Carboxylate-Assisted Ruthenium-Catalyzed C–H Bond *meta*-Alkylations and Oxidative Annulations

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Für meine Eltern

Der Mensch hat dreierlei Wege klug zu handeln:
Erstens durch Nachdenken, das ist der edelste, zweitens durch Nachahmen,
das ist der leichteste, und drittens durch Erfahrung,
das ist der bitterste.

Konfuzius

Contents

1 Introduction

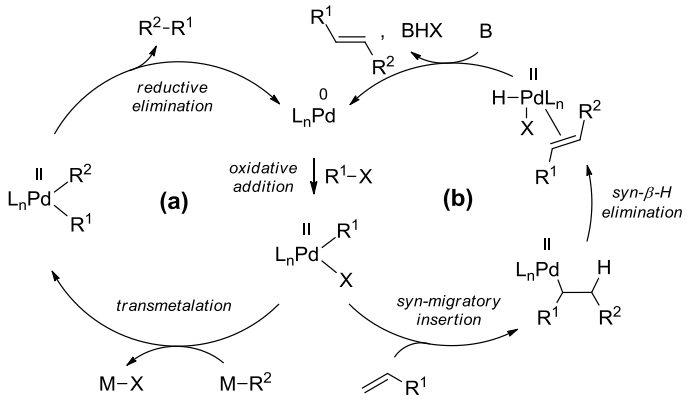
1.1 Transition Metal-Catalyzed C–H Bond Functionalization

Sustainability was declared as one of the major goals within synthetic chemistry.[1] The design of environmentally benign synthetic methods is guided by the '*12 Principles of Green Chemistry*'.[2] Besides safe and non-toxic processes, waste-prevention, as well as atom- and step-economy in combination with catalysis, are all essential requirements for sustainable organic synthesis. From this point of view, transition metal catalysis is an essential step into the desired direction. Thereby, the efficiency of carbon–carbon (C–C) or carbon–heteroatom (C–Het) bond formation can be considerably improved.

For almost half a century, selective transition metal-catalyzed C–C bond formation reactions have attracted significant attention among various research groups around the world. Even in the field of industrial synthesis of pharmaceuticals, these transformations gain more and more attention over classical reaction routes.[3] Certainly, one of the most famous transformations in this research area is the transition metal-catalyzed cross-coupling reaction.[4]

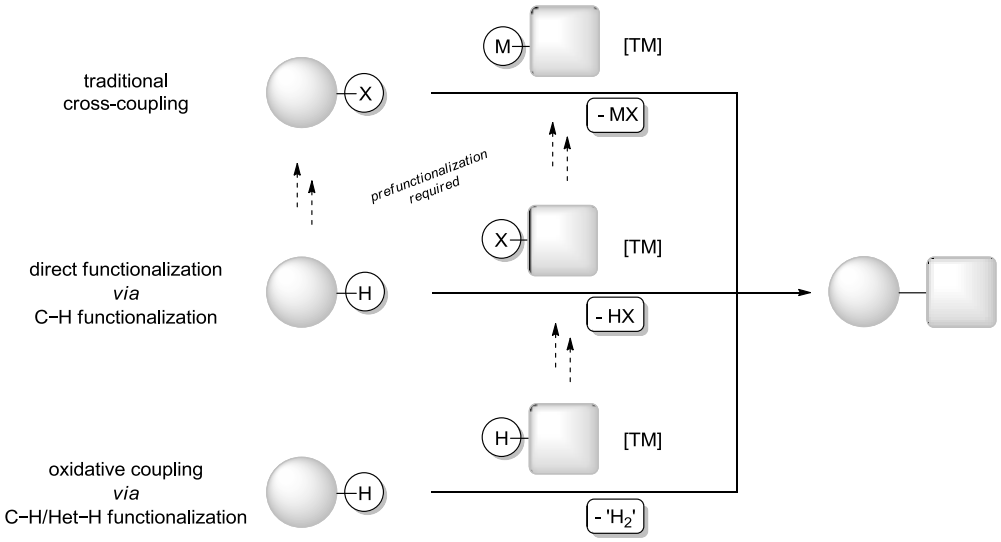
Today, traditional cross-coupling chemistry is a powerful synthetic tool in preparative organic chemistry. This is, for instance, illustrated by the fact that *Heck*, *Negishi* and *Suzuki* have been awarded the Nobel Prize of Chemistry in 2010 for the palladium-catalyzed formation of C–C single bonds *via* cross-coupling chemistry. The major features of these reactions are presented in Scheme 1.1. In general (for the cross-coupling), a (pseudo)halide as an electrophile and an organometallic species as a nucleophile are coupled *via* a Palladium (0)-Palladium (II)-catalytic cycle. The key steps include an oxidative addition, a transmetalation and a reductive elimination (Scheme 1.1, a). For *Mizoroki-Heck*-type couplings (Scheme 1.1, b) a mechanism consisting of a *syn*-insertion followed by σ-bond-rotation and final β-H elimination is generally accepted.[5]

[1] Essen, M.; Metzger, J. O.; Schmidt, E.; Schneidewind, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 414–436.
[2] (a) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2000**, *35*, 686–694. (b) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*, Oxford University Press: Oxford, 1998, p. 30.
[3] Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. *Adv. Synth. Cat.* **2011**, *353*, 1825–1864.
[4] (a) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5086. (b) Metal-*Catalyzed Cross-Coupling Reactions* (Eds. de Meijere, A.; Diederich, F.), 2nd ed., Wiley-VICHY: Weinheim, 2004. (c) *Transition* Metals *for Organic Synthesis* (Eds. Beller, M.; Bolm, C.), 2nd ed., Wiley-VCH: Weinheim, 2004.
[5] Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710.



Scheme 1.1: General catalytic cycles for the cross-coupling (a) and the *Mizoroki-Heck* (b) reaction.

The formation of stoichiometric amounts of potentially harmful metal salts as by-products and the necessity to use prefunctionalized substrates proves to be disadvantageous for the transition metal-catalyzed cross-coupling reaction. To avoid the expensive prefunctionalization steps, transition metal-catalyzed direct functionalizations of C–H bonds represent an excellent alternative (Scheme 1.2).



Scheme 1.2: General comparison of transition metal-catalyzed transformations.

During the last 20 years, direct C–H bond functionalization has become a complementary synthetic tool in organic chemistry, even in the field of the total synthesis of complex natural products and pharmaceuticals.[6]

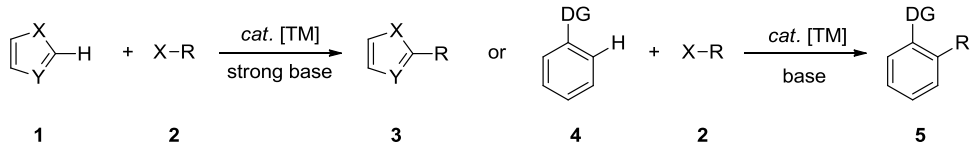
The classical synthetic routes towards the derivatization of arene would for example include electrophilic aromatic substitution (S_E^{Ar}) or directed *ortho*-metalation (DoM)[7] (see below: Chapter

[6] (a) Chen, D. Y.-K.; Youn, S. W. *Chem. Eur. J.* **2012**, *18*, 9452–9474. (b) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788–802. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *5,* 8960–9009. (d) Tran, L. D.; Daugulis, O. *Angew. Chem. Int. Ed*. **2012**, *51*, 5188–5191. (e) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev*. **2011**, *40*, 1885–1898.

[7] Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.

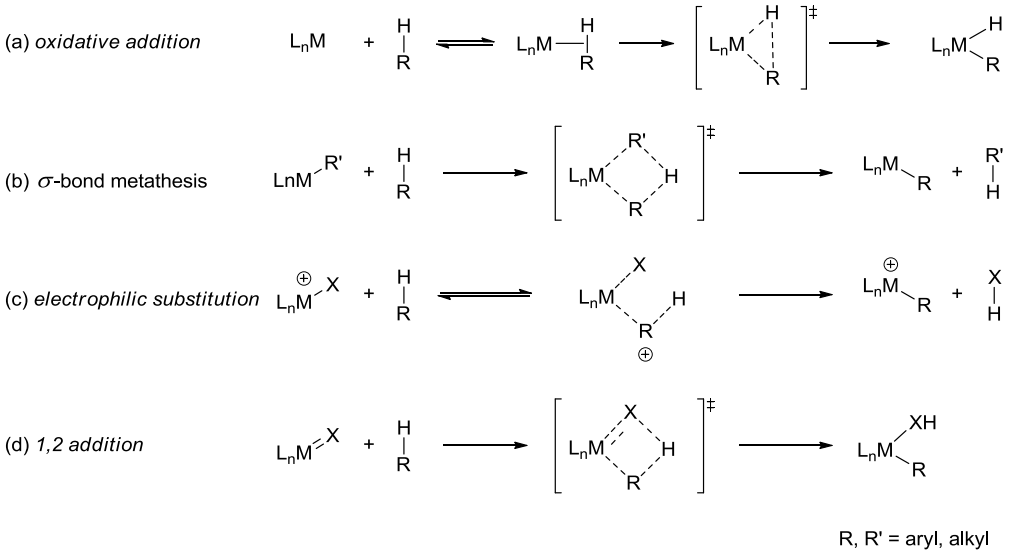
1.2). These reactions are often complicated by harsh reaction conditions and/or side-product formation.

The site-selectivity of catalytic C–H bond functionalizations can be controlled by employing either the enhanced acidity of a specific heteroaromatic C–H bond in substrates of the type **1** or by the directing group (DG) approach for the conversion of substrates **4** into their *ortho*-functionalized derivatives **3** or **5**, respectively (Scheme 1.3, see also Chapter: 1.2).[8] Stoichiometric amounts of bases are necessary in both cases.



Scheme 1.3: Two variants for C–H bond functionalizations.

The C–H bond metalation step can be accomplished by the active metal species L_nM, according to four generally accepted mechanisms (Scheme 1.4). The results of computational studies of these mechanisms on different theoretical levels have been summarized by *Eisenstein* and co-workers.[9]



Scheme 1.4: Possible mechanisms for C–H bond metalation by transition metal complexes.

Oxidative addition (a) is a common process that can mainly be performed by electron-rich, low-valent complexes of late transition metals (Fe, Ru, Os, Ir, Pt, Re). Due to the impossibility of such oxidative transformations for early transition metals with d^0-configuration, σ-bond *meta*thesis (b) appears to be the predominant activation pathway for these metals. In a highly polar reaction medium, late transition metals (e.g. Pd, Pt) might metalate the C–H bond through an electrophilic substitution (c)

[8] (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010,** *110,* 624–655. (b) For a review on removable DG's see: Wang, C.; Huang, Y. *Synlett* **2013**, *24*, 145–149.

[9] Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749–823.

replacing a former ligand on a metal atom with the organic substituent. Alkylidene or amido complexes of early transition metals further possess the possibility to perform the C–H bond activation *via* 1,2-additions (d).[9,10]

Since the aromatic C–H bonds feature enhanced thermodynamic stabilities [D_{H289} (benzene) = 112.9±0.5 kcal·mol^{-1})[11] and low acidities [pK_A (DMSO) = 44.7],[12] marginal differences in reactivity were observed for the different C–H bonds within the same aromatic molecule. Therefore, different strategies have been probed in order to improve the selectivity of transition metal-catalyzed C–H functionalization reactions. Thus, site-selectivity can be achieved *via* chelation, employing Lewis basic directing groups (DG). Alternatively, this effect can be accomplished by the addition of a supplementary reaction partner, for example a base. Pioneering work in the field of stoichiometric base-assisted metalations has been accomplished by the groups of *Shaw*[13] and Reutov[14] in the 1970s. Concerning catalytic base-assisted metalations, it has been proposed that a bidentate base is operating by the *concerted-metalation-deprotonation* pathway (CMD, Fagnou)[15] or by the *ambiphilic metal-ligand activation* (AMLA, Davies & Macgregor) mechanism.[10] Both principles favor a six-membered transition state including very little charge on the aromatic ring. Theoretical calculations on palladium- and iridium- catalyzed[10,16] metalation mechanisms disclose that the metal-acetate complexes have an ambiphilic character due to an intramolecular electrophilic activation of a C–H bond followed by deprotonation with an internal base (Figure 1.1). Furthermore, the function of the transition metal center was also speculated about,[15] as several irida-, rhoda- and ruthenacycles were isolated by *Davies* and co-workers in 2009 upon acetate-assisted C–H-activation reaction of 2-phenylpyridine.[17]

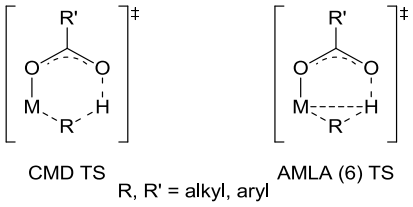
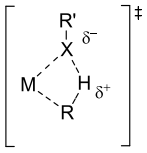


Figure 1.1: Possible transition states during *concerted metalation-deprotonation* (CMD) or *ambiphilic metal-ligand activation* (AMLA) pathways.

[10] Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820–5831.
[11] Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255–263.
[12] Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568–1576.
[13] (a) Duff, J. M.; Shaw, B. L. J. *Chem. Soc., Dalton Trans.* **1972**, 2219–2225. (b) Duff, J. M.; Mann, B. E.; Shaw, B. L.; Turtle, B. J. *Chem. Soc., Dalton Trans.* **1974**, 139–145. (c) Gaunt, J. C.; Shaw, B. L. J. Organomet. Chem. 1975, 102, 511–516.
[14] Sokolov, V. I.; Troitskaya, L. L.; Reutov, O. A. *J. Organomet. Chem*. **1979**, *182*, 537–546.
[15] Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118–1126.
[16] Ess, D. H.; Bischof, S. M.; Oxgaard, J.; Periana, R. A.; Goddard, W. A., III *Organometallics* **2008**, *27*, 6440–6445.
[17] Boutadla, Y.; Al-Duaij, O.; Davies, D. L.; Griffith, G. A.; Singh, K. *Organometallics* **2009**, *28*, 433–440.

The mode of action of monodentate anionic ligands has been explored by the research groups of Goddard as well as Gunnoe.[18] DFT-studies favor an *internal electrophilic substitution* (IES) prior to traditional σ-bond metathesis (Figure 1.2).



IES TS
(X≠ alkyl, aryl)

Figure 1.2: Proposed transition state during the *internal electrophilic substitution* (IES).

During the last decades, the research interest in transition metal-catalyzed C–H bond functionalization as a tool for a variety of C–C bond forming reactions has increased rapidly, especially in the field of biaryl-synthesis.[19]

Among other metals, ruthenium (II) catalysts not only include the remarkably broad substrate scope and the extraordinarily high chemo- and site-selectivity, as reflected by the outstanding functional group tolerance and excellent catalytic activity with water as the reaction medium,[20] but also are significantly less expensive than other transition metal sources. Thus, in 2012, the prices of gold, platinum, rhodium, iridium, palladium and ruthenium were 1730, 1600, 1100, 1050, 669 and 110 US$ per troy oz, respectively.[21]

The *Ackermann* group and others have focused on the application of ruthenium complexes for chelation-assisted direct arylations.[19,22,23] Starting from easily available aryl chlorides as electrophiles and a ruthenium-complex derived from a (hetero-atom-substituted) secondary phosphine oxide [(HA)SPO], they have elaborated the preparative methods for *ortho*-selective direct mono- and bis-

[18] (a) Oxgaard, J.; Trenn, W. J., III; Nielsen R. J.; Periana, R. A.; Goddard, W. A., III *Organometallics* **2007**, *26*, 1565–1567. (b) Conner, D.; Jayaprakash, K. N.; Cundari, T. R.; Gunnoe, T. B. *Organometallics* **2004**, *23*, 2724–2733. (c) for a review, see: Webb, J. R.; BolaÇo, T.; Gunnoe, T. B. *Chem. Sus. Chem.* **2011**, *4*, 37–49.

[19] Selected reviews: (a) Ackermann, L.; Kapdi, A. R.; Potukuchi, H. K.; Kozhushkov, S. I. In *Handbook of Green Chemistry* (Ed. Li, C.-J.), Wiley-VCH: Weinheim, 2012, 259–305. (b) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087–4109; (c) *Modern Arylation Methods* (Ed.: Ackermann, L.), 1st ed., Wiley-VCH: Weinheim, 2009. (d) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (f) Bellina, F.; Rossi R. *Chem. Rev.* **2010,** *110,* 1082–1146. (g) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (h) Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res*. **2012**, *45*, 826–839. (i) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068–5083.

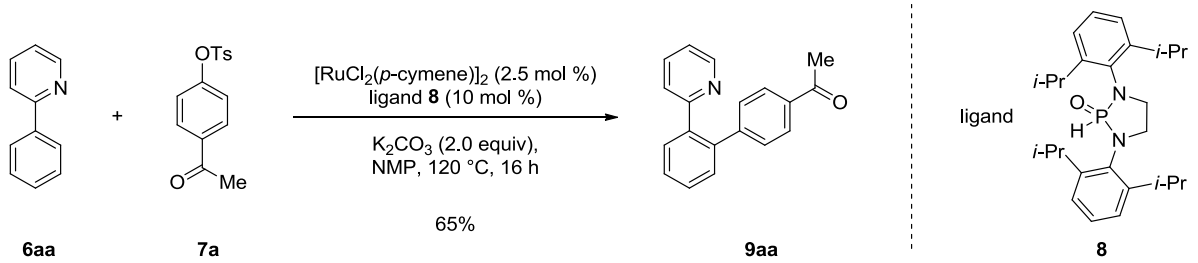
[20] (a) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125. (b) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879–5918.

[21] http://www.platinumgroupmetals.org/

[22] (a) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211–229. (b) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 2619–2622.

[23] (a) Oi, S.; Funayama, R.; Hattori, T.; Inoue, Y. *Tetrahedron* **2008**, *64*, 6051–6059; (b) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783–1785; (c) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org Lett.* **2001**, *3*, 2579–2581.

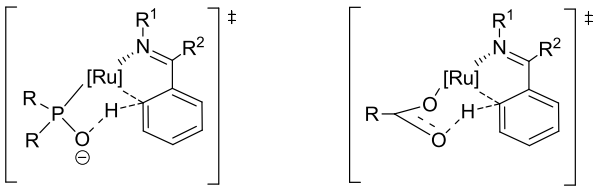
arylation of 2-arylsubstituted pyridines, pyrazoles and ketimines. Even unprecedented direct arylation using tosylates as electrophiles appeared to be successful with a mono-selective outcome (Scheme 1.5).[22]



Scheme 1.5: Ruthenium-catalyzed direct arylation with tosylate **7a** as the electrophiles.

The direct arylation could also be performed *via* initial one-pot *in-situ* tosylation of inexpensive phenol derivatives.[24]

Intensive screening in less polar solvents revealed that sterically demanding carboxylic acids can act in a fashion comparable to the HASPO preligands (Scheme 1.6).[25]



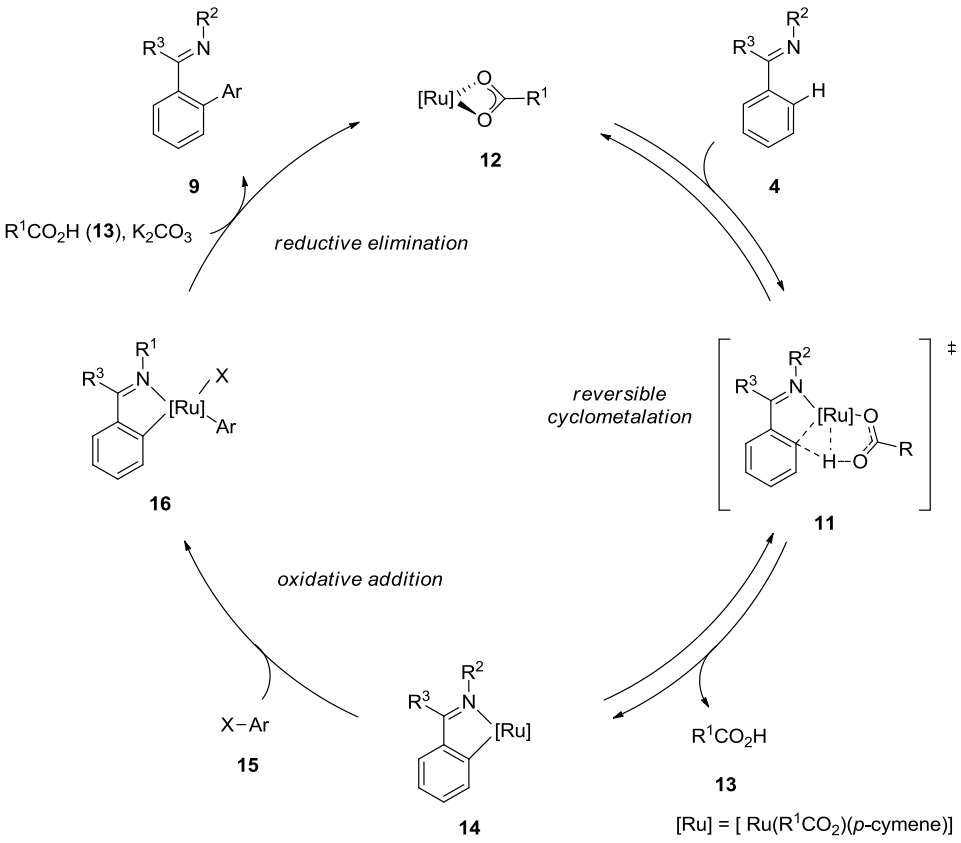
Scheme 1.6: Comparison of C–H metalation transition states between HASPO-preligands and carboxylates.

Mechanistic studies could demonstrate that the direct arylation using carboxylic acids as additives proceeds *via* the *in-situ* formation of a ruthenium-carboxylate complex **12**, which can perform reversible C–H bond functionalization with the substrate. An isolated cycloruthenated complex **14** proved to be catalytically active and is thus expected to participate in the proposed catalytic cycle (Scheme 1.7).[25,26]

[24] (a) Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043–5045; (b) Review: Kozhushkov, S. I.; Potukuchi, H. K.; Ackermann, L. *Catal. Sci. Technol.* **2013**, *in press*. DOI: 10.1039/C2CY20505.

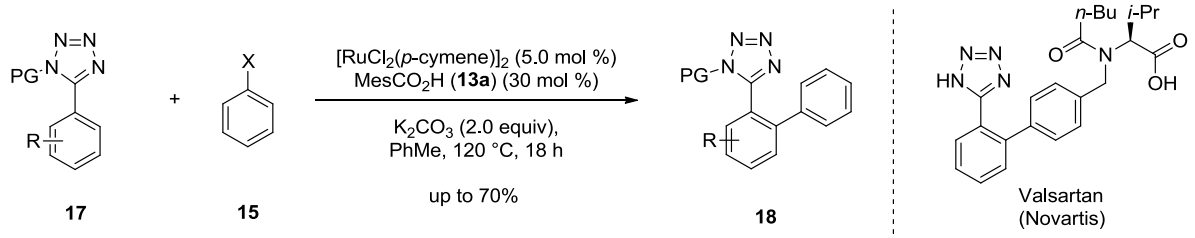
[25] Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299–2302.

[26] (a) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032–5035. For recent reports highlighting the participation of similar ruthenacycles **14** in ruthenium-catalyzed C–H bond functionalizations, see: (b) Li, B.; Feng, H.; Wang, N.; Ma, J.; Song, H.; Xu, S.; Wang, B. *Chem. Eur. J*. **2012**, *18*, 12873–12879. (c) Li, B.; Roisnel, T.; Darcel, C.; Dixneuf, P. H. *Dalton Trans*. **2012**, 41, 10934–10937.



Scheme 1.7: Proposed mechanism for carboxylate-assisted ruthenium-catalyzed direct arylation.

In 2011, *Seki* reported an alternative catalytic system for the ruthenium-catalyzed direct arylation reactions. The use of inexpensive $RuCl_3 \cdot xH_2O/PPh_3$ catalyst resulted in elaborated efficient protocols towards the synthesis of the biaryl unit **18** in angiotensin II receptor blockers like valsartan.[27] Very recently, the group of *Ackermann* showed a carboxylate-assisted complementary ruthenium-catalyzed procedure using mono-protected aryl-tetrazoles as substrate (Scheme 1.8).[28]



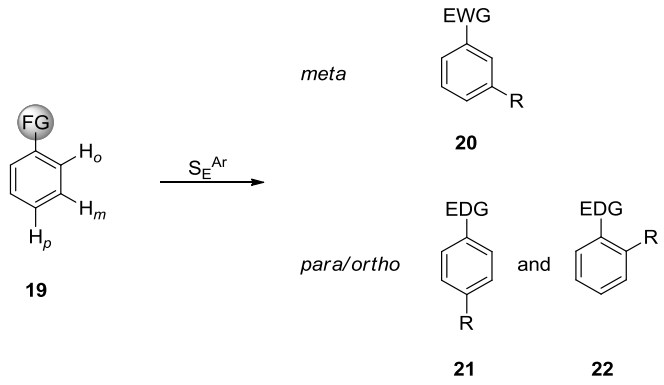
Scheme 1.8: Ruthenium-catalyzed direct arylation towards the synthesis of pharmaceutically important biaryl-structures **18**.

[27] (a) Seki, M. *ACS Catal.* **2011**, *1*, 607–610. For $RuCl_3 \cdot xH_2O$ as catalyst, see also: (b) Ackermann, L.; Althammer, A.; Born, R. *Synlett* **2007**, 2833–2836. (c) Ackermann, L.; Althammer, A.; Born, R. *Tetrahedron* **2008**, *64*, 6115–6124.

[28] Diers, E.; Kumar, N. Y. P.; Mejuch, T.; Marek, I.; Ackermann, L. *Tetrahedron* **2013**, *in press*, DOI:10.1016/j.tet.2013.01.006.

1.2 Site-Selectivity in C–C Bond Formations

When employing classical synthetic methods, such as electrophilic aromatic substitution, the site-selectivity of aromatic C–H bond functionalizations strongly relies on the substitution pattern of the substrate **19**. Depending on the electronic and steric properties of these substituents, the substrate can get *para*- (**21**), *ortho*- (**22**) *or meta*-substituted (**20**)(Scheme 1.9).

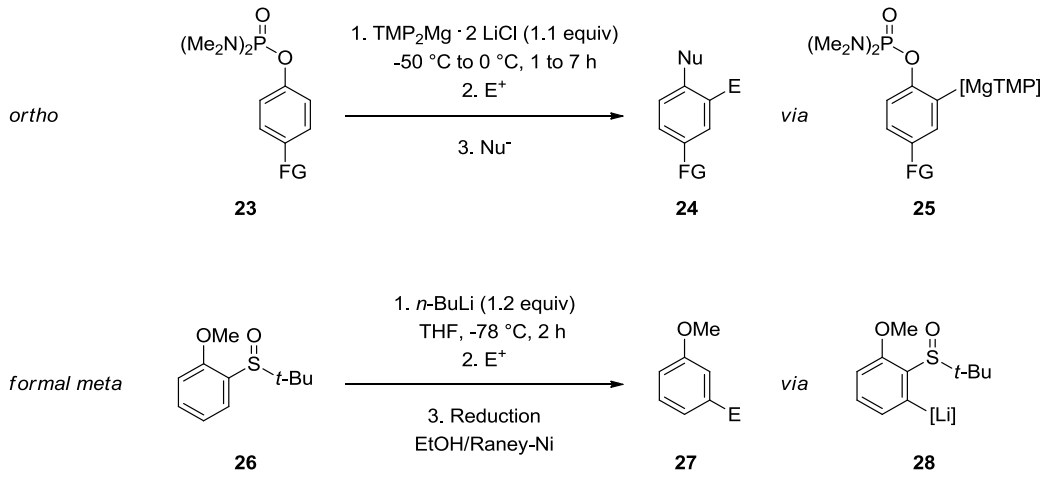


Scheme 1.9: Usual site-selectivity of the electrophilic aromatic substitution.

The research aim of discovering reaction conditions that provide pathways which do not depend on the substitution pattern of the substrate, or in which one can directly functionalize a specific C–H bond remains to be of prime importance.[29] One approach for such a site-selective insertion of a substituent is the use of main group metals in combination with directing groups. This so called '*Directed ortho Metalation*' (DoM) approach has been independently developed in the 1940ies by *Gilman*[30] and *Wittig*[31], and furnished usually *ortho*-functionalized products. Recently, *Knochel* could demonstrate that the use of DoM with organomagnesium compounds in combination with a variety of removable directed-metalation groups (DMG) could be employed for the functionalization of *meta* and *para* C–H bonds as well (Scheme 1.10).[32,33]

Simultaneously, the group of *Brown* reported the site-selective *meta*-substitution using DoM applying organolithiums, and a removable sulfoxide group as DMG.[34] Two simplified examples are shown in Scheme 1.10.

[29] Mahatthananchai, J.; Dumas, A. M.; Bode, J. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 10954–10990.
[30] Gilman, H.; Bebb, R.L. *J. Am. Chem. Soc.* **1939**, 61, 109–112.
[31] Wittig, G.; Fuhrmann, G. *Chem. Ber.* **1940**, *73*, 1197–1218.
[32] Rohbogner, C. J.; Clososki, G. C.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1503–1507.
[33] Monzón, G.; Tirotta, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 10624–10627.
[34] Flemming, J. P.; Berry, M. B.; Brown, J. M. *Org. Biomol. Chem*. **2008**, *6*, 1215–1221.

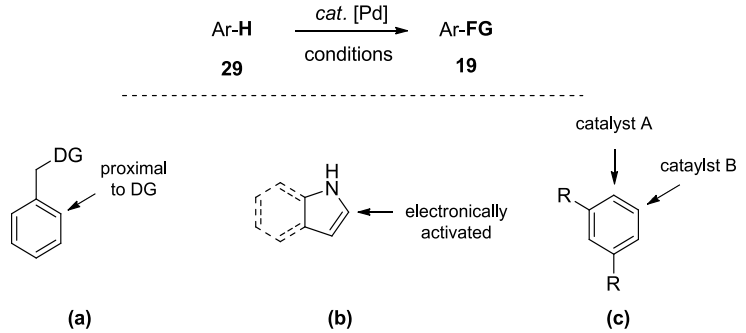


Scheme 1.10: Examples for site-selective C–H deprotonations *via* DoM.

In spite of the generally high selectivities and efficiency of this DoM strategy, the necessity to use stoichiometric amounts of highly reactive main group metal compounds, such as *n*-BuLi, the low reaction temperatures and the need for the removal of the DMG group certainly restricts this approach from the viewpoint of step- and atom-economy.[35]

As an opportunity to avoid disadvantageous stoichiometric amounts of main group metal sources as reactants, transition metal-catalyzed C–H bond functionalization could give access to site-selective incorporations of substituents into arenes.

Due to its high ability for selective C–C bond formations, palladium, one of the most often applied transition metals in catalysis, has been studied intensively by the *Sanford* group. Thus, recently this group has published an overview on the predictive control of site-selectivities in oxidative palladium-catalyzed transformations.[36] The authors differentiate between three the types of control possibilities (Scheme 1.11): Substrate-based through directing groups (a), substrate-based through electronic properties (b), and catalyst-controlled (c).

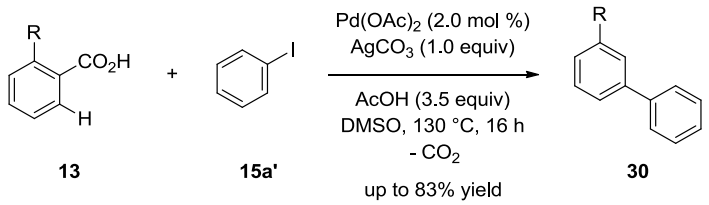


Scheme 1.11: Three possible ways to influence the regioselectivity of palladium-catalyzed C–H bond functionalization according to *Sanford*.

[35] Atom economy: (a) Trost, B. M. *Science* **1991**, *254*, 1471–1477. (b) Trost, B. M. *Acc. Chem. Res*. **2002**, *35*, 695–705.

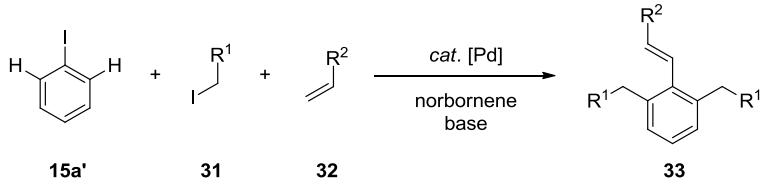
[36] Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res*. **2012**, *45*, 936–946.

These three presented possibilities have been used not only in oxidative couplings, but also in plenty of other transformations. The directing group approach thus usually leads to an *ortho*-functionalization of the substrate. An innovative approach, using carboxylic acids (**13**) as traceless directing groups for formal *meta*-arylation, has been published in 2011 by *Larossa* (Scheme 1.12).[37]



Scheme 1.12: Larossa's formal *meta*-arylation.

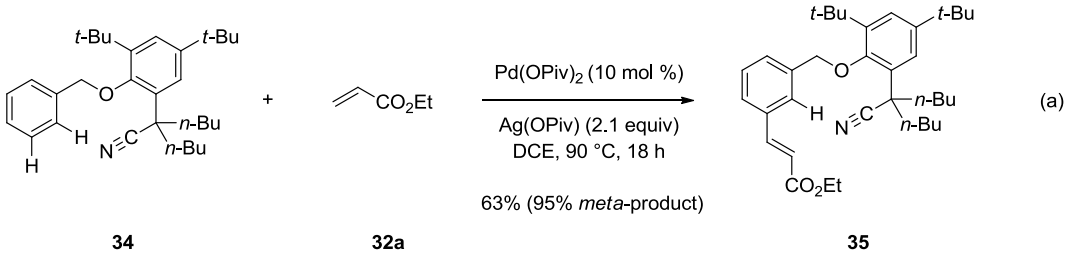
An important example of *ortho*-selective palladium-catalyzed transformation is the so called *Catellani* reaction, in which one can replace both hydrogen atoms in *ortho*-positions to an iodine substituent with diverse nucleophiles followed by *Mizoroki-Heck*-type reaction at the iodine location itself (Scheme 1.13).[38]



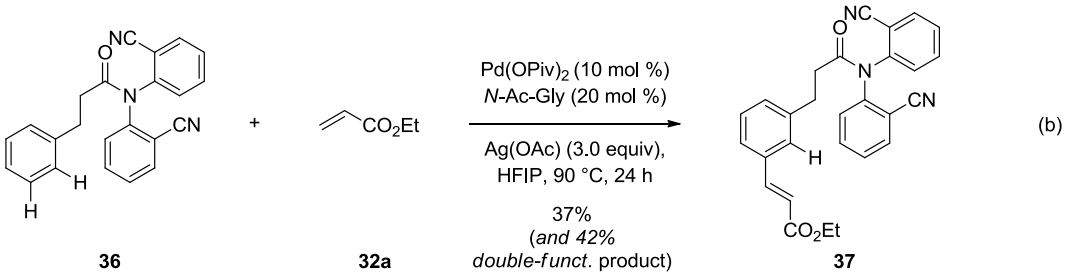
Scheme 1.13: The *Catellani*-reaction in general.

The corresponding cascade mechanism will not be discussed herein.[38] However, it has to be mentioned that a catalytic or stoichiometric amount of norbornene is necessary and that the substrate scope is rather limited, since only iodo arenes (**15a'**), or recently published heteroarenes, can be used exclusively. [39,40]

Besides these approaches for site-selective transition metal-catalyzed functionalization reactions, a recent example for direct *meta*-selective palladium-catalyzed alkenylations using an end-on template have been reported by *Yu* and co-workers in 2012 (Scheme 1.14).[41]



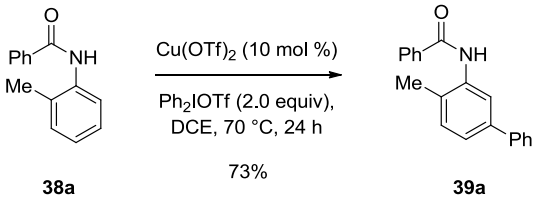
[37] Cornella, J.; Righi, M.; Larossa, I. *Angew. Chem. Int. Ed.* **2011**, *50*, 9429–9432.
[38] Martins, A.; Mariampillai, B.; Lautens, M. *Top. Curr. Chem*. **2010**, *292*, 1–34.
[39] Catellani, M.; Frignani, F.; Rangoni, A. *Angrew. Chem. Int. Ed.* **1997**, *36*, 119–122.
[40] Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990–12993.
[41] (a) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518–522; (b) Highlighted in: Truong, T.; Daugulis, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 11677–11679.



Scheme 1.14: First example of direct *meta*-alkenylation as reported by *Yu*.

This *Fujiwara-Moritani*-type reaction involves the formation of rigid six- or seven-membered cyclic transition states and the use of easily removable nitrile-containing directing groups. In 2009 *Yu et al.* have also reported an approach for *meta*-alkenylation of electron-deficient arenes, wherein the *meta*-selectivity was achieved not due to the *meta*-directing group-effect, but by applying sterically demanding pyridine ligands.[42,43]

Nevertheless, only several *meta*-selective reactions catalyzed by other transition metals, than palladium, have been reported until now. In 2009, the *Gaunt* group has published their findings in the field of copper-catalyzed *meta*-arylations of anilides **38** (Scheme 1.15).[44,45]



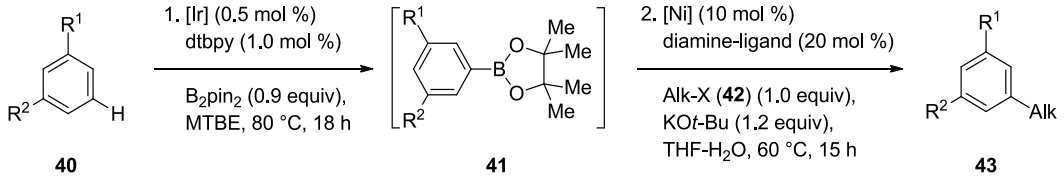
Scheme 1.15: Copper-catalyzed *meta*-arylation according to *Gaunt*.

The reaction mechanism has been discussed controversially and intensively,[46] and in 2011 the group of *Park* has shown the reaction to occur in a *meta*-selective fashion also with heterogeneous recyclable copper catalyst [Cu/AlO(OH)], which was composed from metal nanoparticles.[47] The reaction could proceed smoothly only by raising the temperature (80 °C) and by adding an over-stoichiometric amount (2.0 equiv) of the arylating reagent. It is important to note that even in the absence of a copper-source a high conversion has been detected.

[42] Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072–5074.
[43] For mechanistic DFT calculations, see: Zhang, S.; Shi, L.; Ding, Y. *J. Am. Chem. Soc.* **2011**, *133*, 20218–20229.
[44] (a) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593–1597. (b) Highlighted in: Maleczka, R. E. Jr. *Science* **2009**, *323*, 1573.
[45] For *meta*-alkylation of aromatic α-carbonyl compounds: Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 463–466
[46] For mechanistic DFT calculations, see: (a) Zhang, S.-l.; Ding, Y. *Chin. J. Chem. Phys*. **2011**, *24*, 711–723; (b) Chen, B.; Hou, X.-L.; Li, Y.-X.; Wu, Y.-D. *J. Am. Chem. Soc.* **2011**, *133*, 7668–7671.
[47] Young, E.; Park, J. *Chem. Cat. Chem.* **2011**, *3*, 1127–1129.

Simultaneously, *Gaunt* and co-workers reported also on the copper-catalyzed *para*-selective arylations of phenol and aniline derivatives.[48] The influence of copper in this reaction for the site-selective outcome can be discussed controversially and still remains under question, due to the fact that simple electrophilic aromatic substitution would lead to the observed *para*-selectivity as well.

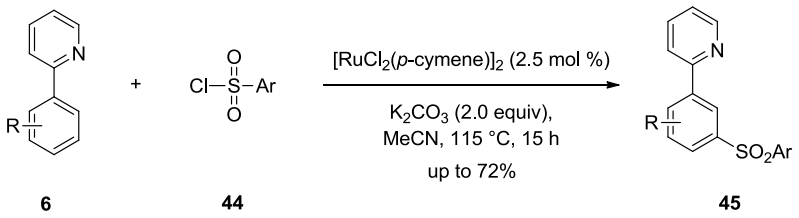
Another transition metal-catalyzed *meta*-selective functionalization of C–H bonds in simple arenes **40** has been invented by the groups of *Marder* and *Hartwig* and consisted of a two-step one-pot procedure. In this particullar case, a stereoselective iridium-catalyzed borylation[49] followed by a *Suzuki-Miyaura*-type cross-coupling reaction was applied (Scheme 1.16). This approach has been used for *meta*-selective arylations,[50] alkylations, allylations, benzylations[51] and halogenations.[52]



Scheme 1.16: Two-step *meta*-selective alkylation of simple arenes **40**.

Obviously, although this transformation can be performed as a one-pot procedure, it needs various reagents and therefore should not be designated as an atom-economical reaction.

Concerning the ruthenium-catalyzed regioselective C–H bond functionalization, only *ortho*-directed reactions, mainly arylations (see above, Chapter 1.1), have been known until recently. In 2011, *Frost* and co-workers have published the first example of a ruthenium-catalyzed *meta*-selective C–S bond formation reaction in sulfonylations of 2-phenylpyridines **6** (Scheme 1.17).[53] The authors proposed a combined C–H activation/S_E^{Ar} mechanism, details of which will be discussed below in chapter 1.1.



Scheme 1.17: Ruthenium-catalyzed *meta*-selective sulfonylation by *Frost et al.*.

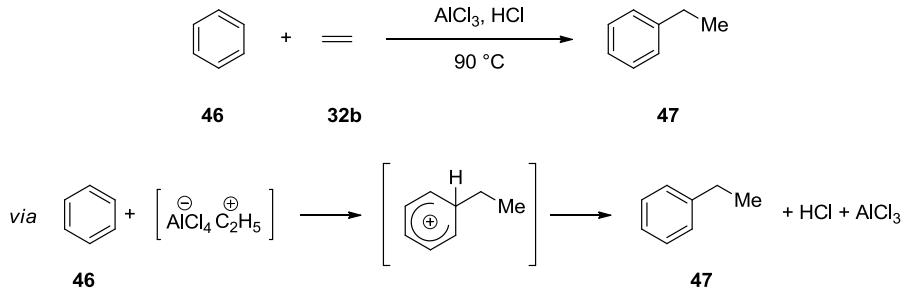
[48] Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M. *J. Angew. Chem. Int. Ed.* **2011**, *50*, 458–462.
[49] Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010,** *110,* 890–931
[50] Morris, J.; Steel, P. G.; Marder, T. B. *Synlett* **2009**, 147–150.
[51] Robbins, D. W.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 933–937.
[52] (a) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129,* 15434–15435; (b) Partridge, B. M.; Hartwig, J. F. *Org. Lett.* **2013**, *15*, 140–143.
[53] Saidi, O.; Marafie, J.; Ledger, A. E. W.; Liu, P. M.; Mahon, M. F.; Kociok-Köhn, G.; Whittlesey, M. K.; Frost, C. G. *J. Am. Chem. Soc.* **2011**, *133*, 19298–19301.

Nevertheless, the analogous *meta*-selective ruthenium-catalyzed direct C–C bond formation reactions still remains ellusive.

1.3 Transition Metal-Catalyzed Alkylation Reactions

Friedel-Crafts Alkylation

Until now, the highly chemo- and regioselective introduction of alkyl chains on aromatic substrates remains a rather challeging objective. On industrial scale, the classical *Friedel-Crafts* chemistry is still the major player, although it involves the use of corrosive reagents, harsh reaction conditions and often undesired side-product formation.[54] Scheme 1.18 demonstrates the alkylation of benzene (**46**) with ethylene (**32b**) affording ethylbenzene (**47**). This reaction is still one of the largest tonnage C–C bond forming processes in industry (ca. 27 Mt/a in 2007).



Scheme 1.18*: Friedel-Crafts* alkylation of benzene.

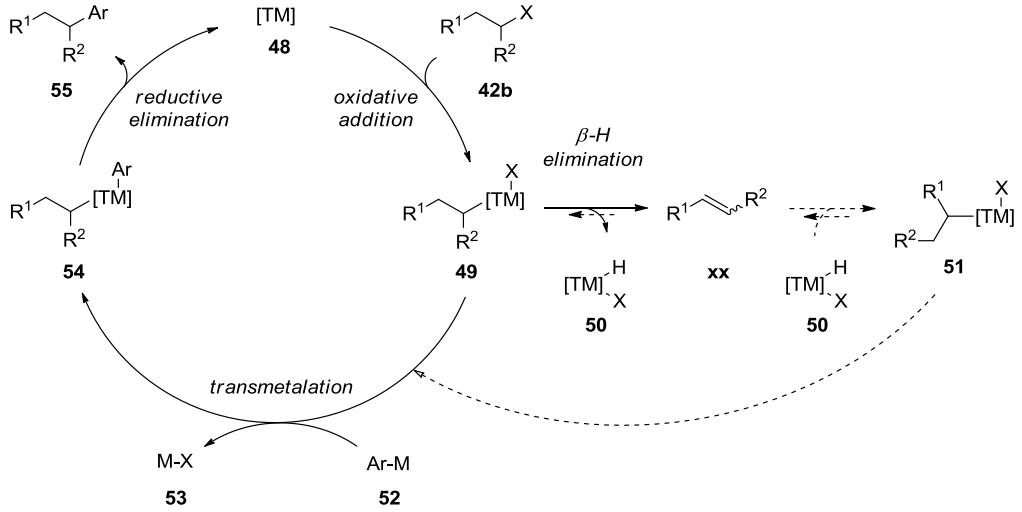
As generally accepted in S_E^{Ar}-type chemistry, electron-donating substituents on the arene moeity favor further substitution by increasing the electron density of the aromatic ring and thus lead to oligoalkylation products. In addition, alkylated carbocations tend to undergo *Wagner-Meerwein* rearrangements, to form the most stable cations, thus leading to a decreased chemoselectivity. Unsatisfactory aspects of this reaction on industrial scale, such as plant corrosion and chloride-containing waste formation, represent an additional problem. In spite of this, tremendous progress has been made in the field of *Friedel-Crafts* alkylation[55] since the first communications[56] in 1877. Beside *Lewis* acids (e.g. $AlCl_3$, $TiCl_4$, BF_3 etc.), strong Brønsted acids (e.g. HF, H_2SO_4 etc.) have been used.

[54] *Metal-Catalysis in Industrial Organic Processes* (*Eds*.: Chiusoli, G. P.; Maitlis, P. M.), RSC: Cambridge, 2007, pp. 163–200.
[55] Rüping, M.; Nachtsheim, B. J. *Beilstein J. Org. Syn.* **2010**, *6*, 1–24.
[56] (a) Friedel, C.; Crafts, J. M. *Compt. Rend*. **1877**, *84*, 1392–1450; (b) Friedel, C.; Crafts, J. M. *J. Chem. Soc.* **1877,** *32,* 725–791.

The first publication of a catalytic *Friedel-Crafts* alkylation using $Sc(OTf)_3$ as *Lewis* acid-catalyst has been reported in 1996.[57] Still immense further developments are ongoing within stereo- and enatioselective catalytic *Friedel-Crafts* alkylation.[58] However, to circumvent the disadvantages of the acid-catalyzed reactions one can either switch to heterogeneous catalysts (for example, acidic zeolites) or use homogeneous transition metal catalysts as a promising alternative.

Cross-Coupling Chemistry

With regard to homogenous catalysis, metal-catalyzed cross-coupling chemistry is an important alternative to acid-catalyzed reactions between arenes and alkyl halides.[59] A general catalytic cycle is represented in Scheme 1.19. In this introduction, only selected examples of alkylations *via* cross-coupling will be discussed.



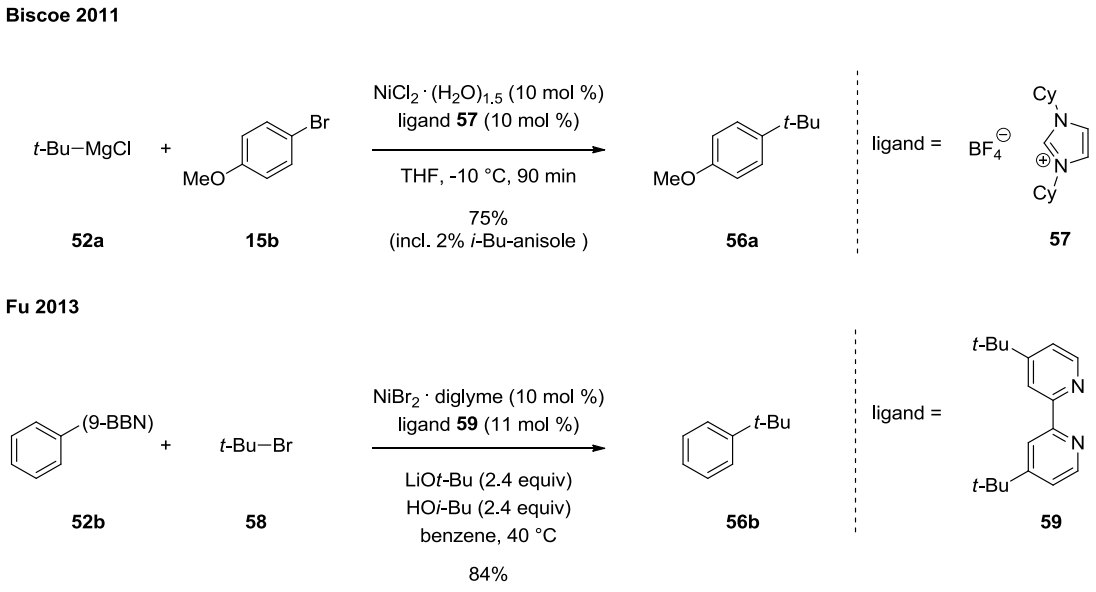
Scheme 1.19: General catalytic cycle for transition metal-catalyzed alkylation of arenes with alkyl halides.

Transition metal-catalyzed cross-couplings with unactivated alkyl (pseudo)halides bearing β-hydrogen atoms are not as easily accomplished as with aryl (pseudo)halides as electrophiles. On the one hand, these electrophiles may undergo competitive reactions like β-hydrogen elimination, which lead to a decreased efficiency and selectivity. On the other hand, they are less prone to undergo the oxidative addition due to their electron-rich character.[60] Of course, advantages of alkylations through traditional cross-coupling reactions can be listed: (a) Control of regioselectivity due to pre-functionalization of arenes, (b) milder reaction conditions as compared to classical *Friedel-Crafts*

[57] Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S.-I. *Synlett* **1996**, 557–559.
[58] *Catalytic Asymmetric Friedel-Crafts Alkylations* (Eds.: Bandini, M.; Umani-Ronchi, A.), Wyley-VCH: Weinheim, 2009.
[59] Reviews: (a) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417–1492. For the use of secondary alkyl halides, see: (b) Rudolph, A.; Lautens, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 2656–2670.
[60] Ackermann, L. *Chem. Comm.* **2010**, *46*, 4866–4877.

chemistry and (c) a broad functional group tolerance.[61] Until recently, most transition metals used in this type of chemistry were palladium, nickel, iron, copper and cobalt.

The great potential of nickel-complexes as the catalyst for alkylations *via* cross-coupling reactions has recently been demonstrated by *Xile Hu*.[62] After publishing several examples for primary and secondary alkyl halides as coupling-partners, the research groups of *Biscoe* and *Fu* finally reported on nickel-catalyzed *Kumada-Corriu* and *Suzuki-Miyaura* cross-couplings with tertiary alkyl halides (**58**) as the electrophiles (Scheme 1.20). Thus, *Biscoe* disclosed the employment of air- and moisture-stable NHC-preligands.[63] However, the products **56a** were contaminated with isomerized *p*-alkylanizoles. On the contrary, such isomerization was not detected by *Fu* and co-workers, but the reaction needed overstoichiometric amounts of *tert*-butoxides to achieve efficient transformation.[64]



Scheme 1.20: Examples of nickel-catalyzed *tert*-alkylations *via* traditional cross-couplings.

Mechanistically these nickel-catalyzed reactions were shown to proceed *via* radical pathways.[65]

Furthermore, *Fu et al.* have made impressive progress within the field of nickel-catalyzed asymmetric alkylation-reactions. This group demonstrated the broad applicability of nickel catalysis for alkyl-alkyl

[61] (a) *Modern Arylation Methods* (Ed.: L. Ackermann), 1st ed., Wiley-VCH: Weinheim, 2009, pp. 155–181. For selected recent reviews on traditional cross-coupling reactions, see: (b) Li, H.; Johansson Seechurn, C. C. C.; Colacot, T. J. *ACS Catal*. **2012**, *2*, 1147−1164. (c) Shaikh, T. M.; Weng, C.-M.; Hong, F.-E. *Coord. Chem. Rev*. **2012**, *256*, 771–803. (d) *Chem. Soc. Rev*. **2011**, *40*, Special Issue 10 "Cross coupling reactions in organic synthesis", 4877–5208. (e) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346–1416. (f) *Acc. Chem. Res*. **2008**, *41*, Special Issue 11 "Cross Coupling", 1439–1564.

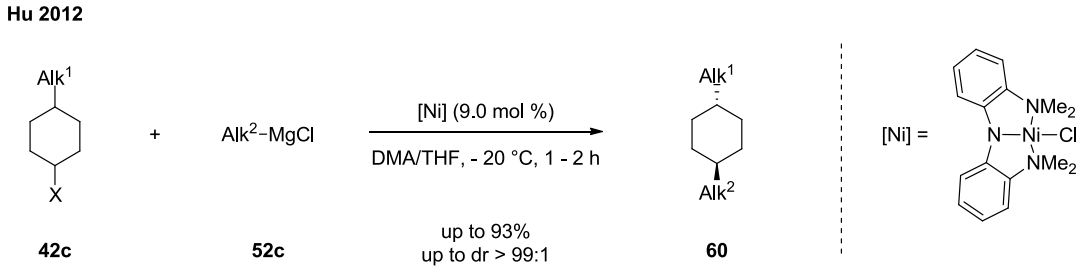
[62] Hu, X. *Chem. Sci.* **2011**, *2*, 1867–1886.

[63] Joshi-Pangu, A.; Wang, C.-Y; Biscoe, M. R. *J. Am. Chem. Soc.* **2011**, *133*, 8478–8481.

[64] Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.*, **2013**, *135, 624–627.*

[65] Taylor, B. L. H.; Jarvo, E. R. *Synlett* **2011**, *19*, 2761–2765.

Negishi[66]- and *Suzuki-Miyaura-type*[67] couplings, while *Hu* and co-workers have published a diastereoselective *Kumada-Corriu-type*[68] coupling in 2012 (Scheme 1.21).



Scheme 1.21: Nickel-catalyzed stereoselective alkyl-alkyl *Kumada-Corriu*-type cross-coupling.[68]

Palladium complexes as the catalyst has been studied most intensively,[69] however, these results will not be discussed herein. Very recently there has also been some evidence of using cobalt[70] and copper[71] as catalysts by the groups of *Nakamura*, *Liu* and *Hu*.

As an inexpensive alternative to the catalytic systems discussed above, iron complexes seem to be the most promising catalysts for the introduction of alkyl chains into arene moieties. Besides the classical (pseudo)nucleophiles like aryl halides, the groups of *Cook*[72] and *Garg*[73] have successively applied several phenol-based substrates, such as **7b** and **15d** in iron-catalyzed *Kochi*-like[74] couplings (Scheme 1.22).

[66] (a) Binder, J. T.; Cordier, C. J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 17003–17006. (b) Choi, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 9102–9105. (c) Oelke, A. J.; Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 2966–2969. (d) Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645–12647.

[67] (a) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794–5797. (b) Zultanski S. L.; Fu, G. C. *J. Am. Chem. Soc.*, **2011**, *133*, 15362–15364. (c) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694–6695. (d) Lu, S.; Fu, G. C. *Angew Chem. In. Ed.* **2010**, *49*, 6676–6678. (e) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602–9603.

[68] Perez Garcia, P. M.; Di Franco, T.; Orsino, A.; Ren, P.; Hu, X. *Org. Lett.* **2012**, *14*, 4286–4289.

[69] (a) *Palladium in Organic Synthesis* (Ed.: Tsuji, J.) Springer-Verlag: Berlin-Heidelberg, 2005, pp. 85–108. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: Negishi, E.), Wiley-Interscience: New York, 2002, pp. 597–618.

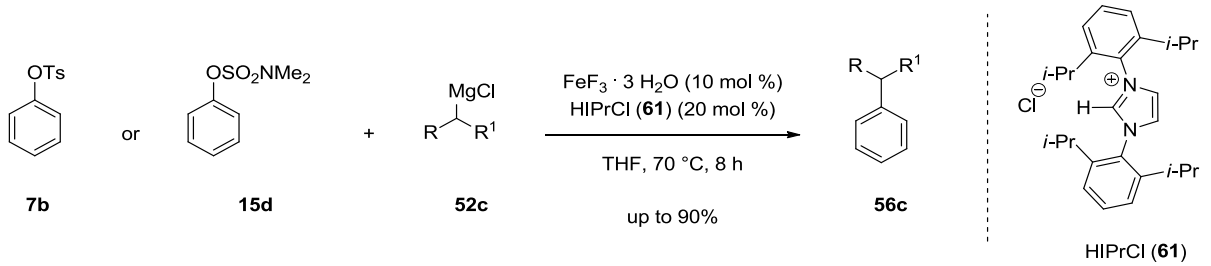
[70] (a) Chen, Q.; Ilies, L.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2011**, *13*, 3232–3234. (b) Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428–429.

[71] (a) Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* **2012**, *134*, 11124–11127. (b) Ren, P.; Stern, L.-A.; Hu, X. *Angew. Chem. Int. Ed.* **2012**, *51*, 9110–9113.

[72] Agrawal, T.; Cook, S. P. *Org. Lett.* **2013**, *15*, 96–99.

[73] Silberstein, A. L.; Ramgren, S. D.; Garg, N. K. *Org. Lett.* **2012**, *14*, 3796–3799.

[74] Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487–1489.



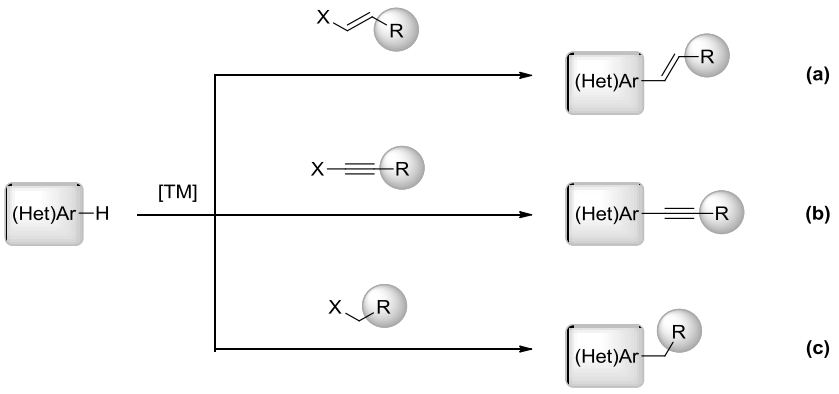
Scheme 1.22: Iron-catalyzed alkylation of arenes using phenol-derived substrates **7b** or **15d.**

Although these reactions give high yields and utilize easily accessible starting materials, like tosylates, and easy-to-prepare air-stable NHC-preligands, they still face the main obstacles of transition metal-catalyzed cross-coupling chemistry in that they employ prefunctionalized substrates. However, certain progress has been made by several research groups to overcome these limitations discussed above in Chapter 1.1.

Transition Metal-Catalyzed Alkylation *via* C–H Bond Functionalization

Because of the disadvantages of classical cross-coupling chemistry, significant progress is expected in the development of direct C–H bond alkylations of arenes and heteroarenes as an environmentally benign and economically more attractive strategy.

In contrast to the sufficiently well elaborated methods for transition metal-catalyzed direct C–H bond arylations (see above, Chapter 1.1), the direct introduction of non-aromatics, especially saturated substituents, has received significant less attention.



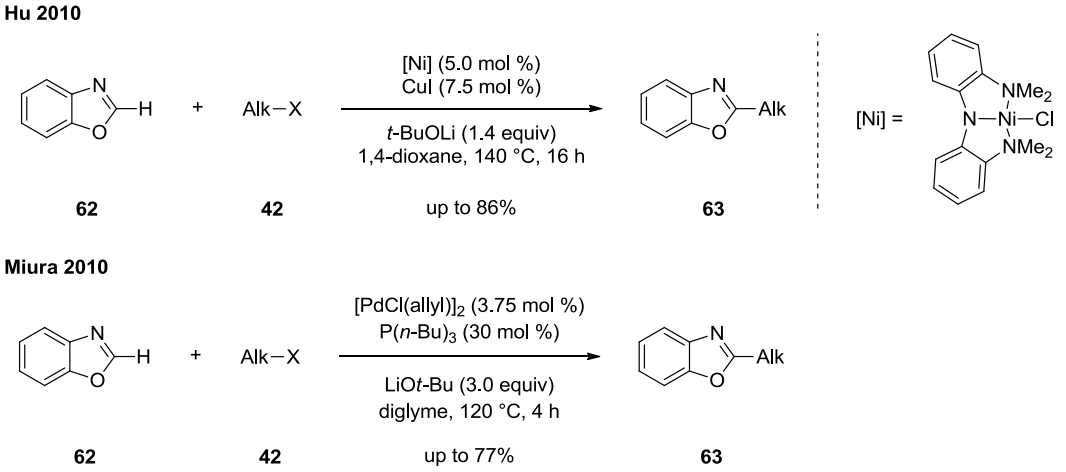
Scheme 1.23: Direct intermolecular alkenylation (a), alkynylation (b) and alkylation (c) of arenes.

Only few methods have been designed for direct alkenylation, alkynylation or even benzylation and alkylation using palladium, rhodium, ruthenium, nickel and copper catalysis (Scheme 1.23).[75]

As indicated above, the present study is focused on the catalytic activity of ruthenium complexes. Among the most prominent examples obtained employing other transition metals, impressive

[75] (a) Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 6495–6516.

progress in the catalytic direct alkylation of relatively acidic C–H bonds in azoles **62**, as reported by the groups of *Hu*[76,77] as well as of *Satoh* and *Miura*,[78] should be mentioned. Thus, in 2010 *Hu* reported on the nickel/copper-catalyzed alkylations of heteroarenes using primary alkyl halides,[77] and in 2012 the similar reactions were performed using less expensive copper catalysts.[76] *Miura* and *Satoh* employed palladium-allyl complexes with additional phosphine ligands for these transformations (Scheme 1.24). [78]



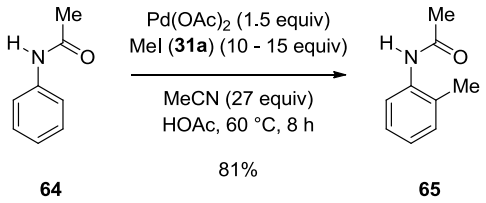
Scheme 1.24: Direct alkylation of acidic C–H bonds in benzo[*d*]oxazole (**62**).

In both cases the authors demonstrated that a broad range of heterocycles could be selectively monoalkylated at the most acidic C–H bond and that a variety of alkyl halides (**42**, X = Cl, Br, I) was reactive under the reported reaction conditions. The main disadvantages herein is the necessity to use over-stoichiometric amounts of strong bases, like lithium *tert*-butoxide, and the impossibility to functionalize all non-acidic positions. A user-friendly modification of the nickel-catalyzed direct alkylation has been reported in 2011 by *Ackermann et al.* using [$NiBr_2$(diglyme)] as the active catalyst.[79]

In 2009, *Fagnou* reported on a palladium-catalyzed benzylation of heterocyclic compounds with benzyl chlorides.[80] The group of *Miura* could also demonstrate that such a palladium-catalyzed benzylation could be performed using benzyl carbonates as reagents in the presence of NaOAc as the base.[81] So far, the described methods strongly rely on the availability of a rather acidic C–H bond.

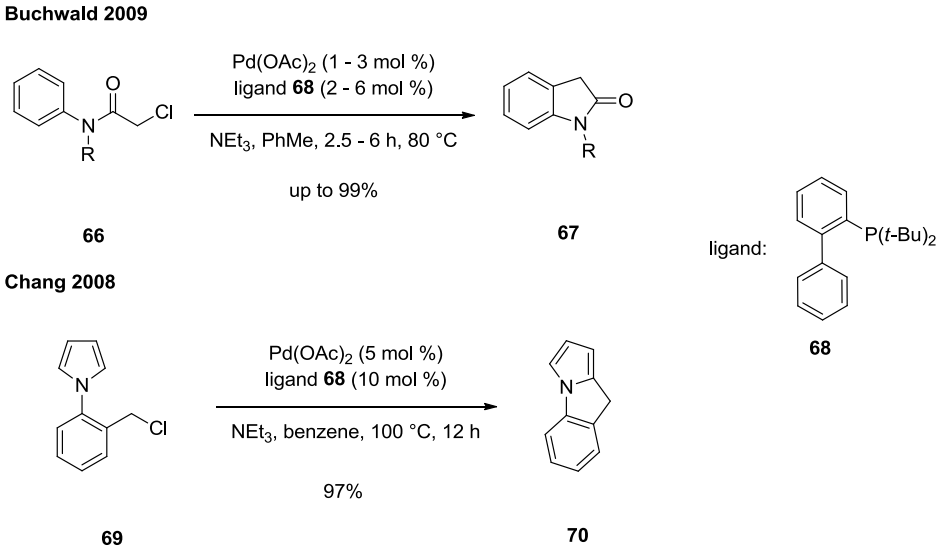
[76] Ren, P.; Salihu, I.; Scopelliti, R.; Hu, X. *Org. Lett,* **2012**, *14*, 1748-1751.
[77] Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem. Int. Ed.* **2010**, *49*, 3061−3064.
[78] Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 12307−12311.
[79] Ackermann, L.; Punji, B.; Song, W. *Adv. Synth. Catal.* **2011**, *353*, 3325–3329.
[80] Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160–4163.
[81] Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 1360–1363. See also: Ackermann, L.; Barfüßer, S.; Pospech, J. *Org. Lett.* **2010**, *12*, 724-726.

Early experiments on palladium-mediated *ortho*-alkylation of acetanilides (**64**) and aldimines employing stoichiometric quantities of palladium acetate have been made by *Tremont* and co-workers in the 1980ies (Scheme 1.25).[82,83]



Scheme 1.25: *ortho*-Methylation of acetanilide (**4g**) mediated by stoichiometric quantities of $Pd(OAc)_2$, as reported by *Tremont*.

In 2003, *Buchwald* elaborated on the catalytic intramolecular cyclisations of anilides **66** towards the synthesis of oxindoles **67**, which can be considered as palladium-catalyzed intramolecular versions of direct alkylation.[84] In 2008, the *Chang* group reported on an analogous synthesis of condensed pyrroloindoles **70** (Scheme 1.26).[85]



Scheme 1.26: Palladium-catalyzed intramolecular direct alkylation reactions.

In 2009, the group of *Yu* disclosed reaction conditions for the palladium-catalyzed *ortho*-alkylation on benzoic acids **13** with selected α,ω-alkyldichlorides or alkyl chlorides (Scheme 1.27). The reaction

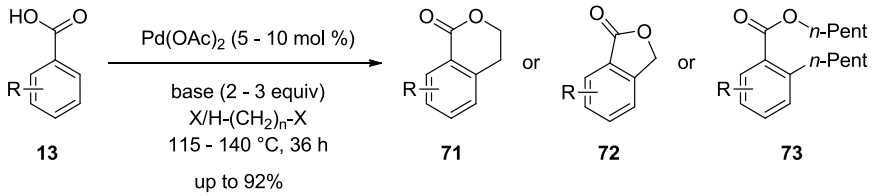
[82] (a) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759–5760; (b) McCallum, J. S.; Gasdaska, J. R.; Liebeskind, L. S.; Tremont, S. J. *Tetrahedron Lett.* **1989**, *30*, 4085–4008.

[83] Nakamura described a similar catalytic alkylation using $Co(acac)_2$ and Grignard-reagents: (a) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428–429; (b) Chen, Q.; Ilies, L.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2011**, *13*, 3232–3234.

[84] Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084–12085.

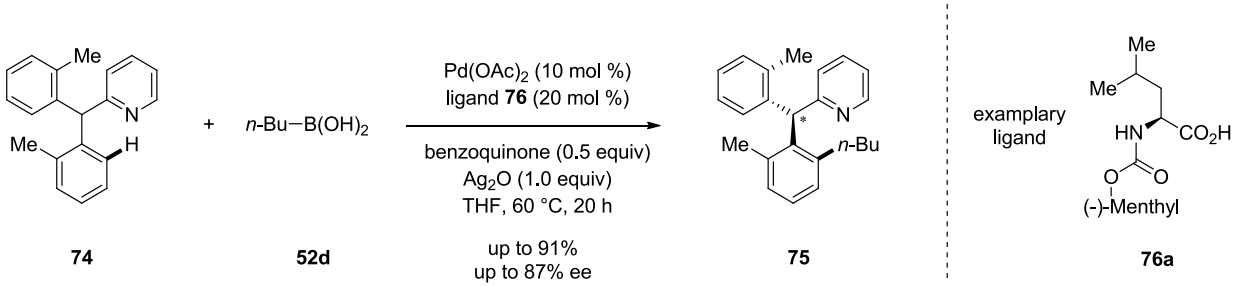
[85] Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 16158–16159.

proceeds *via* an intra- or an intermolecular fashion, after esterification of benzoic acids **13** in a one-pot procedure.[86]



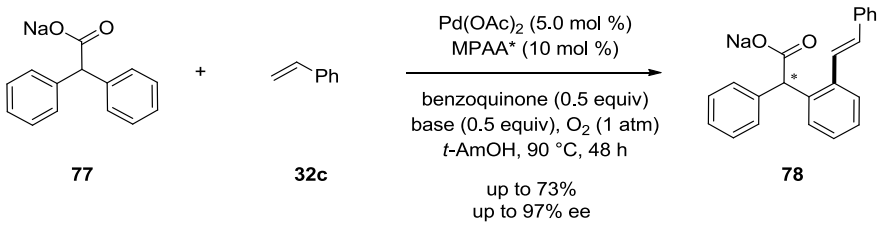
Scheme 1.27: One-pot procedure for esterification/*ortho*-alkylation sequence in benzoic acids **13** through palladium catalysis.

Beside carboxyl *n*-pentyl directing groups, in 2008, *Yu* also demonstrated the possibility to utilize 2-pyridyl directing groups and succeeded in an enatioselective alkylation in substrate **74** using mono-*N*-protected amino acids (MPAA) **76** as chiral ligands (Scheme 1.28).[87]



Scheme 1.28: Site- and eantio-selective palladium-catalyzed alkylation by *Yu*.

Under these reaction conditions, they have also performed an enantioselective C(sp^3)–C(sp^3) bond formation, albeit with moderate yield and enantiomeric excess (38%, 37% ee). Later, in 2010, the *Yu* group has combined both concepts – the application of a carboxyl group as a DG and the enatioselective alkylation using chiral ligands – to accomplish a site- and enantio-selective *Fujiwara-Moritani* alkenylation of sodium diphenylacetates **77** (Scheme 1.29).[88]



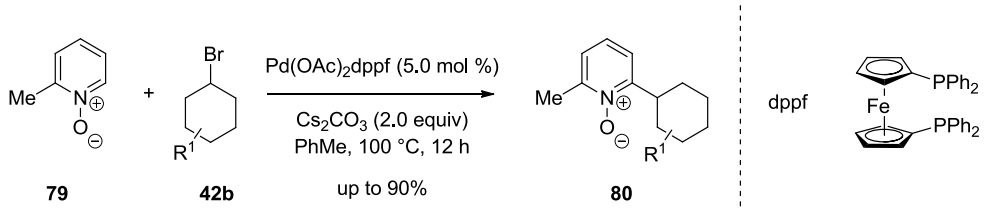
Scheme 1.29: Site- and enantio-selective oxidative alkenylation with carboxylate as the directing group.

[86] Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 6097–6100.

[87] (a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 4882–4886; (b) for mechanistic DFT studies, see: Musaev, D. G.; Kaledin, A.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 1690–1698.

[88] Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460–461.

Very recently, *Fu* described a palladium-catalyzed direct alkylation of pyridine *N*-oxides **79** using the *N*-oxide moiety as the directing group and secondary alkyl bromides **42b** as electrophiles (Scheme 1.30).[89]

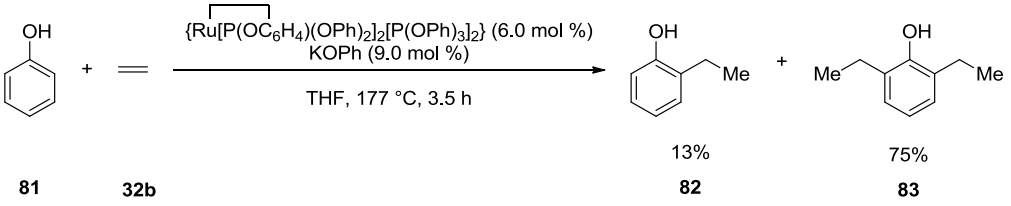


Scheme 1.30: Palladium-catalyzed direct alkylation on pyridine *N*-oxides **79** with cyclohexyl bromide (**42b**).

Ruthenium-Catalyzed Direct Alkylation of Arenes

As this PhD thesis especially deals with ruthenium-catalyzed C–H bond functionalizations, the overview of ruthenium-catalyzed reactions that allow the attachment of certain alkyl groups to the aromatic substrate will be presented below.

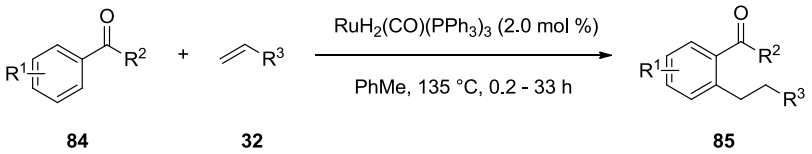
In 1986, the pioneering study by *Lewis* and *Smith* has disclosed the first atom-economical regioselective *ortho*-alkylation of simple phenol derivatives **81** with ethylene, *via* participation of an *in-situ* formed phosphite intermediate (Scheme 1.31).[90,22]



Scheme 1.31: Ruthenium-catalyzed hydroarylation of phenols **81** with ethylene (**32b**) as reported by *Lewis* and *Smith*.

In 1993, *Murai*, *Chatani*, *Kakiuchi* and co-workers reported the addition of various alkenes **32** to aromatic ketones **84** using ruthenium hydride complexes as the catalysts.[91] Today, this hydroarylation reaction is often called the *Murai*-reaction (Scheme 1.32).

[89] Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 616–619.
[90] Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728–2735.
[91] (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529–531. (b) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826–834. For DFT-calculations, see: (c) Helmstedt, U.; Clot, E. *Chem. Eur. J.* **2012**, *18*, 11449–11458. For ruthenium-catalyzed *Murai*-type carbonylations, see: (d) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 2604–2610.



Scheme 1.32: Intermolecular hydroarylation of alkenes **32** with acetophenones **84** (*Murai*-reaction).

The coordination to the ruthenium center by the carbonyl group oxygen promotes the *ortho*-C–H bond cleavage. Subsequent ruthenium coordination to alkene **32** followed by insertion into the Ru–H bond results in the hydroarylation, thereby giving access to anti-Markovnikov alkylation products **70**.

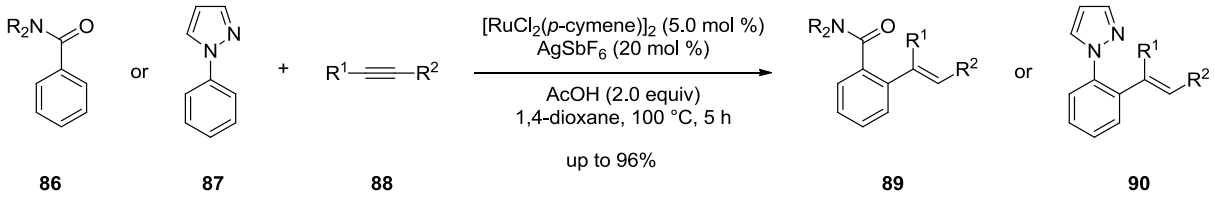
In 2010, the group of *Williamson* has demonstrated the application of the *Murai*-type alkylation towards benzyl alcohols. In this particular case, the ruthenium complex catalyzed two separate reactions, i. e. (i) alcohol oxidation to benzaldehyde by hydrogen transfer to an excess of alkene and (ii) C–H activation/alkene insertion. This reaction afforded the same product **85** (Scheme 1.32); however, *in situ* hydrogenation in the presence of formic acid as hydride source furnished the alkylated benzyl alcohols in high yields.[92] The ruthenium-catalyzed regioselective direct alkylation of perylene bisimides – important class of dyes and pigments – at 2,5,8,11-positions, performed in cooperation of five Japanese research groups obviously demonstrated the user-friendly nature of the *Murai*-reaction.[93]

However, the search for a more convenient pre-catalyst than ruthenium hydride complexes for the *Murai* reaction remains challenging. Thus, an intramolecular ruthenium (III)-catalyzed electrophilic hydro-arylation applying $RuCl_3$/AgOTf as the catalytic system has been elaborated by the group of *Sames* in 2004,[94] who have reported efficient formation of chromanes, tetralins, terpenoids and dihydrocoumarins *via* cyclisation of homo- and dihomoallylarenes.

Darses and *Genet* published a new efficient procedure for the *Murai* reaction in 2009. This protocol operates with the stable, commercially available $[RuCl_2(p\text{-cymene})]_2$ complex as the precatalyst in combination with a phosphine ligand and sodium formiate, to form the catalytically active hydride complex *in situ*.[95]

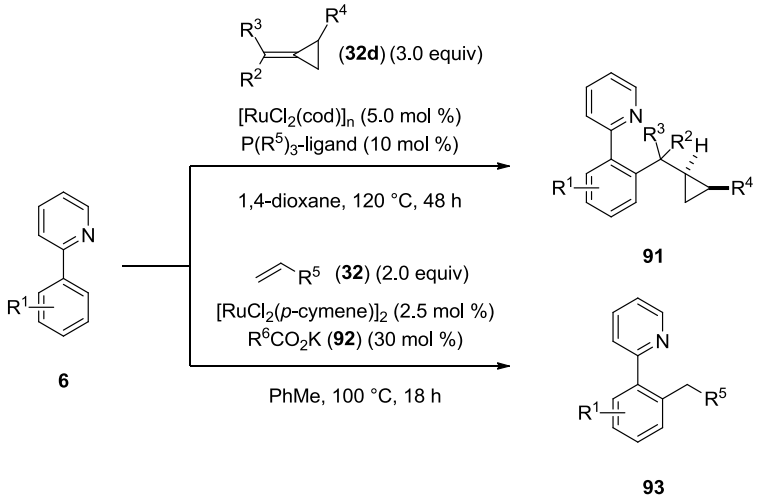
[92] Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2010**, *12*, 3856–3859.
[93] Nakazono, S.; Imazaki, Y.; Yoo, H.; Yang, J.; Sasamori, T.; Tokitoh, N.; Cédric, T.; Kageyama, H.; Kim, D.; Shinokubo, H.; Osuka, A. *Chem. Eur. J.* **2009**, *15*, 7530–7533.
[94] Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581–584.
[95] Martinez, R.; Chevalier, R.; Darses, S.; Genet, J.-P. *Angew. Chem. Int. Ed.* **2006**, *45*, 8232–8235.

Very recently, *Miura* and *Satoh* developed a new procedure for a ruthenium-catalyzed hydroarylation of alkynes **88** using benzamides **86** or 2-phenylpyrazole (**87**) as hydroarylating agents and $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ as the catalytic system (Scheme 1.33).[96]



Scheme 1.33: Ruthenium-catalyzed hydroarylation of alkynes **88**.

Moreover, *Ackermann* and co-workers reported on the ruthenium-catalyzed hydroarylation of methylenecyclopropanes **32d** or unactivated alkenes **32** with 2-phenylpyridines **6** employing $[RuCl_2(cod)]_n$/phosphane and $[RuCl_2(p\text{-cymene})]_2$/carboxylate as the catalysts. Hydroarylations of substrate **6** proceeded smoothly with both types of catalysts and were characterized by complete conservation of all cyclopropane rings in the products **91**, while hydroarylation of simple alkenes **32** required carboxylate assistance (Scheme 1.34).[97]



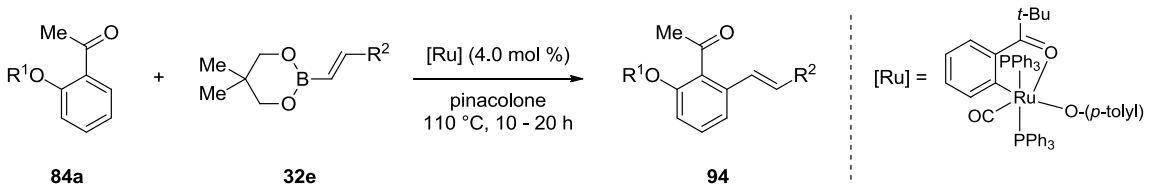
Scheme 1.34: Ruthenium-catalyzed hydroarylation of alkenes **32** according to *Ackermann et al*.

Another synthetic approach towards alkenylated arenes**,** besides the hydroarylation of alkynes (Scheme 1.33), was elaborated by *Kakiuchi* and *Chatani* using the ruthenium-catalyzed alkenylation

[96] (a) Hashimoto, Y.; Hirano, K.; Satoh, T.; Kakiuchi, F.; Miura, M. *J. Org. Chem.* **2013**, *asap*, DOI: 10.1021/jo3025237. (b) Hashimoto, Y.; Hirano, K.; Satoh, T.; Kakiuchi, F.; Miura, M. *Org. Lett.*, **2012**, *14*, 2058–2061. For cobalt-catalyzed alkenylations with stoichiometric amounts of Grignard additives, see: (c) Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 17283–17295. (d) Ding, Z.; Yoshikai, N. *Synthesis* **2011**, *16*, 2561–2566.

[97] (a) Ackermann, L.; Kozhushkov, S. I.; Yufit, D. S. *Chem Eur. J.* **2012**, *18*, 12068–12077; (b) Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Lett.* **2008**, *10*, 3409–3412; (c) Schinkel, M.; Marek, I.; Ackermann, L. *Angew. Chem. Int. Ed*. **2013**, in press; (d) Schinkel, M. *Dissertation*, Universität Göttingen, 2013.

with alkenyl acetates or boronates **32e**.[98] This method could be applied to aromatic ketones **84a** (Scheme 1.35) or 2-phenylheteroarenes with heteroarene as a nitrogen-containing directing group.

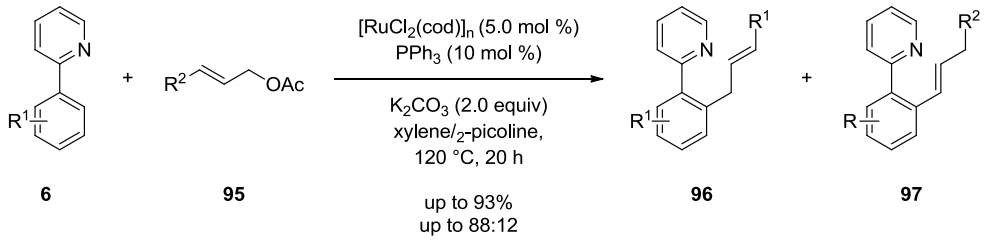


84a **32e** **94**

Scheme 1.35: Ruthenium-catalyzed direct alkenylation with alkenyl boronates **32d** as reported by *Chatani* and *Kakiuchi*.

In 2005, *Inoue*'s group succeeded in an attempt of direct alkenylation of 2-aryloxazolines with alkenyl bromides. The resulting substituted arenes were isolated in moderate to excellent yields, but were contaminated with isomerized arylalkenes in all reported cases.[99] In spite of this, the reaction appears to be promising as a highly step-economical, cost-efficient and sustainable process, and thus demands additional investigations.

An example for the direct ruthenium-catalyzed *ortho*-allylation of arenes **6** has been described by *Oi* and *Inoue* in 2006 (Scheme 1.36).[100] They have demonstrated a direct allylation that proceeds in high yields, but with formation of isomerized by-products, which they believe were formed *via* the reorganization of an *σ*-allyl intermediate to a *π*-allylruthenium complex prior to an C–H cycloruthenation.



6 **95** **96** **97**

Scheme 1.36: Ruthenium-catalyzed allylation with acetates **95** as desribed by *Oi* and *Inoue*.

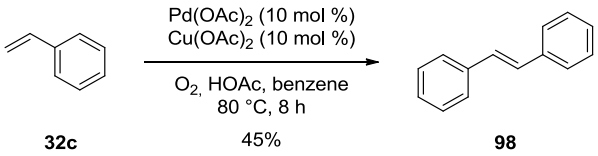
Very recently, the group of *Chatani* reported also on a procedure for a direct alkynylation on substrates bearing a nitrogen-containing DG and using an inexpensive ruthenium (II) complex as the catalyst and caesium pivalate for carboxylate assistance in the C–H activation step.[101]

[98] (a) Ueno, S.; Kochi, T.; Chatani, N.; Kakiuchi F. *Org. Lett.* **2009**, *11*, 855–858; (b) Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M., Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 9858–9859.
[99] Oi, S.; Azaiwa,E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113–3119.
[100] Oi, S.; Tanaka, Y.; Inoue, Y. *Organometallics* **2006**, *25*, 4773–4778.
[101] Ano, Y. ; Tobisu, M.; Chatani, N. *Synlett*, **2012**, *23*, 2763–2767.

1.4 Transition Metal-Catalyzed Oxidative Couplings

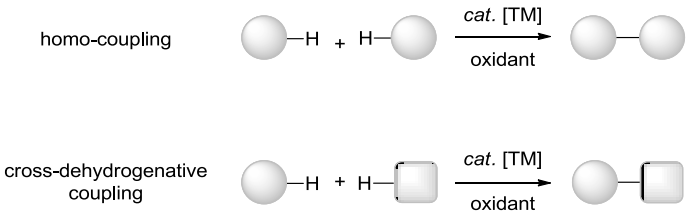
As discussed above, transition metal catalyzed direct functionalizations (see Chapter 1.1), such as direct arylations or alkylations, constitute an important and efficient synthetic method for the chemo- and site-selective C–C bond formation (see above in Chapter 1.1). To enhance the atom economy and the sustainability of transition metal-catalyzed transformations, oxidative methods are promising advancements due to their low waste production and no requirement for prefunctionalization of the substrates.

Thus, in the 1960ies *Fujiwara* and *Moritani* have descibed the palladium-catalyzed oxidative *Heck*-type cross-coupling reaction using various alkenes and arenes as coupling partners (Scheme 1.37).[102] Based on their pioneering work, a broad range of methodologies has been developed during the last decades.



Scheme 1.37: *Fujiwara-Moritani* oxidative alkenylation.

The principle of transition metal-catalyzed oxidative coupling has been extended to metals other than palladium, such as rhodium or gold, and was used for homo- or cross-dehydrogenative couplings (CDC) of variuos substrates (Scheme 1.38).[103]



Scheme 1.38: Homo- and cross-dehydrogenative couplings.

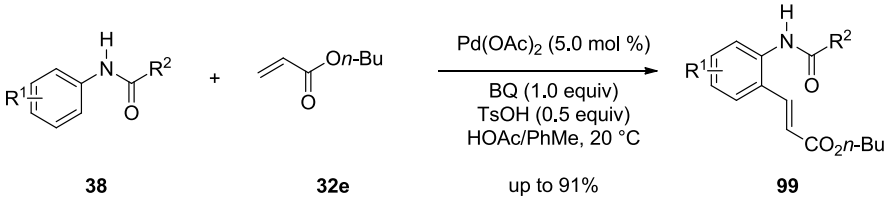
This approach was also found useful for the efficient C–H/Het–H bond functionalizations in an inter- or intramolecular fashion, thus allowing the one-pot preparation of synthetically and practically

[102] (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119–1122. (b) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169. Reviews: (c) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170–1214. (d) Ferreira, E. M.; Zhang, H.; Stolz, B. M. *Oxidative Heck-Type Reactions (Fujiwara-Moritani Reactions)*. In *The Mizoroki-Heck Reaction* (ed.: Oestreich, M.), Wiley: Chichester, 2009, pp. 345–382.

[103] (a) Klussmann, M.; Sureshkumar, D. *Synthesis* **2011**, 353–369. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev*. **2011**, *111*, 1215–1292.

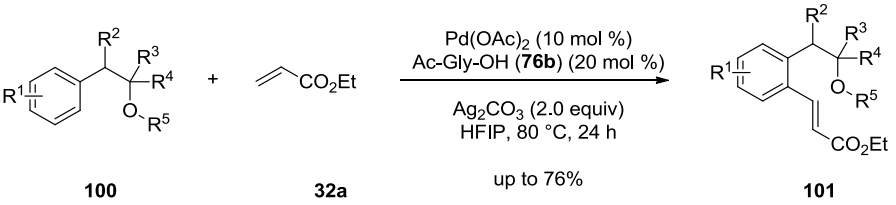
useful heterocycles, such as substituted isoquinolines, isoquinolones, isocoumarins, α-pyrones and 2-pyridones.[104]

Further development of the *Fujiwara-Moritani* reaction[105] resulted in an elaboration of a number of approaches for oxidative alkenylations catalyzed by various transition metals.[102c-f] While the earlier protocols essentially required (super)stoichiometric amounts of peroxides, along with strong acids and/or high reaction temperatures, an important improvement of the oxidative palladium-catalyzed alkenylation has been made by *de Vries* and *van Leeuwen* in 2002,[106] who accomplished selective *ortho*-olefinations of anilides **38** at ambient temperature using *n*-butyl acrylate (**32e**) as a coupling partner (Scheme 1.39).



Scheme 1.39: Palladium-catalyzed *ortho*-alkenylations of anilides **38** under mild reaction conditions.

Among other directing groups, *Yu* recently expanded the substrate scope of this reaction to include aryl urea derivatives.[107] *Yu* also reported on a complementary two-step method for the efficient synthesis of indolines. Beside nitrogen-containing directing groups, he presented in 2013 an oxidative alkenylation of aromatic alkyl ether **100** with weakly coordinating DG in excellent yield, while employing inexpensive MPAAs (**76**) as the ligands (Scheme 1.40).[108]



Scheme 1.40: Palladium-catalyzed oxidative *ortho*-alkenylation with alkyl ether directing groups.

In 2007, *Satoh* and *Miura* reported on the first rhodium-catalyzed oxidative alkenylation using easily accessible benzoic acid **13b** as substrate and acrylates, acryl amides or nitriles as alkenylating reagent

[104] Reviews: (a) Ackermann, L. *Acc. Chem. Res.* **2013**, *46*, DOI:10.1021/ar3002798. (b) Zhu, C.; Wang, R.; Falck, J. R. *Chem. Asian J.* **2012**, *7*, 1502–1514. (c) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev*. **2011**, *40*, 4740–4761. (d) Satoh, T.; M. Miura, M. *Synthesis* **2010**, 3395–3409. (e) Satoh, T.; Ueura, K.; Miura, M. *Pure Appl. Chem*. **2008**, 80, 1127–1134. (f) Nakamura, I., Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. (g) Chiba, S. *Chem. Lett*. **2012**, *41*, 1554–1575.

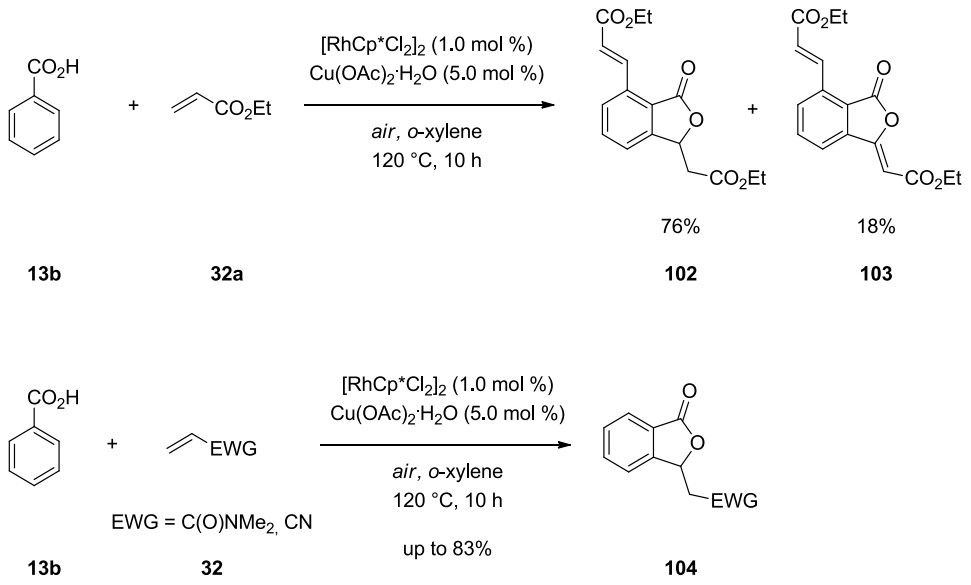
[105] Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992–1995.

[106] Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587.

[107] Wang, L.; Liu, S.; Li, Z.; Yu, Y. *Org. Lett.* **2011**, *13*, 6137–6139.

[108] Li, G.; Leow, D.; Wan, L.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2013**, *52*, 1245–1247.

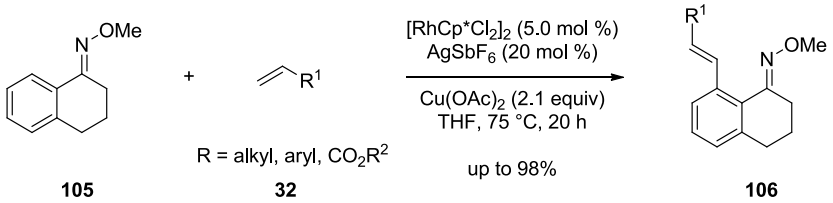
(Scheme 1.41).[109] Herein, a rhodacycle intermediate undergoes alkene insertion followed by β-hydride elimination to form the *ortho*-monovinylated benzoic acid. After a possible second oxidative alkenylation step (for acrylates **32a**), the alkenylation products immediately underwent subsequent intramolecular oxa-*Michael*-reaction, affording divinylated products **102** along with side-product **103** or isobenzofuran-1(3*H*)-ones **104**, respectively.



Scheme 1.41: First rhodium-catalyzed oxidative alkenylation by *Satoh* and *Miura*.

A similar tandem rhodium-catalyzed oxidative olefination-*Michael*-addition between benzamides and alkenes with Ag_2CO_3 as the oxidant was reported in 2010 by the group of *Li*.[110]

Not only ethyl acrylates, but a broad range of alkenes could be used. For example, *Bergman* and *Ellman* succeeded in the first direct oxidative alkenylation of *O*-methyl oximes **105** with a broad range of alkenes **32**, including unactivated ones, employing a highly efficient and selective, yet rather expensive rhodium catalyst (Scheme 1.42).[111]

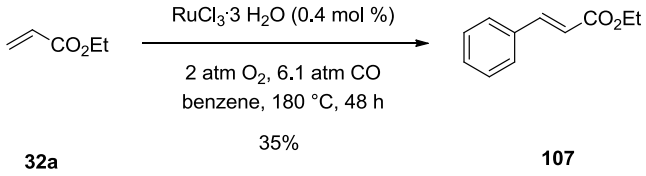


Scheme 1.42: Rhodium-catalyzed oxidative alkenylation of *O*-methyl oximes **105** with alkenes **32**.

[109] Ueura, K.; Satoh, T.; Miura M. *J. Org. Chem.* **2007**, *72*, 5362–5367.
[110] Wang, F.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5430–5433.
[111] Tsai, A. S.; Brasse, M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 540–542.

Alkenylations of acetophenones and benzamides as substrates under comparable reaction conditions have been reported by *Glorius* and co-workers in 2010.[112]

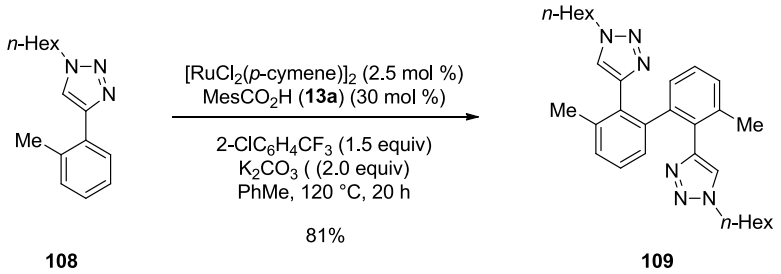
In 2001, *Milstein* discovered the first example of ruthenium-catalyzed oxidative coupling of arenes with olefins under an oxygen atmosphere and harsh reaction-conditions (Scheme 1.43).[113] According to this protocol, moderate yields of up to 47% with low site-selectivities were obtained from substituted arenes and Michael acceptors, while the yields even with activated alkenes were rather low.



Scheme 1.43: First report on ruthenium-catalyzed oxidative alkenylation by *Milstein*.

In 2008, *Inoue* and *Oi* reported on a ruthenium-catalyzed oxidative homocoupling of arenes bearing nitrogen-containing directing groups in their attempted alkenylation with methallyl acetate.[114] In this reaction methallyl acetate served as a hydrogen scavenger, and the homocoupled product was released *via* reductive elimination of a di-cycloruthenated intermediate.

The group of *Li* reported in 2009 on the ruthenium-catalyzed oxidative homo-coupling of 2-phenylpyridines **6** while employing stoichiometric amounts of iron (III) chloride as the oxidant.[115] Further, *Ackermann* et. al could isolate the homocoupling-products, such as **109,** as the main reaction products (Scheme 1.44).[116] These finding have been made during their studies towards carboxylate-assisted ruthenium-catalyzed direct arylations.

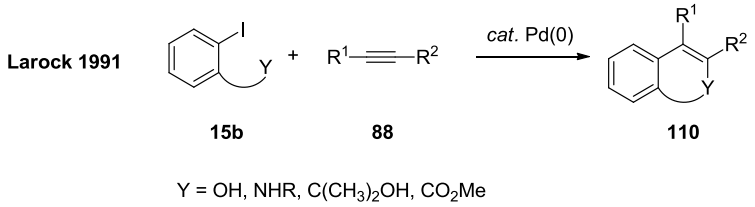


Scheme 1.44: Ruthenium-catalyzed oxidative homo-coupling of phenyltetrazoles (**108**) reported by *Ackermann et al.*.

[112] Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 1064–1067.
[113] (a) Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337–338. Review: (b) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, *DOI*: 10.1039/C2SC21524A.
[114] Oi, S.; Sato, H.; Sugawara, S.; Inoue, Y. *Org. Lett.* **2008**, *10*, 1823–1826.
[115] Guo, X.; Deng, G.; Li, C.-J. *Adv. Synth. Catal.* **2009**, *351*, 2071–2074.
[116] Ackermann, L.; Novák, P.; Vicente, R.; Pirovano, V.; Potukuchi, H. K. *Synthesis* **2010**, 2245–2253.

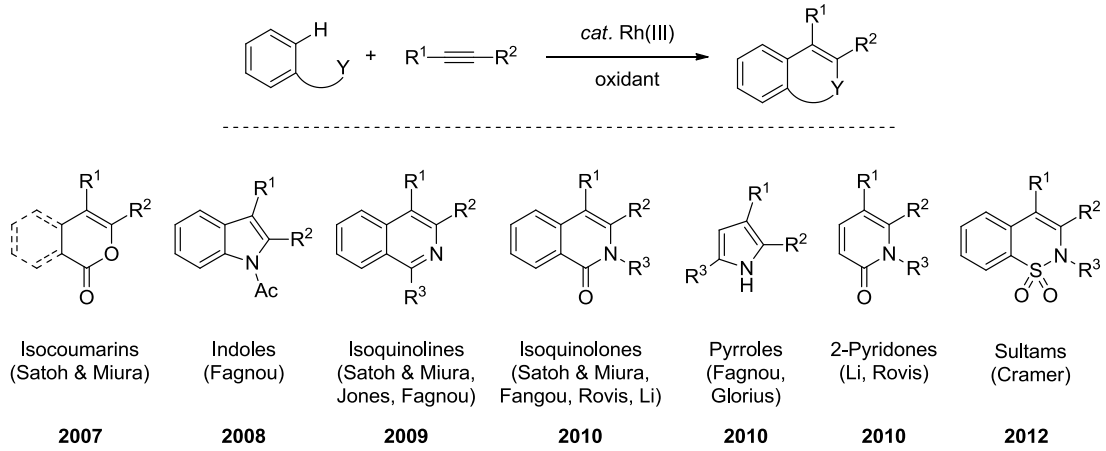
The researchers presented evidence that Ar–X, which normally acted as an arylating agent, in this particular case served as an oxidant, thus promoting the homocoupling. The reaction conditions were optimized to provide broad applicability and moderate to good yields for *ortho*-alkyl-substituted electron-rich substrates. Very recently, a rhodium- as well as a ruthenium-catalyzed oxidative cross-dehydrogenative direct arylation have been published by *You* and co-workers using substrates with nitrogen-containing directing groups and 2-methylthiophenes as the coupling partner.[117]

Revisiting conception of atom-economy and sustainability in organic synthesis, multiple oxidative annulations form the basis for an intelligent approach for diverse heterocycle syntheses. For example, a number of synthetically valuable protocols have been discovered on the basis of the important *Larock*-type heterocyle synthesis (Scheme 1.45).[118]



Scheme 1.45: Intermolecular palladium-catalyzed annulation with alkynes **88** as reported by *Larock*.

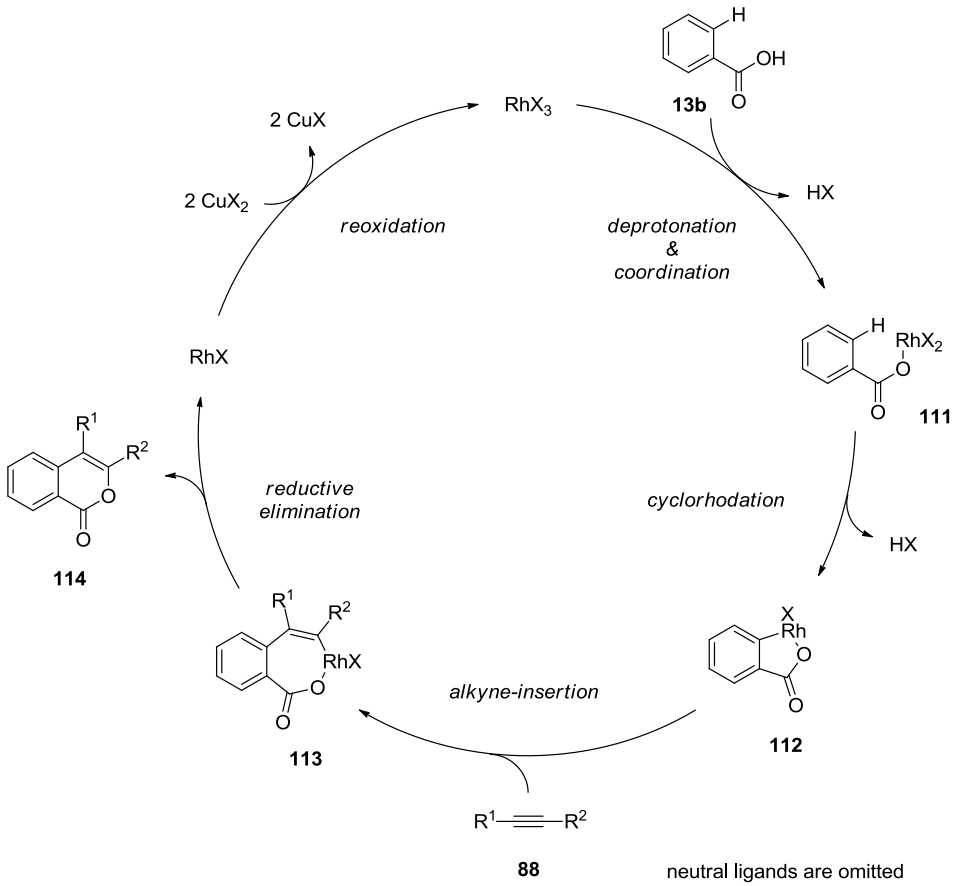
Further development demanded to bypass the well-known limitations of this methodology, such as the prefunctionalization of starting materials **15b**. Thus, a one-pot combination of transition metal-catalyzed C–H bond metalation and annulation steps has become a challenging research target today. Most procedures have been performed with rhodium catalysts and $Cu(OAc)_2 \cdot H_2O$ as the oxidant.[119] For example, *Satoh* and *Miura* have pioneered several practical applications of this synthetic strategy (Scheme 1.46).[120]



Scheme 1.46: Selected examples of oxidative rhodium-catalyzed annulations.

[117] Dong, J.; Long, Z.; Song, F.; Wu, N.; Guo, Q.; Lan, J.; You, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 580–584.
[118] (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690; (b) Larock, R. C. *Top. Organomet. Chem*. **2005**, *14*, 147–182.
[119] Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651–3678.
[120] Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212–11223, and references cited therein.

A general reaction mechanism is presented in Scheme 1.47 for the formation of isocoumarins **114** *via* rhodium-catalyzed oxidative annulation.



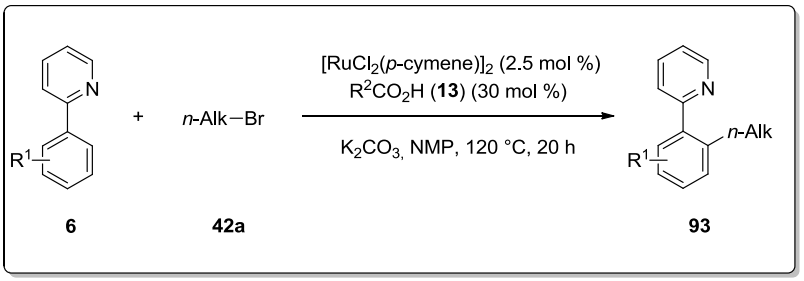
Scheme 1.47: General catalytic cycle for rhodium-catalyzed annulation for the synthesis of isocoumarins.

The catalytic-cycle is initiated *via* the coordination of the rhodium (III) catalyst to the benzoate to form intermediate **111**. After the subsequent formation of intermediate **112** *via* cyclorhodation, coordination of the alkyne moiety followed by alkyne insertion gives intermediate **113**. Reductive elimination releases the isocoumarin **114** and forms a rhodium (I)-species, which undergoes reoxidation by the copper (II) source.

2 Objectives

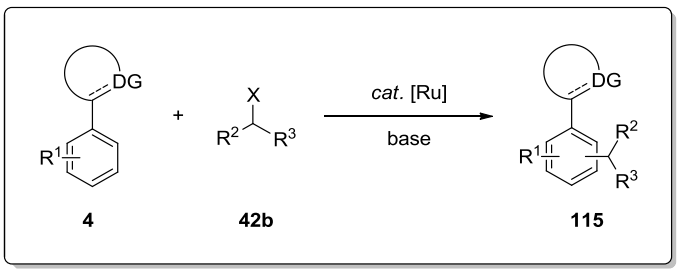
Efficient, chemo- and site-selective C–C bond formations are one of the major instruments in synthetic organic chemistry. Ongoing researches by the group of *Prof. Ackermann* and others showed that transition metal-catalyzed direct C–H bond functionalization is a powerful tool to develop sustainable pathways to meet these challenges. Especially ruthenium catalysts showed remarkable results within the field of direct arylation of (hetero)arenes. Particularly, in the presence of carboxylic acids as cocatalytic additives direct arylations occurred in high yields and in a site-selective fashion.[22]

Recently, the unprecedented ruthenium-catalyzed alkylation of substituted arenes **6** via C–H bond functionalizations applying the challenging unactivated primary alkyl bromides **42a** as electrophiles proved to be viable, in spite of only a small substrate scope had been examined (Scheme 2.1).[121] However, secondary alkyl halides provided only unsatisfactory results under similar reaction conditions.



Scheme 2.1: Ruthenium-catalyzed direct *ortho*-alkylations with unactivated primary alkyl halides **42**.

Hence, a major focus in the presented work was set on the extension of the substrate scope and the development of first generally applicable ruthenium-catalyzed direct alkylations of arenes **4** with secondary alkyl halides **42b** *via* C–H bond cleavages under non-acidic reaction conditions (Scheme 2.2).



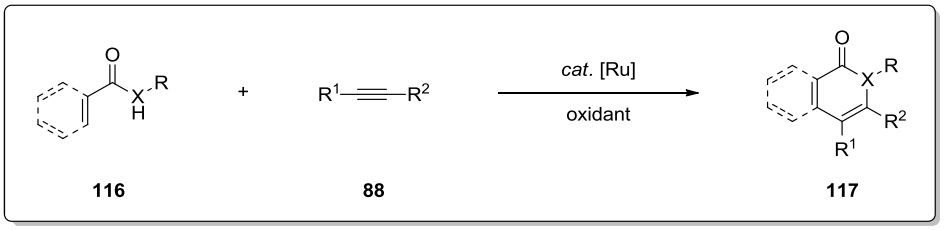
Scheme 2.2: Ruthenium-catalyzed direct alkylation with secondary alkyl halides **42b** under basic reaction conditions.

[121] Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6045–6048.

In order to elucidate the working mode of this *in-situ* generated catalytic system for alkylation reactions in details, preparation of the corresponding intermediate cycloruthenated complexes and experiments with isotopically labeled starting materials were envisioned, which will provide insight into the catalytic cycle of direct alkylations.

Besides the functionalization of arenes with alkyl or aryl moieties, the sustainable heterocycle-synthesis *via* C–H bond functionalizations still remains an under-explored field of research. Thus, several research groups around the world have exploited oxidative rhodium-catalyzed annulation reactions with alkynes to prepare a broad range of heteroarenes in an atom- and step-economic manner.

Since less expensive ruthenium complexes are known to enable the challenging direct double C–H/C–H bond arylations and alkenylations of arenes with ample scope, an additional part of this Ph.D. thesis was devoted to the development of unprecedented ruthenium-catalyzed annulation reactions via C–H/N–H bond functionalizations for the development of new sustainable and economical synthetic approaches to bioactive heterocycles **117** (Scheme 2.3).



Scheme 2.3: Ruthenium-catalyzed oxidative annulation *via* C–H/N–H bond functionalizations for a sustainable heterocycle synthesis.

Furthermore, examination of this new ruthenium-catalyzed reaction towards extension of its substrate scope and detailed mechanistic investigations, including intra- and intermolecular competition experiments, were planned in order to get insight into the catalysts' mode of action.

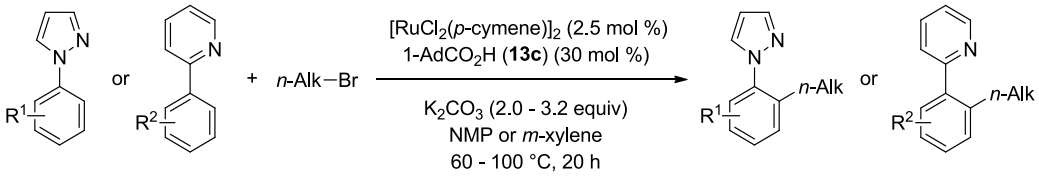
3 Results and Discussion – Ruthenium-Catalyzed Direct Alkylation Reactions

3.1 Ruthenium-Catalyzed Direct *ortho*-Alkylation

Alkyl chains not only dramatically influence the lipophilicity of practically interesting organic compounds, but also affect the penetration rate of biologically active molecules through cell membranes.[122] Due to this reasons, the site-selective C–C bond formation between alkyl and aryl groups is an important goal in synthetic organic chemistry. Complementary to traditional cross-coupling chemistry, direct C–H bond functionalizations are getting more and more into the focus of researcher's activity, however, still remain underdeveloped. The avoidance of a prefunctionalization of starting materials, minimized waste production and fewer side reactions make these transition metal-catalyzed reactions cost-efficient as well as step- and atom-economical.

Since the research group of *Prof. Ackermann* made a lot of progress within the ruthenium-catalyzed direct arylation under carboxylate-assistence (see chapter 1.1), we became attracted by challenging direct alkylations.

Until 2009, sparse reports on direct alkylations with unactivated alkyl halides as electrophiles prompted us to start our own investigations towards this direction keeping the carboxylate assistance effect in mind. An intensive screening for optimized reaction conditions by *Novák, Vicente* and *Hofmann* led to the first results on *ortho*-selective alkylation of 2-arylpyridines **6** and -pyrazoles **87** under relatively mild reaction conditions (Scheme 3.1).[121]



87 **6** **42a** up to 92% **118** **93**

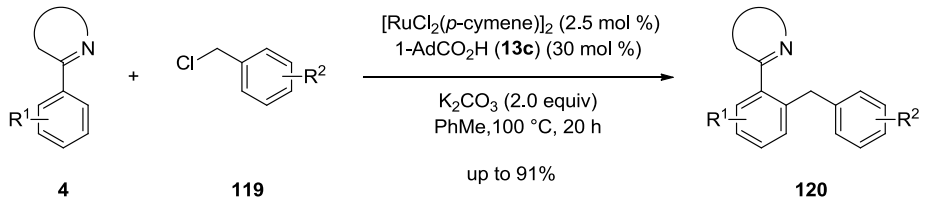
Scheme 3.1: Ruthenium-catalyzed direct alkylation of 2-arylpyridines **6** and -pyrazoles **87** according to *Ackermann et al.*

Detailed optimization studies disclosed that sterically demanding carboxylic acids, such as 1-adamantyl carboxylic acid (**13c**), increased the productivity of the reaction, while NHC or phosphine ligands furnished only poor isolated yields.

[122] Lipinski, C. A. *Drug Discov. Today Technol.* **2004**, *1*, 337–341.

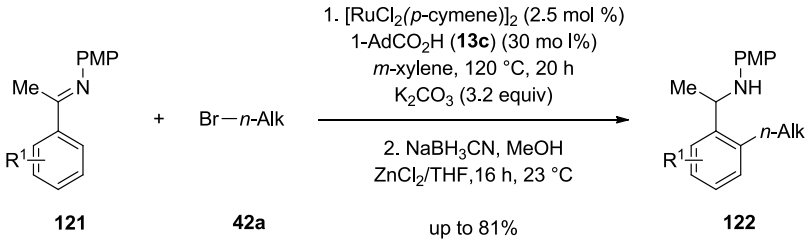
Mechanistic studies excluded an *a priori* likely elimination/hydroarylation mechanism. Thus, simple alkenes did not form the alkylated products **93** and **118** under otherwise identical reaction conditions, and also alkylations with neopentyl bromide could be accomplished. The tolerance towards ester functionalities in the electrophilic reaction partner under these reaction conditions was observed as well.[121]

The efficiency of this method for the benzylation of 2-aryloxazolines, -pyrazoles and -pyridines using benzyl chlorides **119** as inexpensive electrophiles was demonstrated by *Petr Novák* who obtained the desired benzylated products **120** in high yields (Scheme 3.2).[123]



Scheme 3.2: Ruthenium-catalyzed direct benzylation by *Novák.*

Our preliminary studies showed that a variety of ketimines **121** could be monoalkylated under slightly modified reaction conditions as well. Subsequent one-pot reduction under mild reaction conditions yielded the corresponding secondary amines **122** as the product (Scheme 3.3).[121,124,125]



Scheme 3.3: Direct ruthenium-catalyzed *ortho*-alkylation of ketimines **121** and one-pot reduction.

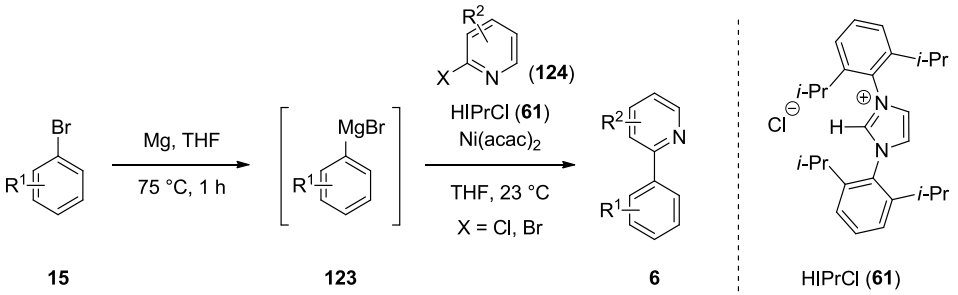
3.1.1 Synthesis of Starting Materials

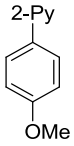
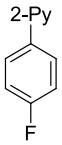
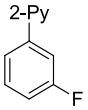
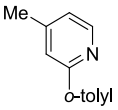
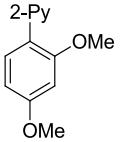
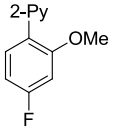
The standard substrates, which were not commercially available, were synthesized according to a published literature procedure without further optimization of the reaction conditions.[126172] For the synthesis of 2-arylpyridines **6**, a *Kumada-Corriu* cross-coupling approach was used. Various aryl

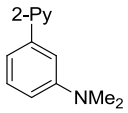
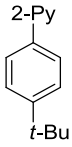
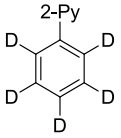
[123] Ackermann, L.; Novák, P. *Org. Lett.* **2009**, *11*, 4966–4969.
[124] Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875–1877.
[125] Hofmann, N. *Palladiumkatalysierte Intramolekulare α-Arylierungen und Rutheniumkatalysierte Intermolekulare Direkte Alkylierungen*. Diplomathesis, Universität Göttingen, 2009.
[126] Böhm, V. P. W.; Weskamp, T.; Gstöttmayr, C. W. K.; Herrmann, W. A. *Angew. Chem. Int. Ed*. **2000**, *39*, 1602–1604.

bromides **15** were converted into the Grignard compounds **123**, which immediately were used for the nickel-catalyzed coupling with 2-halopyridines **124**. As the ligand, *N*-heterocyclic carbene (NHC) HIPrCl (**61**) was employed (Table 3.1).

Table 3.1: *Kumada-Corriu* cross-coupling for the synthesis of differently substituted 2-phenylpyridines **6**.



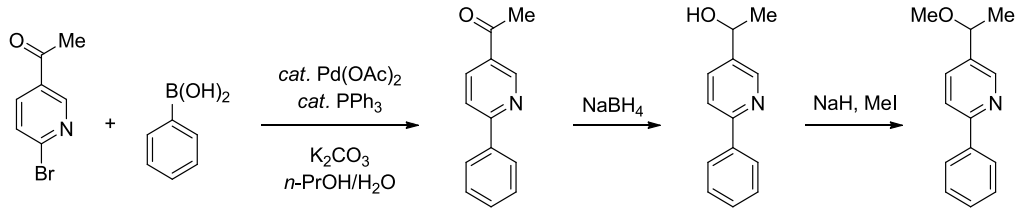
entry	R^1	R^2	product 6	isolated yield[a]
1	4-OMe	H		**94%**
	15b	**124a**	**6ba**	
2	4-F	H		**75%**
	15c	**124a**	**6ca**	
3	3-F	H		**66%**
	15d	**124a**	**6da**	
4	2-Me	4-Me		**88%**
	15e	**124b**	**6ea**	
5	2,4-OMe	H		**69%**
	15f	**124a**	**6fa**	
6	2-OMe-4-F	H		**33%**
	15g	**124a**	**6ga**	

entry	R^1	R^2	product 6	isolated yield[a]
7	3-NMe_2	H		**74%**
	15h	**124a**	**6ha**	
8	4-*t*-Bu	H		**75%**
	15i	**124a**	**6ia**	
9	2,3,4,5,6-D	H		**64%**
	[D_5]-15a	**124a**	**[D_5]-6aa**	

[a] **Reaction conditions:** bromoarene **15** (1.67 equiv), Mg turnings (1.73 equiv), anhydrous THF (2.5 M), 75 °C for 1 h then $Ni(acac)_2$ (3.0 mol %), HIPrCl (**61**) (3.0 mol %), 2-halopyridine **124** (1.0 equiv), anhydrous THF (1.5 M) at 23 °C.

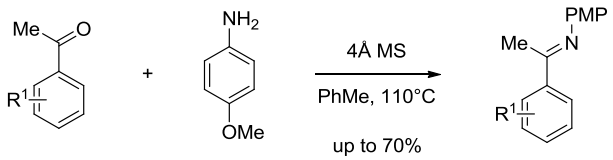
With the exception of phenylpyridine **6ga**, the yields for electron-poor as well as for electron-rich aryl bromides **15** were good to very good.

Because of possible competitive side-reactions upon using *Grignard* compounds, the syntheses of starting materials with acetyl substituents were accomplished *via* palladium-catalyzed *Suzuki-Miyaura* cross-coupling of easily accessible phenyl boronic acid (**52e**) with the appropriate 2-bromo-*n*-acetylpyridine **124**. In several particular cases indicated below, a reduction with inexpensive sodium borohydride followed by *Williamson* methylation with methyl iodide was furthermore performed (Scheme 3.4).



Scheme 3.4: Suzuki-Miyaura cross-coupling for the synthesis of acetyl-substituted 2-phenylpyridines **6bb**.

Ketimines **122**, which studied earlier for direct ruthenium-catalyzed alkylation,[121,124,125] were synthesized from acetophenone derivatives **84** and anisidin (**127**) through dehydration with 4Å molecular sieves. The final purification has been achieved either by recrystallization or column chromatography on silica gel that was deactivated with triethylamine.



84 **127** **121**

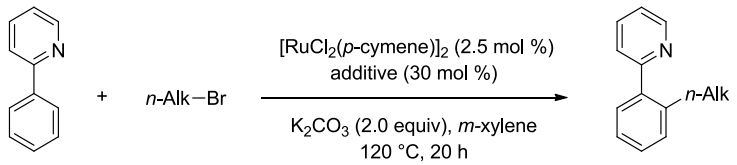
Scheme 3.5: Synthesis of ketimines **121**.

3.1.2 Direct *ortho*-Alkylation: Scope and Limitations

Unprecedented ruthenium-catalyzed *ortho*-alkylations *via* C–H bond activation has preliminary been examined by *Ackermann, Novák, Vicente* and *Hofmann* in 2009.[121] An intensive screening for optimized reaction conditions highlighted a combination of the easy accessible $[RuCl_2[p\text{-cymene})]_2$ as the catalyst and 1-adamantyl carboxylic acid (**13c**) as the additive to be most efficient. Reactions in the presence of stoichiometric amounts of inexpensive potassium carbonate as the base in polar NMP as solvent furnished alkylated arylpyridines **93** and -pyrazoles **118** in up to 92% isolated yield. Alkyl chains ranging from *n*-butyl to *n*-tetradecyl, including neopentyl, could be *ortho*-incorporated 2-phenylpyridines (**6**). Beside alkyl bromides **42a**, the reactivity of alkyl iodides and chlorides have been tested as well, but only more expensive *n*-hexyl iodide proved to be as reactive as the corresponding bromide.[121]

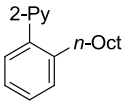
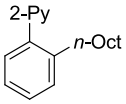
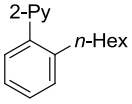
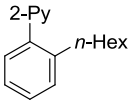
Commercially available NMP containes impurities of its synthetic precursor, γ-butyrolactone (**128**). The latter (or carboxylate resulting from its hydrolysis) acted as a soluble carboxylate source that enhanced the rate of direct arylations in the same extent as did KOAc.[127] To disprove or to support the same effect in direct alkylation reactions, the latter were reproduced in non-polar solvent *m*-xylene with *inter alia* NMP as the additive. The results are summarized in Table 3.1.

Table 3.2: Studies for alternative additives.



6 **42a** **93**

[127] Ouellet, S. G.; Roy, A.; Molinaro, C.; Angelaud, R.; Marcoux, J.-F.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem*. **2011**, *76*, 1436–1439.

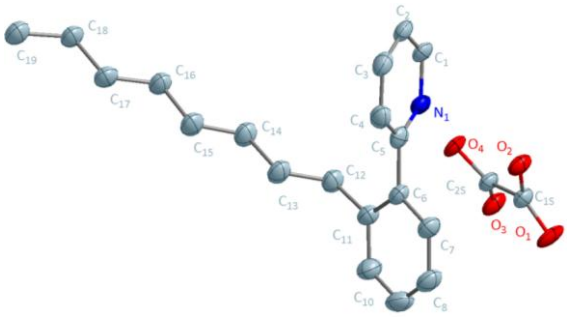
entry	bromide 42a	additive (equiv)	product 93	isolated yield[a]
1	*n*-Oct–Br	1-$AdCO_2H$ (0.3)		**66%**
	42aa	**13c**	**93aa**	
2	*n*-Oct–Br	γ-butyrolacton (0.3)		**(21)[b]**
	42aa	**128**	**93aa**	
3	*n*-Hex–Br	1-$AdCO_2H$ (0.3) + NaI (1.5)		**--**
	42ab	**13c**	**93ab**	
4	*n*-Hex–Br	1-$AdCO_2H$ (0.3) + KPF_6 (0.3)		**--**
	42ab	**13c**	**93ab**	

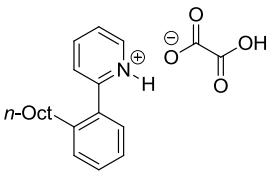
[a] **Reaction conditions:** 2-phenylpyridine (**6aa**) (0.5 mmol), alkyl bromide **42a** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), additive (30 mol %), K_2CO_3 (1.0 mmol), *m*-xylene (2.0 mL), 120 °C, 20 h, yield of isolated product;
[b] conversion determined by GC-MS.

The alkylation in *m*-xylene instead of NMP as the solvent under otherwise identical reaction conditions afforded **93aa** in 66% isolated yield (entry 1) which is comparable to the previously published yield of 80%. This excludes a decisive role of NMP, or of its impurities, for the success of the reaction. Moreover, entry 2 obviously demonstrates that even pure γ-butyrolactone (**128**) as additive is not competent in *m*-xylene. Addition of sodium iodide (entry 3) as well as of cocatalytic amounts of potassium hexafluorophosphate (entry 3) completely shut down the catalytical activity of the ruthenium complex in spite of an expected acceleration due to a possible *in situ Finkelstein*-type reaction of the alkyl bromide (**42a**) or the formation of a more electrophilic, cationic ruthenium catalyst.[128]

To prove the *ortho*-selectivity of the ruthenium-catalyzed direct alkylation with primary alkyl bromides, detailed 2D-NMR studies were conducted side by side with X-ray diffraction analysis of 2(2-octylpheny)pyridinium oxalate (**129**) (Figure 3.1).

[128] Ackermann, L.; Wang, L.; Wolfram R.; Lygin, A.V. *Org. Lett.* **2012**, *14*, 728–731.



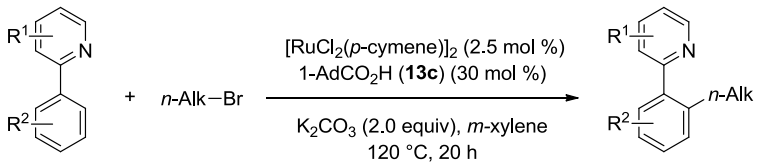


129

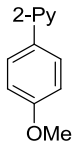
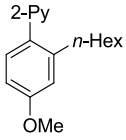
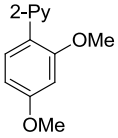
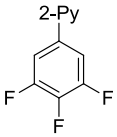
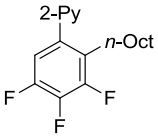
Figure 3.1: ORTEP plots (50% probability thermal ellipsoids) of 2(2-octylpheny)pyridinium oxalate (**129**) in the crystal. All hydrogen atoms have been omitted for clarity. Numbering does not correspond to the IUPAC rules.

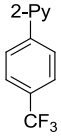
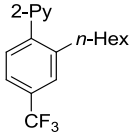
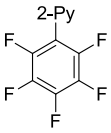
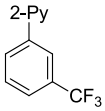
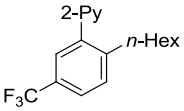
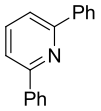
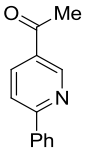
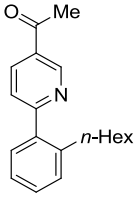
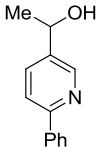
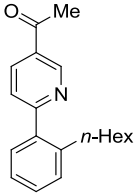
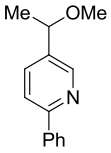
To illustrate the versatility of this new method for the regioselective alkylation of arenes, the substrate scope was tested (table 3.3). Electron-rich, electron-deficient as well as sterically demanding substrates including amino- or carbonyl-substituted 2-phenylpyridines **6** were thus examined.

Table 3.3: Scope of the ruthenium-catalyzed direct alkylation of substituted 2-phenylpyridines **6**.



6 **42a** **93**

entry	substrate 6	bromide 42a	product 93	isolated yield[a]
1	 **6ba**	*n*-Hex–Br **42ab**	 **93bb**	**53%**[b] **[48%]**[c]
2	 **6fa**	*n*-Hex–Br **42ab**	--	--
3	 **6ja**	*n*-Oct–Br **42aa**	 **93ja**	**87%**

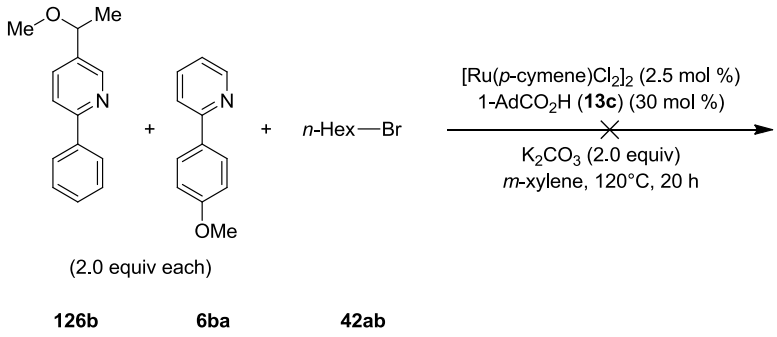
entry	substrate 6	bromide 42a	product 93	isolated yield[a]
4		*n*-Hex–Br		**76%[d]**
	6ka	**42ab**	**93kb**	
5		*n*-Hex–Br	--	--
	6la	**42ab**		
6		*n*-Hex–Br		**52%[d]**
	6ma	**42ab**	**93mb**	
7		*n*-Hex–Br	--	--
	6ab	**42ab**		
8		*n*-Hex–Br		**60%**
	6bb	**42ab**	**94bb**	
9		*n*-Hex–Br		**10%**
	125b	**42ab**	**94bb**	
10		*n*-Hex–Br	--	--
	126b	**42ab**		

[a] **Reaction conditions:** **6** (0.5 mmol), **42a** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), 1-$AdCO_2H$ (**13c**) (30 mol %), K_2CO_3 (1.0 mmol), *m*-xylene (2.0 mL), 120 °C, 20 h, yield of isolated product; [b] in NMP (2.0 mL); [c] $MesCO_2H$ (**13a**) (30 mol %) as the additive in NMP (2.0 mL); [d] at 100 °C.

In accordance with our previously reported results,[121] electron-donating groups, such as methyl or methoxy groups, afforded the desired product **93** in moderate yields (entry 1). A further increase of the electron density on the aromatic moiety leads to complete loss of reactivity (entry 2). In contrast, substrates bearing electron-withdrawing substituents furnished high yields of up to 87% of the

desired product (entries 3 and 4). Not surprisingly, pentafluorinated phenylpyridine **6la** showed no reactivity (entry 5), since this would require a challenging C–F bond cleavage, which is a scarce reaction in ruthenium catalysis.[129] Alkylation of trifluoromethylpyridine (**6ma**, entry 6) delivered the product **93mb** in moderate yield, but with excellent site-selectivity. The alkylation proceeded at the less sterically hindered position, i.e. *para* to the CF_3 substituent.

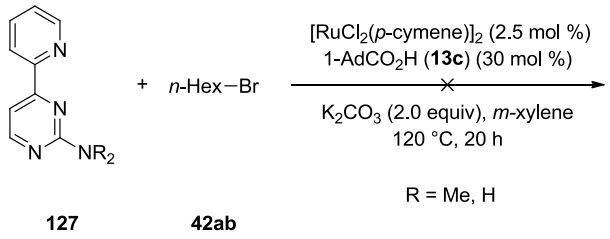
An attempted examination of the influence of the pyridine substituents demonstrated that the second *ortho*-phenyl substituent in 2,6-diphenylpyridine (**6ad**) prevented the direct alkylation (entry 7), probably due to steric interactions, which can impede the formation of intermediate ruthenacycles of the type **14** or **16** (Scheme 1.7). However, the electron-withdrawing acetyl moiety on the pyridine ring in 3-acetyl-6-phenylpyridine (**6bb**) afforded the desired product **94bb** in 60% yield (entry 8). Surprisingly, the direct alkylation of substrate **125b** furnished the same product **94bb**, albeit in poor yield (entry 9), while the corresponding ether **126b** showed no conversion at all (entry 10). Hence, the ruthenium complex catalyzed two separate reactions, that is (i) the alcohol oxidation to the acetyl derivative and (ii) the C–H alkylation. A competition experiment between substrates **126b** and **6ba** indicated no product formation (Scheme 3.6), which can be rationalized by substrate **126b** inhibiting the reaction.



Scheme 3.6: Competition experiment between starting materials **126b** and **6ba**.

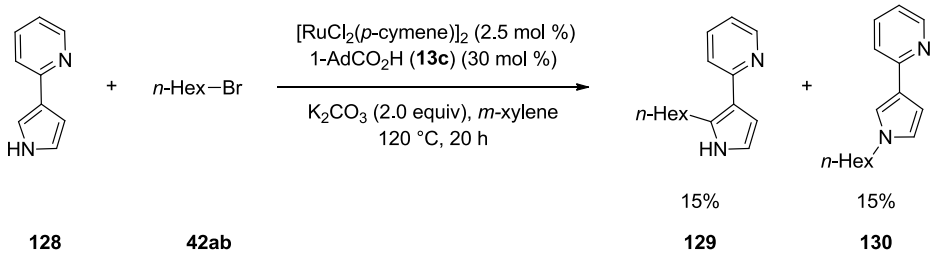
The same result was obtained upon attempted alkylation of guanidine-type substrates **127**. The reactions afforded no alkylated products (Scheme 3.7), probably because of the formation of a rather stable ruthenium complex prior to C–H bond functionalization.

[129] (a) Whittlesey, M. K.; Perutz, R. N.; Greener, B.; Moore, M. H. *Chem. Commun*. **1997**, 187–188. (b) Kirkham, M. S.; Mahon, M. F.; Whittlesey, M. K. *Chem. Commun.* **2001**, 813–814. Review: (c) Clot, E.; Eisenstein, O.; Jasim, N.; Macgregor, S. A.; McGrady, J. E.; R. Perutz, N. *Acc. Chem. Res.* **2011**, *44*, 333–348.



Scheme 3.7: Attempted direct alkylation of nitrogen-rich substrates **127**.

To test whether a free *N–H*-functionality is tolerated by this reaction, the chemical behaviour of substrate **128** was tested under the alkylating reaction conditions (Scheme 3.8). The alkylation proceeded with low conversion, funishing a mixture of two products formed in almost the same isolated yield. The substitution pattern in **129** has been determined *via* careful 2D-NMR analysis. Thus, compound **129** resulted from the desired direct C–H bond alkylation. The site-selective outcome of the alkylation product **129** might arise from the concerted action of the directing group and the higher acidity in α-position to the nitrogen atom position of the pyrrole moiety. Pyrrole **130** was a product of a N–H alkylation probably *via* nucleophilic substitution on hexyl bromide by the deprotonated substrate **128**.[130]



Scheme 3.8: Direct alkylation of (*N–H*)-free pyrrolopyridine (**128**).

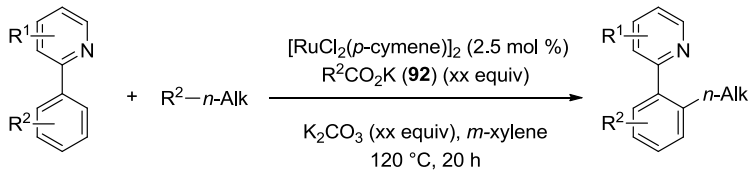
In our previous studies on the direct alkylation of ketimines **122,** the possibility of replacing co-catalytic amounts of 1-adamantyl carboxylic acid (**13c**) with overstoichiometric quantities of inexpensive [131] potassium acetate was demonstrated.[125] Herein, this improvement was also tested for the alkylation of various 2-phenylpyridines **6** (Table 3.4).

First of all, the competence of potassium pivalate in co-catalytic amounts as additive in the presence of additional 2 equivalents of K_2CO_3 was examined (entry 1, 51% yield). In spite of the somewhat lower yield, the level of efficiency was about the same as with 1-adamantyl carboxylic acid (**13c**) (Table 3.2, entry 1, 66% yield). Changing the additive to KOAc in the same cocatalytic amount, but without additional base, only a small amount of the alkylated product **93a** could be isolated (entry 2).

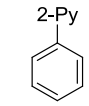
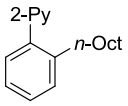
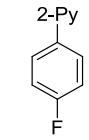
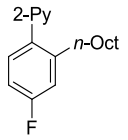
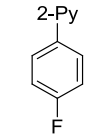
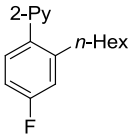
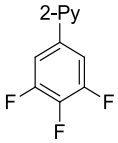
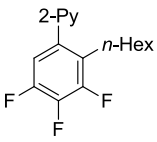
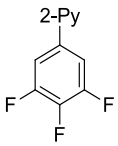
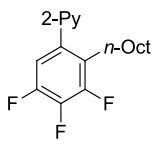
[130] Lea, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* **2004**, 1951–1954.
[131] Price: Sigma-Aldrich.com, 12.01.13: KOAc, 1 kg ≡ 58.30 €; 1-AdCO$_2$H, 100 g ≡ 160.00 €.

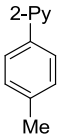
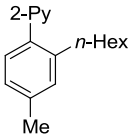
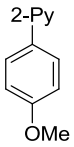
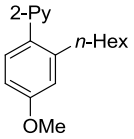
However, when applying 6.4 equivalents of KOAc, high conversion was detected and the yield drastically rose up to 76% (entry 3). The same almost held true for (trifluorophenyl)pyridine **6ja** (entries 4 and 5), while for electron-rich substrates **6oa** and **6ba** the yield ranged from poor to moderate when using KOAc in overstoichiometric amounts (entries 6 and 7; see also Table 3.3, entry 1).

Table 3.4: KOAc as the additive.



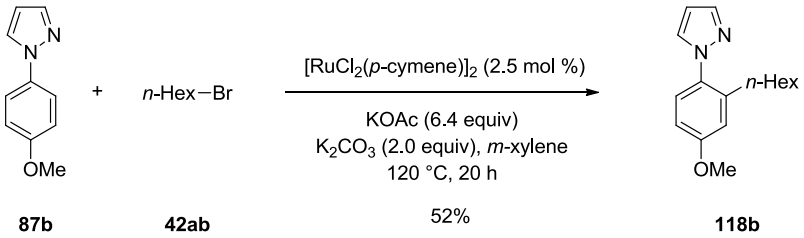
6 **42a** **93**

entry	substrate 6	bromide 42a	additive 92 (equiv)	product 93	isolated yield[a]
1	 **6aa**	*n*-Oct–Br **42aa**	KOPiv (0.3)	 **93aa**	**51%**
2	 **6ca**	*n*-Oct–Br **42aa**	KOAc (0.3)	 **93ca**	**9%[b]**
3	 **6ca**	*n*-Hex–Br **42ab**	KOAc (6.4)	 **93cb**	**76%**
4	 **6ja**	*n*-Hex–Br **42ab**	KOAc (6.4)	 **93jb**	**48%**
5	 **6ja**	*n*-Oct–Br **42aa**	KOAc (6.4)	 **93ja**	**73%**

entry	substrate 6	bromide 42a	additive 92 (equiv)	product 93	isolated yield[a]
6		*n*-Hex–Br	KOAc (6.4)		**15%**
	6oa	**42ab**		**93ob**	
7		*n*-Hex–Br	KOAc (6.4)		**49%**
	6ba	**42ab**		**93bb**	

[a] **Reaction conditions:** **6** (0.5 mmol), **42a** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), additive, K_2CO_3 (1.0 mmol), *m*-xylene (2.0 mL), 120 °C, 20 h, yield of isolated product; [b] no base, 100 °C.

Furthermore, a catalytic system comprising $[RuCl_2(p\text{-cymene})]_2$ and inexpensive KOAc was demonstrated to possess almost a high efficacy in the alkylation of (4-methoxyphenyl)pyrazol (**87b**) as well (Scheme 3.9).



Scheme 3.9: Direct alkylation of (4-methoxyphenyl)pyrazol (**87b**) employing inexpensive KOAc as the additive.

The opportunity to perform organic reactions with water as an inexpensive, environmentally benign, nontoxic reaction medium is attractive.[132] The idea of potential tolerance of ruthenium-catalyzed transformations was postulated by *Ackermann* in his experiments on arylations with K_2CO_3 as the base.[133a] After this, a number of ruthenium-catalyzed reactions such as C–H/X–H-annulations with alkynes,[131b,c] direct oxidative alkenylations[131d,e] and direct arylations[131f] were successively carried out in water. The ruthenium-catalyzed 3-alkylations of indoles in water[134] and the dehydrative alkylation

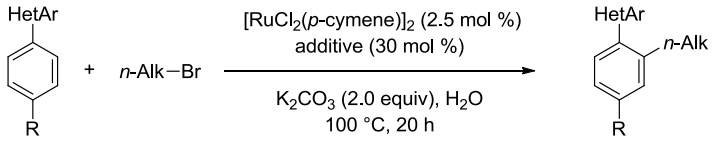
[132] Reviews: (a) Simon, M.-O.; Li, C.-J. *Chem. Soc. Rev.*, 2012, **41**, 1415–1427. (b) *Organic Reactions in Water* (ed.: Lindstorm, U. M.), Wiley-Blackwell: New York, 2007.

[133] (a) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125. (b) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764–767. (c) Ackermann, L; Fenner, S. *Org. Lett.* **2011**, *13*, 6548–6551. (d) Ackermann, L.; Wang, L.; Wolfram, R.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 728–731. (e) Ackermann, L.; Pospech, J. *Org. Lett*. **2011**, *13*, 4153–4155. (f) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 6629–6632.

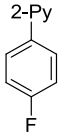
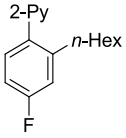
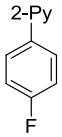
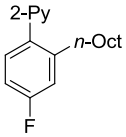
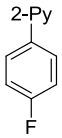
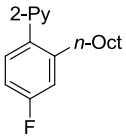
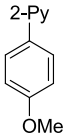
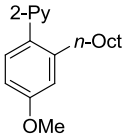
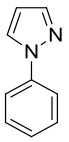
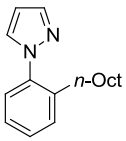
[134] Cadierno, V.; Francos, J.; Gimeno J. *Chem. Commun.* **2010**, *46*, 4175–4177.

of phenols with alcohols[135] have also been reported. However, ruthenium-catalyzed direct alkylation of arenes with alkyl halides in water had proven elusive. Indeed, as the bases were never pre-dried before employing in the ruthenium-catalyzed direct alkylation, it was necessary to examine, whether water could be used as the reaction medium. The results are summarized in Table 3.5.

Table 3.5: Direct alkylation of substrates **6** or **87** employing water as the reaction medium.



6 or **87** **42a** **93** or **118**

entry	substrate	bromide 42a	additive	product	isolated yield[a]
1		*n*-Hex–Br	$MesCO_2H$		**66%**
	6ca	**42ab**	**13a**	**93cb**	
2		*n*-Oct–Br	$1\text{-}AdCO_2H$		**66%**
	6ca	**42aa**	**13c**	**93ca**	
3		*n*-Oct–Br	KOAc		**60%[b]**
	6ca	**42aa**		**93ca**	
4		*n*-Oct–Br	$1\text{-}AdCO_2H$		**61%**
	6ba	**42aa**	**13c**	**93ba**	
5		*n*-Oct–Br	$1\text{-}AdCO_2H$		**62%**
	87a	**42aa**	**13c**	**118a**	

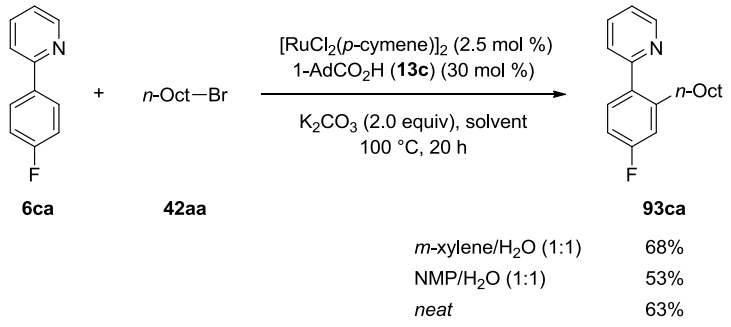
[135] Walton, J. W.; Williams, J. M. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 12166–12168.

[a] **Reaction conditions:** **6** or **87** (0.5 mmol), **42a** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), additive (30 mol %), K_2CO_3 (1.0 mmol), H_2O (2.0 mL), 120 °C, 20 h, yield of isolated product; [b] KOAc (3.2 mmol) as the additive.

Fortunately, while using distilled and degassed water as the reaction medium, electron-poor (entries 1-3) and electron-rich (entry 4) substrates could be alkylated comparable high yield.

The nature of the additive did not significantly affect the outcome of the reaction. Indeed, even superstoichiometric quantities of KOAc can be used as the additive with water as the solvent (entry 3). 2-Phenylpyrazole **87a** could also be alkylated in good yields under these reaction conditions (entry 5).

To estimate, whether a solvent mixture could influence the degree of conversion, mixtures of *m*-xylene or NMP and water were tested (Scheme 3.10). A mixture of water and *m*-xylene furnished essentially the same isolated yield of **93ca** (68%) as in pure water (66%), while in mixtures with NMP the isolated yield slightly decreased (53%). Interestingly, the reactions run under neat conditions, that is in the absence of solvent, did not result in a dramatically decreased yield. However, due to agitation-effects of the reaction mixture, the latter protocol was subsequently not applied.



Scheme 3.10: Solvent effects for the direct alkylation.

A variety of other substrates was tested in the ruthenium-catalyzed direct alkylation reaction, but neither oxygen-containing directing groups (**131**-**136**) nor substrates that would rely on a 7-membered ruthenacycle intermediate (**137**-**141**) were alkylated (Figure 3.2).

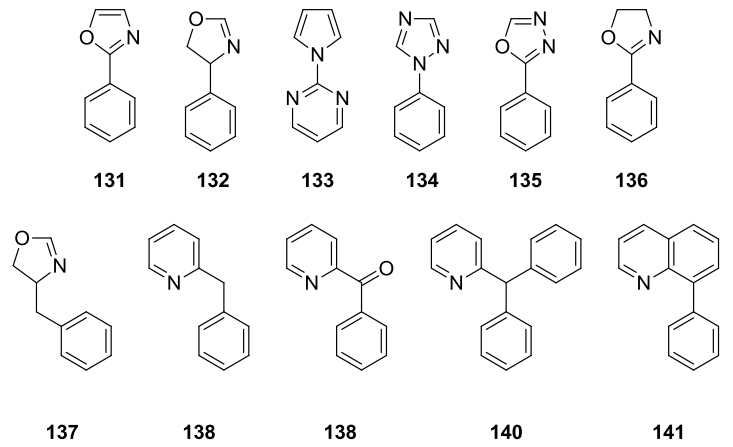
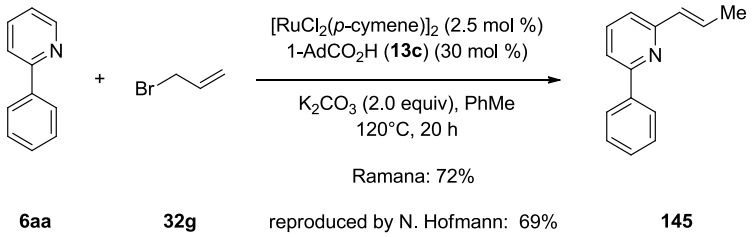


Figure 3.2: Unreactive substrates for the ruthenium-catalyzed direct *ortho*-alkylation.

3.1.2.1 Ruthenium-Catalyzed Direct Allylation

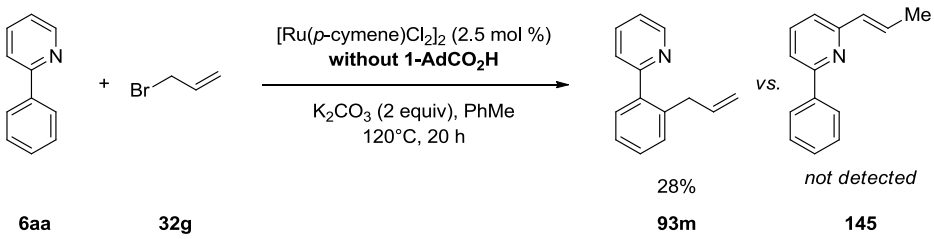
Thereafter, the alkylation with unsaturated bromides was investigated. In 2011, *Ramana* reported on a ruthenium-catalyzed direct propenylation of the pyridine ring in 2-phenylpyridine (**6aa**) under similar reaction conditions, applying allyl bromide (**32g**) (Scheme 3.11).[136]



Scheme 3.11: Ruthenium-catalyzed direct propenylation of 2-phenylpyridine (**6aa**).

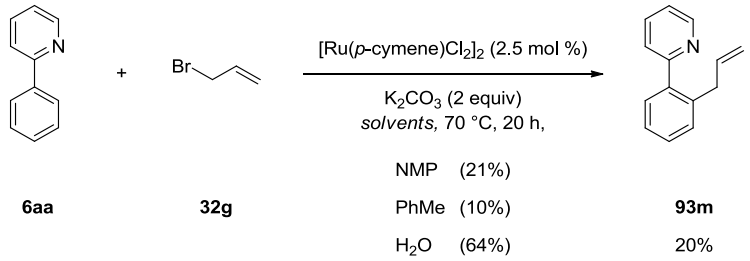
Indeed, compound **145** was formed in comparable yield, as indicated by ^{1}H-NMR spectra. However, it was not possible to separate the product **145** completely from the side-product, presumably allyl adamantilate, by column chromatography. According to *Ramana* and *Gorya*, without adamantyl carboxylic acid the yield of **145** stayed at 72%.[136] Surprisingly, attempted reproduction of these results did not afford any propenylated phenylpyridine **145**. Instead of this, 28% of the *ortho*-allylated 2-phenylpyridine **93m** has been isolated as sole product, albeit in low yield (Scheme 3.12).

[136] Goriya, Y.; Ramana, C. V. *Chem. Eur. J.* **2012**, *18*, 13288–13292.



Scheme 3.12: Ruthenium-catalyzed direct allylation of 2-phenylpyridine (**6aa**).

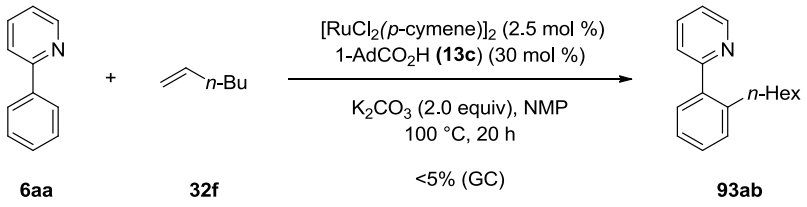
With freshly distilled allyl bromide (**32g**), the formation of this allylated product **93m** could be detected even at 70 °C and without any additive. With water as a solvent, compound **93m** was obtained in 20% isolated yield (Scheme 3.13).



Scheme 3.13: Direct allylation of 2-phenylpyridin (**6aa**) (yields in brackets mean GC-MS-conversions of **6aa**).

3.1.3 Mechanistic Studies

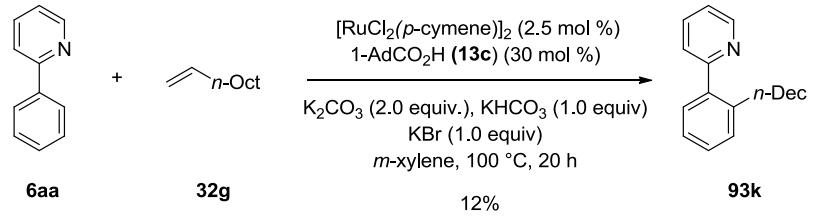
At the outset, the probability of a reaction pathway *via* initial dehydrobromination followed by hydroarylation according to *Murai* and co-workers,[91] but under our optimized reaction conditions, was evaluated (Scheme 3.14).[137]



Scheme 3.14: Attempted hydroarylation.

The conversion of substrate **6aa** to the desired alkylated product **93ab** was not detected when using 1-hexene (**32f**) as alkene, thus excluding a hydroarylation as a possible reaction pathway. To ascertain, whether a one-pot addition/direct alkylation sequence can be accomplished, the reaction was re-tested in the presence of potassium bromide and potassium bi carbonate as the additives (Scheme 3.15).

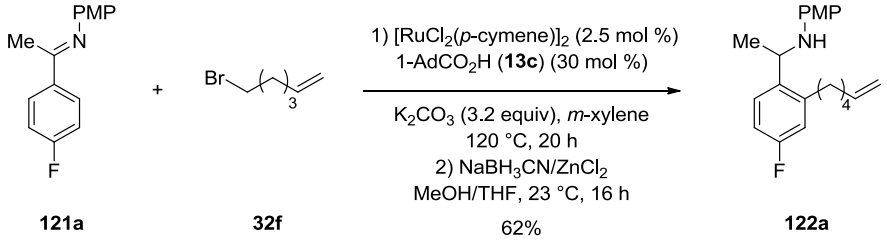
[137] Reaction was performed by Dr. R. Vicente.



Scheme 3.15: Attempted alkylation *via* "one-pot" addition/direct alkylation sequence.

Under these reaction conditions only a very low yield of **93k** (12%) has been obtained, which excluded the one-pot addition/direct alkylation procedure as a viable alternative.

Moreover, a ruthenium-catalyzed direct *ortho*-alkylation with ketimine **121a** and 1-bromohexene **32f** could be accomplished in good yield and high chemoselectivity without the formation of cyclized products (Scheme 3.16).

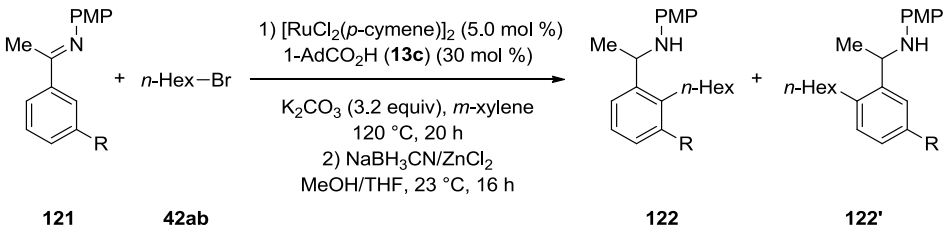


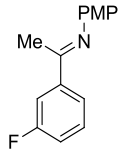
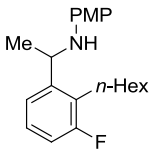
Scheme 3.16: Ruthenium-catalyzed direct alkylation with bromohexene **32f.**

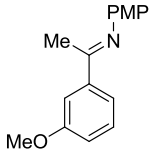
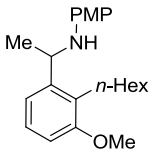
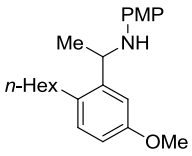
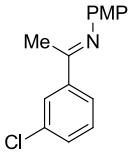
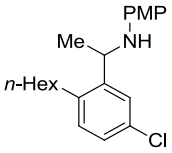
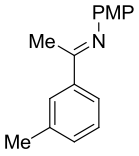
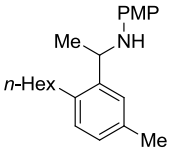
3.1.3.1 Intramolecular Competition Experiments

Intra- and intermolecular competitive direct alkylations of *meta*-substituted ketimines **121** as the substrates were performed with the aim (a) to evaluate the scope of these direct alkylations and (b) to shed light onto the mechanism of direct alkylations through intramolecular competition experiments, which can elucidate sterical and electronical aspects (Table 3.6).

Table 3.6: Intramolecular competition experiments with *meta*-substituted ketimines **121**.



entry	substrate 121	product 122	yield of 122[a]	product 122'	yield of 122'[a]
1			**74%**	--	--
	121b	**122b**			

entry	substrate 121	product 122	yield of 122[a]	product 122'	yield of 122'[a]
2			20%		38%
	121c	**122c**		**122c'**	
3		--	--		68%
	121d			**122d'**	
4		--	--		52%
	121e			**122e'**	

[a] **Reaction conditions: 121** (0.5 mmol), **42ab** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), 1-$AdCO_2H$ (**13c**) (30 mol %), K_2CO_3 (1.6 mmol), *m*-xylene (2.0 mL), 120 °C, 20 h, yield of isolated product.

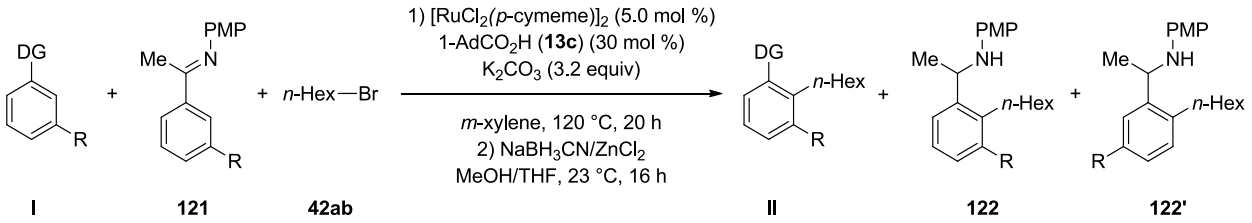
As was shown in earlier studies,[124,125] electron-deficient substrates are more reactive in ruthenium-catalyzed direct alkylation than are electron-rich ones. In the case of *meta*-substituted substrates, the same behavior was detected. A *meta*-fluoro substitution in substrate **121b** resulted in 2-alkylation (entry 1), which most probably resulted from the concerted action of the chelating effect of the imino moiety and the well-documented *ortho*-orienting influence of the fluorine substituents.[138] Conversely, the larger *meta*-chlorine substituent in substrate **121d** (entry 3) or methyl substituent in **121e** (entry 4) directed the alkylations to the less hindered 5-position. As a comparison, the alkylation of the substrate **121c** with a *meta*-methoxy substituent led to a mixture of the 2- (**122c**) and 5-substituted (**122c'**) products (entry 2). Formation of the former might be explained by a secondary chelating effect of the methoxy substituent. Electron-deficient substrates **121b** and **121d** afforded very good yields (entries 1 and 3).

3.1.3.2 Intermolecular Competition Experiments

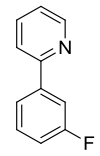
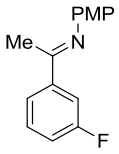
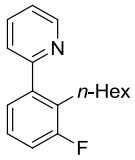
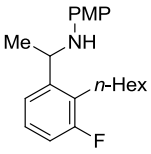
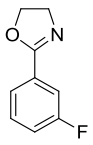
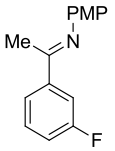
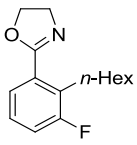
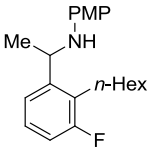
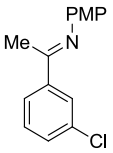
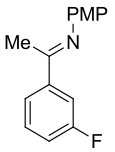
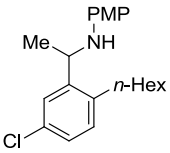
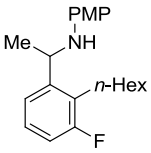
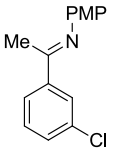
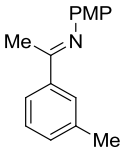
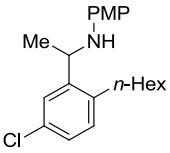
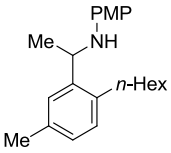
To establish the reactivity-order and to establish priorities for arenes with different substituents and directing groups, intermolecular competition experiments were subsequently carried out (Table 3.7).

[138] (a) Evans, M. E.; Burke, C. L.; Yaibuathes, S.; Clot, E.; Eisenstein, O.; Jones, W. D. *J. Am. Chem. Soc*. **2009**, *131*, 13464–13473; (b) Clot, E.; Mégret, C.; Eisenstein, O.; Perutz, R. N. *J. Am. Chem. Soc*. **2009**, *131*, 7817–7827.

Table 3.7: Intermolecular competition experiments using substrates with various directing groups.



I 121 42ab II 122 122'

entry	substrate I	substrate 121	product II	yield of II[a]	product 122/122'	yield of 122/122'[a]
1				55%		22%
	6da	121b	93db		122b	
2				15%		42%
	136a	121b	143a		122b	
3				20%		56%
	121d	121b	122d'		122b	
4				40%		--
	121d	121e	122d'		122e'	

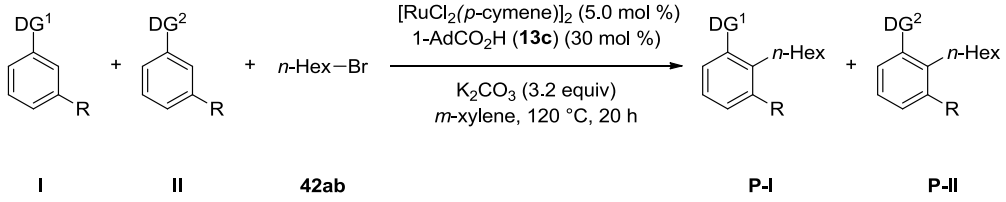
[a] **Reaction conditions**: **I** and **121** (1.0 mmol of each), **42ab** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), 1-$AdCO_2H$ (**13c**) (30 mol %), K_2CO_3 (1.6 mmol), *m*-xylene (4.0 mL), 120 °C, 20 h, yield of isolated product.

Entries 1 and 2 clearly indicate that pyridyl (substrate **6da**) is a more powerful directing group than the ketimine (substrate **121b**), which itself is better than the oxazoline (substrate **136a**). It has to be mentioned, that 2-aryloxazoline (**136**) did not afford any product under the standard reaction conditions in an individual reaction. This led to the assumption that the ketimine moeity also acts as a ligand in this transformation (entry 2). Competition experiments between electron-rich and

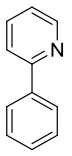
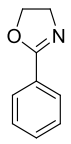
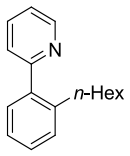
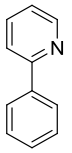
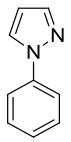
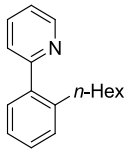
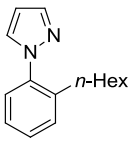
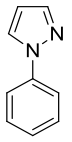
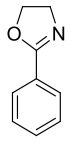
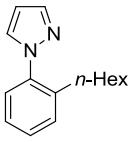
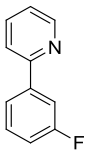
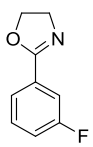
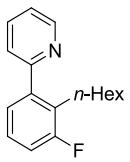
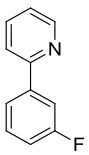
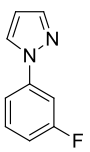
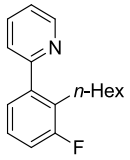
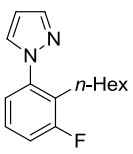
electron-poor ketimines (entries 3 and 4) illustrated that with-drawing substrates were significantly more reactive.

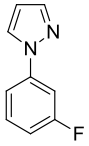
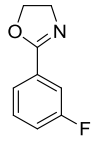
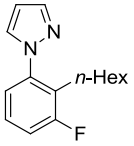
The results of another series of intermolecular competition experiments, which did not require the additional *in situ* reduction step, are show in Table 3.8.

Table 3.8: Intermolecular competition experiments with different directing groups.



I **II** **42ab** **P-I** **P-II**

entry	substrate I	substrate II	product P-I	yield of P-I[a]	product P-II	yield of P-II[a]
1				**24%**	**--**	**--**
	6aa	**136**	**93ab**			
2				**36%**		**9%**
	6aa	**87a**	**93ab**		**118a**	
3				**31%**	**--**	**--**
	87a	**136**	**118a**			
4				**28%**	**--**	**--**
	6da	**136b**	**93db**			
5				**17%**		**17%**
	6da	**87c**	**93db**		**118c**	

entry	substrate I	substrate II	product P-I	yield of P-I[a]	product P-II	yield of P-II[a]
6				48%	--	--
	87c	136b	118c			

[a] **Reaction conditions**: **I** or **II** (1.0 mmol of each), **42ab** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), 1-$AdCO_2H$ (**13c**) (30 mol %), K_2CO_3 (1.6 mmol), *m*-xylene (4.0 mL), 120 °C, 20 h, yield of isolated product.

These results were in line with those summarized in Table 3.7 indicating the efficacy of directing groups to be in the following order: pyridine ≥ pyrazole > ketimine >>> oxazoline (Figure 3.3).

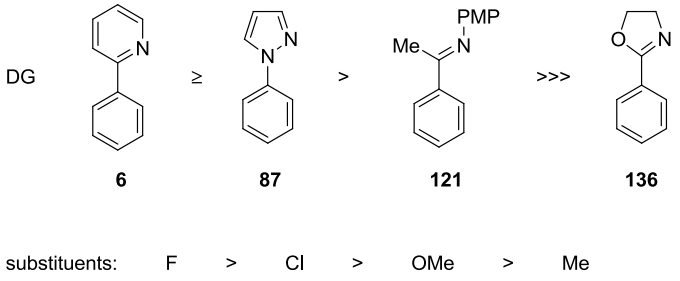
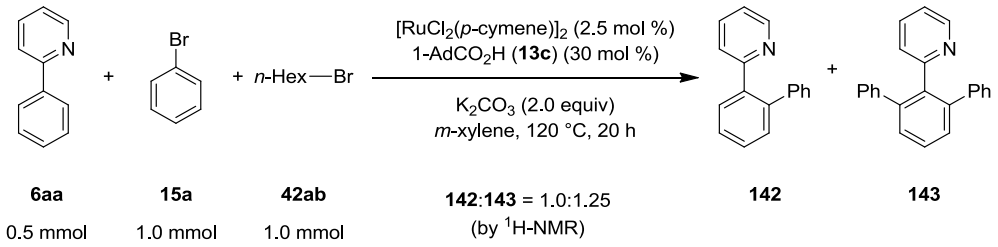


Figure 3.3: Reactivity order for the direct *ortho*-alkylation derived from the results of competition experiments summarized in Table 3.7 and Table 3.8.

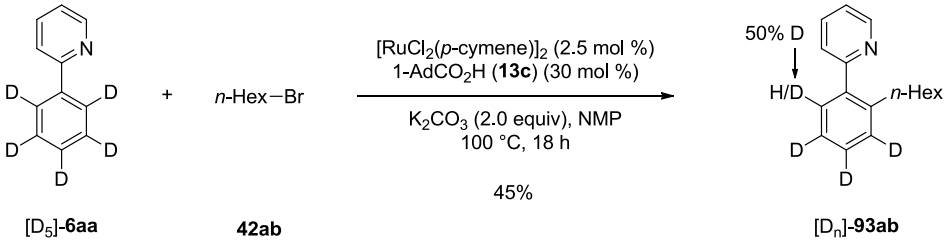
The relative rates of ruthenium-catalyzed direct arylation and direct alkylation have been compared in the competition between bromobenzene (**15a**) and *n*-hexyl bromide (**42ab**) (Scheme 3.17). The reaction led to the formation of an inseparable mixture of mono- (**143**) and bis-arylated (**144**) products, while the alkylation product **93ab** was not detected. This result indicates the direct arylation to be much faster than the direct alkylation reaction.



Scheme 3.17: Competition between direct arylation and alkylation reactions.

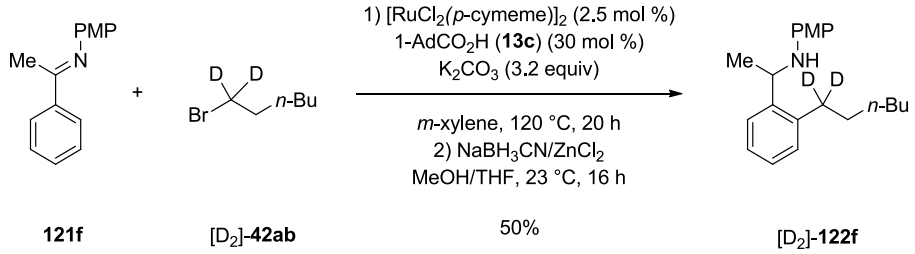
3.1.3.3 Experiments with Deuterium-Labeled Substrates

Previously reported studies by *Dr. Rubén Vicente*[124] on D/H exchange gave strong evidence for a reversible C–H bond metalation step. As displayed in Scheme 3.18, the direct alkylation on deuterated substrate [D_5]-**6aa** under optimized reaction conditions demonstrated 50% of H/D-exchange in the *ortho*-position. It is supposed, that the non-predried K_2CO_3 is acting as an additional proton-source besides the carboxylic acid.



Scheme 3.18: D/H-exchange experiment during direct alkylation of substrate ([D_5]-**6aa**).

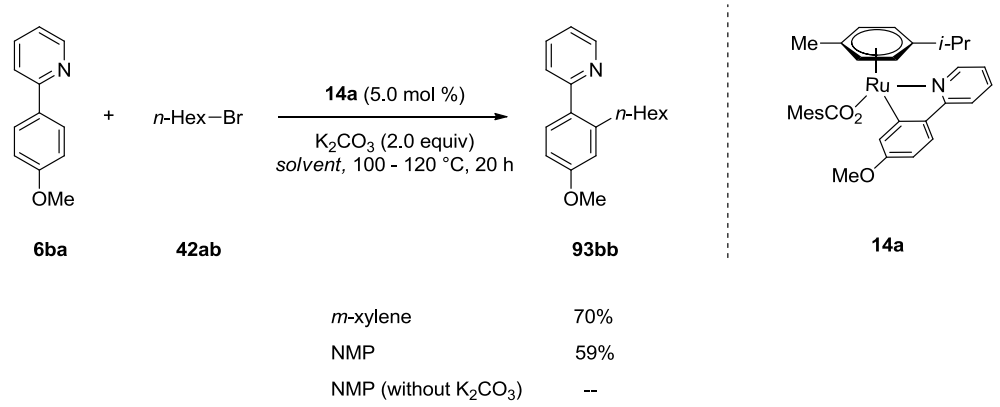
The direct alkylation with [D_2]-**42ab** showed no deuterium scrambling in the product (Scheme 3.19). This result supported once more the elimination/hydroarylation or the formation of carbene intermediates unlikely to be operative.



Scheme 3.19: Direct alkylation with 1,1-dideuteriohexyl bromide ([D_2]-**42ab**).

3.1.3.4 Experiments with Ruthenacycle 14a

Previous studies on the ruthenium-catalyzed direct arylation by the group of *Prof. Ackermann* have demonstrated the capability of the ruthenacycle **14a** to catalyze the desired reaction.[26a] This complex has been synthesized and tested as the catalyst for the direct alkylation (Scheme 3.20).

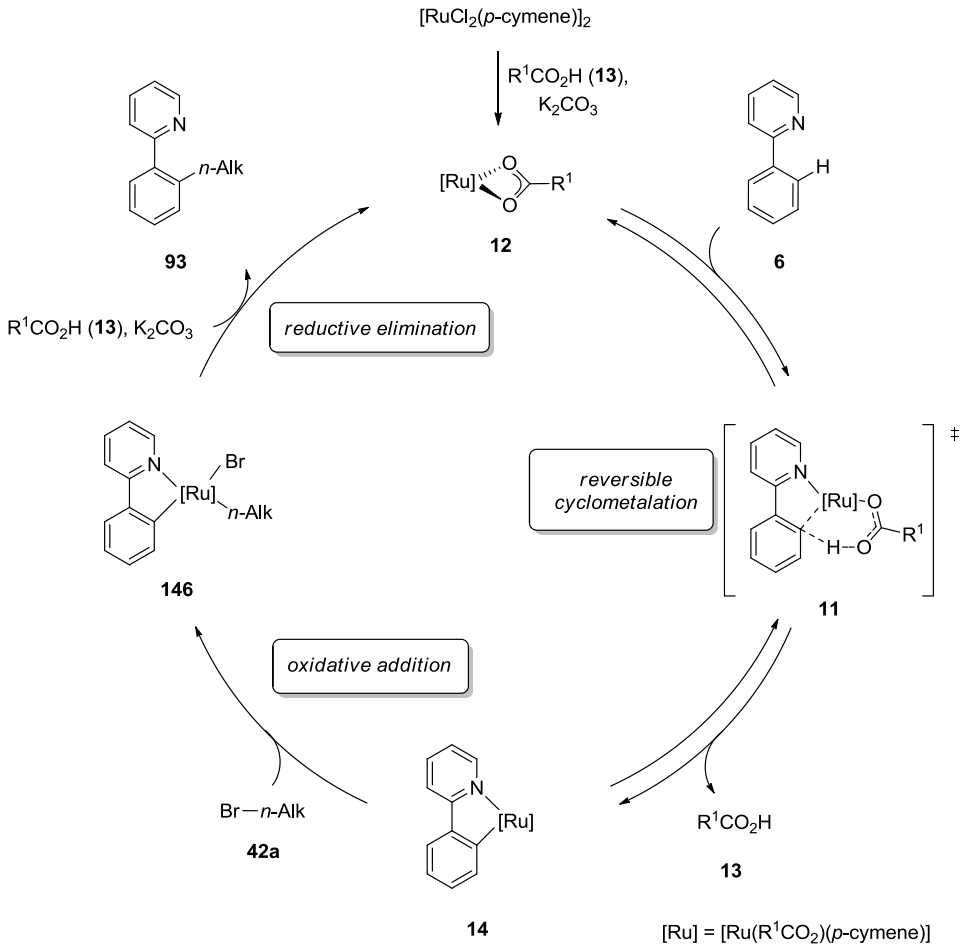


Scheme 3.20: Ruthenium-catalyzed direct alkylation with ruthenacycle **14a** as the catalyst.

As shown in Scheme 3.20, the use of 5.0 mol % of the isolated complex **14a** gave high yields of the alkylated product **93bb** with both *m*-xylene as well as NMP as the solvent. Furthermore, without the base K_2CO_3 no conversion of the substrates occurred. These results lead to the assumption that complex **14a** participates in the catalytic cycle and that a stoichiometric amount of base is necessary.

3.1.3.5 Proposed Catalytic Cycle

Based on the mechanistic studies discussed above, the following catalytic cycle was proposed to account for the chemo- and site-selective outcome of the ruthenium-catalyzed direct alkylation with unactivated primary alkyl halides (Scheme 3.21).



Scheme 3.21: Proposed catalytic cycle for direct ruthenium-catalyzed *ortho*-alkylation.

This catalytic cycle initiates by the formation of a stable ruthenium (II) carboxylate complex **12**, in analogy to the published precedent by *Ackermann et al.*[26] This complex reversibly cyclometalates through a carboxylate-assisted deprotonation through intermediate **11**, affording ruthenacycle **14**. Thereafter, complex **14** reacts with unactivated primary alkyl bromide **42a** *via* either oxidative addition or SET-type process to yield intermediate **146**. Finally, reductive elimination regioselectively gives rise to the alkylated arene **93**, and thereby regenerates the catalytically active species **12**. Importantly, catalytic amounts of carboxylate not only dramatically accelerate the C–H bond activation step affording **14**,[139] but facilitate the C–C bond formation. Unfortunanely, the nature of the activation step with primary alkyl halides (**42a**) still remains unknown, as the corresponding experiments towards its elucidation were not yet successful. Also the nature of the rate-determining step – either the reductive elimination or the activation of the alkyl halide – still remains unknown.

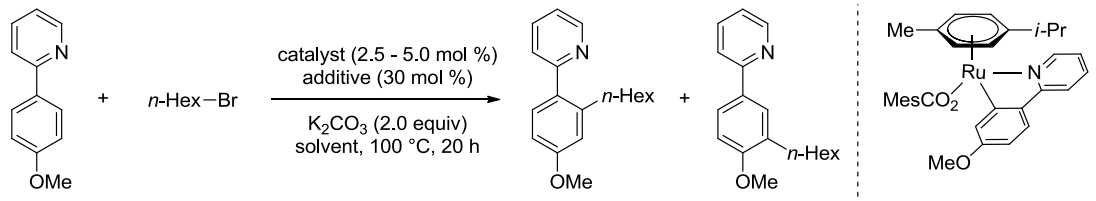
[139] (a) Li, B.; Feng, H.; Wang, N.; Ma, J.; Song, H.; Xu, S.; Wang, B. *Chem. Eur. J.*, **2012**, *18*, 12873–12879. (b) Li, B.; Roisnel, T.; Darcel, C.; Dixneuf, P. H. *Dalton Trans*. **2012**, *41*, 10934–10937.

3.2 Ruthenium-Catalyzed Direct *meta*-Alkylation

3.2.1 Preliminary Observations

As indicated in the introduction, the challenging ruthenium-catalyzed C–H direct alkylations with unactivated primary alkyl halides are an important objective, which appeared to be highly *ortho*-site-selective. Nevertheless, in selected rare cases small quantities of a side-product were isolated (Table 3.9). Careful 2D-NMR studies disclosed these by-products as being formed by an unprecedented ruthenium-catalyzed *meta*-functionalization.

Table 3.9: Observation of *meta*-alkylated side-product **93c'**.



6ba **42ab** **93bb** **93bb'** **14a**

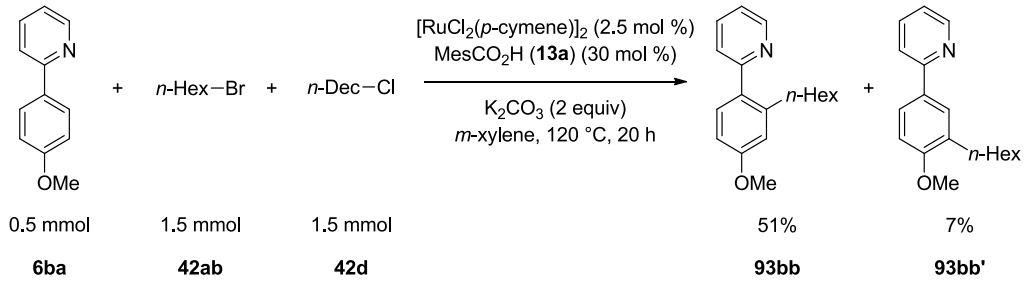
entry	catalyst (mol%)	solvent	additive	yield[a] of 93bb	yield[a] of 93bb'
1	$[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%)	H_2O	$MesCO_2H$ **13a**	**45%**	**7%**
2	$[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%)	neat	$MesCO_2H$ **13a**	**40%**	**6%**
3	$[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%)	H_2O	-	**34%** (**^{1}H-NMR ratio = 7.5:1.0**)	
4	$[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%)	*m*-xylene	$MesCO_2H$ **13a**	**42%** (**^{1}H-NMR ratio = 3.2:1.0**)	
5	**14a** (5.0 mol%)	*m*-xylene	1-$AdCO_2H$ **13c**	**64%**	**4%**

[a] **Reaction conditions:** **6ba** (0.5 mmol), **42ab** (1.5 mmol), [Ru] (5.0 mol %), additive (30 mol %), K_2CO_3 (1.0 mmol), *m*-xylene (2.0 mL), 100 °C, 20 h, yield of isolated products.

Thus, while performing the alkylation of electron rich substrate **6ba** in water as the reaction medium (entry 1), the unexpected *meta*-substituted side-product **93bb'** was isolated in 7% yield. All attempts

to modify the reaction conditions to favor the formation of the *meta*-product were however unsuccessful. Thus, neither changing the solvent (entries 2 - 4) nor employing the highly active ruthenacycle **14a** in combination with the most efficient additive **13c** improved the yield of by-product **93bb'**, while these conditions accelerated the formation of the *ortho*-alkylated product **93bb** (entry 5).

Surprisingly, in a competition experiment between bromo- (**42ab**) and chloroalkane (**42d**) (Scheme 3.22), the side-product **93bb'** could be isolated in comparable amounts as in entry 1, Table 3.9. This experiment again demonstrated the higher reactivity of bromoalkanes as electrophiles in the ruthenium-catalyzed direct alkylation reaction.

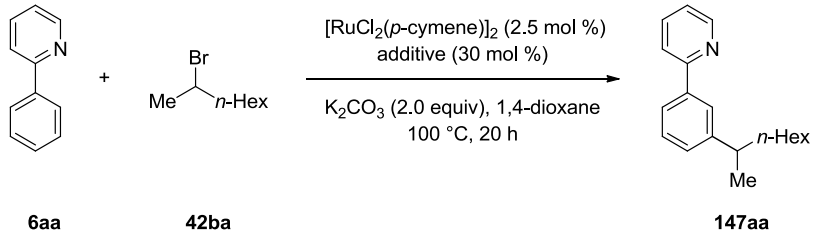


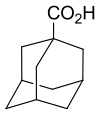
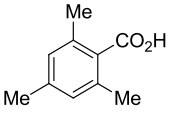
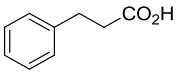
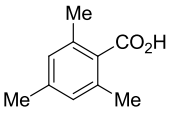
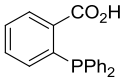
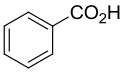
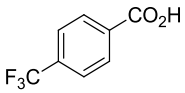
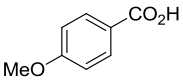
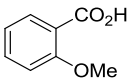
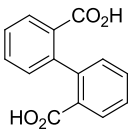
Scheme 3.22: Isolation of *meta*-derivative **93c'** as a side product in a competition experiment.

3.2.2 Optimization Studies for the Direct *meta*-Alkylation

Since the direct alkylation with primary alkyl halides **42a** could not yet be optimized to deliver only the *meta*-alkylated product, we first tested the effect of various reaction conditions on the challenging direct alkylation of arene **6aa** with secondary alkyl halides **42b** (Table 3.10). Inexpensive and readily available carboxylic acids, which appeared to be efficient cocatalysts for ruthenium-catalyzed *ortho*-alkylations with primary alkyl bromides were first explored.

Table 3.10: Optimization studies towards the optimal cocatalyst with 2-bromooctane (**42ba**).



entry	additive	yield of 147a[a]	entry	additive	yield of 147a[a]
1	 **13c**	56%	9	 **13a**	60%
2	 **13d**	34%	10	 **13a**	--[e; f; g]
3	 **13e**	--	11	**TFA** **148**	--
4	 **13b**	38%	12	TfOH **149**	35%
5	 **13f**	55%	13	$MesCO_2K$	47%
6	 **13g**	52%	14	CsOAc	45%[c]
7	 **13h**	46%	15	KOPiv	34%[d]
8	 **13i**	31%	16	KOAc	19%[b]

[a] **Reaction conditions: 6aa** (0.5 mmol), **42ba** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), additive (30 mol %), 1,4-dioxane (2.0 mL), 20 h, 100 °C; [b] KOAc (2.0 equiv), no K_2CO_3; [c] CsOAc (2.0 equiv), no K_2CO_3; [d] PivOK (2.0 equiv); [e] no K_2CO_3; [f] no $[RuCl_2(p\text{-cymene})]_2$; [g] no additive.

As a standard transformation, alkylation of 2-phenylpyridine (**6aa**) – one of the most active substrates in *ortho*-alkylations (Figure 3.3) – with challenging 2-bromooctane (**42ba**) has been selected. The reaction proceeded with most user-friendly $[RuCl_2(p\text{-cymene})]_2$ as the ruthenium

source in the presence of potassium carbonate (2.0 equiv) in 1,4-dioxane. The latter was proven to be the best solvent for these alkylations.[140]

According to 2D-NMR spectra, product **147aa** could be determined to be rather *meta*- than *ortho*-alkylated. For the final prove of this unprecedented site-selectivity, the alkylation product **147aa** was converted to its pyridium salt **148** employing oxalic acid. This salt has been crystallized by slow concentration of their solutions to afford crystals suitable for X-ray crystal structure analysis (Figure 3.4).[141]

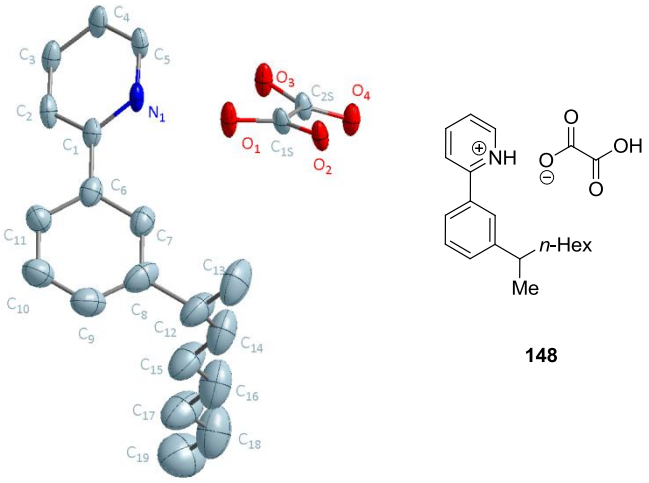
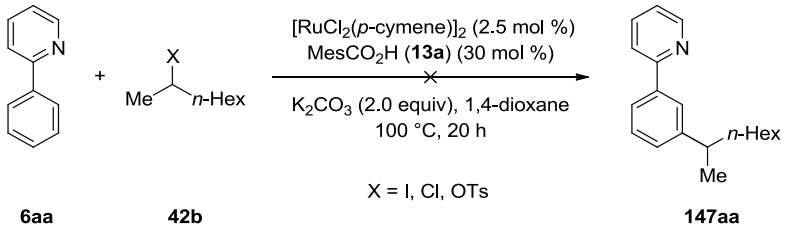


Figure 3.4 ORTEP plots (50% probability thermal ellipsoids) of 2-[2-(octan-2-yl)phenyl]pyridinium oxalate (**148**) in the crystal. All hydrogen atoms have been omitted for clarity. Numbering does not correspond to the IUPAC rules.

The data from Table 3.10 obviously indicate that various aliphatic (entries 1 and 2), aromatic (entries 4–9) and triflic acids (entry 12) as well as their salts (entries 13–16) showed a catalytic activity. Among them, 1-adamantyl (**13c**) (entry 1) and mesityl carboxylic acid (**13a**) (entry 9) gave the best yields, while phosphine-substituted (entry 3) and strong trifluoroacetic acids (entry 11) provided no alkylation. The same effect was observed in the absence of the base, the additive or the ruthenium catalyst (entry 10). Some carboxylates showed high activity, especially potassium mesityl carboxylate, delivered roughly 50% yield (entry 13); however, less than applying *in-situ* generation of this salt (entry 9).

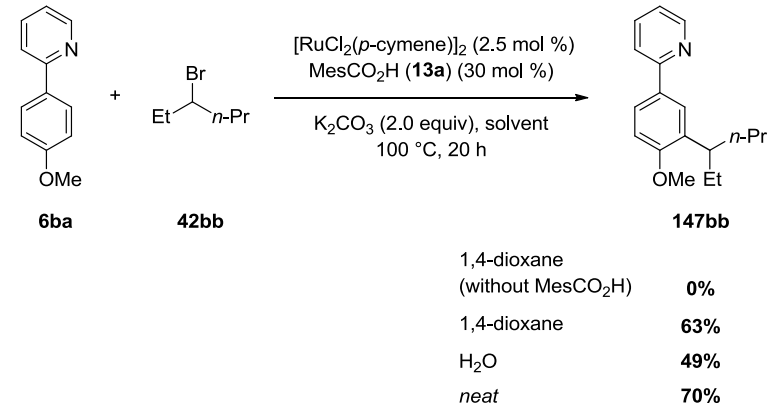
Besides, the reactivity of other electrophiles under these reaction conditions was examined (Scheme 3.23). Unfortunately, neither alkyl iodides or chlorides nor tosylates showed any conversion in the attempted direct ruthenium-catalyzed alkylation.

[140] Preliminary screening for suitable solvents was performed in cooperation with Dr. R. Vicente.
[141] For all other products synthesized by the ruthemiun-catalyzed direct alkylations with secondary alkyl bromides, the substitution pattern was verified applying 2D-NMR analysis and/or nOe-experiments.



Scheme 3.23: Screening of different leaving groups.

As indicated above, a degassed aqueous medium was well accepted for the ruthenium-catalyzed direct alkylation with primary alkyl halides. Therefore, a solvent screening was performed to determine, if water is tolerated to the same extent within the direct *meta*-alkylation (Scheme 3.24).



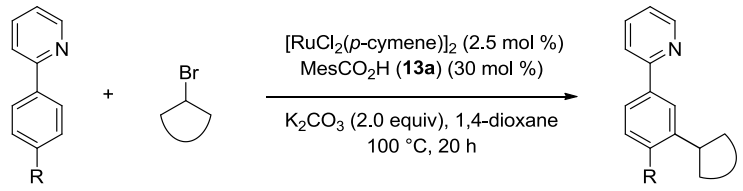
Scheme 3.24: Direct *meta*-alkylation in different reaction media.

Under the standard reaction conditions applying 1,4-dioxane as the solvent, reaction of substrate **6ba** with 3-bromopentane (**42bb**) furnished compound **147bb** in a good yield (63%), while in the absence of the carboxylic acid (**13a**) no product formation was observed. Employment of water as the reaction medium delivered **147bb** in lower, but still good yield (50%), whereas a reaction in the absence of solvent afforded the best yield of 70%. Unfortunately, in further experiments the neat reaction conditions proved to be less suitable due to insufficient solubilities of several organic substrates.

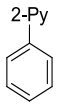
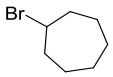
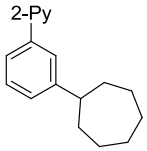
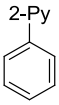
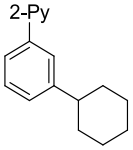
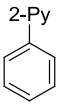
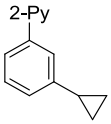
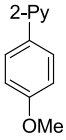
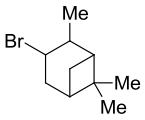
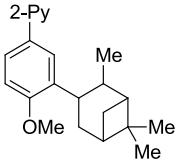
3.2.3 Direct *meta*-Alkylation: Scope & Limitations

In order to explore, to which extend this new reaction type is user-friendly and applicable, various substrates **6** and secondary alkyl bromides **42b** was tested under the optimized reaction conditions. First, the scope of secondary alkyl bromides was explored starting with cyclic aliphatic bromides (Table 3.11).

Table 3.11: Scope of *meta*-alkylation with cyclic secondary alkyl bromides.



6 **42b** **147**

entry	substrate 6	bromide 42b	product 147	yield of 147[a]
1				**76%**
	6aa	**42bc**	**147ac**	
2				**58%**
	6aa	**42bd**	**147ad**	
3				**10%[b]**
	6aa	**42be**	**147ae**	
4				**41%**
	6ba	**42bf**	**147bf**	

[a] **Reaction conditions: 6** (0.5 mmol), **42b** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $MesCO_2H$ (**13a**) (30 mol %), 1,4-dioxane (2.0 mL), 20 h, 100 °C; [b] $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %).

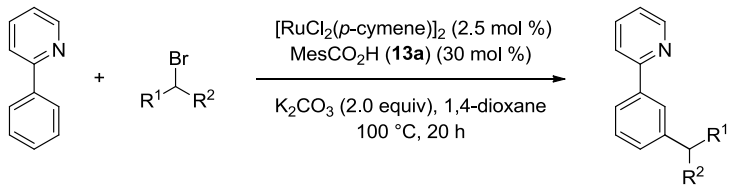
In ruthenium-catalyzed alkylations of 2-phenylpyridine (**6aa**) with bromocycloalkanes **42bc–42bf**, ranging from 7-membered cycloheptyl (**42bc**) to 3-membered cyclopropyl bromide (**42be**) decreasing in the ring size smoothly decreased the yield from 76 to 10%. This was not in line with the strain energies of the parent cyclic hydrocarbons cycloheptane, cyclohexane and cyclopropane, which are equal to 7.6, 1.4, 7.2 and 28.1 kcal·mol^{-1}, respectively.[142] However, this decreasing in yield appeared to be antithetic to the I-strain of corresponding bromides **42bc–42bf**.[143] "I-strain" is that change in internal strain of a ring compound which results from a change in the coordination number (and the

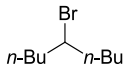
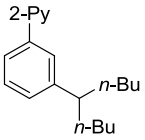
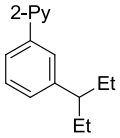
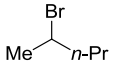
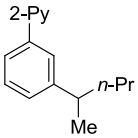
[142] Schleyer, P. von R.; Williams, J. E., Jr.; Blanchard, K. P. *J. Am. Chem. Soc.* **1970**, *92*, 2377–2386.
[143] Brown, H. C.; Fletcher, R. S.; Johannesen, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 212–221.

preferred bond angle) of a ring atom involved in the reaction"[144] and can in the first approximation be characterized by activity of the cyclic bromides in nucleophilic substitution reactions. For example, standard substitution protocols employed in larger ring systems are completely prohibitive in cyclopropane analogs[145] or are highly disfavored in cyclobutane derivatives due to significant *s*-character.[143] It should be mentioned that the formation of ring-opened products has not been detected. Sterically demanding substrate **42bf**, which has been synthesized from the corresponding racemic α-pinen, was only able to alkylate the electron-rich substrate **147bf** (entry 4).

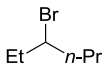
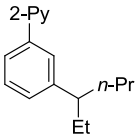
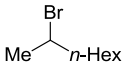
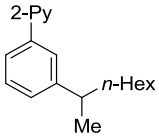
The results of alkylations of 2-phenylpyridine (**6aa**) with acyclic secondary alkyl bromides **42b** are presented in Table 3.12.

Table 3.12: Scope of acyclic 2-bromoalkanes.



entry	bromide 42b	product 147a	isolated yield[a]
1			51%
	42bg	**147ag**	
2			42%
	42bh	**147ah**	
3			43%
	42bi	**147ai**	

[144] Brown, H. C.; Gerstein, M. *J. Am. Chem. Soc*. **1950**, *72*, 2926–2933.
[145] Ryabchuk, P.; Rubina, M.; Xu, J.; Rubin, M. *Org. Lett*. **2012**, *14*, 1752–1755, and references cited therein.

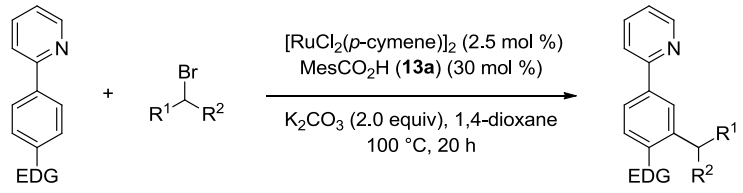
entry	bromide 42b	product 147a	isolated yield[a]
4			26%
	42bb	147ab	
5			60%
	42ba	147aa	

[a] **Reaction conditions: 6aa** (0.5 mmol), **42b** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $MesCO_2H$ (**13a**) (30 mol %), 1,4-dioxane (2.0 mL), 20 h, 100 °C.

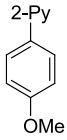
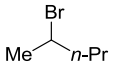
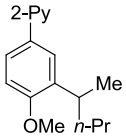
Symmetric as well as unsymmetric secondary alkyl bromides were tested under the standard reaction conditions and provided results. Generally, the bromides **42ba** and **42bg** with longer hydrocarbon chains afforded better yield than homologous compounds **42bi** and **42bh** (entries 1 and 2, entries 3 and 5). Comparing reactivities of 2-bromopentane (**42bi**) (entry 3) and of 3-bromopentane (**42bb**) (entry 4) resulted in the assumption, that the position of the leaving group in bromides **42b** influenced the conversion to some extend as well.

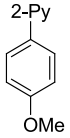
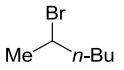
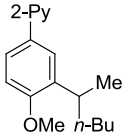
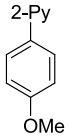
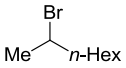
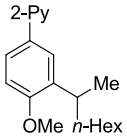
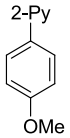
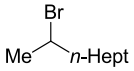
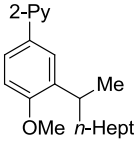
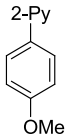
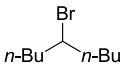
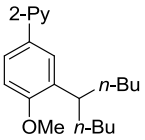
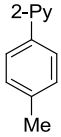
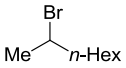
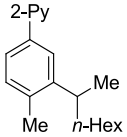
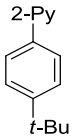
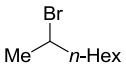
As demonstrated above in Table 3.12 and Table 3.11, unsubstituted 2-phenylpyridine (**6aa**) itself was an appropriate substrate for the ruthenium-catalyzed direct *meta*-alkylation under mild reaction conditions. Furthermore, the influence of electron-donating and electron-withdrawing substituents in the phenyl moiety upon the efficiency of the alkylation was examined. The results of alkylations of electron-rich substrates (**6**) are shown in Table 3.13.

Table 3.13: Scope and limitations with *para*-substituted electron-rich phenylpyridines.



6 **42b** **147**

entry	substrate 6	bromide 42b	product 147	yield of 147[a]
1				62%
	6ba	42bi	147bi	

entry	substrate 6	bromide 42b	product 147	yield of 147[a]
2				**70%**
	6ba	**42bj**	**147bj**	
3				**60%**
	6ba	**42ba**	**147ba**	
4				**56%**
	6ba	**42bk**	**147bk**	
5				**50%**
	6ba	**42bg**	**147bg**	
6				**55%**
	6oa	**42ba**	**147oa**	
7			--	--
	6ia	**42ba**		

[a] **Reaction conditions: 6** (0.5 mmol), **42b** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $MesCO_2H$ (**13a**) (30 mol %), 1,4-dioxane (2.0 mL), 20 h, 100 °C.

In general it can be emphasized that 2-phenylpyridines **6** with electron-donating *para*-substituents, such as methoxy or methyl, can be alkylated with a satisfying efficacy independently from the carbon chain length of the 2-bromoalkane **42b** (entries 1 - 4, 6). Sterically more demanding 5-bromononane (**42bg**) gave slightly lower yields (entry 5), whereas a very bulky *tert*-butyl substituent completely inhibited the desired alkylation (entry 7).

The alkylation product **147ba** was converted to its pyridium salt **149** employing hydrochloric acid. This salt was crystallized by slow evaporation of DCM/*n*-hexane to afford crystals suitable for X-ray crystal structure analysis (Figure 3.5).

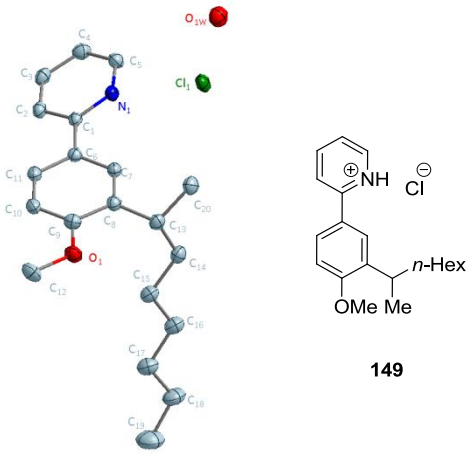
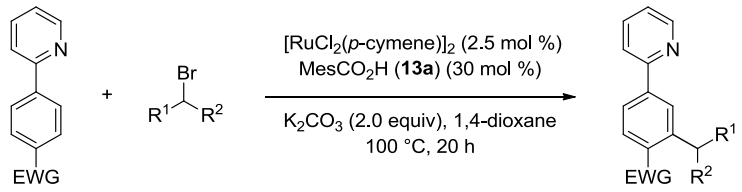


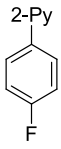
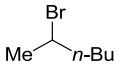
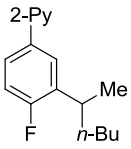
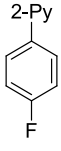
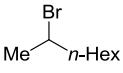
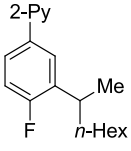
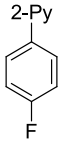
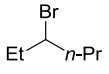
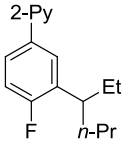
Figure 3.5: ORTEP plots (50% probability thermal ellipsoids) of 2-[4-methoxy-2-(octan-2-yl)phenyl]pyridinium chloride (**149**) in the crystal. All hydrogen atoms have been omitted for clarity. Numbering does not correspond to the IUPAC rules.

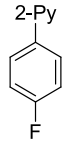
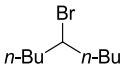
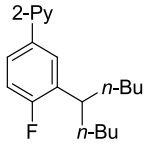
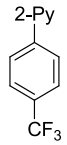
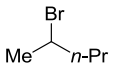
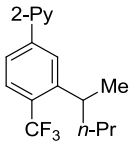
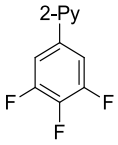
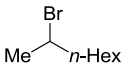
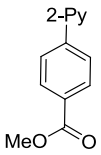
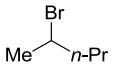
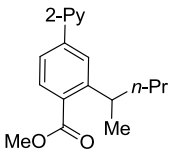
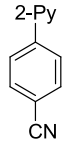
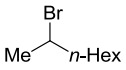
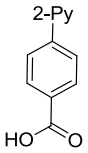
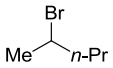
Subsequent examination of electron-deficient 2-phenylpyridines (Table 3.14) showed that steric aspects seemed to affect the yield to larger extent than electronic ones in this newly developed reaction type. Comparison of the results from Table 3.13 with those from Table 3.14 clearly indicated this observation.

Table 3.14: *meta*-Alkylation of *para*-substituted electron-poor 2-phenylpyridines **6**: Scope and limitations.



6 **42b** **147**

entry	substrate 6	bromide 42b	product 147	yield of 147[a]
1				**62%**
	6ca	**42bj**	**147cj**	
2				**56%**
	6ca	**42ba**	**147ca**	
3				**47%**
	6ca	**42bb**	**147cb**	

entry	substrate 6	bromide 42b	product 147	yield of 147[a]
4				50%
	6ca	42bg	147cg	
5				55%
	6ka	42bi	147ki	
6			--	--
	6ja	42ba		
7				63%
	6pa	42bi	147pi	
8			--	--
	6qa	42ba		
9			--	--
	6ra	42bi		

[a] **Reaction conditions: 6** (0.5 mmol), **42b** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mo l%), $MesCO_2H$ (**13a**) (30 mol %), 1,4-dioxane (2.0 mL), 20 h, 100 °C.

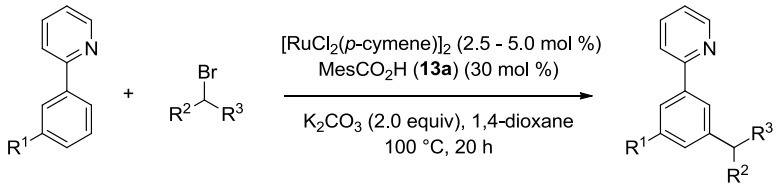
2-(4-Fluorophenyl)pyridine (**6ca**) with decreased electron density of the arene moiety afforded good yields upon alkylation with various alkyl bromides **42b** (entries 1 - 5), independently from the position of the bromine atom as well as from the carbon chain length in **42b**. Not surprisingly that (trifluorophenyl)pyridine **6ja** showed no reactivity (entry 6), as this would involve a C–F bond activation step, which is a scarce reaction type in ruthenium catalysis.[129]

Not surprisingly, the nitrile group (entry 8) was not tolerated by this reaction, and the product formation was not detected. The chemical behavior of substrate **6pa** with an ester functionality (entry 7) was of special interest because of two reasons. On the one hand, it demonstrated tolerance

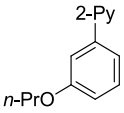
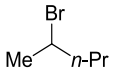
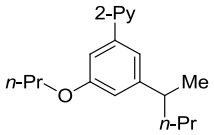
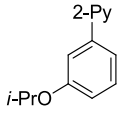
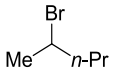
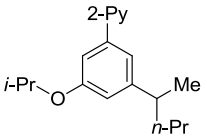
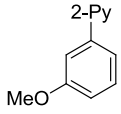
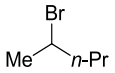
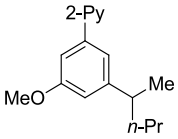
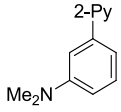
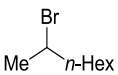
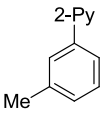
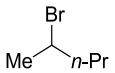
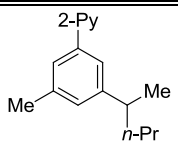
of functional groups towards ruthenium-catalyzed alkylation under basic reaction conditions and, on the other hand, such *meta*-alkylated carboxylate **147pi** cannot be synthesized through *Friedel-Crafts* alkylations. Notably, the substrate **6pa** furnished alkylated compound **147pi** as the sole product without conversion of the ester group. For the comparison, the corresponding free acid did not give rise to any formation of the desired product, but only formed an ester with the alkyl bromide (entry 9).

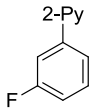
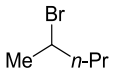
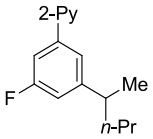
The scope of the ruthenium-catalyzed carboxylate-assisted direct *ortho*-alkylation of *meta*-substituted ketimines **121** with *n*-hexyl bromide (**42ab**) has been discussed above (Table 3.6). Therefore, several *meta*-substituted arylpyridines **6** were alkylated with various 2-bromoalkanes **42b** the optimized reaction conditions (Table 3.15).

Table 3.15: Substrate scope for *meta*-alkylation of *meta*-substituted 2-phenylpyridines.



6 **42b** **147**

entry	substrate 6	bromide 42b	product 147	yield of 147[a]
1				**39%**
	6sa	**42bi**	**147si**	
2				**38%**
	6ta	**42bi**	**147ti**	
3				**40%[b]**
	6ua	**42bi**	**147ui**	
4			--	--
	6ha	**42ba**		
5				**38%[b]**

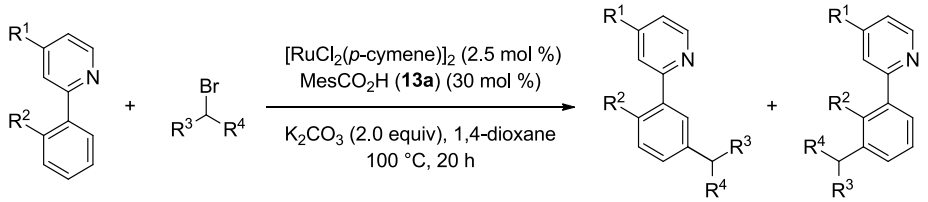
entry	substrate 6	bromide 42b	product 147	yield of 147[a]
	6va	**42bi**	**147vi**	
6				**28%[b]**
	6da	**42bi**	**147ai**	

[a] **Reaction conditions: 6** (0.5 mmol), **42b** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $MesCO_2H$ (**13a**) (30 mol %), 1,4-dioxane (2.0 mL), 20 h, 100 °C; [b] $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %).

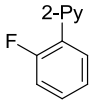
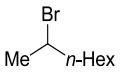
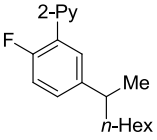
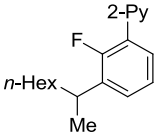
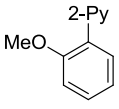
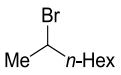
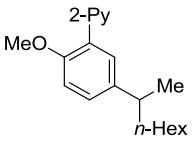
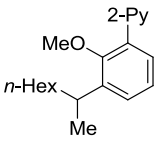
The direct alkylation of *meta*-substituted 2-phenylpyridine **6** proceeded with moderate yields of the desired products **147** (entries 1–3, 5, 6). Table 3.15 indicates, that the yields were almost unaffected by the electronic properties of the substituents in the substrates **6**. The lowest yield of 28% was obtained for electron-poor fluoro-substituted 2-phenylpyridine **6da** (entry 6). Dimethylamin-substituted arene **6ha** completely failed in the direct alkylation (entry 4), presumably due to the formation of a stable ruthenium-complex.

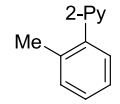
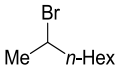
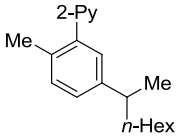
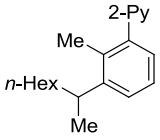
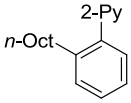
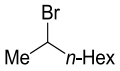
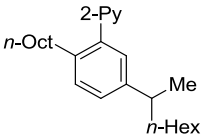
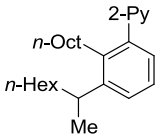
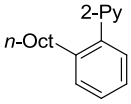
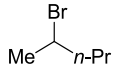
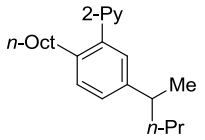
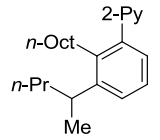
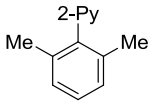
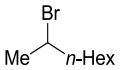
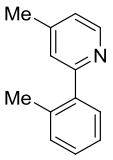
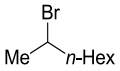
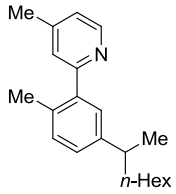
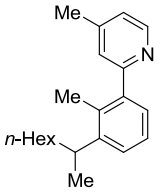
In contrast to *meta*-substituted arylpyridines, in the case of their *ortho*-substituted analogues, two possible products corresponding to the two free *meta*-positions can be formed. The results on the chemical behavior of a variety of substrates **6** are summarized in Table 3.16.

Table 3.16: Substrate scope for *meta*-alkylation of *ortho*-substituted 2-phenylpyridines (**6**).



6 **42b** **147** **147'**

entry	substrate 6	bromide 42b	product 147	product 147'	isolated yield ratio 147:147'[a]
1					**19%** **za:za' = 1.0:5.3**
	6za	**42ba**	**147za**	**147za'**	
2					**43%** **wa:wa' = 1.0:1.2**
	6wa	**42ba**	**147wa**	**147wa'**	

entry	substrate 6	bromide 42b	product 147	product 147'	isolated yield ratio 147:147'[a]
3					60% xa:xa' = 1.0:2.8
	6xa	42ba	147xa	147xa'	
4					32%[b] 150:150' = 1.0:1.3
	93a	42ba	150	150'	
5					31%[b] 151:151' = 1.0:1.2
	93a	42bi	151	151'	
6			--	--	--
	6ya	42ba			
7					62%[b] ea:ea' = 1.0:2.9
	6ea	42ba	147ea	147ea'	

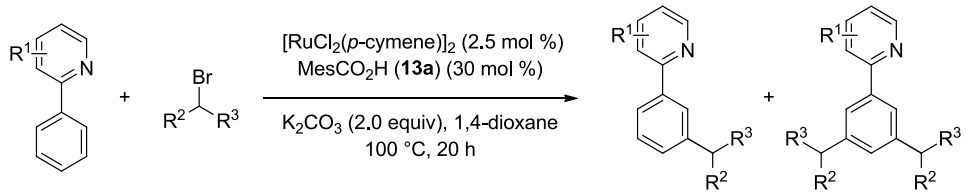
[a] **Reaction conditions: 6** (0.5 mmol), **42b** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $MesCO_2H$ (**13a**) (30 mol %), 1,4-dioxane (2.0 mL), 20 h, 100 °C; see, experimental part for the isolated yields of each isomer;

[b] $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %).

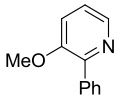
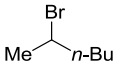
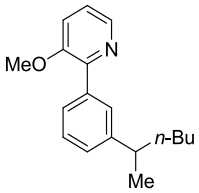
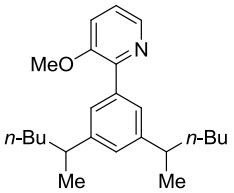
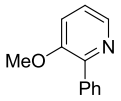
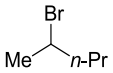
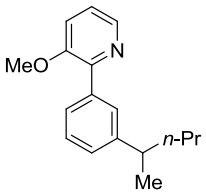
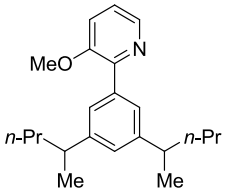
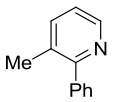
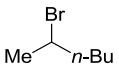
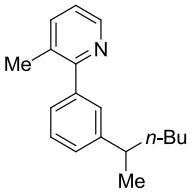
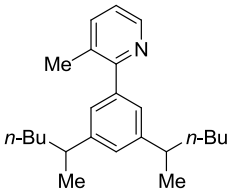
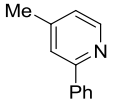
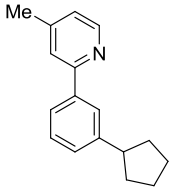
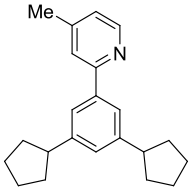
No general preference was detected for one of the two free *meta*-positions for all substrates **6.** Most substrate showed a slight priority for Only for the product **147'**, with three neighboring substituents. Only for the *ortho*-fluoro substrate **6za** the product **147za'** is clearly favoured, but the overall yield is unsatisfactory (entry 1). Yet, this electron-deficient substrate appeared to be less appropriate for alkylation than the electron-rich ones (entries 2–5). Among the latter, better yields were obtained for 2-phenylpyridines with less sterically demanding substituents (entries 2 and 3) than for *n*-octyl-substituted substrates **93a** (entries 4 and 5). No transformation was observed upon attempted alkylation of *ortho*,*ortho*-dimethylated substrate **6ya** (entry 6). In contrast to this, an additional methyl substituent on the pyridine ring did not influence the course of the alkylation (entry 7); an 1:2.9 mixture of compounds **147ea** and **147ea'** was isolated in good yield of 62%

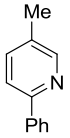
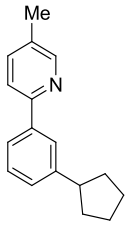
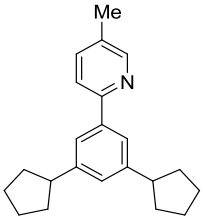
As the next important step, a variety of different directing groups was examined. First, the influence of the substitution pattern on the pyridine moiety was investigated. For this purpose, a broad range of 2-phenylpyridines **6** with substituents on the directing group were tested in alkylation under the optimized reaction conditions (Table 3.17).

Table 3.17 a: Substrate scope for *meta*-alkylation of 2-phenylpyridines substituted on the pyridine moieties.



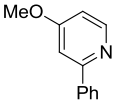
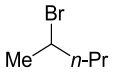
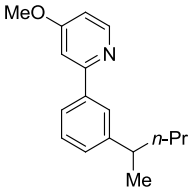
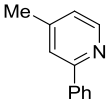
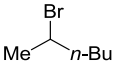
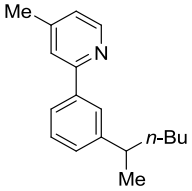
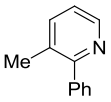
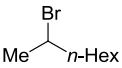
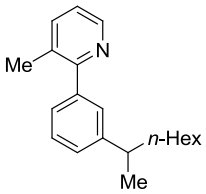
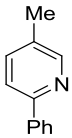
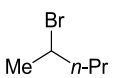
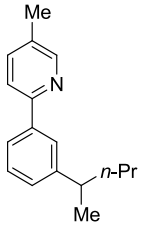
6 **42b** **152** **152'**

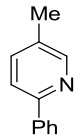
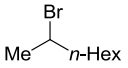
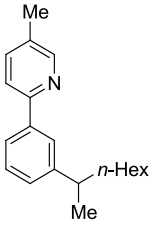
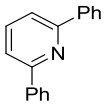
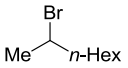
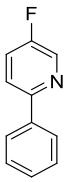
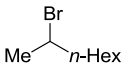
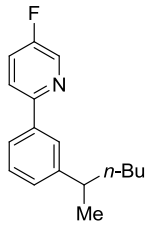
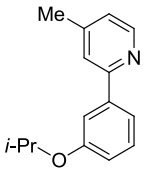
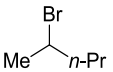
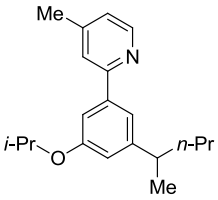
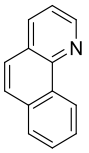
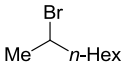
entry	substrate 6	bromide 42b	product 152	yield of 152[a]	by-product 152'	yield of 152'[a]
1				48%		5%
	6cb	**42bj**	**152cj**		**152cj'**	
2				41%[b]		11%[b]
	6cb	**42bi**	**152ci**		**152ci'**	
3				61%		10%
	6db	**42bj**	**152dj**		**152dj'**	
4				38%		6%
	6eb	**42bk**	**152ek**		**152ek'**	

entry	substrate 6	bromide 42b	product 152	yield of 152[a]	by-product 152'	yield of 152'[a]
5				39%		4%
	6fb	42bk	152fk		152fk'	

[a] **Reaction conditions: 6** (0.5 mmol), **42b** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $MesCO_2H$ (**13a**) (30 mol %), 1,4-dioxane (2.0 mL), 20 h, 100 °C; [b] $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %).

Table 3.17 b

entry	substrate 6	bromide 42b	product 152	yield of 152[a]
6				33%[b]
	6gb	42bi	152gi	
7				30%
	6eb	42bj	152ej	
8				56%
	6db	42ba	152da	
9				56%
	6fb	42bi	152fi	

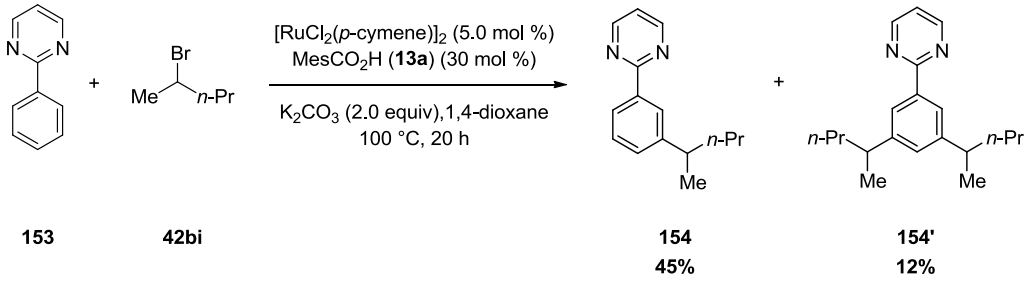
entry	substrate 6	bromide 42b	product 152	yield of 152[a]
10				43%
	6fb	42ba	152fa	
11			--	--
	6ab	42ba		
12				(44%)[c]
	6ib	42ba	152ia	
13				33%[b]
	6ec	42bi	152ei	
14			--	--
	6d	42ba		

[a] **Reaction conditions: 6** (0.5 mmol), **42b** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $MesCO_2H$ (**13a**) (30 mol %), 1,4-dioxane (2.0 mL), 20 h, 100 °C; [b] $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %); [c] GC-MS conversion.

Generally, substitution with methyl or methoxy groups on pyridine resulted in high conversions and moderate to good isolated yields (Table 3.17; entries 1 - 10). In several cases, including alkylations with cyclopentyl bromide (**42bk**) (Table 3.17; entries 4 and 5), formation of bis-alkylated products **152'** in substantial amounts was detected (Table 3.17 a). 4-Methoxy and -methyl substituents (entries 6 and 7) decreased the reactivity of substrates **6** to some extent, while the second electron-donating substituent onto the carbocyclic ring (entry 13) did not affect the yield. Most probably, the higher electron density on the nitrogen atom could influence the stability of the possible intermediate ruthenacycles thus hampering the C–H bond activation step, and this situation cannot

be improved by additional substituent in a carbocyclic ring (entry 13). In contrast to this, 5- (entry 8) and 3-methylated substrates (entries 9 and 10) gave high conversions and afforded products **152fa** and **152fi** in improved yields, whereas 5-fluorosubstituted 2-phenylpyridine **6ib** demonstrated a reduced reactivity (entry 12). The substrate **6ab** with a phenyl substituent in position 6 of the pyridine moiety (entry 11) and benzo[*h*]quinoline (**6d**) (entry 14) did not demonstrate any reactivity towards the desired alkylation. Presumably, sterical interactions and changing electron density on the ruthenium atom are capable to impede the formation of intermediate ruthenacycles in the former case, while rigidity of the skeleton of **6d** completely excluded its *meta*-alkylation in the latter one.

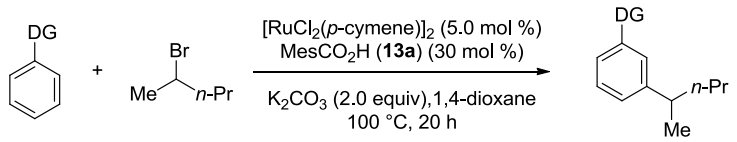
In contrast to 2-arylpyridines **6**, *meta*-alkylation of arenes activated by directing groups with two nitrogen atoms normally required a higher catalyst loading. Thus, 2-phenylpyrimidine (**153**) gave high conversion when using 5.0 mol % of the ruthenium precursor under otherwise identical reaction conditions (Scheme 3.25). Surprisingly, relatively large amount of the bis-alkylated product **154'** was formed.



153 **42bi** **154** 45% **154'** 12%

Scheme 3.25: Ruthenium-catalyzed direct *meta*-alkylation of 2-phenylpyrimidine (**153**).

Since the alkylation of 2-phenylpyrimidine (**153**) proved to be less chemoselective, substrates with other directing groups have been tested (Scheme 3.26 and Figure 3.6).



I **42bi** **II**

Scheme 3.26: Examination of different nitrogen-containing directing groups.

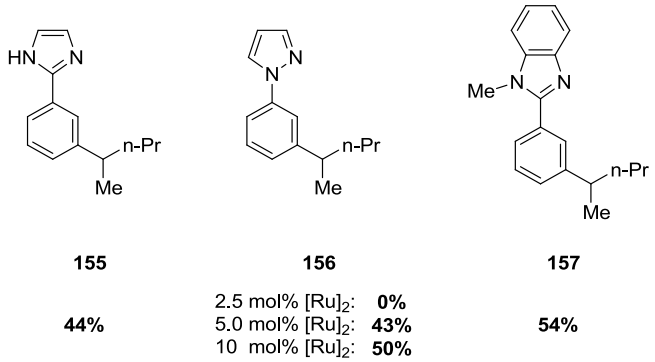
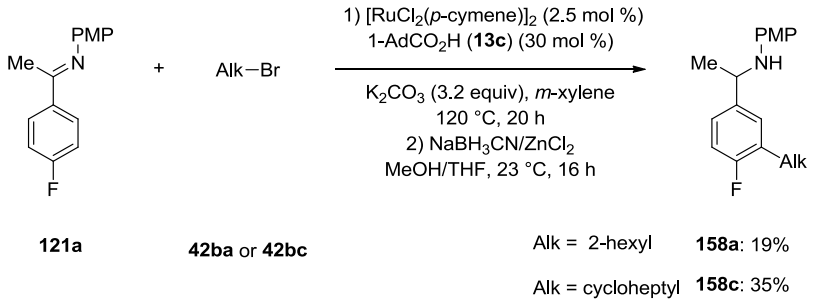


Figure 3.6: Results for substrates with other DG und the conditions mentioned in Scheme 3.26.

Summarizing the data from Figure 3.6, arenes with various directing groups, including unprotected imidazole (**155**), pyrazole (**156**) and *N*-methylated benzimidazole (**157**) proved to be reactive towards *meta*-alkylation under mild reaction conditions. The isolated yields could be raised up to 54% when applying 5.0 mol % of the ruthenium precatalyst. Nevertheless, pyridine is still considered to be the most efficient directing group.

While previous results for the direct *ortho*-alkylation of electron-deficient ketimines **121** with primary alkyl bromides **42a** afforded very good yields, the direct *meta*-alkylation of compound **121a** with secondary alkyl bromides **42ba** and **42bc** delivered unsatisfactory yields (Scheme 3.27).



Scheme 3.27: Attempted ruthenium-catalyzed direct *meta*-alkylation of ketimine **121a** as the substrate.

Among other potentially appropriate substrates **159–166** which were tested towards the direct ruthenium-catalyzed *meta*-alkylation with secondary alkyl bromides under the optimized reaction conditions (Figure 3.7), unfortunately, none of them demonstrated promising conversions to the desired alkylated product.

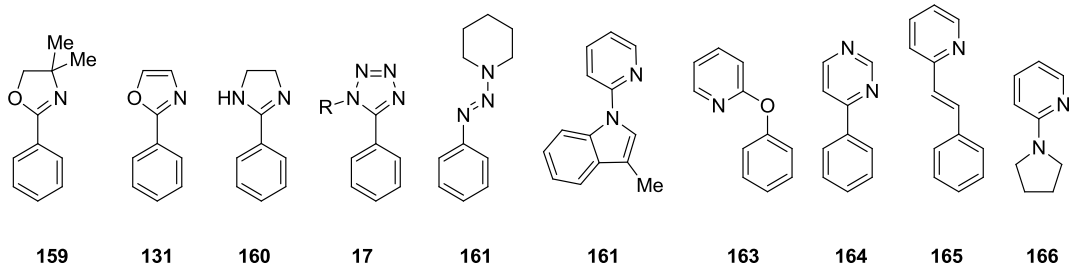
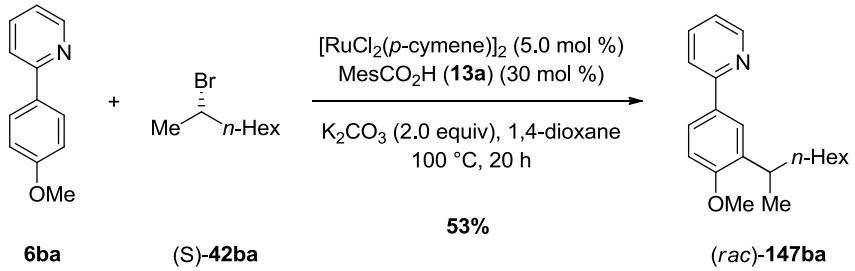


Figure 3.7: Unreactive substrates for the ruthenium-catalyzed direct *meta*-alkylation.

3.2.4 Experiments towards Enantioselective Direct *meta*-Alkylation

Upon this newly developed direct *meta*-selective ruthenium-catalyzed C–C bond forming process, a new stereogenic benzylic carbon centre is generated. Therefore, several experiments towards the enantioselective C–H bond functionalization were conducted.

First, enantiomerically pure 2-bromooctane [(*S*)-**42ba**] was used as electrophile to determine whether the stereochemical information was retained (Scheme 3.28).



Scheme 3.28: Ruthenium-catalyzed direct *meta*-alkylation with enantiopure (*S*)-**42ba**.

The formation of the racemic product was determined under the optimized reaction conditions. A radical pathway or the formation of a planary carbo-cation species can be hypothesized. The yield of the racemic product (*rac*)-**147ba** in this experiment was in the same range as in the preparation with racemic 2-bromooctane (**42ba**) (Table 3.13).

For further experiments, a separation of the two enantiomeric products of the alkylation reaction using preparative chiral HPLC-techniques was carried out. The structure and absolute configuration for arbitrary selected (*R*)-enantiomere of the compound **147bj** was established by X-ray crystal structure analysis of its hydrochloride (Figure 3.8).

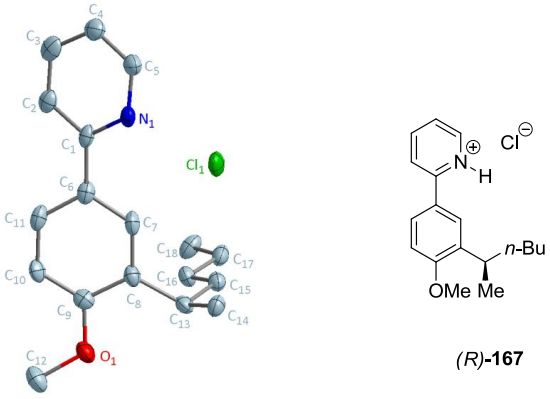
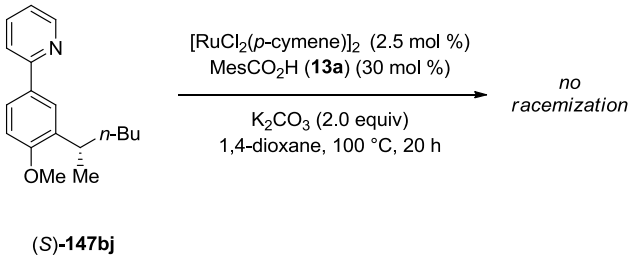


Figure 3.8: ORTEP plots (50% probability thermal ellipsoids) of (*R*)-2-[4-methoxy-2-(hexan-2-yl)phenyl]pyridinium chloride ((*R*)-**167**) in the crystal. Numbering does not correspond to the IUPAC rules. All hydrogen atoms have been omitted for clarity.

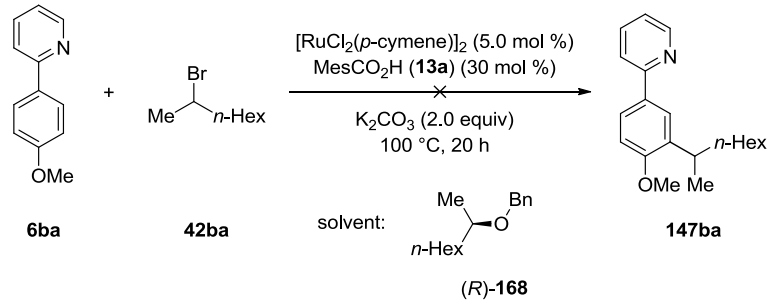
To exclude racemization during the alkylation reaction, an enantioselective pure alkylation product (*S*)-**147bj** was submitted to the standard reaction conditions (Scheme 3.29).



Scheme 3.29: Attempted racemization of (*S*)-**147bj** under standard reaction conditions.

Under these reaction conditions, no racemization on the stereogenic centre was detected, according to results of HPLC analysis on chiral stationary phase. Such a configurative stability of stereogenic centre under the reaction conditions indicates the possibility to elaborate an enantioselective direct alkylation.

Next, it was tested, whether a chiral solvent could give access to enantiomerically an enriched product **147ba**. According to a published protocol,[187187] enantiomerically pure benzyl ether (*R*)-**168** was synthesized and degassed several times applying the *Freeze-Pump-Thaw* degassing procedure. However, no product formation was detected through alkylation under these slightly modified reaction conditions (Scheme 3.30).



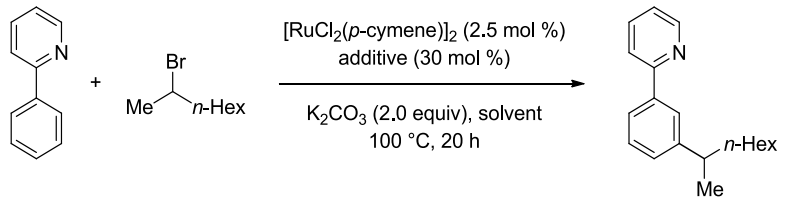
Scheme 3.30: Attempted *meta*-alkylation of **6ba** applying chiral solvent (*R*)-**168**.

3.2.4.1 Chiral Amino Acid-derived Additives

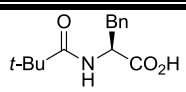
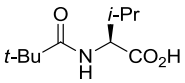
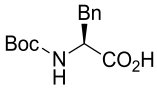
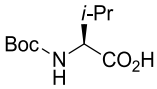
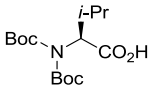
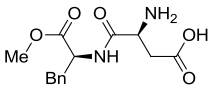
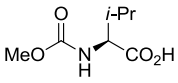
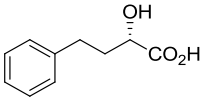
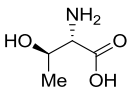
The invention of a enantioselective palladium-catalyzed direct alkylation employing mono-protected amino acids (MPAA) as chiral ligands by *Yu* has attracted considerable attention.[87]

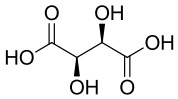
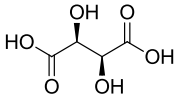
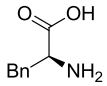
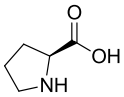
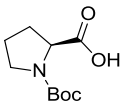
As these transformations afforded relatively high enantioselectivities and excellent yields, several MPAAs (**76**) were synthesized according to the published procedures and tested as additives for the ruthenium-catalyzed direct *meta*-alkylation (Table 3.18) together with chiral carboxylic acids **170**, L-**172** and D-**172** (entries 7, 9 and 10) with water or 1,4-dioxane as reaction medium.

Table 3.18: Screening for most efficient chiral additive.



6aa **42ba** **147aa**

entry	additive	solvent	yield of 147aa[a]
1	 **76b**	H_2O	**53%**
2	 **76c**	H_2O	**73%**
3	 **76d**	H_2O	**36%**
4	 **76e**	H_2O	**48%**
5	 **169**	H_2O	**20%**
6	 **76f**	H_2O	**17%**
7	 **76g**	H_2O	**46%**
8	 **170**	H_2O	**--**
9	 **171**	1,4-dioxane	**--**

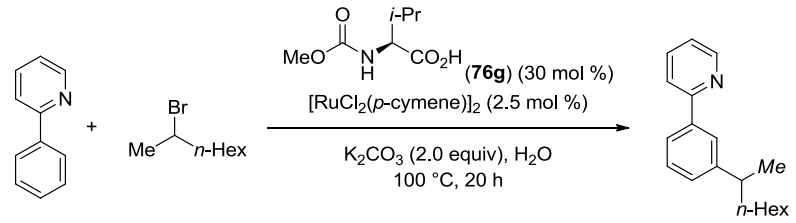
entry	additive	solvent	yield of 147aa[a]
10	 **L-172**	1,4-dioxane	--
11	 **D-172**	1,4-dioxane	--
12	 **173**	1,4-dioxane	--
13	 **174**	1,4-dioxane	--
14	 **76h**	1,4-dioxane	--

[a] **Reaction conditions: 6aa** (0.5 mmol), **42ba** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), additive (30 mol %), solvent (2.0 mL), 20 h, 100 °C.

Several chiral amino acid-derived additives were tested to determine their efficiency as co-catalyst. Mono-*N*-protected phenylalanine- and leucine-derived additives **76b**-**76e** proved to give satisfactory results when using water as the solvent (entries 1 - 4). Among them, pivaloyl-protected leucine (**76c**) (entry 2) gave a better yield than the corresponding Boc-protected amino acid (**76e**) (entry 4).

The use of di-*N*-Boc-protected leucine **169** (entry 5) as well as of dipeptide **76f** (entry 6) did not turn out to be beneficial. Free alcohol functionalities inhibited the reaction, and the product formation was observed neither with water nor with 1,4-dioxane as reaction medium (entries 8 - 10). The same result was obtained using unprotected proline (**174**), phenylalanine (**173**) and Boc-protected proline **76h** as ligands in 1,4-dioxane.

Remarkably, upon alkylation of 2-phenylpyridine (**6aa**) as a standard substrate, MPAA **76c** as a co-catalyst afforded a higher yield (73%, entry 2) than mesityl carboxylic acid (**13a**) (60%, Table 3.10), but with water as the reaction medium. Because of this, several additional screening experiments with mono-protected leucine **76g** towards optimization of the reaction conditions was performed. Thus, the influence of the reagents ratio was investigated (Scheme 3.31).

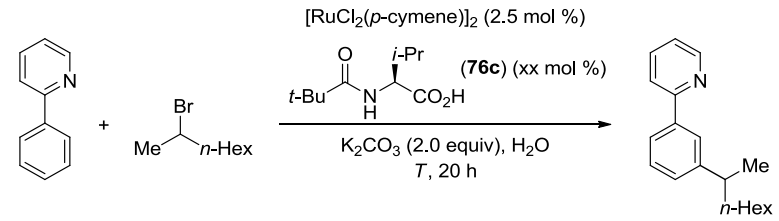


6aa	42ba	147aa
0.5 mmol	0.5 mmol	**26%**
0.5 mmol	1.0 mmol	**40%**
0.5 mmol	1.5 mmol	**46%**

Scheme 3.31: Screening for the optimal ratio between 2-phenylpyridine (**6aa**) and 2-bromooctane (**42ba**).

The results shown in Scheme 3.31 obviously indicate that the ratio of 1:3 still remains the most efficient also for MPAAs as co-catalysts. Furthermore, a screening of co-catalyst loading and reaction temperature was performed with this most efficient amino acid derivative **76c** (Table 3.19).

Table 3.19: Screening for optimal additive loading and reaction temperature.



6aa **42ba** **147aa**

entry	additive 76c [mol %]	T [°C]	isolated yield [a]
1	5	100	--
2	10	100	--
3	20	100	**54%**
5	30	100	**73%**
6	30	40	--
7	30	60	**51%**
8	30	80	**60%**

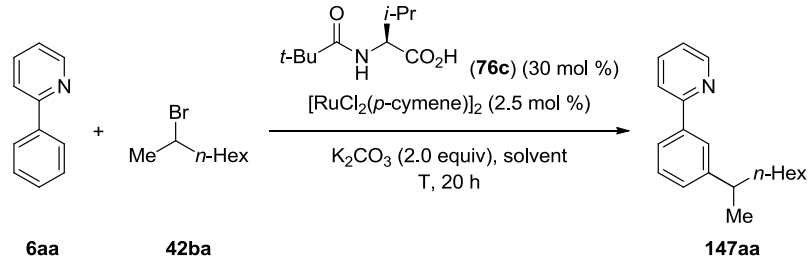
[a] **Reaction conditions: 6aa** (0.5 mmol), **42ba** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), H_2O (2.0 mL), 20 h.

Upon decreasing the cocatalyst loading to 20 mol%, the yield dropped to 54% (entry 3), while no conversion was detected applying less cocatalyst. It was also found that by rising the temperature to 60 °C the reaction still furnished the desired product in good yield.

An additional screening for solvents (Table 3.20) indicated no general rules for the optimal solvent. Thus, non-polar aromatic solvents (entries 2 and 5) appeared to be of similar efficacy as 1,4-dioxane (entry 1), while no transformation proceeded in non-polar *n*-hexane (entry 6), presumably because of

solubility problems, as well as in polar DMA (entry 3), *t*-AmOH (entry 4) or methanol (entry 7). Degassed water still represented the most efficient solvent, however, control experiments without base, additive or ruthenium gave negative results (entry 9). Alternatively, triethylamine as the organic base was tested (entry 10), however, with moderate success.

Table 3.20: Solvent-screening with pivaloyl-protected leucine **76c** as the additive.

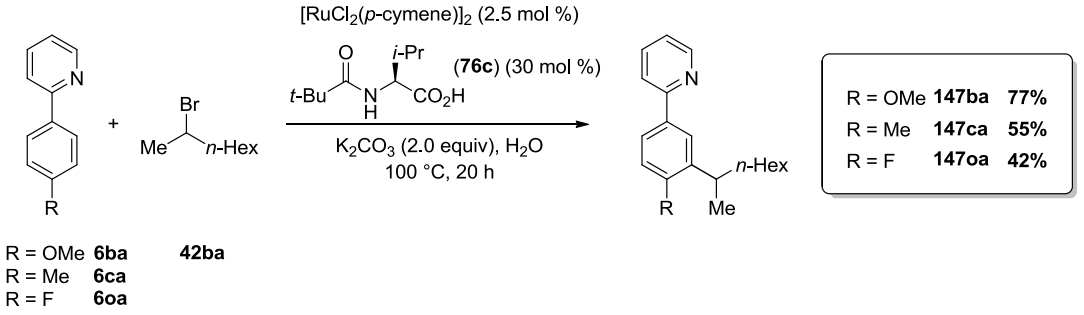


6aa **42ba** **147aa**

entry	solvent	T	isolated yield[a]	entry	solvent	T	isolated yield[a]
1	1,4-dioxane	100 °C	**61%**	**6**	*n*-hexane	65 °C	--
2	PhMe	100 °C	**59%**	**7**	MeOH	65 °C	--
3	DMA	100 °C	--	**8**	H_2O	100 °C	**73%**
4	*t*-AmOH	100 °C	--	**9**	H_2O	100 °C	--[b, c, or d]
5	*m*-xylene	100 °C	**50%**	**10**	H_2O	100 °C	**32%**[e]

[a] **Reaction conditions: 6aa** (0.5 mmol), **42ba** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), H_2O (2.0 mL), 20 h; [b] no catalyst; [c] no additive; [d] no base; [e] NEt_3 as base (2.0 equiv).

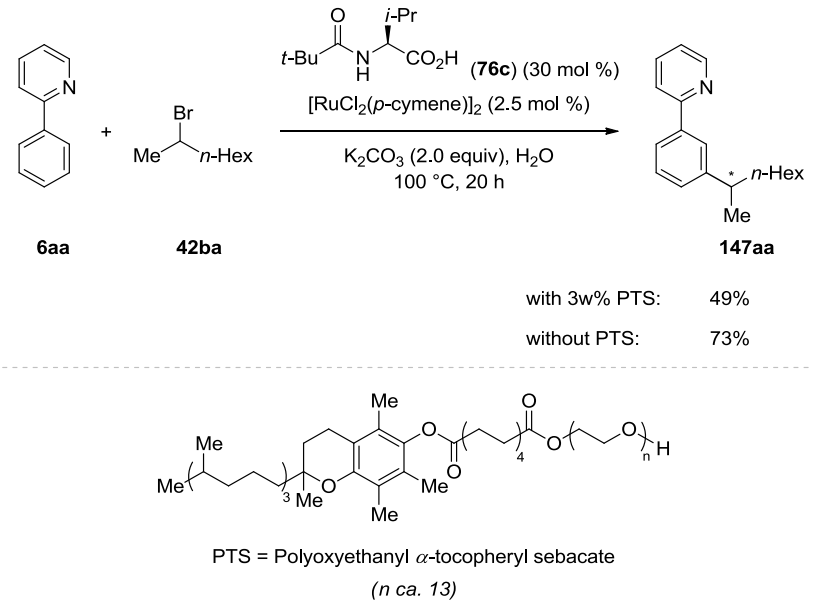
Applying the optimized reaction conditions, the electron-rich substrates **6ba** and **6ca** can be alkylated with higher yields in comparison with electron-deficient one **6oa**, which furnished only moderate yield (Scheme 3.32). With a sterically demanding, but electron-donating substituent the product **147** can be obtained in a good yield, which was in the same range as with mesityl carboxylic acid (**13a**) as additive.



Scheme 3.32: Examples for the direct *meta*-Alkylation with additive **76c**.

Unfortunately, although in all reactions discussed above only enantiomerically pure L-amino acid derivatives were used, HPLC analysis on chiral stationary phase indicated exclusively the formation of racemic products without any enantiomeric excess.

Lipschutz,[146] *Scarso*[147] and others have demonstrated the beneficial effect of phase transfer catalysts, such as polyoxyethanyl α-tocopheryl sebacate (PTS), for transition metal-catalyzed cross-couplings or asymmetric *Bayer-Villiger* oxidation reactions in water. Potential activity of PTS as an additional co-catalyst has also been tested in ruthenium-catalyzed direct *meta*-alkylation of 2-phenylpyridine (**6aa**) with pivaloyl-protected leucine (**76c**) as additive in water as a solvent (Scheme 3.33)



Scheme 3.33: Examining the influence of phase transfer catalyst PTS in the direct *meta*-alkylation with water as the solvent.

Decreasing the yield about roughly one third indicated that the reaction presumably proceeded rather on water than in water.[148]

[146] Lipshutz, B. H.; Ghorai, S.; Leong, W. W. Y.; Taft, B. R.; Krogstad, D. V. *J. Org. Chem.* **2011,** *76*, 5061–5073.

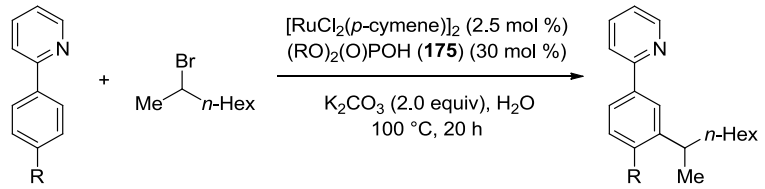
[147] Cavarzan, A.; Bianchini, G.; Sgarbossa, P.; Lefort, L.; Gladiali, S.; Scarso, A.; Giorgio Strukul, G. *Chem. Eur. J*. **2009**, *15*, 7930–7939.

[148] Reviews: (a) Butler, R. N.; Coyne, A. G. *Chem. Rev*. **2010**, *110*, 6302–6337. (b) Narayan, S.; Fokin, V. V.; Sharpless, K. B. In *Organic Reactions in Water: Principles, Strategies and Applications* (ed.: Lindström, U. M), Marcus Blackwell Publishing Ltd: N.-Y., 2007, pp. 350–365.

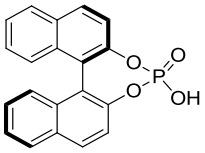
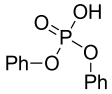
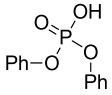
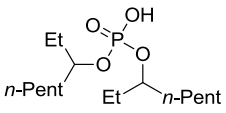
3.2.4.2 Phosphoric Acid Esters as Chiral Additives

Since chiral MPAAs as additives afforded high yields of alkylated 2-phenylpyridines **147**, but unfortunately only in racemic form, other prospective chiral acids were tested. One possibility is displayed by chiral phosphoric acids, which were used in numerous enantioselective transformations, for example in enantioselective organocatalytic reductive aminations.[149] The phosphoric acids **175** appeared to be suitable co-catalysts for the desired direct alkylations performing *meta*-C–H bond functionalization in a comparable fashion to carboxylic acids (Table 3.21).

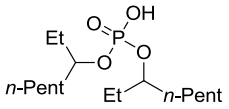
Table 3.21: Phosphoric acids as alternative additives for direct *meta*-alkylation.



6 **42ba** **147**

entry	R	additive	isolated yield[a]
1	OMe	 **175a**	**27%**
2	OMe	 **175b**	**58%**
3	H	 **175b**	**38%**
4	H	 **175c**	**58%**

[149] Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006,** *128,* 84–86.

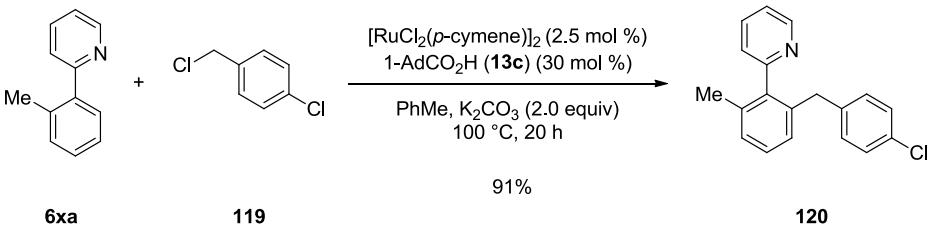
entry	R	additive	isolated yield[a]
5	OMe	 **175c**	**77%**
6	H	H_3PO_4	**24%**

[a] **Reaction conditions: 6** (0.5 mmol), **42ba** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), additive (30 mol %), H_2O (2.0 mL), 20 h, 100 °C.

Thus, acyclic phosphoric acids **175b** and **175c** promoted efficient conversions and ensured high yields of 2-phenylpyridines **147aa** and **147ba** (entries 2, 4 and 5). Unfortunately, the application of enantiomerically pure (*R*)-BINOL-derived phosphoric acid **175a** appeared not only to be less efficient, but resulted in the formation of racemic product, as indicated by HPLC analysis on chiral stationary phase (entry 1).

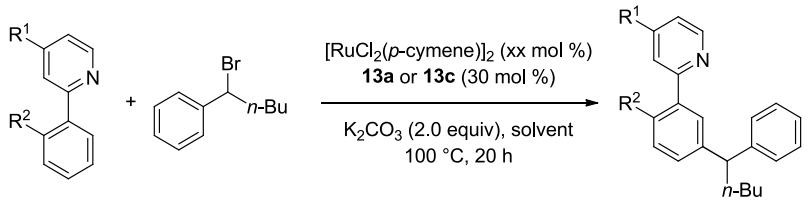
3.2.5 Direct Ruthenium-Catalyzed *meta*-Benzylation

Not only ruthenium-catalyzed alkylation with unactivated alkyl halides, but also direct benzylation represented an interesting objective. The pioneering studies by *Ackermann* and *Novák* demonstrated that arylpyridines **6** can easily be *ortho*-benzylated with primary benzyl chlorides **119** as inexpensive electrophiles. These carboxylate-assisted ruthenium-catalyzed C–H functionalizations afforded benzylated 2-phenylpyridines **120** in good yields under relatively mild conditions (Scheme 3.34).[123]



Scheme 3.34: Ruthenium-catalyzed direct *ortho*-benzylation with *p*-chlorobenzyl chloride (**119**) according to *Ackermann* and *Novák*.

However, ruthenium-catalyzed benzylation reactions with secondary benzyl halides remained unknown until recently, when they were demonstrated to proceed in a *meta*-functionalization mode, similarly to alkylations with unactivated secondary alkyl bromides. The benzylation with (1-bromopentyl)benzene (**176**) - prepared in two steps adopting published procedures - was tested for suitable reaction conditions (Scheme 3.35).



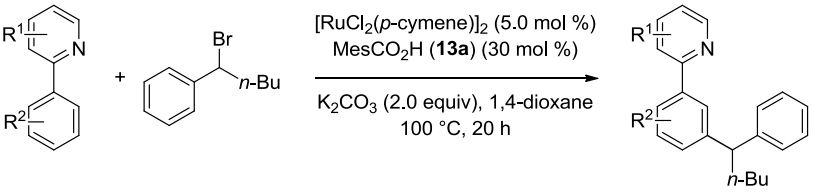
6 **176** **177**

Scheme 3.35: Ruthenium-catalyzed benzylations with (1-bromopentyl)benzene (**176**).

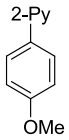
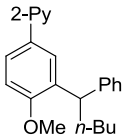
Among the two tested standard acidic additives for the direct benzylation with secondary benzyl bromide **176**, 1-adamantyl- (**13c**) and mesityl carboxylic acid (**13a**), the latter again provided the highest conversion of the starting material **6**. Several solvents were tested, PhMe, NMP, water or 1,4-dioxane, and 1,4-dioxane prove to give the best isolated yields. For high conversions of the subtrate 5 mol % of the ruthenium-catalyst were necessary.

The *meta*-substitution mode in benzylations with secondary benzyl bromides was proved by careful 2D-NMR studies of the isolated products **177**.[150] It has to be emphesized that in spite of the high GC-MS conversion, the isolation of the desired product in a pure form turned out to be difficult. The reason for this are side-reactions of (1-bromopentyl)benzene (**176**), such as dimerization, as indicated by mass spectrometry analyses. These products were not isolated in a pure form. Several examples which demonstrated the limited scope of such direct *meta*-benzylations are presented in Table 3.22.

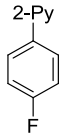
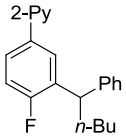
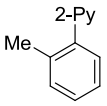
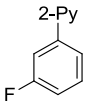
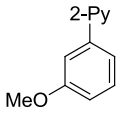
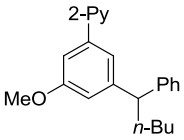
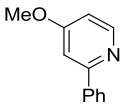
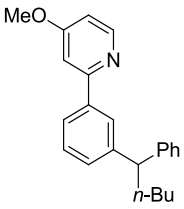
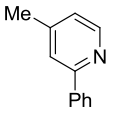
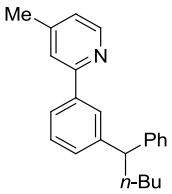
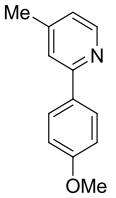
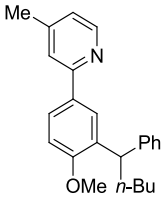
Table 3.22: Scope of direct *meta*-benzylation with (1-bromopentyl)benzene (**176**).



6 **176** **177**

entry	substrate 6	product 176	yield of 177[a]
1	 **6ba**	 **177b**	**15%**

[150] For the detailed information, see: (a) Kuper, C. *Bachelor thesis*, Universität Göttingen, 2011; (b) Malzkuhn, S. *Bachelor thesis*, Universität Göttingen, 2012.

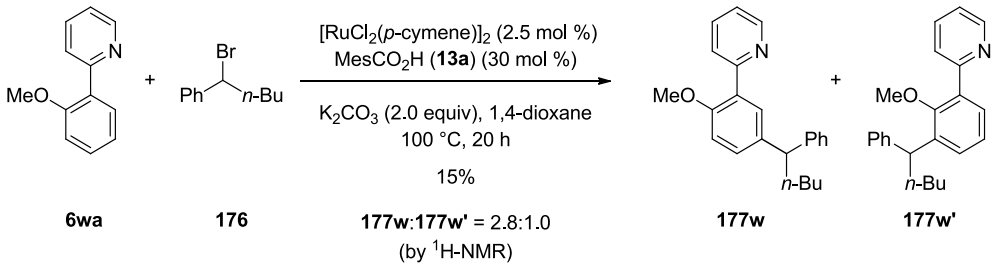
entry	substrate 6	product 176	yield of 177[a]
2			**11%[b]**
	6ca	**177c**	
3		--	--
	6xa		
4		--	--
	6va		
5			**32%**
	6ua	**177u**	
6			**56%**
	6gb	**177g**	
7			**30%**
	6eb	**177e**	
8			**20%**
	6f	**177f**	

[a] **Reaction conditions: 6** (0.5 mmol), **176** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $MesCO_2H$ (**13a**) (30 mol %), H_2O (2.0 mL), 20 h, 100 °C; [b] $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %).

Electron-donating or electron-withdrawing substituents at the *para*-position of the phenyl ring (entries 1, 2) influenced less the isolated yield than the substituents on the pyridine moiety (entries

7 - 9), while *ortho*-methyl (**6xa**) and *meta*-fluoro substituents (**6va**) seemed to inhibit the reaction (entry 3 and 4). Alternatively, methyl and methoxy substituents on the 4-position of pyridine appeared to favor the product formation to some extent (entries 6 - 8). *meta*-Methoxyphenylpyridine **6ua** (entry 5) gave comparable yields for the *meta*-benzylated (32%) and for the *meta*-alkylated products (40%; see entry 3 in Table 3.15).

Nevertheless, the reaction of *ortho*-methoxyphenylpyridine (**6wa**) not only afforded the benzylated products **177w** and **177w'** in a lower isolated yield, but also with inverted regioselectivity, as compared to *meta*-alkylation of the same substrate (Scheme 3.36; entry 2 in Table 3.16).



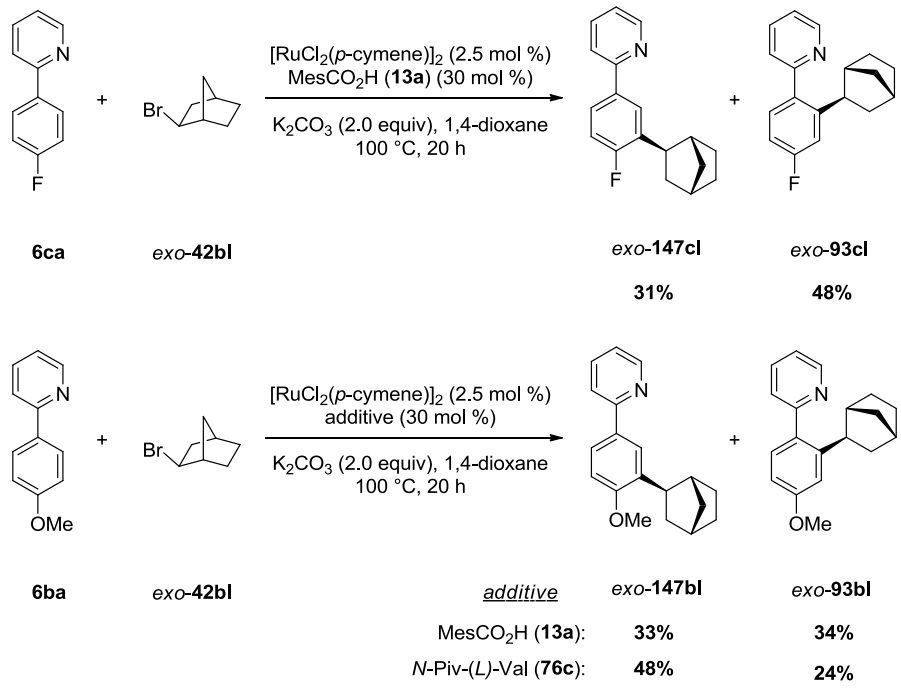
Scheme 3.36: Regioselectivity of the direct *meta*-benzylation of *ortho*-methoxyphenylpyridine **6wa**: intramolecular competition experiment.

3.2.6 Ruthenium-Catalyzed Direct Norbornylation

exo-Bromonorbornane (**42bl**) is especially attractive for ruthenium-catalyzed direct alkylations, as application of this substrate allows to conclude, whether radical steps are involved in C–C bond forming process.[151] Under the standard reaction conditions, alkylations with this bicyclic secondary alkyl bromide **42bl** resulted in high GC-MS conversion, however, isolation of pure products was possible only in a few cases.

Since *para*-fluoro- (**6ca**) and (*para*-methoxyphenyl)pyridine (**6ba**) appeared to be most reactive in reactions with unactivated secondary alkyl halides, they were selected for alkylations with *exo*-norbornyl bromide **42bl** as the electrophile (Scheme 3.37).

[151] Jahn, U. *Top. Curr. Chem.* **2012**, *320*, 121–189.



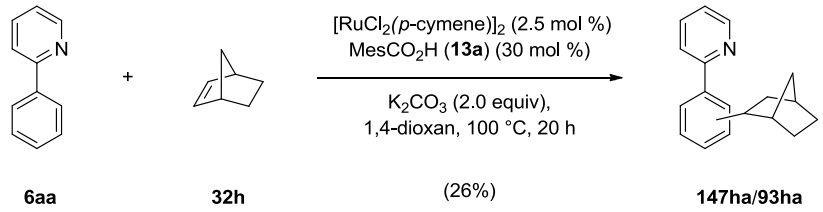
Scheme 3.37: Ruthenium-catalyzed Direct norbornylation of 2-phenylpyridines **6ba** and **6ca**.

Quantitative conversion of substrates **6b** was detected and the products of the direct alkylation were obtained in both reactions. Surprisingly, not only the expected *meta*-alkylated products **147bl** and **147cl**, but also the *ortho*-norbornylated compounds **93bl** and **93cl** were isolated. The *ortho*-alkylation was to some extent preferable for fluoro-substituted 2-phenylpyridine **6ca**, and almost equal amounts of the products were formed from the methoxy-substiututed substrate **6ba**. Interestingly, when *N*-pivalyl-protected L-leucin (**76c**) was used as the additive, the *meta*/*ortho* ratio shifted from 1:1 to 2:1 in favor of the *meta*-alkylated product **147bl**.

Notably, the alkylations proceeded with a retention of configuration of the norbornyl moiety. Thus, only diastereomers with the sterically less demanding *exo*-substituted bicycle[2.2.1]heptyl fragment were obtained in each case.[152]

The catalytic cycle must differ to some extent from the catalytic cycle for secondary alkyl bromides. Indeed, the formation of *ortho*-norbornyl derivatives can be hardly interpreted *via* the proposed cooperative C–H-activation/S_E^{Ar} mechanism (Scheme 3.49). A possible reaction pathway *via* initial dehydrobromination followed by hydroarylation according to the *Murai*-reaction was tested by performing the alkylation with norbornene (Scheme 3.38).

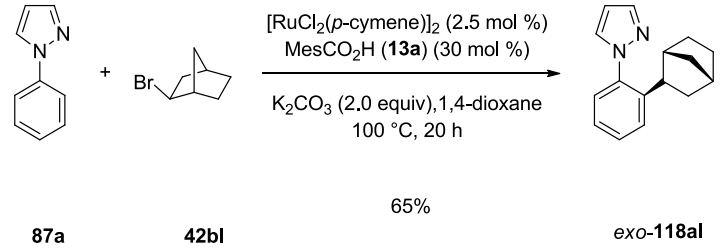
[152] For the discussion on reactivity of exo- and endo-substituted norbornanes see: Schreiner, P. R.; Schleyer, P. v. R.; Schaefer, H. F., III. *J. Org. Chem*. 1997, *62*, 4216–4228. Steric substituent constants are equal to 4.98 (*exo*-norbornyl) and 6.20 (*endo*-norbornyl). See: Beckhaus, H. D. *Angew. Chem. Int. Ed. Engl., 1978, 17,* 593–594.



Scheme 3.38: Attempted norbornylation of 2-phenylpyridine (**6aa**) with norbornene (**32h**).

Under the standard reaction conditions with freshly distilled norbornene, only a low conversion was observed applying GC-MS spectrometry. This almost completely excluded a hydroarylation as a dominating reaction pathway. However, it should be pointed out that in the absence of the ruthenium species or the cocatalyst, 2-phenylpyridine (**6aa**) remained completely unchanged.

Since pyrazole could be used as a directing group for the ruthenium-catalyzed alkylations with primary and secondary alkyl bromides, the direct norbornylation of *N*-phenylpyrazole (**87a**) with *exo*-bromonorbornane (**42bl**) was examined and disclosed to proceed with high efficacy (Scheme 3.39).



Scheme 3.39: Direct ruthenium-catalyzed norbonylation of 2-phenylpyrazole (**87a**).

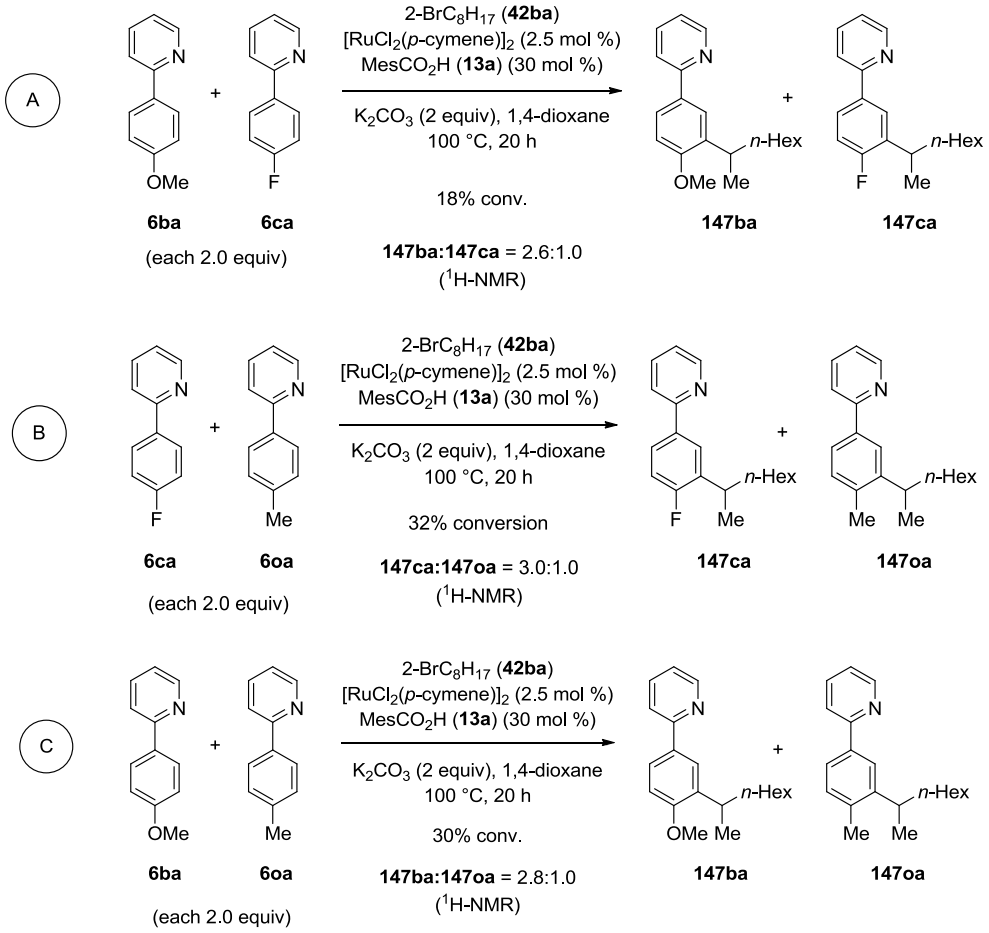
Such an unexpectedly high site- and stereoselectivity of the reaction as well as exclusively high isolated yield of the product **118al** was rather unexpected.

3.2.7 Mechanistic Studies

This newly discovered unexpected *meta*-selective direct ruthenium-catalyzed alkylations with secondary alkyl halides cannot proceed according to the same mechanism as the *ortho*-alkylations with primary alkyl halides. Elucidation of the possible reaction pathway needs mechanistic studies, such as intermolecular as well as intramolecular competition experiments, experiments with isotopically labeled starting materials and test reactions with special ruthenium complexes.

3.2.7.1 Competition Experiments

Intermolecular competition experiments between *para*-substituted 2-phenylpyridines (**6**) were performed, in which a twofold excess of both substrates was treated with 2-bromooctane (**42ba**) as the limiting reagent under otherwise identical reaction conditions (Scheme 3.40). The GC-MS ratio of the products was in accordance with their yield determined by ^{1}H NMR after workup.



Scheme 3.40: Intermolecular competition experiment between substrates **6ba**, **6ca** and **6oa**.

Experiment A disclosed the electron-rich substrate **6ba** to be more reactive in comparison to the fluoro-substituted one **6ca**. The results of experiment B can show steric to be of relevance.[153,154] However, the well-known *ortho*-orienting inductive effect of the fluorine-substituent can also play a certain role.[138] The results of competition in experiments A and C can also be explained by the chelating effect of the methoxy substituent in **6ba** rather than by electronic or steric factors.

[153] Beckhaus, H. D. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 593–594.

[154] For comparable A-values/Conformational Energies for F: 0.25-0.42 kcal/mol; OMe: 0.55 - 0.75 kcal/mol; Me: 1.74 kcal/mol, see: *Stereochemistry of Organic Compounds* (Eds.: Eliel, L. E.; Wilen, S. H.) Wiley: New York, **1994**, pp. 695-697.

The hierarchy of reactivity derived from these experiments is shown here:

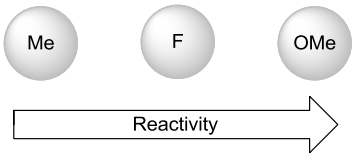
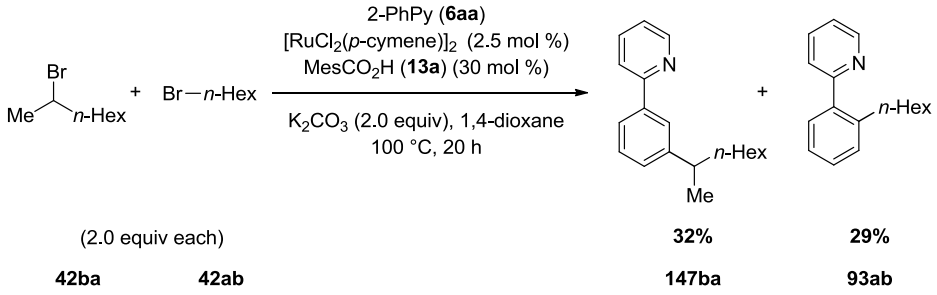


Figure 3.9: Substituents hierarchy as obtained from intermolecular competition experiments for *meta*-alkylation.

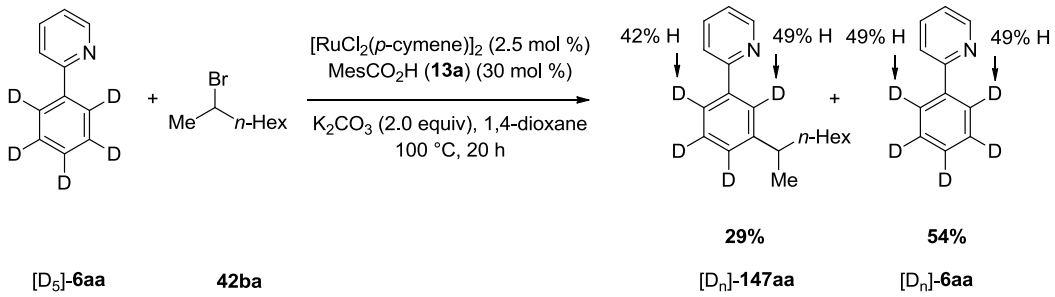
Direct competition experiment between *ortho*- and *meta*-alkylation of 2-phenylpyridine (**6aa**) with primary and secondary alkyl bromides **42ba** and **42ab**, respectively, did not reveal any favorite (Scheme 3.41).[155] The reaction rates appeared to be almost equal for primary as well as for secondary alkyl bromides, while still conserving the individual regioselectivity mode for each electrophile.



Scheme 3.41: Direct competition between ruthenium-catalyzed *meta*- and *ortho*-alkylations.

3.2.7.2 Experiments with Isotopically Labeled Substrates

The determination of the kinetic isotope effect (KIE) is often used as a routine method to decide which is the the rate-determining or the product-determining step in a catalytic cycle.[156] D/H-exchange experiments with deuterium labeled substrates can thus provide valuable informations concerning the mechanistic course of a C–H bond functionalization reaction.

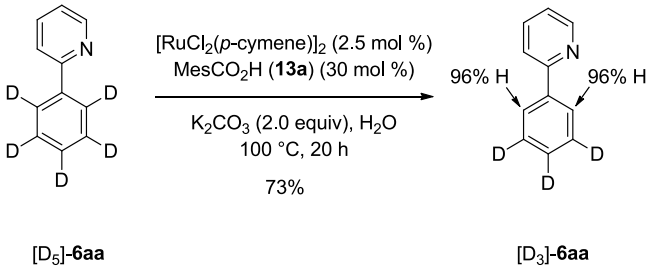


Scheme 3.42. Direct *meta*-alkylation of (pentadeuteriophenyl)pyridine [D_5]-**6aa**.

[155] Additionally, *ortho*-*n*-Octyl-substituted product **93aa** has been isolated in 2% yield.
[156] Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066–3072.

As shown in Scheme 3.42, the direct alkylation of deuterated 2-(pentadeuteriophenyl)pyridine ([D_5]-**6aa**) under the optimized reaction conditions showed almost 50% of D/H-exchange in the *ortho*-position. However, the *meta*-Alkylation of 2-(pentadeuteriophenyl)pyridine ([D_5]-**6aa**) afforded the *meta*-alkylated product [D_n]-**147aa** in a somewhat. Similar to the *ortho*-alkylation of [D_5]-**6aa** with primary alkyl bromides (Scheme 3.18), a significant H/D-exchange in the *ortho* positions was observed to the same extent in both product [D_n]-**147aa** (42% and 47%) and the recovered starting material [D_n]-**6aa** (49%), as determined by ^{1}H-NMR studies. This indicates a reversible C–H bond metalation step in the *ortho*-position to the directing group to proceed with comparable rates in both *meta*- and *ortho*-selective alkylations. While in the latter reaction such a C–H bond activation was considered as a necessary first step in the proposed catalytic cycle (Scheme 3.21), its involvement in the former can only be speculated about (see below). It is assumed that the potassium carbonate can also serve as proton-source for the H/D-exchange.

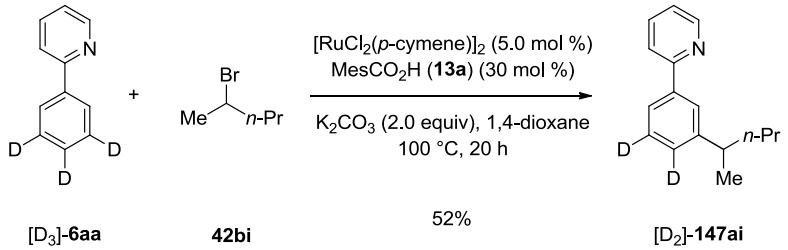
To exclude the C–D activation step from the mechanistic examinations, *meta*-alkylation of (3,4,5-trideuteriophenyl)pyridine ([D_3]-**6aa**) was investigated. The latter has been prepared applying the ruthenium-catalyzed D/H-exchange in substrate [D_5]-**6aa** as a preparative method (Scheme 3.43).



Scheme 3.43: Preparation of (3,4,5-trideuteriophenyl)pyridine [D_3]-**6aa**.

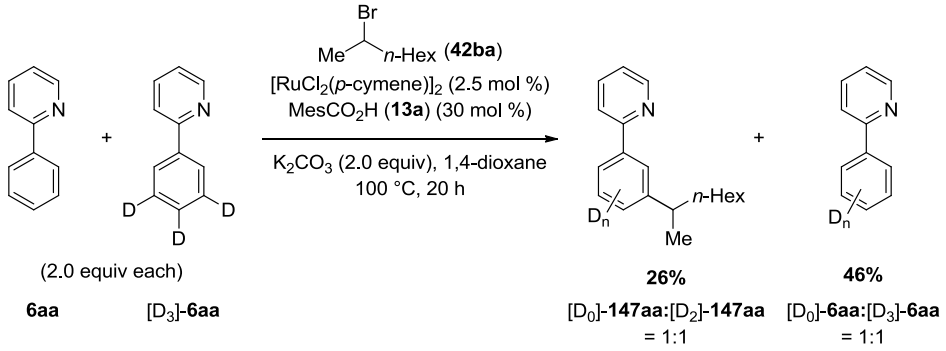
Thus, employing the standard reaction conditions with water as the reaction medium, but in the absence of an organic halide, a regioselective D/H-exchange was accomplished in high yield.

meta-Selective alkylation of the substrate [D_3]-**6aa** under the optimized reaction conditions furnished compound [D_2]-**147ai** in 52% isolated yield (Scheme 3.44), which was comparable with the result obtained applying the undeuterated substrate **6aa**. Moreover, no further D/H-scrambling in the isolated product [D_2]-**147ai** was observed. This allowed the assumption, that the C–C forming step might be not the rate-determining step in the reaction.



Scheme 3.44: Ruthenium-catalyzed direct *meta*-alkylation of (trideiteriophenyl)pyridine [D_3]-**6aa**.

To provide evidence to this hypothesis, an intermolecular competition experiment using 2-phenylpyridines **6aa** and [D_3]-**6aa** in equimolar amounts was performed under the standard reaction conditions (Scheme 3.44).

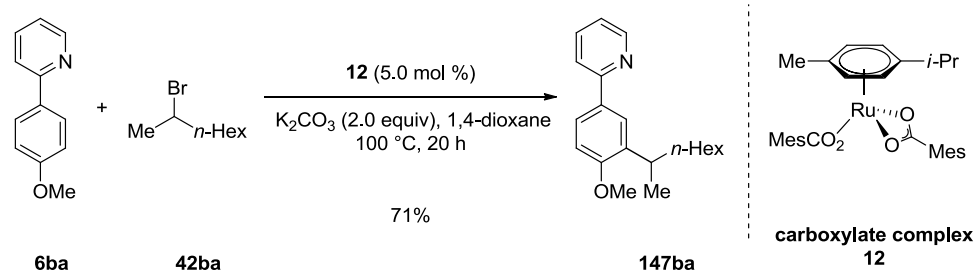


Scheme 3.45: Intermolecular competition experiment between undeuterated 2-phenylpyridine **6aa** and [D_3]-**6aa**.

The slightly lower isolated yield of the *meta*-alkylated product [D_n]-**147aa** in this reaction was not surprising, as commonly observed when applying an excess of the arennes **6**. Careful analysis of the ^{1}H-NMR spectra of the product [D_n]-1**47aa** as well as of the recovered substrate [D_n]-**6aa** revealed both to be an 1:1 mixture of undeuterated and partially deuterated compounds. Moreover, no further H/D-scrambling was detected for both: Therefore, the KIE was determined to be ≈ 1. As a consequence, the C–H bond activation step can neither in the *ortho*- nor in the *meta*-position be rate-determining.

3.2.7.3 Well-Defined Ruthenium (II) Complexes as the Catalysts

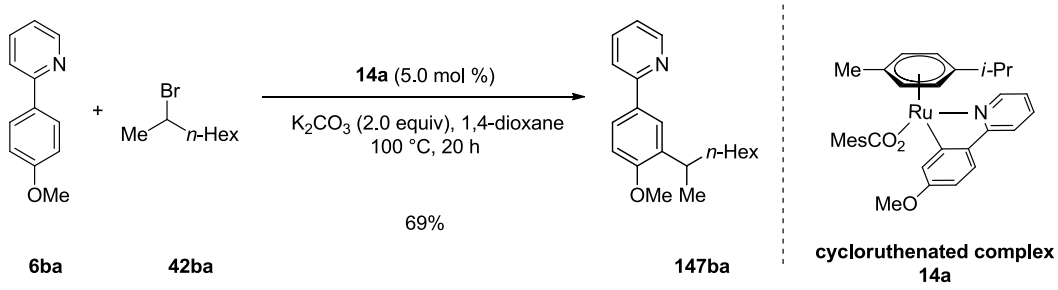
Besides identifying the rate-determining step, the nature of the active ruthenium catalytst should also be elucidated prior to postulating a reaction mechanism. Thus, well-defined ruthenium (II) carboxylate complex **12** was prepared from [$RuCl_2$(*p*-cymene)]$_2$ and mesityl carboxylic acid (**13a**) in a simple one-step procedure,[26a] and was then applied under otherwise identical reaction conditions (Scheme 3.46)



Scheme 3.46: Direct *meta*-alkylation with ruthenium (II) biscarboxylate complex **12**.

The reaction proceeded smoothly and gave aa improved yield of the product **147ba** (71%) as compared to the *in-situ* $[RuCl_2(p\text{-cymene})]_2/MesCO_2H$ system (60%; entry 3 in Table 3.12). This indicated an initial formation of carboxylates **12** from $[RuCl_2(p\text{-cymene})]_2$ and $MesCO_2H$ as most probable initial reaction step. The *in-situ* formed carboxylate **12** might act as the active ruthenium catalyst.

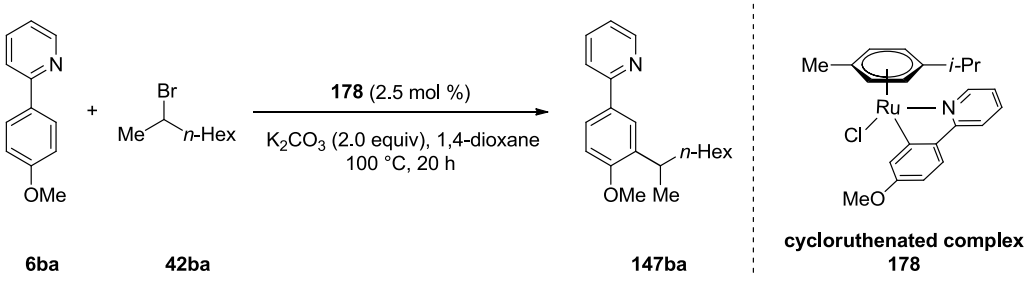
Furthermore, the ruthenacyclic carboxylate complex **14a** was synthesized and examined in the reaction (Scheme 3.47).



Scheme 3.47: Direct *meta*-alkylation with cycloruthenated carboxylate complex **14a**.

Without an additional co-catalysts, this complex **14a** gave product **147ba** in a comparable isolated yield as the simple carboxylate complex **12**. This consequently suggests, that the cyclometalated species **14a** is involved in the catalytic cycle.

As a control experiment, another easily available ruthenacycle **178** of essentially the same structure, but without a carboxylate ligand, was used and did not deliver the alkylated product **147ba** (Scheme 3.48).

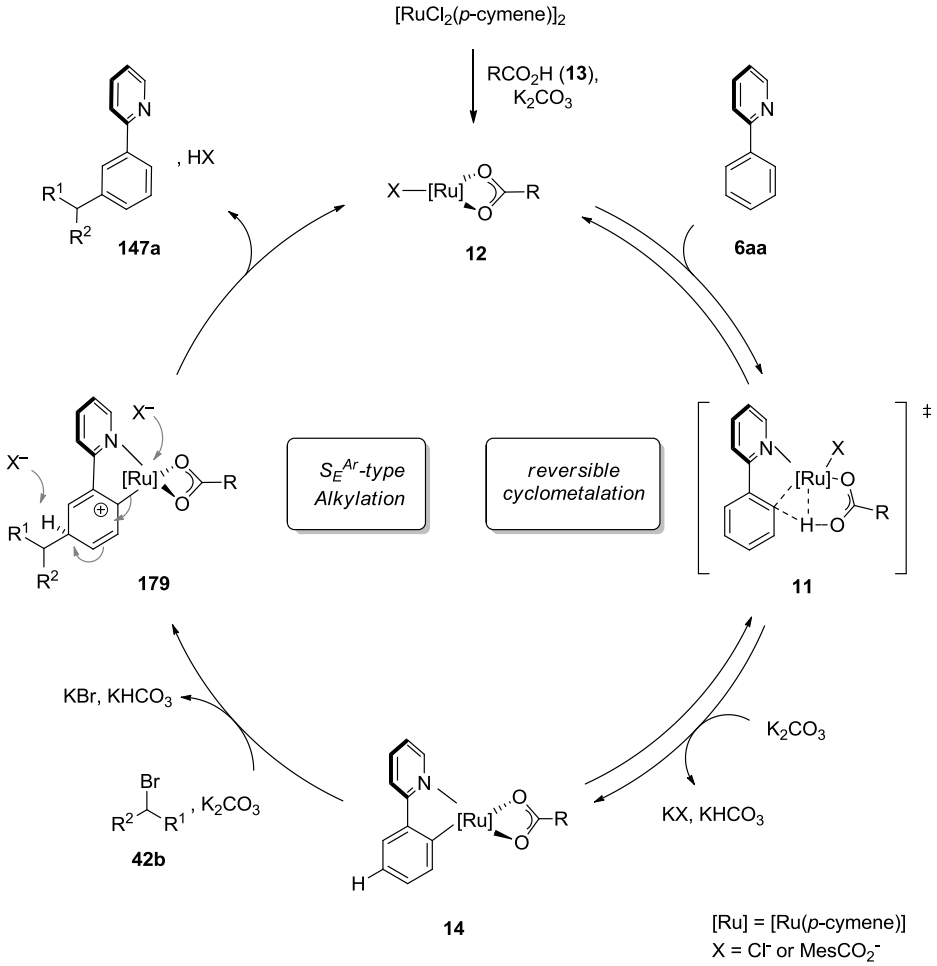


Scheme 3.48: Direct *meta*-alkylation with cycloruthenated chloro complex **178**.

However, upon employing the complex **178** in the presence of mesityl carboxylic acid (**13a**) as additive, isolation of **147ba** in moderate yield was achieved. This indicated the crucial role of carboxylate assistance in the mechanism of *meta*-alkylations.

3.2.7.4 Proposed Catalytic Cycle

Based on the experimental studies summarized above and by comparison of the results obtained by *Frost* and co-workers on the ruthenium-catalyzed *meta*-sulfonylation,[53] the possible mechanistic rationalization of regioselective *meta*-alkylation can be proposed (Scheme 3.49). This mechanism stated below can be described as followed.



Scheme 3.49: Mechanistic proposals for the ruthenium-catalyzed direct *meta*-alkylation of 2-phenylpyridine (**6aa**) with secondary alkyl bromides (**42b**).

Initially, the $[RuCl_2(p\text{-cymene})]_2$ was converted into the ruthenium (II) carboxylate complex **12**, which was coordinated by the nitrogen atom of the pyridine directing group. After the ruthenium centre was in close proximity to the *ortho*-C–H bond, a carboxylate-assisted reversible cyclometalation *via* transition state **11** occurred according to the AMLA mechanism. This resulted in the formation of the

corresponding cyclometalated ruthenium complex **14**. In 1998 *Coudret* and co-workers have reported on stoichiometric electrophilic functionalization of similar ruthenacycles. [157] Remarkably, such complexes underwent selective halogenations, oxidative dimerizations and nitrations on the less sterically hindered reaction center, thus in *meta*-position to the pyridyl and the *para*-position to Ru–C σ-bond.

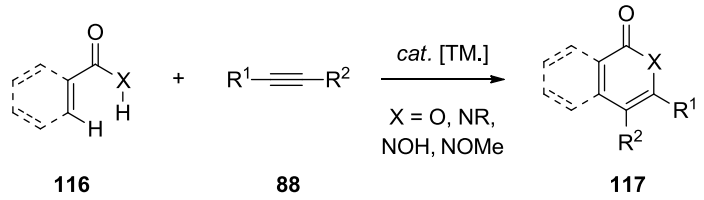
Taking into account these results as well as the results of experiments with isotopically labeled starting materials, the next step in the catalytic cycle can be assumed to proceed through an electrophilic aromatic substitution-type mechanism. Finally, the re-aromatization step regenerates the active species and delivers the *meta*-alkylated product **147a**, presumably *via* protodemetalation. It is still not fully clear, which of the two final steps – the formation of the Wheland-type intermediate **179**[158] or the re-aromatization step – is the rate-determining one. The exact mechanism of activation for the secondary alkyl bromide **42b** must be elucidated as well; for example, a SET radical pathway can be considered. Since the enantioselective fashion of *meta*-alkylation still remains elusive, the formation of a planar carbocationic or radical intermediates from the secondary alkyl halide is not completely excluded.

Recently, *Johnson* and co-workers reported on the Lewis acid-catalyzed shift of a phenyl group to the *meta*-position in substituted arenes.[159] However, no transformation was detected upon attempted isomerization of the *ortho*-alkylated 2-phenylpyridine **147aa** under the reported reaction conditions.

[157] Coudret, C.; Fraysse, S.; Launay, J.-P. *Chem. Commun.* **1998**, 663–664; and references cited therein.
[158] Wheland, G. W. *J. Am. Chem. Soc*. **1942**, *64*, 900–908.
[159] Ajaz, A.; McLaughlin, E. C.; Skraba, S. L.; Thamatam, R.; Johnson, R. P. *J. Org. Chem.* **2012**, *77*, 9487–9495.

4 Ruthenium-Catalyzed Oxidative Transformations *via* C–H/N–H bond Cleavage

Besides direct transition metal-catalyzed C–H bond functionalizations, oxidative transition metal-catalyzed C–H/O–H or C–H/N–H bond functionalizations utilizing arenes or alkenes **88** under mild reaction conditions represent an even more sustainable strategy, since no prefunctionalization steps have to be performed and mild reaction conditions are possible (Scheme 4.1).[104]



Scheme 4.1: Oxidative annulations by C–H/O–H or C–H/N–H bond functionalizations.

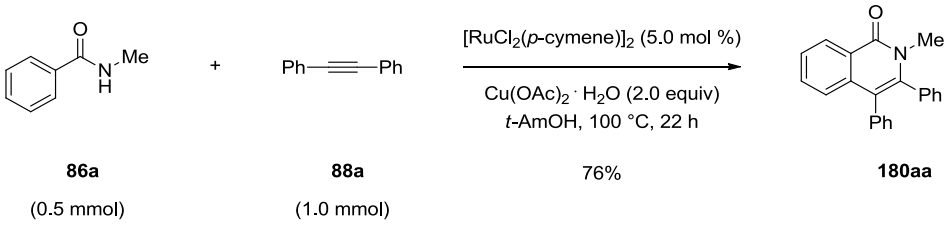
Pioneering research in rhodium-catalysis was accomplished by the groups of *Miura* and *Sato*, *Fagnou* and *Jones*.[120] These groups reported on efficient annulation reactions of alkynes by C–H/O–H or C–H/N–H bond functionalization catalyzed by rather efficient and selective, yet relatively expensive rhodium catalysts. In contrast, significantly less expensive ruthenium complexes previously not been exploited as catalysts for oxidative C–H/O–H or C–H/N–H bond functionalizations.[101a,160]

4.1 Ruthenium-Catalyzed Oxidative Annulations

As demonstrated by *Satoh* and *Miura*,[120] benzamides **86** are suitable substrates for the rhodium-catalyzed annulation with alkynes **88** *via* C–H/N–H bond cleavages, thereby giving sustainable excess to key structural motifs such as isoquinolones **180**.

The alternative ruthenium-based catalytic system for assembling the isoquinolinone skeleton along this route was examined by *Ackermann*, *Lygin* and *Hofmann*. Intensive studies towards optimization of this reaction indicated the conditions shown in Scheme 4.2 to be the most efficient.

[160] http://www.ebullionguide.com (17.01.13; average last 30 days): 1 ounce of ruthenium = 87.85 USD; 1 ounce of rhodium = 1081.90 USD.



Scheme 4.2: Optimized reaction conditions for the ruthenium-catalyzed oxidative synthesis of isoquinolone **180aa**.

Thus, it was disclosed that 5.0 mol % of $[RuCl_2(p\text{-cymene})]_2$ in combination with copper acetate in stoichiometric amounts was a competent catalytic system for the oxidative annulation of alkynes **88** with benzamides **86**. Different oxidants, such as more expensive silver salts, demonstrated rather inhibiting than accelerating effects and afforded ring opened by-products. Detailed description of this newly developed ruthenium-catalyzed reaction required additional investigations to determine scope and limitations of these annulations as well as to explain its mode of action.

4.1.1 Synthesis of starting materials

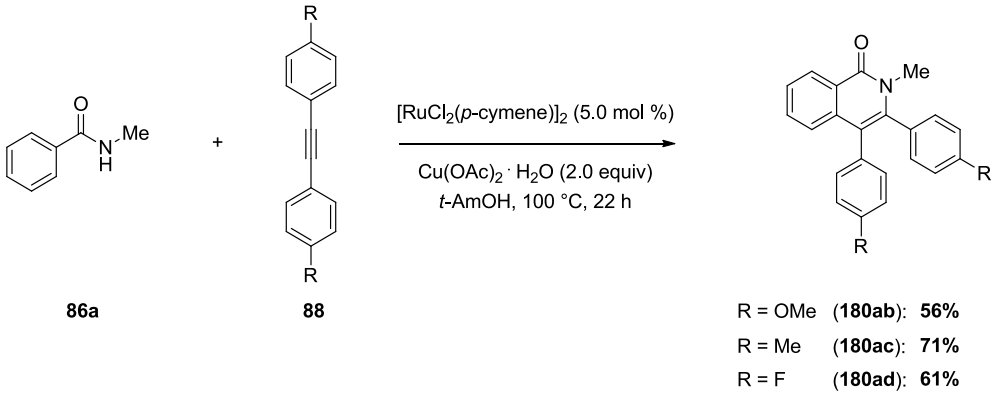
A variety of starting materials was synthesized according to published protocols. Benzamides **86** were prepared from the corresponding carboxylic acids and differentially substituted alkynes **88** by classical organic methods or by transition metal-catalyzed *Sonogashira-Hagihara* coupling.[161,162] The starting material synthesis will not be discussed within this context since no optimization of the reaction conditions was performed.

4.1.2 Ruthenium-Catalyzed Synthesis of Isoquinolin-2-ones: Scope and Limitations

N-methylbenzamide (**86a**) was treated with different symmetrically substituted alkynes **88**, with electron-rich as well as electron-deficient arenes, under the previously optimized reaction conditions. (Scheme 4.3).

[161] Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A. *Org. Lett.* **2002**, *4*, 3199–3202.

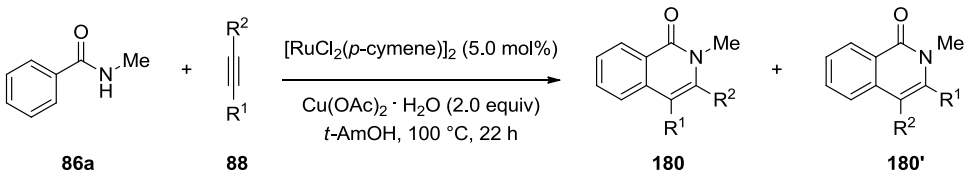
[162] Goeschke, R.; Stutz, S.; Rasetti, V.; Cohen, N.-C.; Rahuel, J.; Rigollier, P.; Baum, H.-P.; Forgiarini, P.; Schnell, C. R.; Wagner, T.; Gruetter, M. G.; Fuhrer, W.; Schilling, W.; Cumin, F.; Wood, J. M.; Maibaum, J. *J. Med. Chem.* **2007**, *50*, 4818−4831.

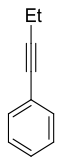
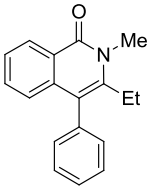
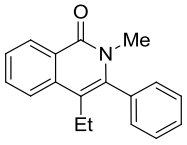
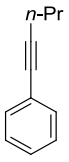
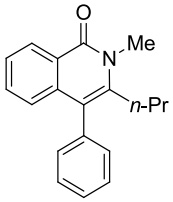
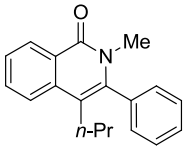


Scheme 4.3: Scope of annulation of *N*-methylbenzamide (**86a**) with symetrically substituted alkynes **88**.

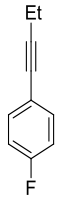
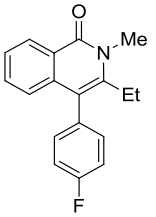
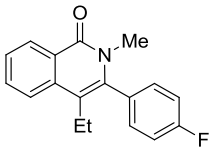
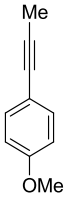
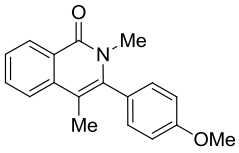
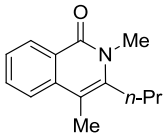
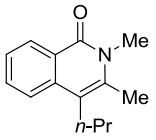
According to these experiments, the electron density on the aryl substituents in alkynes **88** appeared to exert a minimal influence on the formation of the desired products **180ab** – **180ad**, as not only unsubstituted tolane (**88a**), but also electron-rich as well as electron-deficient alkynes **88b**/**88c** and **88d** furnished isoquinolones **180ab** – **180ad** in rather high yields. These promising results prompted us to prove the applicability of unsymmetrically substituted alkynes in these cyclisations (Table 4.1).[163]

Table 4.1: Annulation of unsymetrically substituted alkynes **88** with *N*-methylbenzamide (**86a**).



entry	alkyne 88	product 180	product 180’	ratio 180:180’[b]	combined yield[a]
1				1.0:7.2	80%
	88e	**180ae**	**180ae’**		
2				1.0:9.7	92%
	88f	**180af**	**180af’**		

[163] Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 6379–6382.

entry	alkyne 88	product 180	product 180'	ratio 180:180'[b]	combined yield[a]
3				1.0:7.6	37%
	88g	180ag	180ag'		
4		--		--	66%
	88h		180ah'		
5				1.0:1.4	58%[c]
	88i	180ai	180ai'		

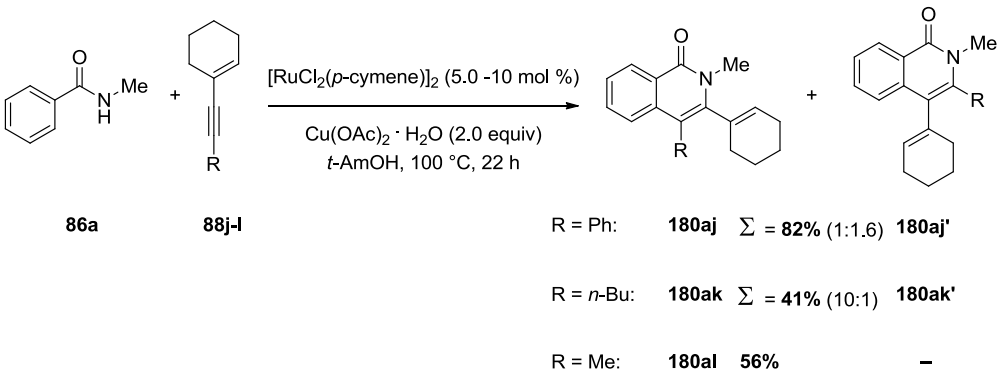
[a] **Reaction conditions: 88** (0.5 mmol), **180** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv), *t*-AmOH (2.0 mL), 22 h, 100 °C; [b] The ratios **180**:**180'** have been determined by nOe, if no separation could be acomplished; [c] Compounds **180ai** and **180ai'** were isolated in pure form in 24 and 34% yield, respectively.

The yields of isoquinolones **180** listed in Table 4.1 ranged from good to very good, except the cyclisation with fluorophenyl alkyne **88g** (entry 3). It is noteworthy that the ruthenium-catalyzed annulation of unsymmetrically substituted Alk–C≡C–Ar **88** delivered mixtures of 4- (**180a**) and 3-arylsubstituted (**180a'**) regioisomeric products in ratios from 1:10 (entry 2) to 1:7 (entry 1). A methoxy substituent in alkyne **88h** resulted in a lower yield, but provided a better regioselectivity of the reaction (entry 4).

Generally, symmetrically substituted dialkylalkynes **88** appeared to be rather suitable substrates for the oxidative annulations.[163] The testing reaction of methyl-*n*-propyl alkyne (**88i**) with *N*-methylbenzamide (**86a**) afforded the 3-*n*-propyl- (**180ai'**) and the 4-*n*-propylisoquinolone (**180ai**) in comparable quantities and in a ratio of 1.4:1.0 (entry 5). This observation is in accordance with the steric substituent constants, being equal to 0.89 (*n*-propyl) and 0.0 (methyl).[153]

The reactivity of the enyne **88j** under the optimized reaction conditions was of special interest, as such experiments could allow (i) to determine the general tolerance of enynes towards C–H/N–H bond functionalizations, (ii) to compare reactivity of a double and of a triple bond in **88j** and (iii) to

open new horizons towards further functionalizations of the products **180**. Several examples of variously substituted (cyclohexen-1-yl)alkynes were studied (Scheme 4.4).



Scheme 4.4: Enynes **88j**-**88l** as coupling partners for the ruthenium-catalyzed annulation with *N*-methylbenzamide (**86a**).

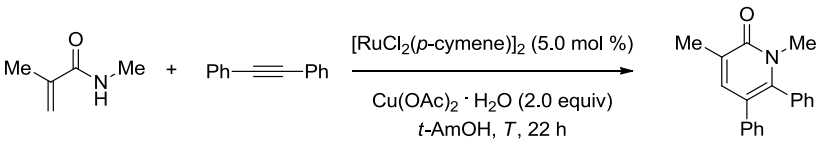
Depending on the nature of the second substituent on the alkyne moiety, moderate to very good total yields of (cyclohexen-1-yl)isoquinolones **180aj** - **180al** were obtained from enynes **88j** - **88l** as cyclization partners. Importantly, while (cyclohexen-1-yl)phenylalkyne (**88j**) afforded the products **180aj** and **180aj'** in high total yield of 82%, but with poor regioselectivity in favor of 3-phenylheterocycle **180aj'**, the yields upon cyclizations with (cyclohexen-1-yl)alkylalkynes **88k** and **88l** were lower (41 and 56%, respectively). However, the latter two transformations demonstrated much better regioselectivity with the predominant formation of the 3-(cyclohexen-1-yl)isoquinolones **180ak** and **180al**. This obviously indicates the very important function of a cyclohexen-1-yl substituent. While a double bond did not participate in the cyclization, cyclohexen-1-yl possessed almost the same regiochemistry-determining orienting power as an aryl substituent (see Table 4.1).

4.1.3 Ruthenium-Catalyzed Synthesis of 2-Pyridones

As this novel ruthenium-catalyzed oxidative annulation showed remarkable potential in the isoquinolone synthesis, other possible heterocycles syntheses were considered to be accomplished by this method. Since pyridone are omnipresent in a number of pharmaceuticals and biologically active natural products,[164] this structural motif represented an intriguing synthetic target. Indeed, ruthenium-catalyzed oxidative annulations with alkynes *via* C–H/N–H bond functionalizations appeared to be possible also with acrylamides as the substrates. Importantly, no product formation was detected without the oxidant or in the absence of the ruthenium catalyst. To elaborate the

[164] (a) Jessen, H. J.; Gademann, K. *Nat. Prod. Rep.* **2010**, *27*, 1168–1185. (b) Nagle, P. S.; Pawar, Y. A.; Sonawane, A. E.; Bhosale, S. M.; More, D. H. *Med. Chem. Res.* **2012**, *21*, 1395–1402. (c) Tamura, R.; Yamada, Y.; Nakao, Y.; Hiyama, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 5679–5682.

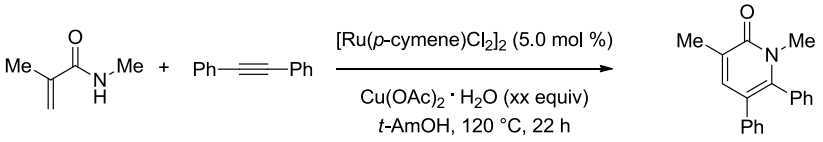
optimized reaction conditions for this transformation, cyclization of *N*-methyl methacrylamide (**181a**) with tolane (**88a**) was selected as the standard reaction (Scheme 4.5).[165]



181a **88a** T = 80 °C **63%** **182aa**
T = 100 °C **60%**
T = 120 °C **77%**

Scheme 4.5: Temperature optimization for ruthenium-catalyzed oxidative synthesis of 2-pyridone **182aa**.

Testing the influence of the reaction temperature upon the course of the annulation, the temperature of 120 °C was revealed to be optimal for this highly chemo-selective oxidative coupling (Scheme 4.5). Further experiments indicated that the amount of oxidant could be reduced with inverted ratio of *N*-methyl methacrylamide (**181a**) and tolane (**88a**). Only one equivalent of copper acetate is actually necessary to obtain product **182aa** in very high yield (Scheme 4.6).

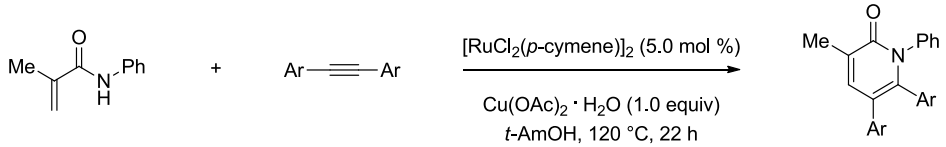


181a **88a** **182aa**
1.0 mmol 0.5 mmol $Cu(OAc)_2 \cdot H_2O$ 1.0 equiv: **92%**
2.0 equiv: **86%**

Scheme 4.6: Effect of $Cu(COA)_2 \cdot H_2O$ on the oxidative annulation.

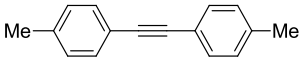
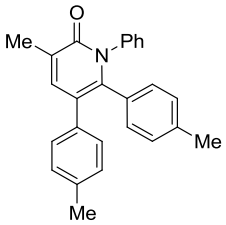
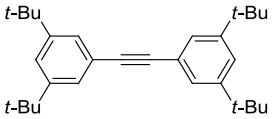
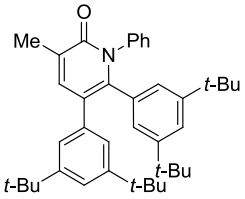
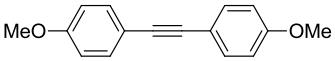
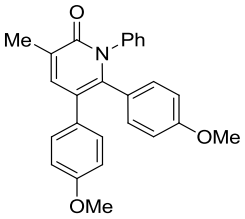
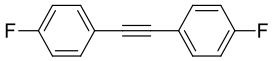
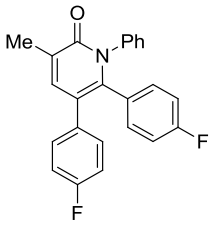
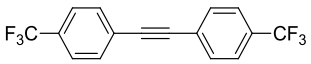
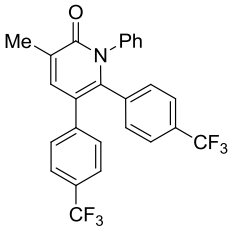
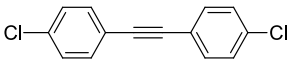
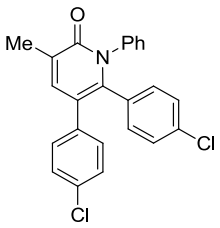
Since rhodium-catalyzed versions of this reaction were known to possess several limitations, such as low selectivities for unsymmetrically substituted alkynes or for *N*-substituted acrylamides with electron-withdrawing substituents, the scope and limitations of this novel ruthenium-catalyzed synthesis of 2-pyridones **182** was tested. First, oxidative cyclization of symmetrically diaryl-substituted alkynes **88** with *N*-phenyl methacrylamide (**181b**) was studied (Table 4.2).

Table 4.2: Synthesis of 2-pyridones **182** with symmetrically substituted diarylalkynes **88**.



181b **88** **182**

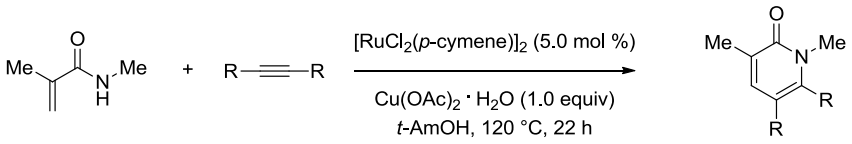
[165] Ackermann, L.; Lygin, A. V.; Hofmann, N. *Org. Lett.* **2011**, *13*, 3278–3281.

entry	alkyne 88	product 182	yield of 182[a]
1			97%
	88c	182bc	
2			62%
	88m	182bm	
3			37%
	88b	182bb	
4			69%
	88d	182bd	
5			71%
	88n	182bn	
6			59%
	88o	182bo	

[a] **Reaction conditions: 181b** (1.0 mmol), **88o** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv), *t*-AmOH (2.0 mL), 20 h, 120 °C.

A broad range of symmetrical diarylsubstituted alkynes **88** gave satisfactory results applying the optimized reaction conditions. Electron-rich (entries 1 - 3) as well as electron-deficient (entries 4 -6) alkynes could be annulated in high yields. The electron-rich di-*p*-tolylacetylene (**88c**) furnished 2-pyridone **182bc** in virtually quantitative yield, whereas the reaction with electron-rich, but sterically demanding alkyne **88m** demonstrated a reduced efficiency (entries 1 and 2). Only the methoxy-substituted substrate **88b** afforded the corresponding product **182bb** in moderate yield (entry 3). Good results were obtained in the annulation of diarylalkynes with electron-withdrawing substituents **88d** and **88n** (entry 4 and 5), and even a chloro-substituted starting material **88o** was tolerated and showed no side-transformations, like direct arylations (entry 6).

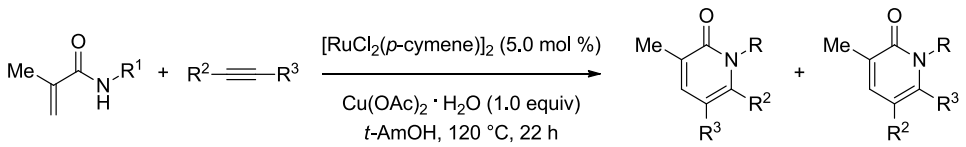
Symmetrical dialkylalkynes such as hex-3-yne (**88p**) and oct-4-yne (**88q**) proved to be feasible substrates for the ruthenium-catalyzed annulation as well (Scheme 4.7).

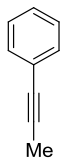
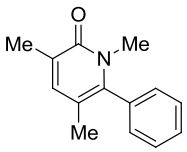
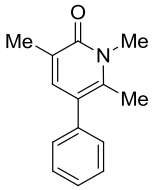


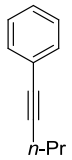
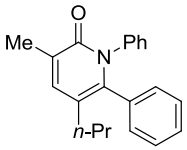
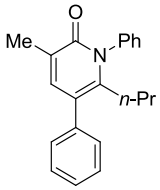
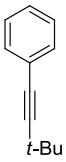
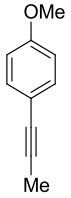
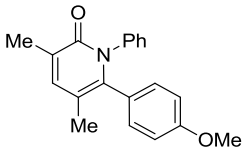
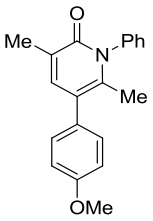
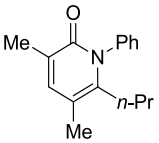
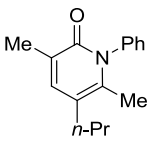
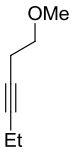
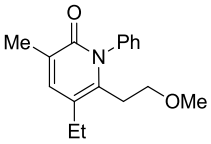
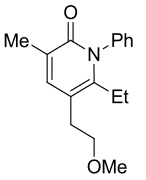
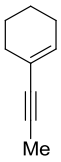
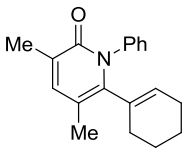
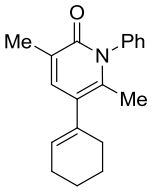
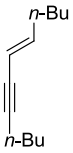
Scheme 4.7: Symmetrical dialkylalkynes **88p** and **88q** as starting materials in ruthenium-catalyzed oxidative synthesis of 2-pyridones **182**.

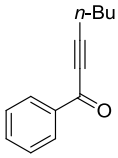
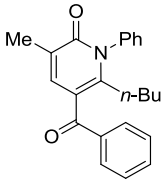
Likewise, the potential application of unsymmetrically-substituted substrates was in the ruthenium-catalyzed oxidative synthesis of 2-pyridones **182** (Table 4.3).

Table 4.3: Ruthenium-catalyzed annulations of acrylamides **181** with unsymmetrically substituted alkynes **88**.



entry	alkyne 88	product 182	product 182'	ratio 180:180'	combined yield[a]
1				1.8:1.0	61%[b]
	88s	182as	182as'		

entry	alkyne 88	product 182	product 182'	ratio 180:180'	combined yield[a]
2				4.7: 1.0	25%[c]
	88f	182bf	182bf'		
3		--	--	--	--
	88t				
4				1.0:5.5	42%[c]
	88h	182bh	182bh'		
5				1.0:2.3	41%[c]
	88i	182bi	182bi'		
6				1.0:1.0	53%[d]
	88u	182bu	182bu'		
7				1.0:7.4	40%[c]
	88l	182bl	182bl'		
8		--	--		--
	88v				

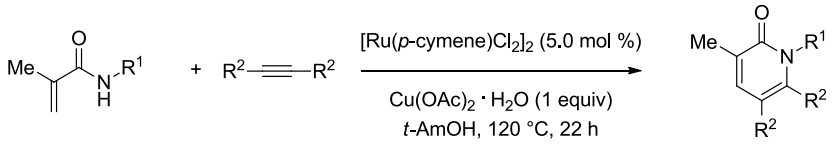
entry	alkyne 88	product 182	product 182'	ratio 180:180'	combined yield[a]
9			--	--	15%
	88w	182bw			

[a] **Reaction conditions: 88** (1.0 mmol), **182** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv), *t*-AmOH (2.0 mL), 20 h, 120 °C; [b] Compounds **182as** and **182as'** were isolated in pure form in 39% and 22% yield, respectively; [c] ratios are calculated by comparision with ^{1}H-NMR-spectra from pure isolated compounds; [d] Products **182bu** and **182bu'** were isolated in pure form in 26% and 27% yield, respectively.

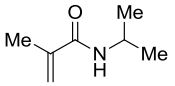
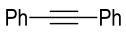
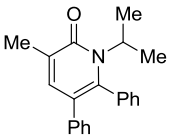
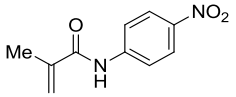
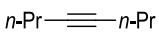
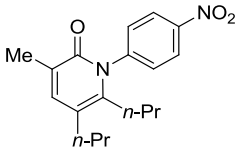
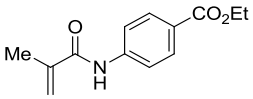
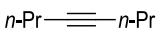
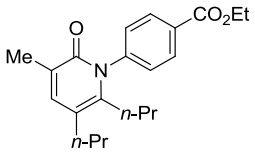
Under these reaction conditions, the scope of unsymmetrically substituted alkynes **88** appeared to be rather limited. While 1-phenyl-1-propyne (**88s**) still gave a good total yield of the products **182as** and **182as'**, albeit with low regioselectivity (entry 1), increasing the size of the alkyl substituent dramatically decreased the conversion (entries 2, 3). Besides the poor regioselectivity, the separation of isomers was only possible in few rare cases (endries 1 and 6). Annulations with unsymetrical dialkylalkynes **88i** and **88u** were almost not regeoselective (entries 5 and 6), although the total yield of the products was still moderate. While the reactivity of 1-(cyclohexen-1-yl)-1-propyne (**88l**) (entry 7)and methylalkylalkynes **88i** (entry 5) was essentially the same as in the annulation with *N*-methylbenzamide (**86a**) (see Scheme 4.4), acyclic enyne **88v** did furnish the desired product (entry 8). However, carbonyl functionality on the acetylenic reactant was tolerated, albeit the isolated yield was rather low (entry 9).

Besides the broad scope for the substitution pattern in the acrylamides **181** in their annulations with aryl-substituted alkynes, as was demonstrated by *Ackermann*, *Lygin* and co-workers,[165] better versatility of these ruthenium-catalyzed oxidative syntheses of 2-pyridones **182** in comparison with the rhodium-catalyzed ones was illustrated by applying the challenging α-methylacrylamides **181d** and **181e** with nitro or ester functionality, respectively (Table 4.4).

Table 4.4: Some examples for the scope of acrylamides **181**.

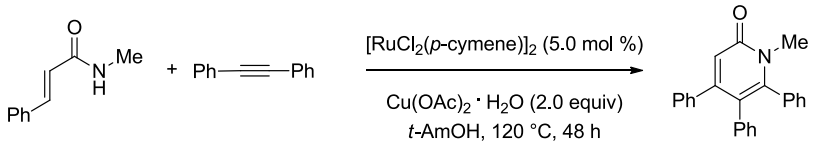


181 **88** **182**

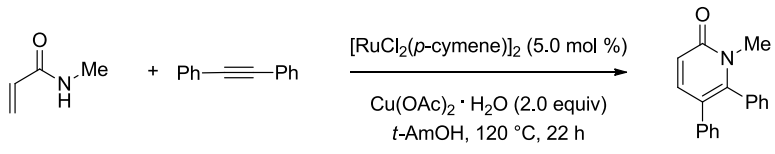
entry	acrylamide 181	alkyne 88	product 182	yield of 182[a]
1				69%
	181c	**88a**	**182ca**	
2				91%
	181d	**88q**	**182dq**	
3				78%
	181e	**88q**	**182eq**	

[a] **Reaction conditions: 181** (1.0 mmol), **88** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv), *t*-AmOH (2.0 mL), 20 h, 120 °C.

The success of these oxidative C–H/N–H bond functionalizations was found to be highly depending upon the substitution mode on a double bond moiety in acrylamide. Thus, while annulations of *α*-phenylacrylamide **181f** with tolane (**88a**) furnished 2-pyridone **182fa** in virtually quantitative yield (Scheme 4.8), an acceptable yield in the reaction of isomeric β-phenylacrylamide **181g** (51%) could be obtained only when using a higher loading of the oxidant and prolonged heating. The unsubstituted acrylamide **181h** demonstrated only poor conversion under the standard condition (Scheme 4.8).[166]



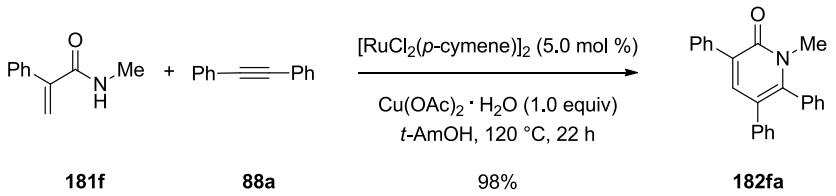
181g **88a** 51% **182ga**



181h **88a** *GC-Conversion < 10%* **182ha**

[166] Reactions performed by Dr. A. V. Lygin.

Scheme 4.8 a: Influence of the substitution on the double bond in acrylamide upon the efficiency of annulation.

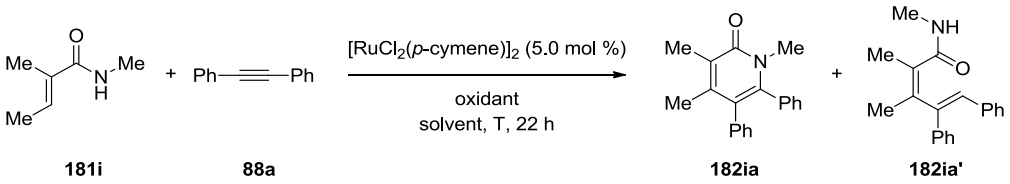


181f **88a** 98% **182fa**

Scheme 4.8: Influence of the substitution on the double bond in acrylamide upon the efficiency of annulation.

Furthermore, annulations of (*E*)-*N*,2-dimethylbut-2-enamide (**181i**) were tested with various solvents, reaction temperature and oxidants, as summarized in Table 4.5.

Table 4.5: Optimization-studies for α,β- dimethylsubstituted *N*-methylacrylamide **181i**.



181i **88a** **182ia** **182ia'**

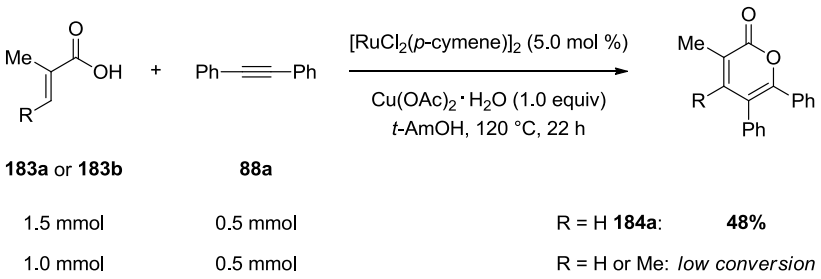
entry	solvent	oxidant (equiv)	T	GC-conversion	yield[a] of 182ia	yield[a] of 182ia'
1	*t*-AmOH	$Cu(OAc)_2$ (0.1)	120 °C	(40)	--[b]	
2	*t*-AmOH	$Cu(OAc)_2$ (2.0)	120 °C	(87)	**57%**	**16%**
3	*t*-AmOH	--	120 °C	(<5)	--	
4	*t*-AmOH	air	120 °C	(<5)	--	
5	*t*-AmOH	AgOAc (2.0)	120 °C	(65)	--[b]	
6	MeOH	$Cu(OAc)_2$ (2.0)	70 °C	(44)	--[b]	
7	DME	$Cu(OAc)_2$ (2.0)	70 °C	(<5)	--	
8	DME	Benzochinone (2.0)	120 °C	(<5)	--	
9	--	Pinacolone (2.0)	120 °C	(<5)	--	

[a] **Reaction conditions: 181i**(1.0 mmol), **88a** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), 22 h; [b] not determined.

Interestingly, only the use of two equivalents of copper acetate gave a satisfactory yield (entry 2). Notably, compound **182ia'** was isolated in 16% yield as well. This ring-opened minor by-product resulted from hydroalkenylation of tolane (**88a**) under these conditions.

Since this novel ruthenium-catalyzed annulation reactions appeared to be highly efficient in a variety of oxidative C–H/N–H bond functionalizations of differently substituted benzamides **86** and

acrylamides **181**, the analogous C–H/O–H bond activations with readily available and inexpensive methacrylic acids **183** was put on the agenda (Scheme 4.9).

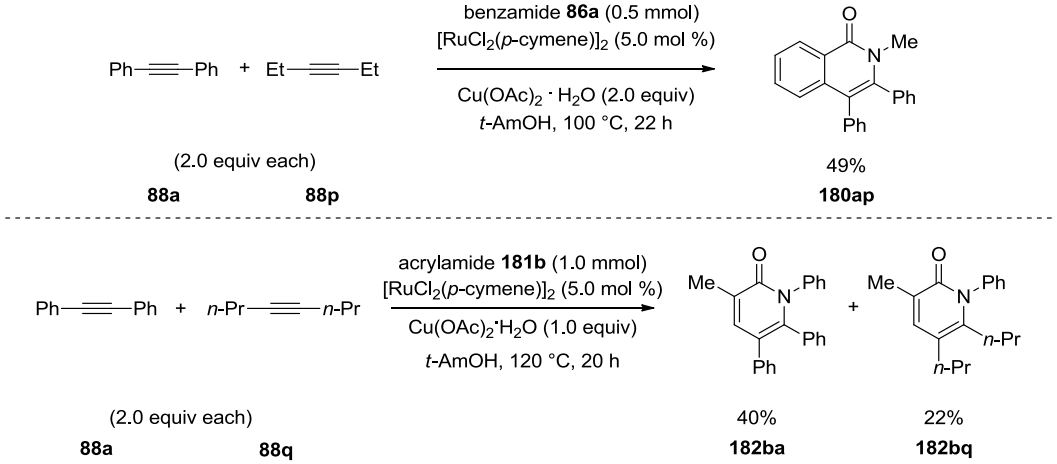


Scheme 4.9: Ruthenium-catalyzed oxidative synthesis of α-pyrones **184a** *via* oxidative C–H/O–H bond functionalizations.

Initial studies indicated that the expected *a*-pyrone **184a** could be obtained in 48% isolated yield when using three equivalents of acrylic acid **183a** already under non-optimized reaction conditions. Upon further developed of this project by the *Ackermann* group, this reaction was adopted towards the synthesis of variously substituted isocoumarines as well.[167]

4.1.4 Mechanistic Studies

To gain insight into the mechanistic course of the ruthenium-catalyzed oxidative annulation of alkynes **88** with benzamides **86** or acrylamides **181** *via* C–H/N–H bond cleavages, several intermolecular competition experiments were performed (Scheme 4.10).



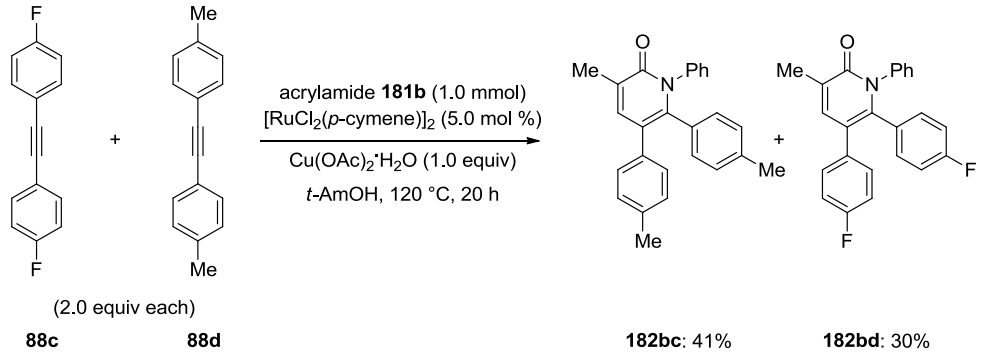
Scheme 4.10: Intermolecular competition experiment between diphenyl- (**88a**) and dialkylalkynes **88p** and **88q**.

The competitive annulation of tolane (**88a**) and diethylacetylene (**88p**) with *N*-methylbenzamide (**86a**) (Scheme 4.10, top) or of tolane (**88a**) and di-*n*-propylacetylene (**88q**) with *N*-

[167] (a) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.* **2012**, *14*, 930–933. (b) Deponti, M.; Kozhushkov, S. I.; Yufit, D.; Ackermann, L. *Org. Biomol. Chem*. **2013**, *11*, 142–148.

phenylmethacrylamide (**181b**) (Scheme 4.10, bottom) showed a predominant formation of the diphenylated product **180ap** or **182ba**, respectively. This might arise from stabilization of an intermediate due to conjugation effects (see below in Scheme 4.12).

Intermolecular competition experiments on reactivity of electron-rich (**88c**) and electron-deficient alkynes (**88d**) towards *N*-phenylmethacrylamide (**181b**) clearly indicated the preferential conversion of the former one (Scheme 4.11).



Scheme 4.11: Intermolecular competition with electron-rich rich (**88d**) and electron-deficient alkyne (**88c**).

Moreover, benzamides with electron-deficient substituents were shown to be favored substrates for the oxidative annulation.[163] This excluded the electrophilic activation of the C–H bond as a possible mechanistic step. Yet, experiments with isotopically labeled substrates and solvents indicated an irreversible C–H bond metalation step with a $k_H/k_D \approx 2.6$,[168] which was of comparable value as for the concerted acetate-assisted metalation.[169] The necessity of such acetate assistance for the success of transformation was also supported in the course of optimization studies, as no product formation was observed in the absence of acetate (Table 4.5; entries 3, 4, 8 and 9).

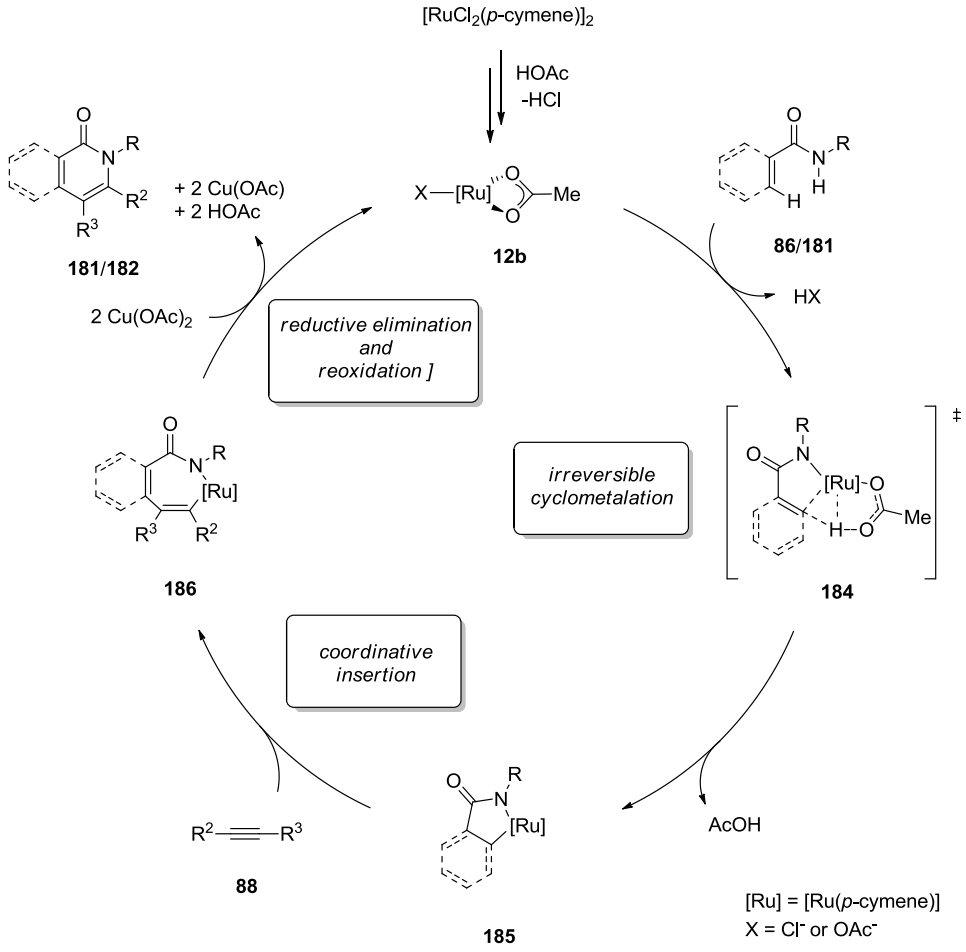
On the basis of these experimental observations, the following catalytic cycle for the ruthenium-catalyzed carboxylate-assisted synthesis of isoquinolones **180** and 2-pyridones **182** *via* oxidative C–H/N–H bond functionalizations is proposed (Scheme 4.12).

Initially, the ruthenium-dimer is expected to form an acetate complex **12b** similar to those observed in the ruthenium-catalyzed carboxylate-assisted direct alkylation (see Scheme 3.21 and Scheme 3.49). Subsequently, carboxylate-assisted irreversible C–H bond metalation *via* transition state **184** with a loss of one molecule of acetic acid upon deprotonation of the amide group formed ruthenacycle **185**. After coordination of alkyne **88**, regioselective migratory insertion deliveres as the

[168] Experiments performed by Dr. A. V. Lygin.

[169] For palladium-catalyzed acetate-assisted C–H metalation, see: Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *Dalton. Trans.* **1985**, 2629–2638.

key intermediate seven-membered rutenacycle **186**. Surprisingly, to the best of our knowledge, no attempts to explain the mechanism and regioselectivity of this migratory insertion has thus far been untertaken, in spite of its prime importance for the general regioselectivity of the annulation. The intermediate **186** releases the desired product **181**/**182** through reductive elimination which is followed by subsequent re-oxidation of the resulting ruthenium (0) species core by the copper (II)-acetate.

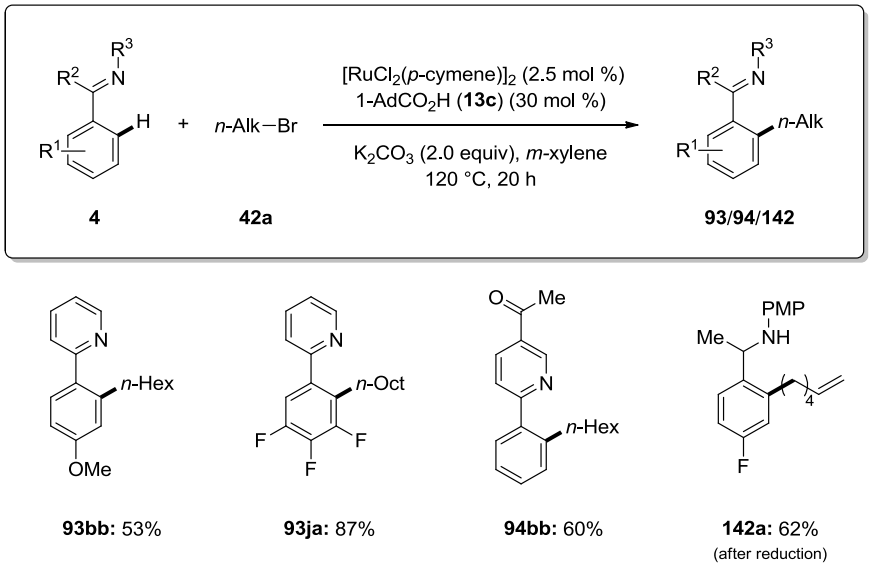


Scheme 4.12: Proposed catalytic cycle for the ruthenium-catalyzed oxidative C–H/N–H bond functionalizations.

5 Summary and Outlook

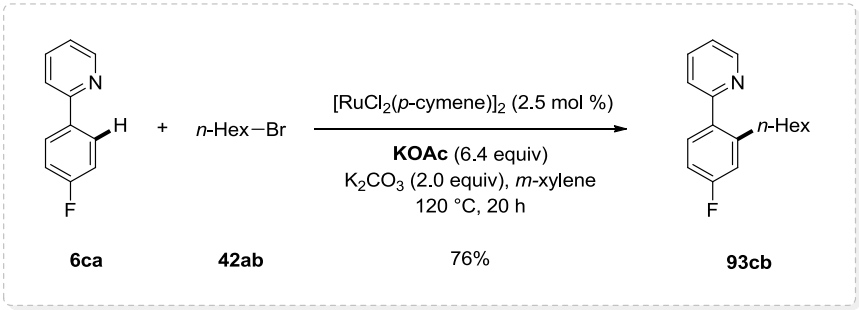
Within this thesis, the development of new synthetic methods has been guided in general by the principles of green chemistry. Among others, the atom- and step-economical ruthenium-catalyzed C–H bond functionalizations in non-toxic reaction media arguably constitute one of the most sustainable synthetic methods in preparative organic chemistry.

In the first project, the main efforts were focused on the ruthenium-catalyzed direct alkylation with unactivated primary alkyl halides **42a** under basic reaction conditions. The development of the generally applicable site-selective formation of C(alkyl)–C(aryl) bonds through direct C–H bond functionalizations was selected as a central goal of this project. Thus, the substrate scope was shown to include unsaturated electrophiles and acetyl-substituted phenylpyridines among others (Scheme 5.1).



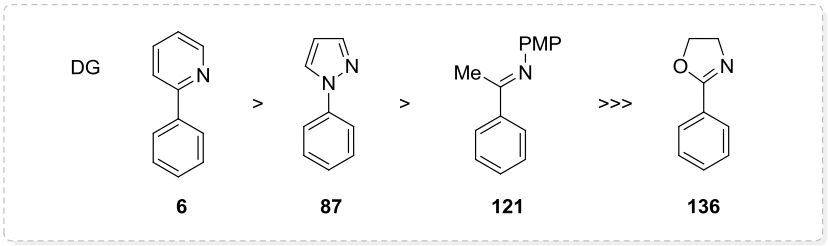
Scheme 5.1: The ruthenium-catalyzed direct *ortho*-alkylation with primary alkyl halides **42a**.

The application of inexpensive KOAc as an additive in the direct alkylation of (*p*-fluorophenyl)pyridine (**6ca**) afforded the desired *ortho*-alkylated product **93cb** in a high yield as well (Scheme 5.2). Furthermore, it was demonstrated that water could be employed as reaction medium.



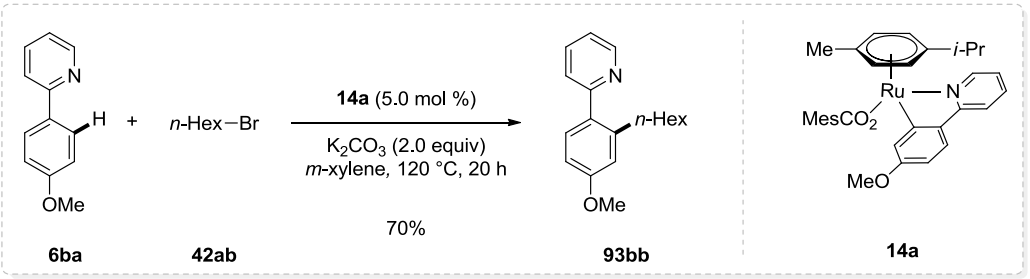
Scheme 5.2: Carboxylate-assisted direct alkylation with inexpensive KOAc as additive.

Mechanistic studies showed the higher reactivity of electron poor substrates. The following order of reactivity of different directing groups (DGs) was derived from intermolecular competition experiments (Scheme 5.3).



Scheme 5.3: Order of reactivity for different DGs.

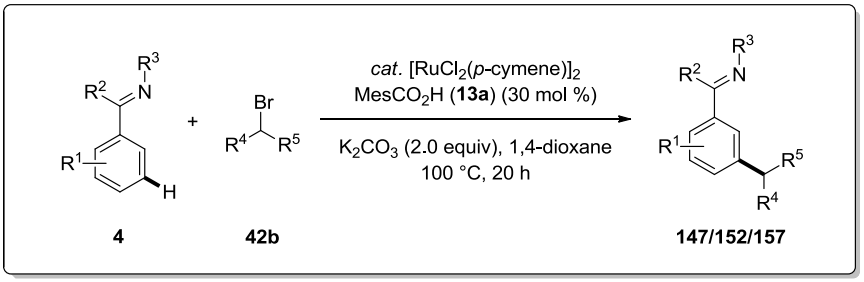
Furthermore, ruthenacycle **14a** was shown to be catalytically competent (Scheme 5.4). Detailed mechanistic studies suggest the catalytic cycle to involve a carboxylate-assisted reversible C–H bond activation followed by activation of the alkyl halide **42a** and final reductive elimination.



Scheme 5.4: Direct *ortho*-alkylation with cycloruthenated complex **14a** as the catalyst.

Future development of the ruthenium-catalyzed direct *ortho*-alkylations with unactivated primary alkyl halides should be focused on extending the substrate scope to include *inter alia* substrates with oxygen-containing directing groups.

Subsequently, an unprecedented *meta*-selective direct alkylation with various cyclic as well as acyclic secondary alkyl bromides **42b** as inexpensive electrophiles was devised (Scheme 5.5).



Scheme 5.5: Ruthenium-catalyzed direct *meta*-alkylation with secondary alkyl bromides **42b**.

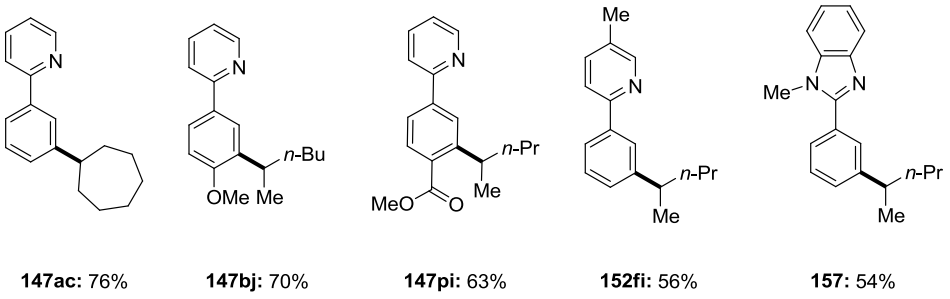
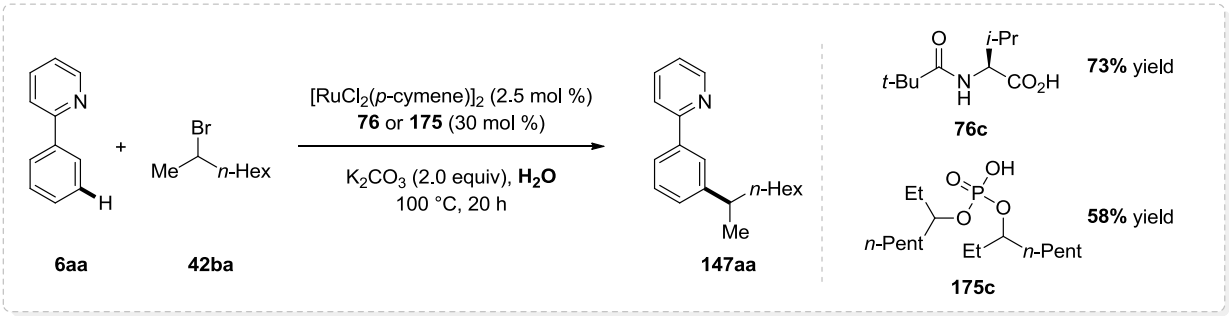


Figure 5.1: Selected examples for the ruthenium-catalyzed direct meta-alkylation.

A broad range of substrates, including ester-substituted arenes and different *N*-containing directing groups were capable of furnishing selectively *meta*-alkylated products. Detailed mechanistic studies were suggested of a reaction manifold, relying on the carboxylate-assisted *ortho*-C–H activation, and subsequent electrophilic aromatic-type substitution.

Various protected amino acids **76** or phosphoric acid diesters **175** were shown to serve as effective ligands for the *meta*-selective direct alkylations, employing water as an environmentally benign reaction medium (Scheme 5.6).

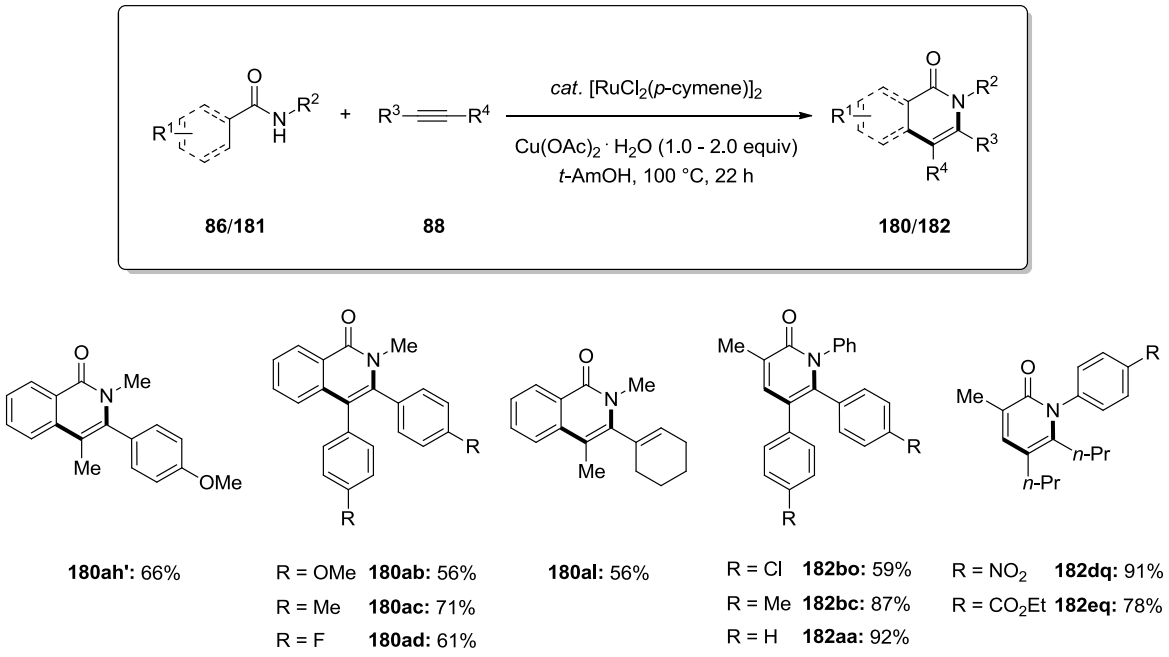


Scheme 5.6: Direct *meta*-alkylation using amino acid **76c** or phosphoric acid diester **175c** as cocatalyst on water.

Further development of the ruthenium-catalyzed direct *meta*-alkylations with unactivated secondary alkyl bromides **42b** should involve enantioselective transformations. As the first step towards achieving enantioselectivity, direct norbornylations bear great potential, which was already demonstrated by high *exo*-stereoselectivities but yet poor regioselectivities.

Further, the future investigations of the ruthenium-catalyzed carboxylate-assisted direct *meta*-alkylation should address understanding of the mode of action of the C–C bond forming step and the activation of the alkyl halide.

In the final project of this thesis, unprecedented ruthenium-catalyzed oxidative alkyne annulations were developed (Scheme 5.7). Application of this new catalytic system allowed for the atom- and step-economical syntheses of isoquinolones **180** and 2-pyridones **182** in high yields and with ample scope.



Scheme 5.7: Ruthenium-catalyzed oxidative annulation for the synthesis of isoquinolones **180** and 2-pyridones **182**.

Thus, variously substituted benzamides **86**, acrylamides **181** and benzoic acids **183** were reacted with dialkyl- and diarylalkynes **88** furnishing the desired isoquinolones **180**, 2-pyridones **182** or *a*-pyrones **184**, respectively, *via* ruthenium-catalyzed carboxylate-assisted C–H/N–H or C–H/O–H bond cleavage.* Since the regioselectivities with unsymmetrically-substituted alkynes remained rather poor, this methodology should be further developed in future studies, towards improving the regioselectivity and towards enlarging the scope for the use of terminal alkynes.

**After publication of the results presented herein, several further developments of this chemistry have been reported by the Ackermann group and others.*[170]

[170] (a) Deponti, M.; Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Biomol. Chem*. **2013**, *11*, 142–148. (b) Wang, L.; Ackermann, L. *Org. Lett*. **2013**, *15*, 176–179. (c) Li, B.; Wang, N.; Yujie, L.; Xu, S.; Wang, B. *Org. Lett*. **2013**, *15*, 136–139. (d) Ma, W.; Graczyk, K.; Ackermann, L. *Org. Lett*. **2012**, *14*, 6318–6321. (e) Chidipudi, S. R.; Khan, I.; Lam, H. W. *Angew. Chem. Int. Ed*. **2012**, *51*, 12115–12119. (f) Zhao, P.; Wang, F.; Han, K.; Li, X. *Org. Lett*. **2012**, *14*, 5506–5509. (g) Kornhaaß, C.; Li, J.; Ackermann, L. *J. Org. Chem.* **2012**, *77*, 9190–9198. (h) Chinnagolla, R. K.; Jeganmohan, M. *Eur. J. Org. Chem*. **2012**, 417–423. (i) Parthasarathy, K.; Senthilkumar, N.; Jayakumar, J.; Cheng, C.-H. *Org. Lett*. **2012**, *14*, 3478–3481. (j) Thirunavukkarasu, V. S.; Donati, M.; Ackermann, L. *Org. Lett*. **2012**, *14*, 3416–3419; (k) Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan, M. *Org. Lett*. **2012**, *14*, 3032–3035. (l) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764–767. (m) Chinnagolla, R. K.; Jeganmohan, M. *Chem. Commun*. **2012**, *48*, 2030–2032. (m) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.* **2012**, *14*, 930–933. (n) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177–180. (o) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548–6551. (p) Li, B.; Feng, H.; Xu, S.; Wang, B. *Chem. Eur. J*. **2011**, *17*, 12573–12577.

6 Experimental Section

6.1 General Remarks

All reactions involving moisture- or air-sensitive reagents or products were performed under a N_2 atmosphere using pre-dried glassware and standard Schlenk techniques. Syringes for handling of dry solvents were flushed with dry nitrogen threefold prior to use.

Solvents

All solvents for reactions involving moisture-sensitive reagents were dried, distilled and stored under inert atmosphere (argon or nitrogen) according to the following standard procedures.

solvent	**drying method**
tert-Amylalcohol	was stirred over sodium chips for 5 h at 120 °C and distilled under ambient pressure.
Dichloromethan	was purified using an solvent purification system (SPS) from MBRAUN.
N,N-Dimethylformamide	was dried over CaH_2 for 8 h, degassed and distilled under reduced pressure.
N-Methyl-2-pyrrolidone	was stirred for 4 h at 150 °C over CaH_2 and subsequently distilled under reduced pressure.
Methanol	was stirred over Mg chips for 3 h at 65 °C prior to distillation.
Tetrahydrofuran	was purified using an SPS solvent purification system from MBRAUN.
Toluene	was either predried over KH followed by distillation from sodium benzophenone ketyl or purified using a solvent purification system from MBRAUN.
Water	was degassed before its use applying repeated Freeze-Pump-Thaw degassing procedure.
1,4-Dioxane	was dried by distillation from sodium benzophenone ketyl.

Vacuum

The following pressures were measured on the used vacuum pump and were not corrected: membrane pump vacuum (MPV): 0.5 mbar, oil pump vacuum (OPV): 0.1 mbar.

Melting Points

Melting points were measured using a *Stuart® Melting Point Apparatus SMP3* from BARLOWORLD SCIENTIFIC. Reported values are uncorrected and are given as a range (M.r.), if the melting occurred not at a specific melting point (M.p.).

Chromatography

Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60F-plates (MACHEREY-NAGEL) with 254 nm fluorescent indicator from MERCK. Plates were visualized under UV-light and developed by treatment with a $KMnO_4$ solution followed by careful applying a heat gun. Chromatographic purification of products was accomplished by flash column chromatography on MERCK silica gel, grade 60 (0.040–0.063 mm and 0.063–0.200 mm, 70–230 mesh astimated).

High Performance Liquid Chromatography

Preparative and analytical separations were performed on an HPLC-System from KNAUER (*Smartline Pump 100*, Dynamic Mixing Chamber, Injection- and Control-Valve, *Smartline UV Detector 2500*). Separation column *ChiralPak IC* (250 × 20 mm or 4.6 × 250 mm) from DAICEL CHEM. IND. (LTD) was used. Organic solvents of HPLC grade were employed. All samples were filtered through Polytetrafluorethylen Filter from ROTH (Ø 25 mm, 0.2 µm) or VWR (Ø 13 mm, 0.2 µm) prior to separation.

Gas Chromatograpgy

The conversion of the reactions was monitored applying coupled gas chromatography/mass spectrometry using *G1800C GCDplus* with mass detector *HP 5971*, *5890 Series II* with mass detector *HP 5972* from HEWLETT-PACKARD and *7890A GC-System* with mass detector *5975C (Triplex-Axis-Detector)* from AGILENT TECHNOLOGIES equipped with *HP-5MS* columns (30 m × 0.25 mm × 0.25 µm) were used.

Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy was performed at 300 or 600 MHz (^{1}H-NMR), 75.5 or 125 MHz (^{13}C-NMR, APT) and 282 MHz (^{19}F-NMR) on BRUKER *AM 250*, VARIAN *Unity-300* and *Inova 500* instruments. Chemical shifts are reported as δ-values in ppm relative to the residual proton peak of the deuterated solvent or its carbon atom, respectively, or the standard trimethylsilyl (TMS) peak.

	^{1}H-NMR	^{13}C-NMR
$CDCl_3$:	7.26 ppm	77.0 ppm
DMSO-D_6 :	2.49 ppm	49.5 ppm

For characterization of the observed resonance multiplicities the following abbrevations were applied: *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *m* (multiplet), *dd* (doublet of doublet), *dt* (doublet of triplet), or analogue representations. The coupling constants *J* are reported in Hertz (Hz).

Infrared Spectroscopy

Infrared spectra were recorded on a BRUKER *Alpha-P* ATR-spectrometer. Liquid probes have been measured as film and solid probes neat. Analysis of the spectral data has been done by using the *OPUS 3.1* software from BRUKER, respectively *OPUS 6*. Absorption ($\tilde{\nu}$) is given in wave numbers (cm^{-1}). Spectra were recorded in the range of 4000 to 400 cm^{-1}.

Mass Spectrometry

EI- and EI-HR-MS spectra were measured on a *Time-of-Flight* mass spectrometer *AccuTOF* from JOEL. ESI-mass spectra were recorded on an *Ion-Trap* mass spectrometer *LCQ* from FINNIGAN or on a *Time-of-Flight* mass spectrometer *microTOF* from BRUKER. ESI-HR-MS spectra were recorded on a BRUKER *APEX IV* or a BRUKER *DALTONIC* (7T, Transform Ion Cyclotron Resonance (FTICR)) mass spectrometer. The ratios of mass to charge are indicated, intensities relative to the base peak (I = 100) are written in parentheses.

Optical Rotatory Power

Optical rotations were measured with digital polarimeters PERKIN-ELMER *241* or JASCO *P-2000* in a 1 dm cell. The optical rotary powers α in the indicated solvents are given in ° at the indicated temperatures.

Crystal Structure Analysis

Crystals for X-ray diffraction crystals of compounds **129**, **148**, **149** and (*R*)-**167** were obtained by slow evaporation of their solutions in DCM/*n*-octane. The single crystal X-ray data were collected on a BRUKER *SMART-CCD 6000* diffractometer at 120.0(2) K using graphite monochromator with Mo-K_α radiation (λ = 0.71073 Å). All structures were solved by direct method and refined by full-matrix least

squares on F^2 for all data. All non-hydrogen atoms were refined with anisotropic displacement parameters. H-atoms were located on the difference map and refined isotropically. Absolute configuration of the compound **147bj** was determined on the basis of X-ray data. Crystal and data collection parameters are summarized in the Table S-1.

Reagents

Chemicals obtained from commercial sources with purity above 95% were used without further purification.

The following compounds were synthesized according to known literature procedures and were pure by comparison with the published The analytical data:

Alkyl halides (**42b**),[171] 2-phenylpyridines (various **6**),[172] 3-methoxy-2-phenylpyridin (**6cb**),[173] alkynes (**88c**-**88o**),[174] complex [bis(2,4,6-trimethylbenzoyloxy)(*p*-cymene)-ruthenium(II)] (**12**) and complex {[5-methoxy-2-(pyridine-2-yl)phenyl](2,4,6-trimethylbenzoyloxy)(*p*-cymene)ruthenium(II)} (**14a**),[175] complex {[2-(pyridine-2-yl)phenyl](*p*-cymene)ruthenium(II)chloride} **178**,[176] amino acid derivatives (variuos **76**),[177] *N*-methylbenzamide (**86a**),[178] (*E*)-*N*,2-dimethylbut-2-enamide (**181i**),[179] pent-1-yn-1-ylbenzene (**88f**),[180] *(E)*-dodec-5-en-7-yne (**88v**),[181] (cyclohex-1-en-1-ylethynyl)-benzene (**88j**),[182] 1-methoxy-4-(prop-1-yn-1-yl)benzene (**88h**),[183] 1-(prop-1-yn-1-yl)cyclohex-1-ene (**88l**),[184] (3*S*)-3-bromo-2,6,6-trimethylbicyclo[3.1.1]heptanes (**42bf**),[185] (*R*)-[(octan-2-yloxy)methyl]benzene (**168**),[186] octan-2-

[171] Sankaranarayanan, S.; Sharma, A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2002**, *13*, 1373–1378.
[172] Böhm, V. P. W.; Weskamp, T.; Gstöttmayr, C. W. K.; Herrmann, W. A. *Angew. Chem. Int. Ed*. **2000**, *39*, 1602–1604.
[173] Finkentey, C.; Langhals, E.; Langhals, F. *Chem. Ber.* **1983**, *116*, 2394–2397.
[174] Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A. *Org. Lett.* **2002**, *4*, 3199–3202.
[175] Ackermann, L.; Vicente, R.; Potukuchi, H.K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032–5035.
[176] Boutadla, Y.; Al-Duaij, O.; Davies, D. L.; Griffith, G. A.; Singh, K. *Organometallics,* **2009**, *28*, 433–440.
[177] Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew.Chem. Int. Ed.* **2008**, *47*, 4882–4886.
[178] Dehmlow, E.V.; Winterfeldt, A. *Z. Naturforsch. B* **1989**, *44*, 455–458.
[179] Beak, P.; Kempf, D. J.; Wilson, K. D. *J. Am. Chem. Soc.* **1985**, *107*, 4745–4756.
[180] Freeburger, M. E.; Spialter, L. *J. Org. Chem.* **1970**, *35*, 652–657.
[181] Yang, C.; Nolan, S. P. *J. Org. Chem.* **2002**, *67*, 591–593.
[182] Yoshida, M.; Hayashi, M.; Shishido, K. *Org. Lett.* **2007**, *9*, 1643–1646.
[183] Zhang, Z.; Orita, A.; Mineyama, H.; Otera, J. *Synlett* **2007**, *12*, 1909–1912.
[184] Tang, X.; Woodward, S.; Krause, N. *Eur. J. Org. Chem.* **2009**, *17*, 2836–2844.
[185] Ranu, B. C.; Jana, R. *Eur. J. Org. Chem.* **2005**, 755–758.
[186] Dellaportas, P.; Jones, R. G.; Holder, S. J. *Macromol. Rapid. Commun.* **2002**, *23*, 99–103.

yl-4-methylbenzenesulfonate,[187] 2-iodooctane,[188] 2-chlorooctane,[189] 2-(1*H*-pyrrol-3-yl)-pyridine (**128**),[190]

The following compounds were obtained by the generous courtesy of the persons named below:

Dr. Alexander V. Lygin: 1,2-Bis(3,5-di-*tert*-butylphenyl)ethyne (**88m**), *N*-*iso*-propylmethacrylamide (**181c**), *N*-phenylmethacrylamide (**181b**)

Dr. Benudhar Punji: 2-(3-*n*-Propoxyphenyl)pyridine (**6sa**), 2-(3-*iso*-propoxyphenyl)pyridine (**6ta**).

Dipl.-Chem. Marvin Schinkel: 2-(3-Fluorophenyl)pyridine (**3da**), 2-(3-methoxyphenyl)pyridine (**6ua**), 3-methoxy-2-phenylpyridine (**6cb**), 3-methyl-2-phenylpyridine (**6db**), 5-methyl-2-phenylpyridine (**6fb**), 2-(3-(trifluoromethyl)phenyl)pyridine (**6ma**), 5-fluoro-2-phenylpyridine (**6ib**), 2,5-diphenylpyridine (**6ab**), 2-phenylpyrimidine (**153**),

B.Sc. Christian Kuper: (1-Bromopentyl)benzene benzene (**176**).

B.Sc. Sabine Malzkuhn: 4-(Pyridin-2-yl)benzonitrile benzene (**6qa**), 2-(4-methoxyphenyl)-4-methylpyridine benzene (**6f**), (1-bromopentyl)benzene benzene (**176**).

B.Sc. Michael Hendrich: 2-(2-Fluorophenyl)pyridine (**6va**).

B.Sc. Kris Bielefeld: 2-(*m*-Tolyl)pyridine (**6va'**).

Karsten Rauch: $[RuCl_2(p\text{-cymene})]_2$.

[187] Jalalian, N.; Olofsson, B. *Tetrahedron* **2010**, *66*, 5793–5800.
[188] Irifune, S.; Kibayashi, T.; Ishii, Y.; Ogawa, M. *Synthesis* **1988**, *5*, 366–369.
[189] Bottoni, A.; Lombardo, M.; Neri, A.; Trombini, C. *J. Org. Chem.* **2003**, *68*, 3397–3405.
[190] Smith, N. D.; Huang, D.; Cosford, N. D. P. *Org. Lett.* **2002**, *4*, 3537–3539.

6.2 General Procedures

General procedure A:

Nickel-Catalyzed Kumada-Corriu Cross-Coupling for the Synthesis of 2-Phenyl-pyridines 6

Under vigorous stirring and an atmosphere of N_2, a solution of bromoarene **15** (1.67 equiv) in anhydrous THF was added dropwise to the suspension of Mg turnings (1.73 equiv) in anhydrous THF (2.5 M with resp. to **15**). The reaction mixture was stirred and heated at 75 °C for an additional 1 h. After cooling to ambient temperature, the obtained Grignard solution was added dropwise to the stirred ice-cold solution of $Ni(acac)_2$ (3.0 mol %), HIPrCl (**61**) (3.0 mol %) and halopyridine **124** in anhydrous THF (1.5 M with resp. to **124**) under an atmosphere of N_2. The resulting solution was stirred at ambient temperature untill complete conversion of the starting material was detected by TLC. A saturated aqueous solution of NH_4Cl (75 mL) was added, and the aqueous layer was extracted with EtOAc (3×75 mL). The combined organic layers were washed with brine (75 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel followed by Kugelrohr distillation to yield the desired product **6**.

General procedure B:

Preparation of Ketimines 121[191]

A solution of the ketone **84** (1.0 equiv) and *para*-methoxyaniline (**127**) (1.25 equiv) in PhMe (0.2 M with resp. to **84**) with 4 Å MS (6 g/25 mL PhMe) was stirred and heated at 110 °C overnight. After cooling to ambient temperature, filtration, concentration under reduced pressure and purification by column chromatography on silica gel deactivated with NEt_3 (10 vol % in *n*-hexane), eluent *n*-hexane, yielded the corresponding ketimines **121**.

General procedure C:

Ruthenium-Catalyzed Direct *ortho*-Selective Alkylation

A suspension of $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $AdCO_2H$ (**13c**) (30 mol %), K_2CO_3 (2.0 equiv), respective substrate **6** (1.0 equiv) and primary alkyl bromide **42a** (3.0 equiv) in *m*-xylene, if not otherwise specified (0.25 M with resp. to **6**) was stirred at 120 °C for 20 h under N_2. EtOAc (50 mL)

[191] Malkov, A. V.; Vranková, K.; Stončius, S.; Kočovský, P. *J. Org. Chem.* **2009**, *74*, 5839–5849.

and H_2O (50 mL) were added to the reaction mixture at ambient temperature. The separated aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield the desired product **93**.

General Procedure D:

Ruthenium-Catalyzed Direct Alkylations of Ketimines 121

A suspension of $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), 1-AdCO_2H (**13c**) (30 mol %), K_2CO_3 (3.2 equiv), respective ketimine **121** (1.0 equiv) and alkyl bromide **42** (3.0 equiv) in *m*-xylene (0.25 M with resp. to **121**) was stirred under N_2 for 20 h at 120 °C. A solution of $ZnCl_2$ in THF (1.7 M, 1.0 equiv with resp. to **121**), $NaBH_3CN$ (2.0 equiv with resp. to **121**) and MeOH (0.25 M with resp. to **121**) were successively added to the reaction mixture at ambient temperature. The reaction mixture was stirred for an additional 16 h at ambient temperature and then distributed between between addition of Et_2O (15 mL) and sat. aq. K_2CO_3 (15 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel.

General procedure E:

Ruthenium-Catalyzed Direct *meta*-Selective Alkylation

A suspension of $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), MesCO_2H (**13a**) (30 mol %), K_2CO_3 (2.0 equiv), substrate **6** (1.0 equiv) and secondary alkyl bromide **42b** (3.0 equiv) in 1,4-dioxane, if not otherwise specified (0.25 M with resp. to **6**), was stirred at 100 °C for 20 h under N_2. After cooling to ambient temperature, the reaction mixture was distributed between EtOAc (50 mL) and H_2O (50 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL), the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield the desired product **147**.

The general procedure F:

Ruthenium-Catalyzed Annulation of Alkynes 88 with Benzamides 86

A mixture of benzamide **86** (1.0 equiv), alkyne **88** (2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv) in *t*-AmOH (0.25 M with resp. to **86**) was stirred at 100 °C for 22 h under N_2 atmosphere. After cooling the reaction mixture to ambient temperature, it was diluted with aq. NH_3 solution (75 mL, 1.0 wt%) and extracted with EtOAc (3 × 75 mL). The combined organic extracts were

washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the residue was purified by column chromatography on silica gel.

The general procedure G:

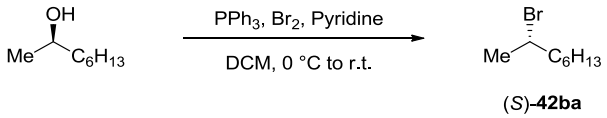
Ruthenium-Catalyzed Annulation of Alkynes 88 with Acrylamides 181

A mixture of acrylamide (**181**) (2.0 equiv), alkyne (**88**) (1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv) in *t*-AmOH (0.25 M with resp. to **88**) was stirred under N_2 atmosphere for 20 h at 120 °C. At ambient temperature, the reaction mixture was diluted with saturated aq. NH_4Cl solution (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the remaining residue was purified by column chromatography on silica gel.

7 Experimental Procedures and Analytical Data

7.1 The Analytical Data for Starting Materials

Synthesis of (*S*)-2-Bromooctane [(*S*)-42ba][171]

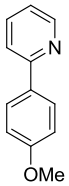


(*S*)-**42ba**

To the stirred solution of PPh_3 (7.93 g, 30.2 mmol) in DCM (25 mL), Br_2 (2.3 mL, 28 mmol) was added dropwise at 0 °C. After stirring for an additional 0.5 h at 0 °C, a solution of (*R*)-octan-2-ol (3.2 g, 25 mmol) and pyridine (2.3 mL, 28 mmol) in DCM (12 mL) was added dropwise at 0 °C, and the mixture was stirred for an additional 3 h at ambient temperature. The reaction mixture was concentrated *in vacuo*, the residue was vigorously stirred with *n*-hexane (50 mL), filtered and concentrated again. This operation was repeated twice. Column chromatography of the residue on silica gel (eluent *n*-hexane) yielded the product [(*S*)-**42ba**] (3.53 g, 73%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.14 (ddd, *J* = 8.1, 6.7, 5.3 Hz, 1H), 1.98-1.64 (m, 5H), 1.56-1.17 (m, 8H), 0.88 (t, *J* = 5.8 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 52.6 (CH), 41.8 (CH_2), 32.3 (CH_2), 29.2 (CH_2), 28.3 (CH_2), 27.0 (CH_3), 23.2 (CH_2), 14.6 (CH_3).
[α^{23}_D] = +34.4° (MeOH).
MS (EI) *m/z* (relative intensity): 113 (26) [M–Br^+], 71 (99), 57 (100), 43 (86).
HR-MS (ESI) *m/z* calculated for $C_8H_{17}Br–H^+$: 191.0435; found: 191.0444.
The The analytical data are in accordance with those reported in the literature.[192]

Synthesis of 2-(4-Methoxyphenyl)pyridine (6ba)



[192] Denton, R. M.; An, J.; Adeniran, B.; Blake, A. J.; Lewis, W.; Poulton, A. M. *J. Org. Chem.* **2011**, *76*, 6749–6767.

The general procedure **A** was followed using 1-bromo-4-methoxybenzene (**15b**) (6.3 mL, 50 mmol) and 2-chloropyridine **124a**) (3.52 g, 34.0 mmol). Purification by column chromatography (*n*-hexane/EtOAc 5:1) followed by Kugelrohr distillation yielded **6ba** (5.25 g, 94%) as a white solid.

M.p.: 53 - 54 °C [Lit.: 53 - 55 °C].[193]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.69 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 7.82-7.67 (m, 2H), 7.63-7.49 (m, 2H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.29-7.18 (m, 1H), 6.97 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 3.90 (s, 3H).

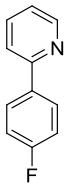
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.1 (C_q), 157.2 (C_q), 149.6 (CH), 140.9 (C_q), 137.0 (CH), 129.7 (CH), 122.2 (CH), 120.7 (CH, 119.3 (CH), 115.1 (CH), 112.0 (CH), 55.4 (CH_3).

MS (EI) *m/z* (relative intensity): 184 (100) [M-H$^+$], 154 (77), 140 (32), 115 (17), 78 (24).

HR-MS (EI): *m/z* calculated for $C_{12}H_{12}NO^+$: 186.0919; found: 186.0915.

The analytical data are in accordance with those reported in the literature.[193]

Synthesis of 2-(4-Fluorophenyl)pyridine (6ca)



The general procedure **A** was followed using 1-bromo-4-fluorobenzene (**15c**) (8.79 g, 50.0 mmol) and 2-chloropyridine (**124a**) (3.39 g, 30.0 mmol). Purification by column chromatography (*n*-hexane/EtOAc 5:1) followed by Kugelrohr distillation yielded **6ca** (3.88 g, 75%) as a white solid.

M.p.: 40 °C [Lit.: 38 - 39 °C].[194]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.53 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.00-7.91 (m, 2H), 7.71 (ddd, *J* = 7.2, 7.4, 1.7 Hz, 1H), 7.67-7.62 (m, 1H), 7.25-7.09 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.3 (d, J_{C-F} = 248 Hz, C_q), 156.3 (C_q), 149.5 (CH), 136.7 (CH), 135.4 (d, J_{C-F} = 3 Hz, C_q), 128.6 (d, J_{C-F} = 8 Hz, CH), 121.9 (CH), 120.1 (CH), 115.5 (d, J_{C-F} = 22 Hz, CH).

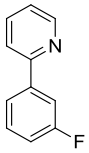
MS (EI) *m/z* (relative intensity): 173 (100) [M$^+$], 146 (7), 121 (5), 75 (6).

HR-MS (EI) *m/z* calculated for $C_{11}H_8FN^+$: 173.0641; found: 173.0639.

The analytical data are in accordance with those reported in the literature.[194]

[193] Riggio, G.; Hopff, W.; Herbert, H.; Alfred, A.; Waser, P. G. *Helv. Chim. Acta* **1983**, *66*, 1039–1045.
[194] Xu, J.; Cheng, G.; Su, D.; Liu, Y.; Wang, X.; Hu, Y. *Chem. Eur. J.* **2009**, 13105–13110.

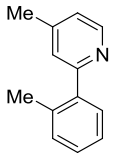
Synthesis of 2-(3-Fluorophenyl)pyridine (6da)



The general procedure **A** was followed using 1-bromo-3-flourobenzene (**15d**) (8.86 g, 51.0 mmol) and 2-chloropyridine (**124a**) (3.37 g, 30.0 mmol). Purification by column chromatography (*n*-hexane/EtOAc 5:1) followed by Kugelrohr distillation yielded **6da** (3.43 g, 66%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.68 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.79-7.63 (m, 4H), 7.41 (ddd, *J* = 8.2, 8.2, 6.0 Hz, 1H), 7.26 (ddd, J_{C-F} = 6.7, 4.8, 1.5 Hz, 1H), 7.11 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.3 (d, J_{C-F} = 245 Hz, C_q), 156.0 (d, J_{C-F} = 3 Hz, C_q), 149.7 (CH), 141.7 (d, J_{C-F} = 8 Hz, C_q), 136.8 (CH), 130.2 (d, J_{C-F} = 8 Hz, CH), 122.6 (CH), 122.4 (d, J_{C-F} = 3 Hz, CH), 120.5 (CH), 115.7 (d, J_{C-F} = 21 Hz, CH), 113.8 (d, J_{C-F} = 23 Hz, CH).
MS (EI) *m/z* (relative intensity): 173 (100) [M^+], 154 (11), 146 (15), 125 (8), 120 (9), 75 (7).
HR-MS (EI): *m/z* calculated for $C_{11}H_8FN^+$: 173.0641; found: 173.0642.
The analytical data are in accordance with those reported in the literature.[172]

Synthesis of 4-Methyl-2-(*o*-tolyl)pyridine (6eb)

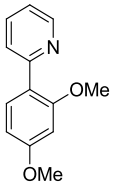


The general procedure **A** was followed using 1-bromo-2-methylbenzene (**15e**) (1.05 g, 6.30 mmol) and 2-bromo-4-methylpyridine (**124b**) (0.59 g, 3.30 mmol). Purification by column chromatography (*n*-hexane/EtOAc 5:1) followed by Kugelrohr distillation yielded **6eb** (0.53 g, 88%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.54 (dd, *J* = 5.1, 0.8 Hz, 1H), 7.41-7.34 (m, 1H), 7.30-7.23 (m, 3H), 7.23-7.18 (m, 1H), 7.07 (ddd, *J* = 5.0, 1.7, 0.8 Hz, 1H), 2.40 (s, 3H), 2.36 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.1 (C_q), 149.1 (CH), 147.3 (C_q), 140.7 (C_q), 135.9 (C_q), 130.8 (CH), 129.7 (CH), 128.3 (CH), 125.9 (CH), 125.1 (CH), 122.8 (CH), 21.3 (CH_3), 20.4 (CH_3).
MS (EI) *m/z* (relative intensity): 183 (62) [M^+], 167 (100), 152 (19), 115 (10), 89 (15).
HR-MS (EI) *m/z* calculated for $C_{13}H_{13}N^+$: 183.1048; found: 183.1047.

The analytical data are in accordance with those reported in the literature.[195]

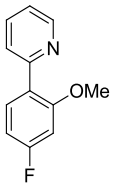
Synthesis of 2-(2,4-Dimethoxyphenyl)pyridine (6fa)



The general procedure **A** was followed using 1-bromo-2,4-dimethoxybenzene (**15f**) (1.89 g, 8.70 mmol) and 2-chloropyridine (**124a**) (0.69 g, 6.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1) followed by Kugelrohr distillation yielded **6fa** (0.91 g, 69%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.92-7.72 (m, 2H), 7.66 (ddd, *J* = 8.1, 7.4, 1.9 Hz, 1H), 7.15 (ddd, *J* = 7.4, 4.9, 1.2 Hz, 1H), 6.62 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.56 (d, *J* = 2.4 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.0 (C_q), 157.8 (C_q), 155.5 (C_q), 148.9 (CH), 135.3 (CH), 131.7 (CH), 124.4 (CH), 121.8 (C_q), 120.8 (CH), 104.9 (CH), 98.6 (CH), 55.3 (CH_3), 55.2 (CH_3).
MS (EI) *m/z* (relative intensity): 214 (100) [M-H$^+$], 200 (14), 185 (47), 170 (47), 142 (53), 80 (30).
HR-MS (EI) *m/z* calculated for $C_{13}H_{13}NO_2$-H$^+$: 214.0868; found: 214.0867.
The analytical data are in accordance with those reported in the literature.[196]

Synthesis of 2-(4-Fluoro-2-methoxyphenyl)pyridine (6ga)



The general procedure **A** was followed using 1-bromo-4-flouro-2-methoxybenzene (**15g**) (2.06 g, 10.0 mmol) and 2-chloropyridine (**124a**) (1.14 g, 9.90 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1) followed by Kugelrohr distillation yielded **6ga** (0.67 g, 33%) as a colorless oil.

[195] Ackermann, L.; Potukuchi, H. K.; Kapdi, A. R.; Schulzke, C. *Chem. Eur. J.* **2010**, *16*, 3300–3303.
[196] (a) Maeyama, K. *Rec. Res. Dev. Org. Chem*. **2003**, *7*, 43–51; (b) Terashima, M. *Chem. Pharm. Bull.* **1985**, *33*, 1009–1015.

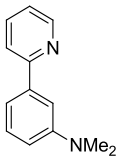
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.67 (ddd, J = 4.9, 1.9, 1.0 Hz, 1H), 7.79-7.72 (m, 2H), 7.67 (ddd, J = 8.0, 7.4, 1.9 Hz, 1H), 7.18 (ddd, J = 7.4, 4.9, 1.3 Hz, 1H), 6.85-6.55 (m, 2H), 3.83 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 164.0 (d, $J_{C\text{-}F}$ = 248 Hz, C_q), 158.2 (d, $J_{C\text{-}F}$ = 10 Hz, C_q), 155.3 (C_q), 149.5 (CH), 135.8 (CH), 132.4 (d, $J_{C\text{-}F}$ = 10 Hz, CH), 125.3 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 124.9 (CH), 121.7 (CH), 107.6 (d, $J_{C\text{-}F}$ = 21 Hz, CH), 99.5 (d, $J_{C\text{-}F}$ = 26 Hz, CH), 55.9 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = -109.40 - 111.63 (m).

HR-MS (ESI) *m/z* calculated for $C_{12}H_{10}FNO+H^+$: 204.0819; found: 204.0824.

Synthesis of *N,N*-Dimethyl-3-(pyridin-2-yl)aniline (6ha)



The general procedure **A** was followed using 3-bromo-*N,N*-dimethylaniline (**15h**) (5.00 g, 25.0 mmol) and 2-chloropyridine (**124a**) (2.24 g, 19.8 mmol). Purification by column chromatography (*n*-hexane/EtOAc 9:1) followed by Kugelrohr distillation yielded **6ha** (2.92 g, 74%) as yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.77-8.54 (m, 1H), 7.81-7.68 (m, 2H), 7.45 (dd, J = 2.7, 1.6 Hz, 1H), 7.39-7.17 (m, 3H), 6.84 (ddd, J = 8.0, 2.7, 1.2 Hz, 1H), 3.04 (s, 6H).

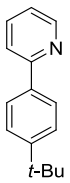
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.5 (C_q), 151.5 (C_q), 149.6 (CH), 140.3 (C_q), 137.5 (CH), 130.0 (CH), 122.6 (CH), 121.6 (CH), 116.2 (CH), 114.2 (CH), 111.9 (CH), 41.4 (CH_3).

MS (EI) *m/z* (relative intensity): 198 (100) [M^+], 183 (72), 168 (12), 154 (38), 127 (14), 91 (14), 43 (15).

HR-MS (EI) *m/z* calculated for $C_{13}H_{14}N_2$-H^+: 197.1079; found: 197.1081.

The analytical data were in accordance with those reported in the literature.[197]

Synthesis of 2-(4-*tert*-Butylphenyl)pyridine (6ia)

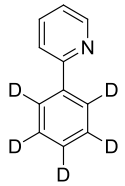


[197] Yoshikai, N.; Asako, S.; Yamakawa, T.; Ilies, L.; Nakamura, E. *Chem. Asian J*. **2011**, *6*, 3059–3065.

The general procedure **A** was followed using 1-bromo-4-*tert*-butylbenzene (**15i**) (5.40 g, 25.3 mmol) and 2-chloropyridine (**124a**) (2.34 g, 20.7 mmol). Purification by column chromatography (*n*-hexane/EtOAc 9:1) followed by Kugelrohr distillation yielded **6ia** (3.3 g, 75%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.68 (dt, *J* = 4.9, 1.4 Hz, 1H), 8.00-7.83 (m, 2H), 7.78-7.64 (m, 2H), 7.58-7.41 (m, 2H), 7.21 (ddd, *J* = 5.8, 4.9, 2.7 Hz, 1H), 1.36 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.6 (C_q), 152.3 (C_q), 149.7 (CH), 136.8 (CH), 136.7 (C_q), 126.7 (2xCH), 125.9 (CH), 121.9 (CH), 120.5 (CH), 34.8 (C_q), 31.5 (CH_3).
MS (EI) *m/z* (relative intensity): 211 (24) [M^+], 196 (100), 181 (10), 168 (11).
HR-MS (ESI) *m/z* calculated for $C_{15}H_{17}N^+$: 211.1361; found: 211.1363.
The analytical data are in accordance with those reported in the literature.[198]

Synthesis of 2-(2,3,4,5,6-Pentadeuterophenyl)pyridin ([D_5]-6aa)

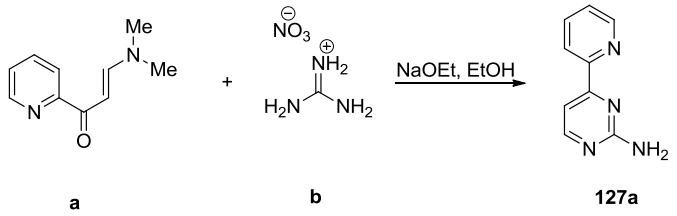


The general procedure **A** was followed using 1-bromo-2,3,4,5,6-pentadeuterobenzene ([D_5]-**15a**) (2.32 g, 14.3 mmol) and 2-chloropyridine (**124a**) (1.21 g, 10.7 mmol). Purification by column chromatography (*n*-hexane/EtOAc 5:1) followed by Kugelrohr distillation yielded [D_5]-**6aa** (1.1 g, 64%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.70 (ddd, *J* = 4.8, 1.4, 0.3, Hz, 1 H), 7.80-7.71 (m, 2 H), 7.25-7.21 (m, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 156.9 (C_q), 149.2 (CH), 138.8 (C_q), 136.3 (CH), 128.0 (t, $J_{C\text{-}D}$ = 25 Hz, C_q), 127.8 (t, $J_{C\text{-}D}$ = 25 Hz, CD), 126.1 (t, $J_{C\text{-}D}$ = 25 Hz, CD), 121.7 (CH), 120.1 (CH).
HR-MS (EI) *m/z* calculated for $C_{11}H_4D_5N^+$: 161.1127; found: 161.1122.
The analytical data were in accordance with those reported in the literature.[199]

[198] Kobayashi, O.; Uraguchi, D.; Yamakawa, T. *Org. Lett.* **2009**, *11*, 2679–2682.
[199] Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Lett.* **2008**, *10*, 3409–3412.

Synthesis of 4-(Pyridin-2-yl)pyrimidin-2-amine (127a)[200]



a **b** **127a**

A solution of guanidinine nitrate **b** (3.14 g, 25.0 mmol) in abs. EtOH (20 mL) was added to a stirred solution of pyridylpropenone **a** (3.5 g, 20.0 mmol) in boiling abs. EtOH (30 mL) and stirring was continued for 20 min. To this mixture Na (0.9 g, 40 mmol) in EtOH (20 mL) was added and the reaction mixture stirred at 80 °C for 16 h. The solution was allowed to cool to ambient temperature and the precipitate was removed by filtration followed by concentration of the filtrate under reduced pressure. After purification by column chromatography (EtOAc/DCM 95:5) the product **127a** (1.72 g, 50%) was isolated as a yellow solid.

M.r.: 133 - 134 °C [Lit: 132 - 137 °C].[200]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.69 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.31 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.80 (td, *J* = 7.8, 1.8 Hz, 1H), 7.62 (d, *J* = 5.2 Hz, 1H), 7.35 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 5.35 (s, 2H).

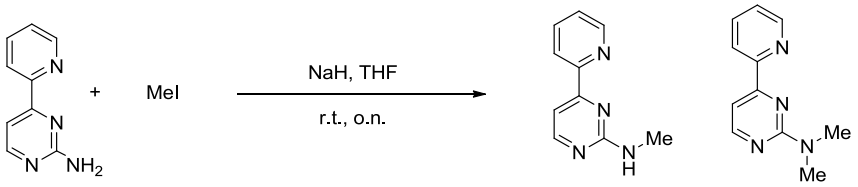
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 164.2 (C_q), 163.3 (C_q), 159.5 (CH), 154.5 (C_q), 149.6 (CH), 137.0 (CH), 125.2 (CH), 121.6 (CH), 108.2 (CH).

MS (EI) *m/z* (relative intensity): 172 (100) [M^+], 145 (12), 131 (10), 103 (19), 79 (21).

HR-MS (EI) *m/z* calculated for $C_9H_8N_4^+$: 172.0749; found: 172.0746.

The analytical data are in accordance with those reported in the literature.[200]

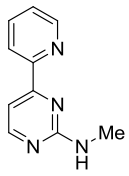
Synthesis of *N*-Methyl-4-(pyridin-2-yl)-pyrimidin-2-amine (127b) & *N,N*-Dimethyl-4-(pyridin-2-yl)-pyrimidin-2-amine (127c)



127a **127b** **127c**

[200] D'Amora, A.; Fanfoni, L.; Cozzula, D.; Guidolin, N.; Zangrando, E.; Felluga, F.; Gladiali, S.; Benedetti, F.; Milani, B. *Organometallics* **2010**, *29*, 4472–4485.

To a stirred solution of **127a** (1.7 g, 10 mmol) in dry THF (50 mL) was added NaH (1.0 g, 25 mmol) in one portion. The reaction mixture was stirred for 8 h at ambient temperature. MeI (1.6 mL, 25 mmol) was added dropwise and the solution was stirred over night. After addition of aq. NH_4Cl-solution (50 mL) and separation of the organic layer, the aq. layer was extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with H_2O (50 mL) and brine (50 mL) and then dried over anhydrous Na_2SO_4. After filtration and evaporation, column chromatography and Kugelrohr distillation gave **127b** (0.48 g, 24%) and **127c** (0.79 g, 43%) as yellow oils.



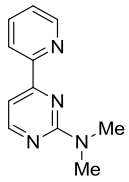
(127b)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.68 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.38 (d, *J* = 7.9 Hz, 1H), 7.80 (td, *J* = 7.7, 1.8 Hz, 1H), 7.56 (d, *J* = 5.1 Hz, 1H), 7.34 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 5.37 (s, 1H), 3.06 (d, *J* = 5.0 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.7 (C_q), 163.3 (C_q), 159.2 (CH), 155.0 (C_q), 149.4 (CH), 136.9 (CH), 125.0 (CH), 121.5 (CH), 106.9 (CH), 28.6 (CH_3).

MS (EI) *m/z* (relative intensity): 186 (100) [M^+], 157 (52), 130 (36), 105 (10), 79 (20).

HR-MS (EI) *m/z* calculated for $C_{10}H_{10}N_4^+$: 186.0905; found: 186.0903.



(127c)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.42 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.79 (td, *J* = 7.7, 1.8 Hz, 1H), 7.50 (d, *J* = 5.0 Hz, 1H), 7.33 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 3.26 (s, 6H).

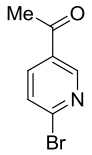
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.5 (C_q), 162.9 (C_q), 159.3 (CH), 155.8 (C_q), 149.7 (CH), 137.3 (CH), 125.3 (CH), 121.9 (CH), 105.7 (CH), 37.6 (2xCH_3).

MS (EI) *m/z* (relative intensity): 200 (100) [M^+], 185 (67), 171 (79), 156 (36), 111 (14), 97 (21), 79 (25), 69 (30), 57 (39), 43 (51).

HR-MS (EI) *m/z* calculated for $C_{11}H_{12}N_4^+$: 200.1062; found: 200.1068.

The analytical data are in accordance with those reported in the literature.[201]

Synthesis of 1-(6-Bromopyridin-3-yl)ethanone (124z)



To a stirred solution of 2,5-dibromopyridine (10.6 g, 44.7 mmol) in dry Et_2O (200 mL) at -78 °C was added dropwise a solution of *t*-BuLi (1.6 M, 29 mL, 45 mmol) in *n*-pentane over 10 min. After 30 min of stirring at -78 °C, DMA (5.2 mL, 50 mmol) was added and stirring continued for 1.5 h. The resulting mixture was warmed to ambient temperature and poured into water (50 mL). The organic phase was washed with water (2 × 30 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a yellow solid (4.1 g, 46%), which was used without further purification.

M.r.: 127 - 128 °C [Lit.: 127 - 128 °C].

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.89 (d, *J* = 2.5 Hz, 1H), 8.07 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.76-7.52 (m, 1H), 2.62 (s, 3H).

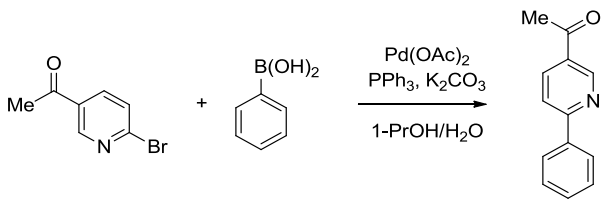
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 195.7 (C_q), 150.5 (CH), 147.1 (C_q), 137.8 (CH), 131.6 (C_q), 128.7 (CH), 26.9 (CH_3).

MS (EI) *m/z* (relative intensity): 199 (35) [M^+], 185 (100), 157 (48), 91 (43), 72 (39).

HR-MS (EI) *m/z* calculated for $C_7H_6BrNO^+$: 198.9633; found: 198.9633.

The analytical data are in accordance with those reported in the literature.[202]

Synthesis of 1-(6-Phenylpyridin-3-yl)ethanone (6ze)



124z **52e** **6bb**

[201] Muller, K.; Schubert, A.; Jozak, T.; Ahrens-Botzong, A.; Schnemann, V.; Thiel, W. R. C*hem. Cat. Chem* **2011**, *3*, 887–892.

[202] El-Deeb, I.M.; Lee, S. H. *Bioorg. Med. Chem.* **2010**, *18*, 3860–3874.

$Pd(OAc)_2$ (80 mg, 0.35 mmol), PPh_3 (0.08 g, 0.25 mmol), aq. solution of K_2CO_3 (2.0 M, 16 mL, 32 mmol) and distilled water (32 mL) were added to a degassed solution of 5-acetyl-6-bromopyridine (**124z**) (4.2 g, 21 mmol) and phenylboronic acid (**52e**) (3.22 g, 27.0 mmol) in 1-propanol (50 mL), and the mixture was refluxed over night. After cooling to ambient temperature, distilled water (50 mL) was added and the mixture was extracted with EtOAc (2 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the crude ketone, which was purified by recrystallisation from MeOH/DCM to give **6ze** (1.9 g, 46%) as colorless plates.

M.p.: 119 °C [Lit.: 119 - 120 °C].

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.23 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.29 (dd, *J* = 8.4, 2.3 Hz, 1H), 8.10-8.02 (m, 2H), 7.84 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.59-7.43 (m, 3H), 2.66 (s, 3H).

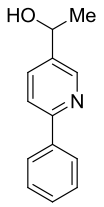
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 197.0 (C_q), 161.5 (C_q), 150.7 (CH), 138.7 (C_q), 136.9 (CH), 131.2 (C_q), 130.6 (CH), 129.5 (2xCH), 127.9 (2xCH), 120.7 (CH), 27.3 (CH_3).

MS (EI) *m/z* (relative intensity): 197 (68) [M^+], 182 (100), 154 (45), 127 (50), 77 (23), 43 (29).

HR-MS (EI) *m/z* calculated for $C_{13}H_{11}NO^+$: 197.0841; found: 197.0837.

The analytical data are in accordance with those reported in the literature.[202]

Synthesis of 1-(6-Phenylpyridin-3-yl)ethanol (125b)



$NaBH_4$ (0.4 g , 10.6 mmol) was added portionwise to a stirred solution of **6xe** (1.8 g, 9.1 mmol) in EtOH (10 mL). The reaction mixture was stirred at ambient temperature for 2 h. After evaporation the remaining residue was washed with brine (10 mL) and extracted with DCM (2 x 25 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. After evaporation of the solvent **125xe** could be isolated quantitatively as a yellow oil and was used without further purification.

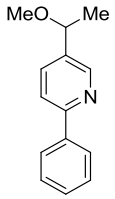
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 2.2 Hz, 1H), 8.01-7.81 (m, 2H), 7.70 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.61 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.49-7.32 (m, 3H), 4.88 (q, *J* = 6.6 Hz, 1H), 3.62 (s, 1H), 1.48 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 156.6 (C_q), 147.3 (CH), 139.8 (C_q), 139.1 (CH), 134.2 (CH), 129.0 (CH), 128.8 (CH), 127.0 (CH), 120.6 (CH), 67.7 (CH), 25.2 (CH_3).

MS (EI) *m/z* (relative intensity): 199 (45) [M^+], 184 (100), 156 (52), 127 (10), 78 (11), 43 (11).

HR-MS (EI) *m/z* calculated for $C_{13}H_{13}NO^+$: 199.0997; found: 199.0992.

Synthesis of 5-(1-Methoxyethyl)-2-phenylpyridine (126b)



To a stirred solution of the respective alcohol **125xe** (1.6 g, 8.0 mmol) in dry THF (25 mL) NaH (0.55 g of a 60% suspension in mineral oil, 13.5 mmol) was added in one portion. The reaction mixture was stirred for 8 h at ambient temperature. MeI (0.85 mL, 13.5 mmol) was added dropwise and the solution was stirred over night. After addition of aq. NH_4Cl-solution (30 mL) and separation of the organic layer, the aq. layer was extracted with EtOAc (2 x 30 mL). The combined organic phase was washed with H_2O (30 mL) and brine (30 mL) and was dried over anhydrous Na_2SO_4. Filtration, evaporation, column chromatography (*n*-hexane/EtOAc 3:2) and Kugelrohr distillation gave **126b** (1.7 g, 99%) as a yellow oil.

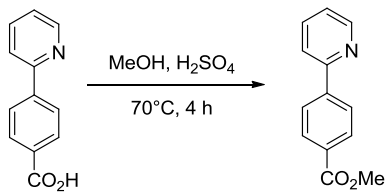
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.61 (dd, *J* = 1.6 Hz, 1H), 8.07-7.91 (m, 2H), 7.73 (d, *J* = 1.6 Hz, 2H), 7.53-7.36 (m, 3H), 4.39 (q, *J* = 6.5 Hz, 1H), 3.27 (s, 3H), 1.50 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.1 (C_q), 148.3 (CH), 139.3 (C_q), 137.2 (C_q), 134.7 (CH), 129.0 (CH), 128.9 (CH), 127.0 (CH), 120.6 (CH), 77.3 (CH), 56.7 (CH_3), 23.7 (CH_3).

MS (EI) *m/z* (relative intensity): 213 (20) [M^+], 198 (100), 182 (37), 154 (12), 127 (12), 43 (13).

HR-MS (EI) *m/z* calculated for $C_{14}H_{15}NO^+$: 213.1154; found: 213.1159.

Synthesis of Methyl-4-(pyridin-2-yl)-benzoate (6pa)[203]



[203] Deshmukh, M.; Patil, S.; Banerjee, K.; Oulkar, D.; Shripanavar, D. *Der Pharmacia Lettre* **2011**, *3*, 264–266.

To a solution of 4-(pyridin-2-yl)benzoic acid (**6ra**) (0.80 g, 4.0 mmol) in MeOH (5.0 mL) conc. H_2SO_4 (0.25 mL) was added and the reaction mixture was stirred at 70 °C for an additional 7 h. After completion of the reaction, the mixture was cooled to ambient temperature and neutralized with aq. $NaHCO_3$ (25 mL). The remaining residue was extracted with chloroform (2 × 50 mL). The solvent was removed under reduced pressure to give **6pa** (0.39 g, 46%) as an off-white solid.

M.p.: 99 °C [Lit.: 98 - 99 °C].[204]

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.72 (ddd, *J* = 4.9, 1.4, 1.3 Hz, 1H), 8.26-8.10 (m, 2H), 8.09-8.00 (m, 2H), 7.83-7.71 (m, 2H), 7.36-7.20 (m, 1H), 3.94 (s, 3H).

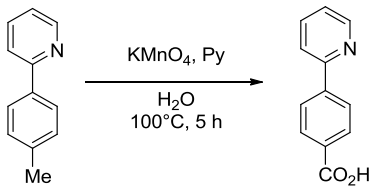
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 167.0 (C_q), 156.3 (C_q), 150.0 (CH), 143.6 (C_q), 137.1 (CH), 130.5 (C_q), 130.2 (CH), 127.0 (CH), 123.0 (CH), 121.1 (CH), 52.3 (CH_3).

MS (EI) *m/z* (relative intensity): 213 (63) [M^+], 182 (100), 154 (54), 127 (24), 77 (11).

HR-MS (EI) *m/z* calculated for $C_{13}H_{11}NO_2^+$: 213.0790; found: 213.0794.

The analytical data are in accordance with those reported in the literature.[204]

Synthesis of 4-(Pyridin-2-yl)benzoic acid (6ra)



6oa **6ra**

A solution of 2-*p*-tolylpyridine (**6oa**) (1.99 g, 11.8 mmol) and pyridine (5.9 mL) in water (30 mL) was heated at 100 °C. $KMnO_4$ (5.88 g, 37.2 mmol) was added in one portion and the reaction mixture was stirred at 100 °C for an additional 5 h. After cooling to ambient temperature, the solution was filtered and the filtrate acidified with conc. aq. HCl to pH 5. Filtration and evaporation yielded **6ra** (0.94 g, 40%) as a white solid.

M.p.: 241 °C. [Lit.: 236–238 °C].[205]

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.96 (s, 1H), 8.71 (d, *J* = 4.7 Hz, 1H), 8.49-7.65 (m, 6H), 7.41 (dd, *J* = 6.1, 6.1 Hz, 1H).

[204] Nunez, A.; Sanchez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron* **2004**, *60*, 6217–6224.
[205] Bailey, T. R. *Tetrahedron Lett*. **1986**, *27*, 4407–4410.

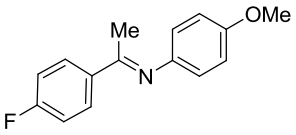
^{13}C-NMR (75 MHz, DMSO-d_6): δ = 167.0 (C_q), 154.7 (C_q), 149.5 (CH), 142.3 (C_q), 137.5 (CH), 131.1 (C_q), 129.6 (CH), 126.6 (CH), 123.3 (CH), 120.9 (CH).

MS (EI) *m/z* (relative intensity): 199 (100) [M^+], 182 (46), 154 (70), 127 (24).

HR-MS (EI) *m/z* calculated for $C_{12}H_9NO_2^+$: 199.0633; found: 199.0637.

The analytical data were in accordance with those reported in the literature.[206]

Synthesis of (*E*)-*N*-[1-(4-Fluorophenyl)ethylidene]-4-methoxyaniline (121a)



The general procedure **B** was followed using 4-fluoroacetophenone (0.71 g, 5.1 mmol) and anisidine (0.77 g, 6.3 mmol) in PhMe (25 mL). Purification by column chromatography (*n*-hexane) yielded **121a** (0.75 g, 60%) as a yellow solid.

M.r.: 75 - 81 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.97-7.92 (m, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.89 (dd, *J* = 9.0, 2.4 Hz, 2H), 6.73 (ddd, *J* = 9.0, 2.4,2.4 Hz, 2H), 3.80 (s, 3H), 2.22 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 164.3 (C_q), 164.1 (d, $J_{C\text{-}F}$ = 259 Hz, C_q), 155.9 (C_q), 144.5 (C_q), 135.8 (C_q), 129.1 (d, $J_{C\text{-}F}$ = 9 Hz, CH), 120.7 (CH), 115.1 (d, $J_{C\text{-}F}$ = 20 Hz, CH), 114.2 (CH), 55.5 (CH_3), 17.3 (CH_3).

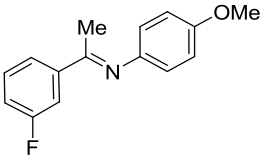
^{19}F-NMR (282 MHz, $CDCl_3$): δ = - 110.7 - -110.8 (m).

IR (ATR): $\tilde{\nu}$ = 3389, 2988, 2945, 2902, 2831, 1716, 1506, 1363, 1028, 840, 813, 729, 567cm^{-1}.

MS (EI) *m/z* (relative intensity): 243 (68) [M^+], 228 (100), 213 (5), 185 (5), 77 (5).

HR-MS (ESI) *m/z* calculated for $C_{15}H_{14}FNO+H^+$: 244.1132; found: 244.1133.

Synthesis of (*E*)-*N*-[1-(3-Fluorophenyl)ethylidene]-4-methoxyaniline (121b)



[206] Gong, Y.; Pauls, H. W. *Synlett* **2000**, 829–831.

The general procedure **B** was followed using 3-fluoroacetophenone (0.65 g, 4.7 mmol) and anisidine (0.79 g, 6.4 mmol) in PhMe (25 mL). Purification by column chromatography (*n*-hexane) yielded **121b** (0.71 g, 62%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.71-7.67 (m, 2H), 7.41-7.31 (m, 1H), 7.16-7.10 (m, 1H), 6.93-6.86 (m, 2H), 6.76-6.72 (m, 2H), 3.79 (s, 3H), 2.22 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 164.2 (C_q), 162.8 (d, $J_{C\text{-}F}$ = 246 Hz, C_q), 156.1 (C_q), 144.2 (C_q), 142.0 (C_q), 129.7 (CH), 122.7 (CH), 120.6 (CH), 117.1 (d, $J_{C\text{-}F}$ = 22 Hz, CH), 114.1 (d, $J_{C\text{-}F}$ = 23 Hz, CH), 113.8 (CH), 55.4 (CH_3), 17.3 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = -113.00 - -113.21 (m).

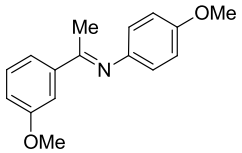
IR (ATR): $\tilde{\nu}$ = 3071, 3036, 3000, 2954, 2910, 2835, 1690, 1631, 1586, 1503, 1442, 843, 755, 686 cm^{-1}.

MS (EI) *m/z* (relative intensity): 243 (61) [M^+], 228 (100), 92 (15), 77 (19), 64 (16).

HR-MS (ESI) *m/z* calculated for $C_{15}H_{14}FNO+H^+$: 244.1138; found: 244.1133.

The analytical data are in accordance with those reported in the literature.[207]

Synthesis of (*E*)-4-Methoxy-*N*-[1-(3-methoxyphenyl)-ethylidene]aniline (121c)



The general procedure **B** was followed using 3-methoxyacetophenone (0.76 g, 5.1 mmol) and anisidine (0.79 g, 6.4 mmol) in PhMe (25 mL). Purification by column chromatography (*n*-hexane) yielded **121c** (0.91 g, 70%) as an orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.65-7.55 (m, 1H), 7.50-7.46 (m, 1H), 7.32 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.01-6.97 (m, 1H), 6.92-6.87 (m, 2H), 6.76-6.71 (m, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 2.22 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.8 (C_q), 159.9 (C_q), 156.2 (C_q), 145.0 (C_q), 141.5 (C_q), 129.5 (CH), 120.9 (CH), 120.0 (CH), 116.9 (CH), 114.5 (CH), 112.0 (CH), 55.7 (CH_3), 55.6 (CH_3), 17.7 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3069, 3033, 2969, 2912, 2840, 1735, 1692, 1635, 1592, 1506, 1235, 920, 806, 720 cm^{-1}.

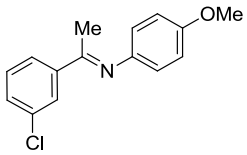
MS (EI) *m/z* (relative intensity): 255 (19) [M^+], 240 (24), 150 (62), 135 (100), 123 (26), 107 (36), 77 (27).

HR-MS (ESI) *m/z* calculated for $C_{16}H_{17}NO_2+H^+$: 256.1338; found: 256.1332.

The analytical data were in accordance with those reported in the literature.[208]

[207] Lee, P. S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 17283–17295.
[208] Moessner, C.; Bolm, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 7564–7567.

Synthesis of *(E)*-*N*-[1-(3-Chlorophenyl)-ethylidene]-4-methoxyaniline (121d)



The general procedure **B** was followed using 3-chloroacetophenone (1.54 g, 10.0 mmol) and anisidine (1.55 g, 12.5 mmol) in PhMe (25 mL). Purification by column chromatography (*n*-hexane) yielded **121d** (1.45 g, 56%) as a yellow solid.

M.r.: 66 °C [Lit.: 64 - 65 °C].

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.97 (dd, *J* = 2.9, 2.3 Hz, 1H), 7.82 (ddd, *J* = 8.0, 1.7, 1.7 Hz, 1H), 7.49-7.30 (m, 2H), 6.95-6.85 (m, 2H), 6.82-6.63 (m, 2H), 3.82 (s, 3H), 2.24 (s, 3H).

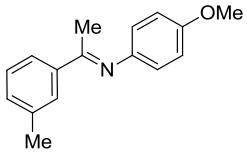
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 164.4 (C_q), 156.2 (C_q), 144.3 (C_q), 141.6 (C_q), 134.6 (C_q), 130.3 (CH), 129.6 (CH), 127.4 (CH), 125.3 (CH), 120.8 (CH), 114.4 (CH), 55.5 (CH_3), 17.4 (CH_3).

MS (EI) *m/z* (relative intensity): 259 (53) [M^+], 244 (100), 148 (15), 92 (15), 64 (13), 43 (40).

HR-MS (EI) *m/z* calculated for $C_{15}H_{14}ClNO^+$: 259.0764; found: 259.0755.

The analytical data are in accordance with those reported in the literature.[209]

Synthesis of (*E*)-4-Methoxy-*N*-(1-*m*-tolylethylidene)aniline (121e)



General procedure **B** was followed using 3-methylacetophenone (0.70 g, 5.2 mmol) and anisidine (0.78 g, 6.3 mmol) in PhMe (25 mL). Purification by column chromatography (*n*-hexane) yielded **121e** (0.59 g, 47%) as a yellow solid.

M.p.: 59 - 61 °C. [Lit.: 60 - 62 °C].[210]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.84 (s, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.37-7.21 (m, 2H), 6.90 (ddd, *J* = 9.3, 2.2, 2.2 Hz, 2H), 6.77 (ddd, *J* = 9.3, 2.2, 2.2 Hz, 2H), 3.78 (s, 3H), 2.41 (s, 3H), 2.23 (s, 3H).

[209] Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem. Int. Ed.* **2009**, *48*, 2925–2928.
[210] Chen, F.; Ding, Z.; He, Y.; Qin, J.; Wang, T.; Fan, Q.-H. *Tetrahedron* **2012**, *68*, 5248–5257.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.5 (C_q), 155.6 (C_q), 144.5 (C_q), 139.4 (C_q), 137.6 (C_q), 130.8 (CH), 127.9 (CH), 127.3 (CH), 124.1 (CH), 120.5 (CH), 113.9 (CH), 55.2 (CH_3), 21.3 (CH_3), 17.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2983, 2926, 2839, 1668, 1504, 1284, 1237, 1054, 1036, 840, 754, 695 cm^{-1}.

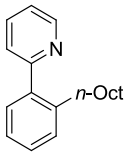
MS (EI) *m/z* (relative intensity): 239 (50) [M^+], 224 (100), 148 (10), 92 (12), 77 (16), 64 (13).

HR-MS (ESI) *m/z* calculated for $C_{16}H_{17}NO+H^+$: 240.1383; found: 240.1383.

The analytical data were in accordance with those reported in the literature.[210]

7.2 The Analytical Data for the Products of the Ruthenium-Catalyzed *ortho*-Alkylation

Synthesis of 2-(2-*n*-Octylphenyl)pyridine (93aa)

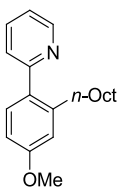


The general procedure **C** was followed using **6aa** (75.6 mg, 0.49 mmol), **42aa** (291 mg, 1.51 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 2.5 mol %) and 1-$AdCO_2H$ (**13c**) (27 mg, 0.15 mmol, 31 mol %) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 15:1) yielded **93aa** (86 mg, 66%) as a colorless oil.

The general procedure **C** was followed using **6aa** (81.6 mg, 0.53 mmol), **42aa** (285 mg, 1.47 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 2.4 mol %) in *m*-xylene (2.0 mL) with KOPiv (20.7 mg, 0.15 mmol) and K_2CO_3 (138 g, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **93aa** (72 mg, 51%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.68 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.71 (td, *J* = 7.7, 1.8 Hz, 1H), 7.54-7.02 (m, 6H), 2.75-2.67 (m, 2H), 1.46-1.43 (m, 2H), 1.36-0.98 (m, 10H), 0.85 (t, *J* = 7.0 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.1 (C_q), 148.8 (CH), 140.5 (C_q), 140.1 (C_q), 135.7 (CH), 129.5 (CH), 129.4 (CH), 128.0 (CH), 125.4 (CH), 123.8 (CH), 121.3 (CH), 32.8 (CH_2), 31.7 (CH_2), 31.1 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 22.5 (CH_2), 14.0 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3059, 2925, 2854, 1586, 1562, 1468, 1425, 751, 449, 420 cm^{-1}.
MS (EI) *m/z* (relative intensity): 267 (31) [M^+], 182 (100), 167 (41).
HR-MS (ESI) *m/z* calculated for $C_{19}H_{25}N+H^+$: 268.2065; found: 268.2060.
The analytical data are in accordance with those reported in the literature.[121]

Synthesis of 2-(4-Methoxy-2-*n*-octylphenyl)-pyridine (93ba)

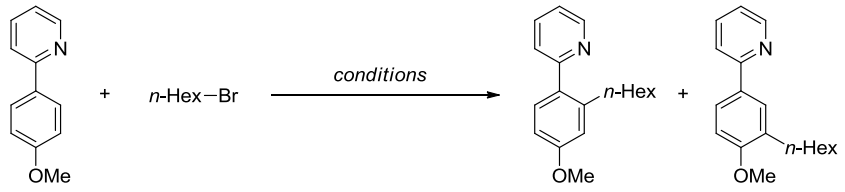


The general procedure **C** was followed using **6ba** (90.0 mg, 0.49 mmol), **42aa** (285 mg, 1.47 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (7.9 mg, 2.6 mol %), in H_2O (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **93ba** (88 mg, 61%) as a colorless oil.

The general procedure **E** was followed using [Ru(*p*-cymene)($MesCO_2$){2-(4-methoxyphenyl)pyridyl}] (**14a**) (15.3 mg, 5.0 mol %), K_2CO_3 (140 mg, 1.01 mmol), **6ba** (95.2 mg, 0.52 mmol) and **42aa** (284 mg, 1.47 mmol) in NMP (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 15:1) yielded **93ba** (91 mg, 59%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.70 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.40-7.26 (m, 2H), 7.20 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 6.96-6.63 (m, 2H), 3.83 (s, 3H), 2.80-2.56 (m, 2H), 1.52-1.36 (m, 2H), 1.31-1.06 (m, 10H), 0.86 (t, *J* = 6.9 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.8 (C_q), 159.2 (C_q), 149.4 (CH), 142.5 (C_q), 135.8 (CH), 133.0 (C_q), 125.6 (CH), 121.6 (2xCH), 112.0 (2xCH), 55.3 (CH_3), 33.9 (CH_2), 32.0 (CH_2), 31.1 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 22.8 (CH_2), 14.24 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3003, 2954, 2923, 1852, 1606, 1587, 1426, 1377, 1277, 1234, 786, 747 cm^{-1}.
MS (EI) *m/z* (relative intensity): 297 (56) [M^+], 226 (12), 212 (100), 197 (41), 168 (12), 154 (22).
HR-MS (ESI) *m/z* calculated for $C_{20}H_{27}NO^+$: 297.2093; found: 297.2100.
The analytical data are in accordance with those reported in the literature.**Fehler! Textmarke nicht efiniert.**

Synthesis of 2-(2-*n*-Hexyl-4-methoxyphenyl)pyridine (93bb) and 2-(3-*n*-Hexyl-4-methoxyphenyl)-pyridine (93bb')



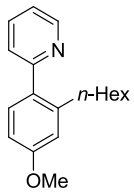
6ba **42ab** **93bb** **93bb'**

The general procedure **C** was followed using $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 2.5 mol %), $MesCO_2H$ (**13a**) (24 mg, 0.15 mmol, 29 mol %), methoxyphenylpyridine **6ba** (94.0 mg, 0.51 mmol) and **42ab** (236 mg, 1.43 mmol) in H_2O (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 15:1) yielded **93bb** (62 mg, 45%) and **93bb'** (9 mg, 7%) as colorless oils.

The general procedure **C** was followed using $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 2.5 mol %), 1-AdCO_2H (**13c**) (24 mg, 0.15 mmol), **6ba** (95.0 mg, 0.51 mmol) and **42ab** (237 mg, 1.44 mmol) in NMP (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 15:1) yielded **93bb** (66 mg, 48%).

The general procedure **E** was followed using [Ru(*p*-cymene)(MesCO_2){2-(4-methoxyphenyl)pyridyl}] **14a** (15.3 mg, 5.0 mol%), K_2CO_3 (140 mg, 1.01 mmol), **6ba** (97.7 mg, 0.53 mmol) and **42ab** (278 mg, 1.68 mmol) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 15:1) yielded **93bb** (100 mg, 70%).

The general procedure **C** was followed using $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 2.5 mol %), **6ba** (94.5 mg, 0.51 mmol) and **42ab** (246 mg, 1.48 mmol) in *m*-xylene (2.0 mL) with KOAc (319 mg, 3.25 mmol). Purification by column chromatography (*n*-hexane/EtOAc 15:1) yielded **93bb** (67 mg, 49%).



(93bb)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.63 (d, *J* = 4.7 Hz, 1H), 7.68 (ddd, *J* = 7.7, 1.9, 1.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.20-7.15 (m, 1H), 6.82 (d, *J* = 2.6 Hz, 1H), 6.78 (dd, *J* = 8.4, 2.7 Hz, 1H), 3.82 (s, 3H), 2.75-2.62 (m, 2H), 1.49-1.34 (m, 2H), 1.22-1.07 (m, 6H), 0.79 (t, *J* = 7.1 Hz, 3H).

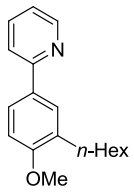
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.0 (C_q), 159.4 (C_q), 149.0 (CH), 142.4 (C_q), 135.9 (CH), 133.1 (C_q), 131.0 (CH), 124.1 (CH), 121.2 (CH), 115.2 (CH), 110.9 (CH), 55.2 (CH_3), 33.1 (CH_2), 31.4 (CH_2), 31.1 (CH_2), 29.0 (CH_2), 22.4 (CH_2), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2927, 2855, 1587, 1505, 1465, 1427, 1280, 1236, 1162, 1045 cm^{-1}.

MS (EI) *m/z* (relative intensity): 269 (33) [M^+], 226 (9), 212 (100), 197 (18), 154 (10).

HR-MS (ESI) *m/z* calculated for $C_{18}H_{23}NO+H^+$: 270.1858; found: 270.1852.

The analytical data are in accordance with those reported in the literature.**Fehler! Textmarke nicht efiniert.**



(93bb')

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.63 (d, *J* = 4.6 Hz, 1H), 7.83-7.74 (m, 2H), 7.60-7.47 (m, 2H), 7.10 (m, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 3.81 (s, 3H), 2.72-2.59 (m, 2H), 1.65-1.54 (m, 2H), 1.41-1.25 (m, 6H), 0.86 (t, *J* = 7.0 Hz, 3H).

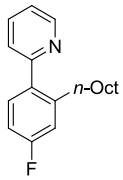
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.4 (C_q) , 157.4 (C_q), 149.4 (CH), 136.6 (CH), 131.7 (C_q), 131.5 (C_q), 128.4 (CH), 125.4 (CH), 121.2 (CH), 119.9 (CH), 110.3 (CH), 55.4 (CH_3), 31.8 (CH_2), 30.4 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3176, 3003, 2954, 1606, 1587, 1426, 1279, 1149, 1129, 1019 cm^{-1}.

MS (EI) *m/z* (relative intensity): 269 (77) [M^+], 226 (16), 198 (100), 168 (65), 154 (19), 43 (15).

HR-MS (ESI) *m/z* calculated for $C_{18}H_{23}NO^+$: 269.1780; found: 269.1780.

Synthesis of 2-(4-Fluoro-2-*n*-octylphenyl)pyridine (93ca)



The general procedure **C** was followed using **6ca** (120 mg, 0.69 mmol), **42aa** (280 mg, 1.45 mmol), $[RuCl_2(p\text{-cymene})]_2$ (8.0 mg, 1.9 mol %), KOAc (20.6 mg, 0.21 mmol, 30 mol %) and K_2CO_3 (190.7 mg, 1.38 mmol) in H_2O (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **93ca** (118 mg, 60%) as a colorless oil.

ortho-Alkylations of (*p*-fluorophenyl)pyridine (**6ca**) with *n*-octyl bromide according to The general procedure **C** in H_2O, *m*-xylene/H_2O (2.0 mL, 1:1), NMP/H_2O (2.0 mL, 1:1) or neat furnished the product **93ca** in 66, 68, 53 and 63% isolated yield, respectively.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.71-8.56 (m, 1H), 7.71 (ddd, *J* = 7.7, 1.9, 1.8 Hz, 1H), 7.41-7.28 (m, 2H), 7.26-7.16 (m, 1H), 7.06-6.86 (m, 2H), 2.74-2.58 (m, 2H), 1.55-1.32 (m, 2H), 1.31-1.07 (m, 10H), 0.96-0.67 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.8 (d, $J_{C\text{-}F}$ = 247 Hz, C_q), 159.5 (C_q), 149.3 (CH) , 143.6 (d, $J_{C\text{-}F}$ = 7 Hz, C_q), 136.5 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 136.2 (CH), 131.5 (d, $J_{C\text{-}F}$ = 8 Hz, CH), 124.2 (CH), 121.8 (CH), 116.2 (d, $J_{C\text{-}F}$ = 21 Hz, CH), 112.6 (d, $J_{C\text{-}F}$ = 21 Hz, CH), 33.0 (d, $J_{C\text{-}F}$ = 2 Hz, CH), 31.9 (CH_2), 31.0 (CH_2), 31.0 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 22.7 (CH_2), 14.2 (CH_3).

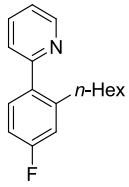
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -107.80 - -124.10 (m).

IR (ATR): $\tilde{\nu}$ = 2954, 2924, 2854, 1588, 1501, 1465, 1219, 1114, 870, 822, 747, 566 cm^{-1}.

MS (EI) *m/z* (relative intensity): 285 (39) [M^+], 256 (10), 214 (11), 200 (100), 185 (67).

HR-MS (ESI) *m/z* calculated for $C_{19}H_{24}FN+H^+$: 286.1971; found: 286.1970.

Synthesis of 2-(4-Fluoro-2-*n*-hexylphenyl)pyridine (93cb)



The general procedure **C** was followed using **6ca** (83.9 mg, 0.48 mmol), **42ab** (247 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.3 mg, 2.5 mol %), $MesCO_2H$ (**13a**) (24.3 mg, 0.15 mmol, 30 mol %) and K_2CO_3 (139 mg, 1.01 mmol) in H_2O (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **93cb** (82 mg, 66%) as a colorless oil.

The general procedure **C** was followed using **6ca** (87.1 mg, 0.50 mmol), **42ab** (255 mg, 1.54 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.9 mg, 2.6 mol%), KOAc (314.1 mg, 3.2 mmol) and K_2CO_3 (138 mg, 1.00 mmol) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **93cb** (98 mg, 76%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.65 (ddd, J = 4.8, 1.9, 0.9 Hz, 1H), 7.70 (ddd, J = 7.7, 1.8, 1.7 Hz, 1H), 7.35-7.14 (m, 3H), 7.02-6.84 (m, 2H), 2.74-2.57 (m, 2H), 1.53-1.32 (m, 2H), 1.25-1.04 (m, 6H), 0.80 (t, J = 8.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.8 (d, $J_{C\text{-}F}$ = 247 Hz, C_q), 159.5 (C_q), 149.3 (CH), 143.6 (d, $J_{C\text{-}F}$ = 8 Hz, C_q), 136.5 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 136.3 (CH), 131.5 (d, $J_{C\text{-}F}$ = 8 Hz, CH), 124.2 (CH), 121.8 (CH), 116.2 (d, $J_{C\text{-}F}$ = 21 Hz, CH), 112.7 (d, $J_{C\text{-}F}$ = 21 Hz, CH), 33.1 (d, $J_{C\text{-}F}$ = 1 Hz, CH_2), 31.5 (CH_2), 31.0 (CH_2), 29.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

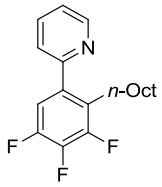
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -114.28 - -114.60 (m).

IR (ATR): $\tilde{\nu}$ = 2955, 2926, 2856, 1608, 1588, 1465, 1427, 1269, 1150, 868, 822, 565 cm^{-1}.

MS (EI) *m/z* (relative intensity): 257 (42) [M^+], 214 (16), 200 (100), 185 (64).

HR-MS (EI) *m/z* calculated for $C_{17}H_{20}FN-H^+$: 256.1502; found: 256.1503.

Synthesis of 2-(3,4,5-Trifluoro-2-*n*-octylphenyl)pyridine (93ja)



The general procedure **C** was followed using **6ja** (106 mg, 0.51 mmol), **42aa** (295 mg, 1.53 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 2.5 mol %), 1-$AdCO_2H$ (**13c**) (27.6 mg, 0.15 mmol, 30 mol %) and K_2CO_3 (141 mg, 1.02 mmol) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **93ja** (142 mg, 87%) as a colorless oil.

The general procedure **C** was followed using **6ja** (103 mg, 0.49 mmol), **42aa** (280 mg, 1.45 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 2.6 mol %), KOAc (320 mg, 3.26 mmol, 6.4 equiv) and K_2CO_3 (138 mg, 1.00 mmol) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **93ja** (115 mg, 73%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.74-8.58 (m, 1H), 7.75 (ddd, *J* = 7.7, 1.8, 1.7 Hz, 1H), 7.35-7.17 (m, 2H), 6.98 (ddd, *J* = 10.6, 7.2, 2.2 Hz, 1H), 2.76-2.58 (m, 2H), 1.50-1.33 (m, 2H), 1.33-1.01 (m, 10H), 0.84 (t, *J* = 7.5 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 157.5 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 151.1 (ddd, $J_{C\text{-}F}$ = 100, 10, 4 Hz, C_q), 149.5 (CH), 147.8 (ddd, *J* = 100, 10, 4 Hz, C_q), 139.8 (ddd, $J_{C\text{-}F}$ = 252, 17, 15 Hz, C_q), 136.6 (CH), 136.4-135.7 (m, C_q), 126.3 (ddd, $J_{C\text{-}F}$ = 14, 4, 1 Hz, C_q), 124.0 (CH), 122.6 (CH) , 113.3 (dd, $J_{C\text{-}F}$ = 18, 4 Hz, CH), 31.9 (CH_2), 30.1 (d, $J_{C\text{-}F}$ = 1 Hz, CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 25.7 (t, $J_{C\text{-}F}$ = 2 Hz, CH_2), 22.7 (CH_2), 14.1 (CH_3).

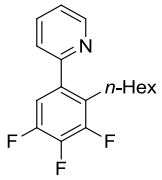
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -136.87 - -138.10 (m), -138.75 (ddd, *J* = 21, 11, 6 Hz), -160.99 (td, *J* = 21, 7 Hz).

IR (ATR): $\tilde{\nu}$ = 3059, 2955, 2925, 2855, 1567, 1515, 1425, 1359, 1151, 1035, 792, 733 cm^{-1}.

MS (EI) *m/z* (relative intensity): 321 (41) [M^+], 292 (10), 245 (12), 236 (100), 221 (76).

HR-MS (EI) *m/z* calculated for $C_{19}H_{22}F_3N^+$: 321.1704; found: 321.1703.

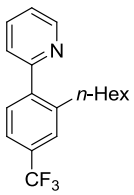
Synthesis of 2-(3,4,5-Trifluoro-2-*n*-hexylphenyl)pyridine (93jb)



The general procedure **C** was followed using **6ja** (105 mg, 0.50 mmol), **42ab** (259 mg, 1.57 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 2.5 mol %), KOAc (314 mg, 3.20 mmol, 6.4 equiv) and K_2CO_3 (138 mg, 1.00 mmol) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **93i** (70 mg, 48%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.67 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.76 (ddd, *J* = 7.8, 1.9, 1.8 Hz, 1H), 7.39-7.26 (m, 2H), 6.99 (ddd, *J* = 10.5, 7.2, 2.2 Hz, 1H), 2.78-2.59 (m, 2H), 1.41 (ddd, *J* = 10.0, 7.5, 5.6 Hz, 2H), 1.29-1.04 (m, 6H), 0.81 (t, *J* = 7.7 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.5 (C_q), 150.5 (ddd, $J_{C\text{-}F}$ = 167, 10, 4 Hz, C_q), 149.5 (CH), 148.5 (ddd, $J_{C\text{-}F}$ = 168, 10, 4 Hz, C_q), 139.9 (ddd, $J_{C\text{-}F}$ = 252, 17, 15 Hz, C_q), 136.6 (CH), 136.2 (dt, $J_{C\text{-}F}$ = 7, 5 Hz, C_q), 126.3 (ddd, $J_{C\text{-}F}$ = 14, 4, 1 Hz, C_q), 124.1 (CH), 122.6 (CH), 113.3 (dd, $J_{C\text{-}F}$ = 18, 4 Hz, CH), 31.4 (CH_2), 30.1 (CH_2), 29.1 (CH_2), 25.7 (CH_2), 22.5 (CH_2), 14.1 (CH_3).
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -136.87 - -138.10 (m), -138.75 (ddd, *J* = 21, 11, 6 Hz), -160.99 (td, *J* = 21, 7 Hz).
IR (ATR): $\tilde{\nu}$ = 2957, 2928, 2857, 1515, 1468, 1443, 1359, 1117, 1059, 791, 747, 665 cm^{-1}.
MS (EI) *m/z* (relative intensity): 292 (24) [M^+], 250 (14), 236 (100), 221 (79).
HR-MS (EI) *m/z* calculated for $C_{17}H_{18}F_3N$-H^+: 292.1313; found: 292.1324.

Synthesis of 2-[2-*n*-Hexyl-4-(trifluoromethyl)phenyl]pyridine (93kb)



The general procedure **C** was followed using **6ka** (113 mg, 0.51 mmol), **42ab** (243 mg, 1.47 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 2.5 mol %), 1-AdCO_2H (**13c**) (28 mg, 0.15 mmol, 30 mol %) and K_2CO_3 (141 mg, 1.02 mmol) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 5:1) yielded **93ka** (119 mg, 76%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.79-8.56 (m, 1H), 7.77 (ddd, *J* = 7.7, 2.1, 0.9 Hz, 1H), 7.59-7.21 (m, 5H), 2.80-2.64 (m, 2H), 1.56-1.34 (m, 2H), 1.31-1.04 (m, 6H), 0.81 (t, *J* = 7.7 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.9 (C_q), 149.3 (CH), 143.6 (C_q), 141.8 (C_q), 136.3 (CH), 130.5 (q, J_{C-F} = 32 Hz, C_q), 130.1 (CH), 126.4 (d, *J* = 4 Hz, CH), 124.2 (q, J_{C-F} = 272 Hz, C_q), 123.9 (CH), 122.5 (d, *J* = 4 Hz, CH), 122.2 (CH), 32.9 (CH_2), 31.4 (CH_2), 30.9 (CH_2), 29.0 (CH_2), 22.4 (CH_2), 13.9 (CH_3).

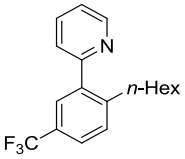
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -62.55 (s).

IR (ATR): $\tilde{\nu}$ = 2956, 2928, 2858, 1587, 1505, 1328, 1162, 1120, 1091, 791 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 637 (20) [2×M+Na^+], 615 (80), 308 (100), 204 (26).

HR-MS (ESI) *m/z* calculated for $C_{18}H_{20}F_3N+H^+$: 308.1621; found: 308.1625.

Synthesis of 2-[2-*n*-Hexyl-5-(trifluoromethyl)phenyl]pyridine (93mb)



The general procedure **C** was followed using **6ma** (110 mg, 0.49 mmol), **42ab** (246 mg, 1.49 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.5 mg, 2.5 mol %), 1-AdCO_2H (**13c**) (28 mg, 0.15 mmol, 31 mol%) and K_2CO_3 (138 mg, 1.00 mmol) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 5:1) yielded **93f** (79 mg, 52%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.77-8.62 (m, 1H), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H), 7.63-7.49 (m, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.32-7.18 (m, 1H), 2.72 (dd, *J* = 9.1, 6.7 Hz, 2H), 1.57-1.34 (m, 2H), 1.27-1.02 (m, 6H), 0.80 (t, *J* = 6.6 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.0 (C_q), 149.5 (CH), 145.2 (d, J_{C-F} = 2 Hz, C_q), 140.9 (C_q), 136.5 (CH), 130.3 (CH), 128.2 (q, J_{C-F} = 32 Hz, C_q), 126.8 (q, J_{C-F} = 4 Hz, CH), 125.0 (q, J_{C-F} = 4 Hz, CH), 124.4 (q, J_{C-F} = 273 Hz, C_q), 124.2 (CH), 122.3 (CH), 33.0 (CH_2), 31.5 (CH_2), 31.1 (CH_2), 29.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

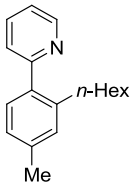
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -62.30 (s).

IR (ATR): $\tilde{\nu}$ = 2956, 2928, 2857, 1467, 1334, 1259, 1119, 1057, 747 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 637 (81) [2×M+Na^+], 616 (100), 330 (64), 308 (54).

HR-MS (ESI) *m/z* calculated for $C_{18}H_{20}F_3N+H^+$: 308.1621; found: 308.1619.

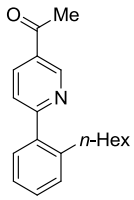
Synthesis of 2-(2-*n*-Hexyl-4-methylphenyl)pyridine (93ob)



The general procedure **C** was followed using **6oa** (88.5 mg, 0.52 mmol), **42ab** (250 mg, 1.51 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (8.0 mg, 2.5 mol %), KOAc (319 mg, 3.25 mmol) and K_2CO_3 (143 mg, 1.04 mmol) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **93ob** (20 mg, 15%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.70 (dt, *J* = 7.7, 1.9 Hz, 1H), 7.34 (td, *J* = 7.8, 1.0 Hz, 1H), 7.25-7.17 (m, 2H), 7.12-7.03 (m, 2H), 2.66 (dd, *J* = 8.1, 7.8 Hz, 2H), 2.36 (s, 3H), 1.48-1.37 (m, 2H), 1.26-1.10 (m, 6H), 0.81 (t, *J* = 6.5 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.3 (C_q), 149.0 (CH), 140.6 (C_q), 137.9 (C_q), 137.5 (C_q), 135.9 (CH), 130.4 (CH), 129.7 (CH), 126.4 (CH), 124.1 (CH), 121.3 (CH), 32.9 (CH_2), 31.5 (CH_2), 31.3 (CH_2), 29.1 (CH_2), 22.5 (CH_2), 21.2 (CH_3), 14.0 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2954, 2925, 2855, 1613, 1586, 1466, 1426, 1026, 823, 787, 748 cm^{-1}.
MS (EI) *m/z* (relative intensity): 253 (20) [M^+], 210 (4), 196 (100), 181 (45), 167 (10), 97 (5).
HR-MS (ESI) *m/z* calculated for $C_{18}H_{23}N+H^+$: 254.1909; found: 254.1902.
The analytical data are in accordance with those reported in the literature.**Fehler! Textmarke nicht efiniert.**

Synthesis of 1-[6-(2-*n*-Hexylphenyl)pyridin-3-yl]ethanone (94bb)

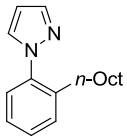


The general procedure **C** was followed using **6bb** (94.5 mg, 0.48 mmol), **42ab** (235 mg, 1.42 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 2.7 mol %), 1-AdCO_2H (**13c**) (28 mg, 0.15 mmol, 31 mol %) and K_2CO_3 (133 mg, 0.96 mmol) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 3:2) yielded **94bb** (81 mg, 60%) as a light brown oil.

The general procedure **C** was followed using 1-[6-(2-hexylphenyl)-pyridin-3-yl]-ethanol (**125b**) (101 mg, 0.51 mmol), **42ab** (253 mg, 1.53 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 2.5 mol %), 1-$AdCO_2H$ (**13c**) (28 mg, 0.15 mmol, 30 mol %) and K_2CO_3 (141 mg, 1.02 mmol) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 5:1 to 1:1) yielded **94bb** (15 mg, 10%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.21 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.27 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.48 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.40-7.17 (m, 4H), 2.77-2.58 (m, 5H), 1.55-1.35 (m, 2H), 1.26-1.05 (m, 6H), 0.79 (t, *J* = 6.8 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 196.7 (C_q), 164.5 (C_q), 149.6 (CH), 141.1 (C_q), 139.4 (C_q), 135.8 (CH), 130.3 (C_q), 130.1 (CH), 129.8 (CH), 129.1 (CH), 126.0 (CH), 124.1 (CH), 33.1 (CH_2), 31.6 (CH_2), 31.4 (CH_2), 29.2 (CH_2), 26.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2954, 2925, 2855, 1686, 1588, 1550, 1466, 1371, 1259, 1087, 750 cm^{-1}.
MS (EI) *m/z* (relative intensity): 281 (26) [M^+], 238 (10), 224 (100), 209 (30), 180 (10), 167 (14).
HR-MS (EI) *m/z* calculated for $C_{19}H_{23}NO^+$: 281.1780; found: 281.1777.

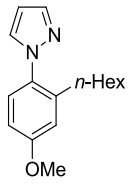
Synthesis of 1-(2-*n*-Octylphenyl)-1*H*-pyrazole (118a)



The general procedure **C** was followed using **87a** (72.1 mg, 0.50 mmol), **42aa** (296 mg, 1.53 mmol), $RuCl_2(p\text{-cymene})]_2$ (7.9 mg, 2.6 mol %), 1-$AdCO_2H$ (**13c**) (27.7 mg, 0.15 mmol, 30 mol %) and K_2CO_3 (139 mg, 1.01 mmol) in H_2O (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **118a** (85 mg, 62%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 1.9 Hz, 1H), 7.55 (d, *J* = 2.3 Hz, 1H), 7.37-7.28 (m, 2H), 7.29-7.20 (m, 2H), 6.41 (dd, *J* = 2.1, 2.1 Hz, 1H), 2.56-2.44 (m, 2H), 1.40 (s, 1H), 1.19 (d, *J* = 4.6 Hz, 11H), 0.85 (t, *J* = 6.8 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 140.2 (CH), 139.8 (C_q), 139.1 (C_q), 130.8 (CH), 130.4 (CH), 128.7 (CH), 126.7 (CH), 126.5 (CH), 106.2 (CH), 31.9 (CH_2), 31.4 (CH_2), 30.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 22.8 (CH_2), 14.2 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2953, 2923, 2854, 1516, 1456, 1393, 1043, 938, 746, 623 cm^{-1}.
MS (EI) *m/z* (relative intensity): 256 (24) [M^+], 185 (10), 171 (100), 158 (19), 130 (17).
HR-MS (EI) *m/z* calculated for $C_{17}H_{24}N_2$-H^+: 255.1861; found: 255.1860.

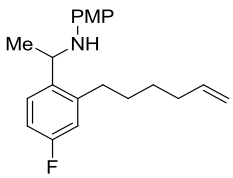
Synthesis of 1-(2-*n*-Hexyl-4-methoxyphenyl)-1*H*-pyrazole (118b)



The general procedure **C** was followed using **87b** (86.9 mg, 0.50 mmol), **42ab** (237 mg, 1.44 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.3 mg, 2.4 mol %), KOAc (314 mg, 3.2 mmol, 6.4 equiv) and K_2CO_3 (138 mg, 1.00 mmol) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **118b** (67 mg, 52%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 1.8 Hz, 1H), 7.51 (dd, *J* = 2.3, 0.6 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 6.83 (d, *J* = 2.8 Hz, 1H), 6.77 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.40 (dd, *J* = 2.1, 2.0 Hz, 1H), 3.83 (s, 3H), 2.51-2.40 (m, 2H), 1.51-1.33 (m, 2H), 1.33-1.08 (m, 6H), 0.83 (t, *J* = 7.5 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.7 (C_q), 140.9 (C_q), 140.0 (CH), 133.2 (C_q), 131.1 (CH), 128.0 (CH), 115.4 (CH), 111.4 (CH), 105.9 (CH), 55.6 (CH_2), 31.6 (CH_2), 31.6 (CH_2), 30.6 (CH_2), 29.2 (CH_2), 22.6 (CH_2), 14.1 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2955, 2927, 2856, 1503, 1464, 1235, 1041, 943, 810, 747, 612 cm^{-1}.
MS (EI) *m/z* (relative intensity): 258 (62) [M^+], 215 (19), 201 (100), 188 (28), 160 (14).
HR-MS (ESI) *m/z* calculated for $C_{16}H_{22}N_2O^+$: 258.1732; found: 258.1731.

Synthesis of *N*-{1-[4-Fluoro-2-(hex-5-en-1-yl)phenyl]ethyl}-4-methoxyaniline (122a)



The general procedure **D** was followed using 4-flouro-*N*-(1-phenylethylidene)-aniline (**121a**) (124 mg, 0.51 mmol), 1-bromohex-5-ene (**32f**) (247 mg, 1.51 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 2.5 mol %), 1-$AdCO_2H$ (**13c**) (28 mg, 0.15 mmol, 30 mol %) in *m*-xylene (2.0 mL). Reduction and purification by column chromato-graphy (*n*-hexane/EtOAc 9:1) yielded **122a** (104 mg, 62%) as a red oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.45 (dd, *J* = 8.5, 6.0 Hz, 1H), 6.95-6.76 (m, 2H), 6.76-6.59 (m, 2H), 6.46 (d, *J* = 9.1 Hz, 2H), 5.82 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.14-4.85 (m, 2H), 4.61 (q, *J* = 6.6 Hz, 1H), 3.71 (s, 3H), 2.70 (td, *J* = 7.3, 3.9 Hz, 2H), 2.23-1.99 (m, 3H), 1.81-1.59 (m, 2H), 1.59-1.41 (m, 5H).

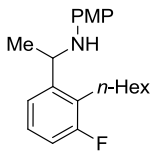
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.8 (d, J_{C-F} = 244 Hz, C_q), 152.5 (C_q), 141.7 (d, J_{C-F} = 7 Hz, C_q), 140.7 (C_q), 138.7 (CH), 137.9 (C_q), 130.7 (CH), 127.0 (d, J_{C-F} = 8 Hz, CH), 125.9 (CH), 116.0 (d, J_{C-F} = 21 Hz, CH), 115.1 (CH), 114.9 (CH), 114.8 (CH_2), 113.3 (d, J_{C-F} = 21 Hz, CH), 55.8 (CH_3), 50.4 (CH), 33.7 (CH_2), 32.0 (CH_2), 30.4 (CH_2), 29.0 (CH_2), 24.1 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$) δ = -116.75 (s).

MS (EI) *m/z* (relative intensity): 327 (10) [M^+], 150 (28), 137 (57), 123 (100), 108 (24), 55 (23).

HR-MS (EI) *m/z* calculated for $C_{21}H_{26}FNO^+$: 327.1998; found: 327.2000.

Synthesis of *N*-[1-(3-Fluoro-2-*n*-hexylphenyl)ethyl]-4-methoxyaniline (122b)



The general procedure **D** was followed using *N*-[1-(3-fluorophenyl)ethylidene]-4-methoxyaniline (**121b**) (122 mg, 0.50 mmol), **42ab** (244 mg, 1.48 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 2.5 mol %), 1-AdCO_2H (**13c**) (27 mg, 0.15 mmol, 30 mol %) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **122b** (122 mg, 74%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 7.7 Hz, 1H), 7.11 (dd, *J* = 8.3, 6.1 Hz, 1H), 6.90 (ddd, *J* = 8.3, 1.7, 1.7 Hz, 1H), 6.71 (d, *J* = 8.9 Hz, 2H), 6.44 (d, *J* = 8.9 Hz, 2H), 4.64 (q, *J* = 6.6 Hz, 1H), 3.71 (s, 3H), 2.87-2.64 (m, 2H), 1.74-1.55 (m, 2H), 1.53-1.23 (m, 9H), 0.92 (t, *J* = 7.0 Hz, 3H).

(N–H was not detected)

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.3 (d, J_{C-F} = 243 Hz, C_q), 151.9 (C_q), 145.0 (C_q), 141.2 (C_q), 127.2 (d, J_{C-F} = 8 Hz, CH), 126.8 (d, J_{C-F} = 16 Hz, C_q), 120.4 (2xCH), 114.7 (2xCH), 114.4 (CH), 113.4 (d, J_{C-F} = 22 Hz, CH), 55.7 (CH_3), 50.2 (CH), 31.7 (CH_2), 30.4 (CH_2), 29.7 (CH_2), 24.9 (CH_2), 24.3 (CH_3), 22.7 (CH_2), 14.1 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = -117.75 - -117.54 (m).

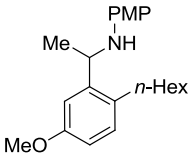
IR (ATR): $\tilde{\nu}$ = 3403, 2960, 2930, 2871, 2859, 2244, 1579, 1512, 1464, 1238, 1040, 910, 739 cm^{-1}.

MS (EI) *m/z* (relative intensity): 329 (17) [M^+], 314 (18), 150 (12), 136 (47), 123 (100), 108 (25).

HR-MS (ESI) *m/z* calculated for $C_{21}H_{28}FNO+H^+$: 330.2233; found: 330.2227.

Synthesis of *N*-[1-(2-*n*-Hexyl-5-methoxyphenyl)ethyl]-4-methoxyaniline (122c) and *N*-[1-(2-*n*-Hexyl-3-methoxyphenyl)ethyl]-4-methoxyaniline (122c')

The general procedure **D** was followed using 4-methoxy-*N*-[1-(3-methoxyphenyl)ethylidene]aniline (**121c**) (117 mg, 0.46 mmol), **42ab** (248 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.0 mg, 2.5 mol %), 1-$AdCO_2H$ (**13c**) (24.9 mg, 0.138 mmol, 30 mol %) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **122c** (60 mg, 38%) and **122c'** (31 mg, 20%) as colorless oils.



(122c)

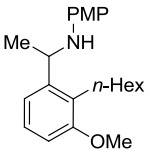
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 8.7 Hz, 1H), 7.02 (d, *J* = 2.8 Hz, 1H), 6.72 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.68 (d, *J* = 8.9 Hz, 2H), 6.43 (d, *J* = 8.9 Hz, 2H), 4.60 (q, *J* = 6.6 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.66 (dt, *J* = 8.7, 4.2 Hz, 2H), 1.71-1.56 (m, 2H), 1.45 (d, *J* = 6.6 Hz, 3H), 1.43-1.23 (m, 6H), 0.91 (t, *J* = 6.9 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.1 (C_q), 151.7 (C_q), 144.0 (C_q), 141.5 (C_q), 131.3 (C_q), 130.4 (CH), 114.7 (CH), 114.3 (CH), 111.6 (CH), 110.6 (CH), 55.7 (CH_3), 55.1 (CH_3), 50.3 (CH), 31.8 (CH_2), 31.5 (CH_2), 31.5 (CH_2), 29.5 (CH_2), 24.2 (CH_3), 22.7 (CH_2), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2985, 2940, 2899, 1741, 1514, 1456, 1373, 1241, 1097, 1047, 847 cm^{-1}.

MS (EI) *m/z* (relative intensity): 341 (50) [M^+], 326 (21), 227 (14), 218 (100), 175 (38), 149 (78), 123 (39), 105 (17).

HR-MS (EI) *m/z* calculated for $C_{22}H_{31}NO_2$+H^+: 342.2433; found: 342.2426.



(122c')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.12 (dd, *J* = 8.0, 7.7 Hz, 1H), 7.08 (dd, *J* =8.0, 1.5 Hz, 1H), 6.75 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.69 (d, *J* = 9.0 Hz, 2H), 6.47 (d, *J* = 9.0 Hz, 2H), 4.67 (q, *J* = 6.6 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 2.89-2.52 (m, 2H), 1.69-1.52 (m, 2H), 1.51-1.22 (m, 9H), 0.92 (t, *J* = 7.0 Hz, 3H).

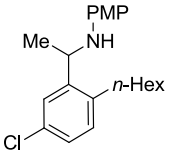
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.6 (C_q), 151.8 (C_q), 143.8 (C_q), 141.5 (C_q), 128.4 (C_q), 126.8 (CH), 117.1 (CH), 114.7 (CH), 114.5 (CH), 108.7 (CH), 55.7 (CH_3), 55.4 (CH_3), 50.4 (CH), 31.7 (CH_2), 29.9 (CH_2), 29.9 (CH_2), 25.4 (CH_2), 24.2(CH_3), 22.6 (CH_2), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3396, 2954, 2926, 2856, 1581, 1465, 1372, 1231, 1177 cm^{-1}.

MS (EI) *m/z* (relative intensity): 341 (55) [M^+], 326 (41), 218 (80), 157 (34), 149 (100), 123 (72), 108 (24), 91 (21).

HR-MS (EI) *m/z* calculated for $C_{22}H_{31}NO_2^+$: 341.2355; found: 341.2363.

Synthesis of *N*-[1-(5-Chloro-2-*n*-hexylphenyl)ethyl]-4-methoxyaniline (122d')



The general procedure **D** was followed using 4-methoxy-*N*-[1-(3-chlorophenyl)ethylidene]aniline (**121d**) (128 mg, 0.51 mmol), **42ab** (243 mg, 1.47 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.5 mg, 2.5 mol %), 1-AdCO_2H (**13c**) (27 mg, 0.15 mmol, 30 mol %) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **122d'** (116 mg, 68%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 1.2 Hz, 1H), 7.14-7.10 (m, 2H), 6.69 (d, *J* = 9.0 Hz, 2H), 6.41 (d, *J* = 9.0 Hz, 2H), 4.58 (q, *J* = 6.6 Hz, 1H), 3.69 (s, 3H), 2.75-2.59 (m, 2H), 1.77-1.54 (m, 2H), 1.49-1.19 (m, 9H), 0.92-0.81 (m, 3H).

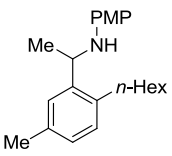
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 152.2 (C_q), 144.5 (C_q), 140.9 (C_q), 137.7 (C_q), 132.2 (C_q), 130.9 (CH), 126.8 (CH), 125.2 (CH), 114.8 (CH), 114.7 (CH), 55.6 (CH_3), 50.5 (CH), 31.7 (CH_2), 31.6 (CH_2), 31.0 (CH_2), 29.4 (CH_2), 24.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3401, 2954, 2927, 2856, 1592, 1509, 1464, 1374, 1233, 1120, 1038, 815, 518 cm^{-1}.

MS (EI) *m/z* (relative intensity): 345 (60) [M^+], 330 (59), 222 (33), 179 (22), 153 (65), 123 (100), 108 (53), 43 (20).

HR-MS (ESI): *m/z* calculated for $C_{21}H_{28}ClNO^+$: 345.1859; found: 345.1860.

Synthesis of *N*-[1-(2-*n*-Hexyl-5-methylphenyl)ethyl]-4-methoxyaniline (122e')

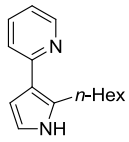


The general procedure **D** was followed using 4-methoxy-*N*-(1-*m*-tolylethylidene)aniline (**121e**) (130 mg, 0.54 mmol), **42ab** (246 mg, 1.49 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.9 mg, 2.4 mol %), 1-$AdCO_2H$ (**13c**) (28 mg, 0.15 mmol, 29 mol %) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **122e'** (92 mg, 52%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 1.6 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 6.97 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 2H), 6.46 (d, *J* = 8.8 Hz, 2H), 4.63 (q, *J* = 6.4 Hz, 1H), 3.69 (s, 3H), 2.73-2.62 (m, 2H), 2.26 (s, 3H), 1.72-1.54 (m, 2H), 1.50-1.22 (m, 9H), 0.90 (t, *J* = 6.9 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 151.7 (C_q), 142.2 (C_q), 141.6 (C_q), 136.2 (C_q), 135.6 (C_q), 129.4 (CH), 127.4 (CH), 125.4 (CH), 114.7 (CH), 114.4 (CH), 55.8 (CH_3), 50.2 (CH), 32.0 (CH_2), 31.8 (CH_2), 31.4 (CH_2), 29.6 (CH_2), 24.1 (CH_3), 22.7 (CH_2), 21.3 (CH_3), 14.2 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3395, 2955, 2928, 2856, 1511, 1464, 1305, 1236, 1168, 1039, 909, 818, 733, 647 cm^{-1}.
MS (EI) *m/z* (relative intensity): 325 (41) [M^+], 310 (26), 202 (57), 159 (19), 133 (100), 123 (62).
HR-MS (ESI): *m/z* calculated for $C_{22}H_{31}NO+H^+$: 326.2484; found: 326.2478.

Synthesis of 2-(2-*n*-Hexyl-1*H*-pyrrol-3-yl)pyridine (129) and 2-(1-*n*-Hexyl-1*H*-pyrrol-3-yl)pyridine (130)

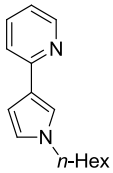
The general procedure **C** was followed using **128** (74.0 mg, 0.51 mmol), **42ab** (248 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 2.5 mol %), 1-$AdCO_2H$ (**13c**) (28 mg, 0.15 mmol, 30 mol%) and K_2CO_3 (141 mg, 1.02 mmol) in *m*-xylene (2.0 mL). Purification by column chromatography (*n*-hexane/EtOAc 5:1) yielded **129** (18 mg, 15%) and **130** (17 mg, 15%) as a colorless oils.



(129)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.55 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 8.21 (s, 1H), 7.66-7.51 (m, 1H), 7.39 (dt, *J* = 8.0, 1.1 Hz, 1H), 6.99 (ddd, *J* = 7.4, 4.9, 1.2 Hz, 1H), 6.72-6.61 (m, 1H), 6.54 (t, *J* = 2.9 Hz, 1H), 3.10-2.87 (m, 2H), 1.71-1.47 (m, 2H), 1.44-1.08 (m, 6H), 0.85 (t, *J* = 7.7 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 156.8 (C_q), 149.7 (CH), 136.5 (CH), 132.9 (C_q), 121.3 (CH), 120.3 (C_q), 120.0 (CH), 116.5 (CH), 109.1 (CH), 32.2 (CH_2), 30.1 (CH_2), 29.7 (CH_2), 27.8 (CH_2), 23.1 (CH_2), 14.6 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3227, 2924, 2854, 1692, 1588, 1497, 1465, 1424, 787, 740 cm^{-1}.

HR-MS (ESI) *m/z* calculated for $C_{15}H_{20}N_2+H^+$: 229.1705; found: 229.1703.



(130)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.50 (ddd, *J* = 5.0, 1.8, 0.9 Hz, 1H), 7.68-7.52 (m, 1H), 7.44 (ddd, *J* = 8.0, 1.1, 1.1 Hz, 1H), 7.31 (dd, *J* = 2.0, 2.0 Hz, 1H), 7.00 (ddd, *J* = 7.4, 4.9, 1.2 Hz, 1H), 6.67 (dd, *J* = 2.5, 2.5 Hz, 1H), 6.60 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.04-3.78 (m, 2H), 1.96-1.61 (m, 2H), 1.43-1.16 (m, 6H), 0.88 (t, *J* = 7.7 Hz, 3H).

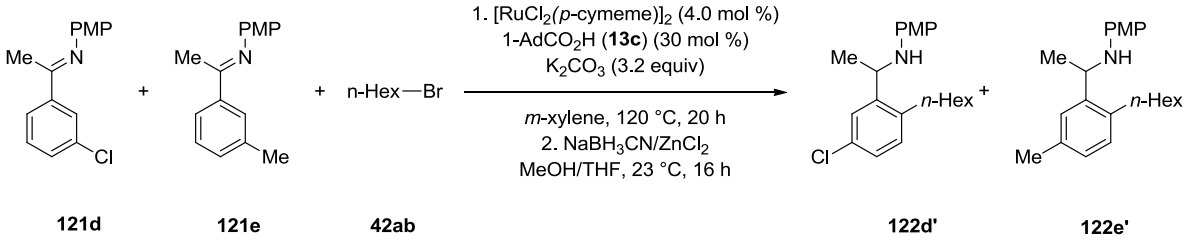
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 154.9 (C_q), 149.4 (CH), 136.4 (CH), 124.9 (C_q), 122.0 (CH), 120.1 (CH), 120.0 (CH), 118.9 (CH), 106.6 (CH), 50.2 (CH_2), 31.5 (CH_2), 31.5 (CH_2), 26.5 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2928, 2857, 1701, 1590, 1544, 1466, 1400, 1365, 1234, 930, 769 cm^{-1}.

HR-MS (ESI) *m/z* calculated for $C_{15}H_{20}N_2+H^+$: 229.1705; found: 229.1704.

Intermolecular Competition Experiments

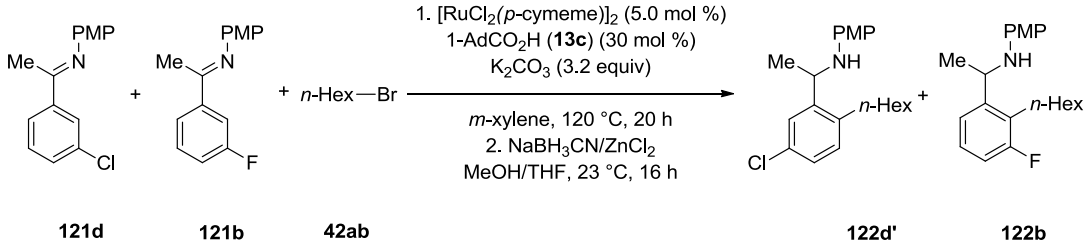
Intermolecular Competition Experiment with *meta*-substituted Ketimines (121e) & (121d)



A suspension of $[RuCl_2(p\text{-cymene})]_2$ (15.4 mg, 25 μmol, 3.9 mol %), 1-$AdCO_2H$ (**13c**) (27.6 mg, 0.15 mmol, 30 mol %), K_2CO_3 (225 mg, 1.62 mmol), **121d** (254 mg, 0.98 mmol), **121e** (224 mg, 0.94 mmol) and **42ab** (106 mg, 0.64 mmol) in *m*-xylene (3.0 mL) was stirred under N_2 for 20 h at 120 °C. A solution of $ZnCl_2$ in THF (0.65 mL, 1.10 mmol, 1.7 M), $NaBH_3CN$ (126 mg, 2.00 mmol) and MeOH (4.0 mL) was added to the cooled reaction mixture and the resulting mixture was stirred at ambient temperature. Analysis by GC showed that **122d'** and **122e'** were formed in a ratio of 4.4:1.0. Et_2O (30 mL) and sat. aq. K_2CO_3 (30 mL) were added to the cold reaction mixture. The separated aqueous phase was extracted with Et_2O (2 × 40 mL). The combined organic layers were dried over Na_2SO_4 and

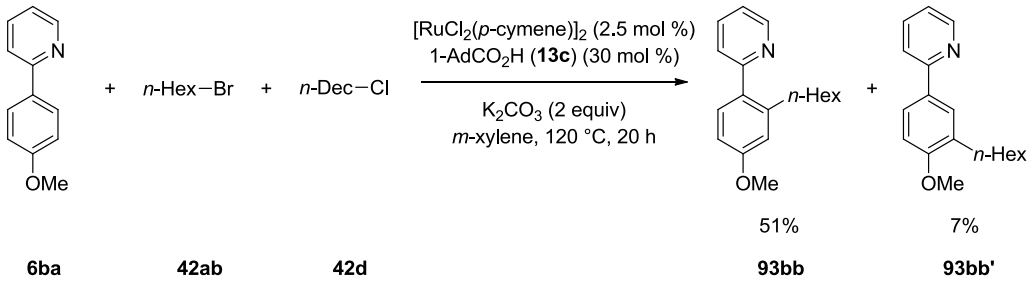
concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 9:1) yielded **122d'** (88 mg, 40%) as a colorless oil.

Intermolecular Competition Experiment with *meta*-substituted Ketimines (121b) & (121d)



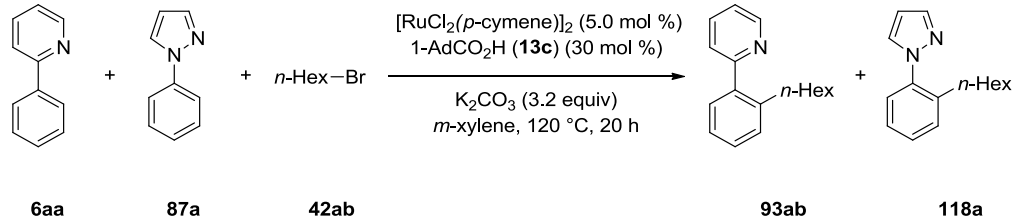
A suspension of $[RuCl_2(p\text{-cymene})]_2$ (15.0 mg, 25 μmol, 4.3 mol %), 1-AdCO_2H (**13c**) (26.3 mg, 0.15 mmol, 30 mol %), K_2CO_3 (226 mg, 1.64 mmol), **121d** (244 mg, 1.00 mmol), **121b** (252 mg, 0.97 mmol) and **42ab** (97 mg, 0.59 mmol) in *m*-xylene (3.0 mL) was stirred under N_2 for 20 h at 120 °C. A solution of $ZnCl_2$ in THF (0.65 mL, 1.10 mmol, 1.7 M), $NaBH_3CN$ (126 mg, 2.00 mmol) and MeOH (4.0 mL) was added to the cooled reaction mixture and the resulting mixture was stirred at ambient temperature. Analysis by GC showed that **122b** and **122d'** were formed in a ratio of 3.2:1.0. Et_2O (30 mL) and sat. aq. K_2CO_3 (30 mL) were added to the cold reaction mixture. The separated aqueous phase was extracted with Et_2O (2 × 40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 10:1) yielded **122b** (107 mg, 56%) and **122d'** (42 mg, 20%) as a colorless oils.

Intermolecular Competition Experiment between 1-Bromohexane (42ab) and 1-Chlorodecane (42d)



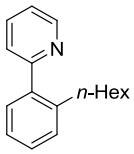
The competition experiment between **42ab** (250 mg, 1.52 mmol) and **42d** (274 mg, 1.55 mmol) with $[RuCl_2[p\text{-cymene})]_2$ (7.9 mg, 13 μmol, 2.5 mol %), 1-AdCO_2H (**13c**) (27.4 mg, 0.15 mmol, 30 mol %), K_2CO_3 (139 mg, 1.00 mmol) and **6ba** (91.7 mg, 0.50 mmol) in *m*-xylene (3.0 mL) yielded after purification by column chromatography (*n*-hexane/EtOAc 9:1 to 3:1) **93bb** (71 mg, 51%) and **93bb'** (9 mg, 7%).

Intermolecular Competition Experiment between 2-Phenylpyridine (6aa) and 1-Phenyl-1*H*-pyrazole (87a)



6aa **87a** **42ab** **93ab** **118a**

The competition experiment between **87a** (135 mg, 0.94 mmol) and **6aa** (140 mg, 0.91 mmol) with $[RuCl_2[p\text{-cymene})]_2$ (15.3 mg, 25 µmol, 4.3 mol %), 1-$AdCO_2H$ (**13c**) (27.8 mg, 0.15 mmol, 30 mol %), K_2CO_3 (137 mg, 0.99 mmol) and **42ab** (96.1 mg, 0.58 mmol) in *m*-xylene (3.0 mL) yielded after and purification by column chromatography (*n*-hexane/EtOAc 9:1) **118a** (12 mg, 9%) and **93ab** (50 mg, 36%) as a colorless oils.



(93ab)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.71 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.69 (td, *J* = 7.7, 1.8 Hz, 1H), 7.50-7.07 (m, 6H), 2.72-2.64 (m, 2H), 1.57-1.29 (m, 2H), 1.29-0.99 (m, 6H), 0.80 (t, *J* = 6.8 Hz, 3H).

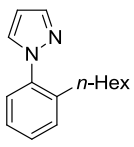
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.2 (C_q), 148.9 (CH), 140.6 (C_q), 140.2 (C_q), 135.8 (CH), 129.5 (CH), 129.5 (CH), 128.1 (CH), 125.5 (CH), 123.9 (CH), 121.4 (CH), 32.7 (CH_2), 31.3 (CH_2), 31.0 (CH_2), 28.9 (CH_2), 22.3 (CH_2), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3059, 2926, 2856, 1586, 1562, 1468, 1377, 795, 751, 474, 457, 441 cm^{-1}.

MS (EI) *m/z* (relative intensity): 239 (21) [M^+], 182 (100), 167 (89).

HR-MS (ESI) *m/z* calculated for $C_{17}H_{21}N+H^+$: 240.1752; found: 240.1746.

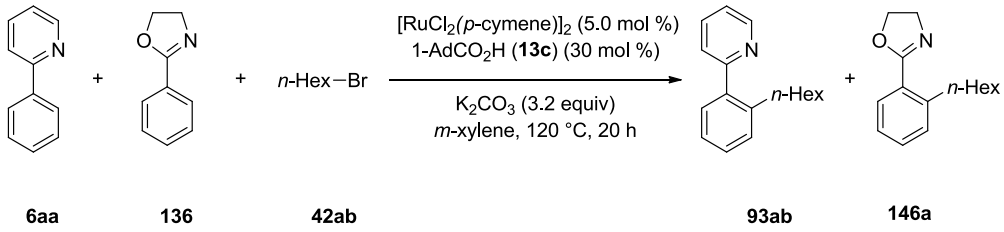
The analytical data are in accordance with those reported in the literature.[121]



(118a)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.71 (ddd, J = 1.8, 0.7, 0.7 Hz, 1H), 7.60-7.49 (m, 1H), 7.41-7.21 (m, 4H), 6.51-6.31 (m, 1H), 2.61-2.45 (m, 2H), 1.51-1.31 (m, 2H), 1.31-1.11 (m, 6H), 0.84 (t, J = 7.4 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 140.3 (CH), 139.8 (C_q), 139.1 (C_q), 130.8 (CH), 130.4 (CH), 128.7 (CH), 126.8 (CH), 126.5 (CH), 106.2 (CH), 31.6 (CH_2), 31.4 (CH_2), 30.7 (CH_2), 29.2 (CH_2), 22.6 (CH_2), 14.2 (CH_2).
IR (ATR): $\tilde{\nu}$ = 2955, 2925, 2856, 1516, 1498, 1418, 1394, 1043, 938, 746 cm^{-1}.
MS (EI) *m/z* (relative intensity): 228 (26) [M^+], 171 (100), 158 (26), 130 (20), 43 (17).
HR-MS (EI) *m/z* calculated for $C_{15}H_{20}N_2$-H^+: 227.1548; found: 227.1549.

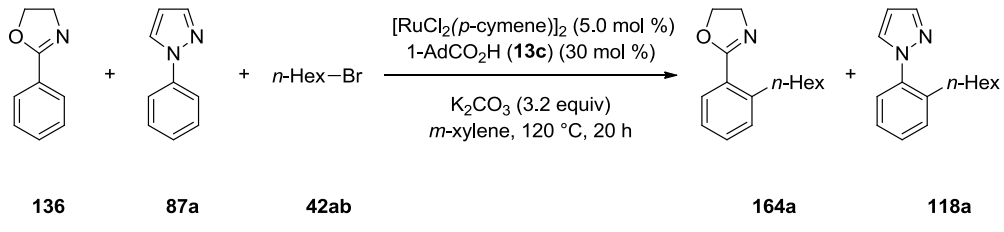
Intermolecular Competition Experiment between 2-Phenylpyridine (6aa) and 2-Phenyl-4,5-dihydrooxazole (136)



6aa **136** **42ab** **93ab** **146a**

The competition experiment between **6aa** (149 mg, 0.96 mmol) and **136** (136 mg, 0.92 mmol) with $[RuCl_2[p\text{-cymene})]_2$ (15.9 mg, 26 µmol, 5.0 mol %) 1-$AdCO_2H$ (**13c**) (27.0 mg, 0.15 mmol, 30 mol %), K_2CO_3 (138 mg, 1.00 mmol) and **42ab** (95.1 mg, 0.58 mmol) in *m*-xylene (3.0 mL) gave after purification by column chromatography (*n*-hexane/EtOAc 9:1) **93ab** (33 mg, 24%) as a colorless oil.

Intermolecular Competition Experiment between 2-Phenyl-4,5-dihydrooxazole (136) an 1-Phenyl-1*H*-pyrazole (118a)

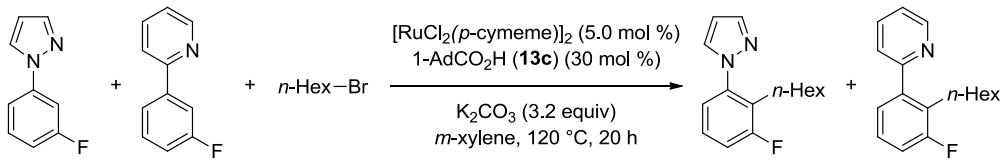


136 **87a** **42ab** **164a** **118a**

The competition-experiment between **136** (138 mg, 0.94 mmol) and **87a** (148 mg, 1.03 mmol) with $[RuCl_2[p\text{-cymene})]_2$ (15.0 mg, 0.025 mmol, 4.5 mol %), 1-$AdCO_2H$ (**13c**) (26.8 mg, 0.15 mmol, 30 mol %), K_2CO_3 (138 mg, 1.00 mmol) and **42ab** (91.0 mg, 0.55 mmol) in *m*-xylene (3.0 mL) gave

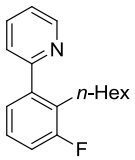
after purification by column chromatography (*n*-hexane/EtOAc 9:1) **118a** (39 mg, 31%) as a colorless oil.

Intermolecular Competition Experiment between 1-(3-Fluorophenyl)-1*H*-pyrazole (87c) an 2-(3-Fluorophenyl)pyridine (6da)



87c **6da** **42ab** **118c** **93db**

The competition experiment between **87c** (165 mg, 1.02 mmol) and **6da** (175 mg, 1.00 mmol) with $[RuCl_2[p\text{-cymene})]_2$ (15.1 mg, 0.025 mmol, 5.0 mol %), 1-$AdCO_2H$ (**13c**) (26.0 mg, 0.14 mmol, 29 mol %), K_2CO_3 (144 mg,1.04 mmol) and **42ab** (89.1 mg, 0.50 mmol) in *m*-xylene (3.0 mL) gave after purification by column chromatography (*n*-hexane/EtOAc 9:1) **93db** (24 mg, 17%) and **118c** (22 mg, 17%) as colorless oils.



(93db)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.79-8.62 (m, 1H), 7.76 (dddd, J = 9.5, 7.6, 4.6, 2.3 Hz, 2H), 7.33-7.00 (m, 4H), 2.79-2.58 (m, 2H), 1.56-1.35 (m, 2H), 1.33-1.00 (m, 6H), 0.81 (t, J = 6.7 Hz, 3H).

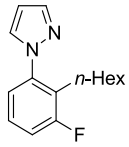
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.7 (d, $J_{C\text{-}F}$ = 244 Hz, C_q), 159.3 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 149.3 (CH), 142.7 (d, $J_{C\text{-}F}$ = 5 Hz, C_q), 136.3 (CH), 128.6 (d, $J_{C\text{-}F}$ = 16 Hz, C_q), 126.9 (d, $J_{C\text{-}F}$ = 9 Hz, CH), 125.5 (d, $J_{C\text{-}F}$ = 3 Hz, CH), 124.2 (CH), 122.1 (CH), 115.2 (d, $J_{C\text{-}F}$ = 24 Hz, CH), 31.5 (CH_2), 30.3 (CH_2), 29.3 (CH_2), 25.8 (d, $J_{C\text{-}F}$ = 3 Hz, CH_2), 22.6 (CH_2), 14.2 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = -117.17 - -117.88 (m).

IR (ATR): $\tilde{\nu}$ = 2954, 2926, 2857, 1564, 1482, 1423, 1277, 991, 883, 772, 746, 700 cm^{-1}.

MS (EI) *m/z* (relative intensity): 257 (41) [M^+], 214 (18), 200 (100), 185 (79), 157 (9).

HR-MS (EI) *m/z* calculated for $C_{17}H_{20}FN\text{-}H^+$: 256.1502; found: 256.1597.



(118c)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, J = 1.8 Hz, 1H), 7.60-7.52 (m, 1H), 7.28-7.16 (m, 1H), 7.16-7.02 (m, 2H), 6.48-6.39 (m, 1H), 2.61-2.44 (m, 2H), 1.53-1.31 (m, 2H), 1.31-1.02 (m, 6H), 0.84 (t, J = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.6 (d, $J_{C\text{-}F}$ = 246 Hz, C_q), 141.1 (d, $J_{C\text{-}F}$ = 7 Hz, C_q), 140.6 (CH), 130.9 (CH), 127.4 (d, $J_{C\text{-}F}$ = 18 Hz, C_q), 127.0 (d, $J_{C\text{-}F}$ = 10 Hz, CH), 122.4 (d, $J_{C\text{-}F}$ = 4 Hz, CH), 115.6 (d, $J_{C\text{-}F}$ = 23 Hz, CH), 106.5 (CH) , 31.4 (CH_2) , 29.9 (d, $J_{C\text{-}F}$ = 1 Hz, CH_2), 29.3 (CH_2), 24.7 (d, $J_{C\text{-}F}$ = 3 Hz, CH_2), 22.6 (CH_2), 14.1 (CH_3).

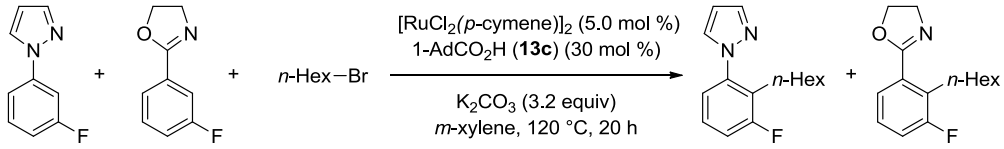
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -114.64 - -116.37 (m).

IR (ATR): $\tilde{\nu}$ = 2956, 2927, 2857, 1517, 1480, 1393, 1240, 1042, 855, 788, 747, 622 cm^{-1}.

MS (EI) *m/z* (relative intensity): 246 (59) [M^+], 203 (24), 189 (100), 176 (39), 148 (36), 135 (14).

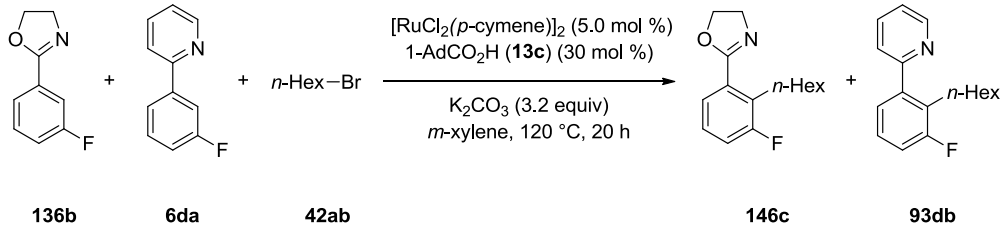
HR-MS (EI) *m/z* calculated for $C_{15}H_{19}FN_2^+$: 246.1532; found: 246.1532.

Intermolecular Competition Experiment between 1-(3-Fluorophenyl)-1*H*-pyrazole (87c) and 2-(3-Fluorophenyl)-4,5-dihydrooxazole (136b)



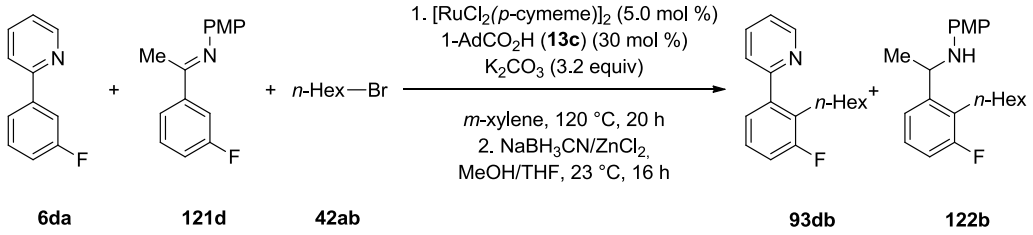
The competition experiment between **87c** (161 mg, 0.99 mmol) and **136b** (146 mg, 0.88 mmol) with [$RuCl_2$[*p*-cymene)]$_2$ (15.0 mg, 0.025 mmol, 4.6 mol %), 1-AdCO_2H (**13c**) (26.7 mg, 0.15 mmol, 30 mol %), K_2CO_3 (140 mg,1.03 mmol) and **42ab** (82.2 mg, 0.54 mmol) in *m*-xylene (3.0 mL) gave after purification by column chromatography (*n*-hexane/EtOAc 9:1) **118c** (59 mg, 48%) as a colorless oil.

Intermolecular Competition Experiment between 2-(3-Fluorophenyl)-4,5-dihydrooxazole (136b) & 2-(3-Fluorophenyl)pyridine (6da)



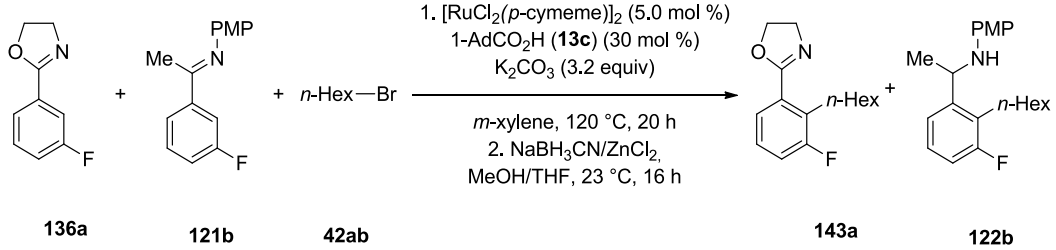
The competition experiment between **136b** (158 mg, 0.96 mmol) and **6da** (166 mg, 0.96 mmol) with $[RuCl_2[p\text{-cymene})]_2$ (15.4 mg, 0.025 mmol, 4.5 mol %), 1-$AdCO_2H$ (**13c**) (27.1 mg, 0.15 mmol, 30 mol %), K_2CO_3 (146 mg, 1.06 mmol) and **42ab** (90.5 mg, 0.55 mmol) in *m*-xylene (3.0 mL) gave after purification by column chromatography (*n*-hexane/EtOAc 9:1 to 1:1) **93db** (39 mg, 28%) as a colorless oil.

Intermolecular Competition Experiment between 2-(3-Fluorophenyl)pyridine (6da) and *(E)*-*N*-[1-(3-Fluorophenyl)ethylidene]-4-methoxyaniline (121b)



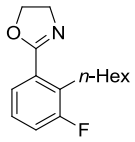
The competition experiment between **121d** (246 mg, 1.01 mmol) and **6da** (182 mg, 1.05 mmol) with $[RuCl_2(p\text{-cymene})]_2$ (15.1 mg, 0.025 mmol, 4.2 mol %), 1-$AdCO_2H$ (**13c**) (27.5 mg, 0.15 mmol, 30 mol %), K_2CO_3 (141 mg, 1.02 mmol) and **42ab** (101 mg, 0.61 mmol) in *m*-xylene (3.0 mL) gave after purification by column chromatography (*n*-hexane/EtOAc 9:1) **93db** (87 mg, 55%) and **122b** (44 mg, 22%) as a colorless oils.

Intermolecular Competition Experiment between *(E)*-*N*-[1-(3-Fluorophenyl)ethylidene]-4-methoxy-aniline (121b) and 2-(3-Fluorophenyl)-4,5-dihydrooxazole (136a)



136a **121b** **42ab** **143a** **122b**

The competition experiment between **136a** (165 mg, 1.00 mmol) and **121b** (253 mg, 1.04 mmol) with $[RuCl_2[p\text{-cymene})]_2$ (15.0 mg, 0.025 mmol, 4.2 mol %), 1-$AdCO_2H$ (27.0 mg, 0.15 mmol, 30 mol %), K_2CO_3 (139 mg, 1.01 mmol) and **42ab** (99.0 mg, 0.60 mmol) in *m*-xylene (3.0 mL) gave after purification by column chromatography (*n*-hexane/EtOAc 9:1 to 1:1) **143a** (22 mg, 15%) and **122b** (83 mg, 42%) as a colorless oils.



2-(3-Fluoro-2-*n*-hexylphenyl)-4,5-dihydrooxazole (143a)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.58-7.48 (m, 1H), 7.22-7.03 (m, 2H), 4.49-4.29 (m, 2H), 4.15-3.97 (m, 2H), 3.09-2.76 (m, 2H), 1.62-1.47 (m, 2H), 1.43-1.19 (m, 6H), 0.91-0.84 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 164.5 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 161.5 (d, $J_{C\text{-}F}$ = 243 Hz, C_q), 131.0 (d, $J_{C\text{-}F}$ = 18 Hz, C_q), 129.5 (d, $J_{C\text{-}F}$ = 5 Hz, C_q), 126.7 (d, $J_{C\text{-}F}$ = 9 Hz, CH), 125.8 (d, $J_{C\text{-}F}$ = 3 Hz, CH), 117.5 (d, $J_{C\text{-}F}$ = 24 Hz, CH), 67.3 (CH_2), 55.5 (CH_2), 31.7 (CH_2), 30.4 (CH_2), 29.5 (CH_2), 26.2 (CH_2), 22.7 (CH_2), 14.2 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = -116.94 - -117.32 (m).

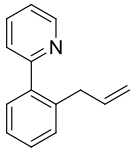
IR (ATR): $\tilde{\nu}$ = 2954, 2928, 2857, 1646, 1512, 1454, 1352, 1254, 1085, 981, 797, 736 cm^{-1}.

MS (EI) *m/z* (relative intensity): 249 (29) [M^+], 206 (25), 192 (100), 179 (32), 164 (23), 149 (65), 135 (18), 123 (22), 109 (24).

HR-MS (EI) *m/z* calculated for $C_{15}H_{20}FNO^+$: 249.1529; found: 249.1520.

Products of Direct Allylation

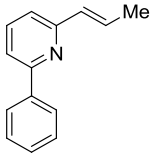
Synthesis of 2-(2-Allylphenyl)pyridine (93m)



$[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 13 μmol, 2.9 mol %) was added to a suspension of **6aa** (68.8 mg, 0.44 mmol, 1.0 equiv) and K_2CO_3 (140 mg, 1.0 mmol, 2.0 equiv) in dry toluene (2 mL). The reaction mixture was degassed with N_2 for 10 min and allyl bromide (**32g**) (300 mg, 2.48 mmol, 5.6 equiv) was added. The resulting solution was stirred for 20 h at 120 °C. The reaction mixture was poured into a mixture of diethyl ether and ice-cold water. The aqueous layer was extracted (3 × 5 mL) with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified using column chromatography through silica gel (5% to 7% EtOAc in *n*-hexane) to afford compound **93m** (24 mg, 28%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.67 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.74-7.63 (m, 1H), 7.42-7.18 (m, 6H), 6.01-5.67 (m, 1H), 5.04-4.75 (m, 2H), 3.47 (dt, *J* = 6.4, 1.6 Hz, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.9 (C_q), 149.2 (CH), 140.5 (C_q), 137.8 (C_q), 137.7 (CH), 136.3 (CH), 130.2 (CH), 130.0 (CH), 128.6 (CH), 126.4 (CH), 124.3 (CH), 121.9 (CH), 115.7 (CH_2), 37.5 (CH_2).
IR (ATR): $\tilde{\nu}$ = 3059, 3007, 2918, 1636, 1585, 1492, 1440, 1023, 989, 911, 746 cm^{-1}.
MS (EI) *m/z* (relative intensity): 194 (78) [M^+], 180 (100), 167 (38), 154 (55), 43 (28).
HR-MS (ESI) *m/z* calculated for $C_{14}H_{13}N+H^+$: 196.1126; found: 196.1124.
The analytical data are in accordance with those reported in the literature.[211]

Attempted Synthesis of (*E*)-2-Phenyl-6-(prop-1-en-1-yl)pyridine (145)Fehler! Textmarke nicht efiniert.[136]



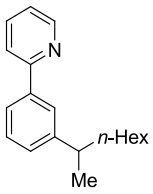
[211] Oi, S.; Tanaka, Y.; Inoue, Y. *Organometallics* **2006,** *25,* 4773–4778.

Following a procedure by Ramana *et al.*, $[RuCl_2(p\text{-cymene})]_2$ (15.4 mg, 25 μmol, 2.3 mol%) was added to a suspension of **6aa** (167 mg, 1.08 mmol, 1.0 equiv), 1-AdCO_2H (55.5 mg, 0.31 mmol, 29 mol%) and K_2CO_3 (277 mg, 2.00 mmol, 1.85 equiv) in dry toluene (5 mL). The reaction mixture was degassed with N_2 for 10 min and allyl bromide (605 mg, 5.00 mmol, 4.6 equiv) was added. The resulting solution was stirred at 120 °C for 20 h. The reaction mixture was poured into a mixture of diethyl ether and ice-cold water. The aqueous layer was extracted (3 x 10 mL) with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified twice by column chromatography through silica gel (5% to 7% EtOAc in *n*-hexane) to afford compound **145** (149 mg, calc. ^{1}H-NMR-yield: 69%) as a yellow oil including remainings of the formed allyl 1-adamantane-1-carboxylate.

The NMR data were in accordance with those reported in the literature.[136]

7.3 Analytical Data for the Ruthenium-Catalyzed *meta*-Alkylation

Synthesis of 2-[3-(Octan-2-yl)phenyl]pyridine (147aa)



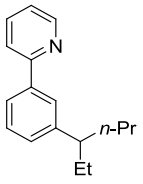
The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.90 mg, 0.013 mmol, 2.5 mol %), **6aa** (87.5 mg, 0.56 mmol), 2-bromooctane (**42ba**) (294 mg, 1.52 mmol), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 26 mol%) and K_2CO_3 (138 mg, 1.00 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147aa** (89 mg, 60%) as a colorless oil.

The general procedure **E** with (*S*)-3-methyl-2-pivalamidobutanoic acid (**76a**) (31.0 mg, 0.15 mmol, 30 mol%) as additive in water (2 mL) at 100 °C gave 73% isolated yield.

The general procedure **E** with di-nonan-3-yl hydrogen phosphate (**175c**) (54.0 mg, 0.17 mmol, 34 mol%) as additive in water (2 mL) at 100 °C gave 58% isolated yield.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.71 (dt, *J* = 4.8, 1.4 Hz, 1H), 7.85 (t, *J* = 1.8 Hz, 1H), 7.79 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.73 (dd, *J* = 4.1, 1.2 Hz, 2H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.31-7.10 (m, 2H), 2.79 (qt, *J* = 7.1, 7.0 Hz, 1H), 1.76-1.55 (m, 2H), 1.38-1.10 (m, 8H), 1.30 (d, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.7 (C_q), 149.4 (CH), 148.5 (C_q), 139.1 (C_q), 136.8 (CH), 128.6 (CH), 127.6 (CH), 125.7 (CH), 124.4 (CH), 121.9 (CH), 120.7 (CH), 40.1 (CH), 38.4 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 27.7 (CH_2), 22.6 (CH_2), 22.3 (CH_3), 14.0 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2956, 2924, 2854, 1584, 1566, 1461, 1434, 772, 742, 700 cm^{-1}.
MS (EI) m/z (relative intensity): 267 (13) [M^+], 196 (32), 182 (100), 167 (58), 78 (13).
HRMS (EI) m/z calculated for $C_{19}H_{25}N+H^+$: 268.2060; found: 268.2063.

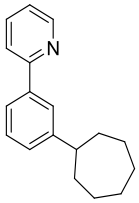
Synthesis of 2-[3-(Hexan-3-yl)phenyl]pyridine (147ab)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.9 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 30 mol %), **6aa** (77.5 mg, 0.50 mmol) and 3-bromohexane (**42bb**) (242 mg, 1.47 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147bb** (31 mg, 26%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.85-8.61 (m, 1H), 7.98-7.64 (m, 4H), 7.49-7.34 (m, 1H), 7.32-7.11 (m, 2H), 2.53 (dt, *J* = 8.7, 5.8 Hz, 1H), 1.85-1.52 (m, 4H), 1.39-1.10 (m, 2H), 0.93-0.74 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.0 (C_q), 149.7 (CH), 146.8 (C_q), 139.4 (C_q), 136.7 (CH), 128.7 (CH), 128.5 (CH), 126.6 (CH), 124.6 (CH), 122.0 (CH), 120.8 (CH), 47.9 (CH), 39.0 (CH_2), 29.8 (CH_2), 20.9 (CH_2), 14.3 (CH_3), 12.4 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3050, 2956, 2926, 2871, 1584, 1566, 1460, 1434, 769, 741 cm^{-1}.
MS (EI) *m/z* (relative intensity): 239 (24) [M^+], 210 (58), 196 (68), 182 (21), 168 (100).
HR-MS (ESI) *m/z* calculated for $C_{17}H_{21}N+H^+$: 240.1752; found: 240.1747.

Synthesis of 2-(3-Cycloheptylphenyl)pyridine (147ac)

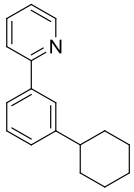


The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.10 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 29 mol %), **6aa** (80.3 mg, 0.52 mmol) and bromocycloheptane (**42bc**) (270 mg, 1.52 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147ac** (99 mg, 76%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.68 (dd, *J* = 4.8, 1.4, 1.4 Hz, 1H), 7.84 (dd, *J* = 1.9, 1.8 Hz, 1H), 7.78-7.65 (m, 3H), 7.36 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.27-7.13 (m, 2H), 2.84-2.65 (m, 1H), 2.06-1.88 (m, 2H), 1.88-1.47 (m, 10H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.0 (C_q), 150.7 (C_q), 149.7 (CH), 139.5 (C_q), 136.7 (CH), 128.8 (CH), 127.5 (CH), 125.6 (CH), 124.3 (CH), 122.0 (CH), 120.8 (CH), 47.3 (CH), 37.0 (CH_2), 28.0 (CH_2), 27.4 (CH_2).
IR (ATR): $\tilde{\nu}$ = 3059, 2918, 2852, 1584, 1564, 1460, 1434, 1151, 990, 769, 741, 699 cm^{-1}.
MS (EI) m/z (relative intensity): 251 (100) [M^+], 236 (15), 222 (40), 208 (65), 194 (77), 182 (74), 169 (75), 155 (38).

HRMS (ESI) m/z calculated for $C_{18}H_{21}N$-H^+: 250.1596; found 250.1594.

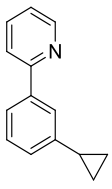
Synthesis of 2-(3-Cyclohexylphenyl)pyridine (147ad)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.70 mg, 0.013 mmol, 2.3 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 27 mol %), **6aa** (86.4 mg, 0.56 mmol) and bromocyclohexane (**42bd**) (271 mg, 1.66 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147ad** (77 mg, 58%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.70 (ddd, *J* = 4.8, 1.4, 1.4 Hz, 1H), 7.88 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.82-7.66 (m, 3H), 7.40 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.31-7.24 (m, 1H), 7.24-7.17 (m, 1H), 2.60-2.61 (m, 1H), 2.04-1.69 (m, 5H), 1.62-1.16 (m, 5H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.8 (C_q), 149.6 (CH), 148.6 (C_q), 139.3 (C_q), 136.6 (CH), 128.6 (CH), 127.4 (CH), 125.6 (CH), 124.4 (CH), 121.9 (CH), 120.6 (CH), 44.7 (CH), 34.4 (CH_2), 26.9 (CH_2), 26.1 (CH_2).
IR (ATR): $\tilde{\nu}$ = 3050, 2921, 2849, 1583, 1564, 1448, 1434, 1414, 1267, 882, 769, 698, 642, 613 cm^{-1}.
MS (EI) *m/z* (relative intensity): 237 (100) [M^+], 208 (36), 194 (38), 182 (71), 169 (27), 155 (16).
HR-MS (ESI) *m/z* calculated for $C_{17}H_{19}N$+H^+: 238.1596; found: 238.1589.

Synthesis of 2-(3-Cyclopropylphenyl)pyridine (147ae)



The general procedure **E** was followed in a sealed tube, using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 28 mol %), **6aa** (82.3 mg, 0.53 mmol) and bromocyclopropane (**42be**) (189 mg, 1.56 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147ae** (10 mg, 10%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.72 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.86-7.63 (m, 1H), 7.55 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.42 (ddd, *J* = 7.2, 1.5, 1.2 Hz, 1H), 7.37-7.15 (m, 3H), 7.00 (dd, *J* = 7.6, 1.4 Hz, 1H), 2.13-1.96 (m, 1H), 0.89-0.74 (m, 2H), 0.74-0.58 (m, 2H).

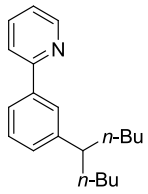
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.7 (C_q), 149.1 (CH), 141.0 (CH), 140.9 (CH), 136.0 (CH), 129.6 (CH), 128.5 (CH), 125.5 (CH), 124.7 (CH), 124.6 (CH), 121.6 (CH), 13.3 (CH), 9.3 (CH_2).

IR (ATR): $\tilde{\nu}$ = 3060, 3003, 1584, 1562, 1467, 1424, 1020, 899, 794, 746 cm^{-1}.

MS (EI) *m/z* (relative intensity): 194 (17) [M-H$^+$], 180 (22), 167 (100), 139 (11).

HR-MS (ESI) *m/z* calculated for $C_{14}H_{13}N+H^+$: 196.1126; found: 196.1122.

Synthesis of 2-[3-(Nonan-5-yl)phenyl]pyridine (147ag)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.20 mg, 0.013 mmol, 2.6 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 30 mol%), **6aa** (71.5 mg, 0.46 mmol) and 5-bromononane (**42bg**) (318 mg, 1.54 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 5:1) yielded **147ag** (66 mg, 51%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.68 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.82-7.75 (m, 2H), 7.74-7.65 (m, 2H), 7.37 (dd, *J* = 8.5, 7.6 Hz, 1H), 7.23-7.14 (m, 2H), 2.64-2.49 (m, 1H), 1.76-1.50 (m, 4H), 1.36-1.01 (m, 8H), 0.81 (t, *J* = 7.0 Hz, 6H).

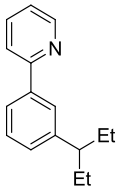
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.9 (C_q), 149.6 (CH), 147.0 (C_q), 139.2 (C_q), 136.6 (CH), 128.5 (CH), 128.2 (CH), 126.3 (CH), 124.4 (CH), 121.9 (CH), 120.6 (CH), 46.2 (CH), 36.6 (CH_2), 29.9 (CH_2), 22.8 (CH_2), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2955, 2925, 2856, 1584, 1566, 1461, 1435, 1416, 770, 741 cm^{-1}.

MS (EI) m/z (relative intensity): 281 (56) [M$^+$], 238 (25), 224 (100), 168 (82).

HRMS (EI) m/z calculated for $C_{20}H_{27}N^+$: 281.2143; found: 281.2140.

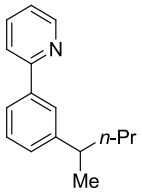
Synthesis of 2-[3-(Pentan-3-yl)phenyl]pyridine (147ah)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.00 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (27 mg, 0.15 mmol, 26 mol %), **6aa** (87.0 mg, 0.56 mmol) and 3-bromopentane (**42bh**) (235 mg, 1.55 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147ah** (53 mg, 42%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.74-8.64 (m, 1H), 7.85-7.76 (m, 2H), 7.75-7.66 (m, 2H), 7.38 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.24-7.12 (m, 2H), 2.51-2.32 (m, 1H), 1.83-1.52 (m, 4H), 0.79 (t, *J* = 8.1 Hz, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.0 (C_q), 149.7 (CH), 146.5 (C_q), 139.3 (C_q), 136.8 (CH), 128.7 (CH), 128.5 (CH), 126.7 (CH), 124.6 (CH), 122.1 (CH), 120.8 (CH), 50.0 (CH), 29.4 (CH_2), 12.4 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3050, 2959, 2926, 2872, 1584, 1565, 1461, 1435, 1152, 767, 700 cm^{-1}.
MS (EI) *m/z* (relative intensity): 225 (29) [M^+], 196 (100), 168 (30), 78 (10), 41 (14).
HR-MS (ESI) *m/z* calculated for $C_{16}H_{19}N+H^+$: 226.1596; found: 226.1593.

Synthesis 2-[3-(Pentan-2-yl)phenyl]pyridine (147ai)



An up-scaled version of The general procedure **E** with less catalyst loading was followed, using $[RuCl_2(p\text{-cymene})]_2$ (14.6 mg, 0.024 mmol, 5.0 mol %), $MesCO_2H$ (**13a**) (24.6 mg, 0.15 mmol, 30 mol %), K_2CO_3 (1.39 mg, 9.80 mmol), **6aa** (0.75 g, 4.82 mmol) and 2-bromopentane (**42bi**) (2.32 g, 15.4 mmol). After 48 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147ai** (0.47 g, 43%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.70 (ddd, *J* = 5.0, 1.5, 1.4 Hz, 1H), 7.89-7.65 (m, 4H), 7.39 (ddd, *J* = 7.6, 3.1, 3.0 Hz, 1H), 7.30-7.15 (m, 2H), 2.81 (qt, *J* = 7.0, 6.9 Hz, 1H), 1.77-1.48 (m, 2H), 1.40-1.11 (m, 2H), 1.30 (d, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H).

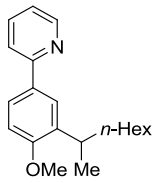
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.9 (C_q), 149.7 (CH), 148.6 (C_q), 139.5 (C_q), 136.7 (CH), 128.8 (CH), 127.7 (CH), 125.9 (CH), 124.5 (CH), 122.0 (CH), 120.7 (CH), 40.8 (CH_2), 39.9 (CH), 22.4 (CH_2), 21.0 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3049, 2956, 2927, 2870, 1603, 1584, 1461, 1434, 1415, 914, 771, 742, 699, 614 cm^{-1}.

MS (70 eV, EI) *m/z* (relative intensity): 225 (34) [M^+], 196 (31), 182 (100), 167 (18), 154 (15), 77 (22), 43 (20).

HR-MS (ESI) *m/z* calculated for $C_{16}H_{19}N^+$: 225.1517; found: 225.1513.

Synthesis of 2-[4-Methoxy-3-(octan-2-yl)phenyl]pyridine (147ba)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.30 mg, 0.012 mmol, 2.3 mol %), $MesCO_2H$ (**13a**) (24 mg, 0.15 mmol, 28 mol %), **6ba** (95.0 mg, 0.51 mmol) and 2-bromooctane (**42ba**) (287 mg, 1.48 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147ba** (91 mg, 60%) as a colorless oil.

The general procedure **E** was followed, using $[Ru(p\text{-cymene})(MesCO_2)_2]$ (**12**) (15.0 mg, 0.027 mmol), **6ba** (96.2 mg, 0.52 mmol) and 2-bromooctane (**42ba**) (282 mg, 1.43 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147ba** (110 mg, 71%).

The general procedure **E** was followed, using $[Ru(p\text{-cymene})(MesCO_2)\{2\text{-(4-methoxy-phenyl)pyridyl}\}]$ (**14a**) (15.8 mg, 0.027 mmol, 5.0 mol %), **6ba** (102.9 mg, 0.56 mmol) and 2-bromooctane (**42ba**) (300 mg, 1.55 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147ba** (114 mg, 69%).

The general procedure **E** was followed, using [Ru(*p*-cymene)(2-phenylpyridyl)Cl] (**178**) (10.9 mg, 0.026 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25.0 mg, 0.15 mmol, 30 mol %), **6ba** (98.0 mg, 0.53 mmol) and 2-bromooctane (**42ba**) (300 mg, 1.55 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1 to 5:1) yielded **147ba** (68 mg, 43%).

The general procedure **E** with (*S*)-3-methyl-2-pivalamidobutanoic acid (**76c**) (31.0 mg, 0.15 mmol) in water (2.0 mL) gave compound **147ba** in 77% isolated yield.

The general procedure **E** with dinona-3-yl hydrogen phosphate (**175c**) (54.0 mg, 0.17 mmol) gave compound **147ba** in 77% isolated yield.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.4, 1.4, 1.0 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.80 (dt, *J* = 8.5, 1.8 Hz, 1H), 7.75-7.63 (m, 2H), 7.19-7.11 (m, 1H), 6.94 (dd, *J* = 8.4, 1.2 Hz, 1H), 3.87 (s, 3H), 3.23 (qt, *J* = 7.1, 6.9 Hz, 1H), 1.79-1.50 (m, 2H), 1.39-1.16 (m, 8H), 1.26 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 6.4 Hz, 3H).

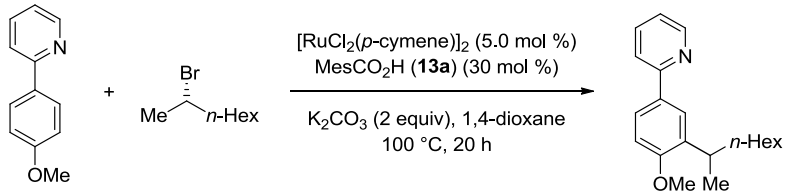
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.0 (C_q), 157.6 (C_q), 149.4 (CH), 136.5 (C_q), 136.5 (CH), 131.7 (CH), 125.5 (C_q), 125.2 (CH), 121.1 (CH), 119.9 (CH), 110.5 (CH), 55.5 (CH_3), 37.1 (CH_2), 32.1 (CH), 31.8 (CH_2), 29.4 (CH_2), 27.7 (CH_2), 22.6 (CH_2), 20.9 (CH_3), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2956, 2927, 2856, 1606, 1563, 1502, 1464, 1431, 1271, 1245, 781 cm^{-1}.

MS (EI) m/z (relative intensity): 297 (27) [M^+], 212 (100), 197 (15), 167 (30).

HRMS (EI) m/z calculated for $C_{20}H_{27}NO^+$: 297.2093; found: 297.2094.

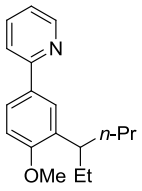
Direct *meta*-Alkylation of 6ba using enantiopure (*S*)-42ba



6ba (*S*)-**42ba** (*rac*)-**147ba**

The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (14.8 mg, 0.024 mmol, 5.0 mol %), **6ba** (94.8 mg, 0.51 mmol) and (*S*)-2-bromooctane (*S*)-**42ba**) (298 mg, 1.54 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded (*rac*)-**147ba** (81 mg, 53%) as a colorless oil. The racemization was confirmed by analytical HPLC on chiral stationary phase.

Synthesis of 2-[3-(Hexan-3-yl)-4-methoxyphenyl]pyridine (147bb)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.10 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (26 mg, 0.13 mmol, 30 mol %), **6ba** (92.4 mg, 0.50 mmol) and 3-bromohexane (**42bb**)

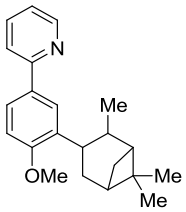
(242 mg, 1.46 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147bb** (85 mg, 63%) as a colorless oil.

The general procedure **E** in water (2.0 mL) gave 49% isolated yield.
The general procedure **E** neat gave 70% isolated yield.

The general procedure **E** was followed, using [Ru(*p*-cymene)($MesCO_2$)$_2$] (**12**) (14.8 mg, 0.026 mmol, 5.0 mol %), **6ba** (98.3 mg, 0.53 mmol) and 3-bromohexane (**42bb**) (256 mg, 1.55 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147bb** (84 mg, 60%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 1.7, 1.2 Hz, 1H), 7.84-7.76 (m, 2H), 7.74-7.62 (m, 2H), 7.15 (ddd, *J* = 6.7, 4.9, 2.0 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 3.85 (s, 3H), 3.13-2.98 (m, 1H), 1.80-1.49 (m, 4H), 1.38-1.09 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.80 (t, *J* = 7.4 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.8 (C_q), 157.7 (C_q), 149.5 (CH), 136.5 (CH), 134.6 (C_q), 131.7 (C_q), 126.2 (CH), 125.1 (CH), 121.2 (CH), 119.9 (CH), 110.6 (CH), 55.6 (CH_3), 39.3 (CH), 37.7 (CH_2), 28.5 (CH_2), 20.7 (CH_2), 14.2 (CH_3), 12.1 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3003, 2956, 2870, 1605, 1585, 1502, 1462, 1430, 1242, 1028, 779 cm^{-1}.
MS (EI) m/z (relative intensity): 269 (61) [M^+], 240 (32), 226 (84), 212 (24), 198 (100), 167 (34).
HRMS (EI) m/z calculated for $C_{18}H_{23}NO^+$: 269.1780; found: 269.1778.

Synthesis of 2-{4-Methoxy-3-(2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)phenyl}pyridine (147bf)



The general procedure **E** was followed, using [$RuCl_2$(*p*-cymene)]$_2$ (7.60 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 28 mol %), **6ba** (96.7 mg, 0.52 mmol) and 3-bromo-2,6,6-trimethylbicyclo[3.1.1]heptane (**42bf**) (332 mg, 1.53 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147bf** (68 mg, 41%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.75-8.59 (m, 1H), 7.96 (d, *J* = 2.4 Hz, 1H), 7.80 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.76-7.63 (m, 2H), 7.23-7.12 (m, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 3.59 (dt, *J* = 8.2, 8.1 Hz, 1H),

2.49-2.22 (m, 3H), 2.08-1.81 (m, 3H), 1.39 (d, *J* = 9.4 Hz, 1H), 1.29 (s, 3H), 1.22 (s, 3H), 0.98 (t, *J* = 7.1 Hz, 3H).

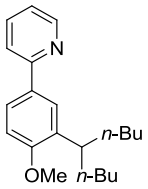
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.6 (C_q), 157.6 (C_q), 149.5 (CH), 137.4 (C_q), 136.9 (CH), 131.9 (C_q), 128.6 (CH), 125.5 (CH), 121.4 (CH), 120.1 (CH), 111.0 (CH), 55.6 (CH_3), 48.7 (CH), 44.0 (CH), 42.5 (CH), 39.5 (C_q), 37.6 (CH), 36.0 (CH_2), 34.5 (CH_2), 28.9 (CH_3), 23.3 (CH_3), 21.4 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2899, 2869, 2836, 1723, 1586, 1463, 1440, 1270, 1244, 1128, 1029, 779, 600 cm^{-1}.

MS (EI) *m/z* (relative intensity): 321 (51) [M^+], 290 (20), 266 (100), 252 (63), 238 (70), 222 (27), 211 (83), 196 (32), 167 (26), 147 (43).

HR-MS (EI) *m/z* calculated for $C_{22}H_{27}NO^+$: 321.2093; found: 321.2105.

Synthesis of 2-[4-Methoxy-3-(nonan-5-yl)phenyl]pyridine (147bg)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.70 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 30 mol %), **6ba** (92.5 mg, 0.50 mmol) and 5-bromononane (**42bg**) (312 mg, 1.51 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147bg** (66 mg, 42%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.69-8.61 (m, 1H), 7.85-7.76 (m, 2H), 7.76-7.62 (m, 2H), 7.15 (ddd, *J* = 6.6, 4.8, 1.9 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 3.85 (s, 3H), 3.19-3.04 (m, 1H), 1.72-1.59 (m, 4H), 1.38-1.05 (m, 8H), 0.83 (t, *J* = 7.1 Hz, 6H).

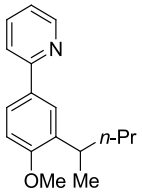
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.7 (C_q), 157.7 (CH), 149.5 (CH), 136.5 (C_q), 135.1 (C_q), 131.7 (CH), 126.2 (CH), 125.1 (CH), 121.1 (CH), 119.9 (CH), 110.7 (CH), 55.6 (CH_3), 37.8 (CH), 35.5 (CH_2), 29.8 (CH_2), 22.8 (CH_2), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2954, 2927, 2856, 1586, 1502, 1463, 1431, 1269, 1242, 1028, 779 cm^{-1}.

MS (EI) *m/z* (relative intensity): 311 (32) [M^+], 254 (76), 198 (100), 168 (27).

HR-MS (EI) *m/z* calculated for $C_{21}H_{29}NO^+$: 311.2249; found: 311.2251.

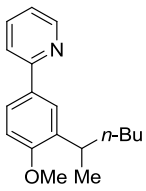
Synthesis of 2-[4-Methoxy-3-(pentan-2-yl)-phenyl]-pyridine (147bi)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.10 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 29 mol %), **6ba** (95.0 mg, 0.51 mmol) and 2-bromopentane (**42bi**) (223 mg, 1.48 mmol). After 20 h, purification by chromatography (*n*-hexane/EtOAc 9:1) yielded **147bi** (81 mg, 62%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.66 (dt, *J* = 4.9, 1.5 Hz, 1H), 7.86 (d, *J* = 2.4 Hz, 1H), 7.80 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.75-7.54 (m, 2H), 7.15 (ddd, *J* = 6.1, 4.8, 2.5 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 3.87 (s, 3H), 3.27 (qt, *J* = 7.1, 7.0 Hz, 1H), 1.82-1.46 (m, 2H), 1.42-1.15 (m, 2H), 1.27 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.9 (C_q), 157.6 (CH), 149.4 (CH), 136.5 (C_q), 136.4 (CH), 131.7 (CH), 125.5 (CH), 125.1 (CH), 121.1 (CH), 119.8 (CH), 110.5 (CH), 55.4 (CH_3), 39.4 (CH_2), 31.8 (CH), 20.8 (CH_2), 20.8 (CH_3), 14.2 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2956, 2929, 2869, 2837, 1584, 1501, 1462, 1243, 1158, 1028 cm^{-1}.
MS (EI) m/z (relative intensity): 255 (59) [M^+], 212 (100), 197 (17), 167 (36).
HRMS (EI) m/z calculated for $C_{17}H_{21}NO^+$: 255.1623; found: 255.1623.

Synthesis of 2-[3-(Hexan-2-yl)-4-methoxyphenyl]pyridine (147bj)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.70 mg, 0.013 mmol, 2.8 mol %), $MesCO_2H$ (**13a**) (26 mg, 0.15 mmol, 28 mol %), **6ba** (98.4 mg, 0.53 mmol) and 2-bromohexane (**42bj**) (249 mg, 1.51 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147bj** (100 mg, 70%) as a colorless oil.

The enantiomers of **147bj** were separated using preparative chiral HPLC [column: Chiralpak IC: eluent: *n*-hexane/EtOAc 97:3, 15 ml/min; t_{ret} = 14.2 and 15.8 min]. The absolute configuration of the arbitrary selected enantiomer with t_{ret} = 14.2 min was established to be (*R*)-**147bj** by means of X-ray crystal structure analysis of its hydrochloride **149**.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.66 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.84 (d, *J* = 2.4 Hz, 1H), 7.82-7.77 (m, 1H), 7.75-7.64 (m, 2H), 7.16 (ddd, *J* = 6.4, 4.8, 1.5 Hz, 1H), 6.94 (dd, *J* = 8.5, 1.1 Hz, 1H), 3.87 (s, 3H), 3.22 (qt, *J* = 7.0, 6.9 Hz, 1H), 1.81-1.47 (m, 2H), 1.42-1.09 (m, 4H), 1.26 (d, *J* = 7.0 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H).

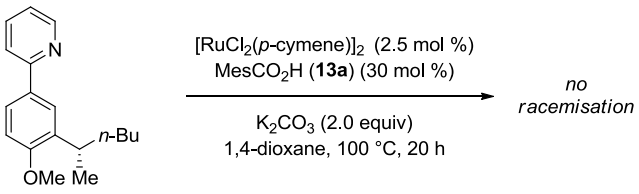
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 171.2 (C_q), 158.1 (C_q), 157.8 (C_q), 149.6 (CH), 136.6 (CH), 131.9 (C_q), 125.7 (CH), 125.3 (CH), 121.3 (CH), 120.0 (CH), 110.7 (CH), 55.6 (CH_3), 36.9 (CH_2), 32.3 (CH), 30.1 (CH_2), 22.9 (CH_2), 21.0 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2956, 2927, 2869, 2857, 1585, 1501, 1462, 1242, 1156, 1028, 604 cm^{-1}.

MS (EI) m/z (relative intensity): 269 (55) [M^+], 212 (100), 197 (23), 182 (11), 167 (36).

HRMS (EI) m/z calculated for $C_{18}H_{23}NO^+$: 269.1780; found: 269.1784.

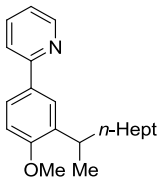
Attempted Racemisation of Compound (*S*)-(147bj) under Optimized Reaction Conditions



(S)-**147bj**

Following the general procedure **E** with (*S*)-**147bj** (t_{ret} = 15.8 min)(20.0 mg, 0.07 mmol), $MesCO_2H$ (**13a**) (3.8 mg, 0.02 mmol, 31 mol%) and $[RuCl_2(p\text{-cymene})]_2$ (1.3 mg, 2.8 mol%). Analysis by analytical HPLC on chiral stationary phase displayed no racemisation of (*S*)-**147bj**.

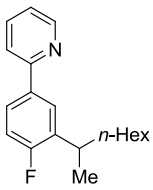
Synthesis of 2-[4-Methoxy-3-(nonan-2-yl)phenyl]pyridine (147bk)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.00 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 30 mol %), **6ba** (95.1 mg, 0.51 mmol) and 2-bromononane (**42bk**) (316 mg, 1.53 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147bk** (89 mg, 56%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.66 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.84 (d, *J* = 2.4 Hz, 1H), 7.80 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.74-7.65 (m, 2H), 7.15 (ddd, *J* = 6.7, 4.9, 2.1 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 3.87 (s, 3H), 3.22 (qt, *J* = 7.1, 6.9 Hz, 1H), 1.78-1.46 (m, 2H), 1.33-1.16 (m, 10H), 1.26 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 6.6 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.0 (C_q), 157.6 (C_q), 149.5 (CH), 136.5 (C_q), 136.5 (CH), 131.7 (C_q), 125.5 (CH), 125.2 (CH), 121.2 (CH), 119.9 (CH), 110.5 (CH), 55.5 (CH_3), 37.1 (CH_2), 32.1 (CH), 31.9 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 27.7 (CH_2), 22.6 (CH_2), 20.9 (CH_3), 14.1 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2956, 2924, 2854, 1606, 1585, 1563, 1501, 1463, 1028, 779, 740 cm^{-1}.
MS (EI) m/z (relative intensity): 311 (39) [M^+], 226 (15), 212 (100), 198 (17), 167 (25).
HRMS (EI) m/z calculated for $C_{21}H_{29}NO^+$: 311.2249; found: 311.2254.

Synthesis of 2-[4-Fluoro-3-(octan-2-yl)phenyl]pyridine (147ca)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.60 mg, 0.013 mmol, 2.4 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 29 mol %), **6ca** (89.8 mg, 0.52 mmol) and 2-bromooctane (**42ba**) (291 mg, 1.51 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 19:1 to 5:1) yielded **147ca** (83 mg, 56%) as a colorless oil.

The general procedure **E** with (*S*)-3-methyl-2-pivalamidobutanoic acid (**76c**) (31.0 mg, 0.15 mmol, 30 mol %) as additive in water (2 mL) at 100 °C gave 42% isolated yield.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.68 (dt, *J* = 4.9, 1.3 Hz, 1H), 7.87 (dd, *J* = 7.2, 2.3 Hz, 1H), 7.79-7.62 (m, 3H), 7.29-7.15 (m, 1H), 7.09 (dd, *J* = 10.1, 8.5 Hz, 1H), 3.11 (qt, *J* = 7.2, 7.1 Hz, 1H), 1.79-1.57 (m, 2H), 1.41-1.12 (m, 8H), 1.31 (d, *J* = 7.1 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.6 (d, $J_{C\text{-}F}$ = 247 Hz, C_q), 156.9 (C_q), 149.6 (CH), 136.6 (CH), 135.4 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 134.7 (d, $J_{C\text{-}F}$ = 15 Hz, CH), 126.9 (d, $J_{C\text{-}F}$ = 6 Hz, CH), 125.8 (d, $J_{C\text{-}F}$ = 9 Hz, CH), 121.8 (CH),

120.3 (CH), 115.6 (d, $J_{C\text{-}F}$ = 24 Hz, CH), 37.1 (CH_2), 33.0 (CH), 31.8 (CH_2), 29.3 (CH_2), 27.7 (CH_2), 22.6 (CH_2), 20.9 (CH_3), 14.0 (CH_3).

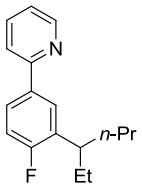
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -117.62 - -119.83 (m).

IR (ATR): $\tilde{\nu}$ = 2958, 2926, 2856, 1586, 1464, 1433, 1262, 1224, 825, 779 cm^{-1}.

MS (EI) m/z (relative intensity): 285 (14) [M^+], 214 (31), 200 (100), 185 (50), 78 (17).

HRMS (ESI) m/z calculated for $C_{19}H_{24}FN+H^+$: 286.1971; measured: 286.1975.

Synthesis of 2-[4-Fluoro-3-(hexan-3-yl)-phenyl]-pyridine (147cb)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.70 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (26 mg, 0.15 mmol, 30 mol %), **6ca** (85.3 mg, 0.50 mmol) and 3-bromohexane (**42bb**) (252 mg, 1.52 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147cb** (60 mg, 47%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.68 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.86-7.64 (m, 4H), 7.20 (ddd, *J* = 7.0, 4.8, 1.5 Hz, 1H), 7.09 (dd, *J* = 9.9, 8.5 Hz, 1H), 2.92 (dt, *J* = 8.8, 6.0 Hz, 1H), 1.85-1.56 (m, 4H), 1.29-1.13 (m, 2H), 0.95-0.74 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 62.2 (d, $J_{C\text{-}F}$ = 247 Hz, C_q), 156.9 (C_q) , 149.6 (CH) , 136.6 (CH) , 135.4 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 132.8 (d, $J_{C\text{-}F}$ = 15 Hz, C_q), 127.4 (d, $J_{C\text{-}F}$ = 6 Hz, CH), 125.7 (d, $J_{C\text{-}F}$ = 9 Hz, CH), 121.8 (CH), 120.3 (CH), 115.6 (d, $J_{C\text{-}F}$ = 24 Hz, CH), 40.2 (CH), 37.7 (d, $J_{C\text{-}F}$ = 2 Hz, CH_2), 28.6 (d, $J_{C\text{-}F}$ = 1 Hz, CH_2), 20.7 (CH_2), 14.1 (CH_3), 12.2 (CH_3).

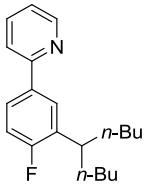
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -117.53 - -119.88 (m).

IR (ATR): $\tilde{\nu}$ = 3053, 2958, 2930, 2872, 1586, 1433, 1403, 1225, 778, 741 cm^{-1}.

MS (EI) *m/z* (relative intensity): 257 (23) [M^+], 228 (36), 214 (41), 186 (100).

HR-MS (ESI) *m/z* calculated for $C_{17}H_{20}FN+Na^+$: 280.1477; found: 280.1472.

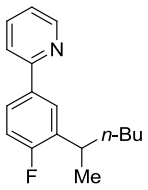
Synthesis of 2-[4-Fluoro-3-(nonan-5-yl)phenyl]pyridine (147cg)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.30 mg, 0.013 mmol, 2.6 mol %), $MesCO_2H$ (**13a**) (24 mg, 0.15 mmol, 28 mol %), **6ca** (90.1 mg, 0.52 mmol) and 5-bromononane (**42bg**) (313 mg, 1.51 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 5:1) yielded **147cg** (78 mg, 50%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.86-7.59 (m, 4H), 7.19 (ddd, *J* = 7.2, 4.8, 1.5 Hz, 1H), 7.07 (dd, *J* = 9.9, 8.5 Hz, 1H), 3.05-2.84 (m, 1H), 1.73-1.56 (m, 4H), 1.37-1.03 (m, 8H), 0.82 (t, *J* = 7.1 Hz, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.0 (d, $J_{C\text{-}F}$ = 246.7 Hz, C_q), 156.9 (CH), 149.6 (CH), 136.7 (CH), 135.4 (d, $J_{C\text{-}F}$ = 3.2 Hz, C_q), 133.2 (d, $J_{C\text{-}F}$ = 15.5 Hz, C_q), 127.4 (d, $J_{C\text{-}F}$ = 6.0 Hz, CH), 125.8 (d, $J_{C\text{-}F}$ = 8.7 Hz, CH), 121.8 (CH), 120.3 (CH), 115.6 (d, $J_{C\text{-}F}$ = 24.2 Hz, CH), 38.7 (CH), 35.5 (CH_2), 29.9 (CH_2), 22.7 (CH_2), 14.0 (CH_3).
^{19}F-NMR (282 MHz, $CDCl_3$) δ = -118.34 (m).
IR (ATR): $\tilde{\nu}$ = 2956, 2929, 2857, 1586, 1567, 1499, 1463, 1433, 1225, 825, 779 cm^{-1}.
MS (EI) m/z (relative intensity): 299 (18) [M^+], 256 (11), 242 (100), 200 (14), 186 (69).
HRMS (EI: m/z calculated for $C_{20}H_{26}FN^+$: 299.2049; found 299.2059.

Synthesis of 2-[4-Fluoro-3-(hexan-2-yl)phenyl]pyridine (147cj)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.70 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 30 mol %), **6ca** (87.3 mg, 0.50 mmol) and 2-bromohexane (**42bj**) (253 mg, 1.53 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 7:1) yielded **147cj** (80 mg, 62%) as a colorless oil.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.68 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.87 (dd, *J* = 7.2, 2.4 Hz, 1H), 7.80-7.64 (m, 3H), 7.21 (ddd, *J* = 7.1, 4.9, 1.4 Hz, 1H), 7.09 (dd, *J* = 10.1, 8.5 Hz, 1H), 3.11 (qt, *J* = 7.1, 6.9 Hz, 1H), 1.77-1.55 (m, 2H), 1.39-1.13 (m, 4H), 1.31 (d, *J* = 6.9 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.7 (d, $J_{C\text{-}F}$ = 247 Hz, C_q), 157.0 (C_q), 149.7 (CH), 136.8 (CH), 135.6 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 134.8 (d, $J_{C\text{-}F}$ = 15 Hz, C_q), 127.0 (d, $J_{C\text{-}F}$ = 6 Hz, CH), 125.9 (d, $J_{C\text{-}F}$ = 9 Hz, CH), 121.9 (CH), 120.3 (CH), 115.7 (d, $J_{C\text{-}F}$ = 24 Hz, CH), 37.0 (CH_2), 33.1 (CH), 30.0 (CH_2), 22.8 (CH_2), 21.0 (CH_3), 14.1 (CH_3).

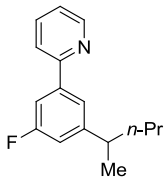
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -117.64 - 119.88 (m).

IR (ATR): $\tilde{\nu}$ = 2959, 2928, 2971, 2858, 1586, 1567, 1499, 1464, 1433, 1261, 1225, 1099, 779 cm^{-1}.

MS (EI) m/z (relative intensity): 257 (20) [M^+], 214 (16), 200 (100), 185 (39).

HRMS (EI) m/z calculated for $C_{17}H_{20}FN^+$: 257.1580, found: 257.1576.

Synthesis of 2-[3-Fluoro-5-(pentan-2-yl)phenyl]pyridine (147di)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (15.1 mg, 0.025 mmol, 5.0 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 31 mol %), **6da** (83.7 mg, 0.48 mmol) and 2-bromopentane (**42bi**) (234 mg, 1.55 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147di** (33 mg, 28%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.67 (ddd, J = 4.8, 1.8, 1.0 Hz, 1H), 7.77-7.65 (m, 2H), 7.61-7.57 (m, 1H), 7.48 (ddd, J = 9.9, 2.5, 1.6 Hz, 1H), 7.22 (ddd, J = 7.2, 4.8, 1.5 Hz, 1H), 6.98-6.87 (m, 1H), 2.78 (qt, J = 7.1, 6.9 Hz, 1H), 1.76-1.41 (m, 2H), 1.41-1.10 (m, 2H), 1.27 (d, J = 6.9 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.4 (d, $J_{C\text{-}F}$ = 245 Hz, C_q), 156.5 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 151.0 (d, $J_{C\text{-}F}$ = 7 Hz, C_q), 149.7 (CH), 141.3 (d, $J_{C\text{-}F}$ = 8 Hz, C_q), 136.8 (CH), 122.4 (CH), 121.4 (d, $J_{C\text{-}F}$ = 2 Hz, CH), 120.6 (CH), 114.1 (d, $J_{C\text{-}F}$ = 21 Hz, CH), 111.2 (d, $J_{C\text{-}F}$ = 23 Hz, CH), 40.5 (CH_2), 39.8 (d, $J_{C\text{-}F}$ = 2 Hz, CH), 22.1 (CH_2), 20.7 (CH_3), 14.1 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = -113.84 (t, J = 9.9 Hz).

IR (ATR): $\tilde{\nu}$ = 2958, 2929, 2872, 1718, 1585, 1438, 1439, 1265, 1171, 1082, 783, 543 cm^{-1}.

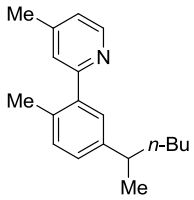
MS (EI) m/z (relative intensity): 243 (45) [M^+], 214 (15), 200 (100), 185 (62), 164 (13), 146 (22).

HRMS (EI) m/z calculated for $C_{16}H_{18}FN^+$: 243.1423; found: 243.1424.

2-[5-(Hexan-2-yl)-2-methylphenyl]-4-methylpyridine (147ea) and 2-[3-(Hexan-2-yl)-2-methylphenyl]-4-methylpyridine (147ea')

The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5.0 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 26 mol %), **6eb** (105 mg, 0.57 mmol) and 2-bromohexane (**42ba**)

(251 mg, 1.52 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147ea** (25 mg, 16%) and **147ea'** (70 mg, 46%) as a colorless oils.



2-[5-(Hexan-2-yl)-2-methylphenyl]-4-methylpyridine (147ea)

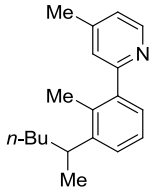
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.54 (dd, *J* = 5.1, 0.7 Hz, 1H), 7.23-7.15 (m, 3H), 7.15-7.09 (m, 1H), 7.09-7.02 (m, 1H), 2.68 (qt, *J* = 7.0, 6.9 Hz, 1H), 2.41 (s, 3H), 2.32 (s, 3H), 1.65-1.49 (m, 2H), 1.35-1.08 (m, 4H), 1.26 (d, *J* = 6.9 Hz, 3H), 0.90-0.80 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.8 (C_q), 149.5 (CH), 147.6 (C_q), 146.0 (C_q), 140.9 (C_q), 133.5 (C_q), 131.1 (CH), 128.8 (CH), 127.2 (CH), 125.6 (CH), 123.1 (CH), 40.1 (CH_3), 38.7 (CH_2), 30.6 (CH_2), 23.4 (CH_2), 22.9 (CH_3), 21.7 (CH), 20.4 (CH_3), 14.6 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2956, 2924, 2857, 1599, 1559, 1500, 1454, 1378, 886, 821 cm^{-1}.

MS (EI) *m/z* (relative intensity): 266 (100) [M-H$^+$], 252 (13), 210 (75), 195 (36), 181 (14).

HR-MS (ESI) *m/z* calculated for $C_{19}H_{25}N$-H$^+$: 266.1909; found: 266.2064.



2-[3-(Hexan-2-yl)-2-methylphenyl]-4-methylpyridine (147ea')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.53 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.29-7.21 (m, 2H), 7.21-7.17 (m, 1H), 7.14 (dd, *J* = 6.7, 2.3 Hz, 1H), 7.06 (ddd, *J* = 5.1, 1.7, 0.8 Hz, 1H), 3.07 (qt, *J* = 7.0, 6.9 Hz, 1H), 2.40 (d, *J* = 0.7 Hz, 3H), 2.24 (s, 3H), 1.78-1.48 (m, 2H), 1.38-1.15 (m, 4H), 1.26 (d, *J* = 6.9 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H).

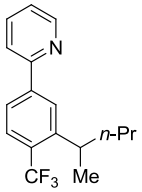
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.2 (C_q), 148.8 (CH), 147.1 (C_q), 146.9 (C_q), 141.4 (C_q), 133.0 (C_q), 127.0 (CH), 125.6 (CH), 125.4 (CH), 125.3 (CH), 122.5 (CH), 37.7 (CH_2), 34.6 (CH_3), 30.1 (CH_2), 23.0 (CH_2), 21.9 (CH_3), 21.2 (CH), 16.2 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3049, 2957, 2925, 2858, 1601, 1557, 1458, 1377, 991, 826, 797, 727, 519 cm^{-1}.

MS (EI) *m/z* (relative intensity): 266 (35) [M-H$^+$], 252 (27), 238 (30), 224 (100), 210 (70), 195 (25), 181 (16).

HR-MS (ESI) *m/z* calculated for $C_{19}H_{25}N\text{-}H^+$: 266.1909; found: 266.1918.

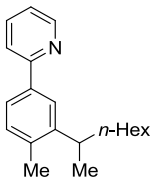
Synthesis of 2-[3-(Pentan-2-yl)-4-(trifluoromethyl)phenyl]pyridine (147ki)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.50 mg, 0.012 mmol, 2.3 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 30 mol %), **6ka** (113 mg, 0.51 mmol) and 2-bromopentane (**42bi**) (218 mg, 1.45 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147ki** (82 mg, 55%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 4.9 Hz, 1H), 8.07-8.04 (m, 1H), 7.85-7.80 (m, 1H), 7.80-7.70 (m, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.26 (ddd, *J* = 7.1, 5.0, 2.0 Hz, 1H), 3.22 (qt, *J* = 6.8, 6.7 Hz, 1H), 1.84-1.50 (m, 2H), 1.45-1.02 (m, 2H), 1.29 (d, *J* = 6.8 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 156.3 (C_q) 149.8 (CH), 147.9 (C_q), 142.7 (C_q), 136.8 (CH), 128.3 (q, $J_{C\text{-}F}$ = 29.2 Hz, C_q), 126.0 (q, $J_{C\text{-}F}$ = 5.6 Hz, CH), 126.0 (CH), 124.7 (q, $J_{C\text{-}F}$ = 273.8 Hz, C_q), 124.0 (CH), 122.8 (CH), 120.9 (CH), 40.5 (CH_2), 34.6 (q, $J_{C\text{-}F}$ = 2.0 Hz, CH), 22.8 (CH_3), 20.8 (CH_2), 14.1 (CH_3).
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -58.53 (m).
IR (ATR): $\tilde{\nu}$ = 2960, 2930, 2873, 1614, 1587, 1564, 1467, 1309, 1142, 1110, 1032, 781 cm^{-1}.
MS (EI) m/z (relative intensity): 293 (24) [M^+], 264 (17), 250 (100), 230 (43), 224 (42), 210 (20).
HRMS (ESI) m/z calculated for $C_{17}H_{18}F_3N^+$: 293.1391; found: 293.1391.

Synthesis of 2-[4-Methyl-3-(octan-2-yl)phenyl]pyridine (147oa)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.20 mg, 0.013 mmol, 2.6 mol %), $MesCO_2H$ (**13a**) (26 mg, 0.15 mmol, 30 mol %), **6oa** (83.0 mg, 0.49 mmol) and 2-bromooctane (**42ba**) (283 mg, 1.47 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147oa** (76 mg, 55%) as a colorless oil.

The general procedure **E** with (*S*)-3-methyl-2-pivalamidobutanoic acid (**76c**) (31.0 mg, 0.15 mmol, 30 mol %) as additive in water (2 mL) at 100 °C gave 55% isolated yield.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.70 (ddd, *J* = 6.4, 3.4, 2.1 Hz, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.74-7.68 (m, 3H), 7.38-7.01 (m, 2H), 3.02 (qt, *J* = 7.1, 6.9 Hz, 1H), 2.38 (s, 3H), 1.79-1.54 (m, 2H), 1.42-1.01 (m, 8H), 1.28 (d, *J* = 6.9 Hz, 3H), 0.87 (t, *J* = 6.0 Hz, 3H).

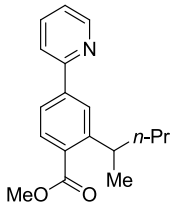
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.9 (C_q), 149.5 (CH), 146.5 (C_q), 137.3 (C_q), 136.5 (CH), 136.3 (C_q), 130.5 (CH), 123.8 (CH), 123.8 (CH), 121.6 (CH), 120.3 (CH), 37.8 (CH_2), 34.6 (CH_3), 31.8 (CH_2), 29.4 (CH_2), 27.8 (CH_2), 22.6 (CH_2), 21.5 (CH), 19.4 (CH_3), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2956, 2924, 2854, 1585, 1501, 1465, 909, 777, 732 cm^{-1}.

MS (EI) m/z (relative intensity): 281 (22) [M^+], 210 (19), 196 (100), 181 (26), 40 (14).

HRMS (ESI) m/z calculated for $C_{20}H_{27}N+H^+$: 282.2222; found: 282.2216.

Synthesis of Methyl 2-(pentan-2-yl)-4-(pyridin-2-yl)benzoate (147pi)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 30 mol %), **6pa** (109 mg, 0.51 mmol) and 2-bromopentane (**42bi**) (232 mg, 1.54 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147pi** (91 mg, 63%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.70 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 8.00 (dd, *J* = 1.1 Hz, 1H), 7.80 (d, *J* = 1.1 Hz, 2H), 7.78-7.70 (m, 3H), 7.24 (ddd, *J* = 6.1, 4.8, 2.4 Hz, 1H), 3.89 (s, 3H), 3.64 (qt, *J* = 7.0, 6.9 Hz, 1H), 1.81-1.49 (m, 2H), 1.43-1.11 (m, 2H), 1.30 (d, *J* = 6.9 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H).

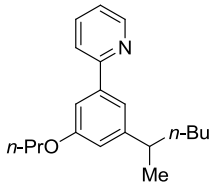
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.7 (C_q), 156.6 (C_q), 149.7 (CH), 149.5 (C_q), 142.2 (C_q), 136.8 (CH), 130.6 (C_q), 130.2 (CH), 125.3 (CH), 123.8 (CH), 122.6 (CH), 120.9 (CH), 52.0 (CH_3), 40.6 (CH_2), 34.5 (CH), 22.1 (CH_3), 20.8 (CH_2), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2955, 2929, 2870, 1718, 1586, 1559, 1464, 1431, 1242, 1078, 772 cm^{-1}.

MS (EI) m/z (relative intensity): 283 (24) [M^+], 252 (42), 240 (55), 222 (62), 208 (100), 180 (40), 167 (19), 152 (14).

HRMS (EI) m/z calculated for $C_{18}H_{21}NO_2^+$: 283.1572; found: 283.1582.

Synthesis of 2-[3-(Hexan-2-yl)-5-*n*-propoxyphenyl]pyridine (147si)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.70 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25mg, 0.15 mmol, 32 mol %), **6sa** (104 mg, 0.47 mmol) and 2-bromohexane (**42bi**) (243 mg, 1.48 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 5:1) yielded **147si** (57 mg, 39%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.69 (ddd, *J* = 4.8, 1.4, 1.4 Hz, 1H), 7.78-7.68 (m, 2H), 7.45-7.35 (m, 2H), 7.25-7.17 (m, 1H), 6.86-6.75 (m, 1H), 4.02 (t, *J* = 6.6 Hz, 2H), 2.73 (qt, *J* = 6.9, 6.9 Hz, 1H), 1.94-1.76 (m, 2H), 1.71-1.48 (m, 2H), 1.37-1.14 (m, 4H), 1.28 (d, *J* = 6.9 Hz, 3H), 1.06 (t, *J* = 7.4 Hz, 3H), 0.86 (t, *J* = 8.0 Hz, 3H).

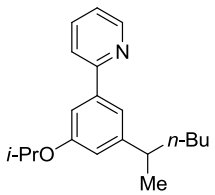
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.6 (C_q), 157.7 (C_q) 150.0 (C_q), 149.5 (CH), 140.5 (C_q), 136.6 (CH), 122.0 (CH), 120.7 (CH), 118.3 (CH), 114.4 (CH), 109.8 (CH), 69.5 (CH_2), 40.2 (CH), 38.0 (CH_2), 30.0 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 22.3 (CH_3), 14.0 (CH_3), 10.6 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2958, 2926, 2872, 1584, 1566, 1440, 1330, 1214, 1170, 1057, 993, 865, 782 cm^{-1}.

MS (EI) *m/z* (relative intensity): 297 (38) [M^+], 254 (20), 241 (100), 198 (38), 183 (26).

HR-MS (EI) *m/z* calculated for $C_{20}H_{27}NO^+$: 297.2093; found: 297.2094.

Synthesis of 2-[3-(Hexan-2-yl)-5-*iso*-propoxyphenyl]pyridine (147ti)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.90 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (24 mg, 0.15 mmol, 28 mol %), **6ta** (114 mg, 0.53 mmol) and 2-bromohexane (**42bi**) (276 mg, 1.67 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 5:1) yielded **147ti** (60 mg, 38%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.73-8.60 (m, 1H), 7.76-7.64 (m, 2H), 7.39-7.30 (m, 2H), 7.22-7.13 (m, 1H), 6.77 (dd, *J* = 2.4, 1.6 Hz, 1H), 4.66 (hept, *J* = 6.0 Hz, 1H), 2.71 (qt, *J* = 7.1 Hz, 1H), 1.67-1.49 (m, 2H), 1.35 (d, *J* = 6.1 Hz, 6H), 1.33-1.11 (m, 7H), 0.83 (t, *J* = 7.0 Hz, 3H).

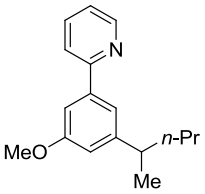
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.3 (C_q), 157.7 (C_q), 150.1 (C_q), 149.5 (CH), 140.5 (C_q), 136.6 (CH), 122.0 (CH), 120.7 (CH), 118.3(CH), 115.7 (CH), 111.4 (CH), 69.8 (CH), 40.2 (CH), 38.1 (CH_2), 30.0 (CH_2), 22.8 (CH_2), 22.2 (CH_3), 22.1 (2xCH_3), 14.03 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2957, 2926, 2871, 2857, 1584, 1566, 1439, 1325, 1116, 993, 782 cm^{-1}.

MS (EI) *m/z* (relative intensity): 297 (29) [M^+], 255 (15), 241 (21), 212 (21), 199 (100), 183 (29), 43 (19).

HR-MS (EI) *m/z* calculated for $C_{20}H_{27}NO^+$: 297.2093; found: 297.2102.

Synthesis of 2-(3-Methoxy-5-pentan-2-ylphenyl)pyridine (147ui)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %), $MesCO_2H$ (**13a**) (26 mg, 0.15 mmol, 32 mol %), **6ua** (77.1 mg, 0.42 mmol) and 2-bromopentane (**42bi**) (227 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147ui** (43 mg, 40%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.69 (d, *J* = 4.8 Hz, 1H), 7.79-7.68 (m, 2H), 7.39 (dd, *J* = 3.4, 1.9 Hz, 2H), 7.23 (ddd, *J* = 6.8, 4.9, 2.3 Hz, 1H), 6.81 (s, 1H), 3.89 (s, 3H), 2.77 (qt, *J* = 7.1, 6.9 Hz, 1H), 1.70-1.49 (m, 2H), 1.39-1.11 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H).

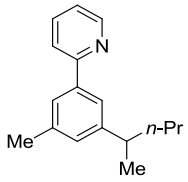
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.0 (C_q), 157.5 (C_q), 150.0 (C_q), 149.3 (CH), 140.4 (C_q), 136.6 (CH), 122.0 (CH), 120.8 (CH), 118.4 (CH), 114.0 (CH), 109.1 (CH), 55.4 (CH), 40.6 (CH_2), 40.0 (CH_3), 22.3 (CH_3), 20.9 (CH_2), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2956, 2927, 2870, 1584, 1566, 1453, 1417, 1339, 1217, 1168, 1056, 864, 781cm^{-1}.

MS (EI) m/z (relative intensity): 255 (46) [M^+], 213 (100), 197 (26), 182 (18), 168 (26), 154 (14).

HRMS (EI) m/z calculated for $C_{17}H_{21}NO^+$: 255.1623; found: 255.1626.

Synthesis of 2-[3-Methyl-5-(pentan-2-yl)phenyl]pyridine (147vi)

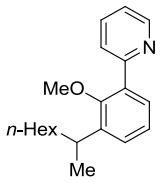


The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (16.0 mg, 0.026 mmol, 4.8 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 28 mol %), **6va** (96.6 mg, 0.57 mmol) and 2-bromopentane (**42bi**) (229 mg, 1.52 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **147vi** (52 mg, 38%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.69 (ddd, *J* = 4.9, 1.4, 1.4 Hz, 1H), 7.79-7.66 (m, 2H), 7.65-7.55 (m, 2H), 7.25-7.16 (m, 1H), 7.09-7.02 (m, 1H), 2.76 (qt, *J* = 7.0, 6.9 Hz, 1H), 2.42 (s, 3H), 1.71-1.48 (m, 2H), 1.41-1.13 (m, 2H), 1.26 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.1 (C_q), 149.7 (CH), 148.6 (C_q), 139.5 (C_q), 138.4 (C_q), 136.8 (CH), 128.6 (CH), 125.4 (CH), 123.1 (CH), 122.0 (CH), 120.9 (CH), 40.8 (CH_2), 39.9 (CH_3), 22.4 (CH_3), 21.7 (CH), 21.1 (CH_2), 14.3 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2956, 2925, 2869, 1585, 1566, 1446, 1377, 991, 781, 742, 704, 671 cm^{-1}.
MS (EI) *m/z* (relative intensity): 239 (22) [M^+], 210 (11), 196 (100), 181 (42), 167 (12).
HR-MS (EI) *m/z* calculated for $C_{17}H_{21}N^+$: 239.1674; found: 239.1672.

2-[2-Methoxy-3-(octan-2-yl)phenyl]pyridine (147wa') and 2-[2-Methoxy-5-(octan-2-yl)phenyl]-pyridine (147wa)

The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.00 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 30 mol %), **6wa** (90.3 mg, 0.49 mmol) and **42ba** (293 mg, 1.52 mmol). After 20 h, purification by chromatography (*n*-hexane/EtOAc 9:1) yielded a mixture of **147wa** and **147wa'** (^{1}H-NMR ratio **147wa**: **147wa' =** 1.0:2.1; 62 mg, 43%) as colorless oils. To get pure compounds some of the mixture was separated by HPLC (*n*-hexane/EtOAc = 97:3).



2-[2-Methoxy-3-(octan-2-yl)phenyl]pyridine (147wa')

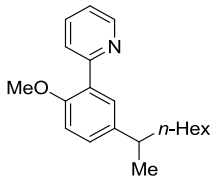
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.71 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.72 (ddd, *J* = 7.4, 1.8, 1.0 Hz, 1H), 7.50 (dd, *J* = 7.4, 2.0 Hz, 1H), 7.35-7.07 (m, 3H), 3.41 (s, 3H), 3.29-3.20 (m, 1H), 1.69-1.50 (m, 2H), 1.41-1.06 (m, 8H), 1.24 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 6.6 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.0 (C_q), 155.5 (C_q), 149.4 (CH), 141.3 (C_q), 135.9 (CH), 133.3 (C_q), 128.5 (CH), 127.5 (CH), 124.5 (CH), 124.4 (CH), 121.7 (CH), 61.6 (CH_3), 38.1 (CH_2), 31.9 (CH_2), 31.8 (CH), 29.5 (CH_2), 28.0 (CH_2), 22.7 (CH_2), 22.3 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2956, 2925, 2855, 1586, 1452, 1430, 1217, 1008, 775, 746 cm^{-1}.

MS (EI) m/z (relative intensity): 297 (29) [M^+], 282 (49), 226 (100), 212 (53), 196 (66), 184 (17), 167 (30).

HRMS (EI) m/z calculated for $C_{20}H_{27}NO$-H^+: 296.2014; found: 296.2026.



2-[2-Methoxy-5-(octan-2-yl)phenyl]pyridine (147wa)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.69 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.73-7.61 (m, 1H), 7.55 (d, *J* = 2.4 Hz, 1H), 7.23-7.11 (m, 2H), 6.92 (d, *J* = 8.5 Hz, 1H), 3.82 (s, 3H), 2.69 (qt, *J* = 7.1, 6.8 Hz, 1H), 1.64-1.48 (m, 2H), 1.37-1.05 (m, 8H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.84 (t, *J* = 6.9 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 156.4 (C_q), 155.0 (C_q), 149.5 (C_q), 149.3 (CH), 140.6 (C_q), 135.6 (CH), 129.8 (CH), 128.0 (CH), 125.2 (CH), 121.5 (CH), 111.4 (CH), 55.7 (CH_3), 39.2 (CH), 38.6 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 27.8 (CH_2), 22.7 (CH_2), 22.4 (CH_3), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2955, 2924, 2854, 1586, 1500, 1462, 1238, 1061, 1027, 812, 746 cm^{-1}.

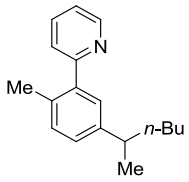
MS (EI) m/z (relative intensity): 297 (50) [M^+], 226 (12), 212 (100), 197 (29), 183 (20), 167 (17), 80 (25).

HRMS (EI) m/z calculated for $C_{20}H_{27}NO$-H^+: 296.2014; found: 296.2028.

2-[5-(Hexan-2-yl)-2-methylphenyl]pyridine (147xa) and 2-[3-(Hexan-2-yl)-2-methylphenyl]pyridine (147xa')

The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.30 mg, 0.013 mmol, 2.7 mol %), $MesCO_2H$ (**13a**) (24 mg, 0.15 mmol, 30 mol %), **6xa** (76.2 mg, 0.45 mmol) and **42ba** (242 mg,

1.47 mmol). After 20 h, purification by chromatography (*n*-hexane/EtOAc 9:1) yielded **147xa** (18 mg, 16%) and **147xa'** (51 mg, 44%) as colorless oils.



2-[5-(Hexan-2-yl)-2-methylphenyl]pyridine (147xa)

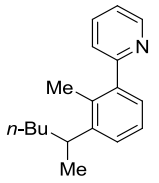
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.70 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.74 (ddd, *J* = 7.7, 1.9 Hz, 1H), 7.42-7.37 (m, 1H), 7.24-7.17 (m, 3H), 7.13 (dd, *J* = 7.9, 1.9 Hz, 1H), 2.69 (qt, *J* = 7.0, 7.0 Hz, 1H), 2.32 (s, 3H), 1.77-1.45 (m, 2H), 1.40-1.08 (m, 4H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.4 (C_q), 149.1 (CH), 145.5 (C_q), 140.2 (C_q), 136.0 (C_q), 132.9 (CH), 130.6 (C_q), 128.3 (CH), 126.8 (CH), 124.1 (CH), 121.5 (CH), 39.5 (CH), 38.1 (CH_2), 30.0 (CH_2), 22.8 (CH_2), 22.3 (CH_3), 19.8 (CH_3), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2955, 2924, 2857, 1587, 1563, 1466, 1426, 894, 823, 792, 748, 639 cm^{-1}.

MS (EI) m/z (relative intensity): 252 (100) [M-H$^+$], 196 (98), 181 (61), 167 (27).

HRMS (EI) m/z calculated for $C_{18}H_{23}N^+$: 253.1830, found: 253.1826.



2-[3-(Hexan-2-yl)-2-methylphenyl]pyridine (147xa')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.69 (ddd, *J* = 4.8, 1.9, 1.0 Hz, 1H), 7.72 (td, *J* = 7.7, 1.8 Hz, 1H), 7.37 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.32-7.19 (m, 3H), 7.16 (dd, *J* = 6.7, 2.3 Hz, 1H), 3.08 (qt, *J* = 7.0, 6.9 Hz, 1H), 2.25 (s, 3H), 1.78-1.50 (m, 2H), 1.40-1.16 (m, 4H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.2 (C_q), 149.0 (CH), 146.8 (C_q), 141.2 (C_q), 135.9 (CH), 132.9 (C_q), 126.9 (CH), 125.5 (CH), 125.3 (CH), 124.4 (CH), 121.3 (CH), 37.6 (CH_2), 34.4 (CH), 30.0 (CH_2), 22.9 (CH_2), 21.7 (CH_3), 16.0 (CH_3), 14.0 (CH_3).

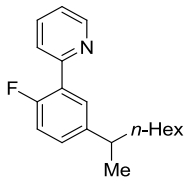
IR (ATR): $\tilde{\nu}$ = 2957, 2926, 2857, 1580, 1563, 1458, 1422, 1377, 1002, 777, 748, 728 cm^{-1}.

MS (EI) m/z (relative intensity): 281 (50) [M$^+$], 266 (21), 224 (20), 210 (100), 196 (75), 181 (33), 167 (38), 84 (27), 41 (41).

HRMS (ESI) m/z calculated for $C_{18}H_{23}N$+H$^+$: 254.1909; found: 254.1911.

2-[2-Fluoro-5-(octan-2-yl)phenyl]pyridine (147za) and 2-[2-Fluoro-3-(octan-2-yl)phenyl]pyridine (147za')

The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.70 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 28 mol %), **6za** (93.5 mg, 0.54 mmol) and 2-bromooctane (**42ba**) (297 mg, 1.54 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 19:1) yielded **147za** (4 mg, 3%) and **147za'** (24 mg, 16%) as colorless oils.



2-[2-Fluoro-5-(octan-2-yl)phenyl]pyridine (147za)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.71 (ddd, *J* = 4.8, 1.7, 1.1 Hz, 1H), 7.83-7.65 (m, 3H), 7.26-7.20 (m, 1H), 7.20-7.12 (m, 1H), 7.06 (dd, *J* = 11.0, 8.4 Hz, 1H), 2.73 (qt, *J* = 7.1, 7.0 Hz, 1H), 1.71-1.46 (m, 2H), 1.23 (dd, *J* = 6.3, 2.8 Hz, 8H), 1.26 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H).

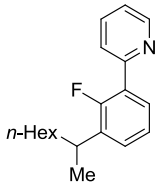
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.0 (d, $J_{C\text{-}F}$ = 247 Hz, C_q), 154.1 (d, $J_{C\text{-}F}$ = 2 Hz, C_q), 150.0 (CH), 144.5 (d, $J_{C\text{-}F}$ = 4 Hz, C_q), 136.6 (CH), 129.7 (d, $J_{C\text{-}F}$ = 3 Hz, CH), 128.9 (d, $J_{C\text{-}F}$ = 8 Hz, CH), 127.2 (d, $J_{C\text{-}F}$ = 12 Hz, C_q), 125.0 (d, $J_{C\text{-}F}$ = 9 Hz, CH), 122.6 (CH), 116.3 (d, $J_{C\text{-}F}$ = 23 Hz, CH), 39.9 (CH), 39.0 (CH_2), 32.3 (CH_2), 29.9 (CH_2), 28.2 (CH_2), 23.1 (CH_2), 22.8 (CH_3), 14.6 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = -111.79 - -137.55 (m).

IR (ATR): $\tilde{\nu}$ = 2956, 2925, 2855, 1587, 1568, 1498, 1462, 1441, 1252, 1213, 821, 790, 744 cm^{-1}.

MS (EI) *m/z* (relative intensity): 285 (12) [M^+], 214 (15), 200 (100), 185 (26).

HR-MS (ESI) *m/z* calculated for $C_{19}H_{24}FN^+$: 285.1893; found: 285.1892.



2-[2-Fluoro-3-(octan-2-yl)phenyl]pyridine (147za')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.70 (ddd, *J* = 4.8, 1.5, 1.5 Hz, 1H), 7.79-7.64 (m, 3H), 7.30-7.14 (m, 3H), 3.14 (qt, *J* = 7.0, 6.9 Hz, 1H), 1.69-1.50 (m, 2H), 1.35-1.12 (m, 8H), 1.27 (d, *J* = 6.9 Hz, 3H), 0.83 (t, *J* = 6.5 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.3 (d, $J_{C\text{-}F}$ = 248 Hz, C_q), 154.2 (d, $J_{C\text{-}F}$ = 2 Hz, C_q), 149.6 (CH), 136.1 (CH), 135.0 (d, $J_{C\text{-}F}$ = 16 Hz, C_q), 128.4 (d, $J_{C\text{-}F}$ = 6 Hz, CH), 128.3 (d, $J_{C\text{-}F}$ = 3.2 Hz, C_q), 127.5 (d, $J_{C\text{-}F}$ = 14 Hz, CH), 124.6 (d, $J_{C\text{-}F}$ = 8 Hz, CH), 124.2 (d, $J_{C\text{-}F}$ = 4 Hz, CH), 122.1 (CH), 37.3 (d, $J_{C\text{-}F}$ = 1 Hz, CH_2), 32.4 (d, $J_{C\text{-}F}$ = 3 Hz, CH), 31.8 (CH_2), 29.3 (CH_2), 27.6 (CH_2), 22.6 (CH_2), 21.1 (d, $J_{C\text{-}F}$ = 1 Hz, CH_3), 14.0 (CH_3).

^{19}F-NMR (283 MHz, $CDCl_3$): δ = -124.49 - -124.61 (m).

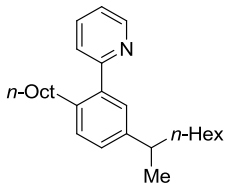
IR (ATR): $\tilde{\nu}$ = 2958, 2926, 2856, 1587, 1567, 1443, 1425, 1198, 1071, 822, 771, 742 cm^{-1}.

MS (EI) *m/z* (relative intensity): 285 (10) [M^+], 214 (18), 200 (100), 185 (18).

HR-MS (ESI) *m/z* calculated for $C_{19}H_{24}FN^+$: 285.1893; found: 285.1888.

2-[5-(Octan-2-yl)-2-(*n*-octyl)phenyl]pyridine (150) and 2-[3-(Octan-2-yl)-2-(*n*-octanyl)phenyl]-pyridine (150')

The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (16.0 mg, 0.027 mmol, 5.0 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 30 mol %), **93a** (138 mg, 0.52 mmol) and 2-bromooctane (**42ba**) (284 mg, 1.47 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 19:1) yielded **150** (28 mg, 14%) and **150'** (36 mg, 18%) as colorless oils.



2-[5-(Octan-2-yl)-2-(*n*-octyl)phenyl]pyridine (150)

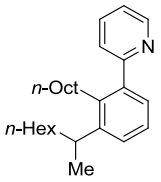
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.68 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.73 (ddd, *J* = 7.7, 1.9, 1.9 Hz, 1H), 7.37 (ddd, *J* = 7.8, 1.1, 1.0 Hz, 1H), 7.23 (dddd, *J* = 5.1, 3.2, 1.6, 1.6 Hz, 2H), 7.17-7.11 (m, 2H), 2.82-2.56 (m, 3H), 1.68-1.37 (m, 4H), 1.37-1.03 (m, 21H), 0.91-0.76 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.8 (C_q), 149.2 (CH), 145.5 (C_q), 140.2 (C_q), 138.1 (C_q), 136.1 (CH), 129.7 (CH), 128.5 (CH), 126.9 (CH), 124.3 (CH), 121.6 (CH), 39.7 (CH), 38.6 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 27.9 (CH_2), 22.8 (CH_2), 22.8 (CH_2), 22.2 (CH_2), 22.2 (CH_2), 14.3 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2955, 2923, 2853, 1587, 1563, 1466, 1426, 1271, 829, 793, 747 cm^{-1}.

MS (EI) *m/z* (relative intensity): 379 (12) [M^+], 294 (100), 208 (14), 194 (22).

HR-MS (EI) *m/z* calculated for $C_{27}H_{41}N^+$: 379.3239; found: 379.3233.



2-[3-(Octan-2-yl)-2-(*n*-octanyl)phenyl]pyridine (150')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.72-8.62 (m, 1H), 7.73 (ddd, *J* = 7.7, 1.8, 1.8 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 1H), 7.24 (dd, *J* = 11.8, 7.7 Hz, 3H), 7.08 (dd, *J* = 7.1, 1.8 Hz, 1H), 3.03 (qt, *J* = 7.1, 7.0 Hz, 1H), 2.67-2.52 (m, 2H), 1.71-1.49 (m, 2H), 1.49-1.01 (m, 23H), 0.87 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.2 (C_q), 149.3 (CH), 147.2 (C_q), 141.6 (C_q), 138.6 (C_q), 136.5 (CH), 127.6 (CH), 126.4 (CH), 126.2 (CH), 124.8 (CH), 122.0 (CH), 39.1 (CH_2), 34.6 (CH), 32.4 (CH_2), 32.4 (CH_2), 31.9 (CH_2), 30.4 (CH_2), 30.1 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 28.5 (CH_2), 23.3 (CH_2), 23.2 (CH_2), 23.2 (CH_3), 14.7 (CH_3), 14.6 (CH_3).

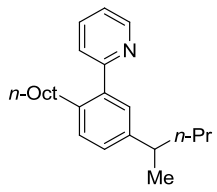
IR (ATR): $\tilde{\nu}$ = 2956, 2922, 2853, 1582, 1563, 1458, 1420, 779, 747, 723 cm^{-1}.

MS (EI) *m/z* (relative intensity): 378 (100) [M-H^+], 308 (78), 294 (41), 266 (21), 208 (48), 194 (50), 180 (30), 43 (50).

HR-MS (ESI) *m/z* calculated for $C_{27}H_{41}N+H^+$: 380.3312; found: 380.3311.

2-[2-(*n*-Octyl)-5-(pentan-2-yl)phenyl]pyridine (151) and 2-[2-(*n*-Octyl)-3-(pentan-2-yl)phenyl]-pyridine (151')

The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (15.0 mg, 0.025 mmol, 5.0 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 29 mol %), **93a** (138 mg, 0.52 mmol) and 2-bromopentane (**42bi**) (236 mg, 1.56 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 30:1) yielded **151** (25 mg, 14%) and **151'** (30 mg, 17%) as colorless oils.



2-[2-(*n*-Octyl)-5-(pentan-2-yl)phenyl]pyridine (151)

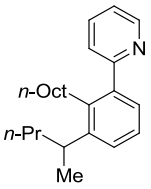
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.73-8.63 (m, 1H), 7.73 (ddd, *J* = 7.5, 1.5, 1.5 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.29-7.17 (m, 2H), 7.17-7.09 (m, 2H), 2.80-2.54 (m, 3H), 1.67-1.34 (m, 4H), 1.34-1.00 (m, 15H), 0.91-0.77 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.7 (C_q), 149.0 (CH), 145.2 (C_q), 140.1 (C_q), 138.0 (C_q), 135.9 (CH), 129.5 (CH), 128.4 (CH), 126.8 (CH), 124.1 (CH), 121.4 (CH), 40.7 (CH_2), 39.2 (CH), 32.6 (CH_2), 31.8 (CH_2), 31.3 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 22.6 (CH_2), 22.2 (CH_2), 20.8 (CH_2), 14.1 (CH_3), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2955, 2924, 2853, 1586, 1563, 1466, 1425, 1101, 897, 747 cm^{-1}.

MS (EI) *m/z* (relative intensity): 337 (31) [M^+], 252 (100), 238 (15), 208 (17), 194 (34), 167 (15), 43 (28).

HR-MS (EI) *m/z* calculated for $C_{24}H_{35}N^+$: 337.2770; found: 337.2755.



2-[2-(*n*-Octyl)-3-(pentan-2-yl)phenyl]pyridine (151')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.78-8.59 (m, 1H), 7.72 (td, *J* = 7.7, 1.9 Hz, 1H), 7.35 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.31-7.17 (m, 3H), 7.07 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.05 (h, *J* = 7.0 Hz, 1H), 2.70-2.51 (m, 2H), 1.66-1.52 (m, 2H), 1.49-1.00 (m, 17H), 0.96-0.79 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.6 (C_q), 148.8 (CH), 146.6 (C_q), 141.0 (C_q), 138.1 (C_q), 135.9 (CH), 127.0 (CH), 125.9 (CH), 125.6 (CH), 124.2 (CH), 121.4 (CH), 40.9 (CH_2), 33.8 (CH), 31.8 (CH_2), 31.7 (CH_2), 31.3 (CH_2), 29.8 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 22.6 (CH_3), 21.0 (CH_2), 14.3 (CH_3), 14.1 (CH_3).

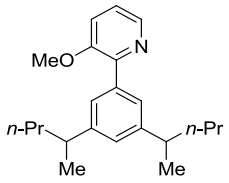
IR (ATR): $\tilde{\nu}$ = 2956, 2923, 2853, 1581, 1563, 1457, 1421, 779, 747 cm^{-1}.

MS (EI) *m/z* (relative intensity): 336 (100) [M-H^+], 308 (71), 294 (29), 266 (23), 252 (98), 208 (44), 194 (54), 180 (30), 167 (33), 43 (31).

HR-MS (EI) *m/z* calculated for $C_{24}H_{35}N^+$: 337.2770; found: 337.2766.

Synthesis of 2-[3,5-Di(pentan-2-yl)phenyl]-3-methoxypyridine (152bi') and 3-Methoxy-2-[3-(pentan-2-yl)phenyl]pyridine (152bi)

The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (15.0 mg, 0.025 mmol, 4.0 mol %), $MesCO_2H$ (**13a**) (26 mg, 0.15 mmol, 24 mol %), **6cb** (115 mg, 0.62 mmol) and 2-bromopentane (**42bi**) (255 mg, 1.69 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 6:1) yielded **152bi'** (23 mg, 11%) and **152bi** (65 mg, 41%) as colorless oils.



(152bi')

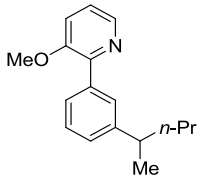
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.32 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.51 (d, *J* = 1.7 Hz, 2H), 7.30-7.14 (m, 2H), 7.04-6.98 (m, 1H), 3.84 (s, 3H), 2.75 (qt, *J* = 7.0, 6.9 Hz, 2H), 1.71-1.45 (m, 4H), 1.38-1.14 (m, 4H), 1.27 (d, *J* = 6.9 Hz, 6H), 0.87 (t, *J* = 7.3 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 153.7 (C_q), 149.2 (C_q), 147.4 (C_q), 141.2 (CH), 128.4 (C_q), 126.1 (CH), 125.7 (CH), 122.7 (CH), 118.7 (CH), 55.6 (CH_3), 40.9 (CH), 39.8 (CH_2), 22.3 (CH_2), 21.0 (CH_3), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2956, 2927, 2871, 1714, 1580, 1420, 1359, 1272, 1218, 1126, 1018, 768 cm^{-1}.

MS (EI) *m/z* (relative intensity): 325 (28) [M^+], 296 (15), 282 (100), 238 (16), 212 (20), 196 (10).

HR-MS (EI) *m/z* calculated for $C_{22}H_{31}NO^+$: 325.2406; found: 325.2406.



(152bi)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.32 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.81-7.65 (m, 2H), 7.36 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.32-7.13 (m, 3H), 3.85 (s, 3H), 2.78 (qt, *J* = 7.1, 6.9 Hz, 1H), 1.75-1.44 (m, 2H), 1.44-1.12 (m, 2H), 1.26 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H).

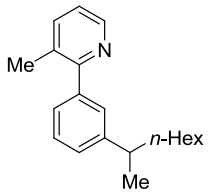
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 153.5 (C_q), 148.6 (C_q), 147.4 (C_q), 141.2 (CH), 137.4 (C_q), 128.2 (CH), 127.7 (CH), 126.9 (CH), 126.9 (CH), 122.7 (CH), 118.4 (CH), 55.4 (CH_3), 40.7 (CH_2), 39.7 (CH), 22.2 (CH_2), 20.8 (CH_3), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3055, 3007, 2957, 2937, 2835, 1578, 1423, 1267, 1195, 1125, 1013, 737, 694 cm^{-1}.

MS (EI) *m/z* (relative intensity): 255 (34), 212 (100), 197 (56), 182 (37).

HR-MS (EI) *m/z* calculated for $C_{17}H_{21}NO^+$: 255.1623; found: 255.1617.

Synthesis of 3-Methyl-2-[3-(octan-2-yl)phenyl]pyridine (152da)

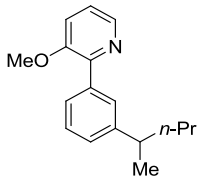


The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.00 mg, 0.013 mmol, 2.4 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 29 mol %), **6db** (90.2 mg, 0.53 mmol) and 2-bromooctane (**42ba**) (282 mg, 1.46 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 4:1) yielded **152da** (84 mg, 56%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.57-8.45 (m, 1H), 7.57 (ddd, *J* = 7.7, 1.7, 0.8 Hz, 1H), 7.44-7.28 (m, 3H), 7.28-7.12 (m, 2H), 2.73 (qt, *J* = 7.0, 6.9 Hz, 1H), 2.35 (s, 3H), 1.70-1.49 (m, 2H), 1.35-1.09 (m, 8H), 1.24 (d, *J* = 6.9 Hz, 3H), 0.92-0.77 (t, *J* = 6.7 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.4 (C_q), 148.0 (C_q), 147.2 (CH), 140.8 (C_q), 138.7 (CH), 131.2 (C_q), 128.4 (CH), 128.0 (CH), 126.9 (CH), 126.7 (CH), 122.3 (CH), 40.4 (CH_3), 38.9 (CH_2), 32.3 (CH_2), 29.9 (CH_2), 28.2 (CH_2), 23.1 (CH_2), 22.8 (CH), 20.6 (CH_3), 14.6 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2956, 2924, 2854, 1583, 1566, 1453, 1417, 1377, 1118, 786, 766, 708, 626 cm^{-1}.
MS (EI): m/z (relative intensity): 281 (28) $[M]^+$, 210 (51), 196 (100), 181 (40), 168 (21).
HRMS (EI) m/z calculated for $C_{20}H_{27}N^+$: 281.2143, found: 281.2143.

Synthesis of 2-[3,5-Di(pentan-2-yl)phenyl]-3-methoxypyridine (152ci') and 2-[3-(Pentan-2-yl)-phenyl]-3-methoxypyridine (152ci)

The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.00 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 30 mol %), **6cb** (92.1 mg, 0.50 mmol) and 2-bromopentane (**42bi**) (250 mg, 1.51 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 5:1) yielded **152ci'**(8 mg, 5%) and **152ci** (62 mg, 48%) as colorless oils.



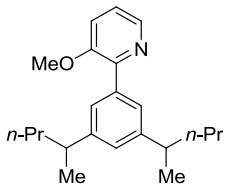
(152ci)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.32 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.75-7.67 (m, 2H), 7.41-7.32 (m, 1H), 7.31-7.17 (m, 3H), 3.85 (s, 3H), 2.76 (qt, *J* = 7.0, 6.9 Hz, 1H), 1.73-1.50 (m, 2H), 1.37-1.10 (m, 4H), 1.28 (d, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 6.8 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 153.5 (C_q), 148.6 (C_q), 147.5 (C_q), 141.3 (CH), 137.5 (C_q), 128.1 (CH), 127.7 (CH), 126.9 (CH), 126.8 (CH), 122.6 (CH), 118.4 (CH), 55.4 (CH_3), 40.0 (CH), 38.1 (CH_2), 29.9 (CH_2), 22.8 (CH_2), 22.2 (CH_3), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3056, 2956, 2925, 2870, 2856, 1579, 1446, 1417, 1268, 1125, 1017, 802, 760, 703 cm^{-1}.

MS (EI) m/z (relative intensity): 269 (44) [M^+], 226 (34), 212 (100), 196 (35), 182 (24), 167 (13), 154 (11).

HRMS (EI) m/z calculated for $C_{18}H_{23}NO^+$: 269.1780; found: 269.1789.



(152ci')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.31 (dd, *J* = 4.6, 1.5 Hz, 1H), 7.51 (d, *J* = 1.7 Hz, 2H), 7.31-7.14 (m, 2H), 7.01 (dd, *J* = 1.8 Hz, 1H), 3.84 (s, 3H), 2.72 (qt, *J* = 7.0, 6.9 Hz, 2H), 1.74-1.44 (m, 4H), 1.44-1.10 (m, 8H), 1.27 (d, *J* = 6.9 Hz, 6H), 0.85 (t, *J* = 6.9 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 153.5 (C_q), 149.2 (C_q), 147.2 (C_q), 141.4 (CH), 137.7 (C_q), 125.9 (CH), 125.6 (CH), 122.5 (CH), 118.4 (CH), 55.5 (CH_3), 40.0 (CH), 38.2 (CH_2), 30.0 (CH_2), 22.8 (CH_2), 22.2 (CH_3), 14.1 (CH_3).

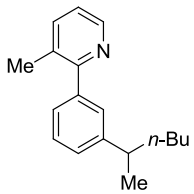
IR (ATR): $\tilde{\nu}$ = 2955, 2925, 2870, 1580, 1457, 1420, 1273, 1181, 1126, 1018, 797 cm^{-1}.

MS (EI) *m/z* (relative intensity): 353 (33) [M^+], 310 (23), 296 (100), 238 (11).

HR-MS (EI) *m/z*calculated for $C_{24}H_{35}NO^+$: 353.2719; found: 353.2720.

Synthesis of 2-[3,5-Di(hexan-2-yl)phenyl]-3-methylpyridine (152dj') & 2-[3-(Hexan-2-yl)phenyl]-3-methylpyridine (152dj)

The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.90 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 30 mol %), **6db** (87.0 mg, 0.51 mmol) and 2-bromohexane (**42bj**) (255 mg, 1.55 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **152dj'** (18 mg, 10%) and **152dj** (79 mg, 61%) as colorless oils.



(152dj)

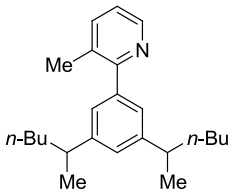
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.54 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.63-7.51 (m, 1H), 7.43-7.25 (m, 3H), 7.25-7.09 (m, 2H), 2.75 (qt, *J* = 7.1, 6.9 Hz, 1H), 2.35 (s, 3H), 1.73-1.48 (m, 2H), 1.38-1.10 (m, 4H), 1.27 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.1 (C_q), 147.7 (C_q), 146.9 (CH), 140.5 (C_q), 138.3 (CH), 130.8 (C_q), 128.0 (CH), 127.6 (CH), 126.5 (CH), 126.3 (CH), 121.9 (CH), 39.9 (CH_3), 38.1 (CH_2), 29.9 (CH_2), 22.7 (CH_2), 22.3 (CH), 20.1 (CH_3), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3047, 2956, 2925, 2857, 1583, 1565, 1448, 1417, 1377, 1118, 900, 786, 765 cm^{-1}.

MS (EI) m/z (relative intensity): 253 (38) [M^+], 210 (46), 196 (100), 181 (43), 168 (23).

HRMS (EI) m/z calculated for $C_{18}H_{23}N$-H^+: 252.1752; found: 252.1751.



(152dj')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.59-8.48 (m, 1H), 7.57 (ddd, *J* = 7.7, 1.8, 0.9 Hz, 1H), 7.22-7.10 (dd, *J* = 7.7, 4.8 Hz, 2H), 7.12 (d, *J* = 1.7 Hz, 1H), 7.00 (t, *J* = 1.8 Hz, 1H), 2.71 (qt, *J* = 7.0, 6.9 Hz, 2H), 2.33 (s, 3H), 1.68-1.47 (m, 4H), 1.37-1.09 (m, 8H), 1.26 (d, *J* = 6.9 Hz, 6H), 0.92-0.80 (m, 6H).

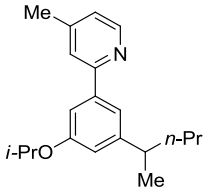
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.7 (C_q), 147.5 (C_q), 146.8 (CH), 140.3 (C_q), 138.3 (CH), 130.8 (C_q), 125.5 (CH), 124.9 (CH), 121.7 (CH), 39.9 (CH_3), 38.2 (CH_2), 30.0 (CH_2), 22.7 (CH_2), 22.3 (CH), 20.1 (CH_3), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2955, 2924, 2857, 1598, 1583, 1566, 1421, 1376, 716 cm^{-1}.

MS (EI) m/z (relative intensity): 337 (68) [M^+], 294 (67), 280 (100), 252 (32), 222 (31), 196 (19), 181 (11).

HRMS (EI) m/z calculated for $C_{24}H_{35}N$-H^+: 336.2691; found: 336.2702.

Synthesis of 2-[3-Isopropoxy-5-(pentan-2-yl)phenyl]-4-methylpyridine (152ei)

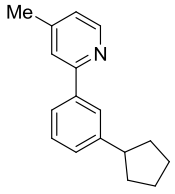


The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (15.2 mg, 0.025 mmol, 5.1 mol %), $MesCO_2H$ (**13a**) (24 mg, 0.15 mmol, 31 mol %), **6ec** (109 mg, 0.48 mmol) and 2-bromopentane (**42bi**) (235 mg, 1.56 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 19:1) yielded **152ei** (47 mg, 33%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.53 (dd, *J* = 5.0, 0.7 Hz, 1H), 7.51 (ddd, *J* = 1.6, 0.8, 0.8 Hz, 1H), 7.37-7.29 (m, 2H), 7.04 (ddd, *J* = 5.0, 1.6, 0.8 Hz, 1H), 6.78 (dd, *J* = 1.9, 1.9 Hz, 1H), 4.68 (hept, *J* = 6.0 Hz, 1H), 2.75 (qt, *J* = 7.0, 6.9 Hz, 1H), 2.41 (s, 3H), 1.74-1.43 (m, 2H), 1.37 (d, *J* = 6.1 Hz, 6H), 1.31-1.10 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.2 (C_q), 157.6 (C_q), 150.0 (C_q), 149.3 (CH), 147.6 (C_q), 140.7 (C_q), 123.0 (CH), 121.7 (CH), 118.4 (CH), 115.6 (CH), 111.4 (CH), 69.8 (CH), 40.6 (CH_2), 39.9 (CH), 22.2 (CH_3), 22.1 (CH_3), 21.2 (CH_3), 20.8 (CH_2), 14.1 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2957, 2926, 2871, 2857, 1584, 1566, 1439, 1325, 1116, 993, 782 cm^{-1}.
MS (EI) *m/z* (relative intensity): 297 (20) [M^+], 255 (32), 213 (100), 197 (21), 43 (47).
HR-MS (EI) *m/z* calculated for $C_{20}H_{27}NO^+$: 297.2093; found: 297.2086.

Synthesis of 2-(3,5-Dicyclopentylphenyl)-4-methylpyridine (152ek') & 2-(3-Cyclopentylphenyl)-4-methylpyridine (152ek)

The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (16.3 mg, 0.027 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (52 mg, 0.31 mmol, 30 mol %), **6eb** (166 mg, 0.98 mmol) and bromocyclopentane (**42bk**) (449 mg, 3.01 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 19:1) yielded **152ek'** (19 mg, 6%) and **152ek** (88 mg, 38%) as colorless oils.



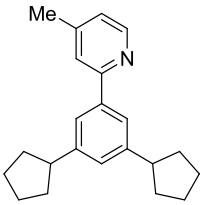
(152ek)
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 5.0 Hz, 1H), 7.88 (d, *J* = 2.0 Hz, 1H), 7.84-7.68 (m, 1H), 7.62-7.49 (m, 1H), 7.38 (dd, *J* = 7.6, 7.5 Hz, 1H), 7.34-7.27 (m, 1H), 7.15-6.97 (m, 1H), 3.21-2.94 (m, 1H), 2.41 (s, 3H), 2.23-2.04 (m, 2H), 1.94-1.56 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.7 (C_q), 149.3 (CH), 147.6 (C_q), 146.9 (C_q), 139.4 (C_q), 128.5 (CH), 127.5 (CH), 125.8 (CH), 124.3 (CH), 122.9 (CH), 121.6 (CH), 46.1 (CH_3), 34.6 (CH_2), 25.5 (CH_2), 21.2 (CH).

IR (ATR): $\tilde{\nu}$ = 3045, 2949, 2866, 1599, 1558, 1449, 825, 793, 698, 455 cm^{-1}.

MS (EI) *m/z* (relative intensity): 237 (29) [M^+], 208 (48), 196 (100), 181 (14), 168 (22).

HR-MS (EI) *m/z* calculated for $C_{17}H_{19}N$-H^+: 236.1439; found: 236.1449.



(152ek')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.52 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.63 (d, *J* = 1.7 Hz, 2H), 7.57-7.45 (m, 1H), 7.19-7.10 (m, 1H), 7.05-6.99 (m, 1H), 3.04 (dt, *J* = 9.7, 7.3 Hz, 2H), 2.40 (s, 3H), 2.14-2.03 (m, 4H), 1.88-1.55 (m, 12H).

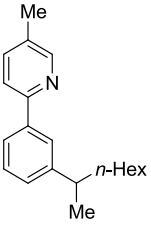
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.1 (C_q), 149.3 (CH), 147.5 (C_q), 146.8 (C_q), 139.4 (C_q), 126.6 (CH), 123.3 (CH), 122.8 (CH), 121.7 (CH), 46.2 (CH_3), 34.7 (CH_2), 25.6 (CH_2), 21.2 (CH).

IR (ATR): $\tilde{\nu}$ = 2952, 2865, 1712, 1595, 1440, 1360, 1220, 876, 828, 529 cm^{-1}.

MS (EI) *m/z* (relative intensity): 305 (30) [M^+], 277 (28), 264 (100), 208 (14), 43 (15).

HR-MS (EI) *m/z* calculated for $C_{22}H_{27}N^+$: 305.2143; found: 305.2128.

Synthesis of 5-Methyl-2-[3-(octan-2-yl)phenyl]pyridine (152fa)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (3.70 mg, 0.006 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (13 mg, 0.8 mmol, 29 mol %), **6hb** (41.6 mg, 0.25 mmol) and 2-bromooctane (**42ba**) (151 mg, 0.78 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **152ha** (30 mg, 43%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.52 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.80 (d, *J* = 1.8 Hz, 1H), 7.75 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.63 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.58-7.51 (m, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.22 (dd, *J* = 7.6, 1.5 Hz, 1H), 2.77 (qt, *J* = 7.1, 6.9 Hz, 1H), 2.37 (s, 3H), 1.73-1.51 (m, 2H), 1.40-1.05 (m, 8H), 1.29 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 6.7 Hz, 3H).

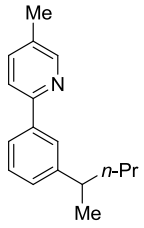
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.1 (C_q), 149.9 (CH) 148.5 (C_q), 139.3 (CH), 137.2 (C_q), 131.4 (CH), 128.6 (CH), 127.2 (CH), 125.5 (CH), 124.2 (CH), 120.2 (CH), 40.1 (CH_3), 38.4 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 27.7 (CH_2), 22.6 (CH_2), 22.3 (CH), 18.1 (CH_3), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3061, 3032, 3001, 2922, 2862, 1475, 1444, 1378, 1027, 774, 734, 691 cm^{-1}.

MS (EI) m/z (relative intensity): 281 (48) [M^+], 210 (37), 196 (100), 181 (60).

HRMS (EI) m/z calculated for $C_{20}H_{27}N^+$: 281.2143; found: 281.2140.

Synthesis of 5-Methyl-2-[3-(pentan-2-yl)phenyl]pyridine (152fi)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.10 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (23 mg, 0.14 mmol, 28 mol %), **6hb** (86.5 mg, 0.51 mmol) and 2-bromopentane (**42bi**) (233 mg, 1.54 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **152hi** (68 mg, 56%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.53 (dd, *J* = 2.3, 1.1 Hz, 1H), 7.81 (t, *J* = 1.9 Hz, 1H), 7.75 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.63 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.55 (dd, *J* = 7.9, 2.2 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.23 (dd, *J* = 7.5, 1.5 Hz, 1H), 2.80 (qt, *J* = 7.0, 6.9 Hz, 1H), 2.37 (s, 3H), 1.74-1.48 (m, 2H), 1.41-1.12 (m, 2H), 1.28 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.1 (C_q), 149.9 (CH), 148.4 (C_q), 139.3 (C_q), 137.2 (CH), 131.4 (C_q), 128.6 (CH), 127.2 (CH), 125.5 (CH), 124.2 (CH), 120.1 (CH), 40.7 (CH_2), 39.8 (CH_3), 22.2 (CH_2), 20.8 (CH), 18.1 (CH_3), 14.1 (CH_3).

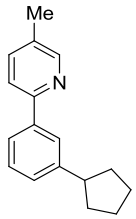
IR (ATR): $\tilde{\nu}$ = 2956, 2925, 2870, 1600, 1564, 1470, 1429, 1377, 794, 701cm^{-1}.

MS (EI) m/z (relative intensity): 239 (41) [M^+], 210 (14), 196 (100), 181 (59), 69 (10), 43 (24).

HRMS (EI) m/z calculated for $C_{17}H_{21}N^+$: 239.1674; found: 239.1672.

Synthesis of 2-[3,5-Dicyclopentylphenyl]-5-methylpyridine (152fk') & 2-(3-Cyclopentylphenyl)-5-methylpyridine (152fk)

The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (14.2 mg, 0.023 mmol, 2.3 mol %), $MesCO_2H$ (**13a**) (50 mg, 0.29 mmol, 29 mol %), **6fb** (176 mg, 1.04 mmol) and bromocyclopentane (**42bk**) (453 mg, 3.03 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 19:1) yielded **152fk'** (12 mg, 4%) and **152fk** (96 mg, 39%) as a colorless oils.



(152fk)

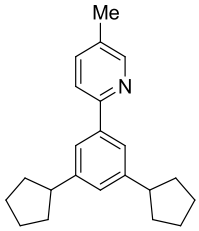
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.56-8.47 (m, 1H), 7.88 (dd, *J* = 1.9, 1.9 Hz, 1H), 7.75 (ddd, *J* = 7.6, 1.6, 1.5 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.54 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.39 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.29 (ddd, *J* = 7.7, 1.6, 1.6 Hz, 1H), 3.09 (dt, *J* = 9.3, 7.4 Hz, 1H), 2.37 (s, 3H), 2.19-2.02 (m, 2H), 1.94-1.57 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.1 (C_q), 149.9 (CH), 146.9 (C_q), 139.3 (C_q), 137.2 (CH), 131.3 (C_q), 128.5 (CH), 127.3 (CH), 125.6 (CH), 124.1 (CH), 120.1 (CH), 46.0 (CH), 34.6 (CH_2), 25.5 (CH_2), 18.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2950, 2866, 1600, 1564, 1470, 1429, 1377, 1223, 833, 792, 753, 699 cm^{-1}.

MS (EI) *m/z* (relative intensity): 237 (42) [M^+], 208 (56), 196 (100), 169 (17).

HR-MS (EI) *m/z* calculated for $C_{17}H_{19}N^+$: 237.1517; found: 237.1507.



(152fk')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.51 (dd, *J* = 2.2, 1.0 Hz, 1H), 7.67-7.57 (m, 3H), 7.53 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.16 (dd, *J* = 1.7, 1.7 Hz, 1H), 3.14-2.96 (m, 2H), 2.36 (s, 3H), 2.20-2.00 (m, 4H), 1.93-1.51 (m, 12H).

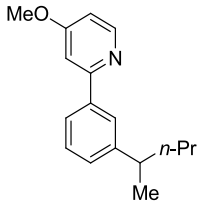
^{13}C-NMR (75 MHz, $CDCl_3$): δ =155.5 (C_q), 149.9 (CH), 146.8 (C_q), 139.3 (CH), 137.1 (C_q), 131.2 (CH), 126.4 (CH), 123.1 (CH), 120.3 (C_q), 46.2 (CH), 34.7 (CH_2), 25.6 (CH_2), 18.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2949, 2867, 1713, 1685, 1599, 1565, 1487, 1449, 1236, 1035, 831 cm^{-1}.

MS (EI) *m/z* (relative intensity): 305 (34) [M^+], 277 (25), 264 (100), 236 (13), 208 (14), 43 (18).

HR-MS (EI) *m/z* calculated for $C_{22}H_{27}N^+$: 305.2143; found: 305.2136.

Synthesis of 4-Methoxy-2-[3-(pentan-2-yl)phenyl]pyridine (152gi)



The general procedure **E** was followed, using [$RuCl_2$(*p*-cymene)]$_2$ (15.0 mg, 0.025 mmol, 5.0 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 26 mol %), **6gb** (106 mg, 0.57 mmol) and 2-bromopentane (**42bi**) (225 mg, 1.49 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 18:1) yielded **152gi** (48 mg, 33%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 5.7 Hz, 1H), 7.80 (d, *J* = 1.9 Hz, 1H), 7.77-7.68 (m, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.29-7.17 (m, 2H), 6.77 (dd, *J* = 5.7, 2.5 Hz, 1H), 3.91 (s, 3H), 2.80 (qt, *J* = 7.0, 6.9 Hz, 1H), 1.72-1.48 (m, 2H), 1.37-1.11 (m, 2H), 1.28 (d, *J* = 6.9 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.3 (C_q), 159.6 (C_q), 150.8 (CH), 148.5 (C_q), 139.3 (C_q), 128.6 (CH), 127.6 (CH), 125.8 (CH), 124.4 (CH), 107.9 (CH), 107.0 (CH), 55.1 (CH_3), 40.6 (CH_2), 39.8 (CH), 22.2 (CH_2), 20.8 (CH_3), 14.1 (CH_3).

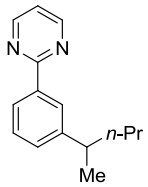
IR (ATR): $\tilde{\nu}$ = 2956, 2928, 2870, 1589, 1562, 1312, 1219, 1036, 797, 701 cm^{-1}.

MS (EI) m/z (relative intensity): 255 (15) [M^+], 226 (14), 212 (100), 182 (17), 169 (14), 69 (16), 43 (28).

HRMS (EI) m/z calculated for $C_{17}H_{21}NO^+$: 255.1623; found: 255.1623.

Synthesis of 2-[3,5-Di(pentan-2-yl)phenyl]pyrimidine (154') and 2-[3-(Pentan-2-yl)phenyl]-pyrimidine (154)

The general procedure **E** was followed, using [$RuCl_2$(*p*-cymene)]$_2$ (15.2 mg, 0.025 mmol, 5.0 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 30 mol %), **153** (76.6 mg, 0.49 mmol) and 2-bromopentane (**42bi**) (229 mg, 1.52 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **154'** (17 mg, 12%) and **154** (50 mg, 45%) as a colorless oils.



(154)

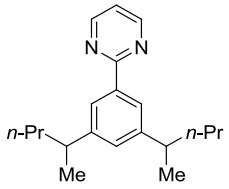
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.80 (d, *J* = 4.8 Hz, 2H), 8.28 (d, *J* = 1.6 Hz, 1H), 8.26 (dd, *J* = 5.7, 1.6 Hz, 1H), 7.42 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.32 (ddd, *J* = 7.6, 1.5, 1.4 Hz, 1H), 7.16 (t, *J* = 4.8 Hz, 1H), 2.82 (qt, *J* = 7.0 Hz, 1H), 1.76-1.49 (m, 2H), 1.42-1.07 (m, 2H), 1.30 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.1 (C_q), 157.3 (CH), 148.5 (C_q), 137.6 (C_q), 129.7 (CH), 128.7 (CH), 126.9 (CH), 125.9 (CH), 119.1 (CH), 40.8 (CH_2), 39.9 (CH), 22.4 (CH_2), 21.0 (CH_3), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2957, 2926, 2871, 1567, 1554, 1453, 1408, 1377, 785, 699, 635 cm^{-1}.

MS (EI) m/z (relative intensity): 226 (20) [M^+], 183 (100), 168 (45), 103 (10), 58 (13), 43 (46).

HRMS (ESI) m/z calculated for $C_{15}H_{18}N_2^+$: 226.1470; found: 226.1461.



(154')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.82 (d, *J* = 4.7 Hz, 2H), 8.09 (d, *J* = 1.7 Hz, 2H), 7.16 (t, *J* = 4.8 Hz, 1H), 7.12 (t, *J* = 1.7 Hz, 1H), 2.79 (qt, *J* = 7.0, 6.9 Hz, 2H), 1.74-1.48 (m, 5H), 1.42-1.11 (m, 4H), 1.29 (d, *J* = 6.9 Hz, 6H), 0.87 (t, *J* = 7.3 Hz, 6H).

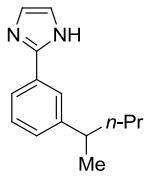
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.9 (C_q), 157.7 (CH), 148.9 (C_q), 137.9 (C_q), 129.2 (CH), 124.9 (CH), 119.4 (CH), 41.3 (CH_2), 40.4 (CH_3), 22.8 (CH), 21.4 (CH_2), 14.7 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2956, 2926, 2871, 1568, 1555, 1455, 1410, 809, 709 cm^{-1}.

MS (EI) m/z (relative intensity): 296 (24) [M^+], 269 (11), 253 (100), 211 (18), 183 (27), 168 (15).

HRMS (EI) m/z calculated for $C_{20}H_{28}N_2^+$: 296.2252; found: 296.2257.

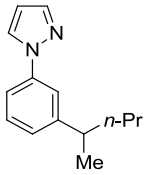
Synthesis of 2-[3-(Pentan-2-yl)phenyl]-1*H*-imidazole (155)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (15.4 mg, 0.025 mmol, 4.9 mol %), $MesCO_2H$ (**13a**) (24 mg, 0.15 mmol, 29 mol %), 2-phenyl-1*H*-imidazole (74.2 mg, 0.52 mmol) and 2-bromopentane (**42bi**) (238 mg, 1.57 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **155** (49 mg, 44%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.92 (dd, *J* = 2.4, 0.6 Hz, 1H), 7.73 (dd, *J* = 1.7, 0.6 Hz, 1H), 7.57 (dd, *J* = 1.9 Hz, 1H), 7.46 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.36 (dd, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.46 (dd, *J* = 2.5, 1.8 Hz, 1H), 2.78 (qt, *J* = 7.0 Hz, 1H), 1.72-1.44 (m, 2H), 1.38-1.12 (m, 2H), 1.28 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 149.9 (C_q), 141.0 (CH), 140.3 (C_q), 129.3 (CH), 127.0 (C_q), 125.4 (CH), 118.3 (CH), 116.8 (CH), 107.5 (CH), 40.7 (CH_2), 39.9 (CH), 22.3 (CH_2), 20.9 (CH_2), 14.2 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2958, 2927, 2871, 1609, 1591, 1519, 1472, 1451, 1393, 1042, 787, 731, 698 cm^{-1}.
MS (EI) m/z (relative intensity): 214 (34) [M^+], 171 (100), 157 (12), 144 (13), 103 (12), 77 (15).
HRMS (EI) *m/z* calculated for $C_{14}H_{18}N_2^+$: 214.1470; found: 214.1475.

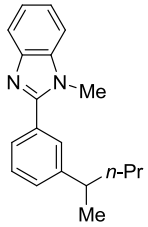
Synthesis of 1-[3-(Pentan-2-yl)phenyl]-1*H*-pyrazole (156)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (16.0 mg, 0.026 mmol, 4.8 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 27 mol %), **87a** (83.8 mg, 0.58 mmol) and 2-bromopentane (**42bi**) (219 mg, 1.45 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 10:1 to 5:1) yielded **156** (54 mg, 43%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.93 (dd, *J* = 2.3, 0.6 Hz, 2H), 7.73 (d, *J* = 1.9 Hz, 1H), 7.56 (s, 1H), 7.46 (ddd, *J* = 8.1, 2.2, 1.1 Hz, 1H), 7.36 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 2.78 (qt, *J* = 7.0, 6.9 Hz, 1H), 1.74-1.46 (m, 2H), 1.39-1.11 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 149.8 (C_q), 141.0 (CH), 140.3 (C_q), 129.3 (CH), 126.9 (CH), 125.3 (CH), 118.3 (CH), 116.7 (CH), 107.5 (CH), 40.7 (CH_2), 39.9 (CH_3), 22.3 (CH), 20.9 (CH_2), 14.2 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2957, 2927, 2871, 1718, 1609, 1591, 1392, 1042, 787, 743 cm^{-1}.
MS (EI) m/z (relative intensity): 214 (59) [M^+], 171 (100), 157 (13), 144 (14).
HRMS (EI) m/z calculated for $C_{14}H_{18}N_2^+$: 214.1470, found: 214.1468.

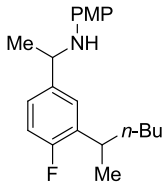
Synthesis of 1-Methyl-2-[3-(pentan-2-yl)phenyl]-1*H*-benzo[*d*]imidazole (157)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (16.0 mg, 0.026 mmol, 5.3 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 31 mol %), 1-methyl-2-phenyl-1*H*-benzo[*d*]imidazole (97.8 mg, 0.47 mmol) and 2-bromopentane (**42bi**) (224 mg, 1.48 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1 to 3:1) yielded **157** (71 mg, 54%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.85-7.80 (m, 1H), 7.59 (dd, *J* = 1.7, 1.6 Hz, 1H), 7.52 (ddd, *J* = 7.6, 1.6 Hz, 1H), 7.42 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.39-7.27 (m, 4H), 3.83 (d, *J* = 1.3 Hz, 3H), 2.79 (qt, *J* = 7.1, 7.0 Hz, 1H), 1.73-1.41 (m, 2H), 1.37-1.09 (m, 2H), 1.27 (d, *J* = 7.0 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 154.7 (C_q), 149.1 (C_q), 143.5 (C_q), 137.1 (C_q), 130.6 (C_q), 129.0 (CH), 129.0 (CH), 128.9 (CH), 127.3 (CH), 123.2 (CH), 122.9 (CH), 120.3 (CH), 110.1 (CH), 41.1 (CH_2), 40.2 (CH_3), 32.2 (CH_3), 22.8 (CH), 21.4 (CH_2), 14.7 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3051, 2956, 2927, 2870, 1588, 1457, 1378, 1324, 1282, 801, 739, 704 cm^{-1}.
MS (EI) m/z (relative intensity): 278 (75) [M^+], 249 (31), 235 (100), 220 (23), 205 (20), 77 (25).
HRMS (EI) *m/z* calculated for $C_{19}H_{22}N_2^+$: 278.1783; found: 278.1786.

Synthesis of *N*-{1-[4-Fluoro-3-(hexan-2-yl)phenyl]ethyl}-4-methoxyaniline (158a)



The general procedure **D** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.3 mg, 0.012 mmol, 2.4 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 30 mol %), **121a** (123 mg, 0.51 mmol) and 2-bromohexane (**42ba**) (246 mg, 1.49 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **158a** [32 mg, 19%; isolated as a set of diastereomers (DS1 ans DS2) in a ratio of 1:1] as a brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.13-6.98 (m, 3H), 6.84 (dd, J = 10.1, 8.3 Hz, 1H), 6.67-6.55 (m, 2H), 6.44-6.30 (m, 2H), 4.29 (qd, J = 6.7, 1.8 Hz, 1H), 3.62 (d, J = 0.9 Hz, 3H), 2.93 (qt, J = 7.1, 7.0 Hz, 1H), 1.64-1.30 (m, 6H), 1.30-0.91 (m, 3H),1.27 (d, J = 7.0 Hz, 3H), 0.86-0.63 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.9 (d, $J_{C\text{-}F}$ = 243 Hz, C_q), 152.3 (C_q), 141.6 (C_q), 140.9 (d, $J_{C\text{-}F}$ = 4 Hz, C_q), 134.4 (dd, $J_{C\text{-}F}$ = 15, 3 Hz, CH), 125.8 (dd, $J_{C\text{-}F}$ = 16, 6 Hz, CH), 124.4 (dd, $J_{C\text{-}F}$ = 8, 6 Hz, CH), 115.4 (dd, $J_{C\text{-}F}$ = 23, 4 Hz, CH), 115.0 (d, $J_{C\text{-}F}$ = 3 Hz, CH), 114.9 (CH), 55.9 (CH_3), 54.2 (DS2, CH), 54.1 (DS1, CH), 36.9 (DS2, CH_2), 36.8 (DS1, CH_2), 32.9 (DS2, CH), 32.7 (DS1, CH), 29.9 (DS2, CH_2), 29.8 (DS1, CH_2), 25.1 (DS2, CH_3), 25.0 (DS1, CH_3), 22.8 (DS2, CH_3), 22.7 (DS1, CH_3), 21.2 (DS2, CH_2), 21.1 (DS1, CH_2), 14.3 (DS2, CH_3), 14.2 (DS1, CH_3).

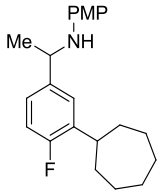
^{19}F-NMR (282 MHz, $CDCl_3$): δ =-121.10 - - 123.33 (m), -123.35 - 125.15 (m).

IR (ATR): $\tilde{\nu}$ = 2958, 2928, 2871, 2859, 1684, 1509, 1461, 1233, 1104, 1035, 817, 517 cm^{-1}.

MS (EI) *m/z* (relative intensity): 329 (74) [M^+], 314 (100), 270 (12), 254 (22), 148 (22), 77 (20).

HR-MS (EI) *m/z* calculated for $C_{21}H_{28}FNO^+$: 329.2155; found: 329.2154.

Synthesis of *N*-[1-(3-Cycloheptyl-4-fluorophenyl)ethyl]-4-methoxyaniline (158c)



The general procedure **D** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.1 mg, 0.013 mmol, 2.4 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 29 mol %), **121a** (129 mg, 0.53 mmol) and bromocycloheptane (**42bc**) (268 mg, 1.51 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded **158c** (64 mg, 35%) as a brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.21 (dd, J = 7.2, 2.4 Hz, 1H), 7.12 (ddd, J = 8.4, 5.0, 2.3 Hz, 1H), 6.92 (dd, J = 10.2, 8.3 Hz, 1H), 6.75-6.68 (m, 2H), 6.52-6.45 (m, 2H), 4.37 (q, J = 6.7 Hz, 1H), 3.72 (s, 3H), 2.98 (dt, J = 10.4, 3.5 Hz, 1H), 2.02-1.51 (m, 12H), 1.48 (d, J = 6.7 Hz, 3H). (N–H was not detected)

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.9 (d, $J_{C\text{-}F}$ = 243 Hz, C_q), 152.0 (C_q), 141.6 (C_q), 140.9 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 136.3 (d, $J_{C\text{-}F}$ = 15 Hz, C_q), 125.5 (d, $J_{C\text{-}F}$ = 6 Hz, CH), 124.0 (d, $J_{C\text{-}F}$ = 8 Hz, CH), 115.2 (d, $J_{C\text{-}F}$ = 24 Hz, CH), 114.7 (CH), 114.7 (CH), 55.7 (CH_3), 54.0 (CH), 39.8 (CH), 39.7 (CH), 35.3 (CH_2), 27.8 (CH_2), 27.1 (CH_2), 25.0 (CH_3).

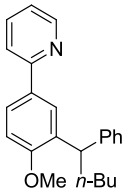
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -121.55 - - 123.63 (m).

IR (ATR): $\tilde{\nu}$ = 3403, 2960, 2930, 2871, 2859, 2244, 1579, 1512, 1464, 1238, 1040, 910, 739 cm^{-1}.

MS (EI) *m/z* (relative intensity): 341 (89) [M^+], 326 (100), 270 (10), 254 (11), 148 (17), 92 (18), 77 (25).
HR-MS (EI) *m/z* calculated for $C_{22}H_{28}FNO^+$: 341.2155; found: 341.2159.

Products of Direct Benzylation

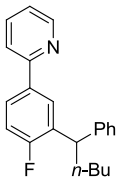
Synthesis of 2-[4-Methoxy-3-(1-phenylpentyl)phenyl]pyridine (177b)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (15.1 mg, 0.025 mmol, 4.5 mol %), $MesCO_2H$ (**13a**) (24 mg, 0.15 mmol, 27 mol %), **6ba** (101 mg, 0.55 mmol) and (1-bromopentyl)benzene (**176**) (344 mg, 1.51 mmol). After 20 h, purification by column chromatography (*n*-hexane/Et_2O 19:1 to 9:1) yielded **177b** (29 mg, 16%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.67-8.65 (m, 1H), 7.95-7.94 (m, 1H), 7.83 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.70-7.60 (m, 2H), 7.35-7.23 (m, 4H), 7.17-7.11 (m, 2H), 6.91 (t, *J* = 8.5 Hz, 1H), 4.43 (t, *J* = 8.0 Hz, 1H), 3.80 (s, 3H), 2.19-2.05 (m, 2H), 1.44-1.24 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.0 (C_q), 157.4 (C_q), 149.4 (CH), 145.1 (C_q), 136.5 (CH), 134.0 (C_q), 131.6 (C_q), 128.1 (CH), 128.0 (CH), 126.2 (CH), 125.7 (CH), 125.6 (CH), 121.2 (CH), 119.9 (CH), 101.7 (CH), 55.5 (CH_3), 43.4 (CH), 34.7 (CH_2), 30.2 (CH_2), 22.7 (CH_2), 14.0 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3051, 2936, 2915, 1579, 1513, 1460, 1431, 775, 736, 717, 556, 485 cm^{-1}.
MS (EI) *m/z* (relative intensity): 331 (17) [$M]^+$, 274 (100), 185 (12), 91 (74).
HR-MS (ESI) *m/z* calculated for $C_{23}H_{25}NO^+$: 331.1936; found: 331.1937.

Synthesis of 2-[4-Fluoro-3-(1-phenylpentyl)phenyl]pyridine (177c)

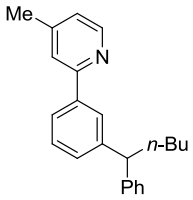


The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (16 mg, 0.026 mmol, 5.3 mol %), 1-$AdCO_2H$ (**13c**) (28 mg, 0.16 mmol,33 mol %), **6ca** (85.1 mg, 0.49 mmol) and (1-bromopentyl)-benzene

(**176**) (357 mg, 1.57 mmol). After 20 h, purification by column chromatography (*n*-hexane/Et_2O 9:1) yielded **177c** (18 mg, 11%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.68 (dd, *J* = 4.6, 1.8 Hz, 1H), 8.03-8.83 (m, 1H), 7.85-7.56 (m, 3H), 7.42-6.88 (m, 7H), 4.36-4.22 (m, 1H), 2.19-2.02 (m, 2H), 1.49-1.06 (m, 4H), 0.89 (t, *J* = 7.5 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.6 (d, $J_{C\text{-}F}$ = 248 Hz, C_q), 156.9 (C_q), 149.7 (CH), 144.1 (C_q), 136.6 (CH), 35.6 (d, $J_{C\text{-}F}$ = 4 Hz, C_q), 132.6 (d, $J_{C\text{-}F}$ = 15 Hz, C_q), 128.4 (CH), 128.0 (CH), 127.5 (d, $J_{C\text{-}F}$ = 5 Hz, CH), 126.3 (d, $J_{C\text{-}F}$ = 9 Hz, CH), 126.2 (CH), 121.8 (CH), 120.2 (CH), 115.8 (d, $J_{C\text{-}F}$ = 24 Hz, CH), 44.1 (CH), 34.4 (CH_2), 30.2 (CH_2), 22.6 (CH_2), 13.9 (CH_3).
^{19}F-NMR (282 MHz, $CDCl_3$) δ = -117.4 - -117.5 (m).
IR (ATR): $\tilde{\nu}$ = 2955, 2930, 2859, 1586, 1566, 1497, 1464, 1433, 1257, 1235, 1152, 780, 742 cm^{-1}.
MS (EI) *m/z* (relative intensity): 319 (36) [M^+], 276 (15), 262 (100), 183 (14).
HR-MS (ESI) *m/z* calculated for $C_{22}H_{22}FN^+$: 319.1736; found: 319.1732.

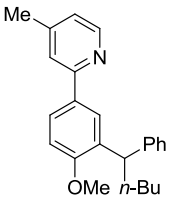
Synthesis of 4-Methyl-2-[3-(1-phenylpentyl)phenyl]pyridine (177e)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 4.8 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 25 mol %), **6eb** (104 mg, 0.61 mmol) and (1-bromopentyl)benzene (**176**) (361 mg, 1.59 mmol). After 20 h, purification by column chromatography (*n*-hexane/Et_2O 19:1) yielded **177e** (58 mg, 30%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 5.0 Hz, 1H), 7.87-7.86 (m, 1H), 7.75-7.71 (m, 1H), 7.48-7.46 (m, 1H), 7.34 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.17-7.09 (m, 5H), 7.01-6.99 (m, 1H), 3.97 (t, *J* = 7.9 Hz, 1H), 2.36 (s, 3H), 2.16-2.01 (m, 2H), 1.39-1.19 (m, 4H), 0.84 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.6 (C_q), 149.4 (CH), 147.7 (C_q), 145.9 (C_q), 145.3 (C_q), 139.7 (C_q), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 126.8 (CH), 126.1 (CH), 124.8 (CH), 121.1 (CH), 121.7 (CH), 51.7 (CH), 35.7 (CH_2), 30.5 (CH_2), 23.0 (CH_2), 21.5 (CH_3), 14.3 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3025, 2927, 2858, 1599, 1493, 1379, 1032, 835, 699, 589 cm^{-1}.
MS (EI) *m/z* (relative intensity): 315 (20) $[M]^+$, 258 (100), 242 (5), 165 (10), 91 (8).
HR-MS (ESI) *m/z* calculated for $C_{23}H_{25}NO+H^+$: 316.2065; found: 316.2060.

Synthesis of 2-(4-Methoxy-3-(1-phenylpentyl)phenyl)-4-methylpyridine (177f)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (15.8 mg, 0.026 mmol, 4.6 mol %), $MesCO_2H$ (**13a**) (24 mg, 0.15 mmol, 27 mol %), **6f** (111 mg, 0.56 mmol) and (1-bromo-pentyl)-benzene (**176**) (360 mg, 1.58 mmol). After 20 h, purification by column chromatography (*n*-hexane/Et_2O 19:1 to 9:1) yielded **177f** (38 mg, 20%) as a white solid.

M.r.: 109 - 110 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 5.0 Hz, 1H), 7.91-7.90 (m, 1H), 7.80 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.46-7.42 (m, 1H), 7.33-7.22 (m, 4H), 7.16-7.11 (m, 1H), 7.00-6.99 (m, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 4.40 (t, *J* = 8.0 Hz, 1H), 3.81 (s, 3H), 2.40 (s, 3H), 2.14-2.07 (m, 2H), 1.40-1.23 (m, 4H), 0.87 (t, *J* = 6.8 Hz, 3H).

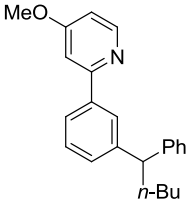
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.9 (C_q), 157.4 (C_q), 149.2 (CH), 147.5 (C_q), 145.2 (C_q), 133.9 (C_q), 131.8 (CH), 128.2 (CH), 128.0 (C_q), 126.2 (CH), 125.7 (CH), 125.6 (CH), 122.3 (CH), 120.9 (CH), 110.8 (CH), 55.6 (CH_3), 43.4 (CH), 34.7 (CH_2), 30.2 (CH_2), 22.7 (CH_2), 21.2 (CH_3), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3082, 3025, 3000, 2928, 2858, 1602, 1557, 1500, 1278, 1245, 1202, 1132, 1028, 812, 698, 413 cm^{-1}.

MS (EI) *m/z* (relative intensiy): 345 (29) $[M]^+$, 288 (100), 272 (8), 91 (46).

HR-MS (ESI) *m/z* calculated for $C_{24}H_{27}NO+H^+$: 346.2171; found: 346.2165.

Synthesis of 4-Methoxy-2-[3-(1-phenylpentyl)phenyl]pyridine (177g)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (15.8 mg, 0.026 mmol, 5.1 mol %), $MesCO_2H$ (**13a**) (24 mg, 0.15 mmol, 30 mol %), **6gb** (88.2 mg, 0.48 mmol) and (1-bromopentyl)-benzene (**176**) (338 mg, 1.49 mmol). After 20 h, purification by column chromatography (*n*-hexane/Et_2O 9:1) yielded **177g** (89 mg, 56%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 5.7 Hz, 1H), 7.86 (dd, *J* = 1.7, 1.6 Hz, 1H), 7.71 (ddd, *J* = 7.6, 1.6, 1.6 Hz, 1H), 7.37-7.07 (m, 7H), 6.71 (dd, *J* = 5.9, 2.5 Hz, 1H), 4.13-4.05 (m, 1H), 4.00-3.91 (m, 1H), 3.82 (s, 3H), 2.12-1.99 (m, 2H), 1.41-1.81 (m, 4H), 0.84 (t, *J* = 6.7 Hz, 3H).

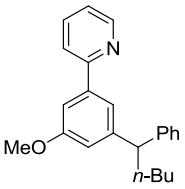
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.3 (C_q), 159.3 (C_q), 150.8 (CH), 145.8 (C_q), 145.1 (C_q), 139.4 (C_q), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 126.7 (CH), 126.0 (CH), 124.7 (CH), 107.9 (CH), 107.3 (CH), 55.0 (CH_3), 51.4 (CH), 35.4 (CH_2), 30.2 (CH_2), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3024, 2998, 2587, 1590, 1563, 1451, 1310, 1219, 1164, 1035, 989, 796 cm^{-1}.

MS (EI) *m/z* (relative intensity): 331 (11) [M^+], 274 (100), 230 (7).

HR-MS (ESI) *m/z* calculated for $C_{23}H_{25}NO$-H^+: 330.1858; found: 330.1873.

Synthesis of 2-[3-Methoxy-5-(1-phenylpentyl)phenyl]pyridine (177u)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (14.9 mg, 0.025 mmol, 4.9 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 26 mol %), **6ua** (107 mg, 0.58 mmol) and (1-bromopentyl)benzene (**176**) (339 mg, 1.49 mmol). After 20 h, purification by column chromatography (*n*-hexane/Et_2O 9:1) yielded **177u** (62 mg, 32%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.69-8.67 (m, 1H), 7.76-7.66 (m, 2H), 7.46-7.45 (m, 1H), 7.38-7.37 (m, 1H), 7.29-7.26 (m, 6H), 6.87-6.86 (m, 1H), 3.95 (t, *J* = 8.1 Hz, 1H), 3.86 (s, 3H), 2.12-2.04 (m, 2H), 1.43-1.22 (m, 4H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.1 (C_q), 157.4 (C_q), 149.5 (CH), 147.3 (C_q), 145.0 (C_q), 140.7 (C_q), 136.6 (CH), 128.3 (CH), 127.8 (CH), 126.0 (CH), 122.1 (CH), 120.7 (CH), 119.3 (CH), 115.0 (CH), 109.2 (CH), 55.3 (CH_3), 51.4 (CH), 35.4 (CH_2), 30.2 (CH_2), 22.7 (CH_2), 14.0 (CH_3).

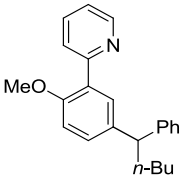
IR (ATR): $\tilde{\nu}$ = 3059, 3002, 2954, 1584, 1451, 1417, 1149, 867, 782, 703 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 331 (31) [M^+], 274 (100), 259 (52), 230 (42), 91 (34).

HR-MS (ESI) *m/z* calculated for $C_{23}H_{25}NO^+$: 331.1936; found: 331.1927.

2-[2-Methoxy-5-(1-phenylpentyl)phenyl]pyridine (177w) and 2-[2-Methoxy-3-(1-phenylpentyl)-phenyl]pyridine (177w')

The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (30 mg, 0.025 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (49 mg, 0.30 mmol, 30 mol %), **6wa** (186 mg, 1.00 mmol) and (1-bromopentyl)benzene (**176**) (676 mg, 2.98 mmol). After 20 h, purification by column chromatography (*n*-hexane/Et_2O 19:1) yielded **177w** (36 mg, 11%) and **177w'** (14 mg, 4%) as colorless oils.



2-[2-Methoxy-5-(1-phenylpentyl)phenyl]pyridine (177w)

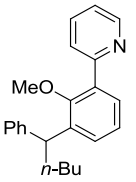
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.70 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.77 (ddd, *J* = 8.0, 1.2, 1.2 Hz, 1H), 7.71-7.63 (m, 2H), 7.33-7.10 (m, 7H), 6.92 (d, *J* = 8.5 Hz, 1H), 3.93 (t, *J* = 7.8 Hz, 1H), 3.81 (d, *J* = 1.1 Hz, 3H), 2.12-1.97 (m, 2H), 1.43-1.16 (m, 4H), 0.86 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 156.5 (C_q), 155.5 (C_q), 149.6 (CH), 145.8 (C_q), 138.2 (C_q), 135.7 (CH), 130.9 (CH), 129.1 (C_q), 129.0 (CH), 128.6 (CH), 128.1 (CH), 126.1 (CH), 125.4 (CH), 121.8 (CH), 111.7 (CH), 56.0 (CH_3), 50.9 (CH), 36.0 (CH_2), 30.8 (CH_2), 23.1 (CH_2), 14.4 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2956, 2929, 2859, 1586, 1566, 1444, 1433, 1257, 1235, 1152, 782, 742, 464 cm^{-1}.

MS (EI) *m/z* (relative intensity): 331 (70) [M^+], 288 (35), 258 (62), 240 (23), 230 (25), 91 (23).

HR-MS (EI) *m/z* calculated for $C_{23}H_{25}NO$-H^+: 330.1858; found: 330.1867.



2-[2-Methoxy-3-(1-phenylpentyl)phenyl]pyridine (177w')

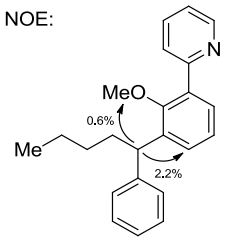
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.68 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.78 (ddd, *J* = 8.0, 1.2, 1.2 Hz, 1H), 7.68 (ddd, *J* = 7.9, 7.4, 1.9 Hz, 1H), 7.51 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.37 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.31-7.09 (m, 7H), 4.43 (t, *J* = 7.8 Hz, 1H), 3.14 (s, 3H), 2.02 (td, *J* = 9.0, 8.5, 7.1 Hz, 2H), 1.43-1.18 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.1 (c_q), 156.2 (C_q), 149.7 (CH), 145.7 (C_q), 138.7 (C_q), 136.2 (CH), 133.7 (C_q), 129.4 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 126.0 (CH), 124.6 (CH), 124.4 (CH), 122.0 (CH), 61.4 (CH_3), 43.8 (CH), 35.8 (CH_2), 30.5 (CH_2), 22.9 (CH_2), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2954, 2928, 2857, 1584, 1498, 1461, 1249, 1061, 1025, 745, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity): 331 (17) [M^+], 316 (21), 28 (60), 274 (100), 240 (32), 165 (16), 91 (32).

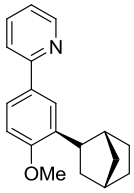
HR-MS (EI) *m/z* calculated for $C_{23}H_{25}NO^+$: 331.1936; found: 331.1933.



Products of Direct Norbornylation

Synthesis of 2-{3-[(1*RS*,2*RS*,4*SR*)-Bicyclo[2.2.1]heptan-2-yl]-4-methoxyphenyl}pyridine (*exo*-147bl) and 2-{2-[(1*RS*,2*RS*,4*SR*)-Bicyclo[2.2.1]heptan-2-yl]-4-methoxyphenyl}pyridine (*exo*-93bl)

The general procedure **E-1** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.3 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (24 mg, 0.15 mmol, 27 mol %), **6ba** (103 mg, 0.56 mmol) and *exo*-2-bromonorbornane (*exo*-**42bl**) (265 mg, 1.51 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1 to 4:1) yielded *exo*-**147bl** (51 mg, 33%) and *exo*-**93bl** (53 mg, 34%) as colorless oils.



(*exo*-147bl)

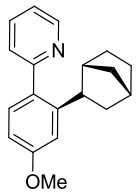
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.86 (dd, *J* = 2.3, 0.7 Hz, 1H), 7.79 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.75-7.62 (m, 2H), 7.15 (ddd, *J* = 6.7, 4.9, 1.8 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 3.10-2.96 (m, 1H), 2.45 (d, *J* = 3.5 Hz, 1H), 2.35 (q, *J* = 3.9, 3.0 Hz, 1H), 1.87-1.78 (m, 1H), 1.70-1.49 (m, 3H), 1.50-1.18 (m, 4H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.8 (C_q), 158.4 (C_q), 150.1 (CH), 137.1 (CH), 136.7 (C_q), 131.9 (C_q), 125.6 (CH), 125.0 (CH), 121.7 (CH), 120.5 (CH), 110.8 (CH), 56.1 (CH_3), 41.7 (CH), 41.1 (CH), 39.2 (CH_2), 37.5 (CH), 37.0 (CH_2), 31.0 (CH_2), 29.6 (CH_2).

IR (ATR): $\tilde{\nu}$ = 2947, 2868, 1715, 1609, 1586, 1503, 1462, 1231, 1144, 790 cm^{-1}.

MS (EI) *m/z* (relative intensity): 279 (56) [M^+], 250 (100), 223 (57), 210 (28), 167 (20).

HR-MS (ESI) *m/z* calculated for $C_{19}H_{21}NO+H^+$: 280.1701; found: 280.1700.



(*exo*-93bl)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.67 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.71 (ddd, *J* = 7.7, 1.9, 1.9 Hz, 1H), 7.32 (ddd, *J* = 7.9, 1.1, 1.0 Hz, 1H), 7.29-7.17 (m, 2H), 6.95 (d, *J* = 2.6 Hz, 1H), 6.77 (dd, *J* = 8.4, 2.6 Hz, 1H), 3.84 (s, 3H), 3.06-2.94 (m, 1H), 2.42-2.32 (m, 1H), 2.32-2.19 (m, 1H), 1.70-1.60 (m, 1H), 1.57-1.25 (m, 4H), 1.25-1.13 (m, 1H), 1.16-1.00 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.7 (C_q), 159.7 (C_q), 149.1 (CH), 147.2 (C_q), 136.1 (CH), 133.7 (C_q), 131.1 (CH), 124.7 (CH), 121.4 (CH), 112.6 (CH), 109.7 (CH), 55.4 (CH_3), 43.4 (CH), 42.8 (CH), 40.2 (CH_2), 37.0 (CH), 36.7 (CH_2), 30.5 (CH_2), 28.7 (CH_2).

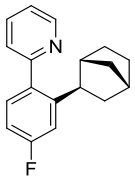
IR (ATR): $\tilde{\nu}$ = 2948, 2868, 1605, 1561, 1462, 1426, 1279, 1224, 1166, 1040, 786, 747 cm^{-1}.

MS (EI) *m/z* (relative intensity): 279 (100) [M^+], 248 (33), 212 (61), 198 (35), 167 (44).

HR-MS (ESI) *m/z* calculated for $C_{19}H_{21}NO+H^+$: 280.1701; found: 280.1697.

Synthesis of 2-{2-((1*RS*,2*RS*,4*SR*)-Bicyclo[2.2.1]heptan-2-yl)-4-fluorophenyl}pyridine (*exo*-147cl) and 2-{3-((1*RS*,2*RS*,4*SR*)-Bicyclo[2.2.1]heptan-2-yl)-4-fluorophenyl}pyridine (*exo*-93cl)

The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (8.3 mg, 0.013 mmol, 2.6 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 30 mol %), **6ca** (87.1 mg, 0.50 mmol) and *exo*-2-bromonorbornane (*exo*-**42bl**) (282 mg, 1.61 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded *exo*-**147cl** (42 mg, 31%) and *exo*-**93cl** (64 mg, 48%) as colorless oils.



(*exo*-**93cl)**

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.69 (s, 1H), 7.73 (ddd, *J* = 7.7, 1.9, 1.9 Hz, 1H), 7.37-7.20 (m, 3H), 7.10 (dd, *J* = 11.1, 2.6 Hz, 1H), 6.92 (ddd, *J* = 8.3, 2.6, 2.6 Hz, 1H), 2.95 (dd, *J* = 9.0, 5.9 Hz, 1H), 2.36-2.29 (m, 1H), 2.29-2.20 (m, 1H), 1.59 (dt, *J* = 9.9, 2.0 Hz, 1H), 1.53-1.30 (m, 4H), 1.20 (ddd, *J* = 9.9, 2.4, 1.4 Hz, 1H), 1.14-0.99 (m, 2H).

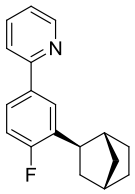
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.9 (d, $J_{C\text{-}F}$ = 246 Hz, C_q), 160.0 (C_q), 149.3 (CH), 148.3 (d, $J_{C\text{-}F}$ = 7 Hz, C_q), 136.8 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 136.2 (CH), 131.5 (d, $J_{C\text{-}F}$ = 8 Hz, CH), 124.6 (CH), 121.8 (CH), 112.9 (d, $J_{C\text{-}F}$ = 22 Hz, CH), 112.1 (d, $J_{C\text{-}F}$ = 21 Hz, CH), 43.4 (d, $J_{C\text{-}F}$ = 1 Hz, CH), 42.8 (CH), 40.2 (CH_2), 36.9 (CH), 36.6 (CH_2), 30.4 (CH_2), 28.6 (CH_2).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = -113.44 - -113.81 (m).

IR (ATR): $\tilde{\nu}$ = 3051, 2949, 2869, 1586, 1462, 1426, 1274, 1212, 939, 787, 747, 591 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 557 (92) [2M+Na^+], 535 (100), 290 (71), 268 (75) [M+H^+].

HR-MS (ESI) *m/z* calculated for $C_{18}H_{18}FN+H^+$: 268.1502; found: 268.1499.



(*exo*-**147cl)**

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.32-8.05 (m, 1H), 7.42 (dd, *J* = 7.4, 2.3 Hz, 1H), 7.34-7.12 (m, 3H), 6.85-6.69 (m, 1H), 6.62 (dd, *J* = 10.0, 8.4 Hz, 1H), 2.62-2.47 (m, 1H), 2.00 (d, *J* = 3.6 Hz, 1H), 1.93 (d, *J* = 3.9 Hz, 1H), 1.38 (ddd, *J* = 11.7, 8.9, 2.2 Hz, 1H), 1.27-1.04 (m, 4H), 1.03-0.90 (m, 1H), 0.89-0.71 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.8 (d, $J_{C\text{-}F}$ = 247 Hz, C_q), 157.2 (C_q), 149.7 (CH), 136.7 (CH), 135.2 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 134.6 (d, $J_{C\text{-}F}$ = 15 Hz, C_q), 125.8 (d, $J_{C\text{-}F}$ = 5 Hz, CH), 125.6 (d, $J_{C\text{-}F}$ = 9 Hz, CH), 121.9 (CH), 120.4 (CH), 115.4 (d, $J_{C\text{-}F}$ = 23 Hz, CH), 41.8 (CH), 40.1 (d, $J_{C\text{-}F}$ = 2 Hz, CH), 38.4 (CH), 37.1 (CH_2), 36.6 (CH_2), 30.6 (CH_2), 29.1 (CH_2).

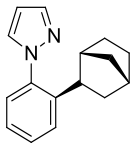
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -116.21 - -116.64 (m).

IR (ATR): $\tilde{\nu}$ = 2951, 2871, 1608, 1575, 1464, 1427, 1275, 788 cm^{-1}.

MS (EI) *m/z* (relative intensity): 267 (38), [M^+], 238 (100), 211 (76), 198 (64), 185 (62), 170 (24), 78 (26).

HR-MS (ESI) *m/z* calculated for $C_{18}H_{18}FN+Na^+$: 290.1321; found: 290.1315.

Synthesis of 1-{2-[(1*RS*,2*RS*,4*SR*)-Bicyclo[2.2.1]heptan-2-yl]phenyl}-1*H*-pyrazole (*exo*-118al)



The general procedure **E** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (7.80 mg, 0.013 mmol, 2.3 mol %), $MesCO_2H$ (**13a**) (24 mg, 0.15 mmol, 27 mol %), **87a** (81 mg, 0.56 mmol) and *exo*-2-bromonorbornane (*exo*-**42bl**) (265 mg, 1.51 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded *exo*-**118al** (87 mg, 65%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 1.8 Hz, 1H), 7.54 (d, *J* = 2.3 Hz, 1H), 7.45-7.31 (m, 2H), 7.28-7.17 (m, 2H), 6.41 (dd, *J* = 2.1, 2.1 Hz, 1H), 2.73-2.61 (m, 1H), 2.31 (dd, *J* = 3.4, 1.6 Hz, 1H), 2.28-2.20 (m, 1H), 1.61-1.30 (m, 5H), 1.23-1.02 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 143.5 (C_q), 139.8 (CH), 139.4 (C_q), 130.8 (CH), 128.5 (CH), 126.9 (CH), 126.3 (CH), 125.7 (CH), 105.7 (CH), 42.2 (CH), 41.3 (CH), 39.2 (CH_2), 36.5 (CH), 36.1 (CH_2), 30.1 (CH_2), 28.2 (CH_2).

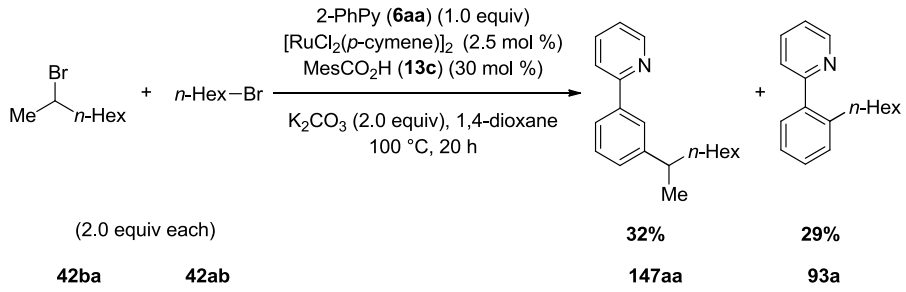
IR (ATR): $\tilde{\nu}$ = 2950, 2869, 1515, 1493, 1453, 1393, 1328, 1042, 938, 745, 728, 623 cm^{-1}.

MS (EI) *m/z* (relative intensity): 238 (199) [M^+], 209 (48), 197 (32), 182 (49), 144 (54), 115 (25), 77 (57), 51 (44).

HR-MS (ESI) *m/z* calculated for $C_{16}H_{18}N_2+Na^+$: 261.1368; found: 261.1366.

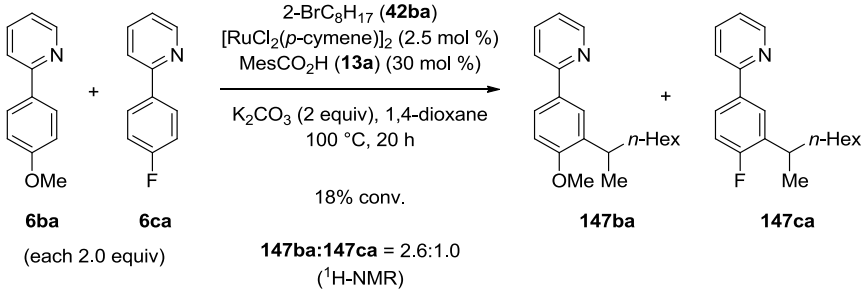
Mechanistic Studies

Intermolecular Competition Experiment between 2-Bromooctane (42ba) and 1-Bromohexane (42ab)



A suspension of $[RuCl_2(p\text{-cymene})]_2$ (16.0 mg, 0.026 mmol, 2.6 mol %), $MesCO_2H$ (**13a**) (48.5 mg, 0.30 mmol, 30 mol %), K_2CO_3 (277 mg, 2.00 mmol), **42ba** (157 mg, 1.02 mmol), **42ab** (375 mg, 1.94 mmol) and **6aa** (328 mg, 1.98 mmol) in dry 1,4-dioxane (4.0 mL) was stirred under N_2 for 20 h at 100 °C. EtOAc (50 mL) and H_2O (50 mL) were added to the reaction mixture at ambient temperature. The separated aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 19:1) to yield **147aa** (88 mg, 32%) and **93a** (80 mg, 29%) as colorless oils.

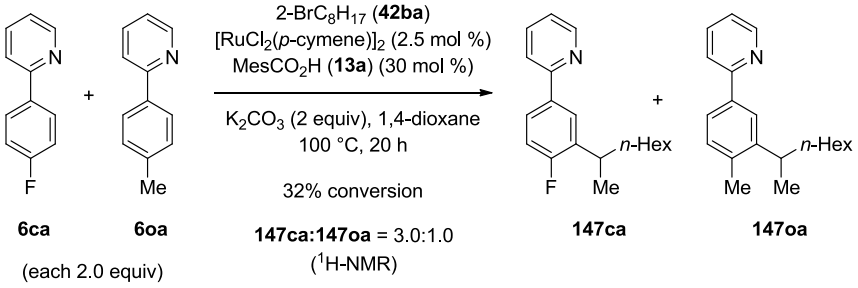
Intermolecular Competition Experiment between 2-(4-Methoxyphenyl)pyridine (6ba) & 2-(4-Fluorophenyl)pyridine (6ca)



A suspension of $[RuCl_2(p\text{-cymene})]_2$ (15.9 mg, 0.026 mmol, 2.6 mol %), $MesCO_2H$ (**13a**) (50.1 mg, 0.30 mmol, 30 mol %), K_2CO_3 (274 mg, 2.00 mmol), **6ba** (370 mg, 2.00 mmol), **6ca** (347 mg, 2.00 mmol) and **42ba** (200 mg, 1.04 mmol) in dry 1,4-dioxane (4.0 mL) was stirred under N_2 for 20 h at 100 °C. EtOAc (50 mL) and H_2O (50 mL) were added to the reaction mixture at ambient temperature. The separated aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The

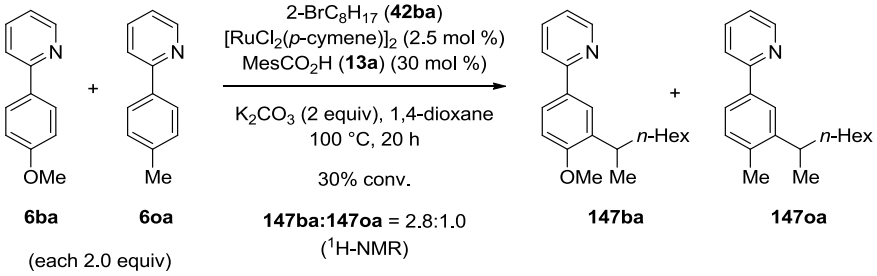
remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 19:1) to yield a mixture of **147ba** and **147ca** (18% conv.) in a ratio of 2.6:1.0 as determined by ^{1}H-NMR spectroscopy.

Intermolecular Competition Experiment between 2-(4-Methylphenyl)pyridine (6oa) & 2-(4-Fluorophenyl)pyridine (6ca)



A suspension of $[RuCl_2(p\text{-cymene})]_2$ (15.5 mg, 0.025 mmol, 2.0 mol %), $MesCO_2H$ (50.0 mg, 0.30 mmol, 23.6 mol %), K_2CO_3 (280 mg, 2.02 mmol), **6ca** (374 mg, 2.02 mmol), **6oa** (333 mg, 1.97 mmol) and **42ba** (245 mg, 1.27 mmol) in dry 1,4-dioxane (4 mL) was stirred under N_2 for 20 h at 100 °C. EtOAc (50 mL) and H_2O (50 mL) were added to the reaction mixture at ambient temperature. The separated aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 19:1). Careful ^{1}H-NMR analysis gave a NMR-yield of 24% for **147ca** and 8% for **147oa**.

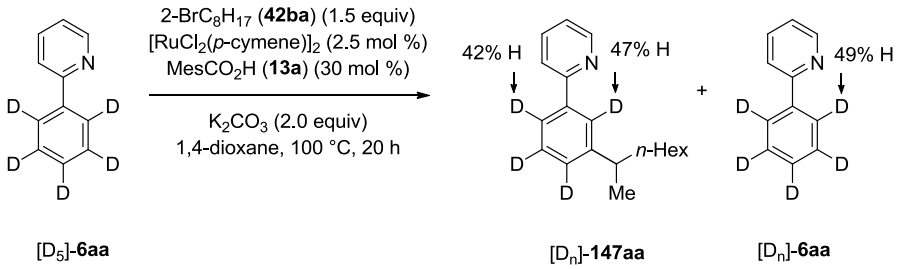
Intermolecular Competition Experiment between 2-(4-Methoxyphenyl)pyridine (6ba) & 2-(4-Methylphenyl)pyridine (6oa)



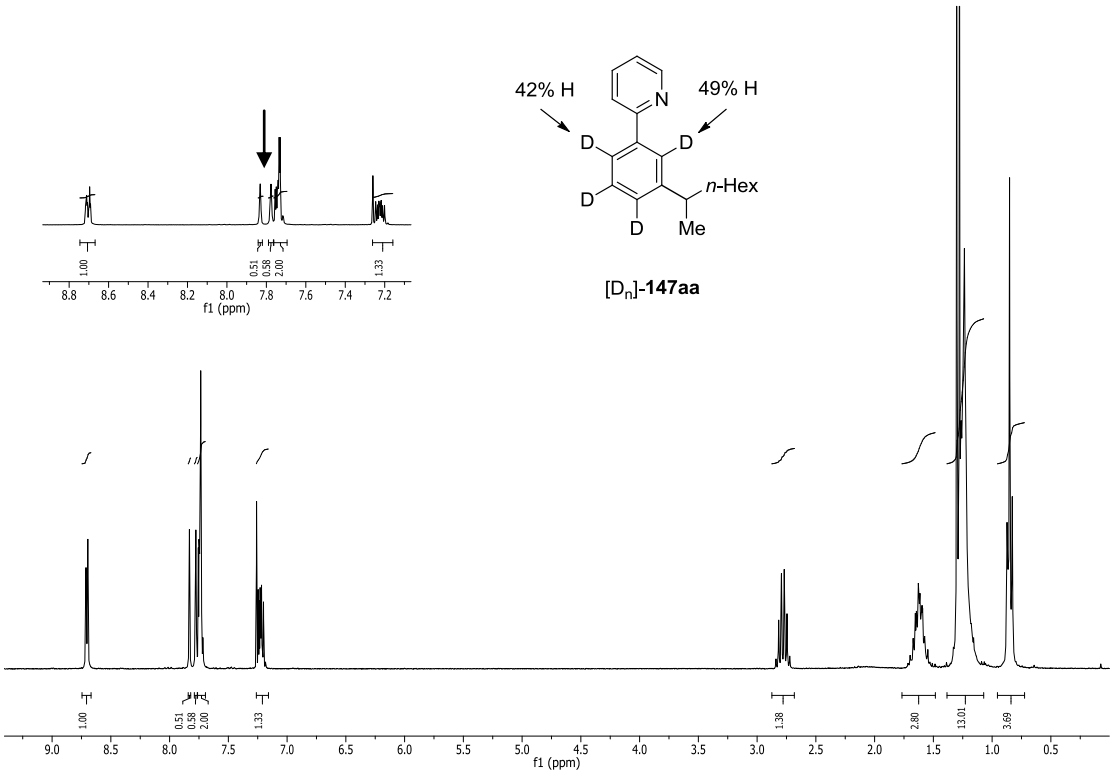
A suspension of $[RuCl_2(p\text{-cymene})]_2$ (15.8 mg, 0.026 mmol, 2.8 mol %), $MesCO_2H$ (48.7 mg, 0.30 mmol, 32 mol %), K_2CO_3 (277 mg, 2.00 mmol), **6ba** (343 mg, 2.03 mmol), **6oa** (372 mg, 2.01 mmol) and **42ba** (180 mg, 0.93 mmol) in dry 1,4-dioxane (4.0 mL) was stirred under N_2 for 20 h

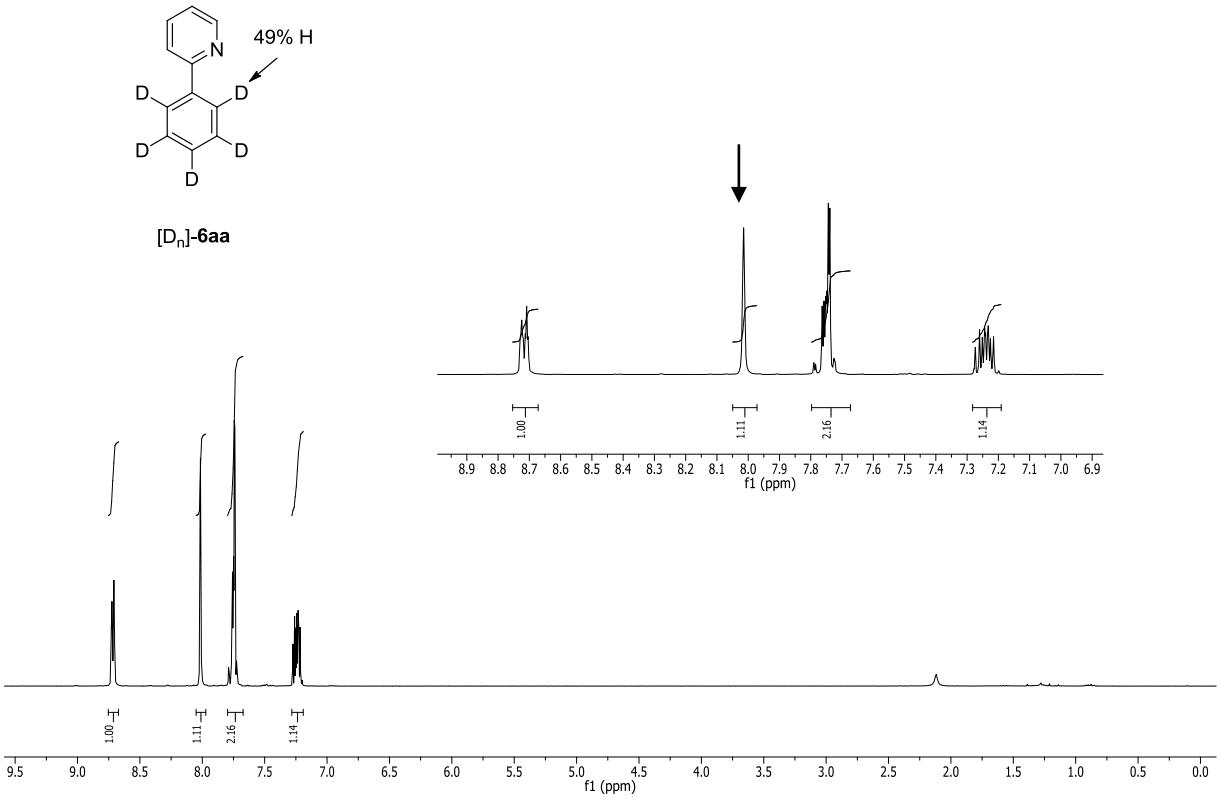
at 100 °C. EtOAc (50 mL) and H_2O (50 mL) were added to the reaction mixture at ambient temperature. The separated aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 9:1) to yield a mixture of **147ba** and **147oa** (30% conv.) in a ratio of 2.8:1.0 as determined by ^{1}H-NMR spectroscopy.

Experiment with Deuterium-Labeled Phenylpyridine [D_5]-6aa



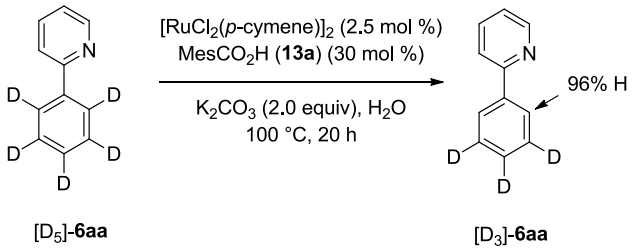
The general procedure **E** was followed, using [$RuCl_2$(*p*-cymene)]$_2$ (7.9 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 23 mol %), [D_5]-**6aa** (104 mg, 0.65 mmol) and 2-bromooctane (**42ba**) (288 mg, 1.49 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 19:1) yielded [D_n]-**147aa** (50 mg, 29%) and reisolated [D_n]-**6aa** (55 mg, 54%) as colorless oils.





Experiments with Deuterium-Labeled 2-(3,4,5-Trideuterophenyl)pyridine ([D_3]-6aa)

Synthesis of 2-(3,4,5-Trideuterophenyl)pyridine ([D_3]-6aa)



A suspension of [$RuCl_2$(*p*-cymene)]$_2$ (73.0 mg, 0.119 mmol, 2.5 mol %), $MesCO_2H$ (**13a**) (244 mg, 1.49 mmol, 31 mol %), K_2CO_3 (1.36 mg, 9.86 mmol) and [D_5]-**6aa** (0.78 g 4.84 mmol) in degassed H_2O (20 mL) was stirred under N_2 for 20 h at 100 °C. EtOAc (50 mL) and H_2O (50 mL) were added to the reaction mixture at ambient temperature. The separated aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) and Kugelrohr-distillation to yield [D_3]-**6aa** (0.56 g, 73%) as a colorless oil.

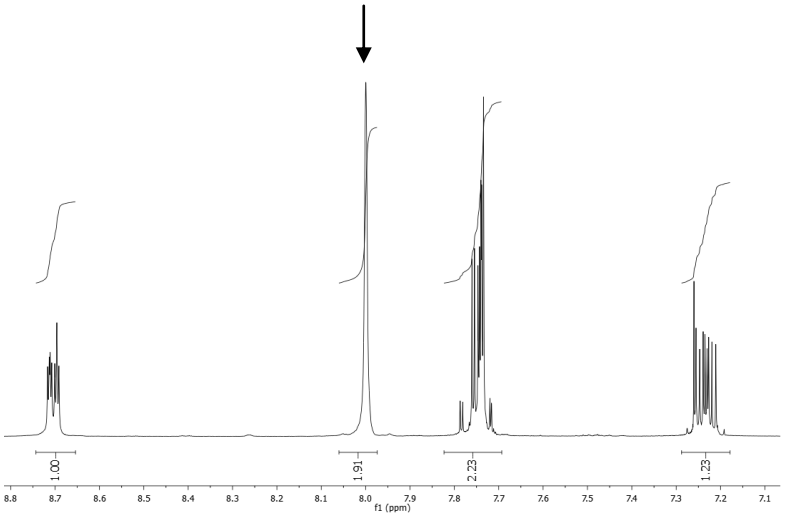
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.74-8.65 (m, 1H), 8.00 (s, 2H), 7.82-7.69 (m, 2H), 7.29-7.18 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.4 (C_q), 149.6 (CH), 139.3 (C_q), 136.7 (CH), 128.3 (C_q), 128.0 (C_q) 126.8 (CH), 122.1 (CH), 120.5 (CH).

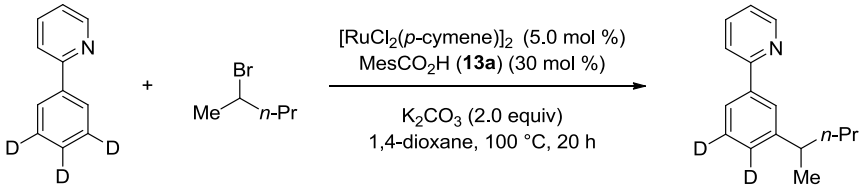
IR (ATR): $\tilde{\nu}$ = 3053, 3003, 2272, 2256, 1582, 1472, 1420, 783, 741, 610 cm^{-1}.

MS (EI) *m/z* (relative intensity): 158 (100) [M^+], 129 (12), 78 (14), 71 (12), 57 (29), 43 (60).

HR-MS (ESI) *m/z* calculated for $C_{11}H_6D_3N+H^+$: 159.1002; found: 159.0995.



Synthesis of 2-[4,5-Dideutero-3-(pentan-2-yl)phenyl]pyridine ([D_2]-147ai)



[D_3]-**6aa** **42bi** [D_2]-**147ai**

The general procedure **E** was followed, using [$RuCl_2$(*p*-cymene)]$_2$ (16.3 mg, 0.027 mmol, 5.2 mol %), $MesCO_2H$ (**13a**) (25 mg, 0.15 mmol, 29 mol %), [D_3]-**6aa** (82.4 mg, 0.52 mmol) and 2-bromopentane (**42bi**) (219 mg, 1.45 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 9:1) yielded [D_2]-**147ai** (61 mg, 52%) as a colorless oil.

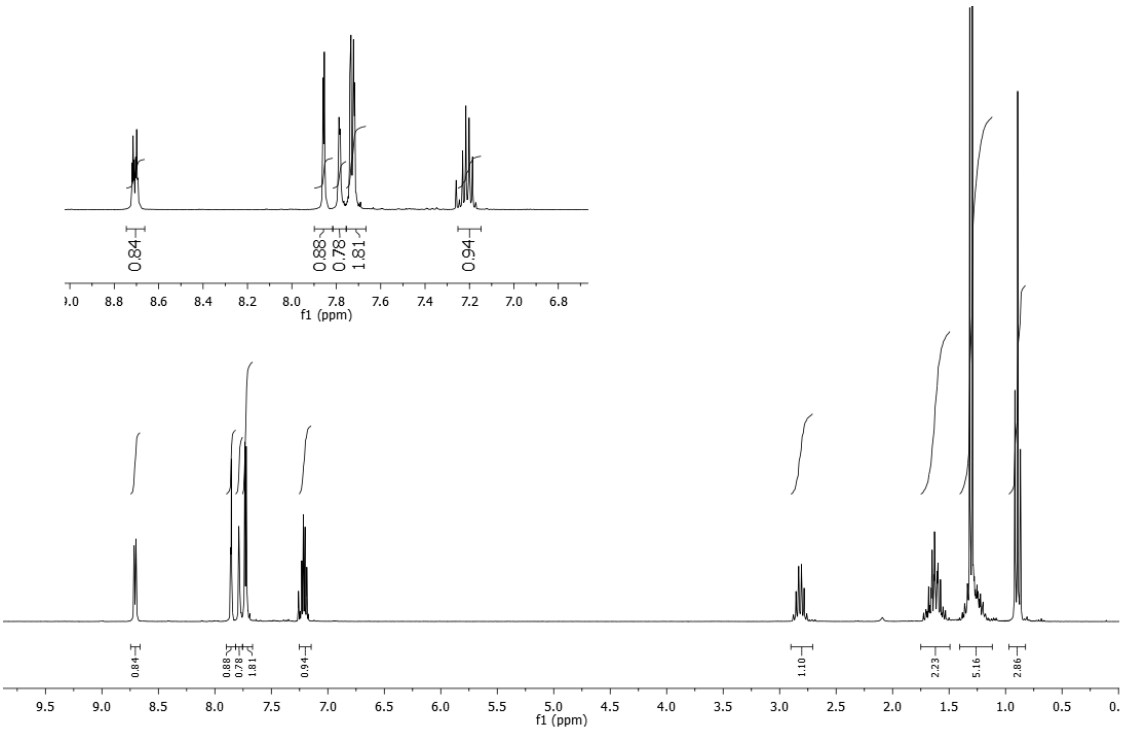
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.71 (ddd, *J* = 4.8, 1.4, 1.4 Hz, 1H), 7.86 (d, *J* = 1.9 Hz, 1H), 7.79 (d, *J* = 1.8 Hz, 1H), 7.76-7.67 (m, 2H), 7.25-7.15 (m, 1H), 2.82 (qt, *J* = 7.0, 6.9 Hz, 1H), 1.75-1.49 (m, 2H), 1.41-1.12 (m, 2H), 1.26 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 158.0 (C_q), 149.7 (CH), 148.5 (C_q), 139.5 (C_q), 136.7 (CH), 128.4 (t, $J_{C\text{-}D}$ = 24 Hz, C_q), 127.3 (t, $J_{C\text{-}D}$ = 24 Hz, C_q), 125.9 (CH), 124.4 (CH), 122.0 (CH), 120.8 (CH), 40.8 (CH_2), 39.9 (CH) , 22.4 (CH_2), 21.0 (CH_3), 14.3 (CH_3).

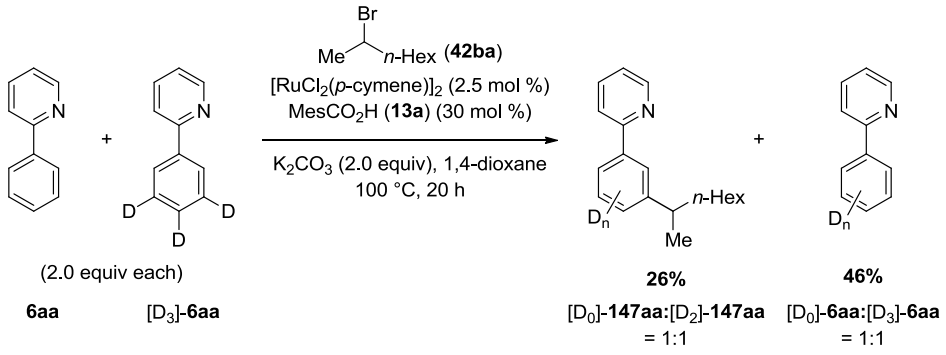
IR (ATR): $\tilde{\nu}$ = 2957, 2927, 2871, 1585, 1560, 1472, 1426, 907, 782, 732, 587 cm^{-1}.

MS (EI) *m/z* (relative intensity): 227 (37) [M^+], 198 (11), 184 (100), 169 (54), 78 (11).

HR-MS (ESI) *m/z* calculated for $C_{16}H_{17}D_2N^+$: 227.1643; found: 227.1641.



Intermolecular Competition Experiment between 2-(3,4,5-Trideuterophenyl)pyridine ([D_3]-6aa) and 2-Phenylpyridine (6aa)

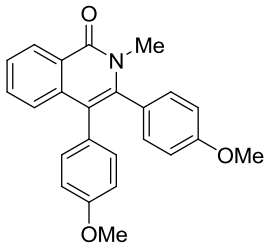


A suspension of [$RuCl_2$(*p*-cymene)]$_2$ (7.90 mg, 0.013 mmol, 2.5 mol %), $MesCO_2H$ (25.3 mg, 0.15 mmol, 30 mol %), K_2CO_3 (139 mg, 1.01 mmol, 2.0 equiv), **6aa** (162 mg, 1.05 mmol), [D_3]-**6aa** (155 mg 0.93 mmol) and **42ba** (106 mg, 0.55 mmol) in 1,4-dioxane (4.0 mL) was stirred under N_2 for

20 h at 100 °C. EtOAc (50 mL) and H_2O (50 mL) were added to the reaction mixture at ambient temperature. The separated aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 19:1) to yield a mixture of [D_0]-**147aa** and [D_2]-**147aa** (^{1}H-NMR ratio 1:1, 38 mg, 26%) and a mixture of re-isolated [D_0]-**6aa** and [D_3]-**6aa** (^{1}H-NMR ratio 1:1, 47 mg, 46%).

7.4 The Analytical Data for the Ruthenium-Catalyzed Oxidative Annulations

Synthesis of 3,4-Bis(4-methoxyphenyl)-2-methylisoquinolin-1(2*H*)-one (180ab)



The general procedure **F** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %), *N*-methylbenzamide (**86a**) (68.0 mg, 0.50 mmol) and 1,2-bis(4-methoxyphenyl)ethyne (**88b**) (194.8 mg, 0.82 mmol). After 22 h, purification by column chromatography (*n*-hexane/EtOAc 3:1) gave **180ab** (104 mg, 56%) as an orange solid.

M.r.: 160 - 162 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.54 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.59- 7.41 (m, 2H), 7.20- 7.14 (m, 1H), 7.09-6.90 (m, 4H), 6.84-6.69 (m, 4H), 3.76 (s, 6H), 3.35 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.8 (C_q), 159.1 (C_q), 158.1 (C_q), 141.3 (C_q), 137.5 (C_q), 132.5 (CH), 131.9 (CH), 131.1 (CH), 128.9 (C_q), 127.8 (CH), 127.6 (C_q), 126.4 (CH), 125.3 (CH), 124.9 (C_q), 118.7 (C_q), 113.6 (CH), 113.4 (CH), 55.1 (CH_3), 55.1 (CH_3), 34.3 (CH_3).

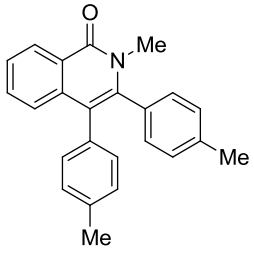
IR (ATR): $\tilde{\nu}$ = 3002, 2957, 2925, 2853, 1788, 1644, 1506, 1328, 1291, 1173, 862, 731 cm^{-1}.

MS (EI) *m/z* (relative intensity): 371 (100) [M^+], 355 (11), 267 (9), 239 (16), 165 (12), 135 (16).

HR-MS (EI) *m/z* calculated for $C_{24}H_{21}NO_3^+$: 371.1521; found: 371.1515.

The spectral data were in accordance with those reported in the literature.[212]

Synthesis of 2-Methyl-3,4-di-*p*-tolylisoquinolin-1(2*H*)-one (180ac)



[212] Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565–10569.

The general procedure **F** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %), *N*-methylbenzamide (**86a**) (66.7 mg, 0.49 mmol) and 1,2-di-*p*-tolylethyne (**88c**) (207.1 mg, 1.00 mmol). After 22 h, purification by column chromatography (*n*-hexane/EtOAc 4:1) gave **180ac** (118 mg, 71%) as a white solid.

M.r.: 194 - 197 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.53 (d, J = 7.1 Hz, 1H), 7.54-7.39 (m, 2H), 7.07-6.85 (m, 9H), 3.30 (s, 3H), 2.26 (s, 6H).

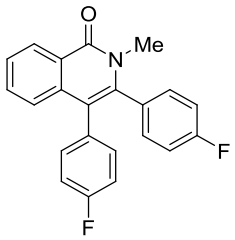
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.8 (C_q), 141.3 (C_q), 137.8 (C_q), 137.4 (C_q), 136.2 (C_q), 133.5 (C_q), 132.3 (C_q), 131.9 (CH), 131.3 (CH), 129.7 (CH), 128.9 (CH), 128.6 (CH), 127.7 (CH), 126.4 (CH), 125.4 (CH), 124.9 (C_q), 118.7 (C_q), 34.3 (CH_3), 21.2 (CH_3), 21.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3022, 2947, 2919, 2863, 1640, 1480, 1284, 1022, 996, 817, 705, 690 cm^{-1}.

MS (EI) *m/z* (relative intensity): 339 (100) [M^+], 246 (8), 178 (12), 132 (17), 91 (13).

HR-MS (EI) *m/z* calculated for $C_{24}H_{21}NO^+$: 339.1623; found: 339.1617.

Synthesis of 3,4-Bis(4-fluorophenyl)-2-methylisoquinolin-1(2*H*)-one (180ad)



The general procedure **F** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %), *N*-methylbenzamide (**86a**) (66.6 mg, 0.49 mmol) and 1,2-bis(4-fluorophenyl)ethyne (**88d**) (217.1 mg, 1.01 mmol). After 22 h, purification by column chromato-graphy (*n*-hexane/EtOAc 3:1) gave **180ad** (107 mg, 61%) as a white solid.

M.r.: 172 - 173 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.54 (d, J = 7.2 Hz, 1H), 7.56-7.45 (m, 2H), 6.99 (m, 9H), 3.33 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.6 (C_q), 162.2 (d, $J_{C\text{-}F}$ = 248 Hz, C_q), 161.6 (d, $J_{C\text{-}F}$ = 244 Hz, C_q), 140.5 (C_q), 136.93 (C_q), 133.0 (d, $J_{C\text{-}F}$ = 8 Hz, CH), 132.2 (C_q), 131.7 (d, $J_{C\text{-}F}$ = 9 Hz, CH), 131.0 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 130.7 (CH), 127.9 (CH), 126.9 (CH), 125.1 (CH), 125.0 (C_q), 118.2(C_q), 115.5 (d, $J_{C\text{-}F}$ = 21 Hz, CH), 115.2 (d, $J_{C\text{-}F}$ = 20 Hz, CH), 34.3 (CH_3).

^{19}F-NMR (283 MHz, $CDCl_3$): δ = -112.0 - -112.2 (m), - 114.7 - -115.1 (m).

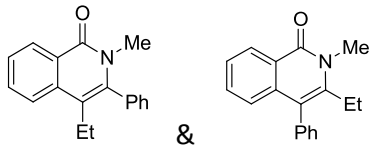
IR (ATR): $\tilde{\nu}$ = 3058, 3040, 2855, 1639, 1603, 1224, 1159, 1054, 866, 771, 728, 701, 688 cm^{-1}.

MS (EI) *m/z* (relative intensity): 346 (100) [M-H^+], 303 (8), 250 (10), 183 (14), 136 (12), 95 (13).

HR-MS (EI) *m/z* calculated for $C_{22}H_{14}F_2NO$-H^+: 346.1043; found: 346.1043.

Synthesis of 4-Ethyl-2-methyl-3-phenylisoquinolin-1(2*H*)-one (180ae) and 3-Ethyl-2-methyl-4-phenylisoquinolin-1(2*H*)-one (180ae')

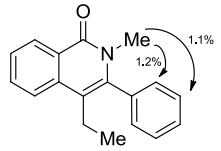
The general procedure **F** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %), *N*-methylbenzamide (**86a**) (68.1 mg, 0.50 mmol) and but-1-yn-1-ylbenzene (**88e**) (140 mg, 1.07 mmol). After 22 h, purification by column chromatography (*n*-hexane/EtOAc 9:1 to 4:1) yielded **180ae** and **180ae'** as a mixture (106 mg, 80%, ratio 7.2:1.0 by ^{1}H-NMR) and was isolated as a grey solid. (NMR spectra were analyzed only for the major regioisomer **180ae'**).



(180ae) **(180ae')**

Major isomer:

nOe:



(180ae')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.52 (ddd, *J* = 8.1, 1.5, 0.7 Hz, 1H), 7.76-7.58 (m, 2H), 7.54-7.30 (m, 4H), 7.28-7.19 (m, 2H), 3.19 (s, 3H), 2.39 (q, *J* = 7.5 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.3 (C_q), 140.0 (C_q), 135.9 (C_q), 135.4 (C_q), 131.9 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.2 (CH), 126.1 (CH), 125.5 (C_q), 123.0 (CH), 116.4 (C_q), 33.9 (CH_3), 21.4 (CH_2), 14.7 (CH_3).

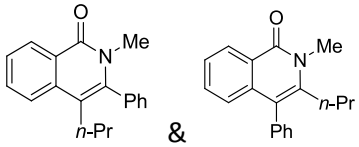
IR (ATR): $\tilde{\nu}$ = 2965, 2929, 2872, 1643, 1556, 1328, 761, 700, 656, 534 cm^{-1}.

MS (EI) *m/z* (relative intensity): 263 (77) [M^+], 248 (100), 233 (20), 178 (11), 77 (13).

HR-MS (EI) *m/z* calculated for $C_{18}H_{17}NO^+$: 263.1310; found: 263.1308.

Synthesis of 2-Methyl-3-phenyl-4-*n*-propylisoquinolin-1(2*H*)-one (180af') & 2-Methyl-4-phenyl-3-*n*-propylisoquinolin-1(2*H*)-one (180af)

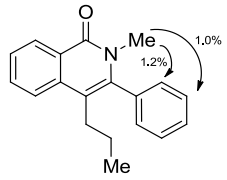
The general procedure **F** was followed using $[RuCl_2(p\text{-cymene})]_2$ (16 mg, 0.026 mmol, 5.1 mol %), *N*-methylbenzamide (**86a**) (67.5 mg, 0.50 mmol) and pent-1-yn-1-ylbenzene (**88f**) (155 mg, 1.07 mmol). After 22 h, purification by column chromatography (*n*-hexane/EtOAc 4:1) yielded **180af'** and **180af** as a mixture (128 mg, 92%, ratio 9.7:1.0 by ^{1}H-NMR) as a white solid.(NMR spectra were analyzed only for the major regioisomer **180af'**.)



(180af) **(180af')**

Major isomer:

nOe:



(180af')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.50 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.68-7.53 (m, 2H), 7.49-7.32 (m, 4H), 7.21 (dd, *J* = 7.5, 2.0 Hz, 2H), 3.18 (s, 3H), 2.37-2.23 (m, 2H), 1.53-1.31 (m, 2H), 0.74 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.2 (C_q), 140.2 (C_q), 136.1 (C_q), 135.4 (C_q), 131.8 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.1 (CH), 126.0 (CH), 125.4 (C_q), 123.0 (CH), 115.1 (C_q), 33.9 (CH_3), 30.4 (CH_2), 23.5 (CH_2), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2953, 2869, 1640, 1588, 1486, 1328, 1072, 1031, 765, 702, 437 cm^{-1}.

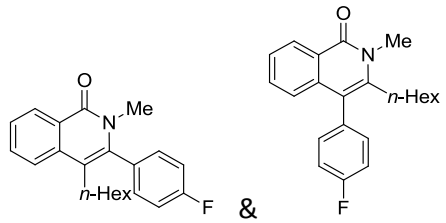
MS (EI) *m/z* (relative intensity): 277 (43) [M^+], 248 (100), 233 (15), 178 (9), 77 (9).

HR-MS (EI): *m/z* calculated for $C_{19}H_{19}NO^+$: 277.1467; found: 277.1466.

Synthesis of 3-(4-Fluorophenyl)-4-*n*-hexyl-2-methylisoquinolin-1(2*H*)-one (180ag) and 4-(4-Fluorophenyl)-3-*n*-hexyl-2-methylisoquinolin-1(2*H*)-one (180ag')

The general procedure **F** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %), *N*-methylbenzamide (**86a**) (68.1 mg, 0.50 mmol) and 1-fluoro-4-(oct-1-ynyl)benzene (**88g**) (261 mg,

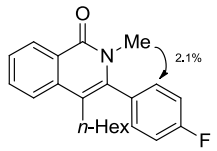
1.23 mmol). After 22 h, purification by column chromatography (*n*-hexane/EtOAc 5:1 to 3:1) yielded **180ag** and **180ag'** as a mixture (62 mg, 37%, ratio 7.6:1.0 by ^{1}H-NMR) as a brown oil. (NMR spectra were analyzed only for the major regioisomer **180ag'**.)



(180ag') & **(180ag)**

Major isomer:

nOe:



(180ag')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.53 (dd, J = 8.1, 1.1 Hz, 1H), 7.72-7.65 (m, 2H), 7.55-7.45 (m, 1H), 7.31-7.14 (m, 4H), 3.23 (s, 3H), 2.41-2.30 (m, 2H), 1.54-1.31 (m, 2H), 1.31-1.02 (m, 6H), 0.82 (t, J = 6.9 Hz, 3H).

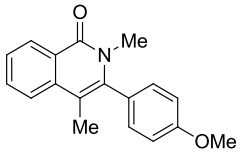
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.7 (d, $J_{C\text{-}F}$ = 249 Hz, C_q), 162.4 (C_q), 139.1 (C_q), 136.1 (C_q), 132.1 (CH), 131.5 (d, $J_{C\text{-}F}$ = 4 Hz, C_q), 131.1 (d, $J_{C\text{-}F}$ = 8 Hz, CH), 128.3 (CH), 126.4 (CH), 125.6 (C_q), 123.2 (CH), 116.0 (d, $J_{C\text{-}F}$ = 22 Hz, CH), 116.0 (C_q), 34.0 (CH_3), 31.2 (CH_2), 30.2 (CH_2), 29.4 (CH_2), 28.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2954, 2927, 2860, 1641, 1590, 1330, 1219, 1160, 858, 776, 708, 542 cm^{-1}.

MS (EI) *m/z* (relative intensity): 337 (53) [M^+], 280 (15), 266 (100), 251 (22), 196 (10).

HR-MS (EI) *m/z* calculated for $C_{22}H_{24}FNO^+$: 337.1842; found: 337.1839.

Synthesis of 3-(4-Methoxyphenyl)-2,4-dimethylisoquinolin-1(2*H*)-one (180ah')



The general procedure **F** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 4.8 mol %), *N*-methylbenzamide (**86a**) (70.0 mg, 0.52 mmol) and 1-methoxy-4-(prop-1-ynyl)benzene (**88h**) (144.6 mg, 0.99 mmol). After 22 h, purification by column chromatography (*n*-hexane/EtOAc 4:1 to 2:1) yielded **180ah'** (96 mg, 66%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 8.0 Hz, 1H), 7.72- 7.58 (m, 2H), 7.53- 7.39 (m, 1H), 7.21-7.08 (m, 2H), 7.06-6.92 (m, 2H), 3.84 (s, 3H), 3.25 (s, 3H), 2.01 (s, 3H).

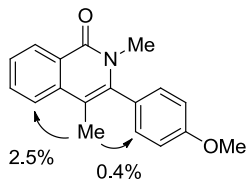
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.5 (C_q), 159.6 (C_q), 140.0 (C_q), 137.0 (C_q), 131.9 (CH), 130.5 (CH), 128.0 (CH), 128.0 (C_q), 126.2 (CH), 125.2 (C_q), 123.1 (CH), 114.2 (CH), 110.7 (C_q), 55.2 (CH_3), 34.1 (CH_3), 14.8 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3038, 2985, 2952, 2935, 1642, 1449, 1411, 1342, 1107, 1029, 693, 639 cm^{-1}.

MS (EI) *m/z* (relative intensity): 278 (100) [M-H$^+$], 263 (53), 248 (20), 220 (11), 178 (10), 165 (11), 148 (19), 86 (15), 77 (16).

HR-MS (EI) *m/z* calculated for $C_{18}H_{17}NO_2^+$: 279.1259; found: 279.1263.

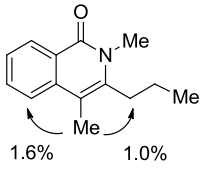
nOe:



Synthesis of 2,4-Dimethyl-3-propylisoquinolin-1(2*H*)-one (180ai) and 2,3-Dimethyl-4-propylisoquinolin-1(2*H*)-one (180ai')

The general procedure **F** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 4.9 mol %)*N*-methylbenzamide (**86a**) (68.7 mg, 0.51 mmol) and hex-2-yne (**88i**) (89.3 mg, 1.09 mmol). After 22 h, purification by column chromatography (*n*-hexane/EtOAc 4:1) yielded **180ai** (26 mg, 24%) as a light brown oil and **180ai'** (37 mg, 34%) as a white solid.

nOe:



(180ai)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 3.4 Hz, 2H), 7.46- 7.34 (m, 1H), 3.65 (s, 3H), 2.80-2.69 (m, 2H), 2.30 (s, 3H), 1.68-1.51 (m, 2H), 1.05 (t, *J* = 7.3 Hz, 3H).

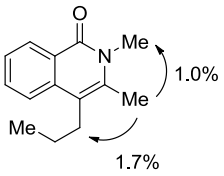
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.0 (C_q), 139.7 (C_q), 137.1 (C_q), 131.9 (CH), 128.1 (CH), 125.7 (CH), 124.5 (C_q), 122.6 (CH), 108.9 (C_q), 32.0 (CH_2), 31.3 (CH_3), 22.1 (CH_2), 14.0 (CH_3), 13.6 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3069, 2961, 2931, 2872, 1772, 1642, 1589, 1486, 1457, 1413, 1370, 1323, 1188, 1075, 1028, 962, 885, 764, 693, 606, 424 cm^{-1}.

MS (EI) *m/z* (relative intensity): 215 (100) [M^+], 200 (88), 11 (80), 172 (30), 156 (34), 147 (40), 129 (24), 115 (28), 102 (50), 77 (28).

HR-MS (EI) *m/z* calculated for $C_{14}H_{17}NO^+$: 215.1310; found: 215.1315.

nOe:



(180ai')

M.r.: 86 - 88 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 8.0 Hz, 1H), 7.69-7.52 (m, 2H), 7.45-7.32 (m, 1H), 3.62 (s, 3H), 2.80-2.59 (m, 2H), 2.38 (s, 3H), 1.69-1.42 (m, 2H), 1.01 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.7 (C_q), 136.4 (C_q), 135.9 (C_q), 131.9 (CH), 128.3 (CH), 125.5 (CH), 124.6 (C_q), 122.4 (CH), 113.9 (C_q), 31.6 (CH_3), 29.8 (CH_2), 23.1 (CH_2), 16.7 (CH_3), 14.1 (CH_3).

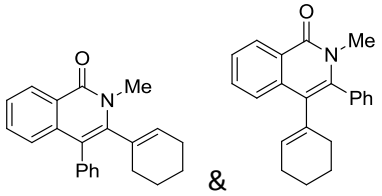
IR (ATR): $\tilde{\nu}$ = 3070, 2953, 2934, 2871, 1724, 1642, 1555, 1457, 1412, 1323, 1029, 699 cm^{-1}.

MS (EI: *m/z* (relative intensity): 215 (36) [M^+], 187 (100), n158 (11), 115 (11), 56 (14).

HR-MS (EI) *m/z* calculated for $C_{14}H_{17}NO^+$: 215.1310; found: 215.1307.

Synthesis of 4-(Cyclohex-1-en-1-yl)-2-methyl-3-phenylisoquinolin-1(2*H*)-one (180aj) & 3-(Cyclohex-1-en-1-yl)-2-methyl-4-phenylisoquinolin-1(2*H*)-one (180aj')

The general procedure **F** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.1 mol %), *N*-methylbenzamide (**86a**) (68.8 mg, 0.51 mmol) and cyclohex-1-en-1-ylethynylbenzene (**88j**) (177 mg, 0.97 mmol). After 22 h, purification by column chromatography (*n*-hexane/EtOAc: 3:1 to 2:1) yielded **180aj** and **180aj'** as an inseperable mixture (42 mg, 26%, ratio by ^{1}H-NMR 1.0:1.3) as an orange oil.

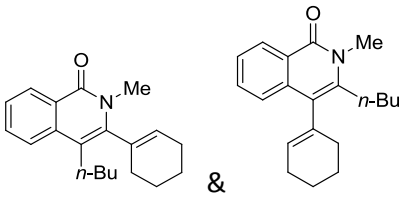


(180aj) **(180aj')**

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.52-8.29 (m, 2H), 7.65-6.91 (m, 18H), 5.61-5.51 (m, 1H), 5.52-5.41 (m, 1H), 3.52 (s, 4H), 3.23 (s, 3H), 2.15-1.86 (m, 7H), 1.86-1.38 (m, 7H), 1.38-1.03 (m, 3H).
Assignment of the resonances was not possible due to their overlapping.
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 162.5 (C_q), 162.3 (C_q), 143.0 (C_q), 139.5 (C_q), 137.2 (C_q), 136.8 (C_q), 136.2 (C_q), 135.0 (C_q), 132.7 (C_q), 132.4 (CH), 132.0 (C_q), 132.0 (CH), 131.8 (CH), 131.6 (CH), 130.9 (CH), 130.5 (CH), 130.0 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.6 (CH), 127.3 (CH), 126.8 (CH), 126.2 (CH), 125.9 (CH), 125.0 (CH), 124.8 (C_q), 124.5 (CH), 124.1 (C_q), 120.8 (C_q), 117.2 (C_q), 34.2 (CH_3), 32.9 (CH_3), 30.3 (CH_2), 29.4 (CH_2), 25.2 (CH_2), 24.8 (CH_2), 22.7 (CH_2), 22.1 (CH_2), 21.7 (CH_2), 21.3 (CH_2).
IR (ATR): $\tilde{\nu}$ = 2939, 2860, 1642, 1606, 1481, 1327, 1026, 777, 756, 702 cm^{-1}.
MS (EI) *m/z* (relative intensity): 315 (100) [M^+], 286 (29), 272 (33), 258 (11), 165 (12), 105 (17).
HR-MS (ESI) *m/z* calculated for $C_{22}H_{21}NO+H^+$: 316.1701; found: 316.1696.

Synthesis of 4-*n*-Butyl-3-(cyclohex-1-en-1-yl)-2-methylisoquinolin-1(2*H*)-one (180ak) & 3-*n*-Butyl-4-(cyclohex-1-en-1-yl)-2-methylisoquinolin-1(2*H*)-one (180ak')

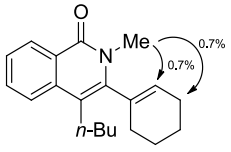
The general procedure **F** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %), *N*-methylbenzamide (**86a**) (68.8 mg, 0.51 mmol) and 1-(hex-1-yn-1-yl)-cyclohex-1-ene (**88k**) (177 mg, 1.10 mmol). After 22 h, purification by column chromatography (*n*-hexane/EtOAc 5:1) yielded **180ak** and **180ak'** as an inseperable mixture (70 mg, 46%, ratio det. by ^{1}H-NMR 10:1.0) which was isolated as an orange oil. (NMR spectra were analyzed only for the major regioisomer **180ak**.)



&

(180ak) **(180ak')**

Major regeoisomer:

nOe:


(180ak)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.47 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.69-7.59 (m, 2H), 7.43 (ddd, *J* = 8.1, 5.0, 3.2 Hz, 1H), 5.81 (dd, *J* = 3.7, 2.0 Hz, 1H), 3.52 (s, 3H), 2.81-2.61 (m, 1H), 2.61-2.44 (m, 1H), 2.33-2.04 (m, 4H), 1.94-1.65 (m, 4H), 1.52-1.33 (m, 3H), 0.96 (t, *J* = 7.0 Hz, 3H).

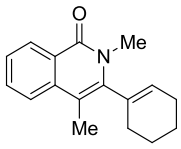
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 162.5 (C_q), 142.0 (C_q), 136.6 (C_q), 132.9 (C_q), 131.7 (CH), 130.5 (CH), 128.0 (CH), 125.8 (CH), 124.9 (C_q), 123.0 (CH), 114.0 (C_q), 33.2 (CH_3), 32.6 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 25.1 (CH_2), 23.0 (CH_2), 22.4 (CH_2), 21.6 (CH_2), 13.8 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3357, 2829, 2859, 1643, 1584, 1555, 1335, 1070, 770, 701 cm^{-1}.

MS (EI) *m/z* (relative intensity): 295 (53) [M^+], 252 (100), 210 (26), 197 (10), 162 (10).

HR-MS (EI) *m/z* calculated for $C_{20}H_{25}NO^+$: 295.1936; found: 295.1942.

Synthesis of 3-Cyclohexenyl-2,4-Dimethylisoquinolin-1(2*H*)-one (180al)



The general procedure **F** was followed using $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 0.051 mmol, 10 mol %), *N*-methylbenzamide (**86a**) (69.0 mg, 0.51 mmol) and 1-(prop-1-ynyl)cyclohex-1-ene (**88l**) (126 mg, 1.05 mmol). After 22 h, purification by column chroma-tography (*n*-hexane/EtOAc: 2:1) yielded **180al** (72 mg, 56%) as an orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 8.3 Hz, 1H), 7.77-7.56 (m, 2H), 7.55-7.36 (m, 1H), 5.86-5.71 (m, 1H), 3.52 (s, 3H), 2.31-2.18 (m, 5H), 2.17-2.05 (m, 2H), 1.76 (s, 4H).

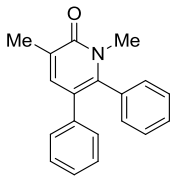
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 162.7 (C_q), 142.1 (C_q), 137.3 (C_q), 133.4 (C_q), 131.8 (CH), 130.8 (CH), 127.9 (CH), 125.9 (CH), 124.8 (C_q), 123.0 (CH), 108.5 (C_q), 32.7 (CH_3), 29.1 (CH_2), 25.2 (CH_2), 22.5 (CH_2), 21.7 (CH_2), 14.2 (CH).

IR (ATR): $\tilde{\nu}$ = 2925, 2858, 2836, 1639, 1588, 1486, 1414, 1341, 1323, 1188, 1030, 919, 765, 728, 694, 644, 564, 424 cm^{-1}.

MS (EI) *m/z* (relative intensity): 253 (100) [M^+], 238 (22), 224 (38), 210 (59), 196 (27), 165 (10), 128 (8), 115 (10), 77 (16).

HR-MS (EI) *m/z* calculated for $C_{17}H_{19}NO^+$: 253.1467; found: 253.1458.

Synthesis of 1,3-Dimethyl-5,6-diphenylpyridin-2(1*H*)-one (182aa)



The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %), *N*-methylmethacrylamide (**181a**) (111 mg, 1.12 mmol) and 1,2-diphenylethyne (**88a**) (89.0 mg, 0.50 mmol). Purification by column chromatography (EtOAc) yielded **182aa** (126 mg, 92%) as a white solid.

M.p.: 135 °C

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 1.0 Hz, 1H), 7.30-7.23 (m, 3H), 7.12-7.03 (m, 5H), 6.95-6.88 (m, 2H), 3.32 (s, 3H), 2.23 (d, *J* = 1.0 Hz, 3H).

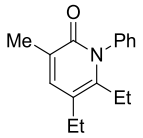
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.1 (C_q), 144.0 (C_q), 139.0 (CH), 138.7 (C_q), 134.5 (C_q), 133.9 (CH), 131.2 (CH), 130.0 (CH), 129.5 (CH), 128.6 (CH), 127.8 (C_q), 126.2 (CH), 119.9 (C_q), 34.7 (CH_3), 17.3 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3057, 2921, 1646, 1597, 1490, 1416, 765, 699 cm^{-1}.

MS (EI) *m/z* (relative intensity): 274 (100) [M-H$^+$], 246 (15), 118 (16), 77 (33), 43 (29).

HR-MS (EI) *m/z* calculated for $C_{19}H_{16}NO^+$: 274.1232, found 274.1238.

Synthesis of 5,6-Diethyl-3-methyl-1-phenylpyridine-2(1*H*)-one (182ap)



The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (16 mg, 0.026 mmol, 5.3 mol %), *N*-phenylmethacrylamide (**181a**) (162 mg, 1.00 mmol) and hex-3-yne (**88p**) (40.0 mg, 0.49 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1) yielded **182ap** (60 mg, 51%) as a brown solid.

M.p.: 93 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.53-7.33 (m, 3H), 7.21-7.08 (m, 3H), 2.41 (q, *J* = 7.5 Hz, 2H), 2.29 (q, *J* = 7.5 Hz, 2H), 2.11 (d, *J* = 0.8 Hz, 3H), 1.18 (t, *J* = 7.5 Hz, 3H), 0.87 (t, *J* = 7.5 Hz, 3H).

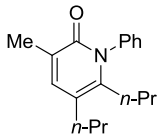
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.5 (C_q), 144.4 (C_q), 139.6 (C_q), 139.5 (CH), 129.3 (CH), 128.5 (CH), 128.3 (CH), 127.1 (C_q), 117.7 (C_q), 23.9 (CH_2), 22.9 (CH_2), 16.9 (CH_3), 15.5 (CH_3), 13.8 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2968, 2930, 1646, 1542, 1315, 773, 695 cm^{-1}.

MS (EI) *m/z* (relative intensity): 241 (100) [M$^+$], 226 (96), 198 (83), 77 (47), 58 (21), 51 (24), 43 (93).

HR-MS (EI) *m/z* calculated for $C_{16}H_{19}NO^+$: 241.1467; found: 241.1461.

Synthesis of 3-Methyl-1-phenyl-5,6-di-*n*-propylpyridin-2(1*H*)-one (182aq)



The general procedure **G** was followed using [$RuCl_2$(*p*-cymene)]$_2$ (15 mg, 0.025 mmol, 4.9 mol %), *N*-phenylmethacrylamide (**181a**) (161 mg, 1.00 mmol) and oct-4-yne (**88q**) (54.0 mg, 0.49 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1 to EtOAc) yielded **182aq** (80 mg, 61%) as a grey solid.

M.p.: 99 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.53-7.36 (m, 3H), 7.21-7.15 (m, 2H), 7.13 (s, 1H), 2.35 (dd, *J* = 8.8, 6.8 Hz, 2H), 2.26-2.15 (m, 2H), 2.12 (d, *J* = 0.8 Hz, 3H), 1.66-1.48 (m, 2H), 1.39-1.23 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.66 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.5 (C_q), 143.4 (C_q), 139.9 (CH), 139.6 (C_q), 129.2 (CH), 128.4 (CH), 128.2 (CH), 126.8 (C_q), 116.5 (C_q), 33.0 (CH_2), 31.8 (CH_2), 24.1 (CH_2), 22.6 (CH_2), 16.9 (CH_3), 14.0 (CH_3), 14.0 (CH_3).

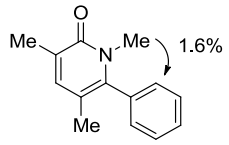
IR (ATR): $\tilde{\nu}$ = 3295, 3053, 1646, 1605, 1541, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity): 269 (47) [M$^+$], 240 (100), 211 (25), 77 (32), 43 (20).

HR-MS (EI) *m/z* calculated for $C_{18}H_{23}NO^+$: 269.1780; found: 269.1782.

Synthesis of 1,3,5-Trimethyl-6-phenylpyridin-2(1*H*)-one (182as) and 1,3,6-Trimethyl-5-phenylpyridin-2(1*H*)-one (182as')

The general procedure **G** was followed using [$RuCl_2$(*p*-cymene)]$_2$ (15 mg, 0.025 mmol, 5.0 mol %), *N*-methylmethacrylamide (**181a**) (101 mg, 1.02 mmol) and prop-1-yn-1-ylbenzene (**88s**) (62.4 mg, 0.54 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1) yielded **182as** (45 mg, 39%) and **182as'** (25 mg, 22%) as white solids.

nOe: 

(182as)

M.p.: 104 °C.

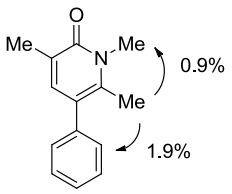
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.55-7.37 (m, 3H), 7.22-7.06 (m, 3H), 3.22 (s, 3H), 2.19 (s, 3H), 1.76 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.5 (C_q), 144.2 (C_q), 140.2 (CH), 135.8 (C_q), 129.6 (CH), 129.5 (CH), 129.3 (CH), 128.2 (C_q), 113.5 (C_q), 35.0 (CH_3), 18.3 (CH_3), 17.8 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2975, 2944, 1643, 1591, 1555, 1254, 1017, 929, 764, 706, 500 cm^{-1}.

MS (EI) *m/z* (relative intensity): 212 (100) [M-H$^+$], 197 (12), 184 (35), 77 (17).

HR-MS (EI) *m/z* calculated for $C_{14}H_{15}NO$-H$^+$: 212.1075; found: 212.1073.

nOe: 

(182as')

M.r.: 77 - 79 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.45-7.28 (m, 3H), 7.28-7.12 (m, 3H), 3.64 (s, 3H), 2.28 (s, 3H), 2.17 (s, 3H).

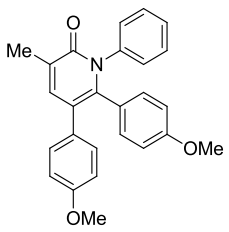
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.4 (C_q), 140.2 (C_q), 139.6 (C_q), 138.7 (CH), 129.6 (CH), 128.4 (CH), 127.0 (CH), 125.5 (C_q), 119.7 (C_q), 31.9 (CH_3), 18.2 (CH_3), 17.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2917, 1639, 1593, 1549, 1416, 1286, 1152, 912, 779, 712, 512 cm^{-1}.

MS (EI) *m/z* (relative intensity): 212 (100) [M-H$^+$], 184 (44), 128 (17), 77 (10), 56 (20).

HR-MS (EI) *m/z* calculated for $C_{14}H_{15}NO$-H$^+$: 212.1075; found: 212.1081.

Synthesis of 5,6-Bis(4-methoxyphenyl)-3-methyl-1-phenylpyridin-2(1*H*)-one (182bb)



The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 4.9 mol %), *N*-phenylmethacrylamide (**181b**) (161 mg, 1.00 mmol) and 1,2-bis(4-methoxyphenyl)-ethyne (**88b**) (121 mg, 0.51 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1 to EtOAc) yielded **182bb** (75 mg, 37%) as a brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.40 (s, 1H), 7.27-7.07 (m, 3H), 7.05-6.98 (m, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 6.46 (d, *J* = 9.2 Hz, 2H), 3.71 (s, 3H), 3.62 (s, 3H), 2.24 (s, 3H).

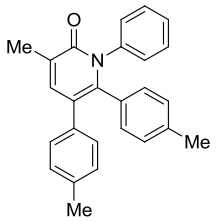
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.1 (C_q), 158.5 (C_q), 157.9 (C_q), 143.3 (C_q), 140.1 (CH), 139.6 (C_q), 132.2 (CH), 131.2 (C_q), 130.6 (CH), 129.1 (CH), 128.7 (CH), 128.5 (C_q), 127.4 (CH), 126.7 (C_q), 119.5 (C_q), 113.3 (CH), 112.9 (CH), 55.1 (CH_3), 54.9 (CH_3), 17.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2933, 2836, 1649, 1609, 1454, 1288, 1027, 831 cm^{-1}.

MS (EI) *m/z* (relative intensity): 397 (100) [M^+], 369 (25), 354 (27), 210 (18), 77 (39).

HR-MS (EI) *m/z* calculated for $C_{26}H_{23}NO_3^+$: 397.1678; found: 397.1671.

Synthesis of 3-Methyl-1-phenyl-5,6-di-*p*-tolylpyridin-2(1*H*)-one (182bc)



The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %), *N*-phenylmethacrylamide (**181b**) (164 mg, 1.02 mmol) and 1,2-di-*p*-tolylethyne (**88c**) (101 mg, 0.49 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1) yielded **182bc** (174 mg, 97%) as a white solid.

M.p.: 168 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.44-7.39 (s, 1H), 7.22-7.08 (m, 3H), 7.04-6.98 (m, 2H), 6.96-6.84 (m, 4H), 6.76-6.68 (m, 4H), 2.25 (s, 3H), 2.23 (s, 3H), 2.11 (s, 3H).

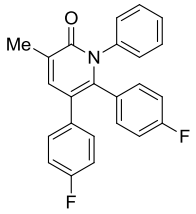
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.0 (C_q), 143.7 (C_q), 140.2 (CH), 139.5 (C_q), 137.2 (C_q), 135.9 (C_q), 135.8 (C_q), 131.3 (C_q), 130.8 (CH), 129.3 (CH), 129.1 (CH), 128.7 (C_q), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.4 (CH), 119.6 (C_q), 21.1 (CH_3), 21.0 (CH_3), 17.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3032, 2921, 1652, 1614, 1503, 1293, 818, 725 cm^{-1}.

MS (EI) *m/z* (relative intensity): 365 (100) [M^+], 337 (29), 194 (19), 77 (37), 43 (23).

HR-MS (EI) *m/z* calculated for $C_{26}H_{23}NO^+$: 365.1780; found: 365.1783.

Synthesis of 5,6-Bis(4-fluorophenyl)-3-methyl-1-phenylpyridin-2(1*H*)-one (182bd)



The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (16 mg, 0.026 mmol, 5.0 mol %), *N*-phenylmethacrylamide (**181b**) (160 mg, 0.99 mmol) and 1,2-bis(4-fluorophenyl)-ethyne (**88d**) (108 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1 to EtOAc) yielded **182bd** (129 mg, 69%) as an off-white solid.

M.p.: 188 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.41 (t, J = 3.8 Hz, 1H), 7.30-7.09 (m, 3H), 6.97 (m, 4H), 6.89-6.75 (m, 4H), 6.75-6.59 (m, 2H), 2.27 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.9 (C_q), 161.8 (d, $J_{C\text{-}F}$ = 248 Hz, C_q), 161.4 (d, $J_{C\text{-}F}$ = 247 Hz, C_q), 142.7 (C_q), 139.6 (CH), 139.2 (C_q), 134.4 (d, $J_{C\text{-}F}$ = 3 Hz, C_q), 132.8 (d, $J_{C\text{-}F}$ = 8 Hz, 2xCH), 131.1 (d, $J_{C\text{-}F}$ = 8 Hz, 2xCH), 130.2 (d, $J_{C\text{-}F}$ = 4 Hz, C_q), 129.6 (C_q), 129.1 (CH), 128.7 (CH), 127.8 (CH), 119.0 (C_q), 115.1 (d, $J_{C\text{-}F}$ = 16 Hz, CH), 114.8 (d, $J_{C\text{-}F}$ = 17 Hz, CH), 17.2 (CH_3) .

^{19}F-NMR (283 MHz, $CDCl_3$): δ = -112.4 (m), -115.6 (m).

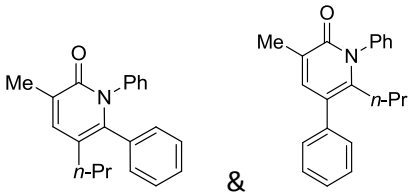
IR (ATR): $\tilde{\nu}$ = 3056, 2920, 1647, 1596, 1544, 1489, 1207, 765 cm^{-1}.

MS (EI) *m/z* (relative intensity): 373 (88) [M^+], 345 (32), 198 (23), 146 (23), 77 (100), 51 (29).

HR-MS (EI) *m/z* calculated for $C_{24}H_{17}F_2NO^+$: 373.1278; found: 373.1279.

Synthesis of the Mixture of 3-Methyl-1,6-diphenyl-5-propylpyridin-2(1*H*)-one (182bf') and 3-Methyl-1,5-diphenyl-6-propylpyridin-2(1*H*)-one (182bf)

The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (16 mg, 0.026 mmol, 4.1 mol %), *N*-phenylmethacrylamide (**181b**) (164 mg, 1.02 mmol) and pent-1-yn-1-ylbenzene (**88f**) (91.1 mg, 0.63 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1) yielded a mixture of **182bf** and **182bf'** (48 mg, 25%) as a slightly brown oil (ratio by ^{1}H-NMR 4.7:1.0).



(182bf) **(182bf')**

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.57-7.30 (m, 2H), 7.32-7.22 (m, 3H), 7.23-7.04 (m, 9H), 7.04-6.91 (m, 6H), 2.23 (d, *J* = 1.0 Hz, 5H), 2.16 (d, *J* = 1.0 Hz, 1H), 2.13-2.02 (m, 4H), 1.51-1.35 (m, 4H), 1.27-1.10 (m, 1H), 0.79 (t, *J* = 7.3 Hz, 4H), 0.43 (t, *J* = 7.3 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.6 (C_q), 162.7 (C_q), 144.4 (C_q), 143.2 (C_q), 139.9 (CH), 139.6 (C_q), 139.3 (CH), 139.1 (C_q), 134.2 (C_q), 130.1 (CH), 129.4 (CH), 129.2 (CH), 129.0 (CH), 128.9 (C_q), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 127.0 (CH), 126.6 (C_q), 119.5 (C_q), 117.6 (C_q), 33.2 (CH_2), 32.6 (CH_2), 24.0 (CH_2), 22.6 (CH_2), 17.3 (CH_2), 16.9 (CH_2), 13.9 (CH_3).

NMR spectra for the mixture of regioisomers have been presented here (NMR-ratio is determined via comparison with comparable substituted pure products.)

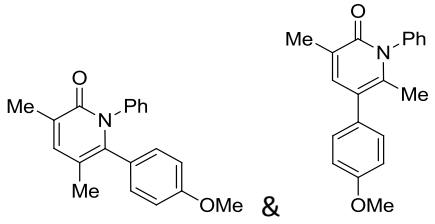
IR (ATR): $\tilde{\nu}$ = 2961, 2928, 2871, 1710, 1652, 1609, 1546, 1361, 1220, 756, 695, 528 cm^{-1}.

MS (EI) *m/z* (relative intensity): 303 (66) [M^+], 274 (100), 246 (19), 180 (17), 128 (12), 77 (45).

HR-MS (ESI) *m/z* calculated for $C_{21}H_{21}NO+H^+$: 304.1701; found: 304.1696.

Synthesis of the Mixture of 6-(4-Methoxyphenyl)-3,5-dimethyl-1-phenylpyridin-2(1*H*)-one (182bh) and 5-(4-Methoxyphenyl)-3,6-dimethyl-1-phenylpyridin-2(1*H*)-one (182bh')

The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %), *N*-phenylmethacrylamide (**181b**) (162 mg, 1.00 mmol) and 1-methoxy-4-(prop-1-yn-1-yl)-benzene (**88h**) (72.7 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1) yielded a mixture of **182bh** and **182bh'** (64 mg, 42%), which could not be separated any further and has been isolated as slightly yellow oil (ratio by ^{1}H-NMR = 1.0:5.5).



(182bh) **(182bh')**

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.57-7.39 (m, 2H), 7.28-7.15 (m, 8H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.00-6.91 (m, 3H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 8.7 Hz, 3H), 3.84 (s, 1H), 3.71 (s, 5H), 2.21 (s, 5H), 2.17 (s, 1H), 1.87 (s, 1H), 1.86 (s, 5H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.9 (C_q), 161.7 (C_q), 158.8 (C_q), 158.6 (C_q), 143.0 (C_q), 140.4 (CH), 139.9 (CH), 139.9 (C_q), 139.9 (C_q), 139.8 (C_q), 131.5 (C_q), 131.2 (CH), 130.6 (CH), 129.6 (CH), 129.0 (CH), 128.7 (C_q), 128.5 (CH), 128.4 (CH), 128.0 (CH), 127.4 (CH), 127.0 (C_q), 126.7 (C_q), 119.0 (C_q), 113.8 (CH), 113.2 (CH), 113.1 (C_q), 55.3 (CH_3), 55.0 (CH_3), 19.2 (CH_3), 17.8 (CH_3), 17.1 (CH_3), 16.8 (CH_3).

NMR spectra for the mixture of regioisomers have been presented here (NMR-ratio is determined via comparison with comparable substituted pure products.)

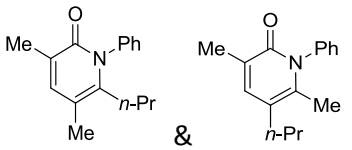
IR (ATR): $\tilde{\nu}$ = 2946, 2917, 2836, 1649, 1606, 1504, 1242, 1030, 841, 694 cm^{-1}.

MS (EI) *m/z* (relative intensity): 305 (100) [M+H$^+$], 290 (23), 277 (32), 262 (38), 77 (30).

HR-MS (EI) *m/z* calculated for $C_{20}H_{19}NO_2$-H$^+$: 304.1338; found: 304.1337.

Synthesis of the mixture of 3,5-Dimethyl-1-phenyl-6-propylpyridin-2(1*H*)-one (182bi) and 3,6-Dimethyl-1-phenyl-5-propylpyridin-2(1*H*)-one (182bi')

The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 3.7 mol %), *N*-phenylmethacrylamide (**181b**) (159 mg, 0.99 mmol) and hex-2-yne (**88i**) (56.1 mg, 0.68 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1) yielded a mixture of **182bi** and **182bi'** (68 mg, 42%) as slightly yellow oil (ratio by ^{1}H-NMR = 1.0:2.3).



(182bi) **(182bi')**

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.46 (dtd, *J* = 15.0, 7.4, 1.7 Hz, 6H), 7.22-7.07 (m, 6H), 2.44-2.31 (m, 2H), 2.25-2.15 (m, 2H), 2.15-2.05 (m, 9H), 1.87 (s, 3H), 1.62-1.45 (m, 2H), 1.41-1.23 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.69 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.7 (C_q), 163.5 (C_q), 143.6 (C_q), 141.0 (CH), 140.1 (CH), 140.1 (C_q), 139.5 (C_q), 139.1 (C_q), 130.8 (CH), 129.5 (CH), 129.2 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.0 (C_q), 126.6 (C_q), 116.8 (C_q), 111.6 (C_q), 33.8 (CH_2), 32.3 (CH_2), 23.7 (CH_2), 21.6 (CH_2), 17.3 (CH_3), 17.1 (CH_3), 16.8 (CH_3), 16.8 (CH_3), 14.0 (CH_3), 13.8 (CH_3).

NMR spectra for the mixture of regioisomers have been presented here (NMR-ratio is determined via comparison with comparable substituted pure products.)

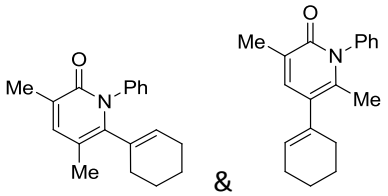
IR (ATR): $\tilde{\nu}$ = 2960, 2929, 2870, 1647, 1602, 1547, 1487, 1293, 1072, 758, 695 cm^{-1}.

MS (EI) *m/z* (relative intensity): 241 (44), 212 (100), 184 (27), 118 (16), 77 (38), 43 (23).

HR-MS (EI) *m/z* calculated for $C_{16}H_{19}NO^+$: 241.1467; found: 241.1464.

Synthesis of the Mixture of 6-(Cyclohex-1-en-1-yl)-3,5-dimethyl-1-phenylpyridin-2(1*H*)-one (182bl) and 5-(Cyclohex-1-en-1-yl)-3,6-dimethyl-1-phenylpyridin-2(1*H*)-one (182bl')

The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (17 mg, 0.026 mmol, 3.7 mol %), *N*-phenylmethacrylamide (**181b**) (161 mg, 1.00 mmol) and 1-(prop-1-yn-1-yl)-cyclohex-1-ene (**88l**) (84.1 mg, 0.70 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1 to 100% EtOAc) yielded a mixture of **182bl** and **182bl'** (73 mg, 40%) which could not be further purified and was isolated as slightly yellow solid (ratio by ^{1}H-NMR = 1.0:7.4).



(182bl) **(182bl')**

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.40-7.30 (m, 3H), 7.22-7.13 (m, 2H), 7.10-7.00 (m, 1H), 5.56-5.51 (m, 1H), 2.14 (s, 3H), 2.00 (s, 3H), 1.87-1.67 (m, 1H), 1.66-1.51 (m, 1H), 1.49-1.32 (m, 2H), 1.28-1.12 (m, 2H), 1.11-0.97 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.0 (C_q), 145.4 (C_q), 140.7 (CH), 139.6 (C_q), 132.5 (CH), 132.3 (C_q), 130.1 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 127.7 (CH), 121.6 (C_q), 111.1 (C_q), 28.7 (CH_2), 24.9 (CH_2), 22.1 (CH_2), 21.4 (CH_2), 17.2 (CH_3), 17.0 (CH_3).

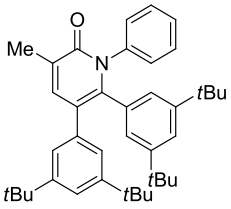
NMR spectra for the mixture of regioisomers have been presented here (NMR-ratio is determined via comparison with comparable substituted pure products.)

IR (ATR): $\tilde{\nu}$ = 2935, 2916, 2850, 2648, 1610, 1546, 1287, 908, 764, 692, 462 cm^{-1}.

MS (EI) *m/z* (relative intensity): 279 (100) [M^+], 250 (53), 208 (17), 77 (45), 43 (29).

HR-MS (EI) *m/z* calculated for $C_{19}H_{21}NO\text{-}H^+$: 278.1545; found: 278.1549.

Synthesis of 5,6-Bis(3,5-di-*tert*-butylphenyl)-3-methyl-1-phenylpyridin-2(1*H*)-one (182bm)



The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (16 mg, 0.026 mmol, 5.1 mol %), *N*-phenylmethacrylamide (**181b**) (164 mg, 1.02 mmol) and 1,2-bis(3,5-di-*tert*-butyl-phenyl)ethyne (**88m**) (201 mg, 0.50 mmol). Purification by column chroma-tography (*n*-hexane/EtOAc: 5/1 → 2/1) yielded **182bm** (173 mg, 62%) as an ivory solid.

M.p.: 215 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 1.1 Hz, 1H), 7.21-7.05 (m, 4H), 7.05-6.99 (m, 2H), 6.90 (dd, *J* = 1.8, 1.8 Hz, 1H), 6.81 (d, *J* = 1.8 Hz, 2H), 6.56 (d, *J* = 1.8 Hz, 2H), 2.28 (d, *J* = 1.0 Hz, 3H), 1.11 (s, 18H), 0.94 (s, 18H).

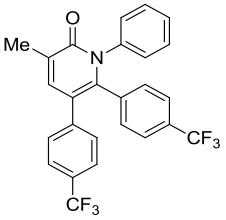
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.1 (C_q), 150.2 (C_q), 149.7 (C_q), 145.1 (C_q), 139.9 (CH), 139.7 (C_q), 138.2 (C_q), 133.4 (C_q), 129.1 (CH), 128.4 (CH), 128.4 (C_q), 127.2 (CH), 125.9 (CH), 124.1 (CH), 120.7 (C_q), 120.5 (CH), 119.8 (CH), 34.6 (C_q), 34.4 (C_q), 31.4 (CH_3), 31.1 (CH_3), 17.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2962, 1655, 1594, 1538, 1362, 875, 719, 699 cm^{-1}.

MS (EI) *m/z* (relative intensity): 546 (80) [M-Me$^+$], 504 (92), 474 (85), 276 (75), 57 (100).

HR-MS (EI) *m/z* calculated for $C_{40}H_{51}NO+Na^+$: 584.3868; found: 584.3863.

Synthesis of 3-Methyl-1-phenyl-5,6-bis{4-(trifluoromethyl)phenyl}pyridin-2(1*H*)-one (182bn)



The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 4.8 mol %), *N*-phenylmethacrylamide (**181b**) (164 mg, 1.02 mmol) and 1,2-bis(4-trifluoromethylphenyl)ethyne (**88n**) (162 mg, 0.52 mmol). Purification by column chroma-tography (*n*-hexane/EtOAc 1:1) yielded **188bn** (175 mg, 71%) as an off-white solid.

M.p.: 158 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.41 (d, J = 1.1 Hz, 2H), 7.38 (s, 1H), 7.28-7.12 (m, 5H), 7.09 (d, J = 8.7 Hz, 2H), 7.04-6.94 (m, 4H), 2.27 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.7 (C_q), 142.5 (C_q), 141.8 (C_q), 139.1 (CH), 138.7 (C_q), 137.4 (C_q), 131.3 (CH), 130.5 (C_q), 130.1 (d, $J_{C\text{-}F}$ = 31 Hz, CH), 130.0 (CH), 129.8 (CH), 129.0 (d, $J_{C\text{-}F}$ = 31 Hz, CH), 129.0 (CH), 128.8 (CH), 125.1 (d, $J_{C\text{–}F}$ = 10 Hz, CH), 124.8 (q, $J_{C\text{-}F}$ = 57 Hz, C_q), 124.7 (d, $J_{C\text{-}F}$ = 11 Hz, CH), 122.6 (d, $J_{C\text{-}F}$ = 58 Hz, C_q), 118.6 (C_q), 17.2 (CH_3).

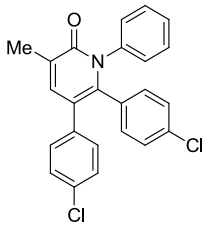
^{19}F-NMR (283 MHz, $CDCl_3$): δ = -62.6 (s), -63.0 (s).

IR (ATR): $\tilde{\nu}$ = 2922, 1652, 1545, 1321, 1082, 1061, 846 cm^{-1}.

MS (EI) *m/z* (relative intensity): 473 (100) [M^+], 445 (20), 77 (60), 43 (55).

HR-MS (EI) *m/z* calculated for $C_{26}H_{17}F_6NO^+$: 473.1214; found: 473.1217.

Synthesis of 5,6-Bis-(4-chlorophenyl)-3-methyl-1-phenylpyridin-2(1*H*)-one (182bo)



The general procedure **G** was followed using [$RuCl_2$(*p*-cymene)]$_2$ (15 mg, 0.025 mmol, 5.0 mol %), *N*-phenylmethacrylamide (**181b**) (164 mg, 1.02 mmol) and 1,2-bis(4-chlorophenyl)ethyne (**88o**) (124 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1) yielded **182bo** (121 mg, 59%) as a white solid.

M.p.: 193 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.37 (d, J = 1.1 Hz, 1H), 7.27-7.07 (m, 5H), 7.03-6.85 (m, 6H), 6.75 (d, J = 9.1 Hz, 2H), 2.24 (d, J = 1.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.8 (C_q), 142.5 (C_q), 139.4 (CH), 138.9 (C_q), 136.7 (C_q), 133.9 (C_q), 132.6 (C_q), 132.4 (C_q), 132.2 (CH), 130.8 (CH), 129.8 (C_q), 129.0 (CH), 128.8 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 118.7 (C_q), 17.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3077, 2915, 1645, 1487, 1124, 694 cm^{-1}.

MS (EI) *m/z* (relative intensity): 405 (62) [M^+], 377 (20), 214 (16), 127 (16), 77 (100), 51 (28).

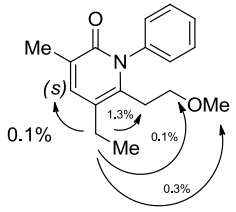
HR-MS (EI) *m/z* calculated for $C_{24}H_{17}Cl_2NO^+$: 405.0687; found: 405.0690.

The spectral data were in accordance with those reported in the literature.

Synthesis of 5-Ethyl-6-(2-methoxyethyl)-3-methyl-1-phenylpyridin-2(1*H*)-one (182bu') and 6-Ethyl-5-(2-methoxyethyl)-3-methyl-1-phenylpyridin-2(1*H*)-one (182bu)

The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (16 mg, 0.026 mmol, 4.3 mol %), *N*-phenylmethacrylamide (**181b**) (159 mg, 0.99 mmol) and 1-methoxyhex-3-yne (**88u**) (67.0 mg, 0.60 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1) yielded **182bu** (42 mg, 26%) as yellow oil and **182bu'** (43 mg, 27%) as white solid.

nOe:



(182bu)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.55-7.34 (m, 3H), 7.24-7.09 (m, 3H), 3.58-3.47 (m, 2H), 3.37 (s, 3H), 2.67 (t, *J* = 7.1 Hz, 2H), 2.33 (q, *J* = 7.5 Hz, 2H), 2.11 (s, 3H), 0.90 (t, *J* = 7.5 Hz, 3H).

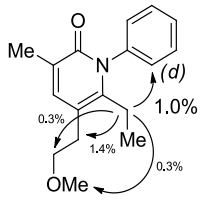
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.7 (C_q), 145.9 (C_q), 140.1 (CH), 139.6 (C_q), 129.5 (CH), 128.6 (CH), 128.5 (CH), 127.2 (C_q), 112.7 (C_q), 73.0 (CH_2), 59.0 (CH_3), 31.3 (CH_2), 23.2 (CH_2), 17.0 (CH_3), 13.8 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2965, 2922, 2876, 2808, 1649, 1605, 1550, 1382, 1195, 1115, 964, 924, 758, 699 cm^{-1}.

MS (EI) *m/z* (relative intensity): 271 (69) [M^+], 256 (100), 240 (16), 226 (73), 198 (36), 77 (50).

HR-MS (EI) *m/z* calculated for $C_{17}H_{21}NO_2^+$: 271.1572; found: 271.1577.

nOe:



(182bu')

M.r.: 107 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.56-7.35 (m, 3H), 7.22-7.12 (m, 3H), 3.25 (t, *J* = 7.4 Hz, 2H), 3.11 (s, 3H), 2.61 (t, *J* = 7.9 Hz, 2H), 2.46 (q, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 1.18 (t, *J* = 7.5 Hz, 3H).

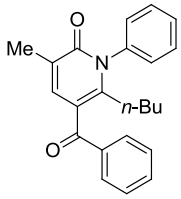
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.7 (C_q), 139.6 (C_q), 139.5 (CH), 138.8 (C_q), 129.6 (CH), 128.7 (CH), 128.7 (CH), 128.2 (C_q), 119.6 (C_q), 70.8 (CH_2), 58.5 (CH_3), 30.1 (CH_2), 24.3 (CH_2), 17.1 (CH_3), 15.5 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3450, 2977, 2927, 2876, 1710, 1651, 1609, 1544, 1363, 1111, 759, 699 cm^{-1}.

MS (EI) *m/z* (relative intensity): 271 (40) [M^+], 226 (100), 211 (14), 132 (19), 77 (27), 45 (37).

HR-MS (EI) *m/z* calculated for $C_{17}H_{21}NO_2^+$: 271.1572; found: 271.1573.

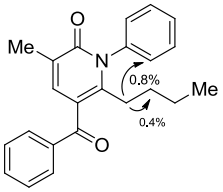
Synthesis of 5-Benzoyl-6-butyl-3-methyl-1-phenylpyridin-2(1*H*)-one (182bw)



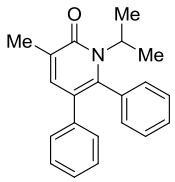
The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 4.9 mol %), *N*-phenylmethacrylamide (**181b**) (163 mg, 1.01 mmol) and 1-phenylhept-2-yn-1-one (**88w**) (95 mg, 0.51 mmol). Purification by column chromatography (*n*-hexane/EtOAc 2:1) yielded **182bw** (27 mg, 15%) as slightly brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.82-7.73 (m, 2H), 7.65-7.41 (m, 5H), 7.32-7.19 (m, 4H), 2.59-2.39 (m, 2H), 2.09 (s, 3H), 1.45-1.27 (m, 2H), 0.98 (h, *J* = 7.3 Hz, 2H), 0.56 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 195.4 (C_q), 163.9 (C_q), 152.9 (C_q), 138.5 (C_q), 138.4 (C_q), 137.9 (CH), 133.0 (CH), 129.9 (CH), 129.7 (CH), 129.1 (CH), 128.7 (CH), 128.5 (CH), 125.7 (C_q), 116.5 (C_q), 31.9 (CH_2), 30.5 (CH_2), 22.6 (CH_2), 17.0 (CH_3), 13.3 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3496, 2959, 2929, 2874, 1708, 1638, 1360, 1220, 910, 759, 697, 529 cm^{-1}.
MS (EI) *m/z* (relative intensity): 345 (47) [M^+], 302 (64), 274 (23), 105 (100), 77 (77), 51 (17), 43 (62).
HR-MS (EI) *m/z* calculated for $C_{23}H_{23}NO_2^+$: 345.1729; found: 345.1725.

nOe:



Synthesis of 1-Isopropyl-3-methyl-5,6-diphenylpyridin-2(1*H*)-one (182ca)



The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %), *N*-isopropylmethacrylamide (**181c**) (124 mg, 0.98 mmol) and 1,2-diphenylethyne (**88a**) (89.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 1:1 to EtOAc) yielded **182ca** (105 mg, 69%) as a yellow solid.

M.p.: 171 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.32-7.22 (m, 4H), 7.15-7.01 (m, 5H), 6.96-6.86 (m, 2H), 4.22-4.06 (m, 1H), 2.20 (d, *J* = 0.6 Hz, 3H), 1.54 (d, *J* = 6.8 Hz, 6H).

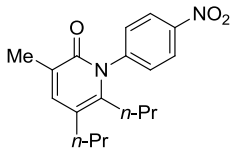
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.3 (C_q), 144.2 (C_q), 139.2 (C_q), 138.5 (CH), 135.2 (C_q), 129.8 (CH), 129.5 (CH), 129.4 (C_q), 128.4 (CH), 128.2 (CH), 127.6 (CH), 126.0 (CH), 120.1 (C_q), 53.9 (CH_3), 19.3 (CH), 17.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2968, 1640, 1608, 1490, 1372, 763, 704 cm^{-1}.

MS (EI) *m/z* (relative intensity): 302 (31) [M-H$^+$], 261 (100), 215 (20), 43 (17).

HR-MS (EI) *m/z* calculated for $C_{21}H_{21}NO$-H$^+$: 302.1545; found: 302.1553.

Synthesis of 3-Methyl-1-(4-nitrophenyl)-5,6-dipropylpyridin-2(1*H*)-one (182dq)



The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (10 mg, 0.016 mmol, 4.9 mol %), *N*-(4-nitrophenyl)-methacrylamide (**181d**) (135 mg, 0.65 mmol) and oct-4-yne (**88q**) (35.0 mg, 0.32 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1) yielded **182dq** (92 mg, 91%) as a yellow solid.

M.p.: 105 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 9.0 Hz, 2H), 7.38 (d, *J* = 9.0 Hz, 2H), 7.15 (d, *J* = 1.1 Hz, 1H), 2.41-2.26 (m, 2H), 2.23-2.14 (m, 2H), 2.10 (d, *J* = 1.0 Hz, 3H), 1.64-1.48 (m, 2H), 1.36-1.20 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.68 (t, *J* = 7.3 Hz, 3H).

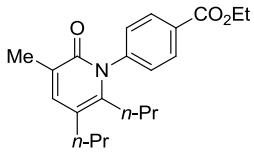
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.2 (C_q), 147.5 (C_q), 145.5 (C_q), 142.2 (C_q), 140.6 (CH), 130.1 (CH), 127.3 (C_q), 124.7 (CH), 117.4 (C_q), 32.9 (CH_2), 31.7 (CH_2), 24.1 (CH_2), 22.6 (CH_2), 16.8 (CH_3), 14.0 (CH_3), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3057, 2921, 1646, 1597, 1490, 1416, 765, 699 cm^{-1}.

MS (EI) *m/z* (relative intensity): 314 (48) [M$^+$], 285 (100), 239 (16), 210 (20), 43 (18).

HR-MS (EI) *m/z* calculated for $C_{18}H_{22}N_2O_3^+$: 314.1630; found: 314.1641.

Synthesis of Ethyl 4-[3-Methyl-2-oxo-5,6-di-*n*-propylpyridin–1(2*H*)-yl]benzoate (182eq)



The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %), ethyl 4-methacrylamidobenzoate (**181e**) (239 mg, 1.02 mmol) and oct-4-yne (**88q**) (55.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 1:1) yielded **182eq** (133 mg, 78%) as a yellow solid.

M.p.: 88 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 1.1 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.38-2.26 (m, 2H), 2.23-2.12 (m, 2H), 2.09 (d, *J* = 1.0 Hz, 3H), 1.63-1.44 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.34-1.17 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.66 (t, *J* = 7.2 Hz, 3H).

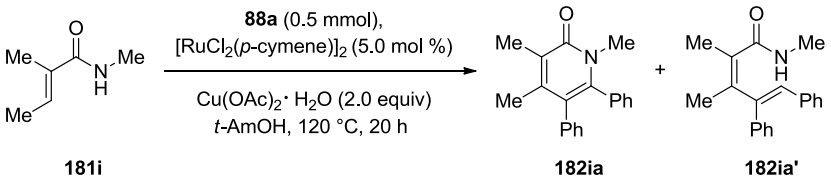
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.8 (C_q), 163.3 (C_q), 143.8 (C_q), 142.8 (C_q), 140.2 (CH), 130.6 (CH), 130.5 (C_q), 128.8 (CH), 127.0 (C_q), 116.9 (C_q), 61.2 (CH_2), 32.9 (CH_2), 31.7 (CH_2), 24.1 (CH_2), 22.7 (CH_2), 16.8 (CH_3), 14.3 (CH_3), 14.0 (CH_3), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2959, 2870, 1713, 1649, 1543, 1269, 1100, 768 cm^{-1}.

MS (EI): *m/z* (relative intensity) 341 (40) [M^+], 312 (100), 285 (28), 210 (15).

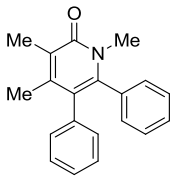
HR-MS (EI) *m/z* calculated for $C_{21}H_{27}NO_3^+$: 341.1991, found 341.1993.

Synthesis of 1,3,4-Trimethyl-5,6-diphenylpyridin-2(1*H*)-one (182ia) and (2*Z*,4*E*)-*N*,2,3-Trimethyl-4,5-diphenyl-penta-2,4-dienamide (182ia')



The general procedure **G** was followed using *(E)-N,*2-dimethylbut-2-enamide (**181i**) (125 mg, 1.11 mmol), 1,2-diphenylethyne (**88a**) (89.0 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (16 mg, 0.026 mmol, 5.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (200 mg, 1.00 mmol, 2.0 equiv) in *t*-AmOH (2.0 mL). Purification by

column chromatography (*n*-hexane/EtOAc 4:1) yielded **182ia** (82 mg, 57%) as a bright brown solid and **182ia'** (23 mg, 16%) as a colorless oil.



1,3,4-Trimethyl-5,6-diphenylpyridin-2(1*H*)-one (182ia)

M.p.: 167 °C.

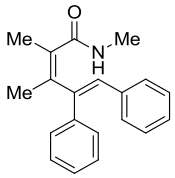
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.21-7.01 (m, 6H), 7.01-6.94 (m, 2H), 6.93-6.84 (m, 2H), 3.25 (s, 3H), 2.22 (s, 3H), 1.88 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.6 (C_q), 145.0 (C_q), 143.3 (C_q), 138.0 (C_q), 134.9 (C_q), 130.9 (CH), 129.5 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 126.5 (CH), 124.7 (C_q), 122.1 (C_q), 34.7 (CH_3), 18.2 (CH_3), 13.4 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3305, 3052, 2943, 1634, 1582, 1441, 763, 703 cm^{-1}.

MS (EI) *m/z* (relative intensity): 288 [M-H$^+$] (100), 260 (18), 115 (12), 77 (24), 43 (44).

HR-MS (EI) *m/z* calculated for $C_{20}H_{19}NO$-H$^+$: 288.1388; found: 288.1398.



(2*Z*,4*E*)-*N*,2,3-Trimethyl-4,5-diphenyl-penta-2,4-dienamide (182ia')

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.28-7.20 (m, 3H), 7.17-7.05 (m, 5H), 7.01-6.93 (m, 2H), 6.61 (s, 1H), 5.64 (br s, 1H), 2.66 (d, *J* = 4.9 Hz, 3H), 1.98 (d, *J* = 1.0 Hz, 3H), 1.71 (d, *J* = 1.0 Hz, 3H) .

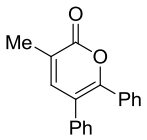
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 172.7 (C_q), 143.0 (C_q), 139.0 (C_q), 138.2 (C_q), 137.0 (C_q), 132.0 (C_q), 130.0 (CH), 129.4 (CH), 128.7 (CH), 128.1 (CH), 128.0 (CH), 127.6 (CH), 126.9 (CH), 26.4 (CH_3), 18.4 (CH_3), 16.8 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3307, 2960, 1655, 1448, 1247, 756, 698 cm^{-1}.

MS (EI): *m/z* (relative intensity) 291 [M$^+$] (100), 233 (84), 214 (96), 202 (44), 91 (33), 77 (50).

HR-MS (EI) *m/z* calculated for $C_{20}H_{21}NO^+$: 291.1623; found: 291.1620.

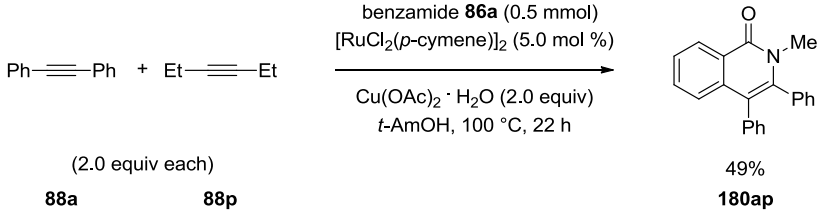
Synthesis of 3-Methyl-5,6-diphenyl-2*H*-pyran-2-one (184a)



The general procedure **G** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %), methacrylic acid (**183a**) (148 mg, 1.72 mmol, 3.44 equiv) and 1,2-diphenylethyne (**88a**) (89.5 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 3:1) yielded **184a** (63 mg, 48%) as slightly yellow oil.

^{1}H-NMR (300 MHz, CDCl3): δ = 7.34 (t, *J* = 1.6 Hz, 1H), 7.32-7.27 (m, 4H), 7.25 (ddd, *J* = 5.0, 2.1, 1.0 Hz, 2H), 7.24-7.19 (m, 2H), 7.18-7.14 (m, 2H), 2.18 (d, *J* = 1.3 Hz, 3H).
^{13}C-NMR (75 MHz, CDCl3): δ = 163.1 (C_q), 155.4 (C_q), 144.0 (CH), 136.6 (C_q), 132.2 (C_q), 129.5 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.1 (CH), 127.7 (CH), 123.7 (C_q), 128.0 (C_q), 16.5 (CH_3).
IR (ATR): $\tilde{\nu}$ = 1708, 1550, 1488, 1443, 1173, 1050, 949, 764, 693, 574 cm^{-1}.
MS (EI) *m/z* (relative intensity): 262 (100) [M^+], 234 (87), 191 (46), 129 (37), 105 (82), 77 (98), 51 (30).
HR-MS (EI) *m/z* calculated for $C_{18}H_{14}O_2^+$: 262.0994; found: 262.1000.
The The analytical data were in accordance with those reported in the literature.[213]

Intermolecular Competition Experiment between Alkynes 88a and 88p



A mixture of *N*-methylbenzamide (**86a**) (69.9 mg, 0.52 mmol), **88a** (180 mg, 1.01 mmol), **88p** (77.0 mg, 0.94 mmol), $[RuCl_2(p\text{-cymene})]_2$ (16.0 mg, 0.026 mmol, 5.0 mol %) and $Cu(OAc)\cdot H_2O$ (202 mg, 1.01 mmol) in *t*-AmOH (4.0 mL) was stirred at 100 °C for 22 h. At ambient temperature, the reaction mixture was diluted with aq. NH_4Cl (75 mL) and extracted with EtOAc (3 x 75 mL). After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) to yield **180ap** (79 mg, 49%) as a colorless solid.

[213] Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 6295–6298.

(180ap)

M.r.: 246 - 247 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.57 (d, J = 4.8 Hz, 1H), 7.52 (m, 2H), 7.28-7.05 (m, 11H), 3.36 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.7 (C_q), 141.2 (C_q), 137.2 (C_q), 136.5 (C_q), 135.1 (C_q), 132.0 (CH), 131.5 (CH), 129.9 (CH), 128.2 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 126.8 (CH), 126.6 (CH), 125.3 (CH), 124.9 (C_q), 118.8 (C_q), 34.3 (CH_3).

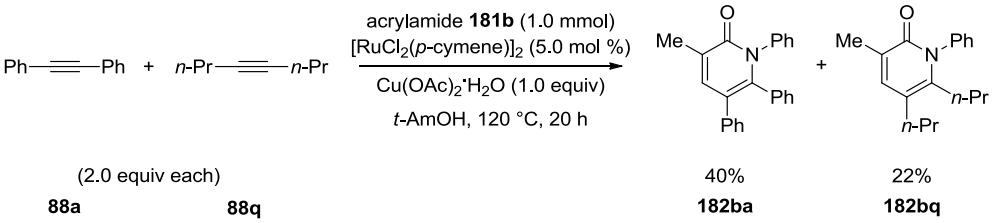
IR (ATR): $\tilde{\nu}$ = 1646, 1604, 1552, 1489, 1414, 1176, 1074, 1025, 924, 781 cm^{-1}.

MS (EI) *m/z* (relative intensity): 311 (100) [M^+], 165 (7), 77 (8).

HR-MS (EI) *m/z* calculated for $C_{22}H_{17}NO^+$: 311.1310; found: 311.1311.

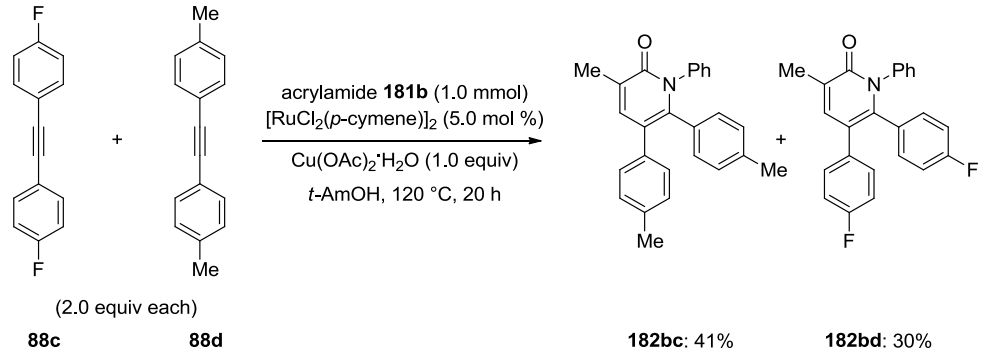
The The analytical data are in accordance with those reported in the literature.[212]

Intermolecular Competition Experiment between Alkynes 88a and 88q



A mixture of *N*-phenylmethacrylamide (**181b**) (81 mg, 0.50 mmol), **88a** (179 mg, 1.00 mmol), **88q** (114 mg, 1.01 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (100 mg, 0.50 mmol) in *t*-AmOH (4.0 mL) was stirred at 120 °C for 20 h. At ambient temperature, the reaction mixture was diluted with aq. NH_4Cl (75 mL) and extracted with EtOAc (3 x 75 mL). After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc 3:1 to EtOAc) to yield **182ba** (67 mg, 40%) and **182bg** (29 mg, 22%) as white solids.

Intermolecular Competition Experiment between Alkynes 88c and 88d



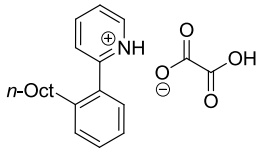
A mixture of *N*-phenylmethacrylamide (**181b**) (85.0 mg, 0.53 mmol), **88c** (214 mg, 1.00 mmol), **88d** (208 mg, 1.01 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol%) and $Cu(OAc)_2 \cdot H_2O$ (100 mg, 0.50 mmol) in *t*-AmOH (4.0 mL) was stirred at 120 °C for 20 h. At ambient temperature, the reaction mixture was diluted with aq. NH_4Cl (75 mL) and extracted with EtOAc (3 x 75 mL). After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc 1:1) to yield **182bd** (59 mg, 30%) and **182bc** (79 mg, 41%) as white solids.

7.5 Crystallographic Details

Preparation of 2-Arylpyridinium Oxalates (129) and (149).

To a stirred solution of (2-*n*-octylphenyl)pyridine (**93aa**) or 2-[3-(octan-2-yl)phenyl]pyridine (**147aa**) (1 equiv), in a mixture of DCM and one drop of MeOH, a solution of anhydrous oxalic acid (1 equiv) in DCM was added in one portion at ambient temperature. After an additional stirring for 10 min, the reaction mixture was concentrated under reduced pressure. The residue was dissolved with DCM/*n*-octane mixture and filtered. Slow evaporation of this solution at ambient temperature afforded crystals suitable for X-ray diffractometry.

2-(2-*n*-Octylphenyl)pyridinium Oxalate (129)



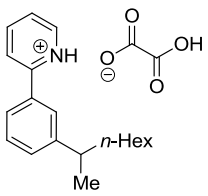
M.r.: 82 - 84 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.10 (s, 1H), 9.00 (s, 1H), 8.29 (t, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.56-7.42 (m, 1H), 7.36 (dd, *J* = 9.9, 7.4 Hz, 3H), 2.71-2.50 (m, 2H), 1.57-1.35 (m, 2H), 1.21 (d, *J* = 27.7 Hz, 12H), 0.85 (t, *J* = 6.1 Hz, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 162.3 (C_q), 158.1 (C_q), 146.3 (CH), 141.2 (C_q), 140.1 (CH), 130.2 (C_q), 130.1 (CH), 130.1 (CH), 130.1 (CH), 126.3 (CH), 126.2 (CH), 123.2 (CH), 33.0 (CH_2), 31.9 (CH_2), 31.2 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3).

HR-MS (ESI) *m/z* calculated for $C_{21}H_{27}NO_4$-$C_2O_4H^+$: 268.2065; found: 268.2060.

2-[3-(Octan-2-yl)phenyl]pyridinium Oxalate (149)



M.r.: 84 - 85 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.89 (s, 1H), 8.14 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.85-7.71 (m, 2H), 7.63-7.51 (m, 1H), 7.48 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 2.79 (qt, *J* = 7.1, 7.0 Hz, 1H), 1.73-1.50 (m, 2H), 1.42-1.11 (m, 8H), 1.26 (d, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 5.9 Hz, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 162.7 (C_q), 156.2 (C_q), 150.0 (C_q), 145.9 (CH), 142.0 (CH), 130.5 (CH), 129.9 (CH), 127.0 (CH), 125.8 (CH), 123.6 (CH), 123.7 (CH), 40.4 (CH), 38.7 (CH_2), 32.1 (CH_2), 28.0 (CH_2), 23.0 (CH_2), 22.6 (CH_2), 22.5 (CH_3), 14.4 (CH_3).

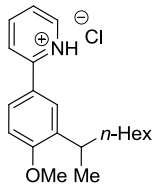
MS (EI) *m/z* (relative intensity): 267 (22) [M-Oxalat$^+$], 196 (20), 182 (100), 167 (52), 43 (13).

HR-MS (EI) *m/z* calculated for $C_{21}H_{27}NO_4$-$C_2H_2O_4^+$: 267.1987; found: 267.1996.

Preparation of 2-Arylpyridinium Chlorides (149) and ((*R*)-167).

To a stirred solution of 2-[4-methoxy-3-(octan-2-yl)-phenyl]pyridine (**147ba**) or enantiomerically pure (*R*)-2-[3-(hexan-2-yl)-4-methoxyphenyl]pyridine [(*R*)-**147bj**], in a mixture of DCM and one drop of MeOH, a concentrated aqueous solution of HCl (1 equiv) was added in one portion at ambient temperature. After an additional stirring for 10 min, the reaction mixture was concentrated under reduced pressure. The residue was dissolved with DCM/*n*-octane mixture and filtered. Slow evaporation of this solution at ambient temperature afforded crystals suitable for X-ray diffractometry.

2-[4-Methoxy-3-(octan-2-yl)-phenyl]pyridinium Chloride (148)



M.r.: 93 - 95 °C.

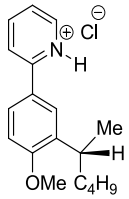
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.89 (d, *J* = 5.8 Hz, 1H), 8.37-8.20 (m, 2H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 2.6 Hz, 1H), 7.66 (ddd, *J* = 7.2, 5.9, 1.1 Hz, 1H), 7.10 (d, *J* = 8.7 Hz, 1H), 3.92 (s, 3H), 3.24 (qt, *J* = 7.1, 7.0 Hz, 1H), 1.81-1.43 (m, 4H), 1.42-1.07 (m, 6H), 1.27 (d, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 6.6 Hz, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 161.2 (C_q), 153.1 (C_q), 144.7 (CH), 141.8 (CH), 138.4 (C_q), 128.1 (CH), 127.0 (CH), 123.6 (CH), 122.7 (CH), 121.7 (C_q), 111.8 (CH), 55.9 (CH_3), 37.2 (CH_2), 32.3 (CH), 32.1 (CH_2), 29.6 (CH_2), 27.8 (CH_2), 22.9 (CH_2), 21.0 (CH_3), 14.3 (CH_3).

MS (EI) *m/z* (relative intensity): 297 (41) [M-HCl$^+$], 212 (100), 197 (17), 167 (30).

HR-MS (EI) *m/z* calculated for $C_{20}H_{28}ClNO$-HCl^+: 297.2093; found: 297.2088.

(*R*)-2-[3-(Hexan-2-yl)-4-methoxyphenyl]pyridinium chloride ((*R*)-167)



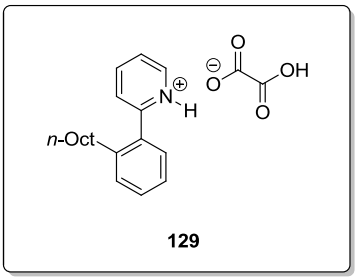
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.87 (d, *J* = 5.7 Hz, 1H), 8.37-8.20 (m, 2H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 2.6 Hz, 1H), 7.66 (ddd, *J* = 7.2, 5.9, 1.1 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 3.92 (s, 3H), 3.24 (qt, *J* = 7.1, 7.0 Hz, 1H), 1.79-1.43 (m, 2H), 1.42-1.07 (m, 4H), 1.27 (d, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 6.7 Hz, 3H).
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 161.2 (C_q), 153.1 (C_q), 144.7 (CH), 141.8 (CH), 138.4 (C_q), 128.1 (CH), 127.0 (CH), 123.6 (CH), 122.7 (CH), 121.7 (C_q), 111.8 (CH), 55.9 (CH_3), 37.2 (CH_2), 32.3 (CH), 29.6 (CH_2), 22.9 (CH_2), 21.0 (CH_3), 14.3 (CH_3).
MS (EI) *m/z* (relative intensity): 269 (41) [M-HCl^+], 184 (100), 197 (22).
HR-MS (EI) *m/z* calculated for $C_{18}H_{24}ClNO$-HCl^+: 269.1780; found: 269.1783.

Table S-1. Crystal and data collection parameters for compounds **129**, **148**, **149** and (*R*)-**167**

Compound	**129**	**148**	**149**	**(*R*)-167**
Empirical formula	$C_{19}H_{26}N^+$ x $C_2HO_4^-$ x $C_2H_2O_4$	$C_{20}H_{28}NO^+$ x Cl^- x H_2O	$[C_{19}H_{26}N]^+$ x $[C_2O_4H]^-$ x 0.5 $[C_2O_4H_2]$	$C_{18}H_{24}ClNO$ x 0.5 H_2O
Molecular mass [g/mol]	447.47	351.90	402.45	314.84
Temperature [K]	120	120	120	100.0
Crystal system	monoclinic	triclinic	triclinic	monoclinic
Space group	*C*2/c	*P*-1	*P*-1	*C*2
a [Å]	32.502(5)	4.9785(3)	5.6937(7)	34.0337(19)
b [Å]	14.839(2)	8.7894(5)	10.2647(12)	5.5726(3)
c [Å]	9.7776(14)	22.6643(14)	19.007(2)	18.2007(11)
***α* [°]**	90.00	87.606(2)	95.608(4)	90.00
***β* [°]**	106.084(4)	86.998(2)	97.574(4)	90.524(2)

Compound	**129**	**148**	**149**	**(*R*)-167**
γ [°]	90.00	77.422(2)	97.614(4)	90.00
Volume [Å^3]	4531.2(11)	966.15(10)	1083.9(2)	3451.7(3)
Z	8	2	2	8
D_{calc} [mg/mm^3]	1.312	1.210	1.233	1.212
μ [mm^{-1}]	0.099	0.209	0.090	1.971
F(000)	1904.0	380.0	430.0	1352.0
Crystal size/mm^3	0.48 × 0.12 × 0.04	0.42 × 0.12 × 0.09	0.44 × 0.06 × 0.001	0.38 × 0.02 × 0.01
2Θ range for data collection	3.04 to 55°	3.6 to 58°	4.04 to 52°	4.86 to 120°
Index ranges	-42 ≤ h ≤ 42, -19 ≤ k ≤ 19, -12 ≤ l ≤ 12	-6 ≤ h ≤ 6, -11 ≤ k ≤ 11, -30 ≤ l ≤ 30	-7 ≤ h ≤ 7, -11 ≤ k ≤ 12, -23 ≤ l ≤ 23	-35 ≤ h ≤ 38, -6 ≤ k ≤ 5, -19 ≤ l ≤ 19
Reflections collected	22812	15955	8319	8125
Independent reflections	5206 [*R*(int) = 0.2062]	5106 [*R*(int) = 0.0320]	4213 [*R*(int) = 0.0566]	4131 [*R*(int) = 0.0503]
Data/ restraints/ parameters	5206/0/406	5106/0/337	4213/0/306	4131/1/588
GoF	0.972	1.013	0.983	1.022
Final *R* indexes [I>2σ (I)]	R_1 = 0.0727, wR_2 = 0.1144	R_1 = 0.0421, wR_2 = 0.1057	R_1 = 0.0756, wR_2 = 0.1886	R_1 = 0.0523, wR_2 = 0.1241
Final R indexes [all data]	R_1 = 0.1694, wR_2 = 0.1314	R_1 = 0.0576, wR_2 = 0.1164	R_1 = 0.1452, wR_2 = 0.2204	R_1 = 0.0681, wR_2 = 0.1323

More detailed illustrations of the different molecular structures of compounds **129**, **148**, **149** and (*R*)-**167** in the crystals including fragments of molecular packings and H-bondings are presented below.



129

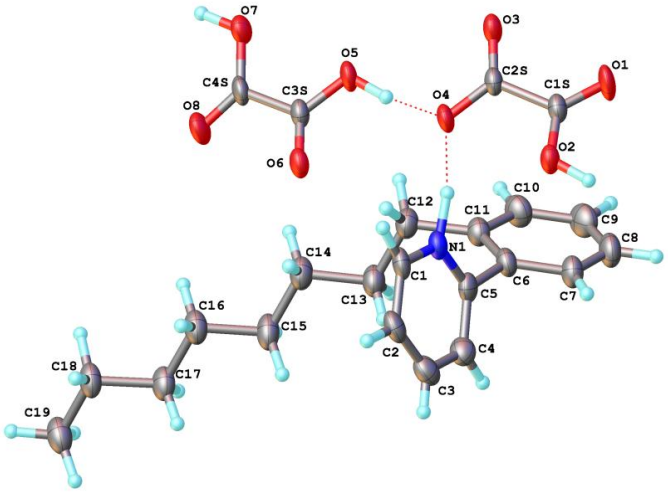


Figure 7.1: Molecular structure of **129** in the crystals. Thermal ellipsoids are shown at 50% probability.

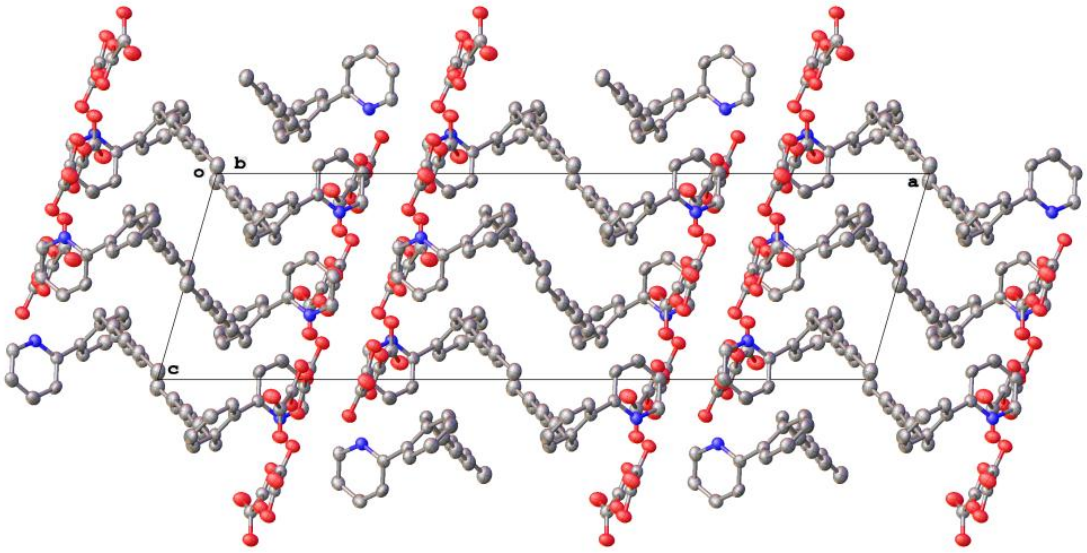


Figure 7.2: Fragment of the molecular packing in extended unit cell of **129**; space group *C*2/c.

Table S-2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 129. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij} tensor.

Atom	*x*	*y*	*z*	U(eq)
N1	6874.6(9)	2772.9(14)	1881(3)	30.5(6)
C1	7147.0(12)	2258.1(17)	1393(4)	35.3(8)
C2	7046.8(12)	2026.8(19)	-13(4)	37.8(8)
C3	6670.9(12)	2331(2)	-895(4)	41.0(9)
C4	6397.3(12)	2842(2)	-383(4)	37.8(8)
C5	6498.4(10)	3056.0(17)	1032(3)	32.0(8)
C6	6221.6(10)	3614.4(18)	1689(3)	33.2(8)
C7	6150.6(11)	4510(2)	1238(4)	39.4(9)
C8	5890.2(12)	5045(2)	1797(4)	45.3(10)
C9	5697.6(12)	4713(2)	2761(4)	48.7(10)
C10	5765.4(12)	3825(2)	3205(4)	44.3(9)
C11	6026.7(10)	3259.3(18)	2683(3)	34.2(8)
C12	6076.8(12)	2277.6(19)	3148(4)	37.0(8)
C13	5760.3(13)	1652.0(19)	2159(4)	40.7(9)
C14	5837.8(13)	662(2)	2591(4)	41.8(9)
C15	5526.5(13)	33(2)	1570(5)	45(1)
C16	5623.8(12)	-958(2)	1916(4)	42.6(9)
C17	5294.4(13)	-1568(2)	967(4)	42.1(9)
C18	5377.0(12)	-2576(2)	1292(4)	41.9(9)
C19	5027.9(14)	-3167(2)	373(5)	50.6(10)
O5	6964.9(7)	1876.7(12)	6205(2)	35.9(6)
O6	6965.8(7)	1005.5(12)	4349(2)	35.1(5)
O7	6951.5(7)	463.2(13)	7779(2)	38.3(6)
O8	6671.7(8)	-355.3(12)	5817(2)	46.9(7)
C3S	6933.7(10)	1112.4(17)	5548(3)	31.3(7)
C4S	6839.2(11)	313.8(17)	6421(4)	32.8(8)
O1	7055.5(8)	5499.0(11)	4891(2)	45.9(6)
O2	7164.9(7)	4557.2(12)	3227(2)	34.8(6)
O3	7096.7(7)	4010.1(11)	6622(2)	37.8(6)
O4	7060.6(7)	3162.4(11)	4720(2)	33.8(5)
C1S	7098.5(10)	4758.4(17)	4458(3)	31.2(7)
C2S	7089.4(10)	3918.0(17)	5374(3)	29.5(7)

Table S-3 Anisotropic Displacement Parameters (Å^2×10^3) for 129. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka\times b\times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	37.8(17)	16.7(11)	38.7(16)	1.2(11)	13.1(14)	1.9(12)
C1	40(2)	14.5(13)	53(2)	0.3(15)	15.8(19)	2.3(15)
C2	47(2)	19.1(15)	51(2)	-7.9(15)	19(2)	-5.2(15)
C3	50(2)	29.5(17)	45(2)	-8.4(17)	16(2)	-8.8(17)
C4	33(2)	31.8(17)	43(2)	-0.2(15)	2.6(18)	-0.8(16)
C5	39(2)	17.6(13)	41(2)	5.2(13)	13.5(17)	-2.0(13)
C6	37(2)	19.9(14)	41.9(19)	-3.5(13)	10.5(16)	-0.4(13)
C7	43(2)	23.9(16)	52(2)	2.4(15)	15.1(19)	4.0(15)
C8	55(3)	23.9(16)	57(2)	0.5(16)	15(2)	7.0(16)
C9	46(2)	40.5(19)	59(3)	-5.0(18)	13(2)	15.6(17)
C10	50(2)	35.3(18)	51(2)	-6.0(17)	20(2)	4.0(17)
C11	36(2)	24.1(15)	42(2)	-0.6(14)	10.8(16)	2.5(14)
C12	39(2)	25.6(15)	46(2)	5.2(15)	10.0(18)	0.8(15)
C13	44(2)	24.0(16)	52(2)	3.9(15)	9(2)	3.0(15)
C14	44(2)	26.4(16)	53(2)	5.4(15)	10(2)	0.4(16)
C15	44(2)	25.1(16)	66(3)	5.3(16)	13(2)	3.0(16)
C16	39(2)	26.2(16)	59(3)	-0.9(17)	9(2)	3.1(16)
C17	42(2)	26.0(17)	58(3)	3.1(16)	14(2)	6.5(15)
C18	41(2)	23.0(16)	61(3)	1.7(16)	13(2)	3.6(15)
C19	50(3)	28.2(18)	72(3)	-2.2(19)	15(2)	3.2(18)
O5	54.3(15)	12.5(9)	43.7(13)	-0.7(9)	18.4(12)	2.2(9)
O6	49.1(15)	16.9(10)	41.8(13)	-0.6(9)	17.1(12)	3.5(9)
O7	57.6(16)	19.1(10)	38.9(15)	-1.4(10)	14.6(12)	-6.3(10)
O8	74.4(18)	17.9(10)	49.6(15)	-3.5(10)	19.2(13)	-9.9(11)

C3S	40(2)	15.3(13)	40(2)	0.9(13)	12.9(17)	1.8(13)
C4S	41(2)	13.2(13)	43(2)	-1.7(14)	10.1(16)	2.6(13)
O1	76.5(18)	11.9(10)	56.5(15)	-0.4(10)	30.2(14)	5.2(11)
O2	51.0(15)	17.4(10)	38.9(14)	2.8(10)	17.2(12)	2.8(10)
O3	59.7(16)	16.2(10)	40.6(14)	1.7(10)	19.0(12)	0.6(10)
O4	50.4(14)	12.8(9)	38.8(13)	-3.0(9)	13.3(11)	0.4(9)
C1S	35.2(19)	18.1(14)	41(2)	0.8(13)	12.0(16)	1.0(13)
C2S	35.5(18)	15.6(14)	39(2)	1.1(13)	12.7(16)	2.1(13)

Table S-4 Bond Lengths for 129.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
N1	**C1**	1.352(4)	**C14**	**C15**	1.527(5)
N1	**C5**	1.341(4)	**C15**	**C16**	1.522(4)
C1	**C2**	1.366(5)	**C16**	**C17**	1.508(5)
C2	**C3**	1.363(5)	**C17**	**C18**	1.538(4)
C3	**C4**	1.365(5)	**C18**	**C19**	1.516(5)
C4	**C5**	1.368(5)	**O5**	**C3S**	1.293(3)
C5	**C6**	1.493(4)	**O6**	**C3S**	1.216(3)
C6	**C7**	1.398(4)	**O7**	**C4S**	1.295(4)
C6	**C11**	1.402(4)	**O8**	**C4S**	1.205(3)
C7	**C8**	1.379(5)	**C3S**	**C4S**	1.540(4)
C8	**C9**	1.359(5)	**O1**	**C1S**	1.200(3)
C9	**C10**	1.386(4)	**O2**	**C1S**	1.314(4)
C10	**C11**	1.388(4)	**O3**	**C2S**	1.222(3)
C11	**C12**	1.521(4)	**O4**	**C2S**	1.281(3)
C12	**C13**	1.518(5)	**C1S**	**C2S**	1.540(4)
C13	**C14**	1.531(4)			

Table S-5 Bond Angles for 129.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C5	**N1**	**C1**	122.2(3)	**C12**	**C13**	**C14**	112.4(3)
N1	**C1**	**C2**	120.0(3)	**C15**	**C14**	**C13**	112.2(3)
C3	**C2**	**C1**	118.4(3)	**C16**	**C15**	**C14**	112.7(3)
C2	**C3**	**C4**	120.8(4)	**C17**	**C16**	**C15**	112.0(3)
C3	**C4**	**C5**	120.1(3)	**C16**	**C17**	**C18**	113.8(3)
N1	**C5**	**C4**	118.4(3)	**C19**	**C18**	**C17**	112.4(3)
N1	**C5**	**C6**	117.6(3)	**O5**	**C3S**	**C4S**	113.6(3)
C4	**C5**	**C6**	124.0(3)	**O6**	**C3S**	**O5**	125.3(3)
C7	**C6**	**C5**	117.3(3)	**O6**	**C3S**	**C4S**	121.2(2)
C7	**C6**	**C11**	120.6(3)	**O7**	**C4S**	**C3S**	113.2(2)
C11	**C6**	**C5**	122.1(2)	**O8**	**C4S**	**O7**	127.1(3)
C8	**C7**	**C6**	119.2(3)	**O8**	**C4S**	**C3S**	119.7(3)
C9	**C8**	**C7**	121.2(3)	**O1**	**C1S**	**O2**	126.6(3)
C8	**C9**	**C10**	119.8(3)	**O1**	**C1S**	**C2S**	120.9(3)
C9	**C10**	**C11**	121.3(4)	**O2**	**C1S**	**C2S**	112.5(2)
C6	**C11**	**C12**	122.4(3)	**O3**	**C2S**	**O4**	125.1(3)
C10	**C11**	**C6**	117.9(3)	**O3**	**C2S**	**C1S**	119.5(2)
C10	**C11**	**C12**	119.6(3)	**O4**	**C2S**	**C1S**	115.4(3)
C13	**C12**	**C11**	113.4(3)				

Table S-6 Hydrogen Bonds for 129.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	**H1**	**O4**	1.08(4)	1.70(4)	2.735(3)	158(3)
O7	**H7A**	**O6**[1]	0.99(4)	1.70(4)	2.659(3)	162(4)
O2	**H2A**	**O3**[2]	0.92(3)	1.70(3)	2.615(3)	170(3)
O5	**H5**	**O4**	0.99(5)	1.48(5)	2.469(3)	174(5)

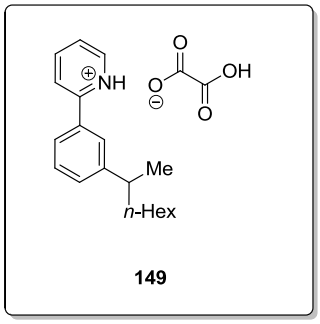
[1]+X,-Y,1/2+Z; [2]+X,1-Y,-1/2+Z

Table S-7 Torsion Angles for 129.

A	B	C	D	Angle/°
N1	C5	C6	C11	-67.9(4)

Table S-8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 129.

Atom	*x*	*y*	*z*	U(eq)
H1A	7422(9)	2106(16)	2110(30)	21(7)
H1	7016(12)	2990(20)	2960(40)	71(12)
H3	6602(13)	2190(20)	-1820(40)	66(13)
H2	7250(10)	1651(19)	-400(30)	44(9)
H4	6135(9)	3010(15)	-1010(30)	14(7)
H7	6318(10)	4693(18)	560(30)	37(9)
H8	5878(10)	5650(20)	1450(30)	40(9)
H9	5477(12)	5080(20)	3210(40)	71(11)
H10	5610(12)	3600(20)	3900(40)	61(11)
H12A	6053(10)	2244(19)	4250(40)	48(9)
H12B	6391(10)	2057(17)	3320(30)	31(8)
H13A	5449(12)	1850(20)	2000(40)	60(11)
H13B	5789(13)	1700(20)	1190(40)	72(13)
H14A	5812(10)	572(17)	3650(30)	34(8)
H14B	6120(11)	550(20)	2590(30)	45(10)
H15A	5257(12)	110(20)	1730(40)	48(10)
H15B	5565(11)	160(20)	450(40)	59(10)
H16A	5626(10)	-1053(19)	2990(40)	49(10)
H16B	5906(10)	-1125(18)	1810(30)	34(8)
H17A	4992(11)	-1435(18)	960(30)	37(9)
H17B	5313(11)	-1460(20)	-70(40)	49(10)
H18A	5391(11)	-2650(20)	2450(40)	54(10)
H18B	5655(10)	-2743(17)	1160(30)	27(8)
H19A	4995(10)	-3050(19)	-790(40)	40(9)
H19B	4775(12)	-3000(20)	600(30)	46(10)
H19C	5075(11)	-3810(20)	600(30)	53(10)
H7A	6900(13)	-50(30)	8360(40)	78(13)
H2A	7147(11)	5020(20)	2590(40)	58(11)
H5	7008(17)	2370(30)	5570(60)	140(20)



149

Beside an oxalate every cell includes another molecule of oxalic acid. These molecules are bound to each other through H-bonding on connect between two layers. Theses layers include the hydrophobic aliphatic chains. This compound could possibly be used as phase transfer catalyst, which should be further examined. The resolution of the structure is not perfect since the crystals have not been of higher quality.

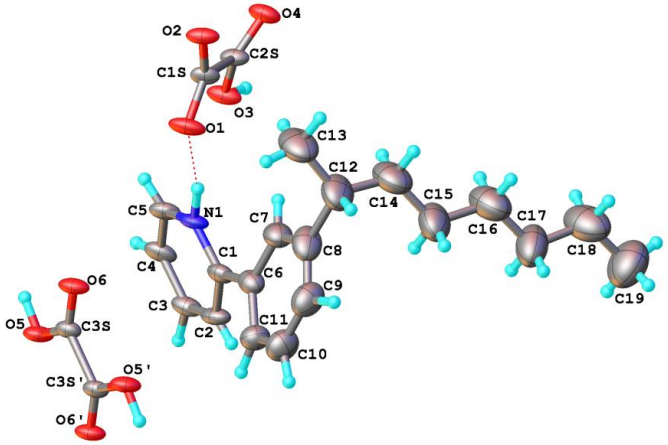


Figure 7.3 Molecular structure of **149** in the crystal. Thermal ellipsoids are shown at 50% probability.

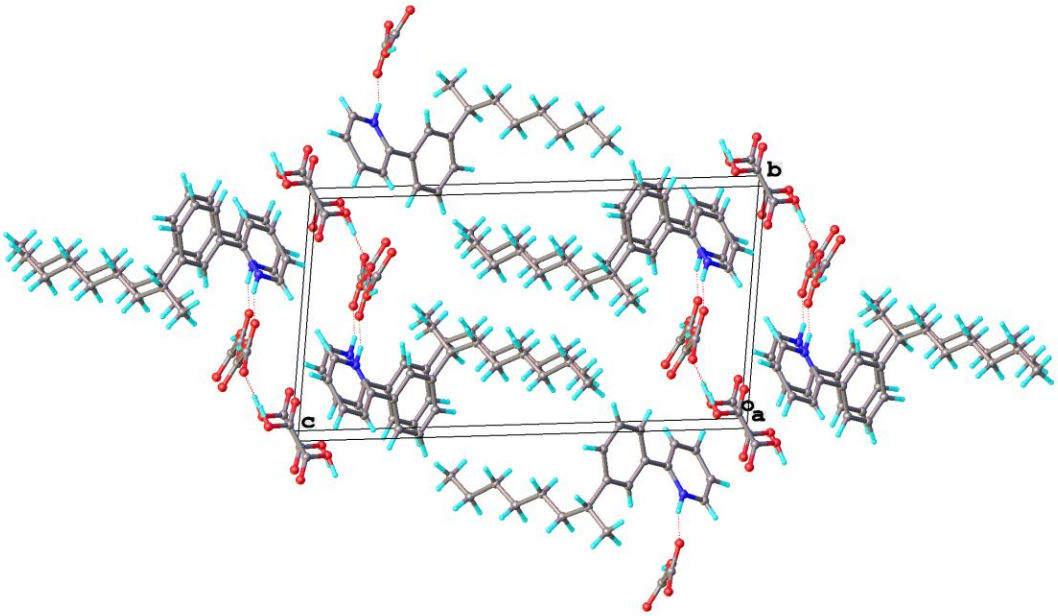


Figure 7.4: Fragment of the molecular packing in extended unit cell of **149**; space group *P*-1.

Table S-9 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 149. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
N1	-790(5)	6899(3)	1146.3(17)	30.7(7)
C1	-413(6)	8087(3)	1547(2)	32.1(9)
C2	-2090(7)	8923(4)	1407(3)	36.9(10)
C3	-4043(6)	8556(4)	898(2)	35.2(9)
C4	-4365(7)	7327(4)	501(2)	37.6(10)
C5	-2678(6)	6526(4)	638(2)	34.4(9)
C6	1747(7)	8437(4)	2092(2)	38.5(10)
C7	2780(8)	7468(5)	2440(2)	46.9(11)
C8	4828(9)	7806(6)	2956(2)	60.8(14)
C9	5873(10)	9124(6)	3104(3)	62.9(14)
C10	4847(9)	10067(5)	2765(3)	56.9(12)
C11	2792(8)	9749(4)	2274(2)	44.1(10)

C12	5858(11)	6745(6)	3349(3)	75.3(17)
C13	6750(12)	5750(6)	2898(3)	88(2)
C14	4411(12)	6331(6)	3886(3)	84.8(19)
C15	3494(12)	7261(6)	4368(3)	85.5(19)
C16	2102(12)	6758(6)	4914(4)	94(2)
C17	1041(13)	7634(7)	5379(3)	95(2)
C18	-386(13)	7049(7)	5913(4)	105(2)
C19	-592(14)	7878(8)	6356(4)	119(3)
O1	2183(4)	4992(2)	1189.3(15)	40.3(7)
O2	3384(4)	3061(2)	1373.9(14)	31.8(6)
O3	-2299(4)	3987(2)	1261.3(15)	35.4(7)
O4	-1018(4)	2271(2)	1761.8(14)	35.9(7)
C1S	1823(6)	3834(3)	1325(2)	27.9(8)
C2S	-693(6)	3259(3)	1471(2)	28.2(8)
O5	-2164(4)	9278(2)	-715.6(14)	32.7(6)
O6	824(4)	8427(2)	-111.2(14)	32.5(6)
C3S	-311(6)	9311(3)	-219.8(19)	26.1(8)

Table S-10 Anisotropic Displacement Parameters ($Å^2×10^3$) for 149. The Anisotropic displacement factor exponent takes the form: $-2π^2[h^2a^{*2}U_{11}+...+2hka×b×U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	30.0(17)	14.9(15)	50.8(19)	11.0(14)	9.8(15)	6.7(12)
C1	31.7(19)	23.0(19)	46(2)	12.4(17)	14.7(17)	4.2(15)
C2	38(2)	19(2)	59(3)	9(2)	21(2)	8.3(17)
C3	25.6(19)	26(2)	60(3)	17.3(19)	13.0(19)	8.1(15)
C4	27(2)	24(2)	63(3)	17.4(19)	8(2)	-0.4(16)
C5	28(2)	17(2)	58(3)	8.5(19)	7.9(19)	0.7(15)
C6	40(2)	37(2)	45(2)	10.9(18)	14.2(19)	14.2(17)
C7	56(3)	40(3)	51(3)	10(2)	11(2)	19(2)
C8	63(3)	80(4)	49(3)	16(3)	7(2)	40(3)
C9	61(3)	70(4)	54(3)	-5(3)	-3(3)	19(3)
C10	54(3)	56(3)	55(3)	-4(3)	-1(2)	5(2)
C11	46(2)	36(2)	49(3)	1(2)	4(2)	4.8(19)
C12	93(4)	85(4)	59(3)	25(3)	8(3)	44(3)
C13	104(5)	78(4)	105(4)	40(4)	37(4)	53(4)
C14	100(5)	67(4)	104(5)	39(4)	32(4)	35(3)
C15	114(5)	95(5)	63(3)	29(3)	23(3)	48(4)
C16	103(5)	75(4)	121(5)	40(4)	43(4)	31(4)
C17	123(5)	116(6)	63(4)	18(4)	27(4)	62(5)
C18	107(5)	85(5)	145(6)	39(5)	48(5)	39(4)
C19	131(7)	135(7)	99(5)	-5(5)	31(5)	46(6)
O1	24.2(13)	17.7(13)	81(2)	15.9(13)	10.6(13)	1.4(10)
O2	17.1(12)	15.7(12)	62.6(17)	4.8(11)	4.8(11)	2.9(9)
O3	16.4(12)	21.4(13)	71.9(19)	15.7(12)	10.7(12)	3.8(9)
O4	28.1(13)	21.4(13)	62.0(17)	16.7(12)	11.8(12)	3.2(10)
C1S	16.4(16)	17.2(17)	48(2)	3.5(15)	2.1(15)	-3.0(13)
C2S	19.1(17)	17.3(17)	49(2)	4.9(16)	6.6(15)	4.2(13)
O5	31.1(14)	15.5(13)	51.8(17)	6.7(12)	2.4(12)	5.7(10)
O6	27.8(13)	15.8(12)	56.0(16)	9.1(11)	8.1(11)	5.9(10)
C3S	21.7(17)	17.3(17)	41(2)	7.6(15)	8.7(16)	1.8(13)

Table S-11 Bond Lengths for 149.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
N1	**C1**	1.348(5)	**C12**	**C14**	1.454(8)
N1	**C5**	1.334(5)	**C14**	**C15**	1.453(8)
C1	**C2**	1.384(5)	**C15**	**C16**	1.478(8)
C1	**C6**	1.480(6)	**C16**	**C17**	1.445(8)
C2	**C3**	1.359(6)	**C17**	**C18**	1.503(8)
C3	**C4**	1.383(6)	**C18**	**C19**	1.439(9)

Table S-11 Bond Lengths for 149.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C4	**C5**	1.361(5)	**O1**	**C1S**	1.238(4)
C6	**C7**	1.398(5)	**O2**	**C1S**	1.267(4)
C6	**C11**	1.389(6)	**O3**	**C2S**	1.302(4)
C7	**C8**	1.402(7)	**O4**	**C2S**	1.206(4)
C8	**C9**	1.390(7)	**C1S**	**C2S**	1.546(4)
C8	**C12**	1.516(6)	**O5**	**C3S**	1.313(4)
C9	**C10**	1.366(7)	**O6**	**C3S**	1.200(4)
C10	**C11**	1.378(6)	**C3S**	**C3S**[1]	1.543(7)
C12	**C13**	1.455(7)			

[1]-X,2-Y,-Z

Table S-12 Bond Angles for 149.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C5	**N1**	**C1**	122.7(3)	**C13**	**C12**	**C8**	114.8(4)
N1	**C1**	**C2**	116.8(4)	**C14**	**C12**	**C8**	111.2(4)
N1	**C1**	**C6**	119.4(3)	**C14**	**C12**	**C13**	119.3(5)
C2	**C1**	**C6**	123.8(4)	**C15**	**C14**	**C12**	122.9(5)
C3	**C2**	**C1**	121.6(4)	**C14**	**C15**	**C16**	119.4(5)
C2	**C3**	**C4**	119.7(4)	**C17**	**C16**	**C15**	121.5(5)
C5	**C4**	**C3**	117.9(4)	**C16**	**C17**	**C18**	118.5(6)
N1	**C5**	**C4**	121.4(4)	**C19**	**C18**	**C17**	120.1(6)
C7	**C6**	**C1**	121.3(4)	**O1**	**C1S**	**O2**	125.3(3)
C11	**C6**	**C1**	120.4(3)	**O1**	**C1S**	**C2S**	119.0(3)
C11	**C6**	**C7**	118.3(4)	**O2**	**C1S**	**C2S**	115.7(3)
C6	**C7**	**C8**	121.0(5)	**O3**	**C2S**	**C1S**	111.7(3)
C7	**C8**	**C12**	120.1(5)	**O4**	**C2S**	**O3**	126.6(3)
C9	**C8**	**C7**	119.0(4)	**O4**	**C2S**	**C1S**	121.7(3)
C9	**C8**	**C12**	120.9(5)	**O5**	**C3S**	**C3S**[1]	110.7(3)
C10	**C9**	**C8**	119.7(5)	**O6**	**C3S**	**O5**	126.7(3)
C9	**C10**	**C11**	121.7(5)	**O6**	**C3S**	**C3S**[1]	122.5(4)
C10	**C11**	**C6**	120.3(4)				

[1]-X,2-Y,-Z

Table S-13 Hydrogen Bonds for 149.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	**H1**	**O1**	1.03(4)	1.75(4)	2.753(4)	165(3)
O3	**H3A**	**O2**[1]	0.82	1.79	2.560(3)	156.6
O5	**H5A**	**O2**[2]	0.88(5)	1.71(6)	2.560(3)	161(5)

[1]-1+X,+Y,+Z; [2]-X,1-Y,-Z

Table S-14 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 149.

Atom	*x*	*y*	*z*	U(eq)
H12	7324	7231	3636	90
H13A	5426	5204	2597	132
H13B	7612	5211	3193	132
H13C	7799	6178	2607	132
H14A	3035	5728	3634	102
H14B	5345	5812	4183	102
H15A	2493	7759	4077	103
H15B	4850	7884	4616	103
H16A	814	6092	4665	112
H16B	3145	6303	5218	112
H17A	3	8101	5080	114
H17B	2320	8290	5641	114
H18A	-1588	6349	5653	126
H18B	688	6632	6229	126

Table S-14 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 149.

Atom	*x*	*y*	*z*	U(eq)
H19A	-2457	8422	6066	179
H19B	-433	8430	6712	179
H19C	-2689	7333	6586	179
H1	420(70)	6260(40)	1250(20)	44(11)
H2	-1940(50)	9540(30)	1634(16)	6(9)
H3	-5200(60)	9240(40)	743(18)	33(9)
H4	-5560(70)	7030(40)	112(19)	30(10)
H5	-2650(60)	5820(40)	364(18)	21(9)
H7	1980(60)	6630(40)	2344(18)	26(10)
H9	7270(90)	9290(50)	3530(30)	66(14)
H10	5660(90)	10930(50)	2950(30)	67(15)
H11	2050(100)	10460(60)	2090(30)	85(17)
H3A	-3543	3750	1417	53
H5A	-2240(90)	8470(50)	-920(30)	75(17)

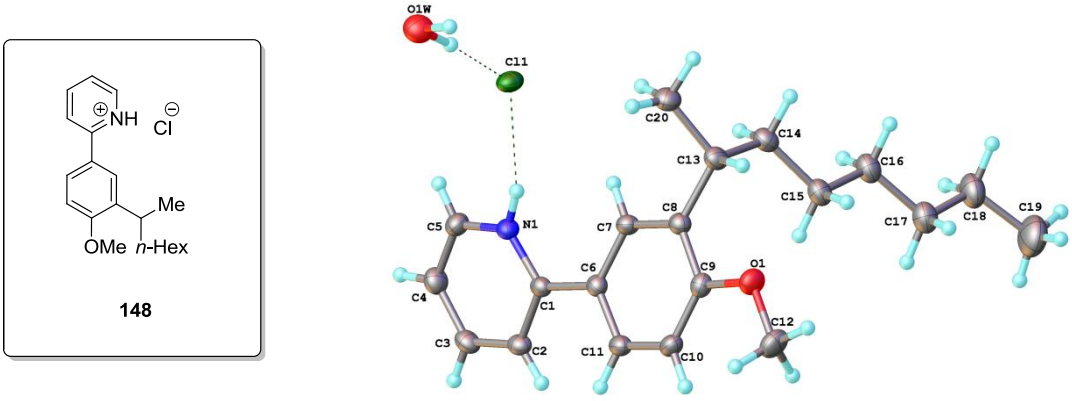


Figure 7.5: Molecular structure of **148** in the crystal. Thermal ellipsoids are shown at 50% probability.

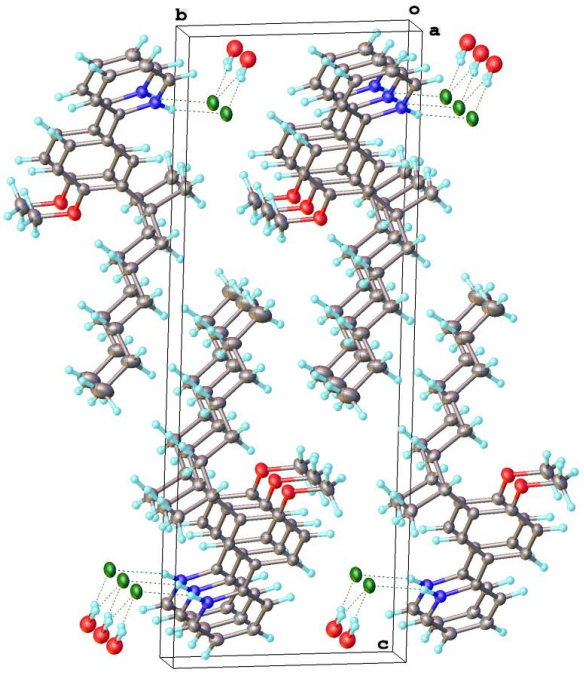


Figure 7.6: Fragment of the molecular packing in extended unit cell of **148**; space group *P*-1.

Table S-15 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 148. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	10730(2)	5862.1(12)	7061.5(5)	29.6(2)
N1	1109(2)	8659.9(14)	8949.3(5)	21.7(2)
C1	1967(3)	7185.7(15)	8765.0(6)	20.1(3)
C2	617(3)	6070.0(17)	9022.5(6)	23.4(3)
C3	-1521(3)	6493.0(18)	9436.9(7)	26.1(3)
C4	-2359(3)	8031.4(19)	9601.8(7)	28.1(3)
C5	-983(3)	9104.4(18)	9349.1(7)	25.9(3)
C6	4224(3)	6837.1(16)	8312.5(6)	20.9(3)
C7	5078(3)	8020.1(16)	7962.7(6)	21.9(3)
C8	7224(3)	7692.9(16)	7540.2(6)	22.5(3)
C9	8595(3)	6130.8(17)	7474.3(6)	23.2(3)
C10	7785(3)	4948.9(17)	7817.3(6)	25.0(3)
C11	5599(3)	5300.5(16)	8226.3(6)	24.1(3)
C12	12179(4)	4285(2)	6992.1(8)	34.5(4)
C13	7958(3)	8975.0(17)	7133.7(6)	25.1(3)
C14	5910(3)	9389.2(18)	6637.6(7)	28.1(3)
C15	5667(3)	8052.5(19)	6251.4(7)	29.5(3)
C16	3687(4)	8592(2)	5757.8(7)	32.6(3)
C17	3431(4)	7320(2)	5342.1(7)	36.0(4)
C18	1439(4)	7925(3)	4856.5(8)	42.5(4)
C19	1290(6)	6721(4)	4404.6(11)	62.4(6)
C20	8084(4)	10447.8(19)	7462.2(8)	30.3(3)
O1W	7014(3)	12950.0(14)	9496.5(6)	37.1(3)
Cl1	2673.2(7)	11819.5(4)	8719.00(16)	27.23(11)

Table S-16 Anisotropic Displacement Parameters (Å^2×10^3) for 148. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka\times b\times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	29.4(5)	27.3(5)	30.5(6)	-4.9(4)	5.6(4)	-3.2(4)
N1	24.5(6)	19.4(6)	22.6(6)	-0.7(4)	-0.8(4)	-8.1(4)
C1	23.2(6)	18.7(6)	19.2(6)	1.0(5)	-4.7(5)	-5.7(5)
C2	26.5(7)	21.1(7)	24.4(7)	1.4(5)	-4.3(5)	-8.9(5)
C3	27.4(7)	27.8(7)	25.7(7)	5.3(6)	-2.9(6)	-12.2(6)
C4	27.0(7)	32.9(8)	25.1(7)	-0.9(6)	2.0(6)	-9.2(6)
C5	29.2(7)	22.5(7)	26.4(7)	-4.5(5)	1.0(6)	-6.5(6)
C6	23.2(7)	21.3(6)	19.3(6)	-0.5(5)	-2.9(5)	-6.9(5)
C7	25.3(7)	17.6(6)	22.6(6)	0.5(5)	-2.3(5)	-4.2(5)
C8	24.5(7)	21.5(6)	22.2(6)	0.3(5)	-2.0(5)	-6.6(5)
C9	23.1(7)	25.2(7)	21.4(6)	-3.8(5)	-0.8(5)	-5.2(5)
C10	30.5(7)	19.0(6)	24.5(7)	-2.5(5)	-3.3(6)	-2.6(5)
C11	31.4(7)	19.3(6)	22.6(7)	0.6(5)	-3.8(6)	-7.1(5)
C12	33.2(8)	30.0(8)	38.9(9)	-11.8(7)	4.5(7)	-3.2(7)
C13	26.0(7)	24.7(7)	24.7(7)	0.9(5)	2.9(5)	-6.8(5)
C14	31.8(8)	27.1(7)	25.6(7)	3.9(6)	-0.5(6)	-7.8(6)
C15	32.0(8)	32.7(8)	23.8(7)	1.8(6)	-1.8(6)	-7.4(6)
C16	34.8(9)	38.6(9)	24.8(7)	2.0(6)	-2.0(6)	-9.3(7)
C17	38.5(9)	42.9(10)	26.8(8)	-1.3(7)	-1.6(7)	-9.3(7)
C18	50.1(11)	55.0(12)	26.0(8)	-0.7(8)	-6.3(8)	-18.2(9)
C19	76.7(18)	76.0(17)	39.5(12)	-13.3(11)	-11.4(12)	-23.4(14)
C20	34.7(8)	26.7(7)	31.2(8)	0.9(6)	0.6(7)	-11.0(6)
O1W	37.2(7)	35.8(6)	39.7(7)	0.4(5)	1.3(5)	-11.7(5)
Cl1	30.21(19)	19.62(17)	33.5(2)	-2.79(13)	2.47(14)	-9.59(13)

Table S-17 Bond Lengths for 148.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C9	1.3660(17)	C8	C9	1.4041(19)
O1	C12	1.4271(19)	C8	C13	1.5196(19)
N1	C1	1.3495(17)	C9	C10	1.389(2)
N1	C5	1.3461(19)	C10	C11	1.382(2)
C1	C2	1.3970(19)	C13	C14	1.536(2)
C1	C6	1.4712(19)	C13	C20	1.534(2)
C2	C3	1.381(2)	C14	C15	1.523(2)
C3	C4	1.386(2)	C15	C16	1.522(2)
C4	C5	1.372(2)	C16	C17	1.522(2)
C6	C7	1.4066(19)	C17	C18	1.521(3)
C6	C11	1.3916(19)	C18	C19	1.519(3)
C7	C8	1.387(2)			

Table S-18 Bond Angles for 148.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C9	O1	C12	117.33(12)	C9	C8	C13	120.78(13)
C5	N1	C1	123.86(12)	O1	C9	C8	116.30(12)
N1	C1	C2	116.86(13)	O1	C9	C10	123.05(13)
N1	C1	C6	119.34(12)	C10	C9	C8	120.65(13)
C2	C1	C6	123.80(13)	C11	C10	C9	120.12(13)
C3	C2	C1	120.43(14)	C10	C11	C6	120.90(13)
C2	C3	C4	120.37(14)	C8	C13	C14	110.38(12)
C5	C4	C3	118.24(14)	C8	C13	C20	113.00(12)
N1	C5	C4	120.22(14)	C20	C13	C14	109.97(13)
C7	C6	C1	121.92(12)	C15	C14	C13	116.03(13)
C11	C6	C1	119.87(12)	C16	C15	C14	112.07(13)
C11	C6	C7	118.20(13)	C15	C16	C17	114.63(15)
C8	C7	C6	121.93(13)	C18	C17	C16	112.38(16)
C7	C8	C9	118.16(13)	C19	C18	C17	114.0(2)
C7	C8	C13	120.95(12)				

Table S-19 Hydrogen Bonds for 148.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	H1	Cl1	0.87(2)	2.23(2)	3.0610(12)	159.5(17)
O1W	H1WA	Cl1[1]	1.02(3)	2.23(3)	3.2309(14)	168(2)
O1W	H1WB	Cl1	1.05(4)	2.15(4)	3.2004(14)	175(3)

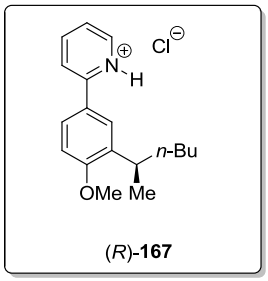
[1] 1+X,+Y,+Z

Table S-20 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 148.

Atom	*x*	*y*	*z*	U(eq)
H1	1880(40)	9420(20)	8822(9)	36(5)
H2	1150(40)	5050(20)	8903(8)	29(4)
H3	-2390(40)	5740(20)	9597(8)	28(4)
H4	-3840(40)	8400(20)	9880(9)	34(5)
H5	-1390(40)	10120(20)	9433(8)	30(5)
H7	4130(40)	9060(20)	8003(8)	27(4)
H10	8750(40)	3910(20)	7780(8)	33(5)
H11	5110(40)	4490(20)	8454(8)	29(4)
H12A	13670(50)	4390(30)	6696(10)	52(6)
H12B	10920(40)	3640(20)	6859(8)	32(5)
H12C	13000(40)	3840(20)	7372(9)	41(5)
H13	9810(40)	8550(20)	6950(8)	31(5)
H14A	6500(40)	10240(20)	6371(9)	35(5)
H14B	4030(40)	9860(20)	6826(8)	32(5)
H15A	7510(40)	7560(20)	6063(9)	37(5)
H15B	5080(40)	7180(20)	6494(8)	34(5)
H16A	4300(40)	9470(20)	5512(8)	36(5)
H16B	1780(40)	9050(20)	5938(8)	32(5)
H17A	2900(40)	6420(20)	5565(9)	41(5)

Table S-20 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 148.

Atom	*x*	*y*	*z*	U(eq)
H17B	5220(50)	6840(30)	5174(10)	50(6)
H18A	2000(50)	8860(30)	4622(11)	60(7)
H18B	-500(50)	8290(30)	5053(10)	57(7)
H19A	-70(70)	7190(40)	4112(15)	100(11)
H19B	720(50)	5810(30)	4583(11)	63(7)
H19C	3290(60)	6370(30)	4195(13)	86(9)
H20A	6310(40)	10970(20)	7646(8)	29(4)
H20B	9210(40)	10320(20)	7793(9)	34(5)
H20C	8720(40)	11210(30)	7183(10)	51(6)
H1WA	8820(60)	12750(30)	9254(12)	72(8)
H1WB	5630(70)	12620(40)	9218(15)	109(11)



(*R*)-**167**

On the basis of X-ray data, the absolute configuration of the compound (*R*)-**147bj** was determined. Hydrochloride (*R*)-**167** is arranged as a hemihydrate.

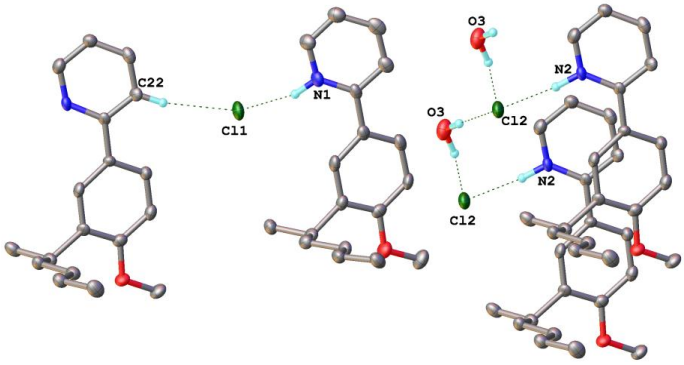


Figure 7.7: Molecular structure of (*R*)-**167** in the crystal including the interesting H-bonding. Thermal ellipsoids are shown at 50% probability.

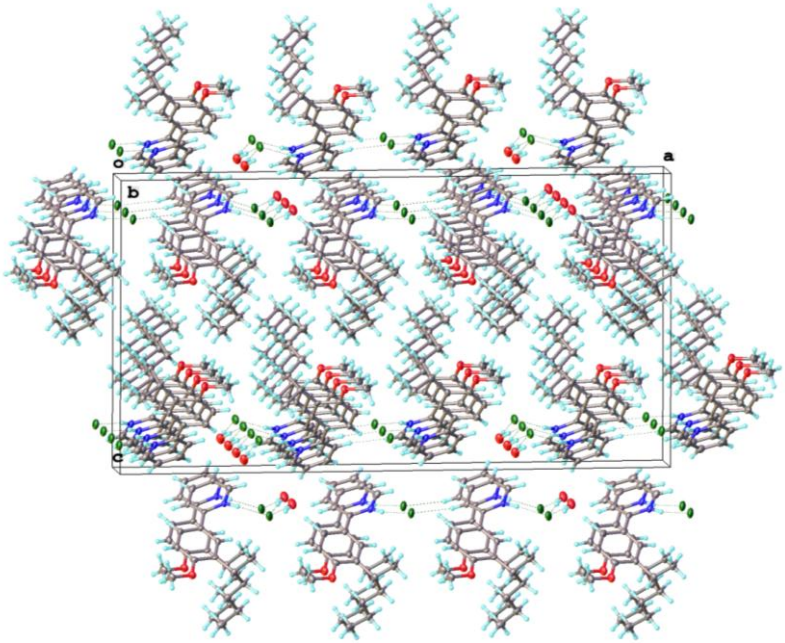


Figure 7.8: Fragment of the molecular packing in extended unit cell of (*R*)-**167**; space group *C*2.

Table S-21 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 167. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Cl1	-192.4(3)	1970(3)	8719.5(7)	33.1(4)
Cl2	2366.8(3)	644(2)	8653.1(7)	32.1(4)
O1	1303.6(9)	6279(6)	6656.0(19)	32.1(10)
N1	497.5(11)	-1276(8)	8813(2)	25.6(10)
C1	875.6(13)	-1136(9)	8594(3)	23.5(12)
C2	1132.8(15)	-2883(11)	8847(3)	28.0(12)
C3	1005.8(16)	-4671(11)	9309(3)	32.6(14)
C4	612.4(16)	-4791(11)	9512(3)	33.0(14)
C5	365.3(15)	-3057(12)	9250(3)	31.4(13)
C6	989.4(13)	814(10)	8093(3)	24.2(12)
C7	714.9(14)	1993(11)	7640(3)	26.2(12)
C8	820.4(13)	3775(10)	7151(3)	24.6(12)
C9	1214.6(14)	4441(10)	7132(3)	24.8(13)
C10	1493.6(14)	3349(10)	7575(3)	27.0(13)
C11	1379.4(14)	1525(11)	8047(3)	29.5(14)
C12	1698.3(16)	7167(14)	6651(4)	38.4(15)
C13	513.0(14)	4788(10)	6627(3)	25.7(13)
C14	172.3(16)	5997(12)	7024(3)	29.1(14)
C15	366.3(14)	2849(10)	6089(3)	25.8(13)
C16	688.4(15)	1472(11)	5690(3)	27.5(14)
C17	533.0(15)	-348(11)	5159(3)	30.2(14)
C18	852.2(17)	-1857(12)	4793(4)	33.4(14)
O2	3846.1(9)	6143(6)	6809.9(17)	25.2(9)
N2	3151.4(10)	-1597(8)	9050(2)	20(1)
C21	3524.9(13)	-1374(9)	8784(2)	19.1(11)
C22	3797.8(14)	-3046(10)	9007(3)	23.0(11)
C23	3690.7(15)	-4866(10)	9480(3)	26.5(13)
C24	3310.7(14)	-5043(10)	9735(3)	24.7(12)
C25	3045.0(15)	-3338(11)	9511(3)	27.7(13)
C26	3610.0(12)	567(10)	8260(2)	18.6(11)
C27	3317.6(13)	1661(10)	7835(3)	22.6(12)
C28	3394.4(12)	3469(10)	7335(2)	20.6(11)
C29	3785.1(13)	4251(9)	7283(3)	23.5(12)
C30	4079.7(15)	3170(10)	7693(3)	25.0(13)
C31	3997.9(13)	1336(9)	8174(3)	22.5(13)
C32	4233.3(16)	7076(13)	6769(3)	30.1(13)
C33	3064.0(13)	4478(10)	6860(3)	23.8(12)
C34	2767.9(16)	5835(12)	7336(3)	28.9(12)
C35	2859.0(14)	2563(10)	6399(3)	24.4(13)
C36	3128.3(16)	1089(11)	5904(3)	26.1(13)
C37	2912.7(16)	-612(11)	5400(3)	28.6(13)
C38	3188.5(18)	-2128(12)	4937(4)	34.8(15)
O3	2024.4(10)	5626(9)	9179(2)	37(1)

Table S-22 Anisotropic Displacement Parameters (Å^2×10^3) for 167. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka\times b\times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl1	16.8(6)	39.4(8)	43.1(8)	-1.6(7)	-3.5(5)	4.3(6)
Cl2	19.9(6)	36.9(8)	39.6(8)	4.5(7)	3.1(5)	8.4(6)
O1	23.3(18)	37(3)	36(2)	1.1(18)	0.8(15)	-8.4(16)
N1	18(2)	31(3)	28(3)	-1(2)	-6.3(19)	-1(2)
C1	21(3)	31(3)	19(3)	-6(2)	-5(2)	6(2)
C2	30(3)	31(3)	22(3)	-7(3)	-7(2)	3(3)
C3	42(3)	31(4)	24(3)	-10(3)	-12(3)	3(3)
C4	37(3)	35(4)	27(3)	1(3)	-7(3)	-4(3)
C5	28(3)	34(3)	32(3)	3(3)	-7(2)	-6(3)
C6	22(3)	32(3)	19(3)	-5(3)	0(2)	5(2)
C7	15(3)	39(3)	25(3)	-5(3)	-2(2)	1(3)
C8	18(2)	33(3)	23(3)	-3(3)	2(2)	-1(2)
C9	28(3)	27(3)	19(3)	-4(2)	5(2)	-2(3)

Table S-22 Anisotropic Displacement Parameters ($Å^2×10^3$) for 167. The Anisotropic displacement factor exponent takes the form: $-2π^2[h^2a^{*2}U_{11}+...+2hka×b×U_{12}]$

C10	15(3)	35(3)	31(3)	-3(3)	4(2)	1(3)
C11	22(3)	41(4)	25(3)	-4(3)	-4(2)	10(3)
C12	27(3)	49(4)	39(4)	-5(4)	5(3)	-11(3)
C13	22(3)	29(3)	26(3)	3(3)	1(2)	-7(2)
C14	22(3)	35(4)	29(3)	3(3)	-3(3)	5(3)
C15	22(3)	31(3)	24(3)	2(3)	-2(2)	-3(3)
C16	19(3)	31(4)	32(3)	1(3)	-1(2)	-4(3)
C17	22(3)	41(4)	28(3)	9(3)	-4(3)	2(3)
C18	35(3)	38(4)	27(4)	1(3)	-2(3)	14(3)
O2	26.1(18)	22(2)	27(2)	4.7(15)	2.4(15)	-4.9(15)
N2	14(2)	23(2)	22(2)	-3(2)	-1.7(17)	4(2)
C21	18(2)	27(3)	12(3)	-4(2)	-3(2)	1(2)
C22	17(3)	28(3)	23(3)	1(3)	-5(2)	-4(3)
C23	23(3)	27(4)	29(3)	-5(3)	-8(2)	4(3)
C24	26(3)	29(3)	18(3)	1(2)	-2(2)	2(2)
C25	20(3)	38(4)	25(3)	-1(3)	2(2)	-3(3)
C26	20(2)	23(3)	14(3)	2(2)	-1.2(19)	0(2)
C27	14(3)	30(3)	24(3)	-3(3)	2(2)	-2(3)
C28	21(2)	29(3)	12(3)	-2(2)	-5(2)	-1(2)
C29	27(3)	26(3)	18(3)	0(2)	1(2)	-2(3)
C30	18(3)	31(3)	26(3)	-4(3)	3(2)	-2(3)
C31	18(2)	28(4)	22(3)	1(2)	-1(2)	1(2)
C32	28(3)	32(4)	30(4)	4(3)	5(3)	-10(3)
C33	22(3)	26(3)	23(3)	2(2)	-4(2)	-4(2)
C34	34(3)	29(3)	23(3)	-1(3)	-10(2)	6(3)
C35	21(3)	33(4)	19(3)	1(2)	-2(2)	3(2)
C36	26(3)	27(4)	26(3)	4(3)	-3(3)	1(3)
C37	29(3)	29(3)	27(3)	2(3)	-3(3)	5(3)
C38	40(3)	37(4)	26(4)	-8(3)	-4(3)	10(3)
O3	29(2)	37(2)	45(2)	-14(2)	5.7(17)	0(2)

Table S-23 Bond Lengths for 167.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	**C9**	1.377(6)	**O2**	**C29**	1.378(6)
O1	**C12**	1.431(6)	**O2**	**C32**	1.419(6)
N1	**C1**	1.353(6)	**N2**	**C21**	1.370(6)
N1	**C5**	1.351(7)	**N2**	**C25**	1.335(7)
C1	**C2**	1.385(7)	**C21**	**C22**	1.374(7)
C1	**C6**	1.473(7)	**C21**	**C26**	1.472(7)
C2	**C3**	1.376(8)	**C22**	**C23**	1.381(7)
C3	**C4**	1.394(8)	**C23**	**C24**	1.381(7)
C4	**C5**	1.364(8)	**C24**	**C25**	1.371(8)
C6	**C7**	1.404(7)	**C26**	**C27**	1.396(7)
C6	**C11**	1.389(7)	**C26**	**C31**	1.398(6)
C7	**C8**	1.383(7)	**C27**	**C28**	1.383(7)
C8	**C9**	1.392(6)	**C28**	**C29**	1.404(6)
C8	**C13**	1.519(7)	**C28**	**C33**	1.520(6)
C9	**C10**	1.380(7)	**C29**	**C30**	1.383(7)
C10	**C11**	1.389(8)	**C30**	**C31**	1.375(7)
C13	**C14**	1.529(7)	**C33**	**C34**	1.534(7)
C13	**C15**	1.538(7)	**C33**	**C35**	1.523(7)
C15	**C16**	1.527(7)	**C35**	**C36**	1.531(7)
C16	**C17**	1.494(8)	**C36**	**C37**	1.505(8)
C17	**C18**	1.531(7)	**C37**	**C38**	1.522(8)

Table S-24 Bond Angles for 167.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C9	**O1**	**C12**	118.2(4)	**C29**	**O2**	**C32**	117.3(4)
C5	**N1**	**C1**	122.6(5)	**C25**	**N2**	**C21**	123.1(4)
N1	**C1**	**C2**	117.5(5)	**N2**	**C21**	**C22**	117.5(5)

Table S-24 Bond Angles for 167.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
N1	**C1**	**C6**	118.8(4)	**N2**	**C21**	**C26**	118.9(4)
C2	**C1**	**C6**	123.7(5)	**C22**	**C21**	**C26**	123.6(4)
C3	**C2**	**C1**	120.7(5)	**C21**	**C22**	**C23**	120.0(5)
C2	**C3**	**C4**	120.3(6)	**C22**	**C23**	**C24**	121.0(5)
C5	**C4**	**C3**	117.6(6)	**C25**	**C24**	**C23**	117.9(5)
N1	**C5**	**C4**	121.2(5)	**N2**	**C25**	**C24**	120.6(5)
C7	**C6**	**C1**	122.1(4)	**C27**	**C26**	**C21**	122.5(4)
C11	**C6**	**C1**	120.3(5)	**C27**	**C26**	**C31**	118.2(5)
C11	**C6**	**C7**	117.6(5)	**C31**	**C26**	**C21**	119.3(4)
C8	**C7**	**C6**	122.6(5)	**C28**	**C27**	**C26**	123.0(4)
C7	**C8**	**C9**	117.6(5)	**C27**	**C28**	**C29**	117.1(4)
C7	**C8**	**C13**	119.3(4)	**C27**	**C28**	**C33**	120.0(4)
C9	**C8**	**C13**	123.0(5)	**C29**	**C28**	**C33**	122.9(4)
O1	**C9**	**C8**	115.5(4)	**O2**	**C29**	**C28**	115.4(4)
O1	**C9**	**C10**	122.7(4)	**O2**	**C29**	**C30**	123.9(4)
C10	**C9**	**C8**	121.8(5)	**C30**	**C29**	**C28**	120.7(5)
C9	**C10**	**C11**	119.2(5)	**C31**	**C30**	**C29**	121.1(5)
C6	**C11**	**C10**	121.2(5)	**C30**	**C31**	**C26**	119.8(5)
C8	**C13**	**C14**	112.8(4)	**C28**	**C33**	**C34**	110.4(4)
C8	**C13**	**C15**	110.9(4)	**C28**	**C33**	**C35**	112.8(4)
C14	**C13**	**C15**	111.6(4)	**C35**	**C33**	**C34**	110.9(4)
C16	**C15**	**C13**	115.2(4)	**C33**	**C35**	**C36**	115.3(4)
C17	**C16**	**C15**	113.4(4)	**C37**	**C36**	**C35**	113.9(4)
C16	**C17**	**C18**	113.9(5)	**C36**	**C37**	**C38**	112.8(5)

Table S-25 Hydrogen Bonds for 167.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	**H1**	**Cl1**	0.97(6)	2.03(6)	2.968(4)	161(5)
N2	**H2A**	**Cl2**	1.01(5)	2.08(5)	3.029(4)	156(4)
O3	**H3A**	**Cl2**	0.97(5)	2.20(5)	3.162(5)	175(4)
O3	**H3B**	**Cl2**[1]	1.04(7)	2.16(7)	3.180(5)	167(5)

[1]+X,1+Y,+Z

Table S-26 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 167.

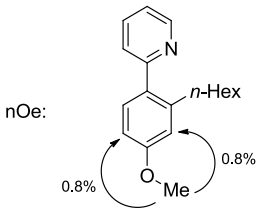
Atom	*x*	*y*	*z*	U(eq)
H1	312(15)	20(110)	8730(30)	45(17)
H5	101(14)	-2870(100)	9360(20)	35(15)
H2	1392(14)	-2800(100)	8700(20)	30(14)
H3	1188(15)	-6010(110)	9460(30)	45(17)
H4	474(19)	-5980(130)	9790(40)	70(20)
H7	468(12)	1550(80)	7640(20)	13(12)
H10	1758(13)	3900(80)	7510(20)	15(12)
H11	1554(15)	640(110)	8300(30)	38(16)
H12A	1688(14)	8610(110)	6310(30)	41(16)
H12B	1769(12)	7760(80)	7110(30)	16(14)
H12C	1888(15)	5820(120)	6530(30)	48(17)
H13	639(12)	5730(90)	6310(20)	12(12)
H14A	-14(14)	6580(100)	6660(30)	33(14)
H14B	33(12)	4900(90)	7350(20)	14(12)
H14C	257(17)	7260(130)	7330(30)	60(20)
H15A	191(12)	1650(90)	6370(20)	24(13)
H15B	179(16)	3660(120)	5770(30)	54(18)
H16A	846(15)	2690(110)	5440(30)	38(16)
H16B	835(17)	650(130)	5990(30)	60(20)
H17A	382(14)	420(110)	4780(30)	35(15)
H17B	332(13)	-1360(90)	5380(20)	18(12)
H18A	723(13)	-3170(100)	4390(30)	35(14)
H18B	987(13)	-2510(90)	5160(30)	19(14)

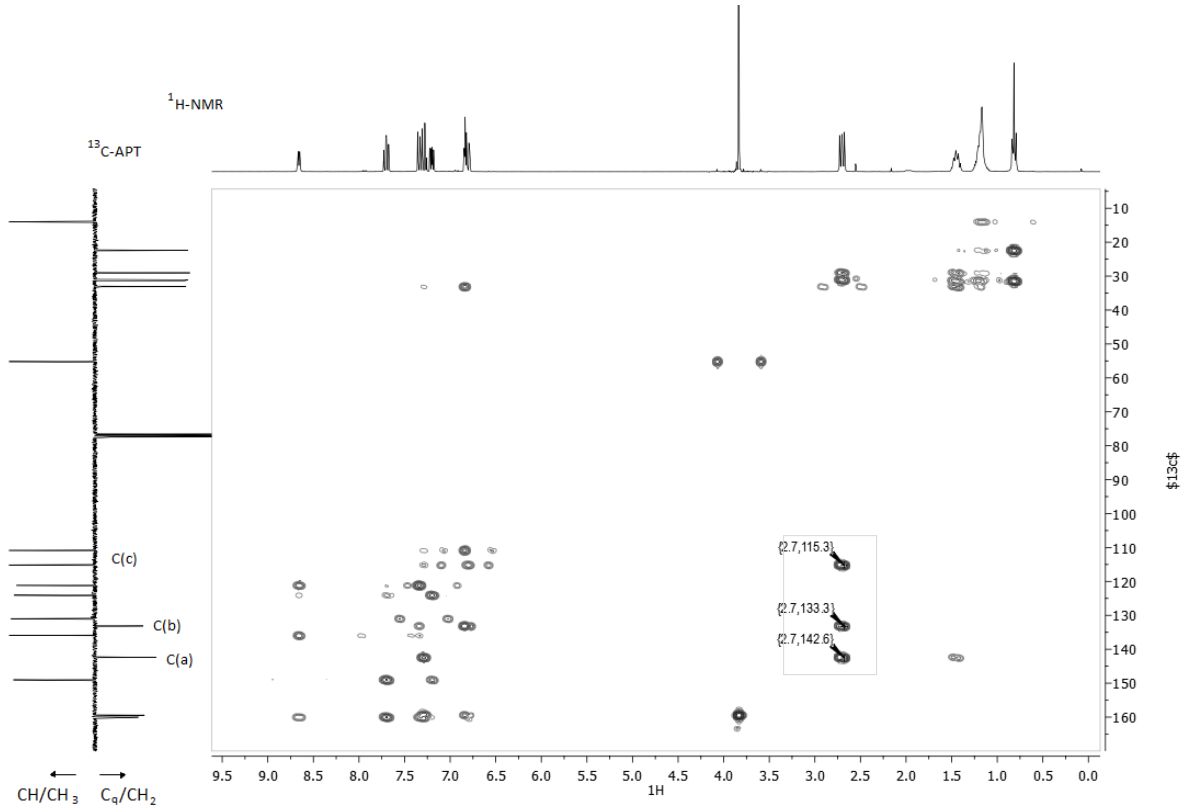
Table S-26 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 167.

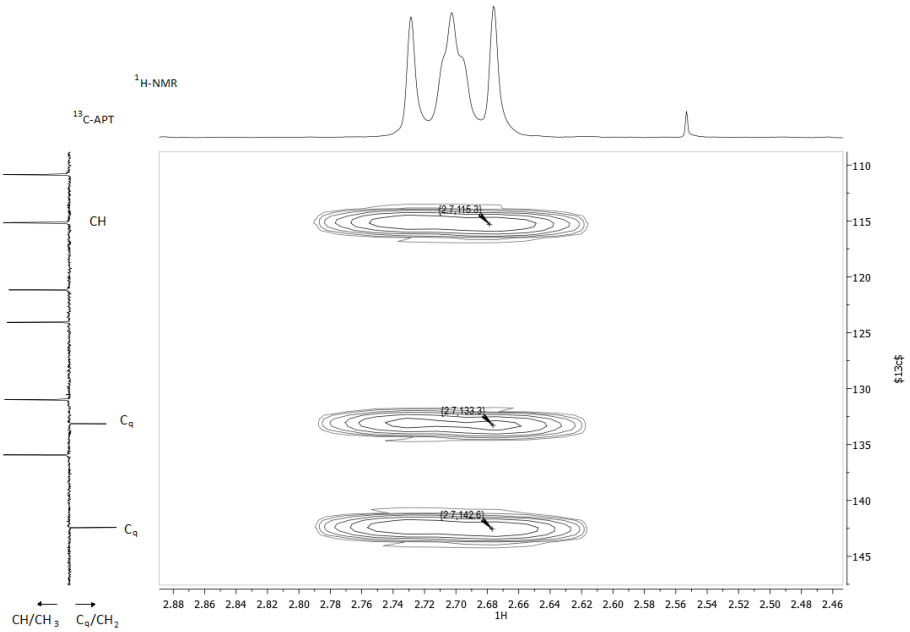
Atom	*x*	*y*	*z*	U(eq)
H18C	1030(20)	-1050(170)	4480(40)	110(30)
H2A	2929(13)	-430(90)	8970(20)	29(14)
H27	3082(17)	1160(120)	7880(30)	70(20)
H22	4063(14)	-2920(100)	8870(20)	29(13)
H23	3853(13)	-5940(90)	9590(30)	21(15)
H24	3229(12)	-6410(100)	10080(30)	24(13)
H25	2769(14)	-3150(90)	9640(20)	24(12)
H30	4299(13)	3800(80)	7670(20)	11(13)
H31	4206(12)	330(90)	8470(20)	17(11)
H32A	4327(12)	7660(90)	7280(30)	19(13)
H32B	4238(14)	8230(110)	6430(30)	33(16)
H32C	4404(13)	5940(90)	6600(30)	19(14)
H33	3187(13)	5790(90)	6520(20)	23(12)
H34A	2881(12)	7210(90)	7660(20)	24(13)
H34B	2637(15)	4510(110)	7650(30)	49(17)
H34C	2565(13)	6540(90)	6980(30)	26(13)
H35A	2703(13)	1480(90)	6720(30)	27(14)
H35B	2639(15)	3370(110)	6130(30)	41(16)
H36A	3280(16)	1890(120)	5600(30)	48(18)
H36B	3291(16)	280(120)	6170(30)	50(19)
H37A	2742(11)	-1470(80)	5710(20)	6(11)
H37B	2751(13)	390(100)	5150(30)	21(13)
H38A	3057(14)	-3160(110)	4590(30)	36(15)
H38B	3368(18)	-1190(140)	4580(40)	80(20)
H38C	3348(16)	-3150(110)	5250(30)	47(17)
H3A	2112(13)	4070(100)	9010(20)	16(13)
H3B	2167(17)	7110(130)	8970(30)	60(20)

7.6 Selected HMBC-Spectra

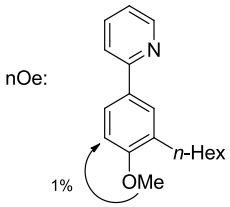
HMBC 93bb







HMBC 93bb'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OMe
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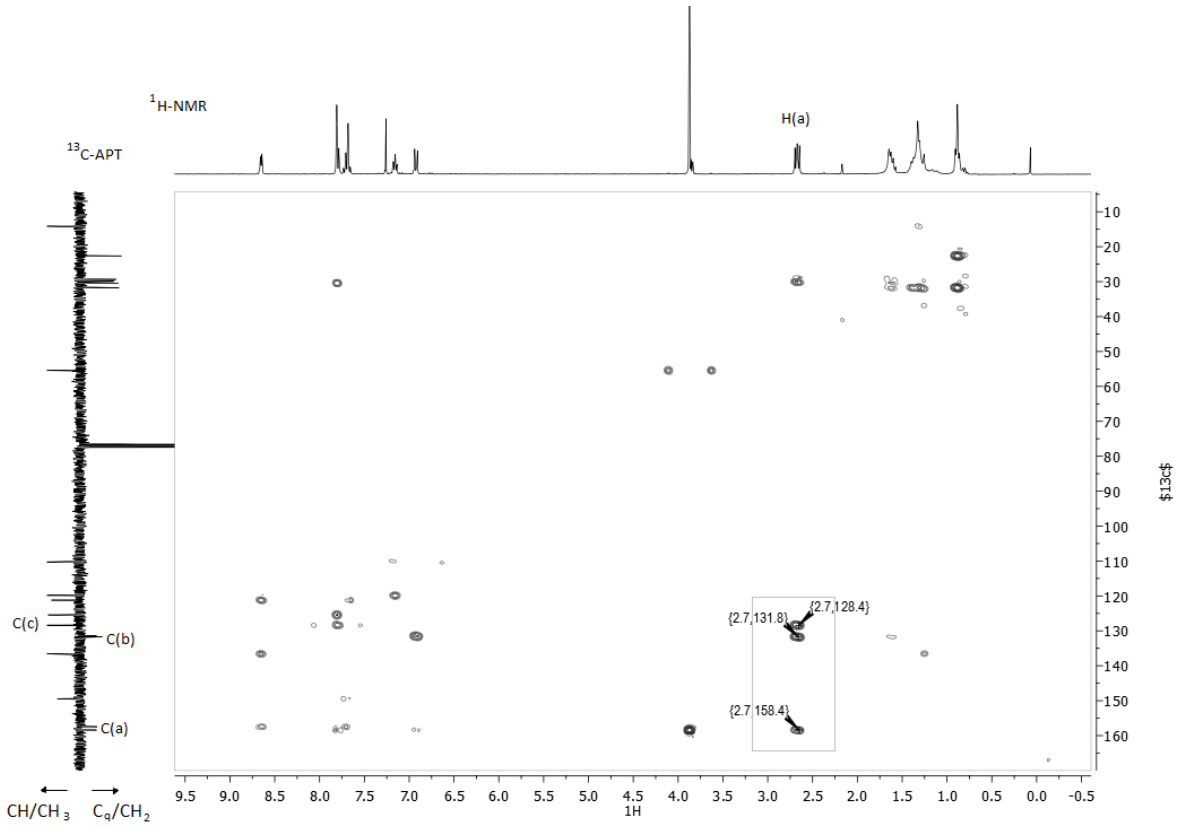
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13C-APT
C(c)
C(b)
C(a)
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{2.7,128.4}
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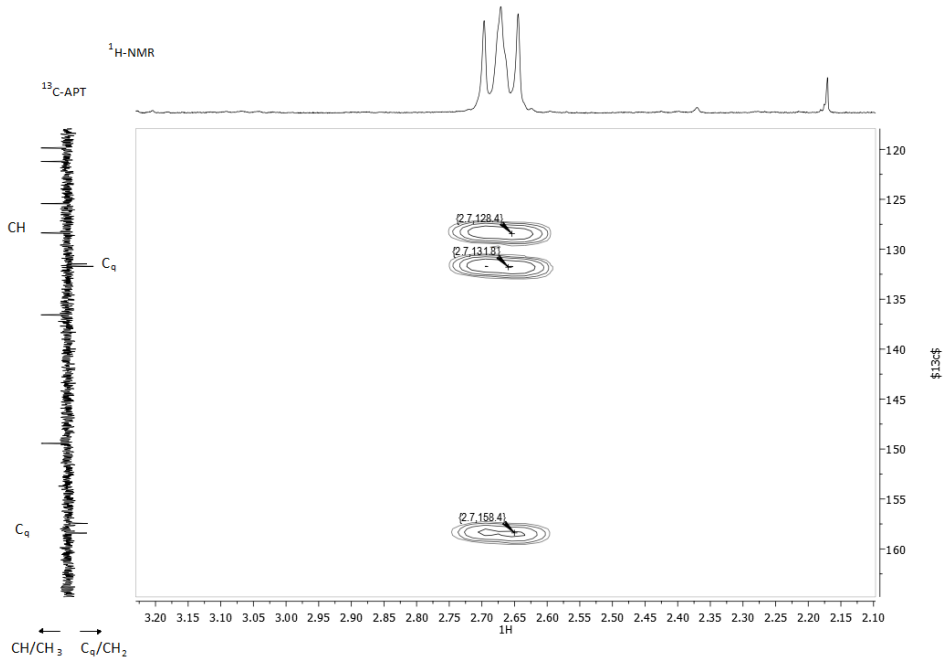
CH/CH3
Cq/CH2
1H
$13c$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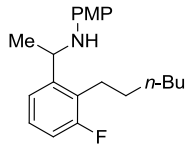
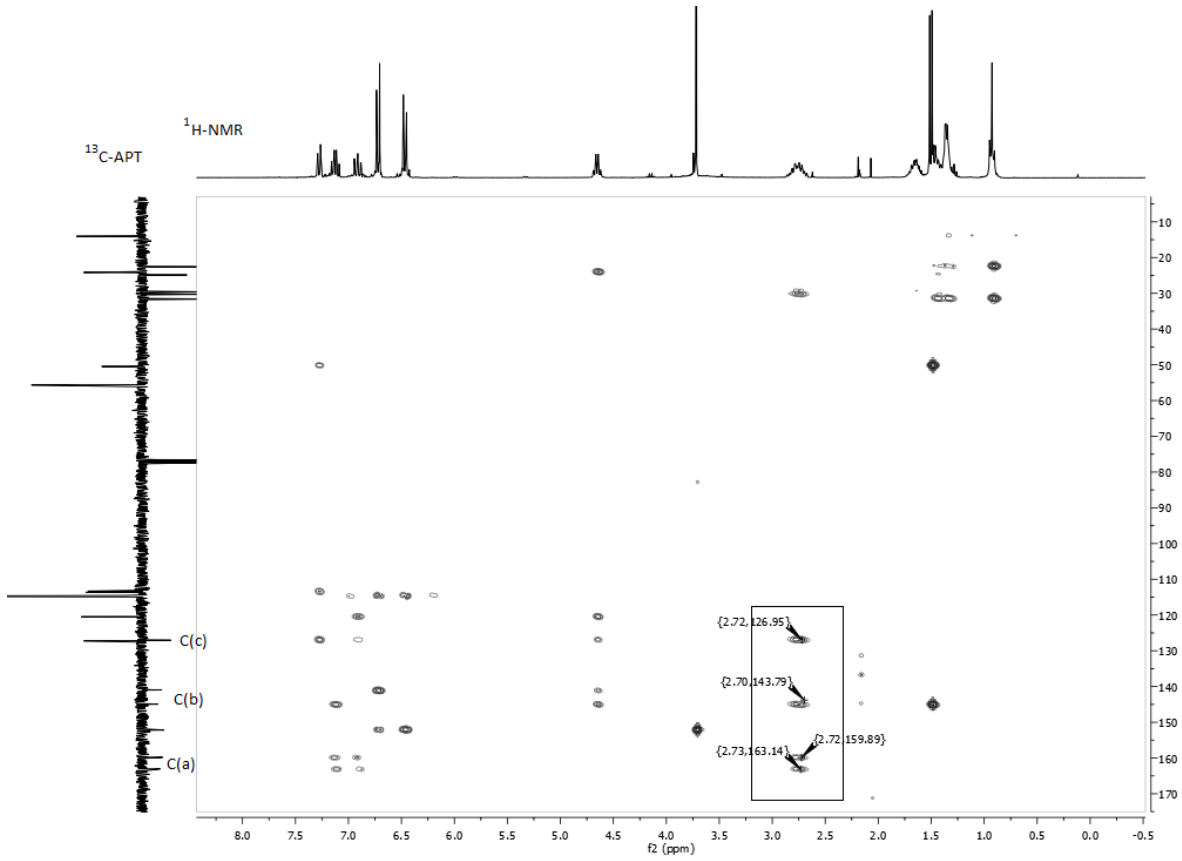
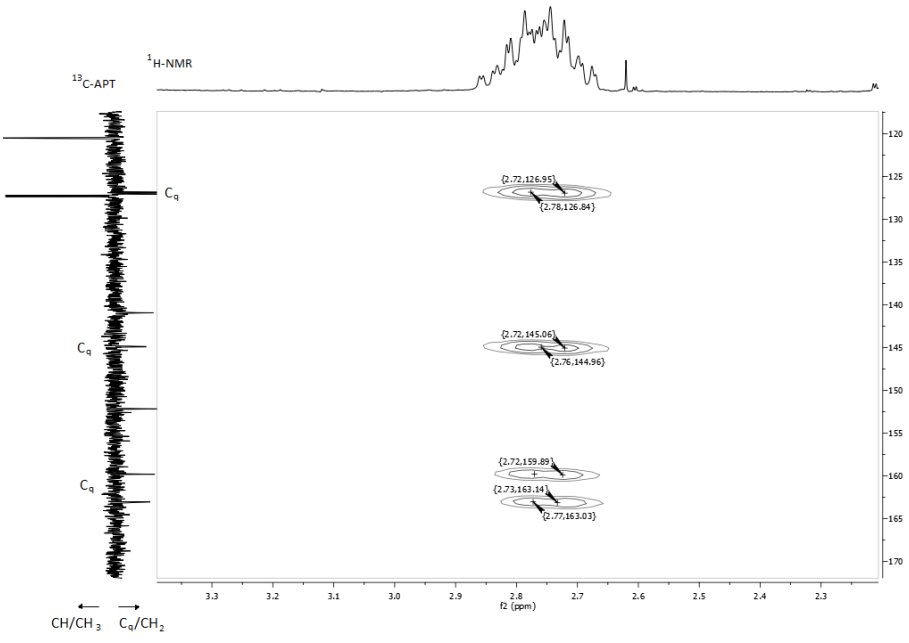
Cq/CH2
1H
$13c$

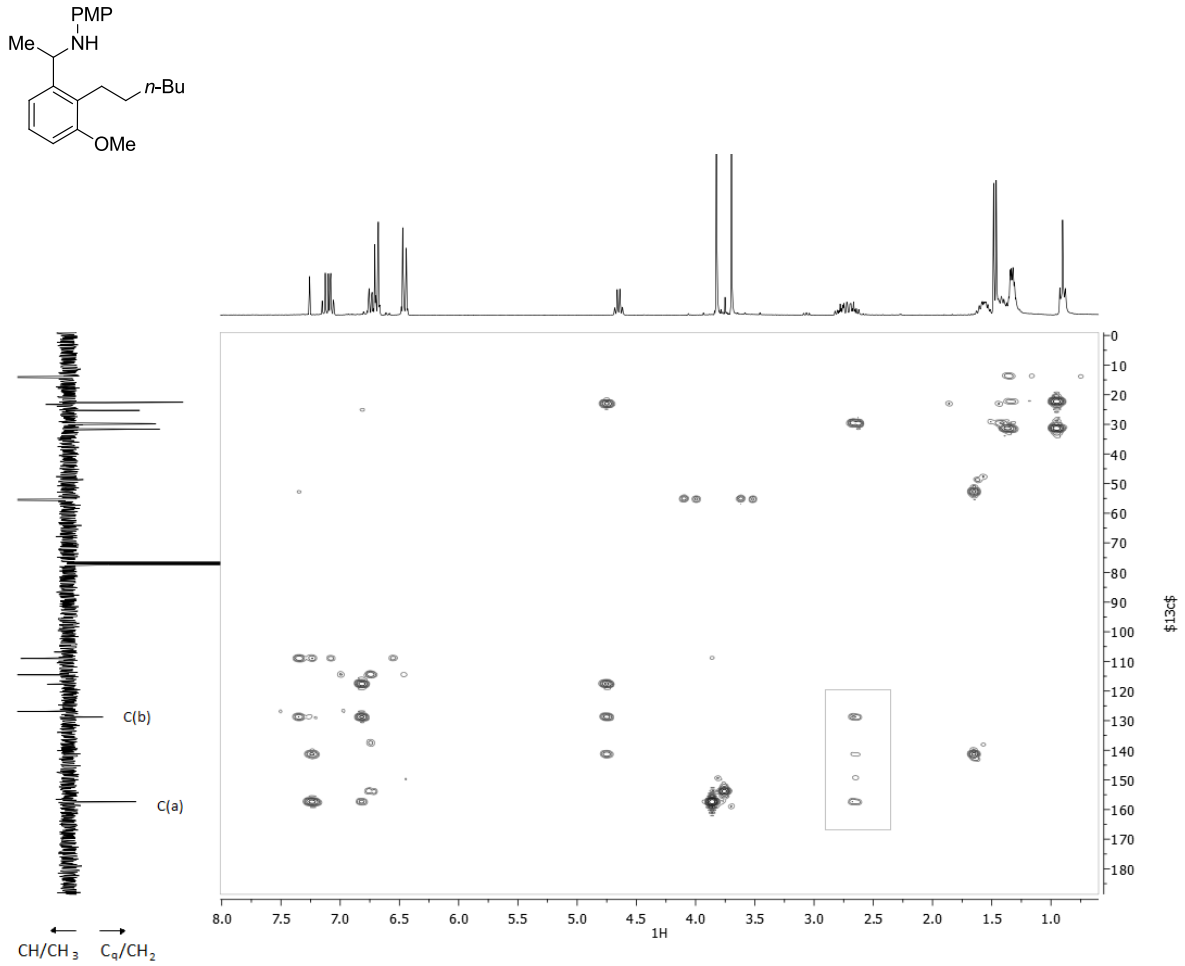
HMBC 122b

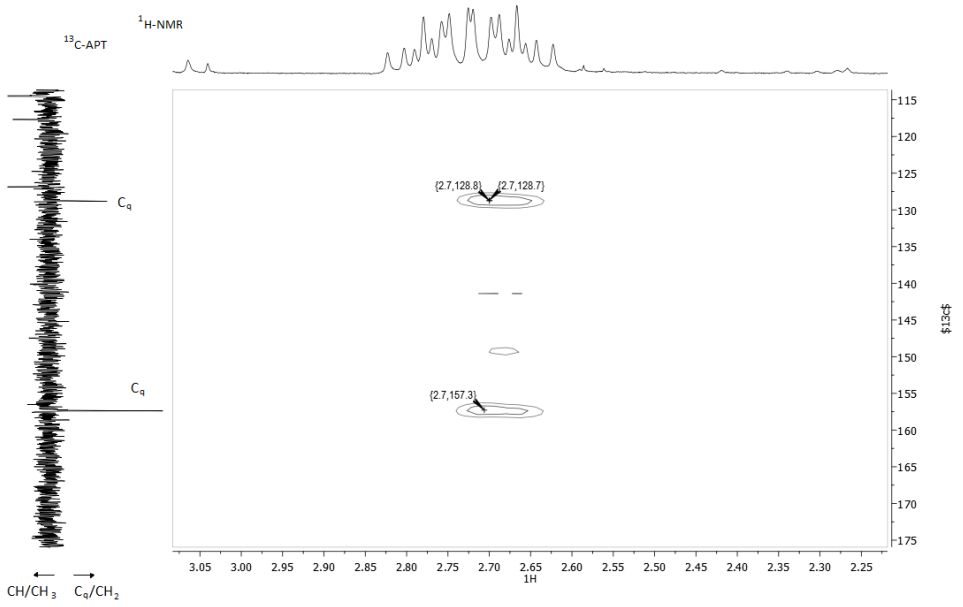

PMP
Me
NH
n-Bu
F


1H-NMR
13C-APT
C(c)
C(b)
C(a)
{2.72,126.95}
{2.70,143.79}
{2.73,163.14}
{2.72,159.89}
f2 (ppm)

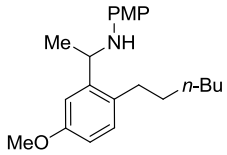

1H-NMR
13C-APT
Cq
Cq
Cq
{2.72,126.95}
{2.78,126.84}
{2.72,145.06}
{2.76,144.96}
{2.72,159.89}
{2.73,163.14}
{2.77,163.03}
f2 (ppm)
CH/CH3
Cq/CH2

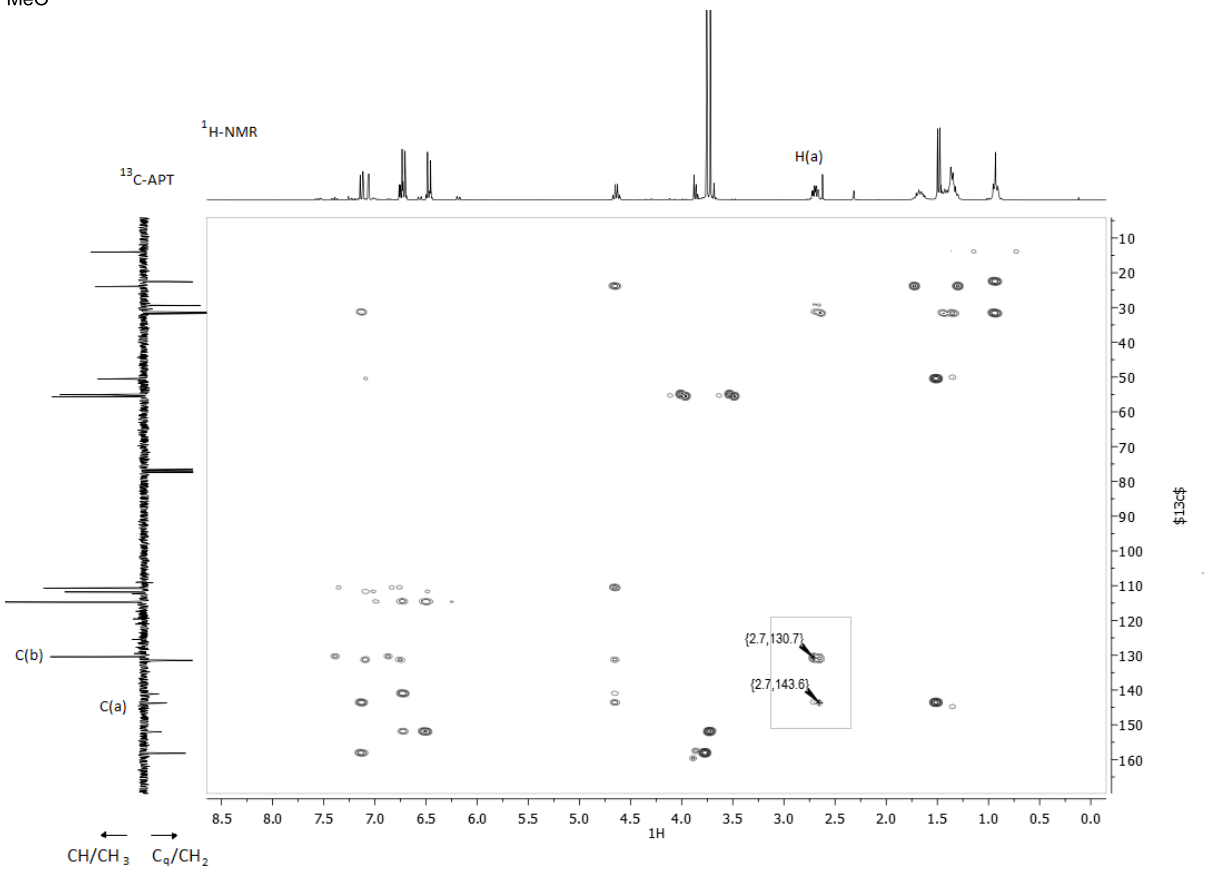
HMBC 122c

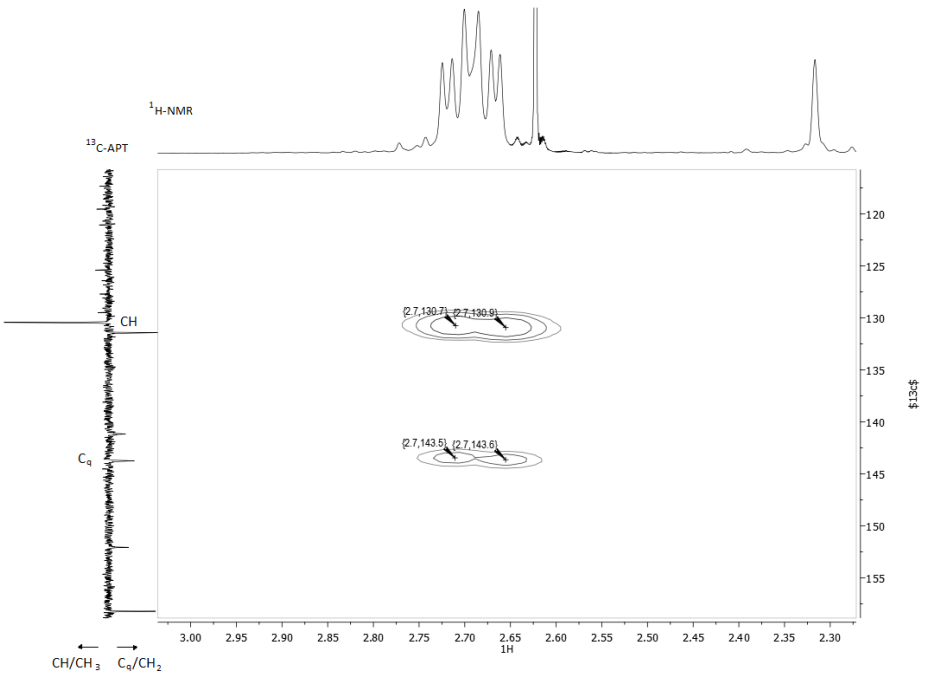

PMP
Me
NH
n-Bu
OMe
C(b)
C(a)
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
Cq
Cq
{2.7,128.8}
{2.7,128.7}
{2.7,157.3}
CH/CH3
Cq/CH2
1H
$13c$

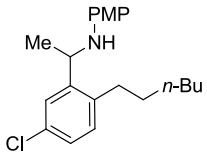
HMBC 122c'

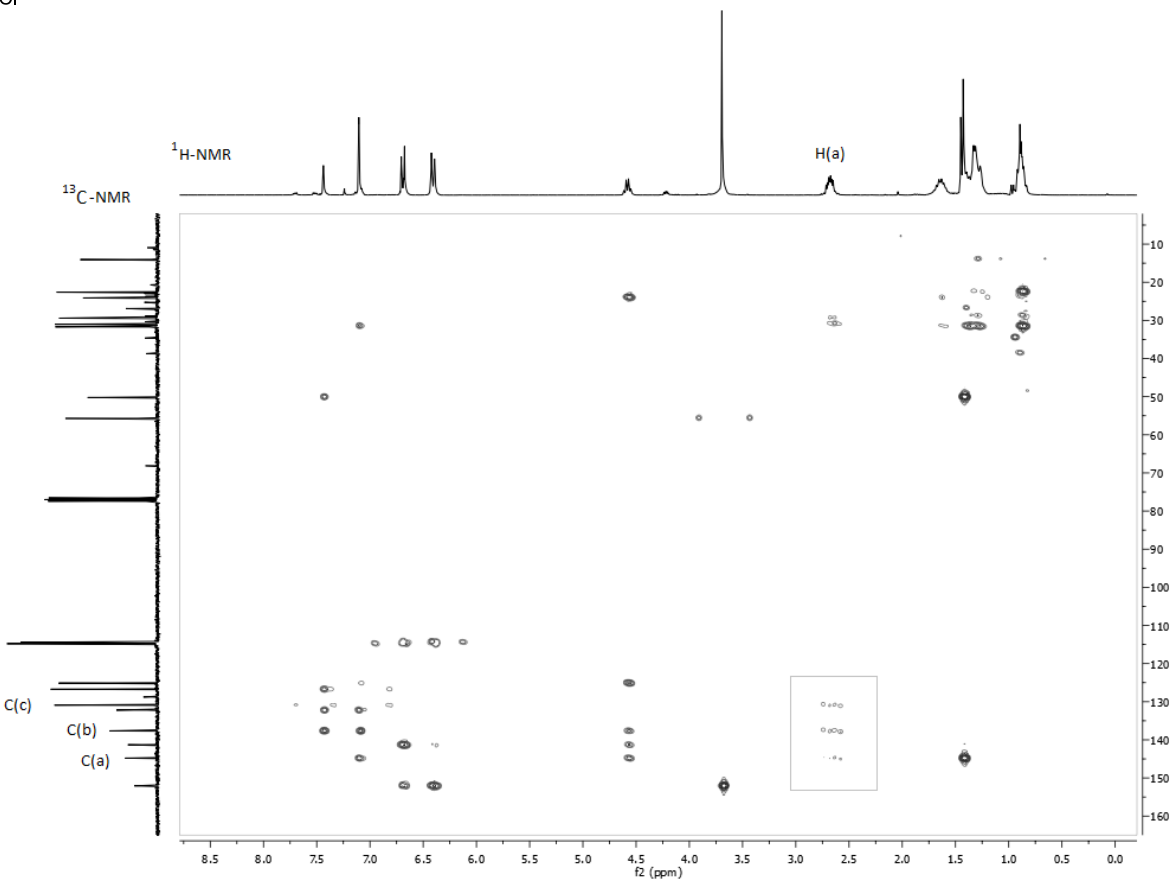

PMP
Me
NH
n-Bu
MeO

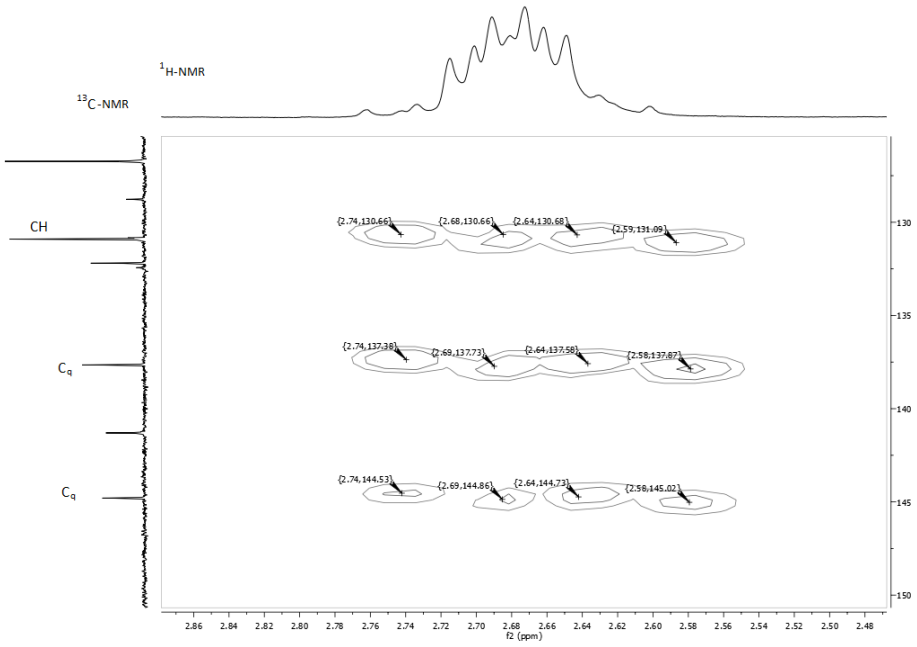

1H-NMR
13C-APT
H(a)
C(b)
C(a)
{2.7,130.7}
{2.7,143.6}
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
CH
Cq
{2.7,130.7}
{2.7,130.9}
{2.7,143.5}
{2.7,143.6}
CH/CH3
Cq/CH2
1H
$13c$

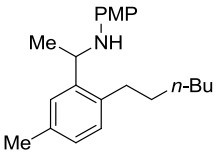
HMBC 122d

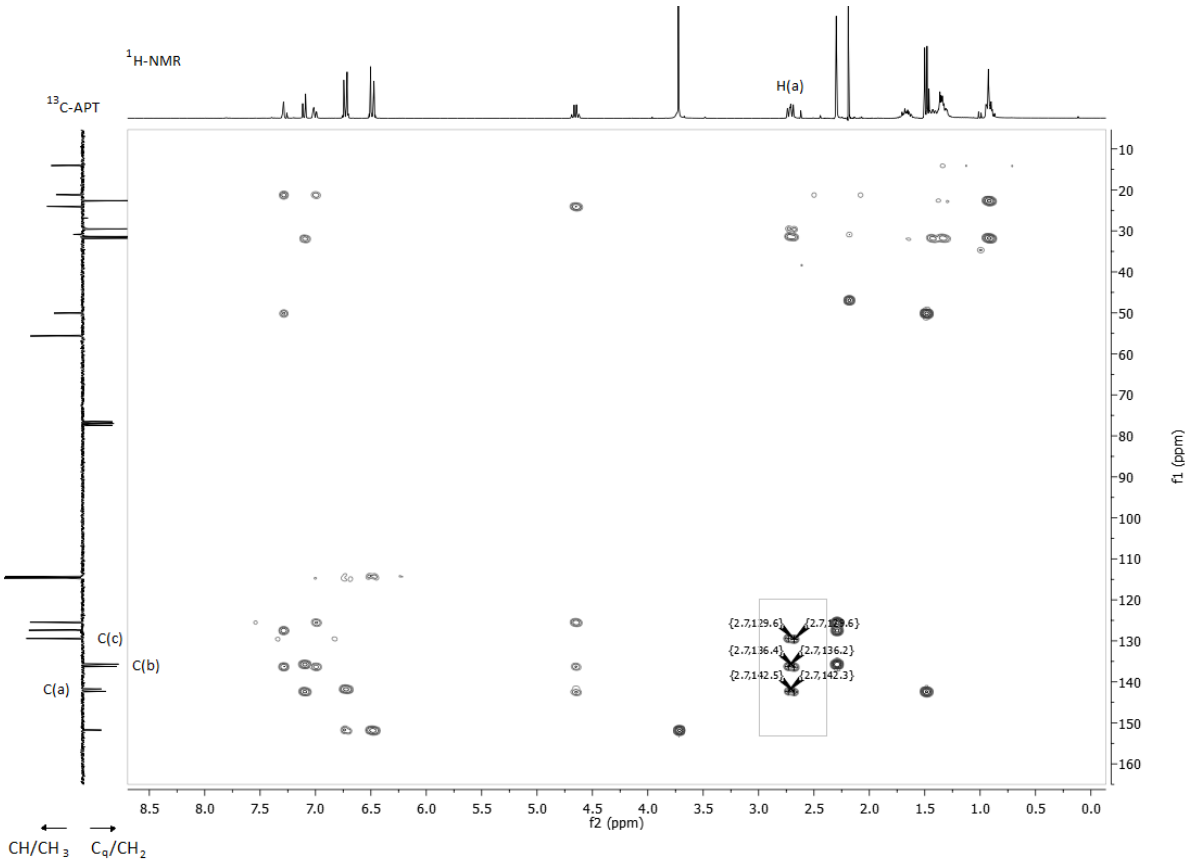

PMP
Me
NH
n-Bu
Cl

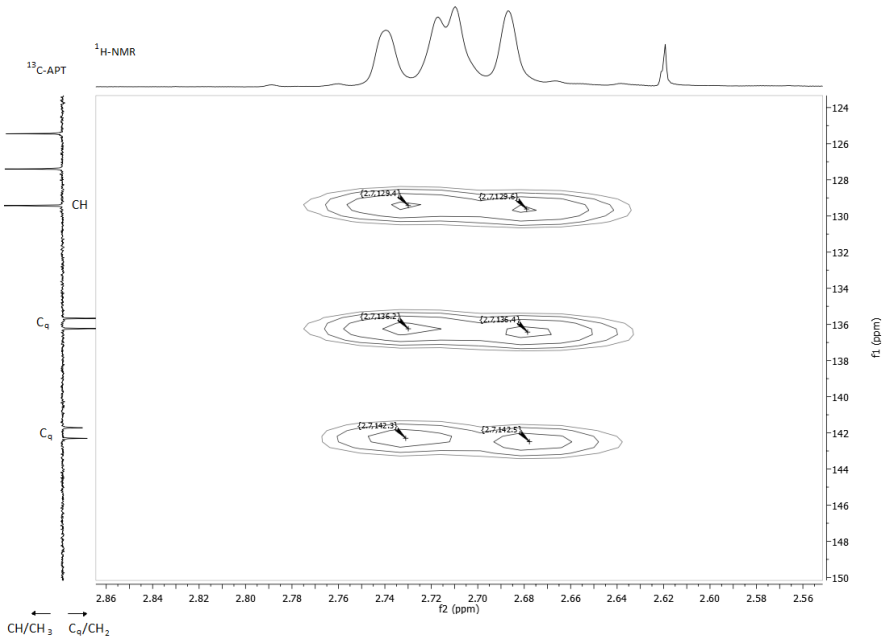

1H-NMR
H(a)
13C-NMR
C(c)
C(b)
C(a)
f2 (ppm)


1H-NMR
13C-NMR
CH
Cq
Cq
{2.74,130.66}
{2.68,130.66}
{2.64,130.68}
{2.59,131.09}
{2.74,137.38}
{2.69,137.73}
{2.64,137.58}
{2.58,137.87}
{2.74,144.53}
{2.69,144.86}
{2.64,144.73}
{2.58,145.02}
f2 (ppm)

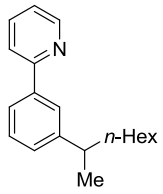
HMBC 122e

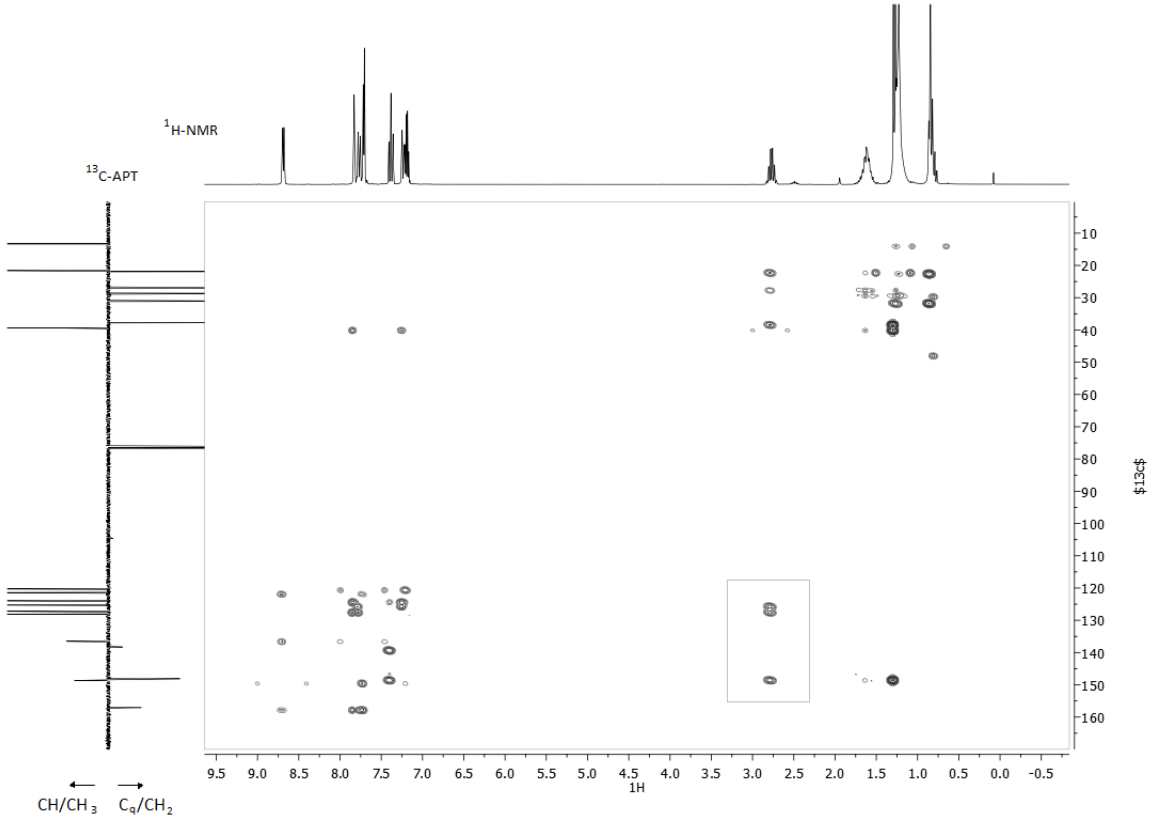

PMP
Me
NH
n-Bu
Me

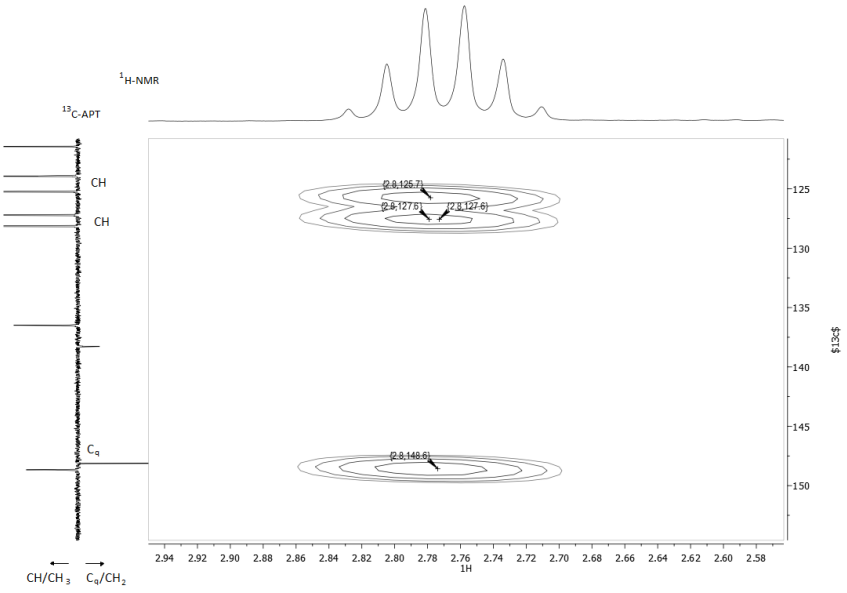

1H-NMR
13C-APT
H(a)
C(c)
C(b)
C(a)
{2.7,129.6}
{2.7,129.6}
{2.7,136.4}
{2.7,136.2}
{2.7,142.5}
{2.7,142.3}
f1 (ppm)
f2 (ppm)
CH/CH3
Cq/CH2


1H-NMR
13C-APT
CH
Cq
Cq
{2.7,129.6}
{2.7,129.6}
{2.7,136.2}
{2.7,136.4}
{2.7,142.3}
{2.7,142.5}
f1 (ppm)
f2 (ppm)
CH/CH3
Cq/CH2

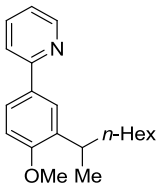
HMBC 147aa

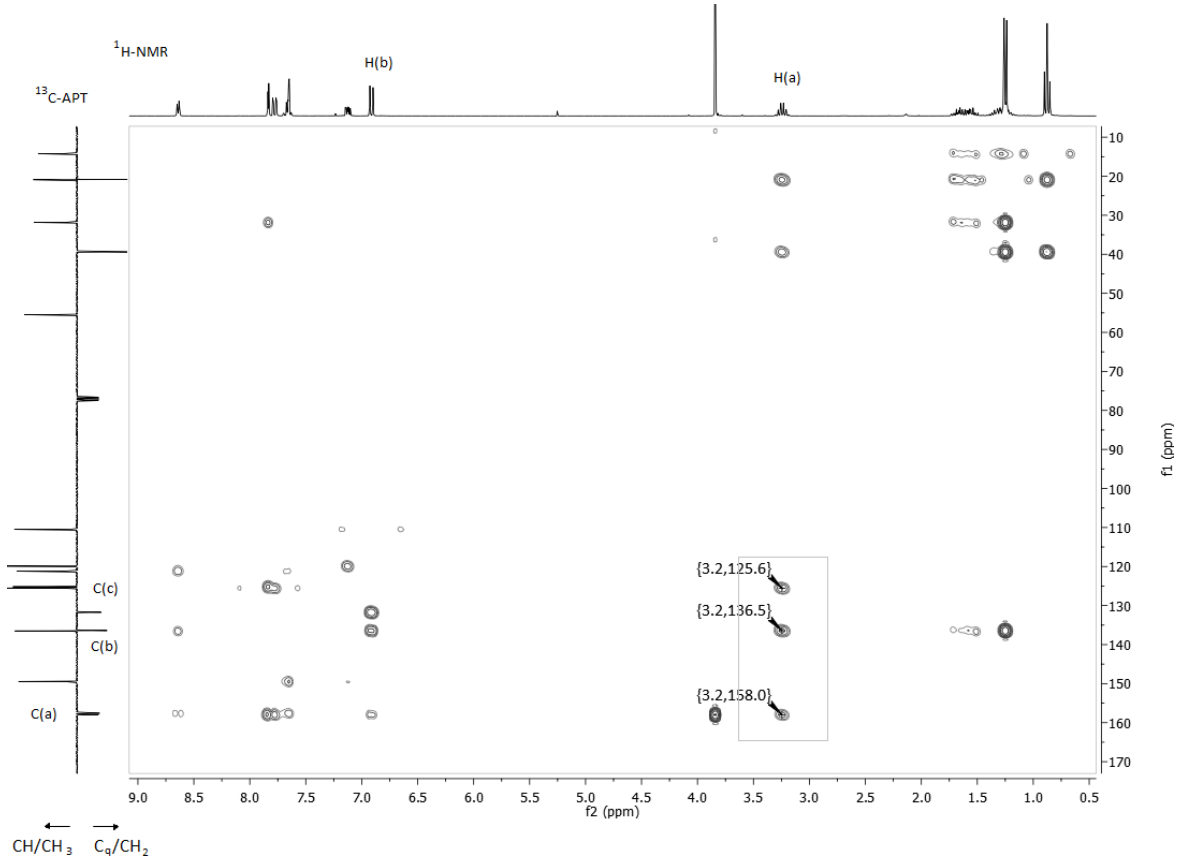

N
n-Hex
Me

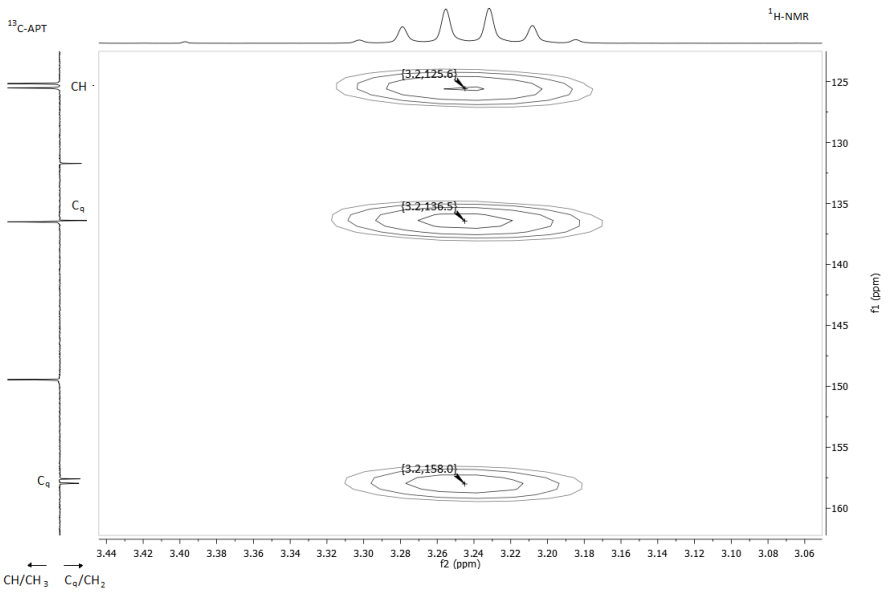

1H-NMR
13C-APT
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
CH
CH
Cq
CH/CH3
Cq/CH2
1H
$13c$

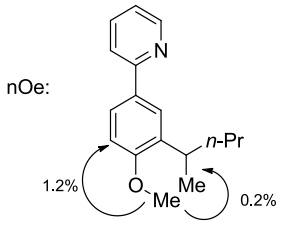
HMBC 147ba

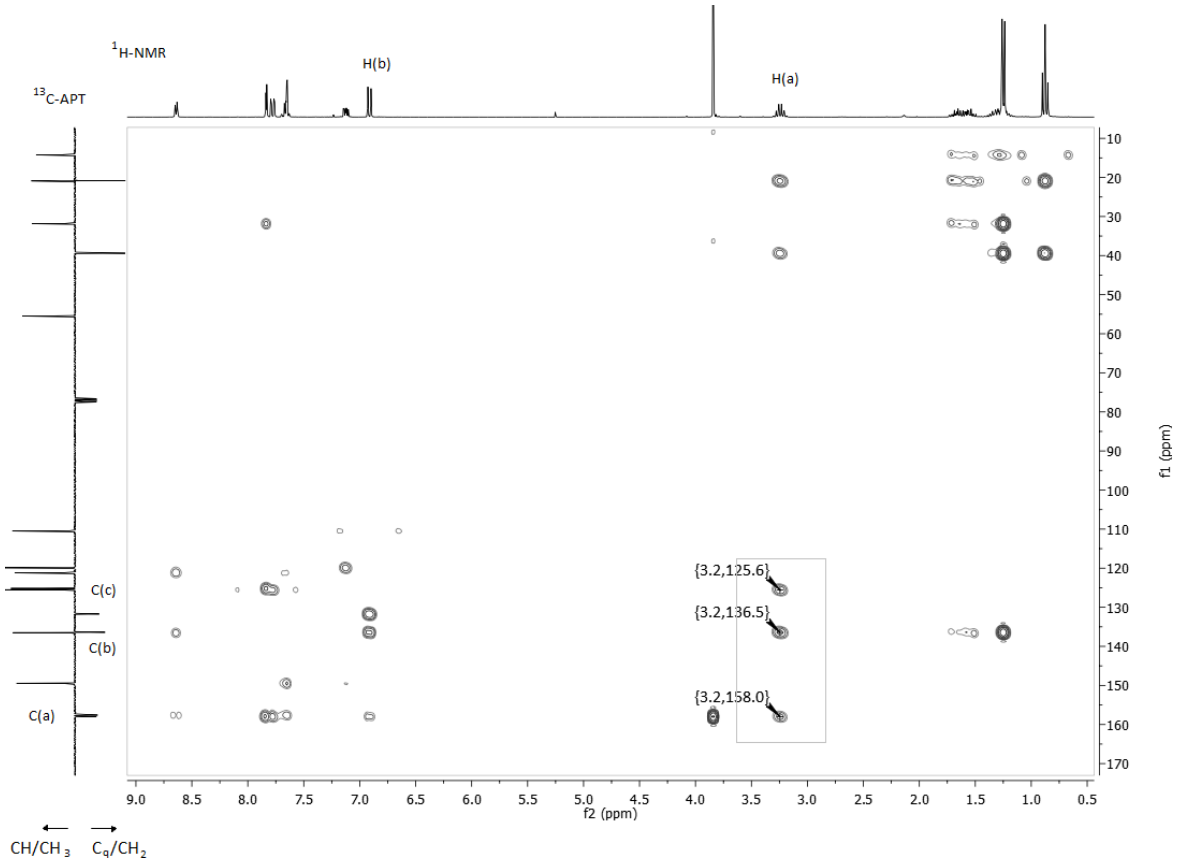

N
n-Hex
OMe Me

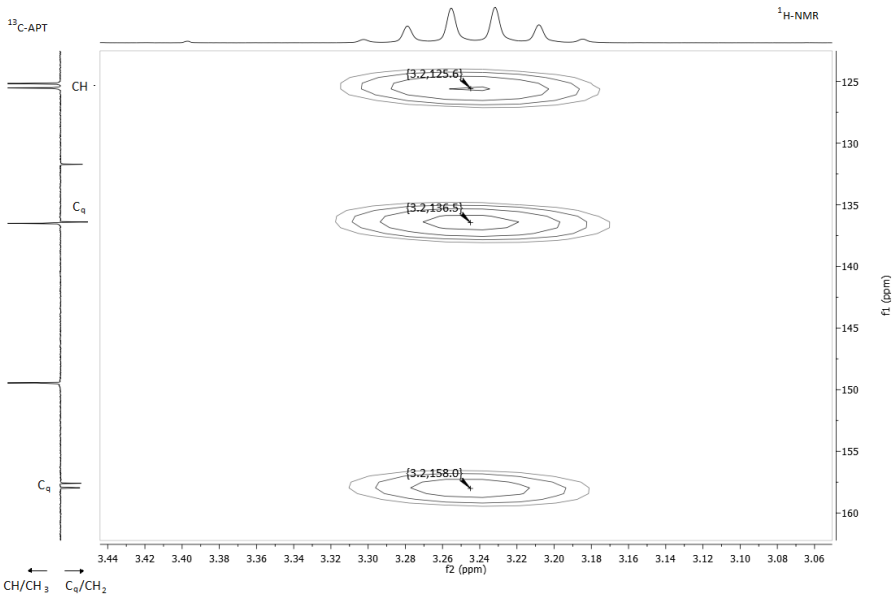

1H-NMR
H(b)
H(a)
13C-APT
C(c)
C(b)
C(a)
{3.2,125.6}
{3.2,136.5}
{3.2,158.0}
f2 (ppm)
f1 (ppm)
CH/CH3
Cq/CH2


13C-APT
1H-NMR
CH
Cq
Cq
{3.2,125.6}
{3.2,136.5}
{3.2,158.0}
f2 (ppm)
f1 (ppm)
CH/CH3
Cq/CH2

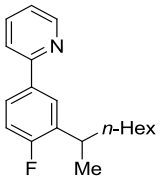
HMBC 147bi

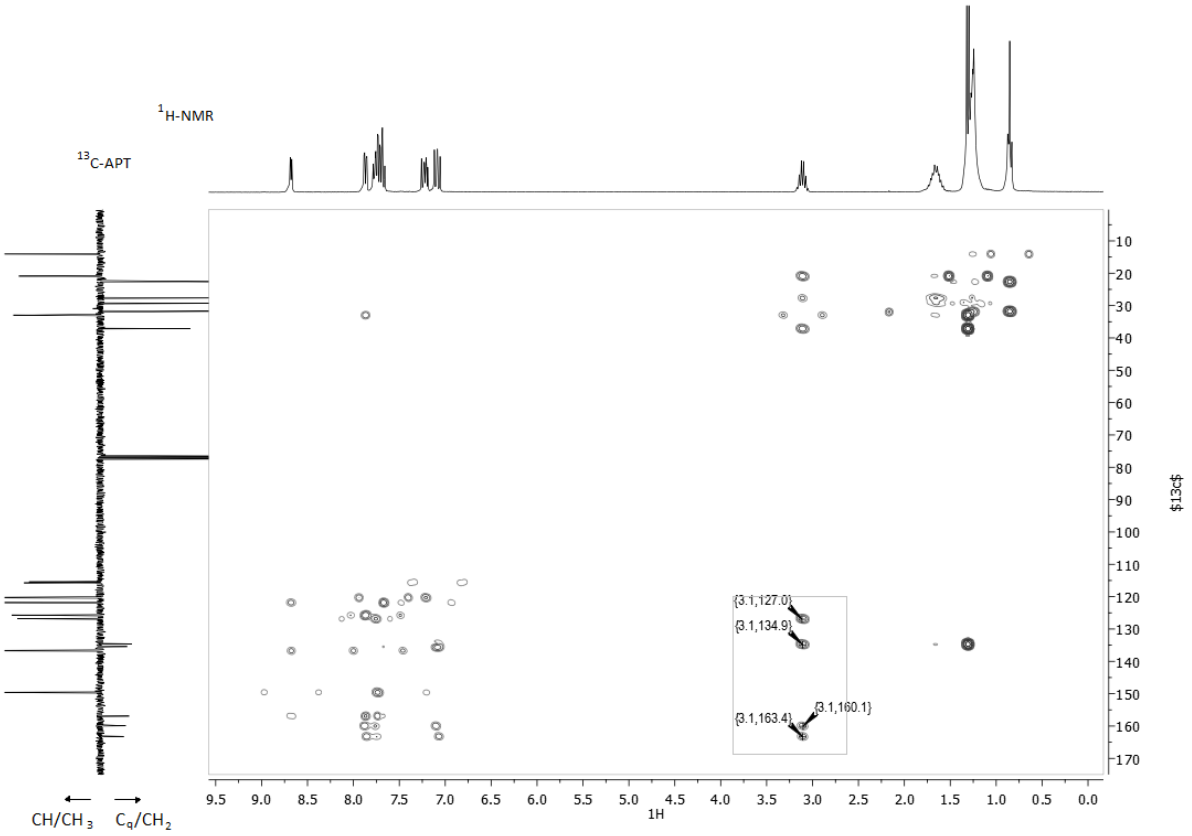

nOe:
N
n-Pr
O
Me
Me
1.2%
0.2%

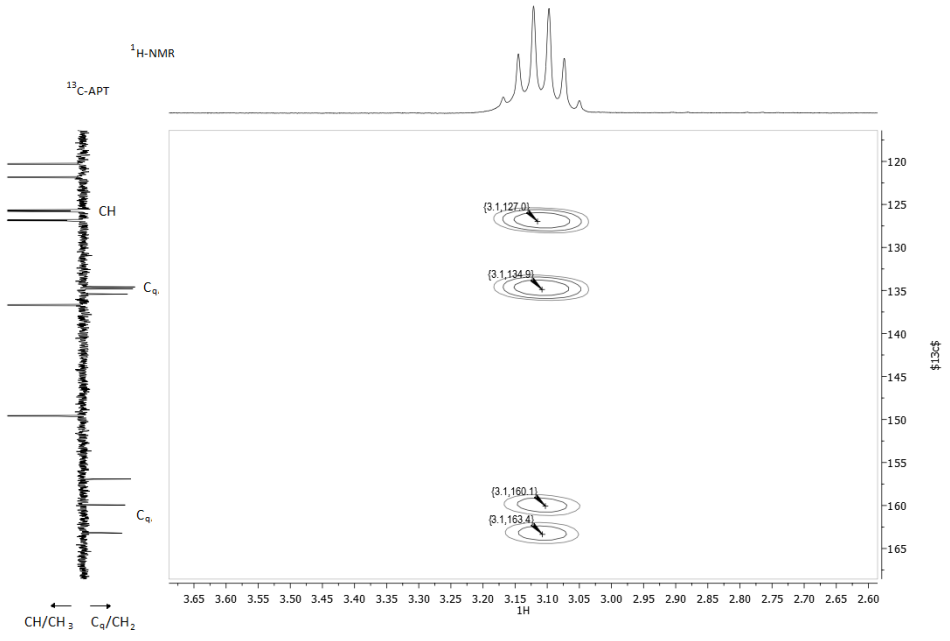

1H-NMR
H(b)
H(a)
13C-APT
C(c)
C(b)
C(a)
{3.2,125.6}
{3.2,136.5}
{3.2,158.0}
f2 (ppm)
f1 (ppm)
CH/CH3
Cq/CH2


13C-APT
1H-NMR
CH
Cq
Cq
{3.2,125.6}
{3.2,136.5}
{3.2,158.0}
f2 (ppm)
f1 (ppm)
CH/CH3
Cq/CH2

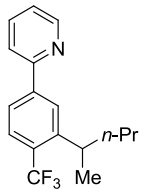
HMBC 147ca

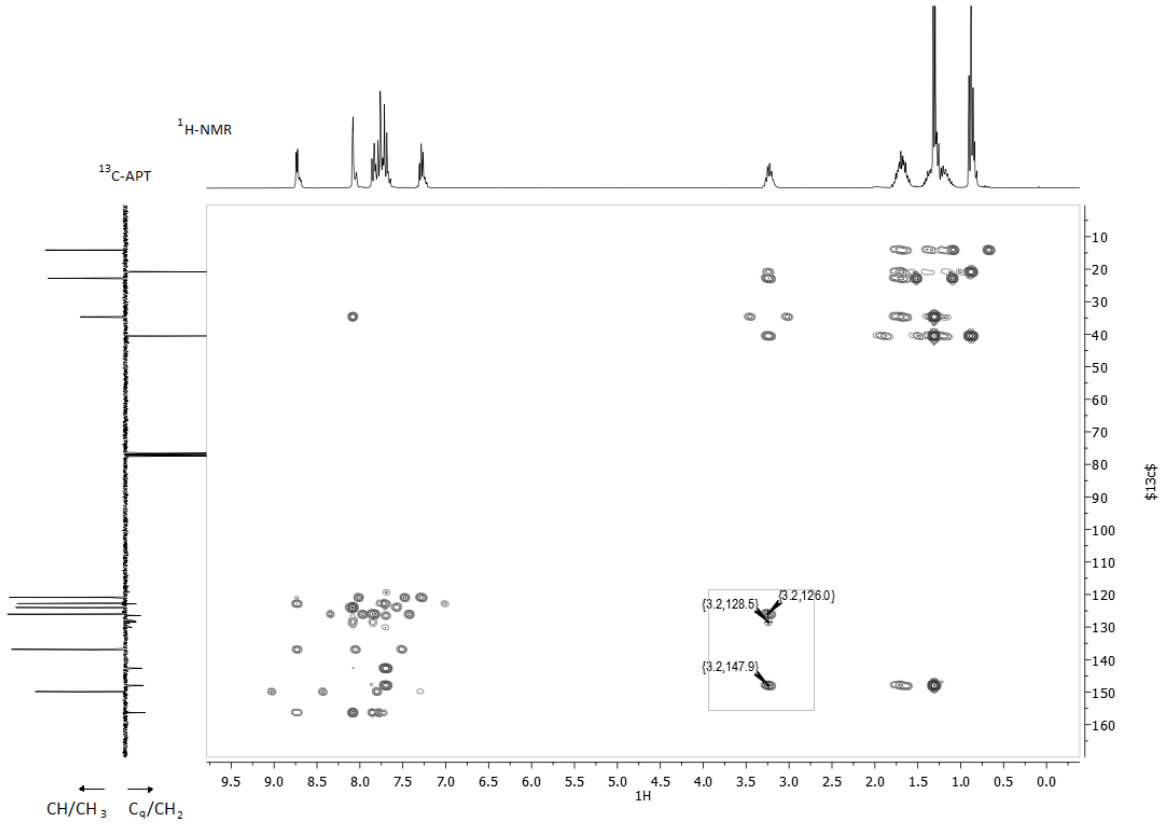

N
n-Hex
F
Me

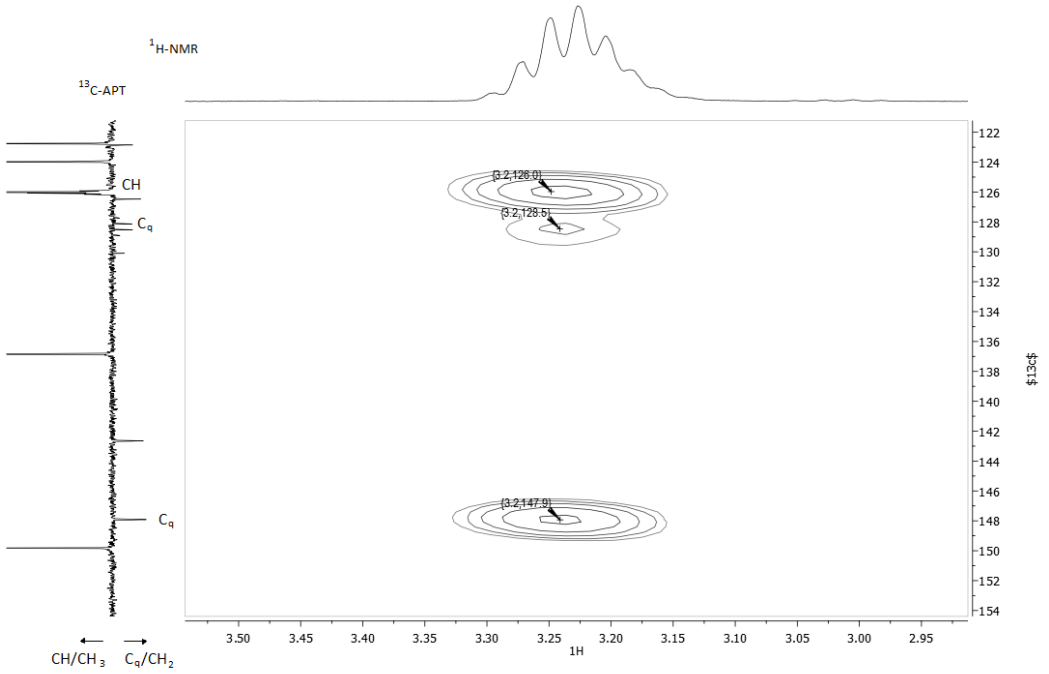

1H-NMR
13C-APT
{3.1,127.0}
{3.1,134.9}
{3.1,163.4}
{3.1,160.1}
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
CH
Cq
Cq
{3.1,127.0}
{3.1,134.9}
{3.1,160.1}
{3.1,163.4}
CH/CH3
Cq/CH2
1H
$13c$

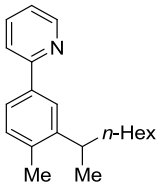
HMBC 147ki

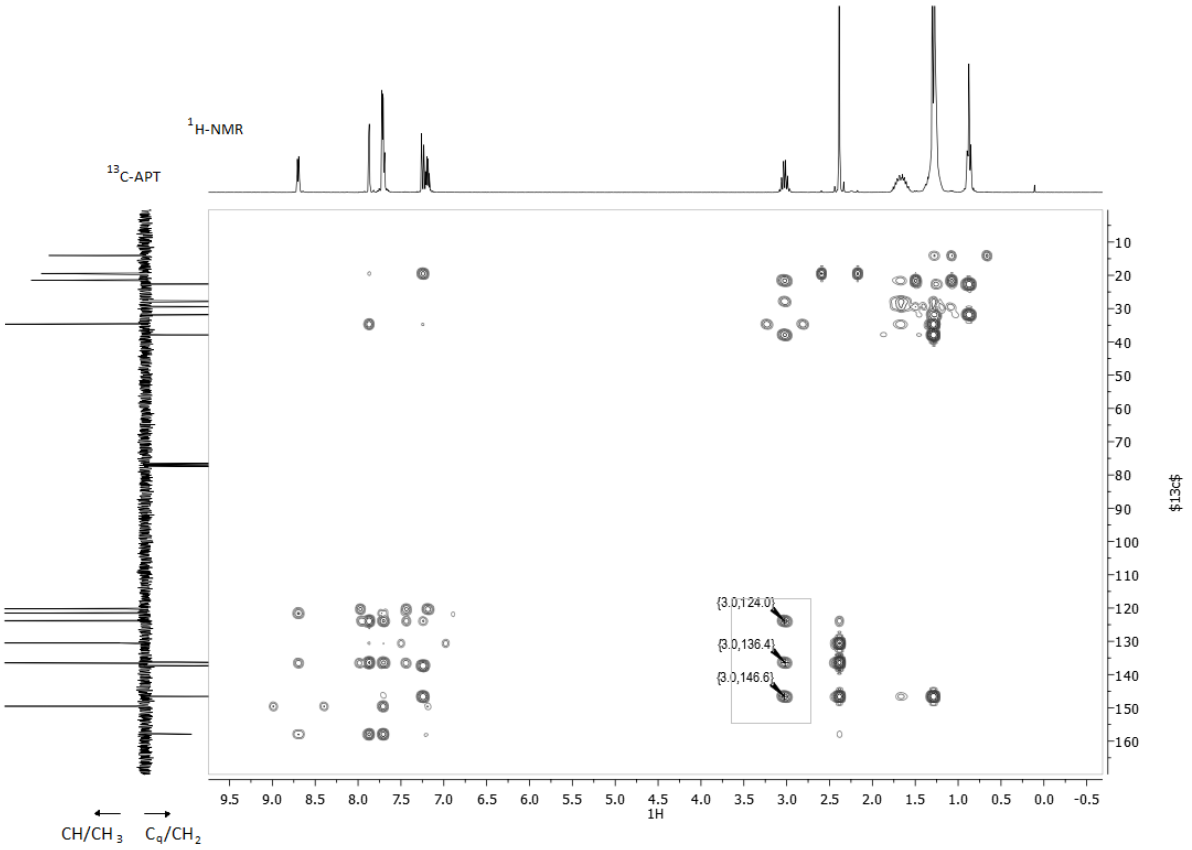

N
n-Pr
CF3
Me

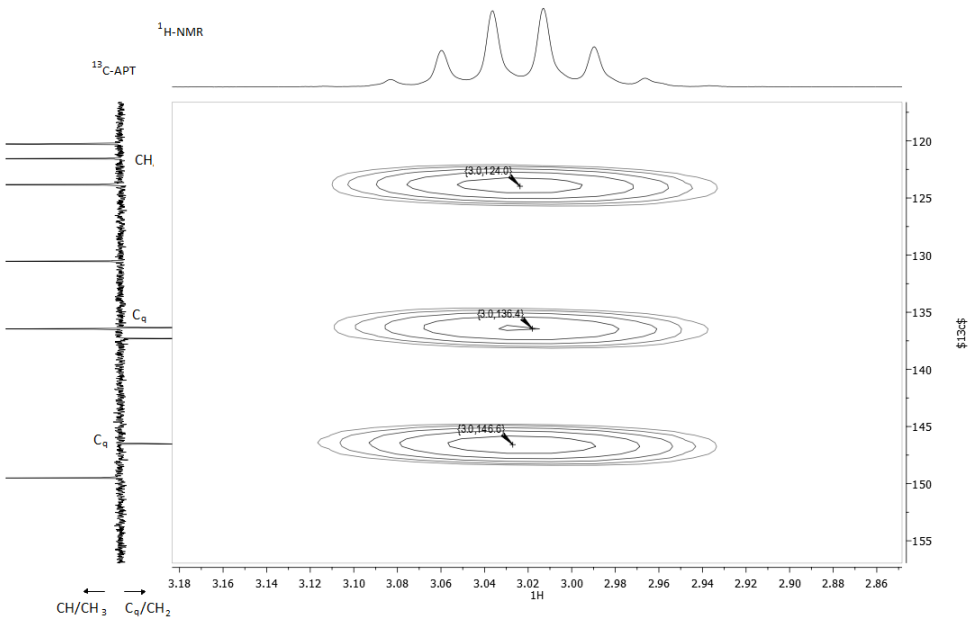

1H-NMR
13C-APT
{3.2,128.5}
{3.2,126.0}
{3.2,147.9}
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
CH
Cq
Cq
{3.2,126.0}
{3.2,128.5}
{3.2,147.9}
CH/CH3
Cq/CH2
1H
$13c$

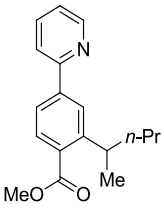
HMBC 147oa

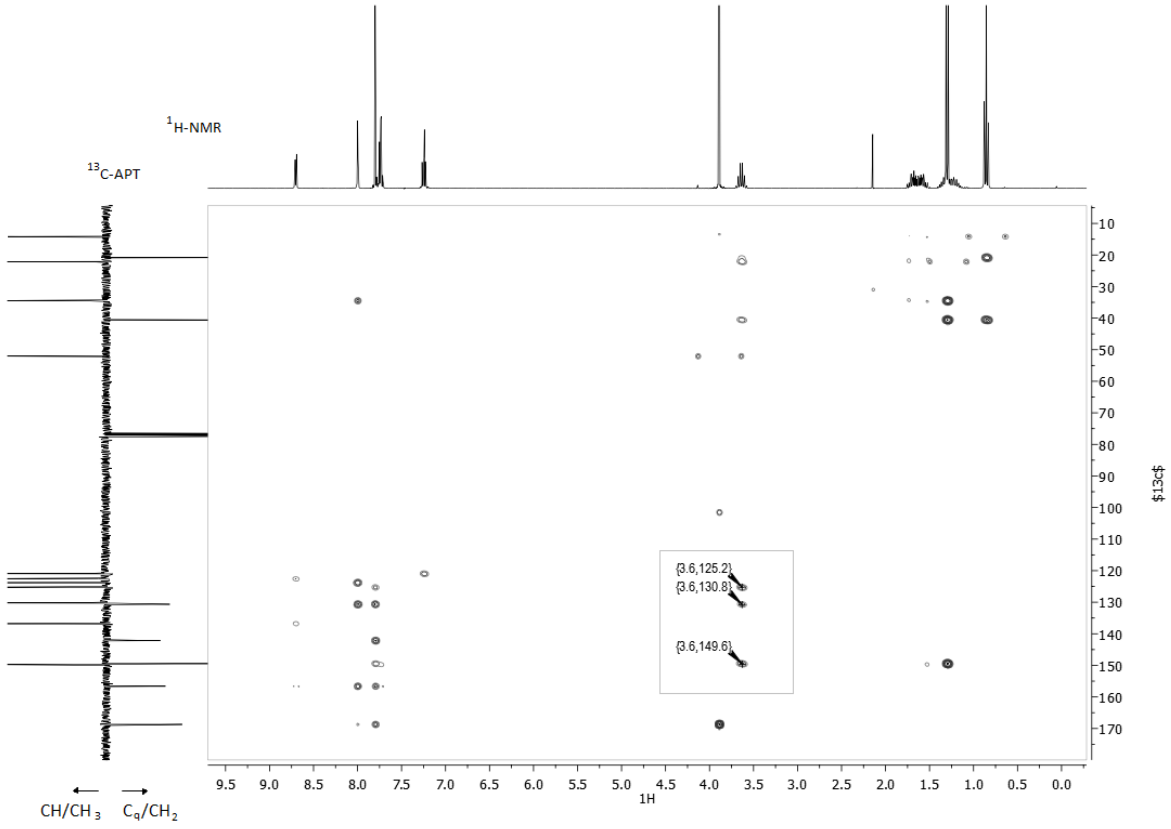

N
n-Hex
Me
Me

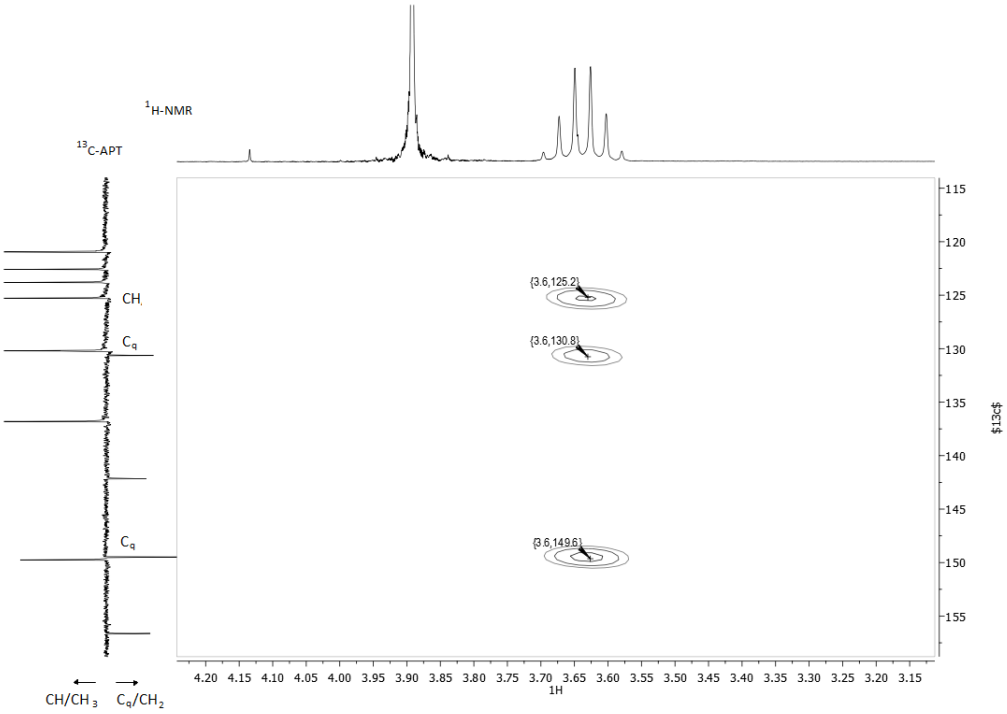

1H-NMR
13C-APT
{3.0,124.0}
{3.0,136.4}
{3.0,146.6}
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
CH
Cq
Cq
{3.0,124.0}
{3.0,136.4}
{3.0,146.6}
CH/CH3
Cq/CH2
1H
$13c$

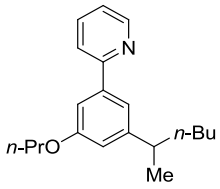
HMBC 147pi

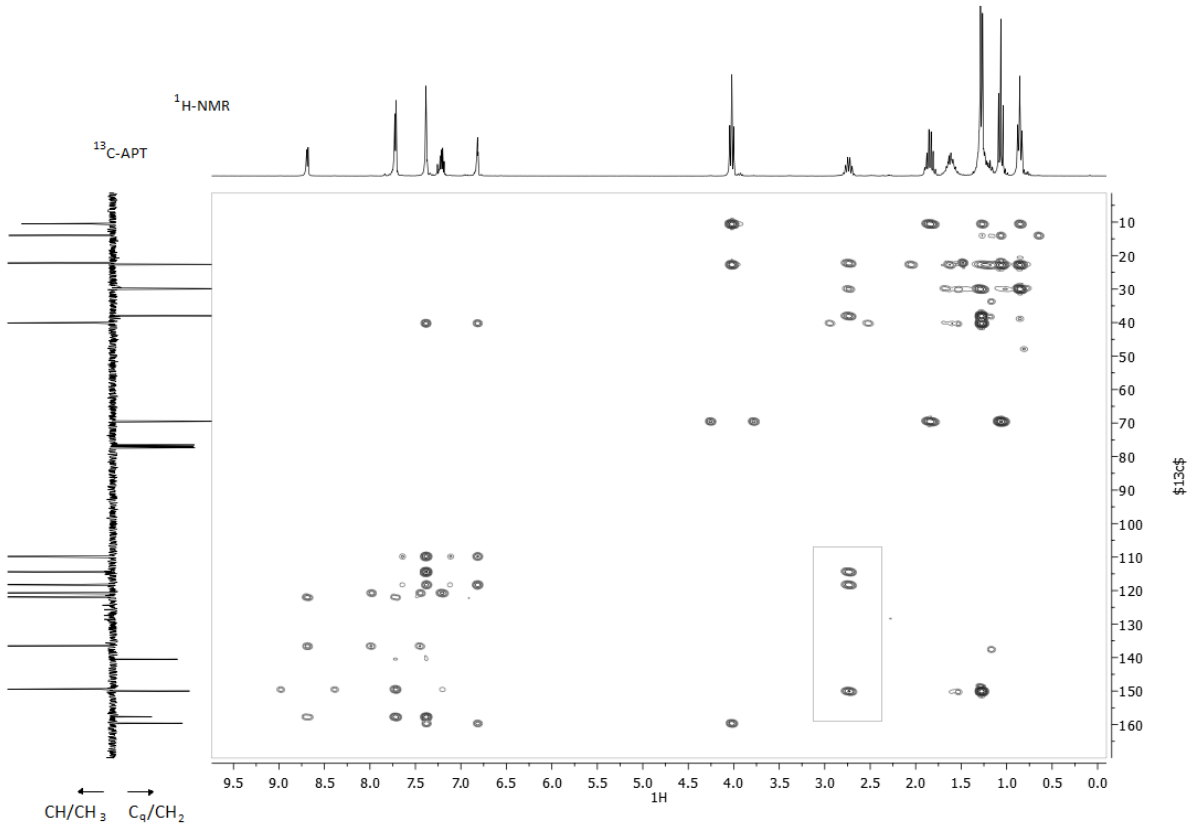

N
n-Pr
Me
MeO
O

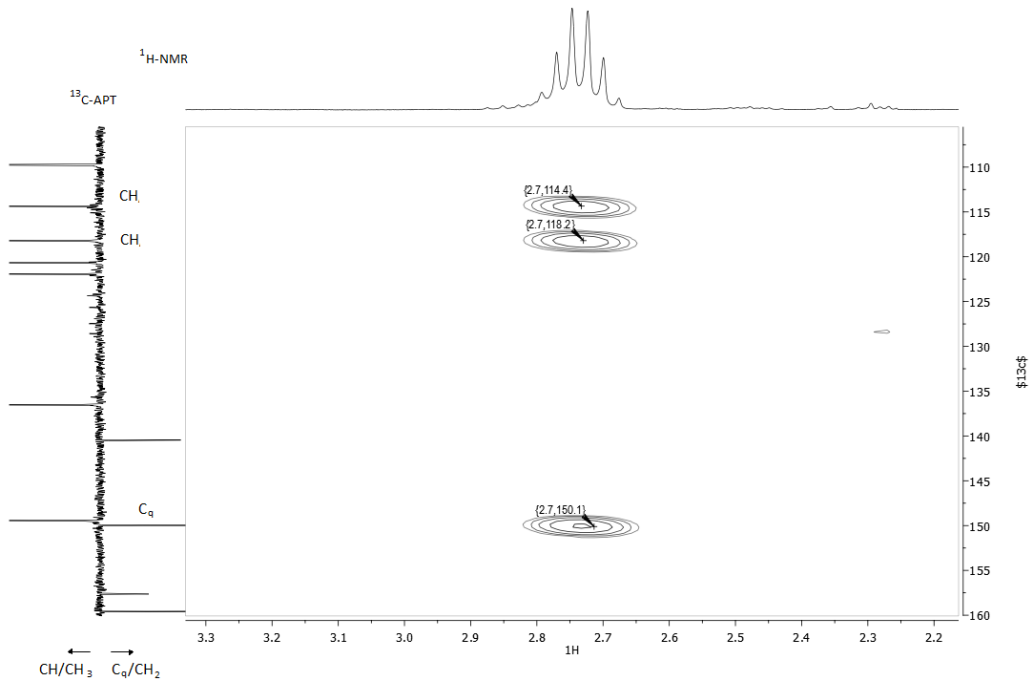

1H-NMR
13C-APT
{3.6,125.2}
{3.6,130.8}
{3.6,149.6}
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
CH
Cq
Cq
{3.6,125.2}
{3.6,130.8}
{3.6,149.6}
CH/CH3
Cq/CH2
1H
$13c$

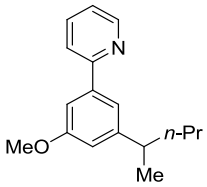
HMBC 147si

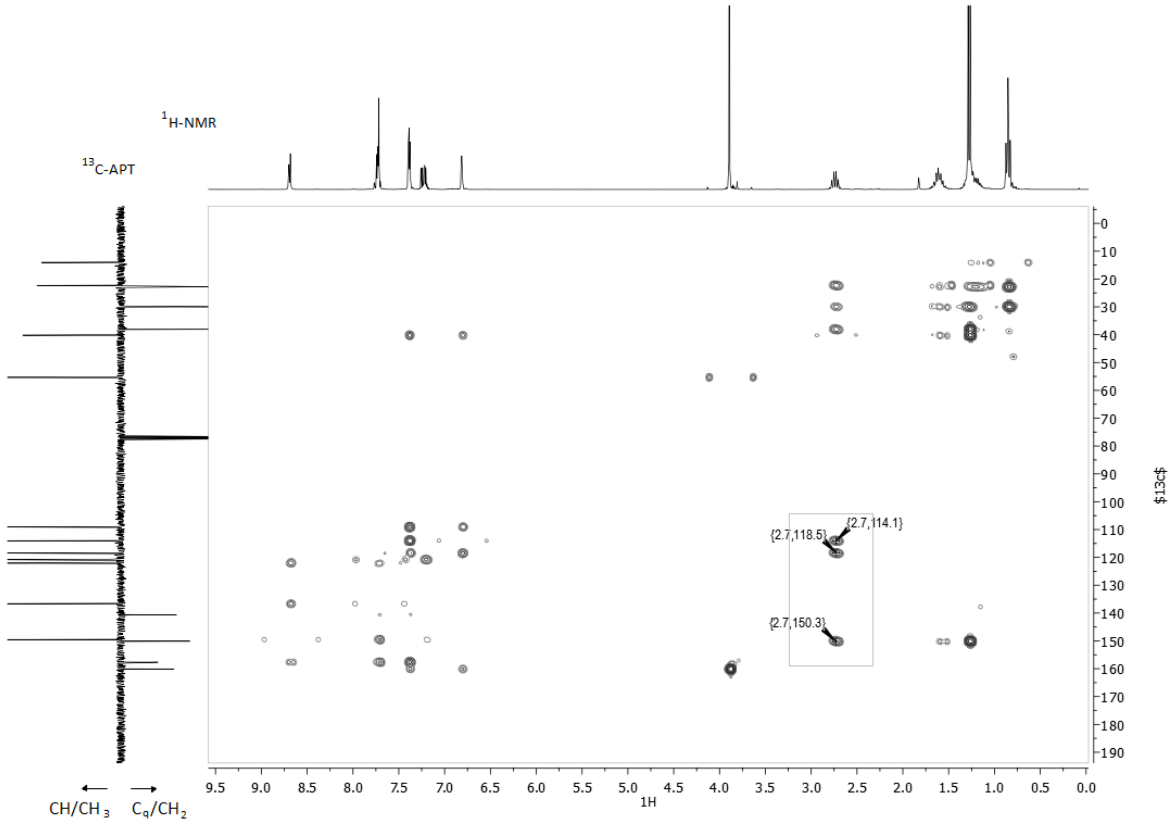

N
n-PrO
n-Bu
Me

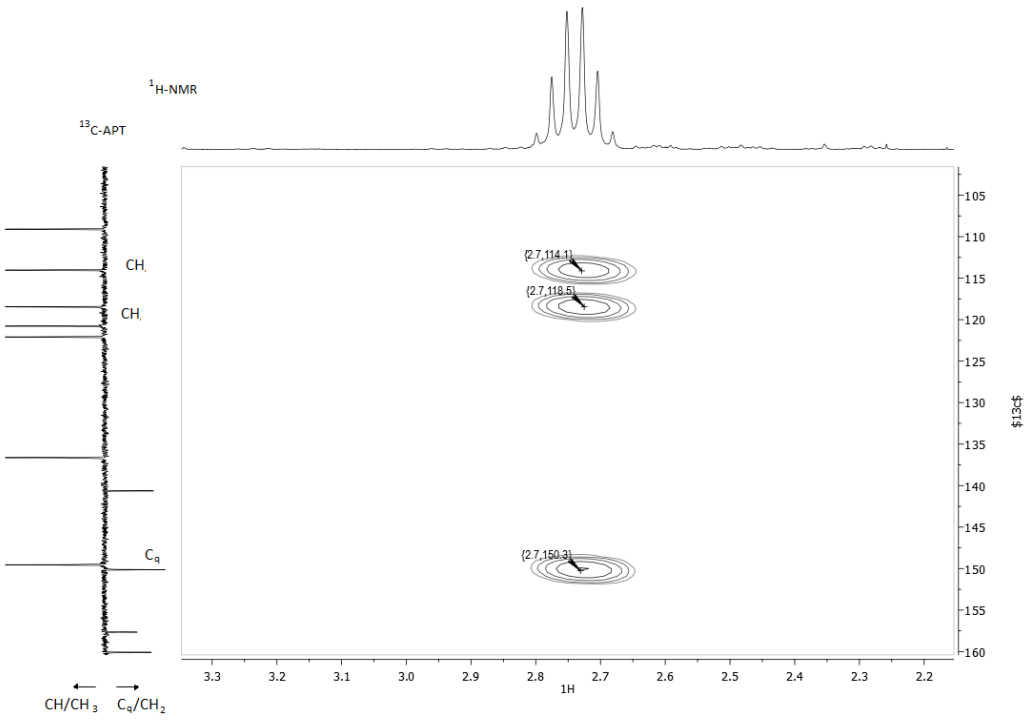

1H-NMR
13C-APT
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
CH
CH
Cq
(2.7,114.4)
(2.7,118.2)
(2.7,150.1)
CH/CH3
Cq/CH2
1H
$13c$

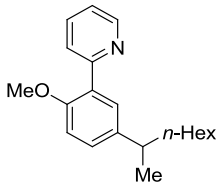
HMBC 147ui

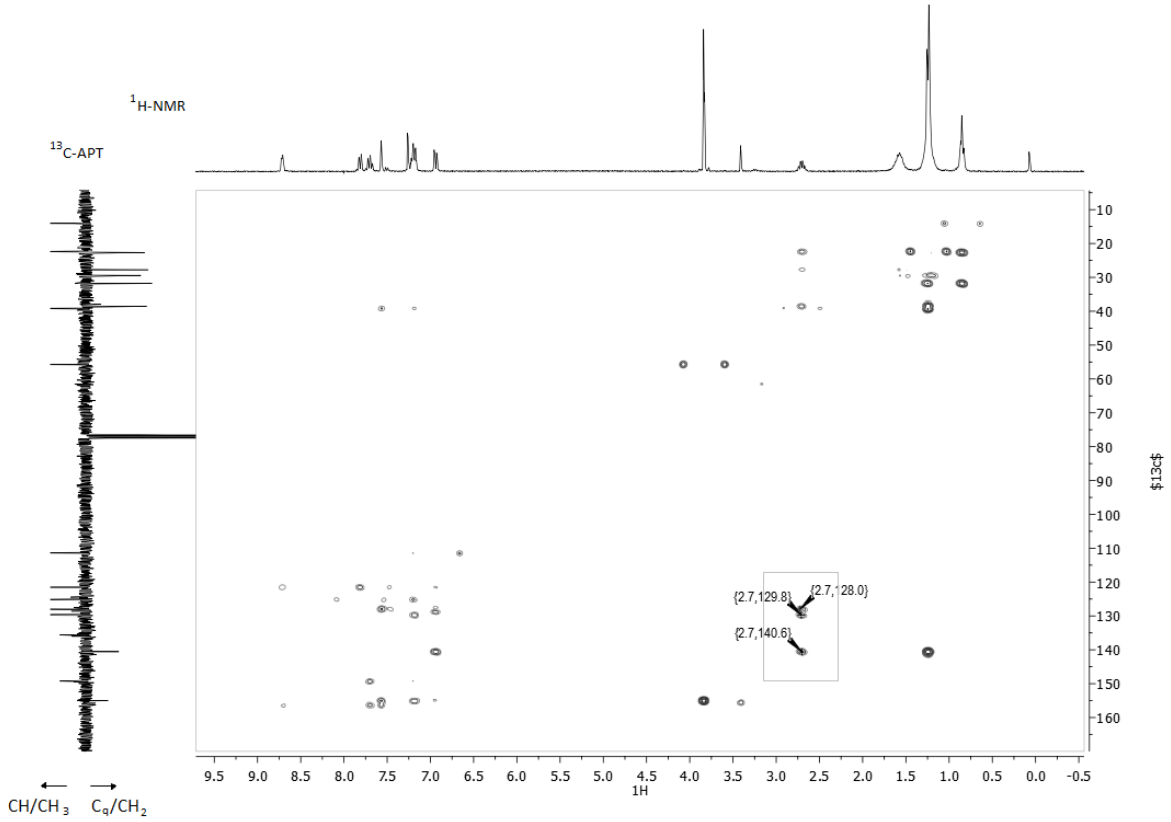

N
MeO
n-Pr
Me

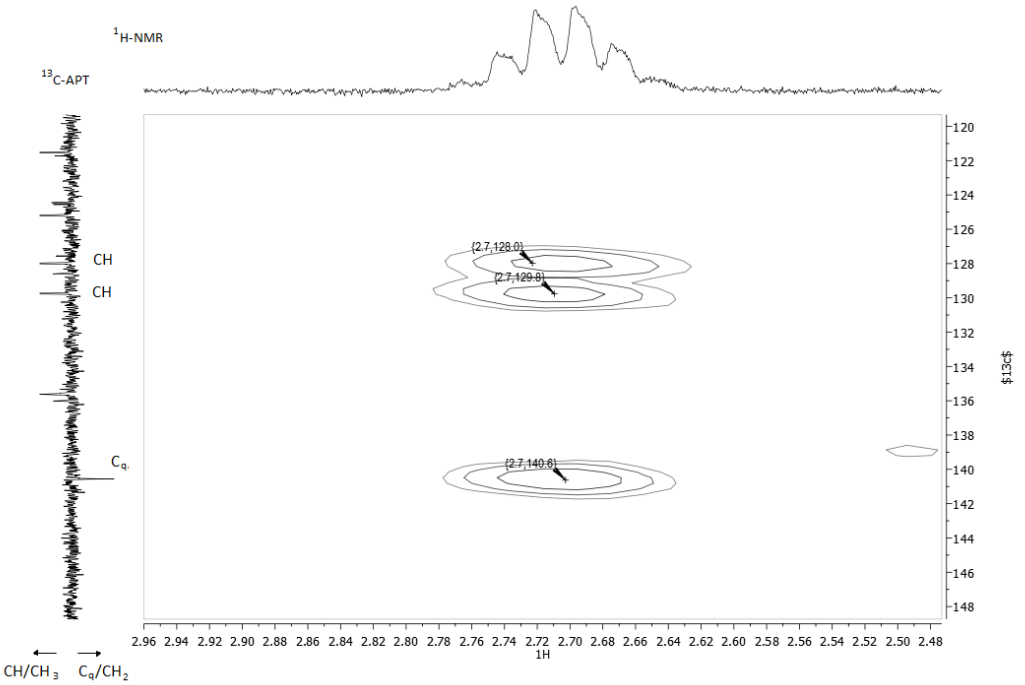

1H-NMR
13C-APT
{2.7,118.5}
{2.7,114.1}
{2.7,150.3}
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
CH
CH
Cq
{2.7,114.1}
{2.7,118.5}
{2.7,150.3}
CH/CH3
Cq/CH2
1H
$13c$

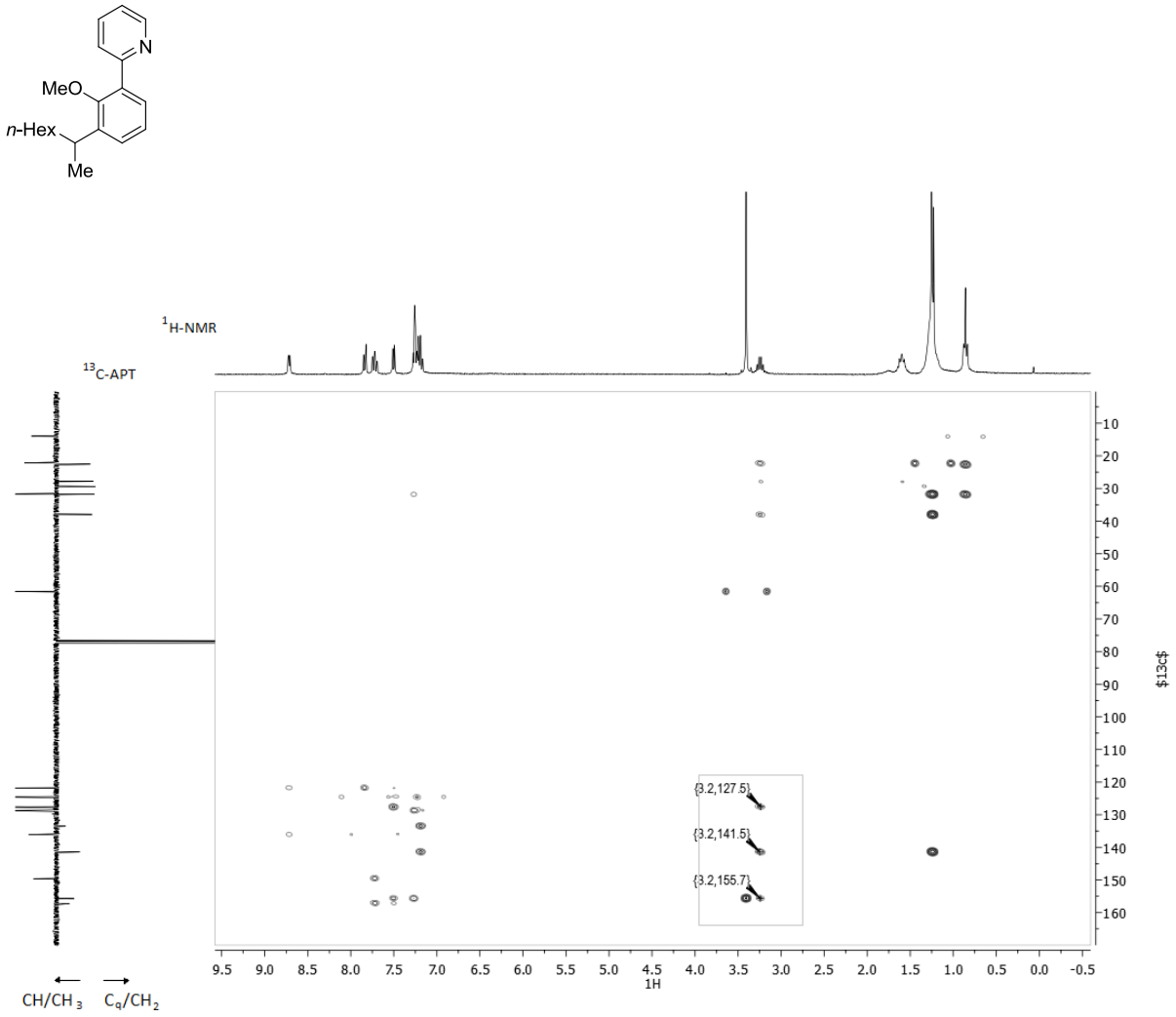
HMBC 147wa

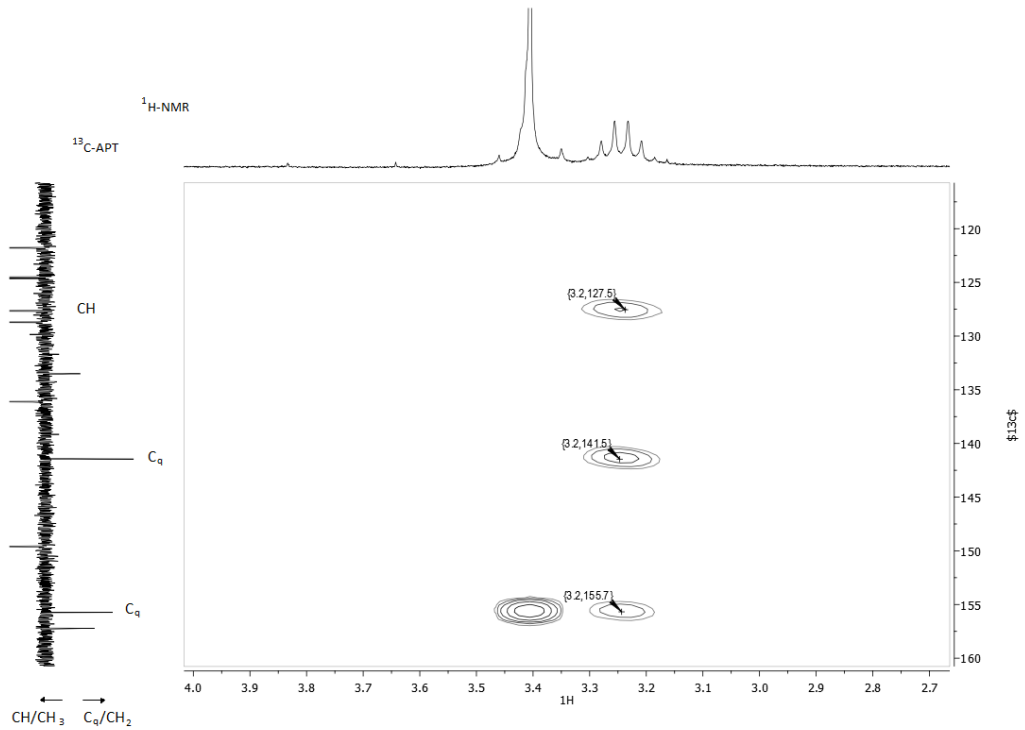

N
MeO
n-Hex
Me


1H-NMR
13C-APT
{2.7,129.8}
{2.7,140.6}
1H
$13c$
CH/CH3
Cq/CH2


1H-NMR
13C-APT
{2.7,128.0}
{2.7,129.8}
{2.7,140.6}
CH
CH
Cq
1H
$13c$
CH/CH3
Cq/CH2

HMBC 147wa‘


N
MeO
n-Hex
Me
1H-NMR
13C-APT
{3.2,127.5}
{3.2,141.5}
{3.2,155.7}
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
CH
Cq
Cq
{3.2,127.5}
{3.2,141.5}
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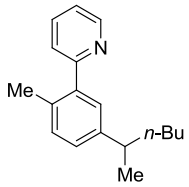
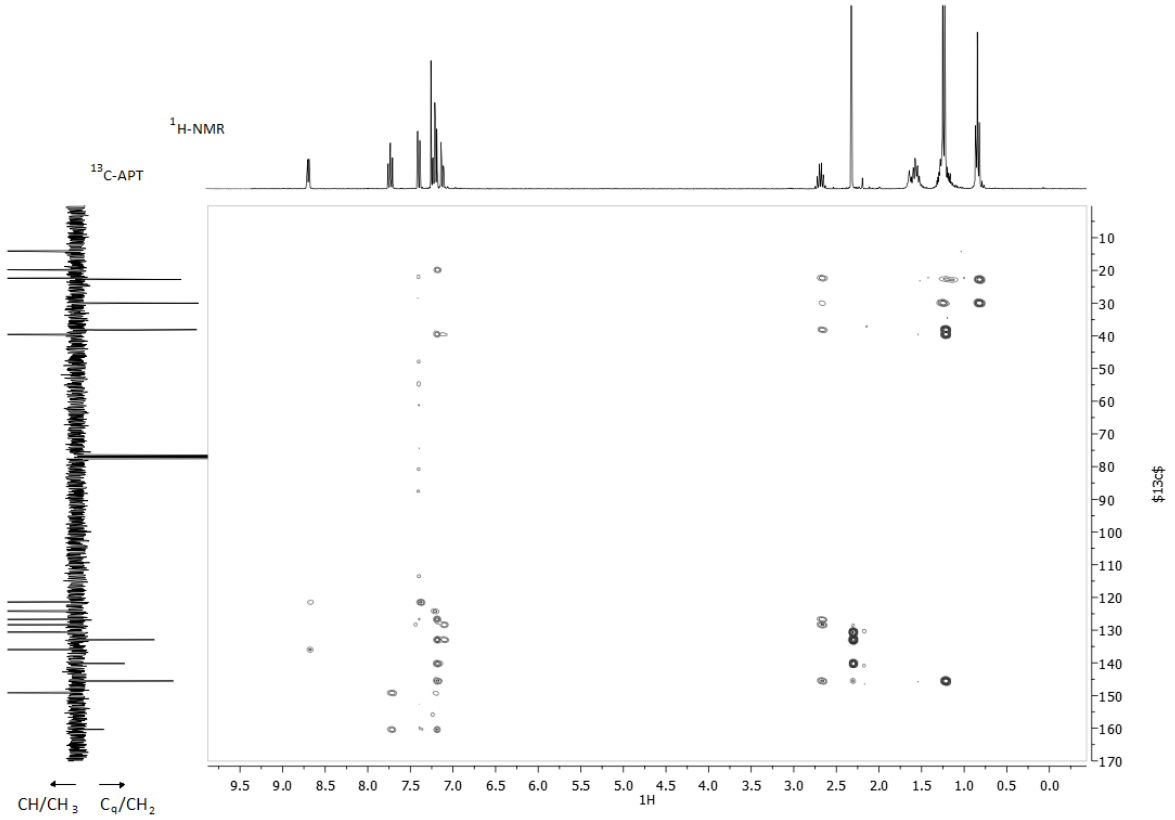
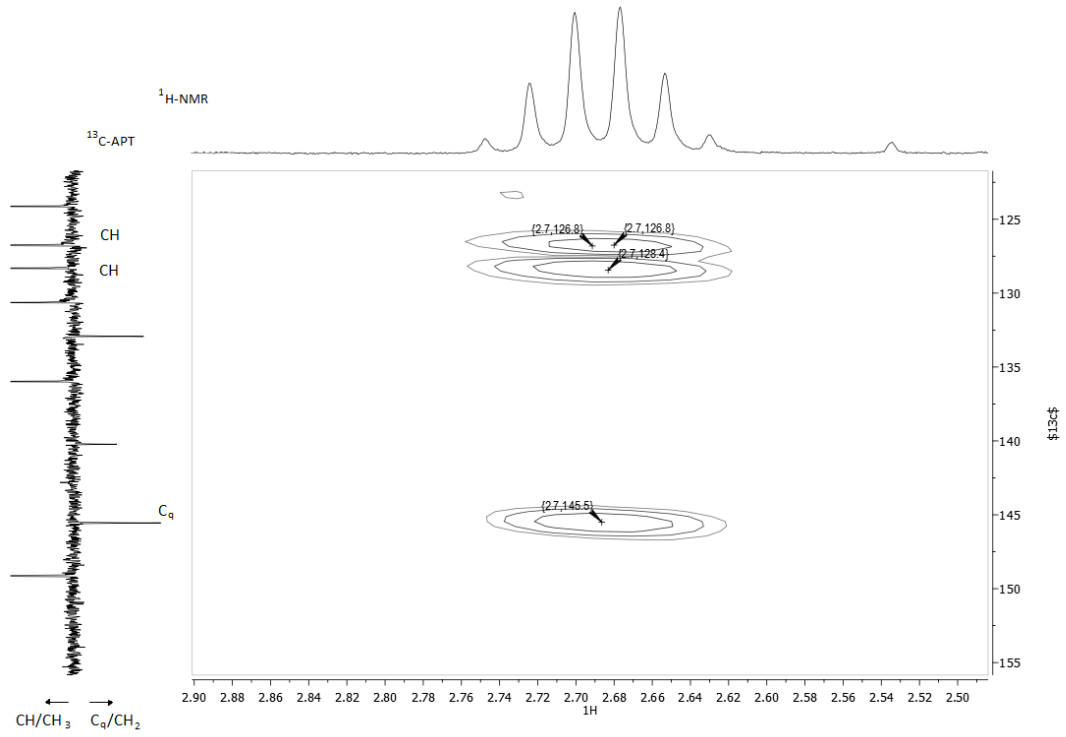
CH/CH3
Cq/CH2
1H
$13c$

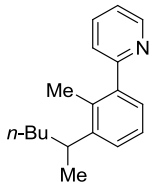
HMBC 147xa

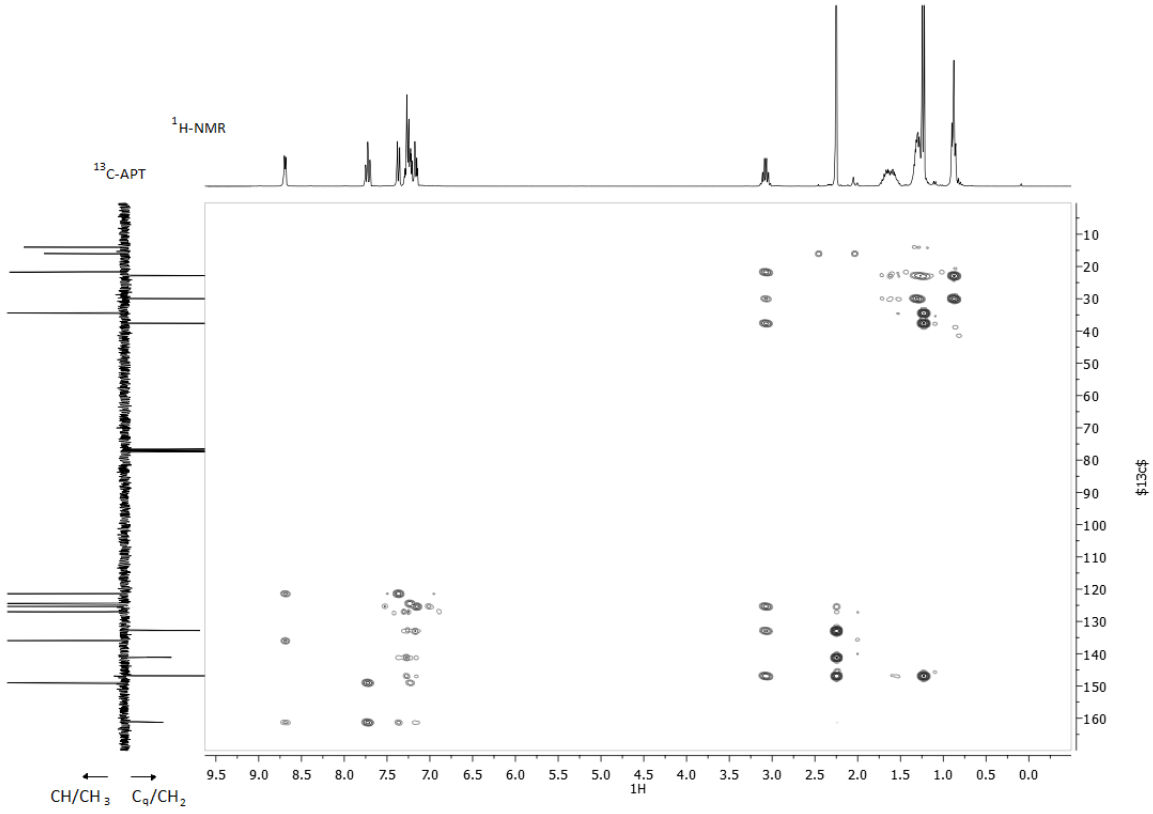

N
Me
n-Bu
Me

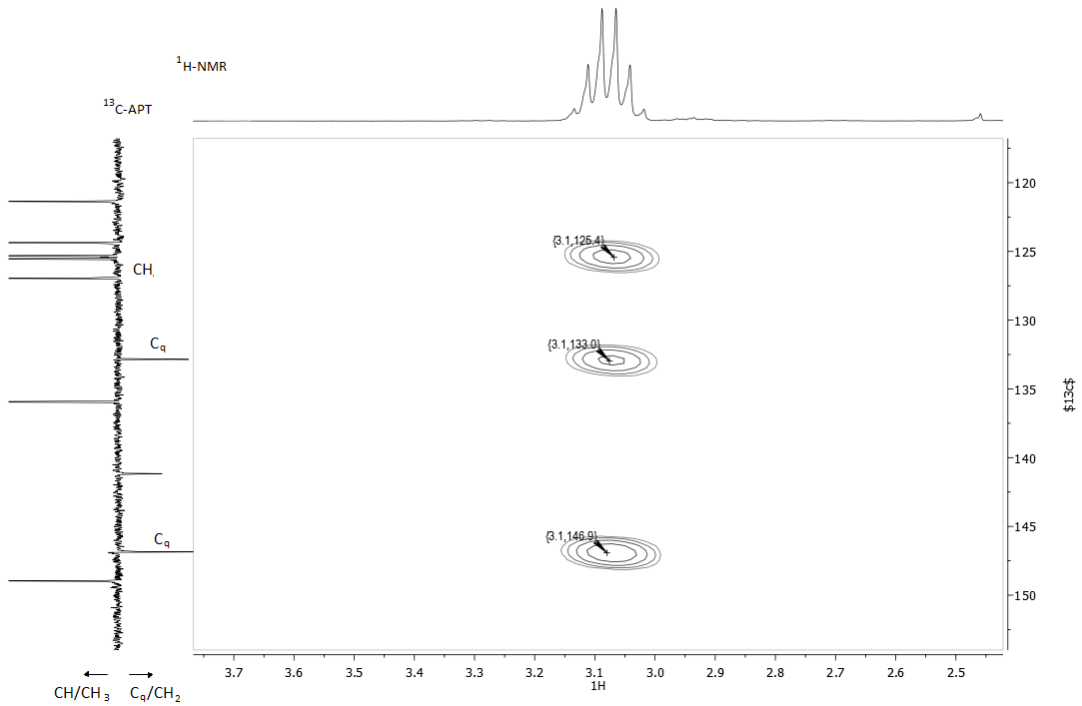

1H-NMR
13C-APT
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
CH
CH
Cq
{2.7,126.8}
{2.7,126.8}
{2.7,128.4}
{2.7,145.5}
CH/CH3
Cq/CH2
1H
$13c$

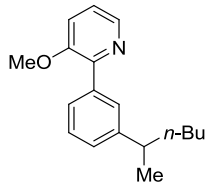
HMBC 147xa'

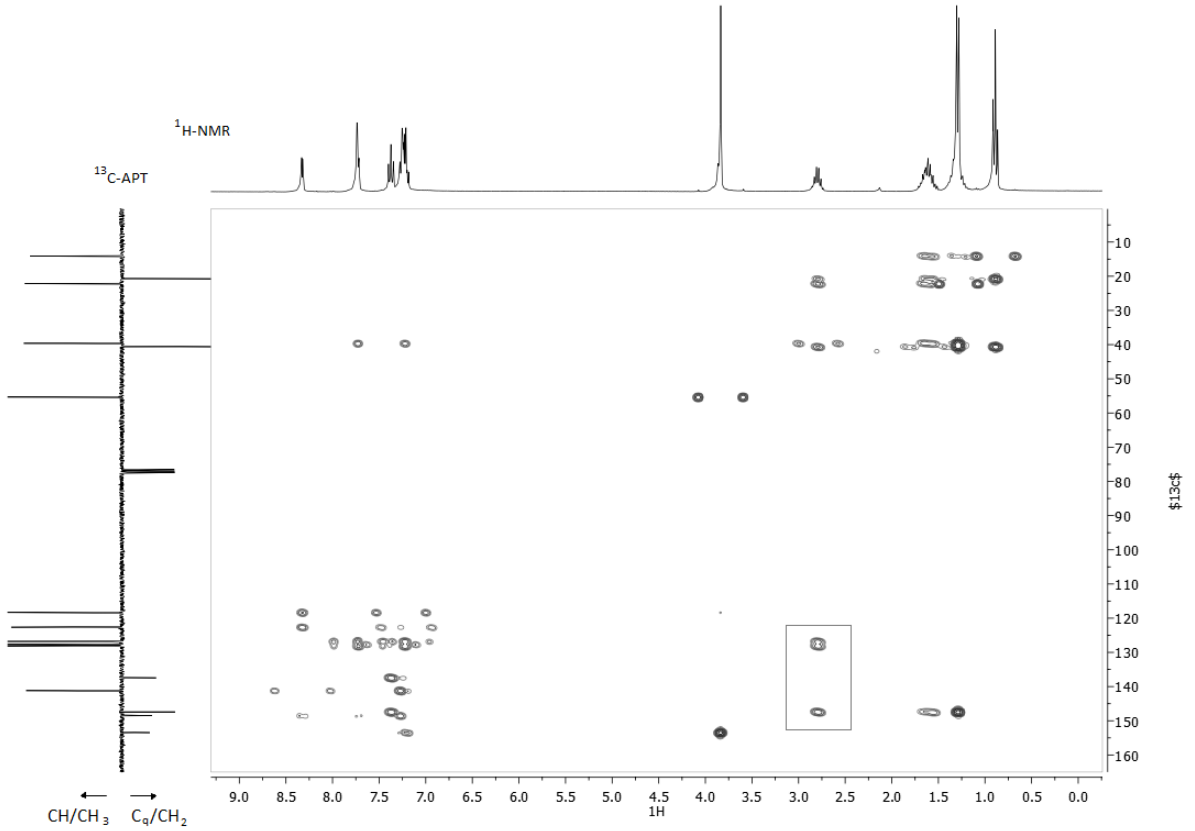

N
Me
n-Bu
Me

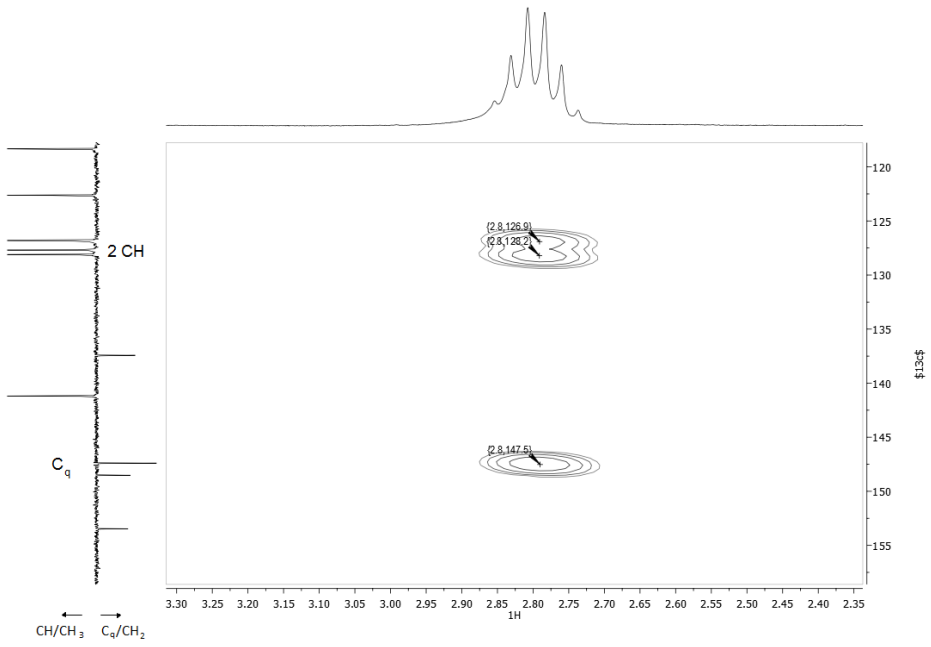

1H-NMR
13C-APT
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
CH
Cq
Cq
{3.1,125.4}
{3.1,133.0}
{3.1,146.9}
CH/CH3
Cq/CH2
1H
$13c$

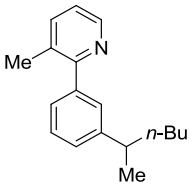
HMBC 152cj

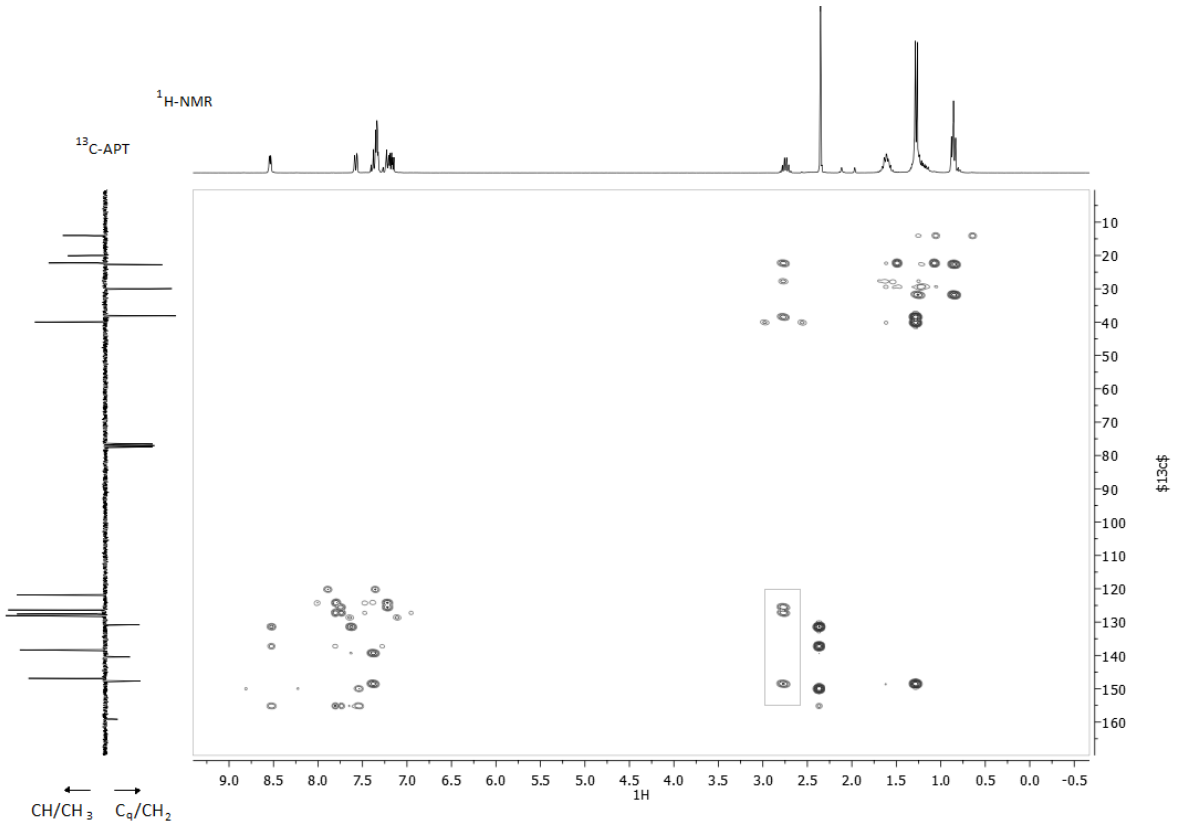

MeO
N
n-Bu
Me

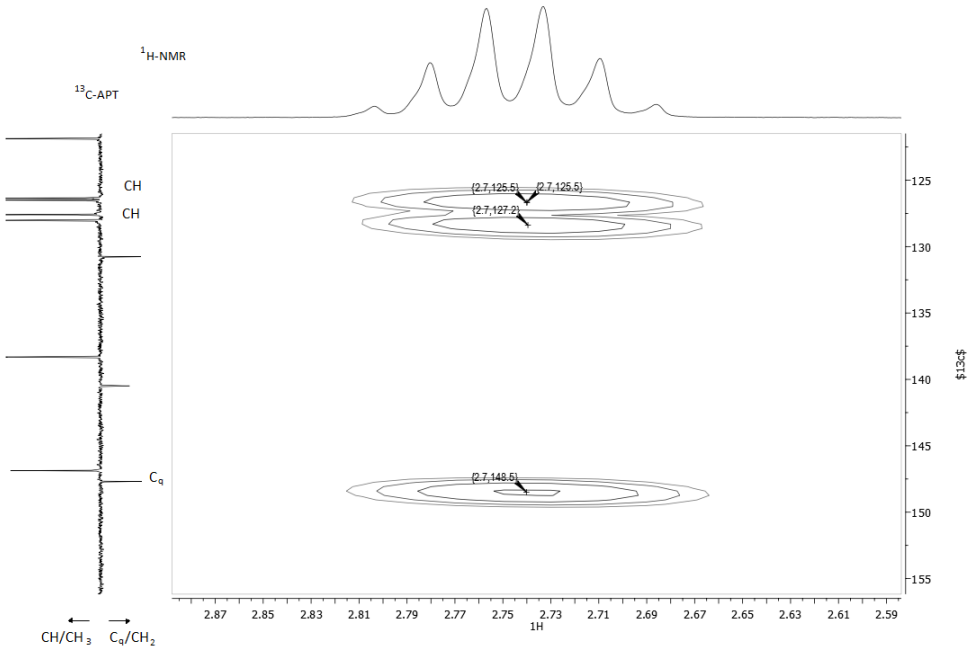

1H-NMR
13C-APT
CH/CH3
Cq/CH2
1H
$13c$


2 CH
Cq
CH/CH3
Cq/CH2
1H
$13c$

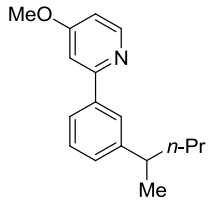
HMBC 152dj

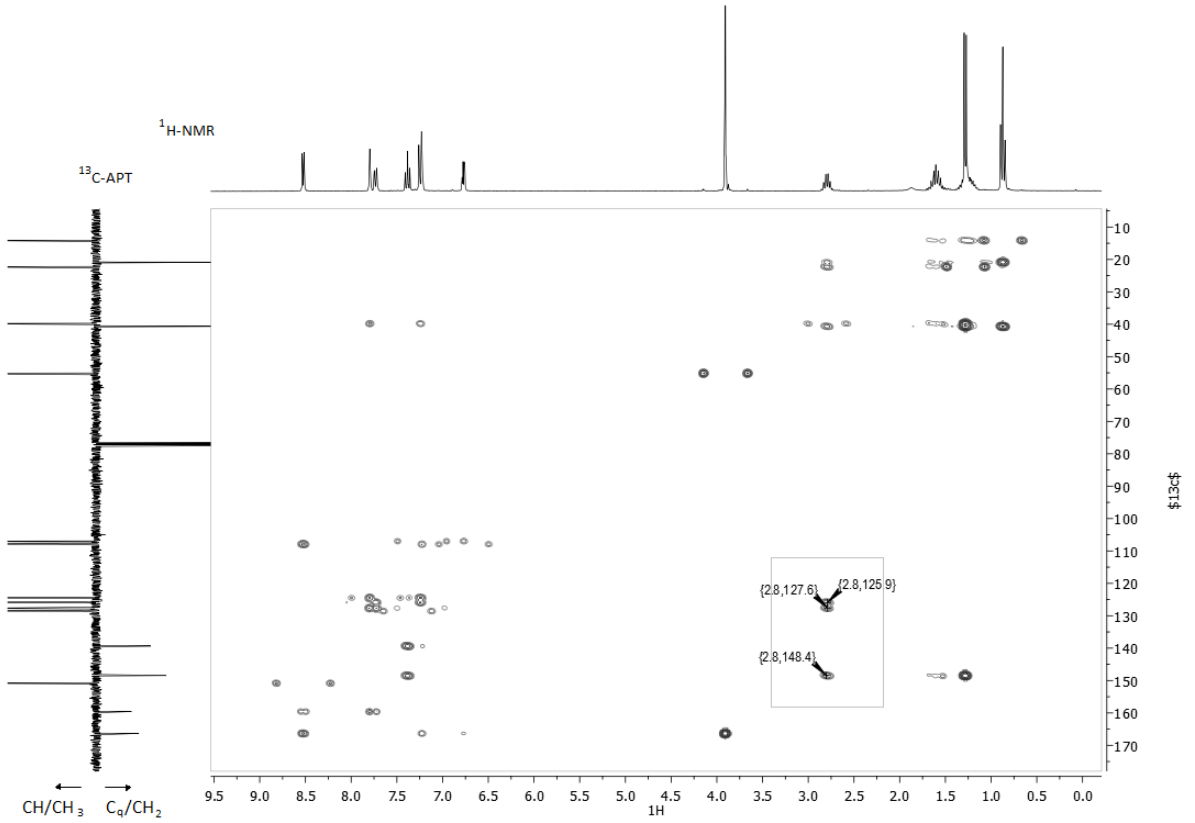

Me
N
n-Bu
Me

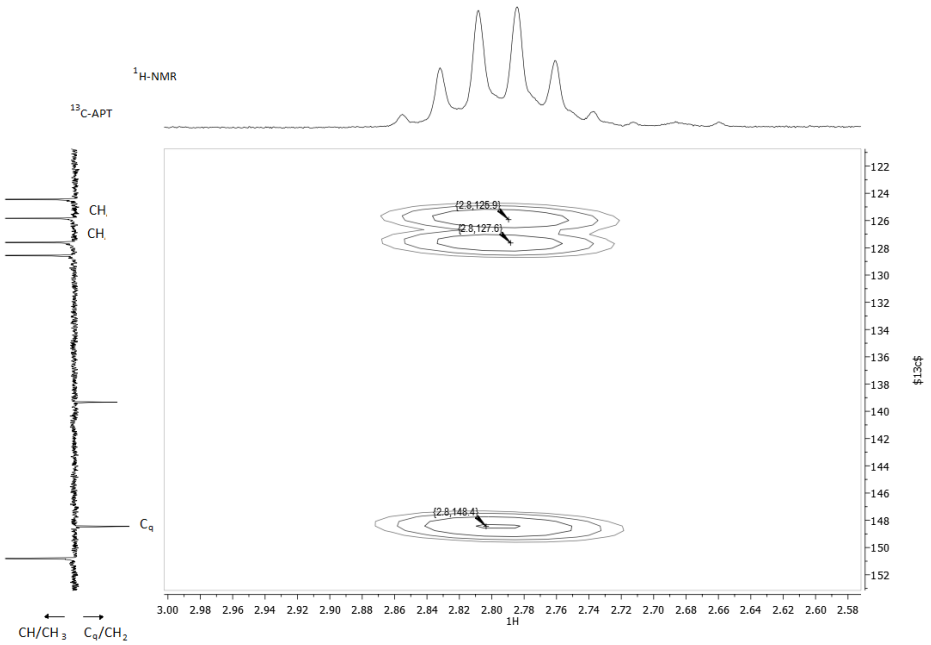

1H-NMR
13C-APT
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
CH
CH
Cq
CH/CH3
Cq/CH2
1H
$13c$

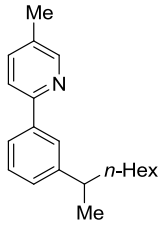
HMBC 152gi

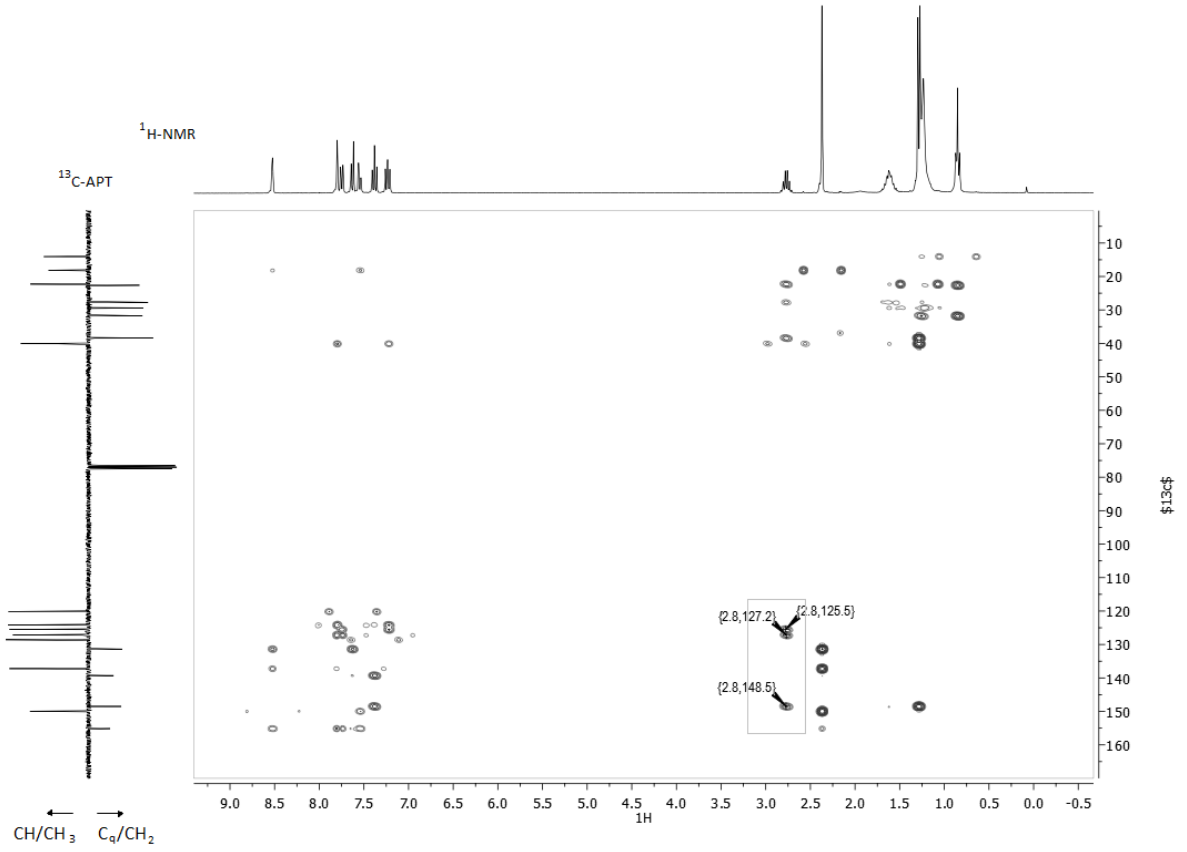

MeO
N
n-Pr
Me

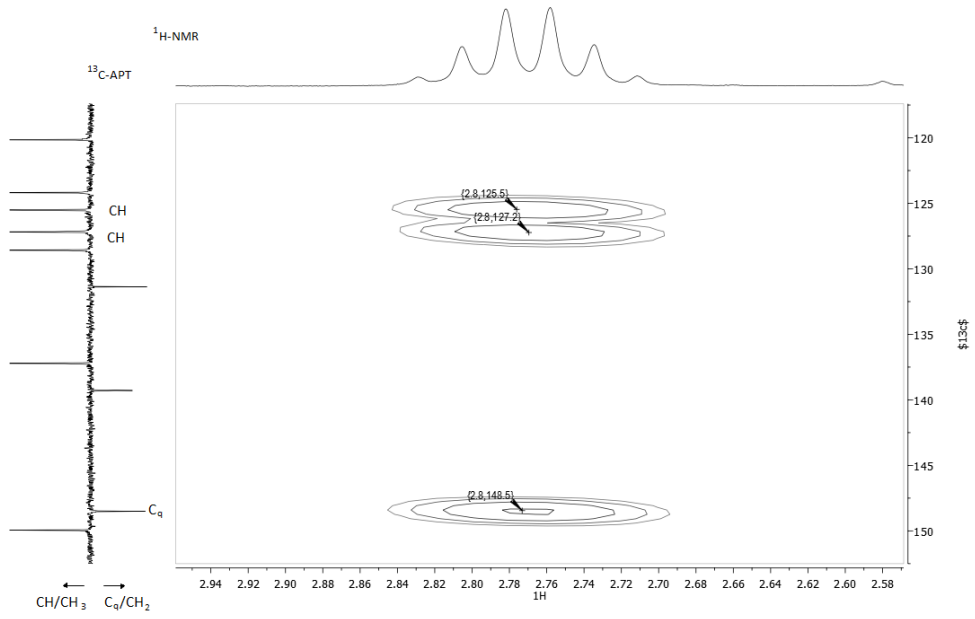

1H-NMR
13C-APT
{2,8,127.6}
{2,8,125.9}
{2,8,148.4}
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
{2,8,126.6}
{2,8,127.6}
{2,8,148.4}
CH
CH
Cq
CH/CH3
Cq/CH2
1H
$13c$

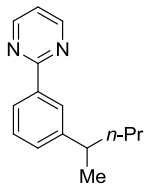
HMBC 152fa


Me
N
n-Hex
Me


1H-NMR
13C-APT
{2.8,127.2}
{2.8,125.5}
{2.8,148.5}
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
CH
CH
Cq
{2.8,125.5}
{2.8,127.2}
{2.8,148.5}
CH/CH3
Cq/CH2
1H
$13c$

HMBC 154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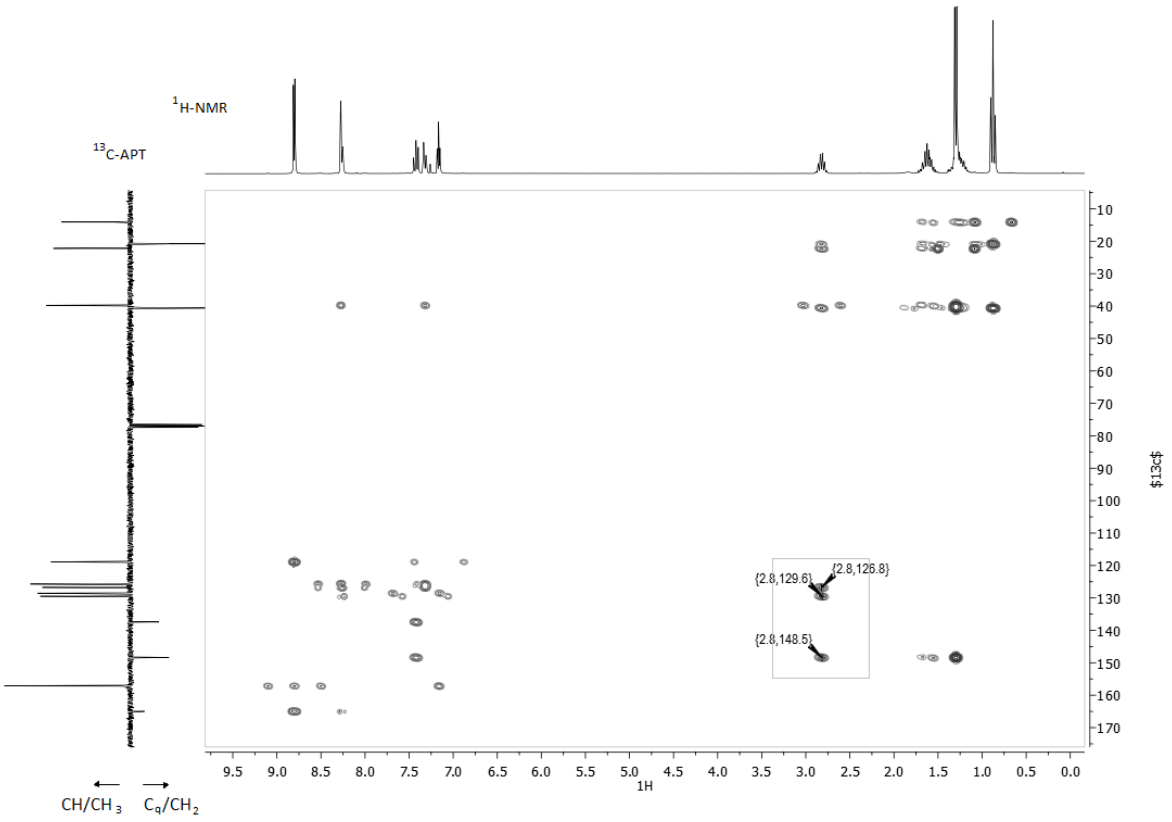
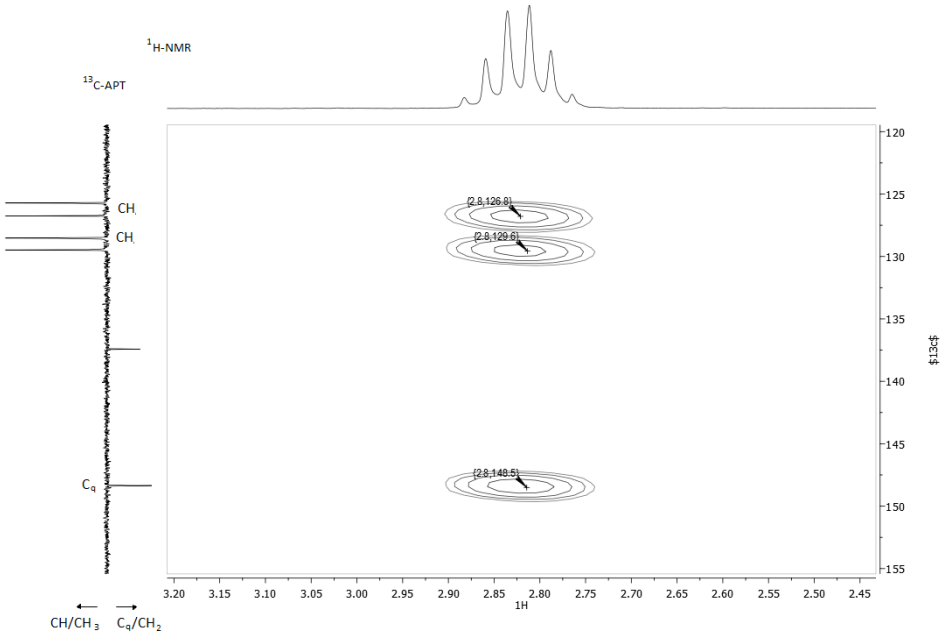
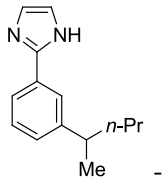
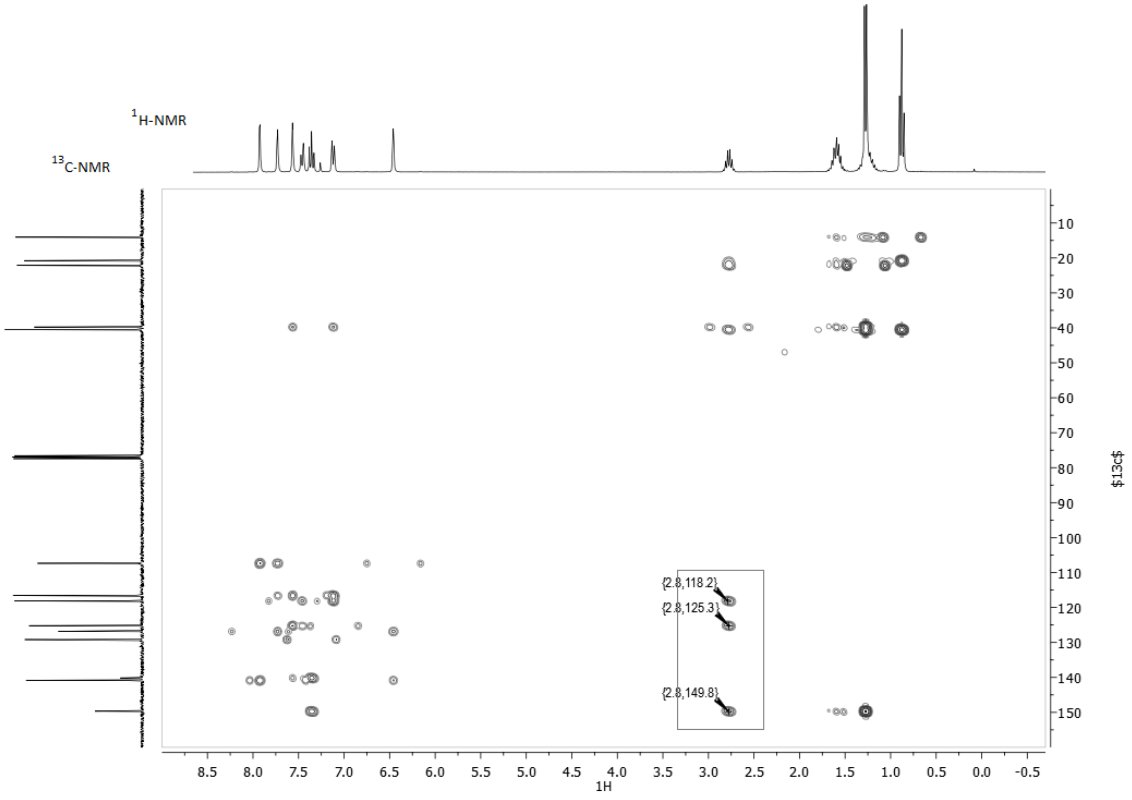
N
n-Pr
Me

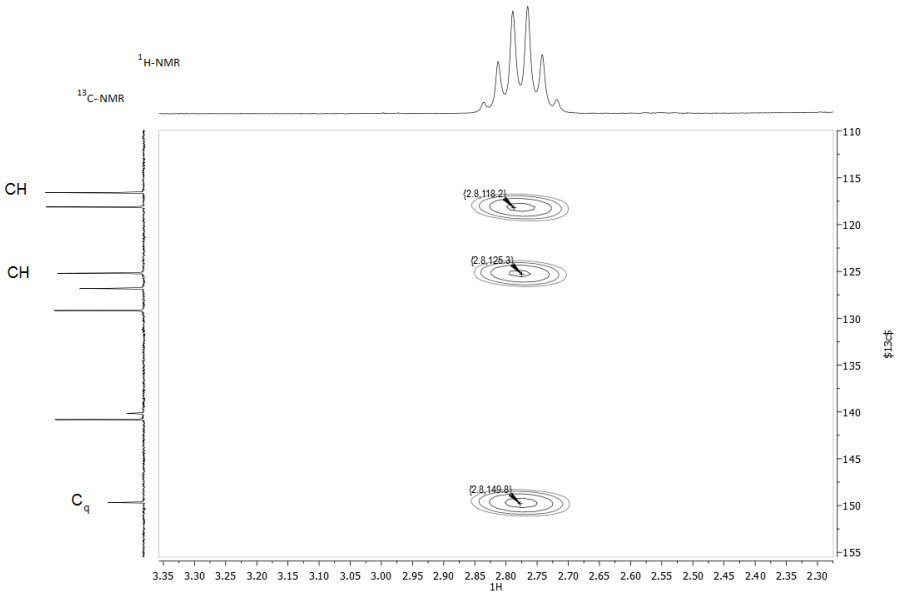

1H-NMR
13C-APT
{2.8,129.6}
{2.8,126.8}
{2.8,148.5}
1H
$13c$
CH/CH3
Cq/CH2


1H-NMR
13C-APT
{2.8,126.8}
{2.8,129.6}
{2.8,148.5}
CH
CH
Cq
1H
$13c$
CH/CH3
Cq/CH2

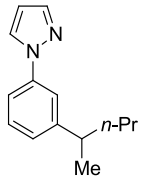
HMBC 155

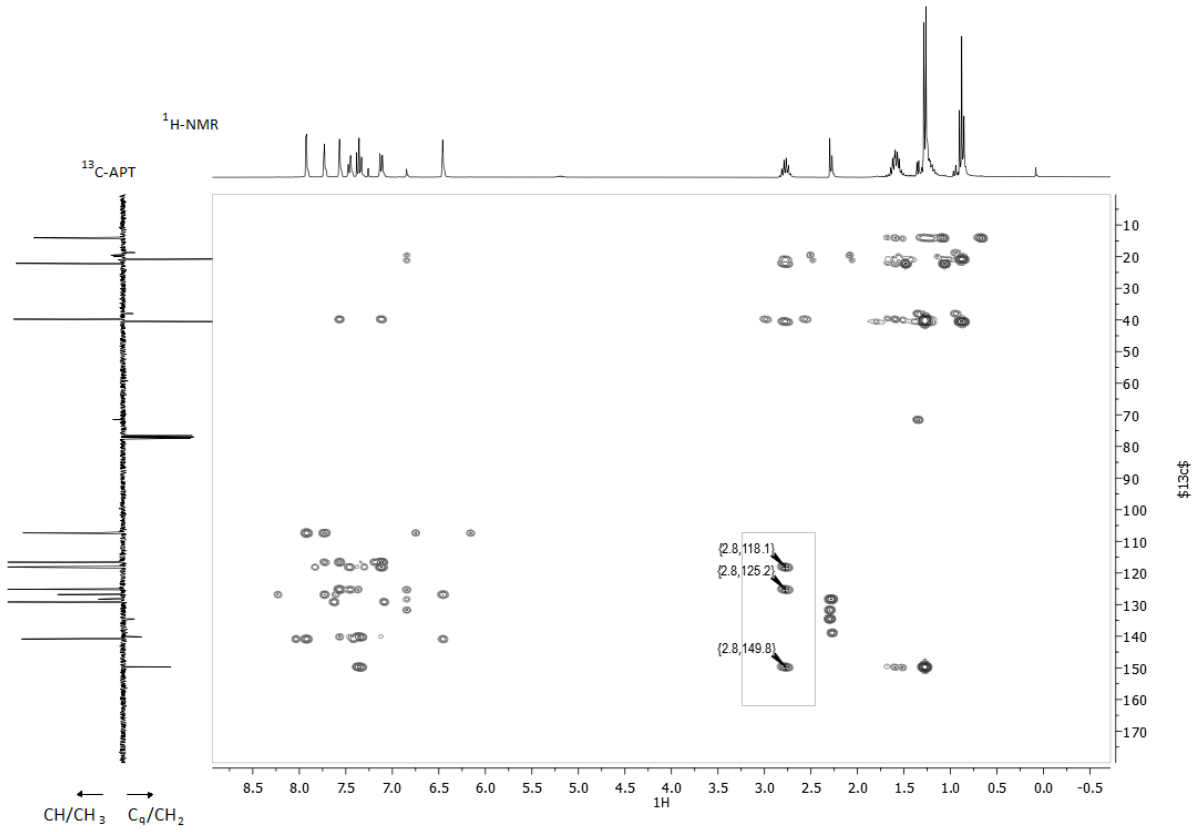

N
NH
n-Pr
Me

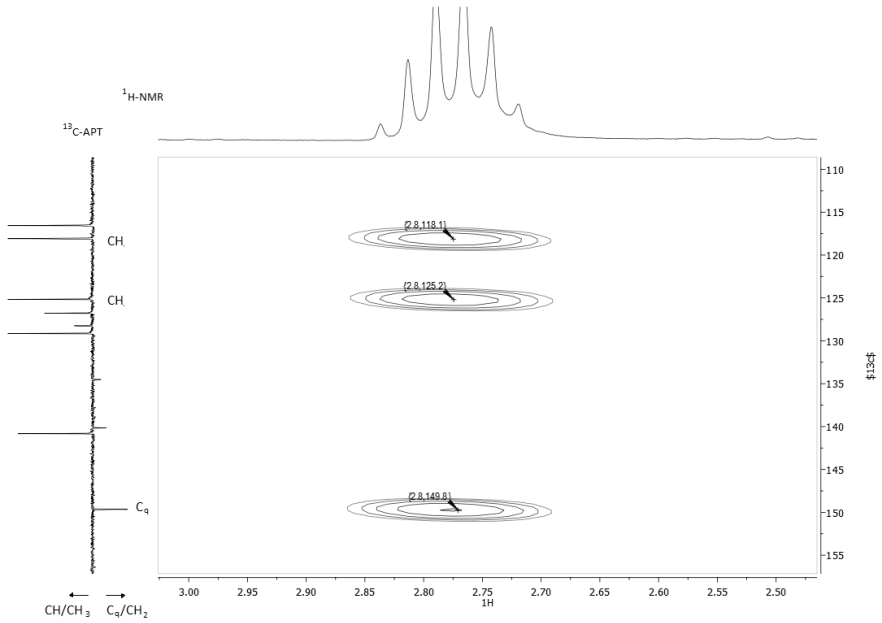

1H-NMR
13C-NMR
{2.8,118.2}
{2.8,125.3}
{2.8,149.8}
1H
$13C$


1H-NMR
13C-NMR
CH
CH
Cq
{2.8,118.2}
{2.8,125.3}
{2.8,149.8}
1H
$13C$

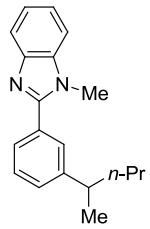
HMBC 156

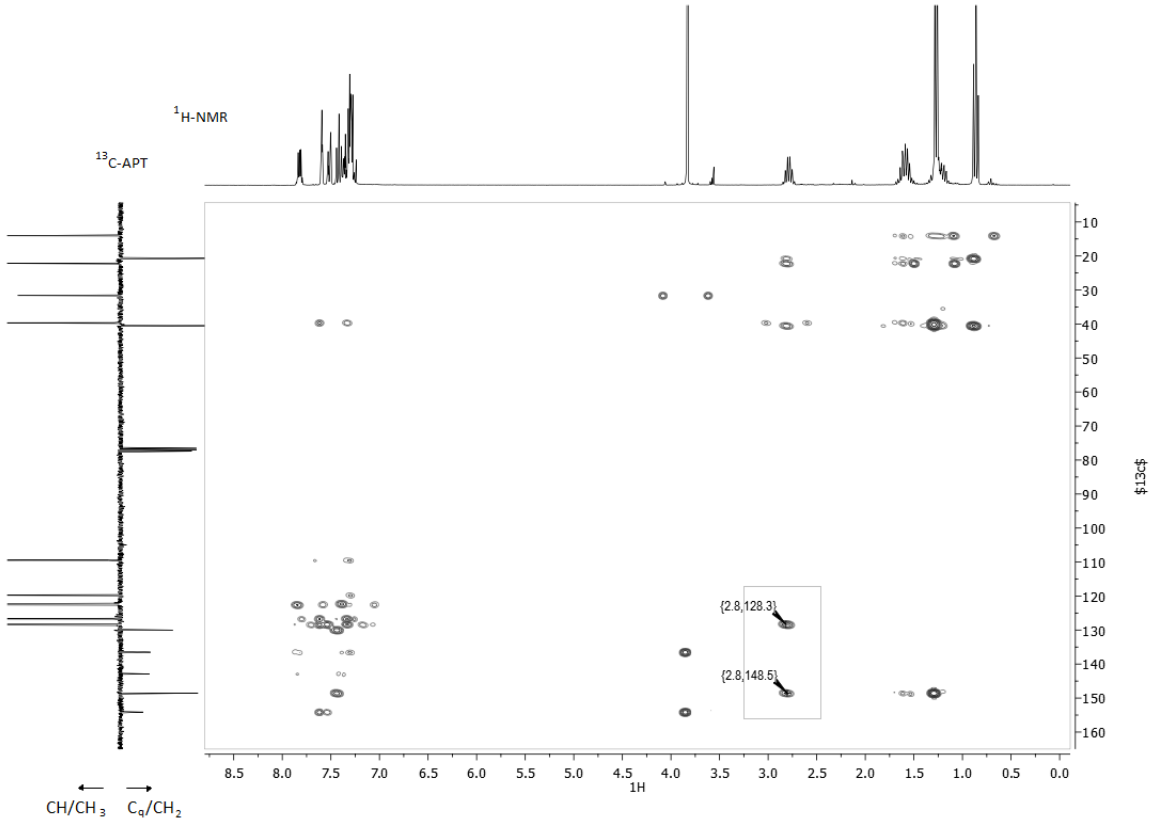

N
N
n-Pr
Me

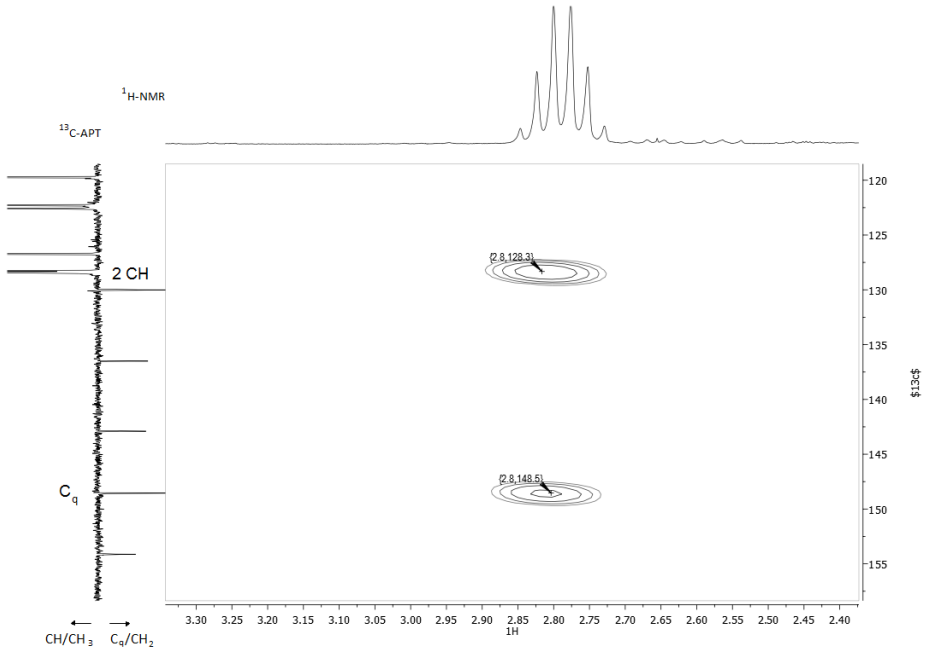

1H-NMR
13C-APT
(2.8,118.1)
(2.8,125.2)
(2.8,149.8)
CH/CH3
Cq/CH2
1H
$13c$


1H-NMR
13C-APT
CH
CH
Cq
(2.8,118.1)
(2.8,125.2)
(2.8,149.8)
CH/CH3
Cq/CH2
1H
$13c$

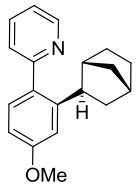
HMBC 157

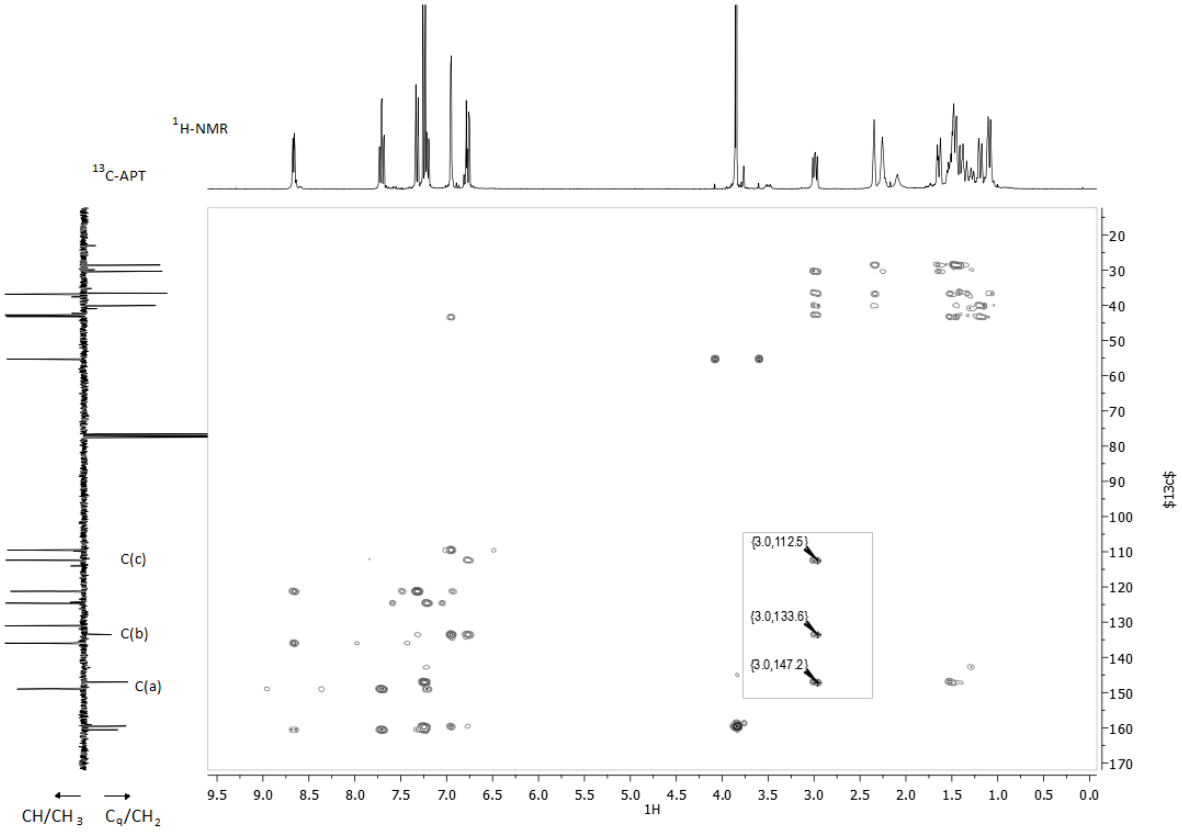

N
N
Me
n-Pr
Me


1H-NMR
13C-APT
{2.8,128.3}
{2.8,148.5}
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
1H
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160
$13c$
CH/CH3 Cq/CH2


1H-NMR
13C-APT
2 CH
Cq
{2.8,128.3}
{2.8,148.5}
3.30 3.25 3.20 3.15 3.10 3.05 3.00 2.95 2.90 2.85 2.80 2.75 2.70 2.65 2.60 2.55 2.50 2.45 2.40
1H
120 125 130 135 140 145 150 155
$13c$
CH/CH3 Cq/CH2

HMBC 93bl


N
H
OMe


1H-NMR
13C-APT
C(c)
C(b)
C(a)
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Cq/CH2
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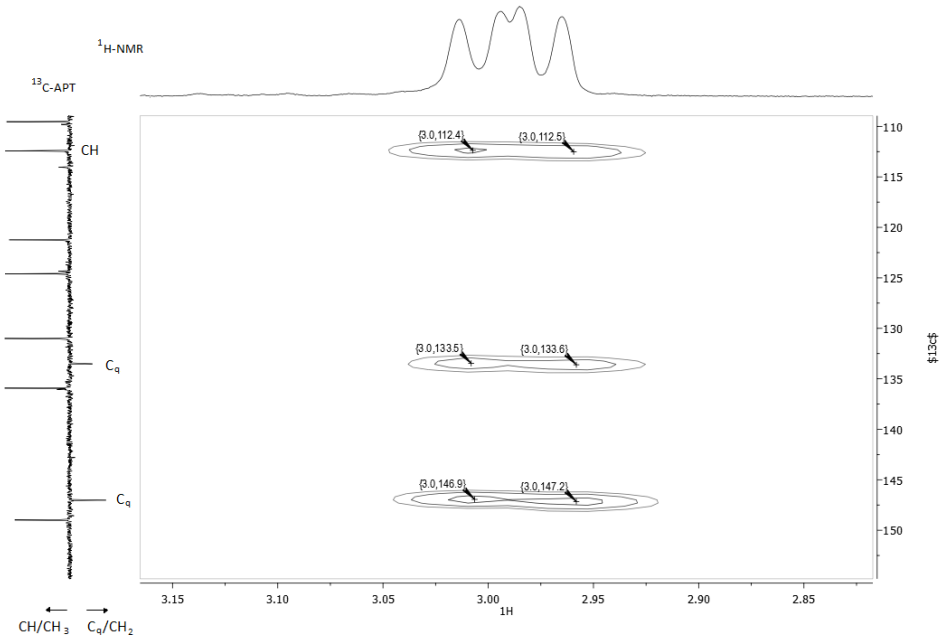
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Cq
Cq
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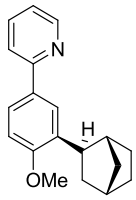
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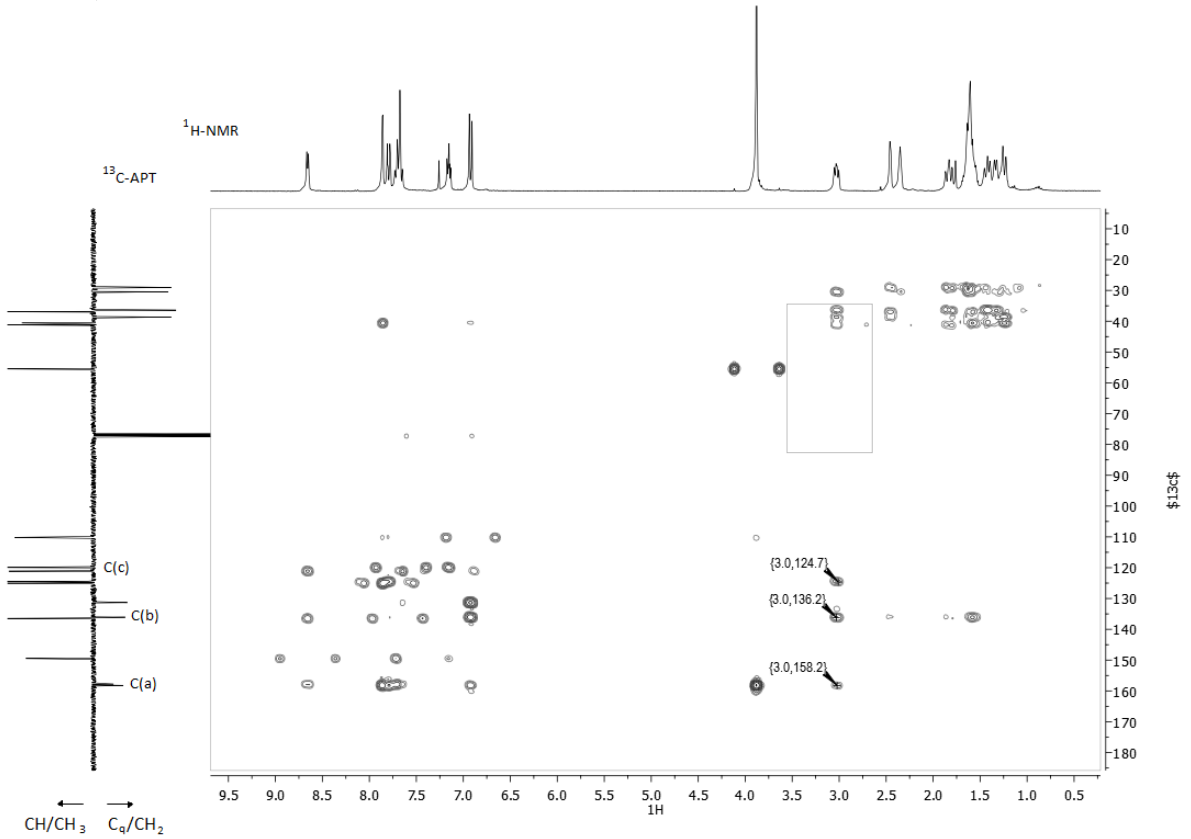
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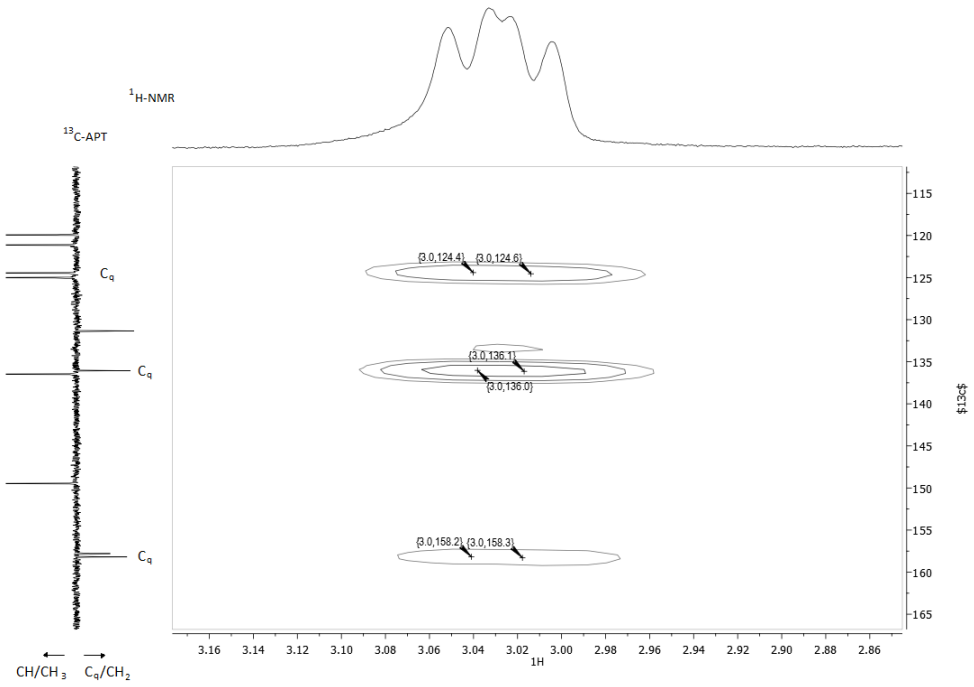
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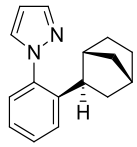

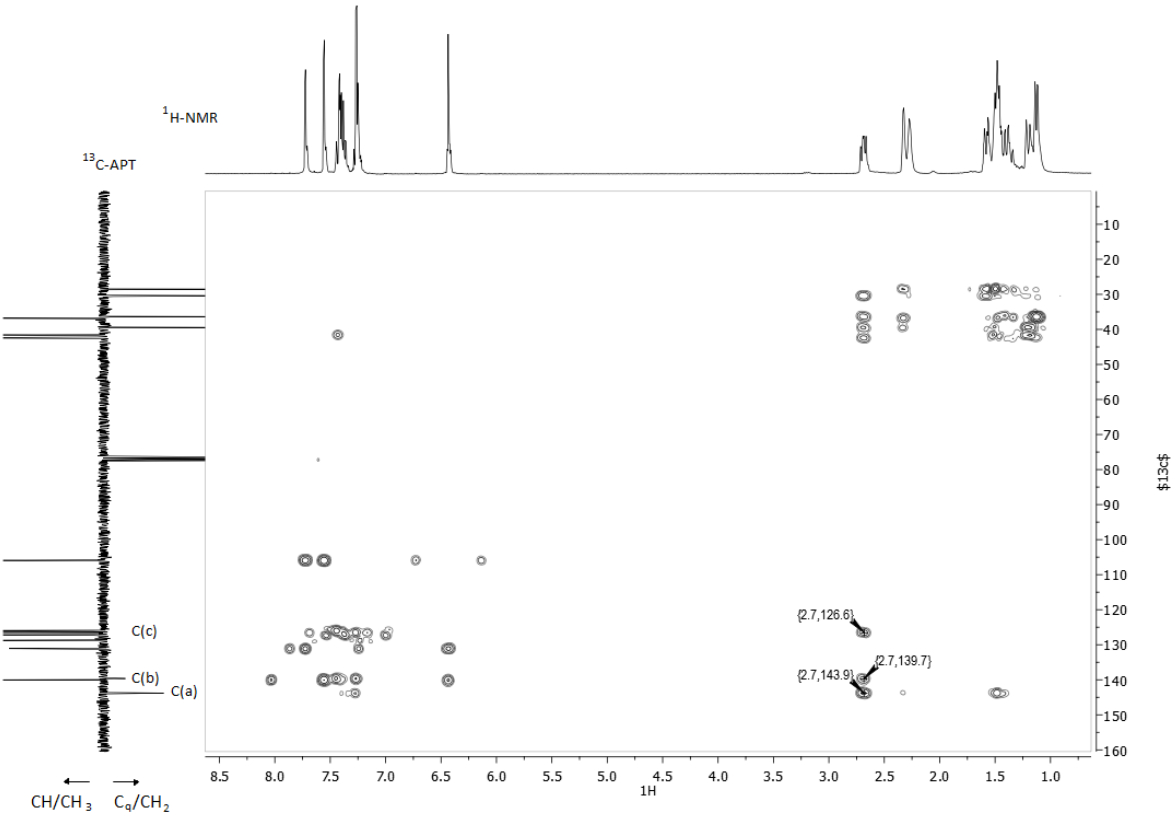
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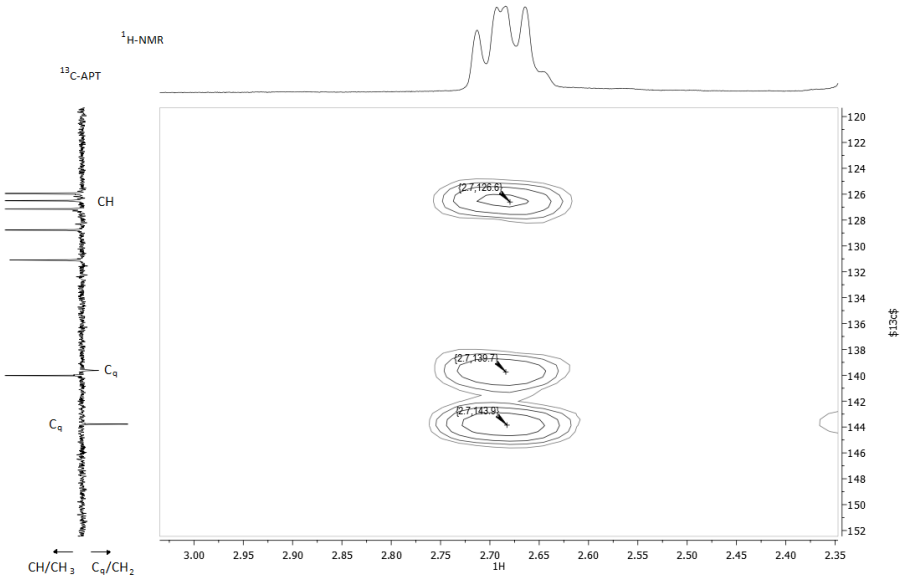
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Cq
Cq
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{2.7,143.9}
CH/CH3
Cq/CH2
1H
$13c$

8 List of Abbreviations

(HA)SPO	(heteroatom) substituted secondary
(Het)Ar	(hetero)arene
[M+]	molecular ion peak
2D	two dimensional
2-Py	2-pyridyl
Å	Angström
acac	acetyl acetonate
Ad	adamantyl
Alk	alkyl
AMLA	ambiphilic metal-ligand activation
AmOH	amyl alcohol
APT	attached proton test
aq.	aqueous
Ar	aryl
B_2Pin_2	bis(pinacolato)diboron
BINOL	1,1'-binaphthol
Bn	benzyl
BQ	benzochinone
Bu	butyl
Boc	*tert*-butyloxycarbonyl
ca.	circa
calc.	calculated
cat.	catalytic
CCD	charge coupled device
CDC	circular dichroism chromatography
CMD	concerted metalation deprotonation
cod	1,5-cyclooctadien
Cp	cyclopentadienyl
δ	chemical shift
DCE	1,2-dichloroethane
DCM	dichloromethane
Dec	decyl
DFT	density functional theory
DG	directing group
D_H^{289}	dissociation enthalphie at 289 K
diglyme	1-methoxy-2-(2-methoxyethoxy)ethane
DMA	N,N-dimethylacetamid
DMG	directed metalation group
DMSO	dimethyl sulfoxide
DoM	directed *ortho* metalation
dppf	1,1'- bis(diphenylphosphino)ferrocen
dr	diastereomeric ratio
dtbpy	4,4'-di-tert-butyl bipyridine
E^+	electrophile
Ed.	editor
EDG	electron donating group
ee	enantiomeric excess
EI	electron ionization
equiv	equivalent
ESI	electronspray ionization
et al.	*et alia*
Et	ethyl
eV	electron-Volt
EWG	electron withdrawing group
FTICR	Fourier transform ion cyclotron resonance
g	gramm
GC	gas chromatography
Gly	glycine
GoF	goodness of fit
h	hours
Hept	heptyl
Het	hetero
Hex	hexyl
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMBC	heteronuclear multiple bond correlation
HR	high resolution
Hz	Hertz
I	intensity
i-	*iso*-
i.e.	*id est*
IPr	1,3-bis(2,6-diisopropylphenyl)
IR	infrared spectroscopy
isol.	isolated
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
K	Kelvin
KIE	kinetic isotope effect
L	ligand
M	metal
M	molar
m	multiplett
M.p.	melting point
M.r.	melting range
m/z	mass-to-charge ratio
Me	methyl
MeCN	acetonitrile
Mes	mesityl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
µm	micrometer
TMP	2,2,6,6-tetramethylpiperidine
tol	tolyl
Ts	*para*-toluenesulfonyl
TS	transition state
Val	valine
wt%	weight by volume
X	(pseudo)halide
X-ray	roentgen-spectroscopy
mm	millimeter
m-	meta-
mmol	millimol
MPAA	monoprotected amino acid
MPV	membrane pump vacuum
MS	mass spectrometry
MS	molecular sieves
Mt/a	million tonnes per year
MTBE	methyl tert-butyl ether
N_2	nitrogen

NHC	nitrogen-containing heterocyclic
nm	nanometer
NMR	nuclear magnetic resonance
n-	*normal*-
nOe	nuclear overhauser effect
Nu^-	nucleophile
Ø	average
Oct	octyl
o-	*ortho*-
OPV	oil pump vacuum
ORTEP	oak ridge thermal-ellipsoid plot program
Pent	pentyl
PG	protecting group
Ph	phenyl
PhMe	toluene
Piv	pivaloyl
pK_A	logarithmic acid dissociation constant
PMP	*para*-methoxyphenyl
p-	*para*-
PPh_3	triphenylphosphine
ppm	parts per million
Pr	propyl
PTC	phase transfer catalyst
PTS	polyoxyethanyl α-tocopheryl sebacate
Py	pyridine
R	rest
sat.	saturated
S_E^{Ar}	electrophilic aromatic substitution
SET	single electron transfer
SIMes	1,3-bis(2,4,6-trimethylphenyl)-imidazolin-2- ylidene
T	temperature
t-	*tert*-
t	time
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	transition metal

9 Danksagung

Zuerst und im Besonderen möchte ich mich bei Herrn Prof. Dr. Lutz Ackermann für die gute Betreuung während der Anfertigung meiner Dissertation, für die mir gegebene Möglichkeit, auf interessanten Themengebieten zu forschen, und für seine Unterstützung im Hinblick auf meinen weiteren Werdegang bedanken.

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10 Curriculum Vitae

Date of birth:	June 7th, 1984 (Berlin)
Nationality:	German

Further Education

11/2009 – *present*	Studies for a doctorate under supervision of Prof. Dr. Lutz Ackermann, Institute of Organic and Biomolecular Chemistry; Georg-August University Göttingen: 'Carboxylate-Assisted Ruthenium-Catalyzed C–H Bond *meta*-Alkylations and Oxidative Annulations'
since 4/2010	scholarship within the international Ph.D. program CaSuS (*Catalysis for Sustainable Synthesis*)
09/2009	Final examinations in chemistry ('Diplom', grade 'very good')
01/2009 – 07/2009	Diploma-thesis under supervision of Prof. Dr. Lutz Ackermann, Institute of Organic and Biomolecular Chemistry; Georg-August University Göttingen: 'Palladium-Catalyzed Intramolecular *α*-Arylation and Ruthenium-Catalyzed Intermolecular Direct Alkylation.'
04/2007 – 09/2007	Erasmus exchange under supervision of Dr. Michael J. Hall, University of Newcastle upon Tyne (UK): 'Studies towards Encapsulated Fluorophores *via* Diels-Alder Reaction.'
10/2006 – 09/2009	Advanced studies in chemistry at the Georg-August University Göttingen
10/2006	Intermediate examination in chemistry ('Vordiplom', grade 'Good')
10/2004 – 09/2006	Studies of Chemistry at the Georg-August University Göttingen

Education

1997 – 2004	Humboldt-Gymnasium Eichwalde • Abitur with grade 1.7 (Major subjects: Chemistry and Mathematics) • Participation at 'Jugend forscht' (Chemistry) in 2003 • Attendance at the 'Deutsche Schülerakademie' in 2002 • Participation at 'Mathematik- & Chemieolympiade' • Awarded with 'Humboldt-prize' in 2001
1994 – 1997	Primary school in Schulzendorf
1991 – 1994	Primary school in Berlin-Treptow

Methods Courses

- *Computer methods in catalysis research* (Prof. M. Holthausen)
- *Spectroscopic methods in catalysis research* (Jun.-Prof. M. Bauer)
- *Kinetic methods for elucidation of reaction mechanisms* (Prof. M. Buback, Prof. P. Vana, Prof. M. Busch)
- *Advanced High-Throughput Screening Techniques in Catalysis* (Prof. O. Trapp)
- *Intercultural competency* (Prof. S. Klein-Franke)
- *Varianten sprecherischer Performance* (ZESS Göttingen)
- *Process Engeneering* (Dr. L. Rodefeld Bayer AG)

Extra Curricular Roles

- Student representative (2005 – 2008; elected member of the 'Fachschaftsrat Chemie', Vice-president of the 'Fachschaftsräte-versammlung', member of the 'Studienkommission')
- CaSuS student representative (09/2010 – 2/2012)
- Member of the organization team of the *Open Day* at the IOBC (09/2011)
- Organisation of Bayer-Workshop *Process Engeneering* for PhD-students (07/2012)

Teaching Experiences

- Guidance of several Bachelor Theses, IOBC, Georg-August University of Göttingen.
- Preparation of weekly written exams in SoSe 2012 for course *„Reaction Mechanisms in Organic Chemistry"*
- Assistant for preparative practical *"Advanced Organic Chemical Laboratory"* in WiSe 11/12*; "Basic Organic Chemical Practical Chemistry"* in SoSe 2010 & SoSe 2011
- Assistant for preparative practical and theoretics in WiSe 2009/2010 "*Chemical Laboratory for Medical Students*"

Conferences

07/2012	Poster presentation 15th ICC (*International Congress on Catalysis),* Munich
09/2011	Poster presentation at the *Summer School on Green Chemistry*, Göttingen
07/2011	Attendance at the *ICIQ Summer School* 2011 (*Institut Català d'Investigació Química*) (holder of a scholarship), Tarragona
10/2010	Poster presentation 1st NiKaS (*Niedersächsisches Katalyse Symposium*), Göttingen
09/2010	Poster presentation 17th OrChem (*Organisch-Chemische Tagung der GDCH*), Weimar

Oral Presentations

06/2011 4th Göttinger Chemie-Forum (GDCH/Jungchemikerforum), Göttingen

11/2010 ASMOS 6 (*Advances in the Synthesis of Molecularly Ordered Structures*), Dijon

06/2010 CaSuS Workshop, Mariaspring

Publications

Dissertation

[6] Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, accepted for publication.

[5] Ackermann, L.; Lygin, A. V.; Hofmann, N. *"Ruthenium-Catalyzed Oxidative Synthesis of 2-Pyridones through C–H/N–H Bond Functionalizations" Org. Lett.* **2011***, 13*, 3278–3281*. (highlighted in Synfacts)*

[4] Ackermann, L.; Lygin, A. V.; Hofmann, N. *"Ruthenium-Catalyzed Oxidative Annulation via C–H/N–H Bond Cleavages" Angew. Chem. Int. Ed.* **2011***, 50*, 6379–6382*. (selected as hot paper)*

[3] Ackermann, L.; Hofmann, N.; Vicente, R. *"Carboxylate-Assisted Ruthenium-Catalyzed Direct Alkylations of Ketimines" Org. Lett.* **2011**, *13,* 1875–1877.

Diplomathesis

[2] Ackermann, L.; Vicente, R.; Hofmann, N. *"Air-Stable Secondary Phosphine Oxide as Preligand for Palladium-Catalyzed Intramolecular α-Arylations with Chloroarenes" Org. Lett.* **2009***, 11*, 4274–4276*. (highlighted in Organic Chemistry Portal)*

[1] Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *"Ruthenium-Catalyzed Regioselective Direct Alkylation of Arenes with Unactivated Alkyl Halides through C–H Bond Cleavage" Angew. Chem. Int. Ed.* **2009***, 48*, 6045–6048. *(selected as hot paper)*