Ruthenium(II)-Catalyzed Direct C–H *meta*-Alkylations, Alkenylations and Alkyne Annulations

Dissertation

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submitted by

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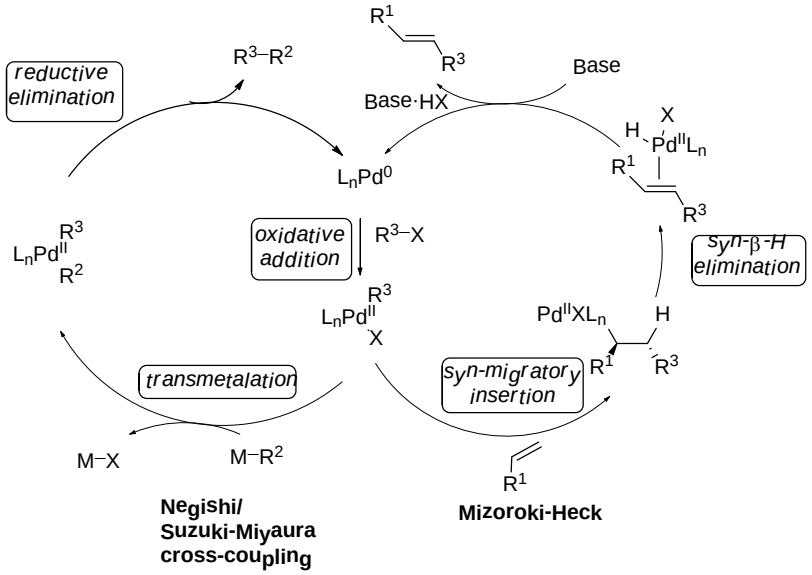
1 Introduction

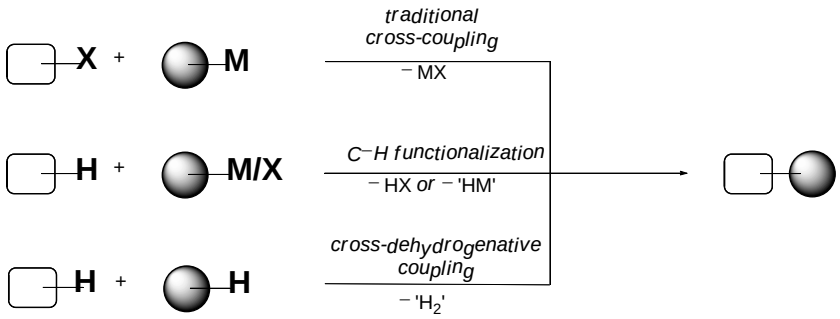
1.1 Transition Metal-Catalyzed C–H Bond Functionalization

In the past decades, transition metal-catalyzed cross-coupling reactions have been considered as one of the most powerful and reliable methods for chemo- and site-selective construction of carbon–carbon (C–C) or carbon–heteroatom (C–Het) bonds.[1-4] Besides academia, these reactions have also been widely employed in pharmaceutical, agrochemical, and fine chemical industries.[5,6] For their magnificent contribution for palladium-catalyzed cross-coupling reactions, *R. F. Heck*, *E. Negishi* and *A. Suzuki* were awarded the Nobel Prize in chemistry in 2010.[7-9] The generally accepted mechanisms for these palladium-catalyzed cross-coupling transformations are illustrated in Scheme 1.1. In both types of coupling reactions, first step is the oxidative addition of the aryl halide (or pseudohalide) to the catalytically active palladium(0) species which initiates the catalytic cycle. At this stage the processes diverge. In the Mizoroki-Heck[10,11] reaction, the reaction progresses by coordination of an alkene to the palladium(II) species followed by *syn*-migratory insertion and *syn*-*β*-hydride elimination to form the substituted alkene product, and subsequently base-assisted elimination to regenerate the active palladium(0). In the Negishi[12] and Suzuki-Miyaura[13] cross-coupling reactions, the oxidative addition is followed by transmetalation of an organometallic or main group element species to generate a Palladium(II) intermediate. Subsequent reductive elimination results in C–C bond formation with the regeneration of palladium(0) species to complete the catalytic cycle.



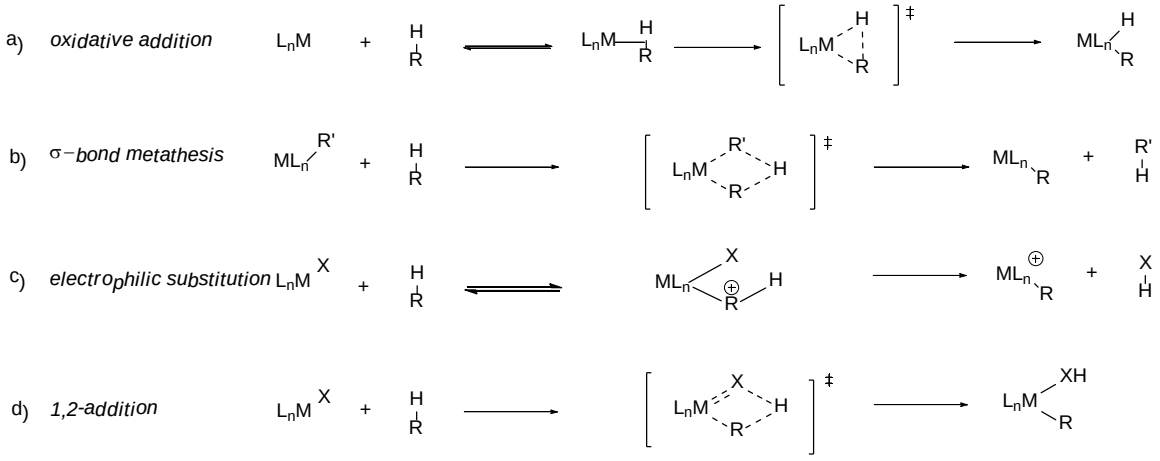
Scheme 1.1: General catalytic cycles for Mizoroki–Heck, Negishi, and Suzuki–Miyaura reactions

Despite the various applications of these reactions, the use of pre-functionalized starting materials and generation of stoichiometric amount of undesired byproducts remain major disadvantages. As a more atom- and step-economical[14,15] alternative, C–H functionalization has recently emerged as a valuable tool allowing the transformation of otherwise unreactive C–H bonds (Scheme 1.2).[16-24] Furthermore, the direct construction of C–C bonds by functionalizing two C–H bonds including C(sp^3)–H bonds, which was termed as cross-dehydrogenative coupling (CDC),[25] has been extensively studied.[26,27]



Scheme 1.2: Strategies for C−C and C−Het bond formation

Depending on the nature of the transition metal M and the ligand set L_n, the elementary step of C−H bond metalation was proposed to proceed via different pathways. *Ackermann* as well as *Eisenstein* and co-workers summarized four generally accepted pathways for this process which are shown in Scheme 1.3.[17,28]

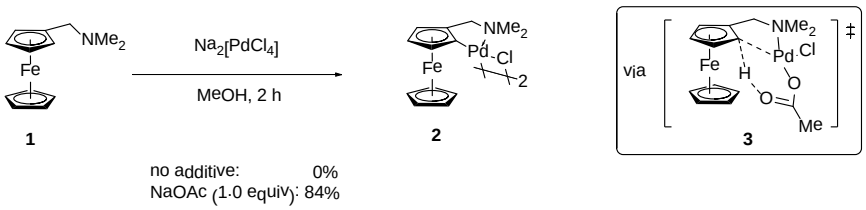


Scheme 1.3: Different mechanisms for C−H metalation

Oxidative addition is a common mechanism in which a C−H bond first coordinates to the metal vacant site and is then cleaved to form a M−H bond and a M−C bond (Scheme 1.3a). This process often occurs for electron-rich, low-valent late transition metals (Re, Fe, Ru, Os, Ir and Pt). However, early group 3 and 4 transition metals as well as lanthanides (d^0 configuration) usually do not undergo oxidative addition. Therefore, for these metals *σ*-bond metathesis (SBM) is more common (Scheme 1.3b). Similar reactivity is observed for late- or post-transition metals (Pd^{2+}, Pt^{2+}, Pt^{4+}, Hg^{2+}) in strongly polar medium, electrophilic attack of the metal occurs in which the metal largely acts as a Lewis acid and thus classified as electrophilic substitution (Scheme 1.3c). C−H bond activation can also proceed *via* 1,2-addition to unsaturated M−X bonds (Scheme 1.3d).

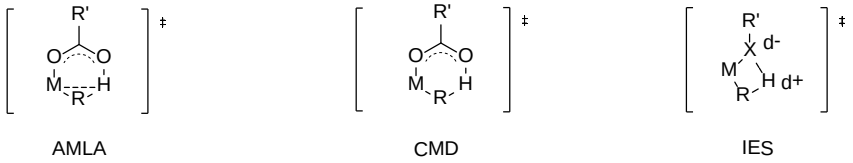
In the early 1970s, work by *Shaw* and *Gaunt* highlighted the importance of stoichiometric amounts of NaOAc for successful cyclometalation of *N*,*N*-dimethylaminomethylferrocene (**1**) (Scheme 1.4).[29] Subsequently, *Reutov* and co-workers found that carboxylic acids are competent additives for the same transformation and furnished products with moderate enantiomeric excess.[30] More importantly, a transition state of concerted carboxylate-assisted intermolecular deprotonation[17] was

first proposed.



Scheme 1.4: Base-assisted cyclometalation and proposed transition state **3**

In this context, theoretical calculations have offered new insight into the mechanism of base-assisted C–H metalation. Based on computational studies, *Davies* and *Macgregor* described such reaction as ambiphilic metal-ligand activation (AMLA),[31] whereas *Fagnou* used the term concerted-metalation-deprotonation (CMD).[32] Both proposals favor a similar six-membered transition state, however, *Davies* and *Macgregor* suggested an agostic interaction between metal center and the C–H bond (Scheme 1.5).

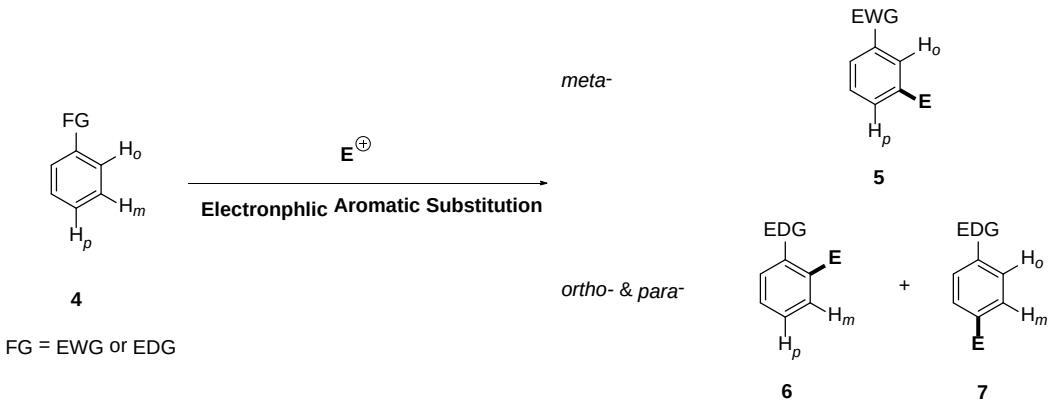


Scheme 1.5: Proposed transition state for base-assisted C–H activation

The groups of *Oxgaard* and *Goddard* reported detailed experimental and computational studies on C–H bond activation of benzene by iridium complexes. Herein, a four-membered transition state was proposed and described as internal electrophilic substitution (IES).[33]

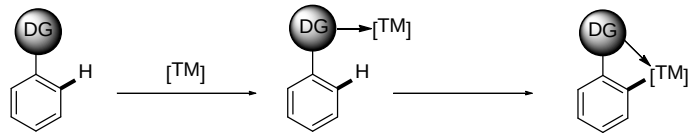
1.2 Site-Selectivity in C–H Bond Functionalization

C–H bonds are ubiquitous in nature, a characteristic which on one hand facilitates their usage as starting material for elaboration of more complex structures. However, on the other hand, this makes controlling the site-selectivity of C–H functionalization a great challenge. In electrophilic aromatic substitution, it has been well established that electron-donating substituents direct incoming electrophiles to the *ortho*- (**6**) and *para*-positions (**7**), whereas electron-withdrawing substituents lead to the *meta*- position (**8**) (Scheme 1.6).



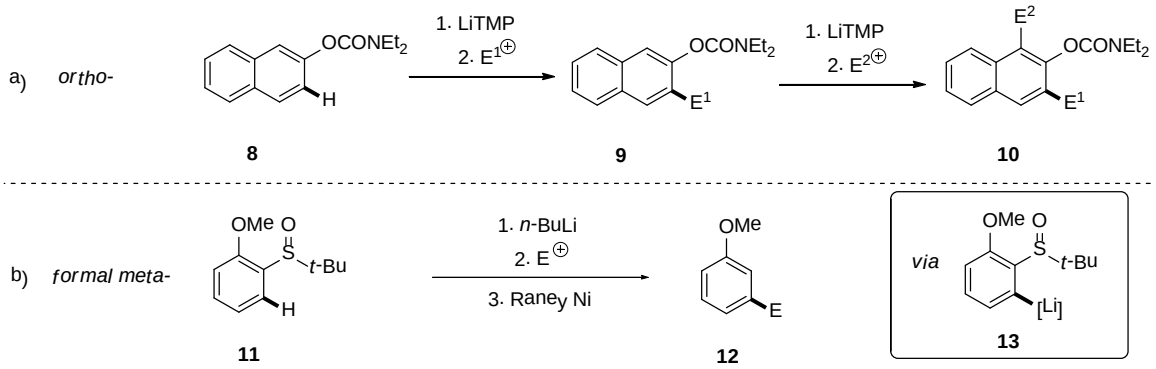
Scheme 1.6: Site-selectivity in electrophilic aromatic substitution

In spite of the synthetic importance of this classic selectivity pattern, accessing the isomers which are not anticipated by these rules remained a challenge. Over the last few decades, C−H functionalization involving the use of directing groups (DGs) has become the most common approach that allows access to *ortho*-functionalized aromatic compounds through chelation-assisted cyclometalation[34,35] or weak coordination.[20] A directing group usually bears a heteroatom of which the lone pair of electrons can coordinate to the transition metal complex [TM] (Scheme 1.7).



Scheme 1.7: Coordination mode of a DG in transition metal-catalyzed C−H functionalization

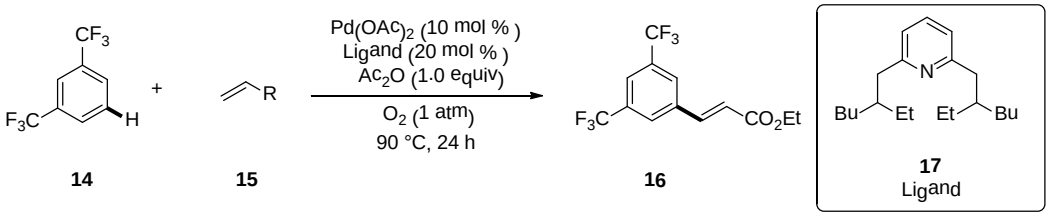
The same principle has previously been utilized in the stoichiometric directed *ortho*-metalation (DoM), discovered independently by *Gilman*[36] and *Wittig*[37] in the late 1930s. In this approach, an aryllithium intermediate is formed by *ortho*-deprotonation following the chelation of lithium by the direct metalation group (DMG). Subsequent attack by an electrophile delivers the *ortho*-functionalized product. Scheme 1.8a shows a recent example of preparing *ortho*-substituted naphthalenes **9** and **10** via carbamate assisted DoM.[38] It is worth noting that the DoM strategy can be employed for the preparation of *meta*-substituted products as well. For example, the group of *Brown* demonstrated that utilizing removable sulfoxide group as DMG smoothly gave rise to *meta*-substituted anisole **12** (Scheme 1.8b).[39]



Scheme 1.8: Examples of site-selective DoMs

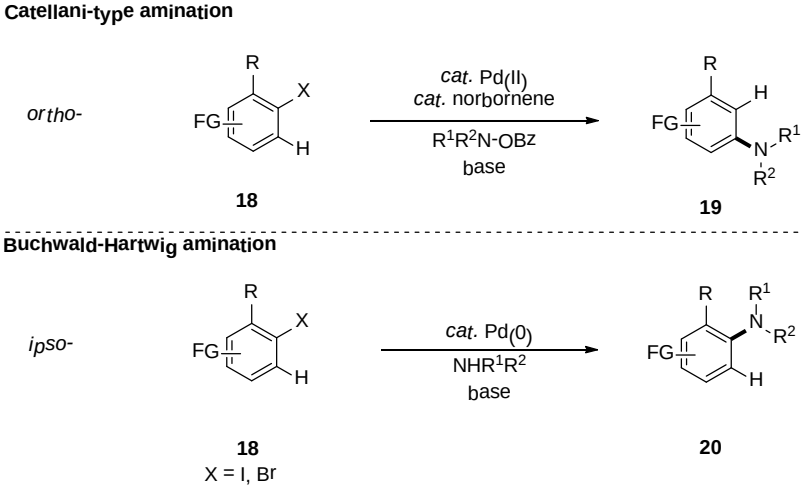
Although the DoM strategy usually exhibits high reactivity and efficiency, there remain certain drawbacks. First, the necessity of using stoichiometric amounts of strong base inevitably produces stoichiometric amounts of salt waste. Second, employing very reactive strong base largely limits the potential substrate scope in terms of functional group tolerance.

Besides using directing groups, the site-selectivity can also be controlled by employing electronically activated substrates.[40] For example, the group of *Yu* developed palladium-catalyzed C−H olefination of electron-deficient arenes **14**,[41] wherein the most acidic *meta*-C−H bond is predominately functionalized (Scheme 1.9). Systematic theoretical study of this reaction has been performed. It was calculated that the initial C−H activation step proceeds via concerted metalation-deprotonation (CMD) pathway.[42]



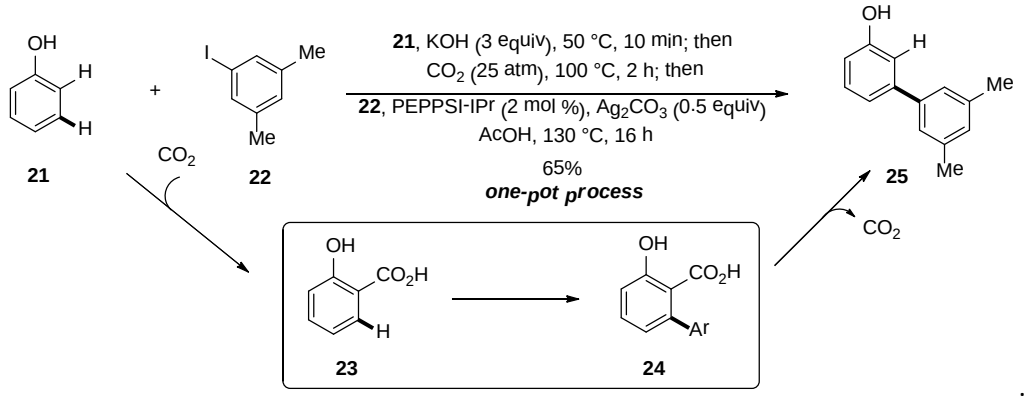
Scheme 1.9: *meta*-Selective C−H alkenylation of electron-deficient arene **14**

Palladium-catalyzed norbornene-mediated *ortho*-selective C−H functionalization of iodobezene derivatives **18**, which is also known as the Catellani reaction, allows for the facile construction of up to three C−C bonds in a site-selective fashion.[43] Given its unique site-selectivity, considerable attention has been drawn in extending the synthetic utility of this transformation over the last decade.[44,45] Recently, the group of *Dong* developed an elegant example of employing Catellani reaction for site-selective C−H amination of arenes **18**.[46] Comparing to the well-known Buchwald-Hartwig amination,[47] this novel approach provided amination products exclusively at *ortho*-position (**19**) rather than *ipso*-position (**20**) (Scheme 1.10). More importantly, this method offers broad implications for developing various dual functionalizations of arenes that involve *ortho*-C−Het bond formation.



Scheme 1.10: Different selectivity patterns in palladium-catalyzed aminations

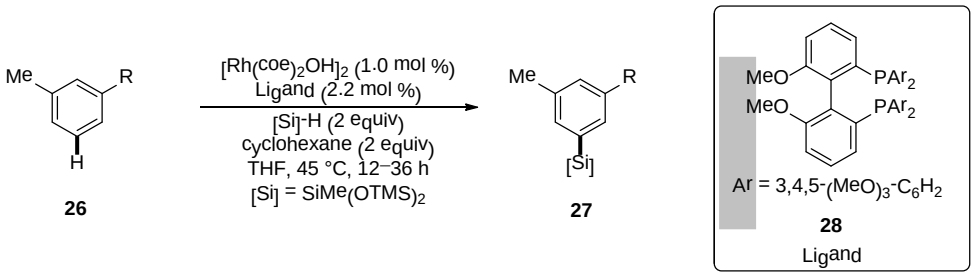
Based on their previous work of using carboxylic acids as directing groups for formal *meta*-selective direct arylation of phenols,[48] in 2014, *Larrosa* and co-workers modified their methodology by installing carboxylic acid as a traceless directing group in situ which enabled palladium-catalyzed *ortho*-selective arylation and can be cleaved under the same reaction conditions (Scheme 1.11). This improved method avoided the pre-functionalized phenols (**21**) and the overall *meta*-arylation process proceeded in a one-pot fashion.[49,50]



Scheme 1.11: One-pot direct *meta*-arylation of phenol **21**

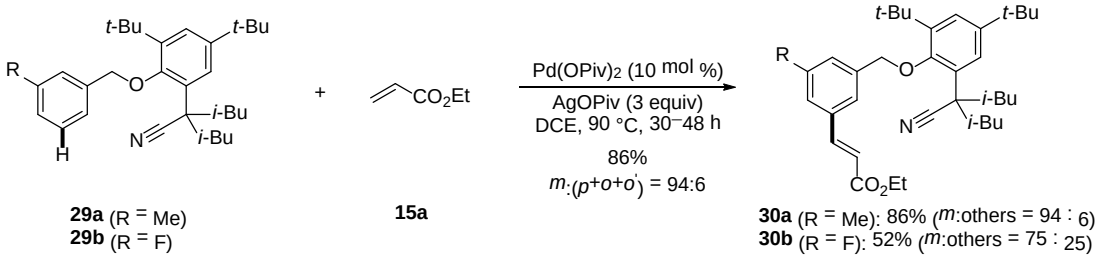
In spite of the above mentioned approaches for achieving *meta*- or formal *meta*-selective C−H bond functionalizations, developing more general methods to directly access *meta*- or *para*-positions of aromatic compounds with high site-selectivity remains a challenge.[51-53]

One major breakthrough was achieved by the groups of *Smith*[54] and *Hartwig.*[55] They have reported one-pot iridium-catalyzed C−H borylation and sequential functionalization of 1,3-disubstituted arenes at C-5 position. Most recently, Hartwig and co-workers disclosed rhodium-catalyzed *meta*-selective C−H silylation of unactivated arenes (**26**).[56,57] The resulted silylarene products **27** are very useful building blocks for organic synthesis (Scheme 1.12). In this type of transformations, regio-selectivity was proposed to be governed by a combination of the steric bulkiness around the catalyst and the substituents on the arenes.[58]



Scheme 1.12: Rhodium-catalyzed *meta*-selective C−H silylation

A second breakthrough in achieving *meta*-selectivity is through coordination of transition metal catalyst to a rational designed template which facilitates the approach of the catalyst to the remote *meta*-C−H bond. This novel method, in which the first palladium-catalyzed *meta*-selective alkenylation assisted by a removable nitrile-containing directing group in substrates **29** via a highly strained, tricyclic-cyclophane-type palladated intermediate was achieved (Scheme 1.13), was developed by the group of *Yu* in 2012.[59]



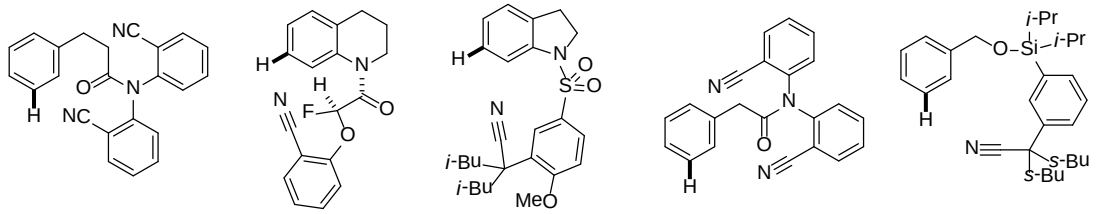
29a (R = Me)
29b (R = F)

15a

30a (R = Me): 86% (*m*:others = 94 : 6)
30b (R = F): 52% (*m*:others = 75 : 25)

Scheme 1.13: Palladium-catalyzed *meta*-selective C−H alkenylation

Subsequently, *Yu* and co-workers developed other nitrile-containing directing groups based on the same strategy (Scheme 1.14). These directing groups successfully promoted *meta*-selective arylation, methylation and alkenylation of phenylpropanoic acid **31** and phenolic derivatives,[60] *meta*-selective olefination and acetoxylation of anilines and tetrahydroquinolines **32**,[61] *meta*-selective olefination, arylation, and acetoxylation of indolines **33**,[62] and, most recently, *meta*-selective olefination of phenylacetic acid derivatives **34**.[63] The group of *Tan* slightly modified the *Yu* template by using a silicon atom for attachment in substrate **35**, allowing for a facile introduction and deprotection strategy and thus increasing the synthetic practicality of the template.[64]



31
Yu, **2013**

32
Yu, **2014**

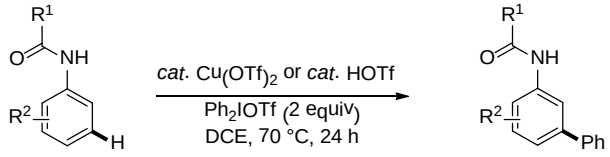
33
Yu, **2014**

34
Yu, **2015**

35
Tan, **2013**

Scheme 1.14: Directing groups for palladium-catalyzed *meta*-C−H functionalization

As an alternative approach, *Gaunt* and co-workers reported copper-catalyzed *meta*-selective C−H arylation of anilides **36**[65,66] and subsequently *α*-aryl carbonyl compounds (Scheme 1.15).[67] Regarding the mechanism of this remarkable transformation, the authors initially proposed a copper intermediate. However, at slightly elevated temperature, this transformation took place smoothly in the absence of any copper catalyst.



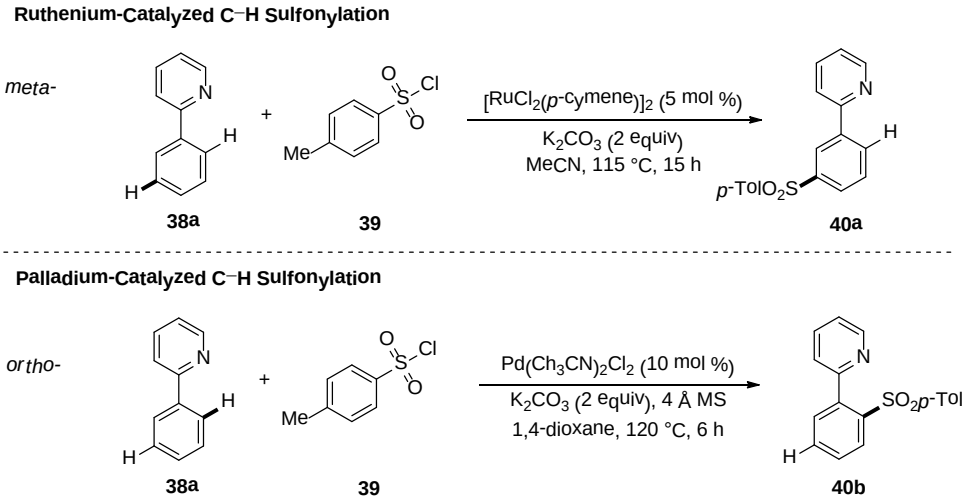
36

37

Scheme 1.15: *meta*-selective C−H arylation of anilides **36**

Subsequently the same group described copper-catalyzed *para*-selective direct arylation of aniline and phenol derivatives.[68] Again, reaction occurred in the absence of copper and *ortho*-arylation was observed when the *para*-position of aniline was blocked. This selectivity pattern is consistent with a classical electrophilic aromatic substitution. However, copper improved the reactivity of this transformation presumably by inducing dissociation of the triflate anion to form an activated aryliodonium species.

In 2011, *Frost* and co-coworkers discovered that in contrast to palladium,[56] ruthenium led to completely different site-selectivity in direct C–H sulfonylation of 2-phenylpyridine derivatives (**38a**) (Scheme 1.16).[69-71] In this novel approach, a cyclometalated ruthenium complex containing a Ru-C_{aryl} σ-bond was initially formed, and then the ruthenium center itself became a directing group,[72,73] thus directing the electrophilic attack to the *para*-position with respect to the ruthenium by inductive and mesomeric effects.

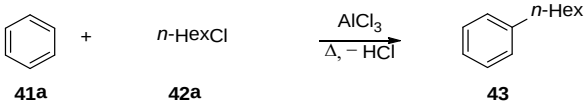


Scheme 1.16: Different selectivity pattern in transition metal-catalyzed C–H sulfonylation

1.3 Transition Metal-Catalyzed Alkylation with Alkyl Halides

Friedel-Crafts Alkylation

Ever since *Friedel* and *Crafts* reported the first $AlCl_3$-mediated electrophilic aromatic substitution of benzene (**41a**) with alkyl chlorides **42** in 1877 (Scheme 1.17),[74] the Friedel-Crafts alkylation has been one of the most powerful C–C bond forming processes in organic synthesis. However, it took more than a century for asymmetric catalytic versions of this transformation to be developed.[75] Meanwhile, the substrate scope has been extended to include various aromatic compounds and alkylating agents.



Scheme 1.17: Electrophilic aromatic alkylation as reported by *Friedel* and *Crafts*

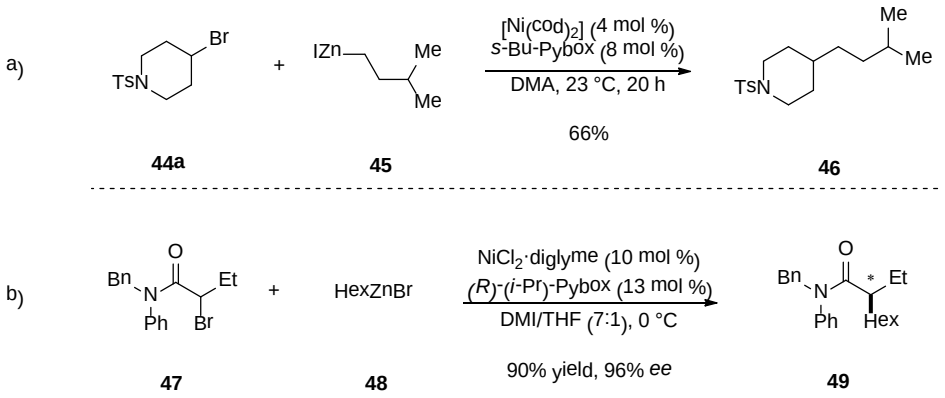
Despite the fact that research towards developing new strategies for catalytic, stereoselective,[76] enantioselective and environmentally benign[77] Friedel-Crafts alkylation is still active, many innate limitations hinder the broader application of these methods. First, acid-labile functional groups are not tolerated. Second, the electrophiles often undergo rearrangements, thus limiting the utility for *n*-alkylations. Third, chemo- or regioselectivity is not perfect, and the electron-deficient arenes are much less reactive than the electron-rich ones. At last, the electronic effects prevent formation of products with alkyl group located *meta*- to electron-donating groups.

Transition Metal-Catalyzed Cross-Coupling

In conventional cross-coupling chemistry, alkyl electrophiles bearing β-hydrogen atoms had been considered unsuitable substrates for mainly two reasons. First, the oxidative addition of alkyl C–Hal bonds to a metal center is more difficult than aryl–Hal and alkenyl–Hal ones due to their electron-rich nature. Second, the thus formed alkyl metal species are substantially less stable owing to a lack of π electrons which can interact with empty *d* orbitals of the metal. This instability easily gives rise to undesired side reactions, most prominently β-hydride eliminations.[78]

However, since the pioneering work of *Kochi*[79] and *Suzuki,*[80] a wide range of transition metals can readily catalyze the coupling of primary alkyl halides and organometallic regents.[81,82] Compared with primary alkyl halides, secondary alkyl halides are more difficult to couple in conventional cross-coupling chemistry due to the increased energy barrier towards oxidative addition, which results from the increased steric hindrance. Nevertheless, tremendous progress has been made in coupling secondary alkyl halides during the past decade.[83]

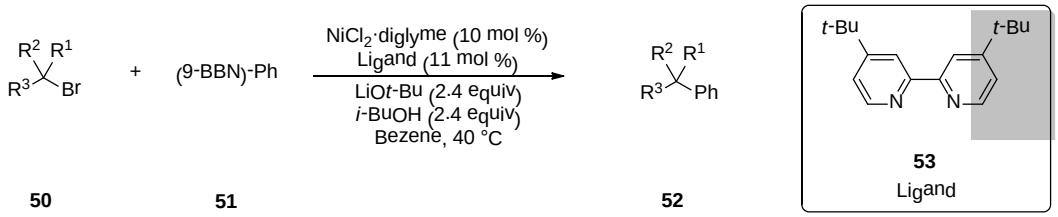
In 2003, the group of *Fu* reported the first nickel-catalyzed Negishi coupling of secondary alkyl bromides **44** and iodides (Scheme 1.18a). This transformation proceeded smoothly in the presence of various functional groups, such as sulfon amides, ethers, acetals, esters, and amides.[84] Shortly thereafter, the same group reported an asymmetric nickel-catalyzed Negishi coupling of secondary electrophiles (Scheme 1.18b).[85] Coupling of racemic α-bromoamides (**47**) under the catalysis with $NiCl_2$ and *i*Pr-Pybox led to a variety of functionalized α-substituted amides (**49**) in good yields and high *ee* values.



Scheme 1.18: Nickel-catalyzed Negishi coupling of secondary alkyl halides

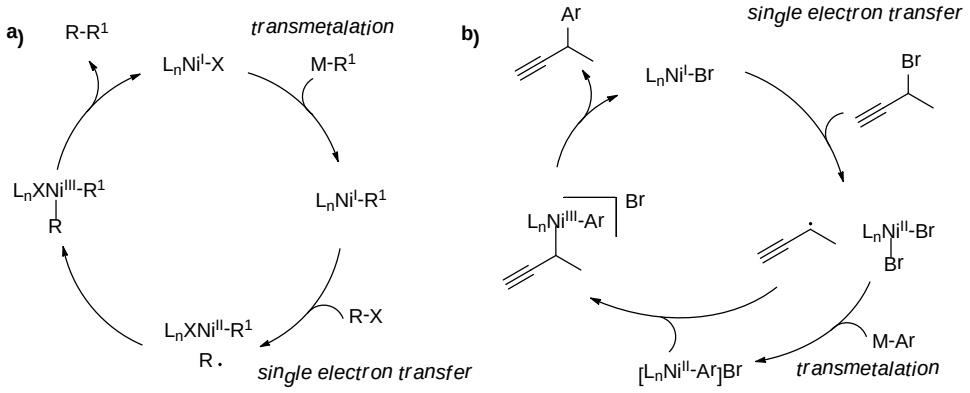
Besides Negishi coupling, nickel-catalyzed Suzuki-,[86] Hiyama-,[87] Kumada-,[88] and Sonogashira-type coupling[89] were also reported in an enantioselective fashion, with major contribution from the *Fu* group. Although nickel has been proven to be the most versatile metal for cross-coupling of alkyl halides,[90] other transition metals, such as copper,[91] iron,[92] cobalt[93] and palladium[94] are also competent.

Although huge progress has been made towards coupling secondary alkyl halides in the past decade, until now, there are only a few publications concerning transition metal-catalyzed C–C bond formation with unactivated tertiary alkyl halides. In 2013, *Fu* and *Zultanski* reported the first nickel-catalyzed Suzuki coupling of tertiary alkyl halides (**50**).[95]



Scheme 1.19: Nickel-catalyzed Suzuki coupling of tertiary alkyl halides **50**

The mechanism of nickel-catalyzed Negishi alkyl-alkyl cross-coupling has been studied independently by the groups of *Vicic*[96] and *Phillips.*[97] Recently, *Fu* and coworkers also examined the pathway for Negishi arylation of secondary propargylic bromides.[98] Both studies proposed catalytic cycles involving the transmetalation of organozinc regents and the reductive elimination to yield the products and most importantly, activation of the alkyl halides by single electron transfer (SET)[99] to form free alkyl radicals. However, *Vicic* found that nickel(II) species were inactive in the alkyl-alkyl coupling and thus proposed transmetalation as the first step (Scheme 1.20a), while in *Fu*'s experiments nickel(II) seemed to be the active catalyst (Scheme 1.20 b).



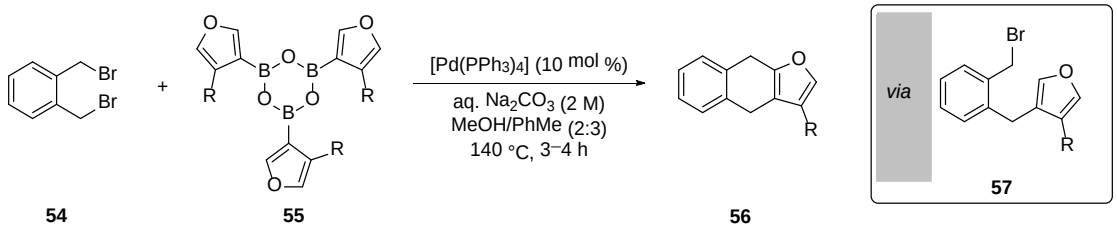
Scheme 1.20: Proposed mechanisms for nickel-catalyzed Negishi coupling: a) alky-alkyl coupling; b) aryl-propargyl coupling

Transition Metal-Catalyzed Direct C–H Alkylation

An innate disadvantage of conventional cross-coupling of alkyl halides is the usage of pre-functionalized nucleophilic substrates which are often not commercially available. Preparation of these nucleophiles as well as the cross-couplings themselves potentially produces undesired byproducts. Thus, direct C–H bond alkylation represents an economically attractive alternative. Indeed, during the last few years, tremendous progress has been achieved in the field of direct C–H bond alkylation of (hetero)arenes, and different transition metals proved to be competent.[100]

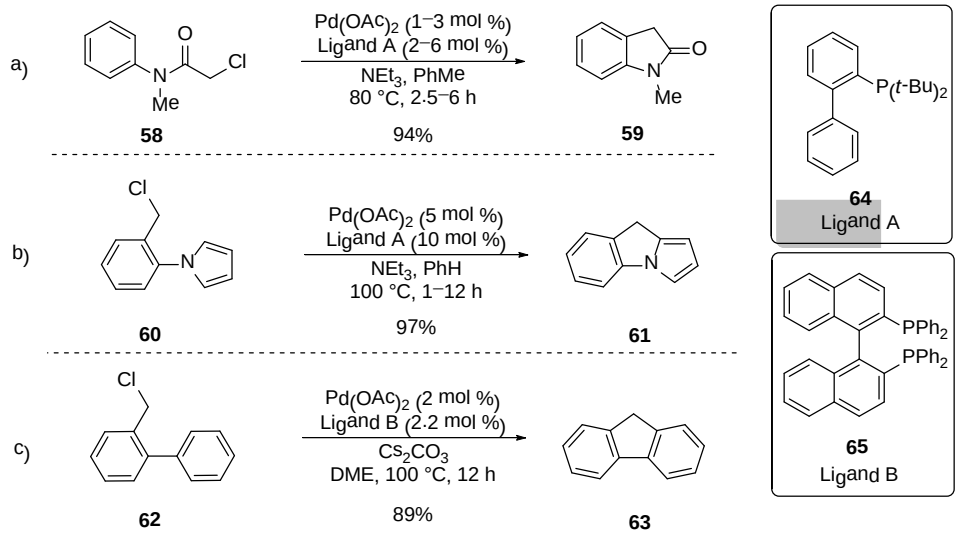
Intramolecular Direct C–H Alkylation

One of the early examples of transition metal-catalyzed intramolecular C–H benzylation was developed by the group of *Wong.*[101] Initial intermolecular Suzuki–Miyaura cross-coupling afforded intermediate **57**, which set the stage for a palladium-catalyzed intramolecular direct benzylation (Scheme 1.21).



Scheme 1.21: Palladium-catalyzed direct intramolecular benzylation

In 2003, *Buchwald* and co-workers disclosed palladium-catalyzed oxindoles synthesis through intramolecular alkylation of α-chloroacetanilides **58** (Scheme 1.22a).[102] *ortho*- or *meta*-Substituted α-chloroacetanilides delivered oxindoles **59** of which the less hindered *ortho*-positions were selectively alkylated. Subsequently, the group of *Chang* also reported synthesis of pyrroloindoles **61** via palladium-catalyzed intramolecular benzylation of pyrroles **60** under similar reaction conditions (Scheme 1.22b).[103] Pyrroles bearing electron-withdrawing substituents were observed to react faster than the corresponding electron-rich derivatives, thus indicating a CMD-type mechanism.

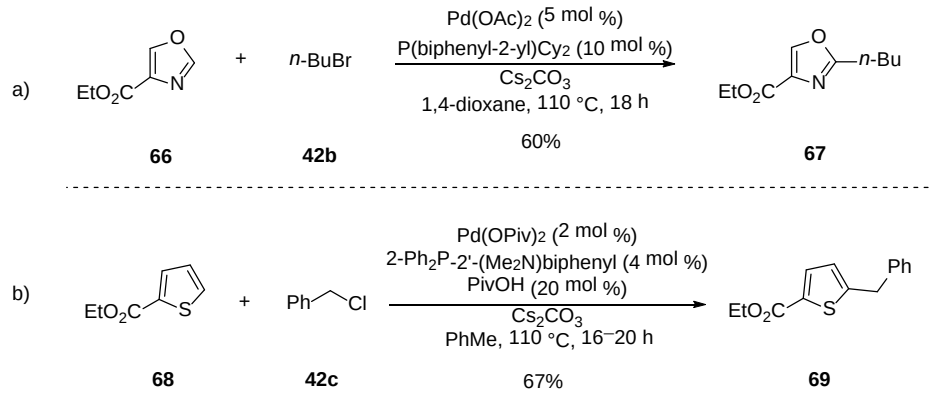


Scheme 1.22: Palladium-catalyzed direct intramolecular cyclizations

In a follow-up work, *Chang* and co-workers demonstrated that simple arenes **62** could also be cyclized with an optimized palladium/BINAP system (Scheme 1.22c).[104] It is noteworthy that in all these intramolecular reactions described above, the halides were activated and thus underwent facile oxidative addition.

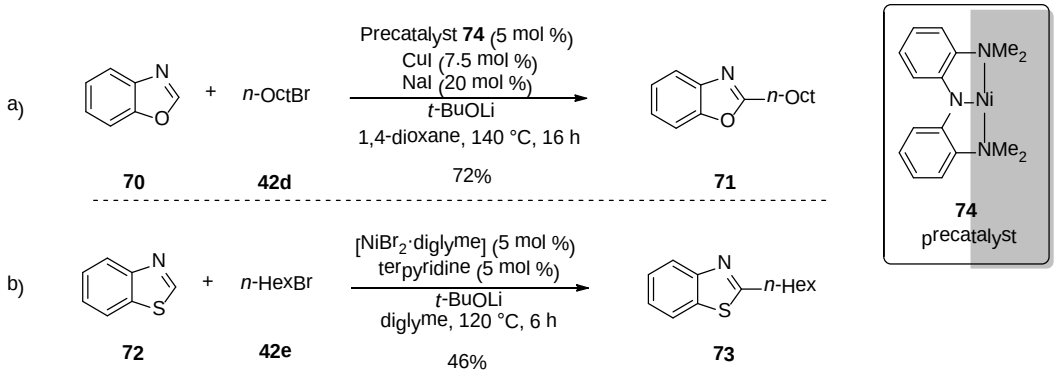
Direct C–H Alkylation of Heteroarenes

Besides arenes, heteroarenes were demonstrated as suitable substrates for transition metal-catalyzed direct C–H alkylation as well. In 2009, *Hoarau* and co-workers developed one of the earliest examples of palladium-catalyzed alkylation and benzylation of oxazoles **66** (Scheme 1.23a).[105] The scope of heteroarenes for this transformation was significantly expanded by the group of *Fagnou*; various five-membered heteroarenes were functionalized at the most acidic C–H bond (Scheme 1.23b).[106] Addition of pivalic acid turned out to be beneficial for the overall efficiency, which indicated a CMD-type mechanism.



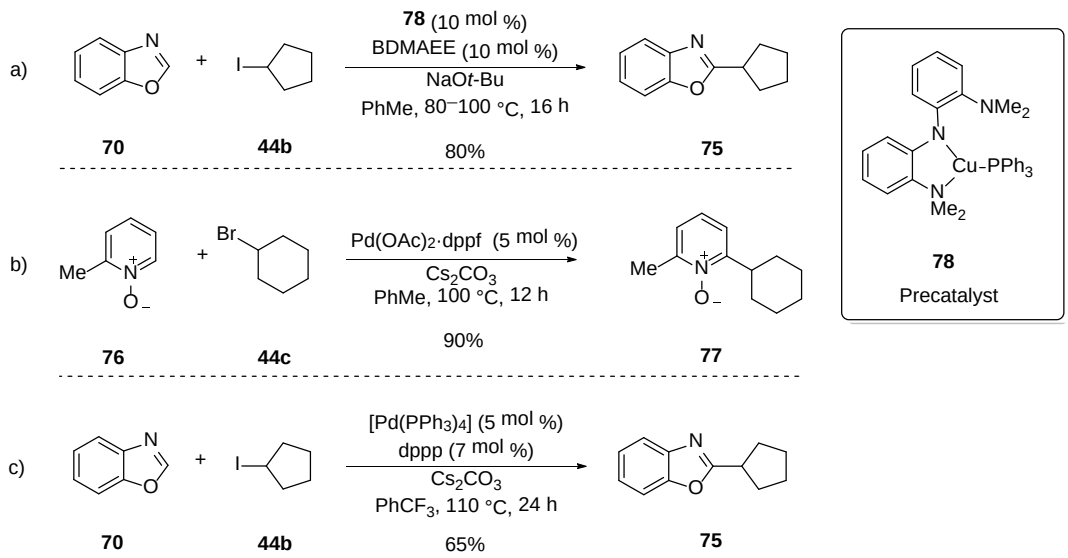
Scheme 1.23: Palladium-catalyzed direct alkylations of heteroarenes

Shortly thereafter, *Hu* and co-workers demonstrated that nickel complexes are also capable of promoting direct alkylation of heteroarenes.[107] Interestingly, addition of cocatalytic amounts of CuI proved to be essential for achieving high yields (Scheme 1.24a). The groups of *Miura*[108] and *Ackermann*[109] independently showed that user-friendly [(Diglyme)$NiBr_2$] also allowed for the effective direct C–H alkylation of heteroarenes (Scheme 1.24b).



Scheme 1.24: Nickel-catalyzed direct alkylation of heteroarenes

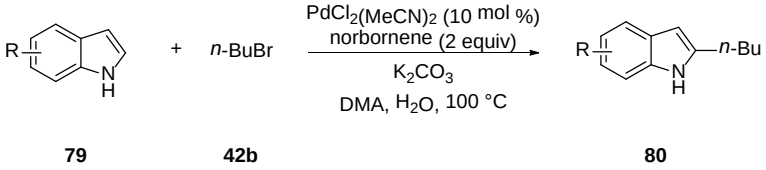
Furthermore, in 2012, *Hu* and co-workers showed that not only primary alkyl halides, but also secondary alkyl halides **44** are suitable substrates for copper-catalyzed direct alkylation of heteroarenes **70** (Scheme 1.25a).[110] Reactions with radical scavengers and other mechanistic studies suggested a radical mechanism. Recently, palladium-catalyzed direct alkylation of pyridine *N*-oxides **76** and other heteroarenes with unactivated secondary alkyl halides were also independently reported by the groups of *Fu*[111] and *Wu*[112] (Scheme 1.25b,c).



Scheme 1.25: Palladium or copper-catalyzed direct alkylation with secondary alkyl halides **44**

Norbornene-Mediated Direct C–H Alkylation

While the electron-rich C3-position of indoles **79** can be easily alkylated by Friedel-Crafts alkylation, regioselective direct alkylation at C2-position of free *N*-H indoles is not straightforward. As already discussed in Chapter 1.2, Catellani reaction displays unique site-selectivity *via* manipulation of norbornene. Thus, *Bach* and co-workers took advantage of this strategy and achieved for the first time direct C2-alkylation of free *N*–*H* indole derivatives **79** (Scheme 1.26).[113]

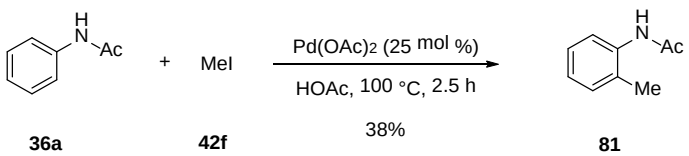


Scheme 1.26: Norbornene-mediated direct C2 alkylation of free *N*-H indoles **79**

The C2-alkylation process was originally assumed to initiate by the well-established C3-palladation. However, after comprehensive mechanistic study, Bach and co-workers proposed *N*-palladation of indole to be the first step.[114] The synthetic utility of this protocol for 2-alkylation of indoles was also demonstrated by its application in the total synthesis of *Aspidosperma* alkaloids.

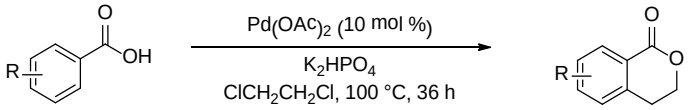
Monodentate Directing Group Assisted Direct C–H Alkylation

With respect to directing group-assisted C–H alkylation, *Tremont* and co-workers discovered that stoichiometrically palladated acetanilides reacted smoothly with alkyl iodides.[115] Further investigation achieved a catalytic version of this transformation, albeit with a low turnover number of 1.5 (TON) (Scheme 1.27).



Scheme 1.27: Palladium-catalyzed direct alkylation of acetanilide **36b**

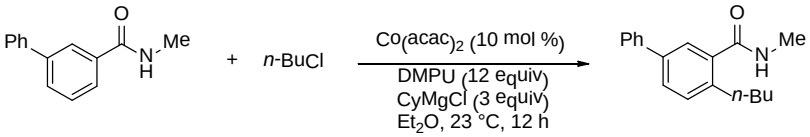
In 2009, Yu and co-workers disclosed palladium-catalyzed direct alkylation of benzoic acids **82** with either 1,2-dichloroethane or dibromomethane (Scheme 1.28).[116] Mechanistic studies showed that o*rtho-s*elective alkylation took place first and subsequent intramolecular S_N2 cyclization delivered desired lactones **83**. Using alkyl bromides and chlorides instead of iodides allowed the catalytic cycle to be closed without using stoichiometric amounts of AgOAc.



82 **83**

Scheme 1.28: Palladium-catalyzed direct alkylation of benzoic acids **82**

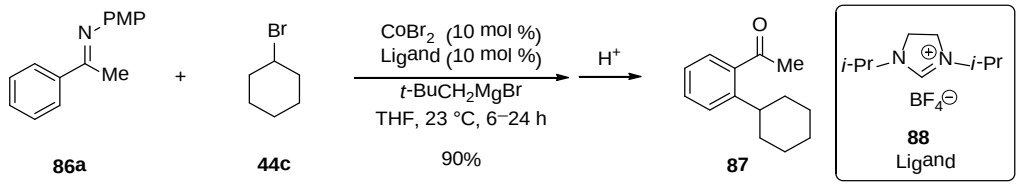
Besides palladium catalysts, the group of *Nakamura* developed a cobalt-catalyzed direct alkylation of secondary benzamides **84**, an important functional group and structure motif which can be further transformed (Scheme 1.29).[117] Inexpensive DMPU was used as ligand and the reaction proceeded under very mild conditions.



84a **42g** 81% **85**

Scheme 1.29: Nickel-catalyzed direct alkylation of secondary benzamide **84a**

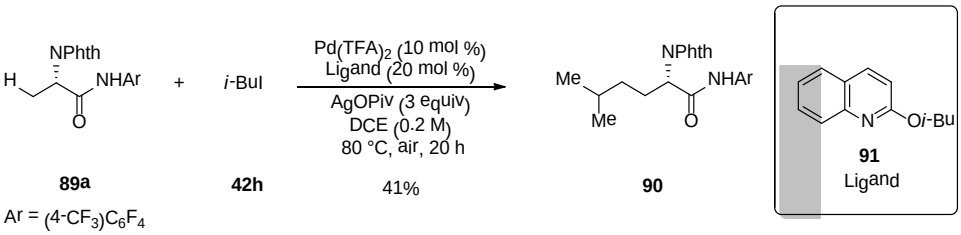
In 2013, the groups of *Ackermann* and *Yoshikai* reported cobalt/*N*-heterocyclic carbene catalytic systems for the *ortho*-alkylation of arenes **38** and **86** with both primary and secondary alkyl chlorides and bromides, independently (Scheme 1.30).[118-120] A radical mechanism was proposed based on the fact that both *trans*- and *cis*-isomers of 1-(*tert*-butyl)-4-cyclohexane afforded products with the same *trans*/*cis* isomeric ratio.



86a **44c** 90% **87**

Scheme 1.30: Cobalt-catalyzed direct alkylation with secondary alkyl bromide **44c**

Recently, *Yu* and co-workers achieved palladium-catalyzed direct C(sp^3)–H alkylation of electron-deficient secondary benzamides **89a** with pyridine- and quinoline-based ligands **91** as crucial promoters (Scheme 1.31).[121] Furthermore, this protocol allowed for the preparation of unnatural amino acids as well.



89a **42h** 41% **90**

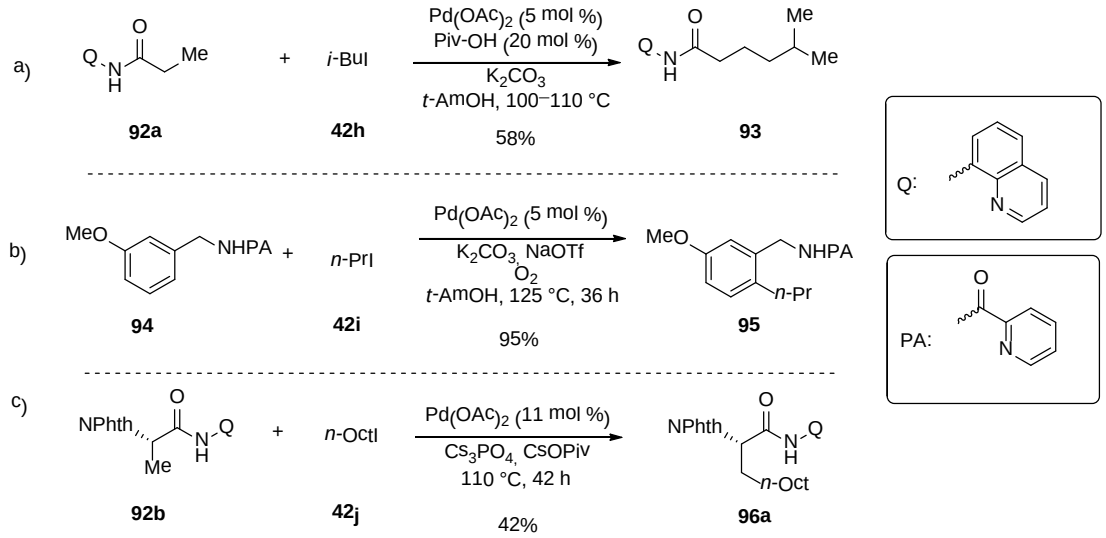
Ar = $(4\text{-}CF_3)C_6F_4$

Scheme 1.31: Palladium-catalyzed direct alkylation of C(sp^3)−H bond

Bidentate Directing Group-Assisted Direct C−H Alkylation

Ever since *Daugulis* and co-workers' work on utilizing 8-aminoquinoline (Q) and picolinamides (PA) as bidentate directing groups for promoting palladium-catalyzed C(sp^3)−H and C(sp^2)−H arylation of amides,[122] many research groups have been intensively exploring the potential of this strategy in transition metal-catalyzed C−H bond functionalization.[123,124]

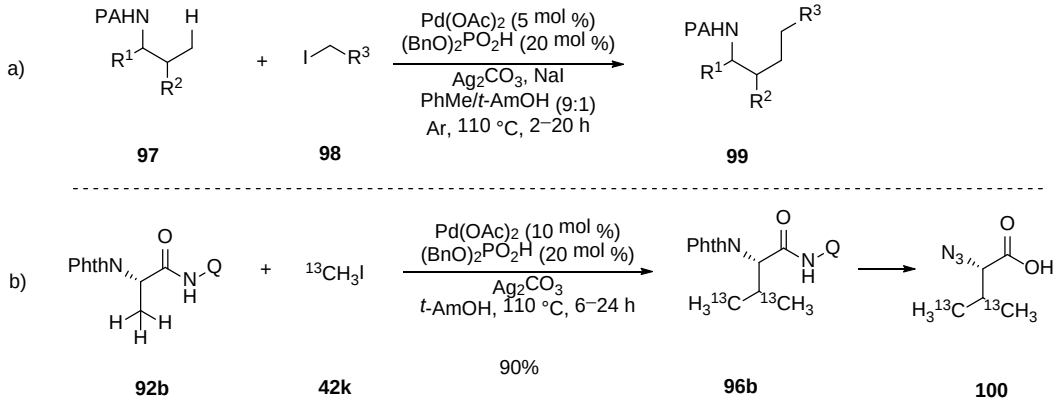
In 2010, the group of *Daugulis* reported several examples of palladium-catalyzed C(sp^3)−H alkylation of amides **92** assisted by 8-aminoquinoline (Scheme 1.32a).[125] Shortly thereafter, *Chen* and co-workers extended the scope of palladium-catalyzed C(sp^2)−H alkylation by picolinamide assistance in substrate **94**, various primary alkyl iodides were tolerated and the directing group could easily be cleaved (Scheme 1.32b).[126] In 2012, *Daugulis* and co-workers published another method for unnatural amino acid preparation. However, only moderate yields were obtained via this C(sp^3)−H alkylation (Scheme 1.32c).[127]



Scheme 1.32: Bidentate DG-assisted palladium-catalyzed direct alkylations

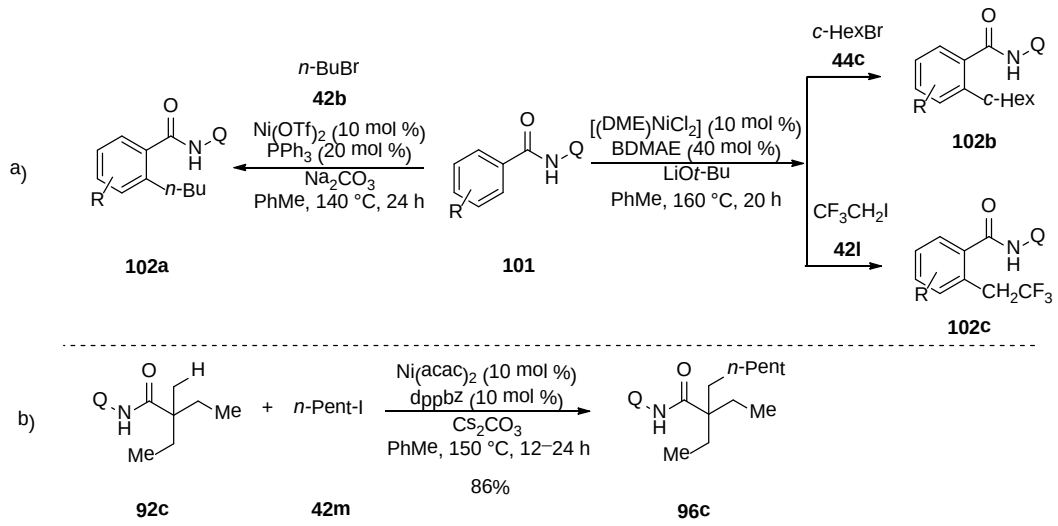
Following their previous publication of direct C(sp^2)−H alkylation, *Chen* and co-workers disclosed efficient palladium catalyst for the alkylation of C(sp^3)−H bonds of aliphatic amine substrates **97** via picolinamide assistance.[128] Ag_2CO_3 and dibenzyl phosphate $(BnO)_2PO_2H$ were determinant promoters of this reaction (Scheme 1.33a). This research group also succeeded in optimizing *Daugulis*' work on unnatural amino acids synthesis under essentially the same conditions (Scheme 1.33b). This approach provided a convenient and powerful solution to site-selective incorporation of isotopically labeled moieties into the carbon scaffolds of amino acids.[129] Similar transformations were also

reported by the group of *Shi.*[130,131]



Scheme 1.33: Bidentate DG-assisted palladium-catalyzed direct alkylation of C(sp^3)–H bond

Besides palladium, *Chatani* and co-workers reported the first example of bidentate directing group-assisted nickel-catalyzed C–H alkylation of benzamide derivatives **101** (Scheme 1.34a).[132] A variety of functionalized primary alkyl bromides **42** were applicable in the alkylation reaction. Shortly thereafter, the group of *Ackermann* successfully utilized challenging secondary alkyl bromides **44** and trifluoroethyl iodide (**42l**) in this reaction (Scheme 1.34a).[133] Furthermore, *Ge* and co-workers achieved nickel-catalyzed direct alkylation of unactivated C(sp^3)–H bonds with the assistance of 8-aminoquinoline (Scheme 1.34b).[134] The reaction favored the C–H bonds of methyl groups over the methylene C–H bonds and tolerated various functional groups. It should be mentioned that inexpensive iron catalysts were also demonstrated to be competent in promoting bidentate directing group-assisted direct C–H alkylation of C(sp^2)–H bonds with both primary and secondary alkyl electrophiles, as was independently reported by the groups of *Nakamura*[135] and *Cook.*[136,137]

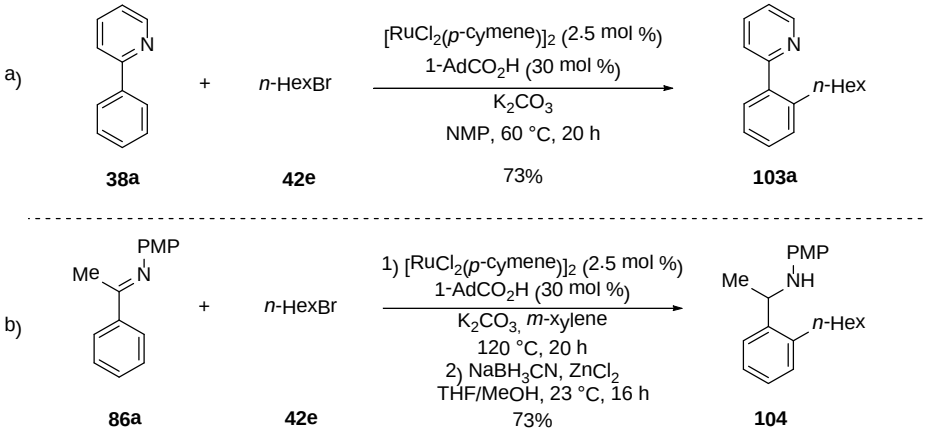


Scheme 1.34: Bidentate DG-assisted nickel-catalyzed direct alkylation

Ruthenium(II)-Catalyzed Direct C–H Alkylation

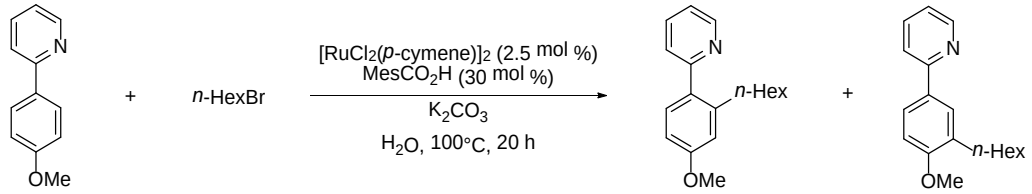
Based on their research on carboxylate-assisted ruthenium(II)-catalyzed direct arylations,[138,139] *Ackermann* and co-workers successfully extended this catalytic system to unprecedented ruthenium(II)-catalyzed direct C–H alkylation and benzylation of 2-phenylpyridines **38**.[140,141] Among various screened carboxylates, sterically bulky 1-AdCO_2H proved to be the most efficient. Primary

alkyl iodides, bromides, chlorides served as viable substrates, while alkyl bromides **42e** provided the best yields (Scheme 1.35a).



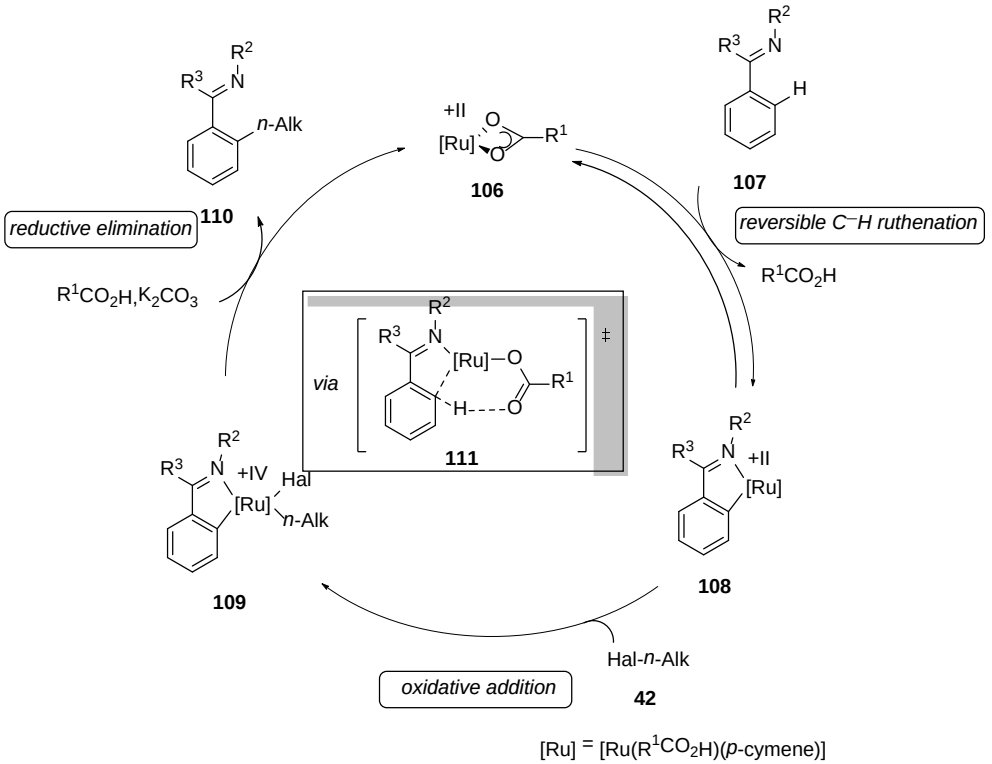
Scheme 1.35: Ruthenium(II)-catalyzed direct alkylation with primary alkyl halide **42e**

Furthermore, aromatic ketimines **86** could also be efficiently alkylated, which was exploited for the synthesis of secondary amines **104** through a sustainable one-pot-process (Scheme 1.35b). Further investigation by performing this direct alkylation in water yielded *meta*-alkylated by-product **105a** (Scheme 1.36),[142] This *meta*-alkylation took place under solvent-free reaction conditions as well, albeit in low yields.



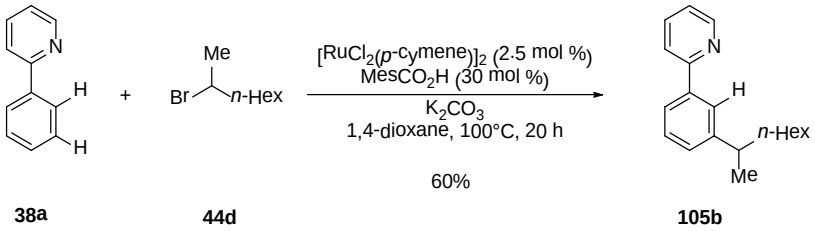
Scheme 1.36: Preliminary observation of ruthenium(II)-catalyzed direct *meta*-alkylation

Based on the mechanistic studies, a catalytic cycle proposed by *Ackermann* and co-workers is shown below in Scheme 1.37. This catalytic cycle initiated with the formation of a ruthenium(II) carboxylate complex **106**, which reversibly activated the *ortho*-C−H bond through carboxylate-assisted deprotonation (**109**) to form cyclometalated intermediate **108**. Thereafter, complex **108** reacted with primary alkyl halides **42** via formal oxidative addition to yield intermediate **109**. Finally, reductive elimination regioselectively gave rise to the alkylated arene **110**, and thereby regenerated the active catalyst **106**.



Scheme 1.37: Proposed catalytic cycle for ruthenium(II)-catalyzed direct alkylation

However, shortly thereafter, *Ackermann* and *Hofmann* demonstrated that *meta*-alkylation products can be isolated in high yields by using secondary alkyl halides **44**.[143] The direct alkylations occurred under mild conditions with ample scope and tolerated valuable functional groups (Scheme 1.35).



Scheme 1.38: Ruthenium(II)-catalyzed direct *meta*-alkylation with secondary alkyl halide **44d**

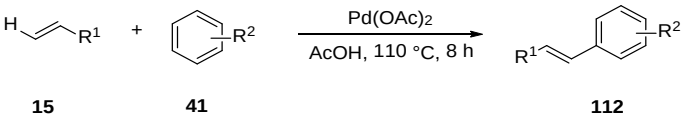
Concerning the mechanism, the authors proposed that cyclometalation activated the arene for a S_EAr-type alkylation with the secondary alkyl halides through the strong directing group effect of the Ru−C σ-bond, thus leading to a functionalization in the *para*- or *ortho*-position with respect to the Ru−C bond. The detailed mechanism will be discussed in Chapter 3.1.

1.4 Transition Metal-Catalyzed Oxidative C−H Alkenylation

Encouraged by the need for green and sustainable chemistry,[144] synthetic chemists are constantly seeking more efficient ways to construct C−C bonds, the essential link in all organic molecules. In the early 1970s, *Mizoroki*[10] and *Heck*[11] disclosed palladium-catalyzed C−C bond forming reaction between an aryl halide and an alkene (see above). In fact, before achieving insertion of palladium into Ar−X bond under catalytic condition, *Heck* also performed in situ synthesis of ArPdX complexes from

palladium salts and aryl-metal complexes in the late 1960s.[145,146] However, both methods produce stoichiometric amounts of byproducts. In consideration of the atom economy principle,[147] direct C–C bond formation from two C–H bonds would be the most promising approach.

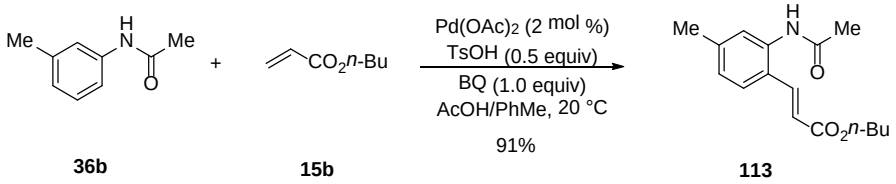
In this context, in 1967 *Fujiwara* and *Moritani* achieved the synthesis of stilbene employing the reaction of the styrene-$PdCl_2$ complex with benzene[148] and, in 1968, the oxidative coupling between styrene **15** and benzene **41** with two turnovers of palladium.[149] Shortly thereafter, they reported a catalytic version of this reaction (Scheme 1.39).[150]



15 **41** **112**

Scheme 1.39: Palladium-catalyzed Fujiwara–Moritani reaction

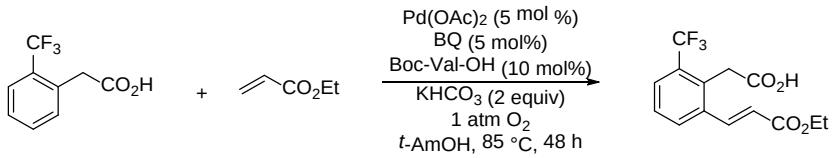
Since *Fujiwara* and *Moritani*'s seminal work, enormous efforts have been devoted to optimizing and extending the scope of this reaction.[26,151] In 2002, the groups of *de Vries* and *van Leeuwen* reported an exceptionally mild Fujiwara-Moritani reaction which employed anilide directing groups to control reactivity and site-selectivity (Scheme 1.40). The addition of TsOH played an important role in improving the reactivity, which was believed to increase the electrophilicity of the palladium catalyst and thus to facilitate C–H palladation.[152]



36b **15b** **113**

Scheme 1.40: Palladium-catalyzed direct alkenylation of anilide **36b**

In 2010, *Yu* and co-workers disclosed the oxidative coupling between phenylacetic acid derivatives **114** and alkenes **15** (Scheme 1.41).[153] Weak coordination between C=O bond of the carboxylate and $Pd(OAc)_2$ was proposed to facilitate the *ortho*-C–H functionalization. Notably, introducing mono-protected amino acids (MPAAs) **116** as ligands enhanced both site-selectivity and reactivity. Electron-deficient substrates **114**, which were previously inactive, could then undergo facile olefination.

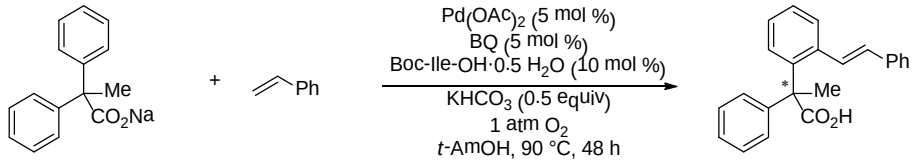


114a **15a** **115a**

Scheme 1.41: Palladium-catalyzed direct alkenylation of phenylacetic acid **114a**

Moreover, MPAAs **116** are not only limited to enhance the reaction rate and regioselectivity, but can also function as chiral ligand to control enantioselectivity.[154,155] *Yu* and coworkers demonstrated that alkenylation of diphenylacetate sodium salt **114b** was accompanied by desymmetrization to afford

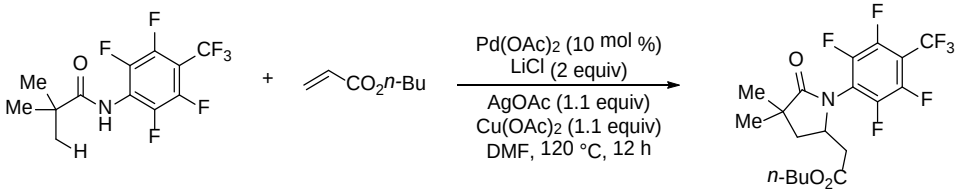
product **115b** with modest to excellent enantioselectivities (Scheme 1.42).



114b **15c** 73% yield, 97% *ee* **115b**

Scheme 1.42: Enantioselective palladium-catalyzed oxidative C−H alkenylation

Subsequently, *Yu* and co-workers achieved the challenging C(sp^3)−H bond alkenylation of aliphatic secondary amides **89** (Scheme 1.43).[156] As regards the mechanism, initial formation of a five-membered palladacycle assisted by amide directing group was proposed. LiCl served as a source of chloride anions which stabilized palladium(0) and facilitated the formation of chloride-bridged bimetallic palladium species.

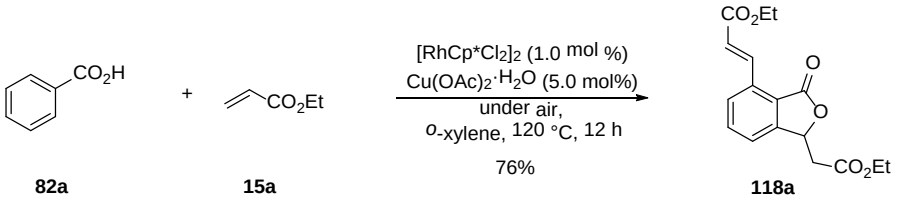


89b **15b** 88% **117**

Scheme 1.43: Palladium-catalyzed direct alkenylation of C(sp^3)−H bond

Besides palladium, other transition metal catalysts have been reported for enabling the oxidative C−H alkenylation reactions as well. In recent years, great effort has been devoted to rhodium-catalyzed oxidative C−H alkenylation.[157,158] Despite the relatively high cost of rhodium catalysts, it is still of major interests owing to the high efficiency, reactivity, and functional group tolerance.

An early contribution by *Matsumoto*, *Yoshida*, and coworkers achieved rhodium-catalyzed oxidative C−H olefination of benzene with ethylene.[159] In 2007, *Satoh* and *Miura* reported an example of rhodium-catalyzed C(sp^2)−H bond alkenylation (Scheme 1.44).[160] At low catalyst loadings, the olefination of benzoic acid **82a** resulted in *ortho*-alkenylated lactone **118a**, which arose from di-*ortho*-substitution and subsequent intramolecular oxa-Michael addition.

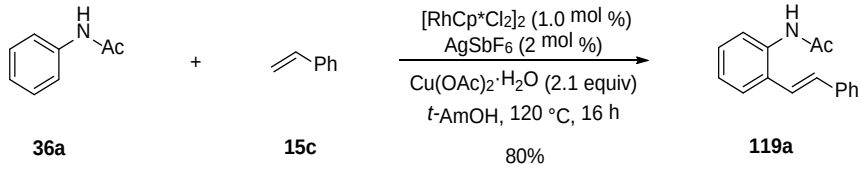


82a **15a** 76% **118a**

Scheme 1.44: Rhodium-catalyzed C−H alkenylation of benzoic acid (**82a**)

Patureau and *Glorius* reported a related rhodium-catalyzed *ortho*-alkenylation of anilides **36** using an in-situ generated cationic rhodium complex (Scheme 1.45).[161] Comparing to palladium catalysts, lower catalyst loadings, good functional group tolerance and higher reactivity of electron-neutral olefins were realized. Under elevated pressure, ethylene reacted to yield the corresponding

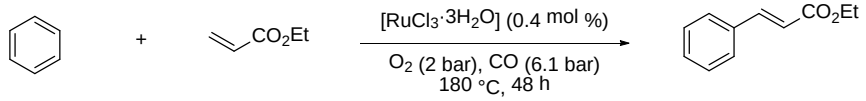
acetanilido-substituted styrene in moderate yield.



36a **15c** **119a**

Scheme 1.45: Rhodium-catalyzed C−H alkenylation of anilide **36a**

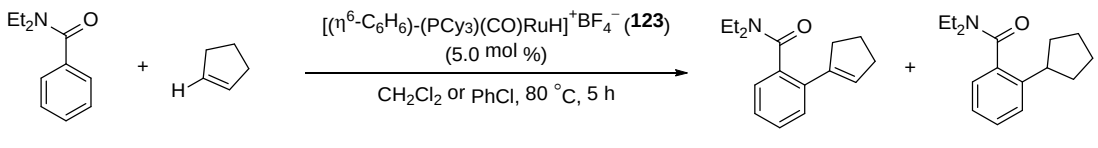
In contrast, significantly less expensive, yet highly reactive ruthenium catalysts have only recently been developed for facilitating oxidative C−H bond alkenylations on arenes.[162] In 2001, *Milstein* and co-workers reported an example of synthesizing styrene derivatives (**112a**) via ruthenium-catalyzed oxidative coupling of arenes (**41a**) with olefins (Scheme 1.46).[163] Whereas a range of ruthenium complexes, such as $RuCl_3 \cdot H_2O$, $[Ru(CO)_3Cl_2]_2$, $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$, $Ru(NO)Cl_3 \cdot 5H_2O$ and $Ru(F_3CCOCHCOCF_3)_3$, enabled similar catalytic reactivities, yet $Ru_3(CO)_{12}$ exhibited low efficiency. Carbon monoxide was proposed to stabilize a cationic ruthenium species, and a value of KIE ≈ 2 was established with substrates C_6H_6 (**41a**) and C_6D_6, indicating the C−H bond metalation to be the rate-determining step. Unfortunately, low reactivity of the simple alkenes as well as the low regioselectivity limited this approach for practical application. Furthermore, this strategy was limited by the high temperature and high pressure of molecular oxygen and carbon monoxide.



41a **15a** 35% **112a**

Scheme 1.46: Ruthenium-catalyzed C−H alkenylation of simple arene **41a**

Fortunately, this limitation of low selectivity observed in alkenylations of simple arenes was successfully addressed by employing substrates with directing groups for chelating assistance. In 2010, the group of *Yi* reported on oxidative C−H alkenylation of benzamide derivatives **120** with unactivated alkenes (**15d**) enabled by cationic ruthenium hydride complex $[(\eta^6\text{-}C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ (**123**) (Scheme 1.47).[164] In contrast to previous work of the *Milstein* group, a negligible KIE of 1.1 was observed for the competition reaction between $C_6H_5C(O)NEt_2$ (**120a**) and its deuterated analogue $C_6D_5C(O)NEt_2$, thus suggesting a reversible arene C−H bond metalation step. In the absence of an external oxidant, an excess of alkene **15** as well as the alkenylated product **121** served as the hydrogen scavenger. Unfortunately, participation of **121** led to a mixture of the products **121** and **122**.

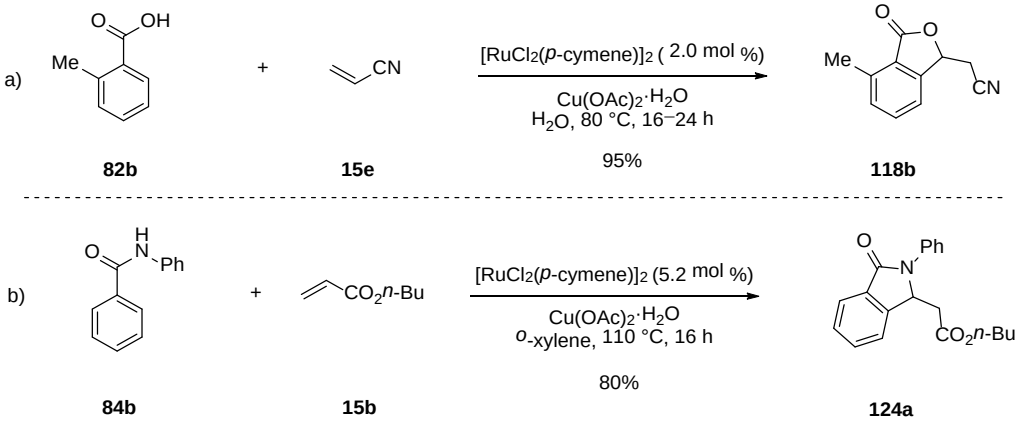


120a **15d** **121a** **122**

Scheme 1.47: Ruthenium-catalyzed C−H alkenylation of benzamide **120a**

In 2011, *Ackermann* and *Pospech* disclosed the lactone synthesis via ruthenium(II)-catalyzed oxidative

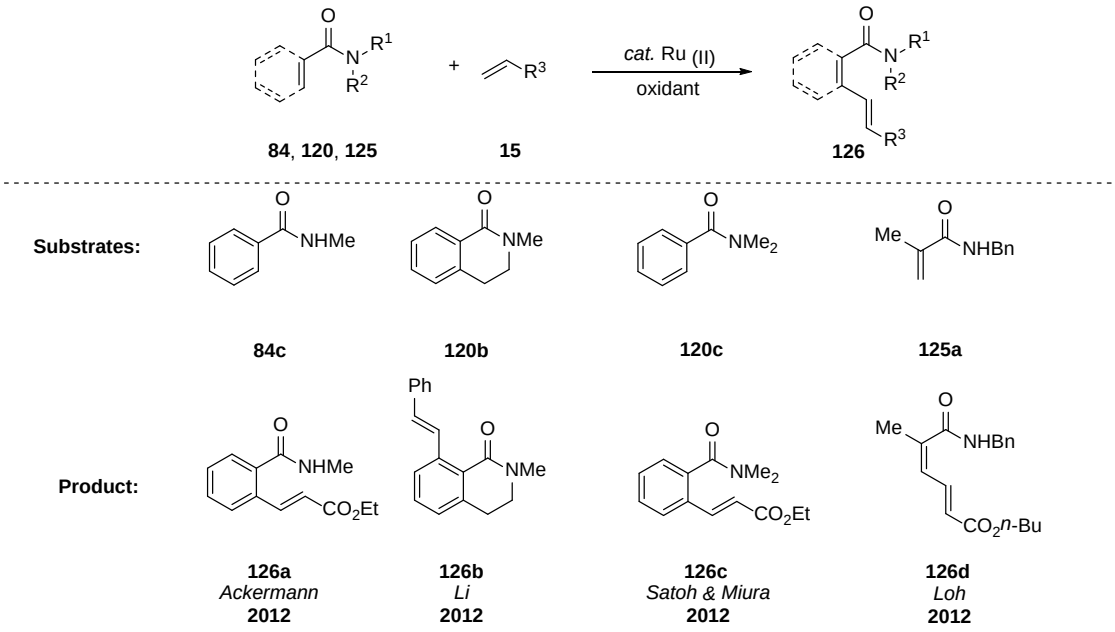
C−H bond alkenylation of benzoic acids **82** with acrylates or acrylonitrile (**15e**) in water (Scheme 1.48a).[165] With stoichiometric amounts of $Cu(OAc)_2 \cdot H_2O$ as the oxidant, the reaction proceeded smoothly under mild reaction conditions. The *ortho*-alkenylated intermediate underwent immediate intramolecular oxa-Michael reaction and delivered lactone derivatives **118** in good yields.



Scheme 1.48: Ruthenium(II)-catalyzed C−H alkenylation of benzoic acid (**82b**) and benzanilide (**84b**)

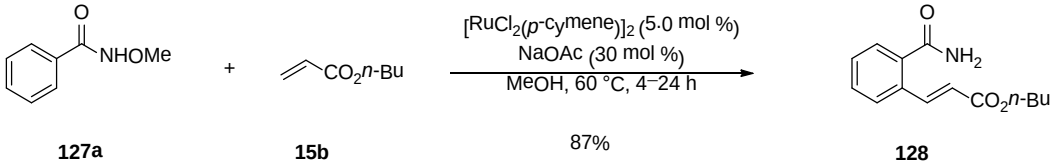
A similar phenomenon was observed by the groups of *Satoh/Miura* and *Ackermann* in the ruthenium(II)-catalyzed oxidative alkenylation of benzanilide (**84b**) (Scheme 1.48b).[166] Indeed, the initially formed alkenylated derivative underwent intramolecular Michael reaction to give bicyclic benzamide **124a**.

Subsequently, ruthenium(II)-catalyzed oxidative alkenylation of various amide derivatives were studied (Scheme 1.49). *Satoh*, *Miura* and co-workers demonstrated the oxidative alkenylation of *N*,*N*-dimethylbenzamide (**120c**) in the presence of co-catalytic $AgSbF_6$, $[RuCl_2(p\text{-cymene})]_2$ and $Cu(OAc)_2 \cdot H_2O$.[167] Notably, no reaction would occur in the absence of the silver salt. *Li* and co-workers achieved alkenylation of cyclic *N*-protected isoquinolones **120b** under similar reaction conditions.[168] The *Ackermann* group showed that the use of less expensive KPF_6 instead of $AgSbF_6$ enabled olefination of *N*-monosubstituted benzamides **84c** using environmentally benign water as solvent.[169] Moreover, this approach was not limited to aromatic amides. Ruthenium(II)-catalyzed oxidative alkenylation of acrylamines (**125a**) was also developed by *Zhang* and *Loh,*[170] and moderate to good yields and excellent site-selectivity were obtained.



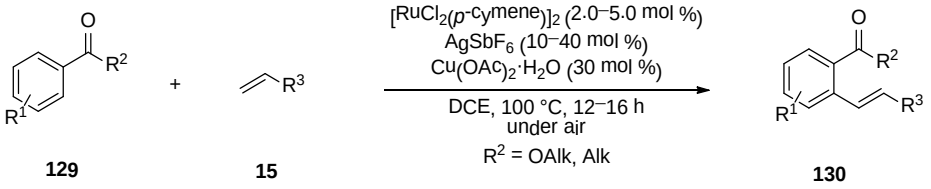
Scheme 1.49: Ruthenium(II)-catalyzed C−H alkenylation of benzamide derivatives

Alternatively, ruthenium(II)-catalyzed C−H alkenylation of benzamides could be realized without external oxidant. Pre-functionalized starting materials bearing an internal oxidizing directing groups such as *N*-methoxybenzamide (**127a**)[171] and *N*-hydroxybenzamides[172] smoothly delivered olefinated N−deprotected benzamide (**128**) (Scheme 1.50).



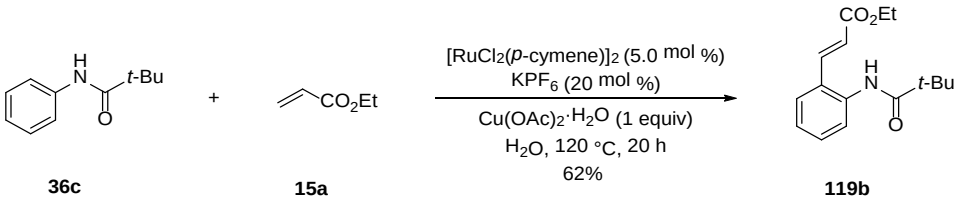
Scheme 1.50: Ruthenium(II)-catalyzed C−H alkenylation of *N*-methoxybenzamide (**127a**)

In addition to chelation-assisted olefination of benzamides, the groups of *Ackermann* and *Jeganmohan* independently studied ruthenium(II)-catalyzed oxidative alkenylation of readily available, yet weakly coordinating[21] esters,[173,174] and phenones.[175] Thus, a catalytic system consisting of $[RuCl_2(p\text{-cymene})]_2$, $AgSbF_6$, and co-catalytic amounts of $Cu(OAc)_2 \cdot H_2O$ utilizing air as terminal oxidant allowed for efficient aerobic C−H bond alkenylations of aryl esters, phenones **129** (R^2 = OAlk, Alk, respectively) utilizing air as a terminal oxidant (Scheme 1.51). Most recently, *Loh* and coworkers disclosed ruthenium(II)-catalyzed oxidative cross-coupling of acrylates. This protocol offered a straightforward and atom-economical synthesis of functionalized (*Z*,*E*)-muconate derivatives with good stereo- and chemo-selectivities.[176]



Scheme 1.51: Ruthenium(II)-catalyzed C−H alkenylation of esters, phenones and aldehydes **129**

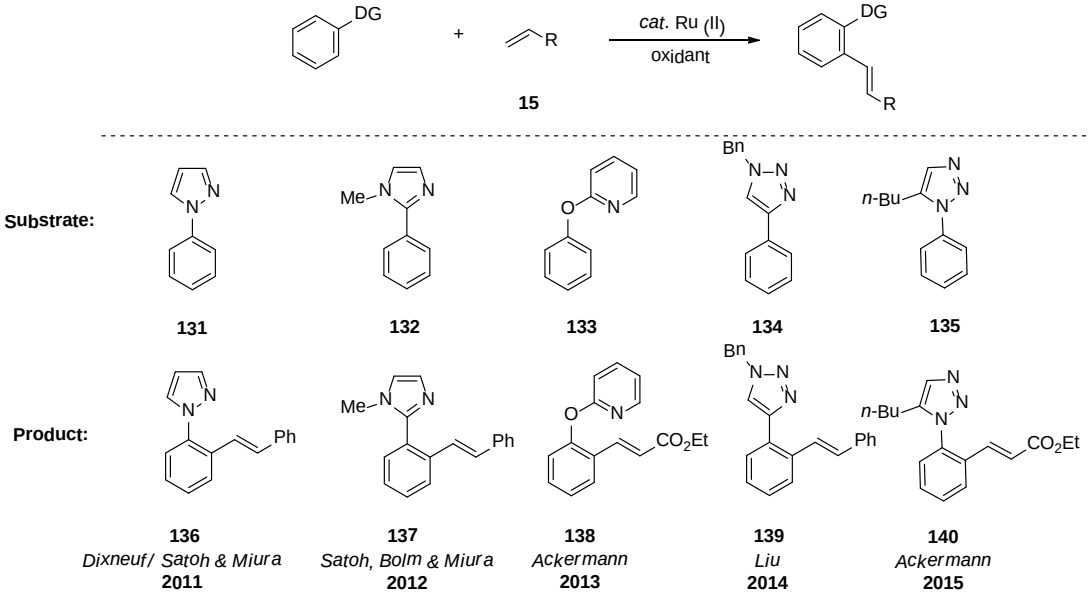
Moreover, not only arenes bearing electron-withdrawing groups, but also electron-rich substrates could undergo facile alkenylation under ruthenium(II) catalysts. In 2012, *Ackermann* and co-workers reported on the first ruthenium(II)-catalyzed oxidative alkenylation of anilides **36** with alkenes **15** in water (Scheme 1.52).[169] Intramolecular competition experiments with *N*-benzoyl anilides delivered solely alkenylated products on the benzamide moieties.



36c **15a** **119b**

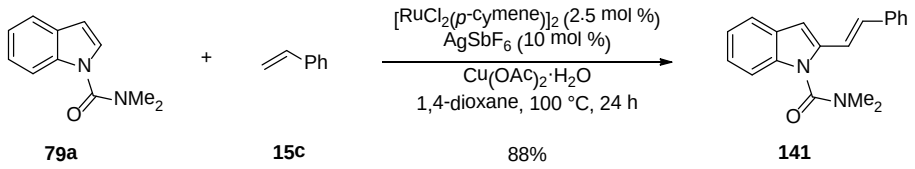
Scheme 1.52: Ruthenium(II)-catalyzed C−H alkenylation of anilide **36c**

Ruthenium(II)-catalyzed oxidative alkenylation of arenes also proved viable by utilizing heterocyclic directing groups (Scheme 1.53). *N*-Arylpyrazoles **131**,[166,177] 2-arylimidazoles **132**[167] were demonstrated to be suitable substrates by the groups of *Dixneuf, Bolm*, *Satoh* and *Miura*. It should be mentioned that *Ackermann* and *Ma* reported on the ruthenium(II)-catalyzed oxidative olefination of phenol derivatives **133** bearing a pyridine directing group which can easily be removed.[178] Recently, the groups of *Liu* and *Ackermann* disclosed ruthenium(II)-catalyzed oxidative alkenylation of arenes **134** and **135** assisted by 1,2,3-triazole directing group.[179-181]



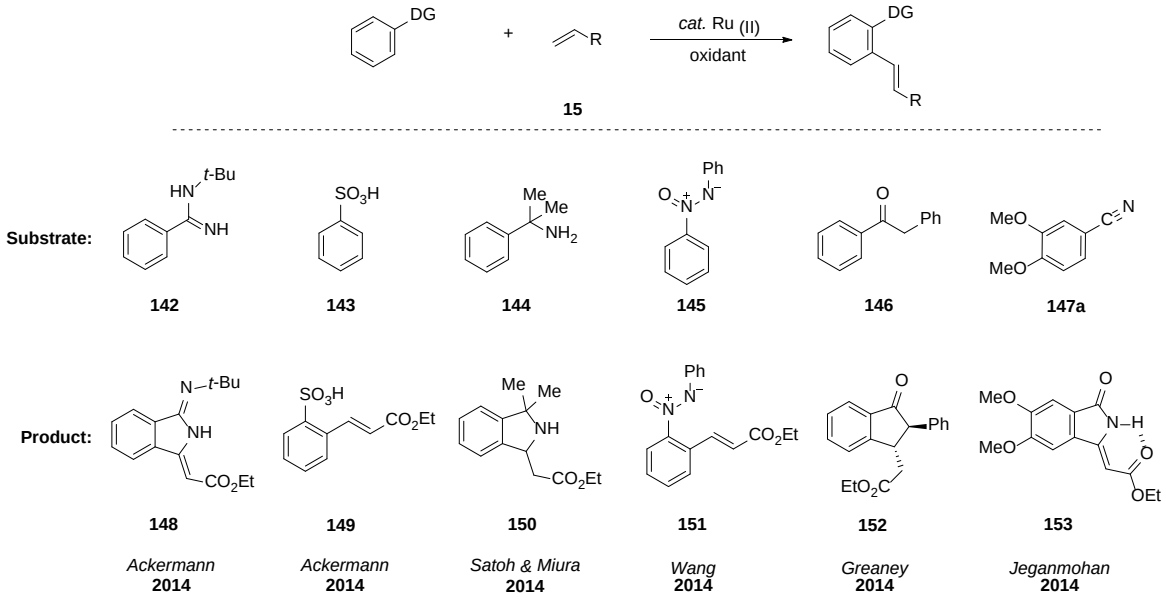
Scheme 1.53: Ruthenium(II)-catalyzed C−H alkenylations directed by heterocyclic DGs

Ruthenium(II)-catalyzed oxidative alkenylations of heterocyclic compounds were achieved with assistance of various directing groups employing the catalytic system described above, albeit with different catalytic efficacies. Thus, *Satoh, Miura* and co-workers disclosed carboxylic acid-directed ruthenium(II)-catalyzed oxidative alkenylation of thiophenes, benzothiophenes, benzofurans, pyrroles, and indoles.[182] Subsequently, the groups of *Prabhu* and *Wang* reported on the ruthenium(II)-catalyzed C-2 alkenylation of indoles using either *N*-benzoyl[183] or *N*-carbamoyl (**79a**)[184] moiety as a directing group, respectively (Scheme 1.54).



Scheme 1.54: Ruthenium(II)-catalyzed C−H alkenylation of *N*-carbamoylindole **79a**

Most recently, novel and synthetically useful directing groups have been utilized for ruthenium(II)-catalyzed oxidative alkenylations (Scheme 1.55). For instance, *Ackermann* and co-workers achieved direct C−H olefination of amidines **142**[185] and of sulfonic acids **143**.[186] The group of *Satoh* and *Miura* disclosed free amino group-directed *ortho*-alkenylation and successive cyclization to produce (isoindol-1-yl)acetic acid derivatives **150**.[187] Azoxybenzenes **145** also underwent smooth oxidative alkenylation under ruthenium(II) catalysis.[188] The group of *Greaney* reported on the cascade C−H bond functionalization based on ruthenium(II)-catalyzed oxidative alkenylation.[189] 1-Indanones **152**, indeno-indenes, and indeno-furanones became accessible via this approach. Moreover, *Jeganmohan* and co-workers demonstrated a highly regio- and stereoselective synthesis of (*Z*)-3-methyleneisoindolin-1-ones **153** by ruthenium(II)-catalyzed annulation of aromatic nitrile **147a**.[190]

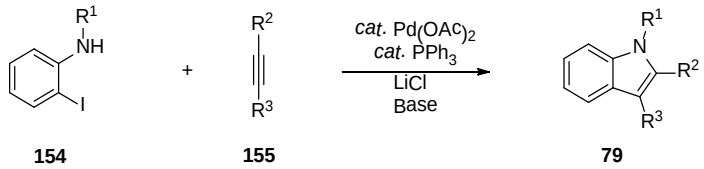


Scheme 1.55: Recent examples of ruthenium(II)-catalyzed oxidative C−H alkenylation

1.5 Transition Metal-Catalyzed Alkyne Annulations by C−H/Het−H Functionalizations

Aromatic heterocycles represent structural motifs which can be found in a great number of biologically active natural and synthetic compounds, pharmaceuticals, and agrochemicals.[191] Moreover, aromatic heterocycles are widely used for synthesis of polymeric materials and dyes of high value. Chemists have been making great effort towards preparation of these heterocyclic compounds for decades. Among a variety of new synthetic methodologies, transition metal-catalyzed reactions are of particular interests for direct constructions of complex structures from readily

accessible starting materials.[192-194] Inspired by the traditional cross-coupling chemistry, palladium-catalyzed processes have emerged as a powerful tool in heterocycle synthesis,[195,196] among which, the *Larock* indole-synthesis is extremely versatile and can be utilized in preparing a variety of indole derivatives **79** (Scheme 1.56).[197] However, the same as in the traditional cross-coupling chemistry requirement of prefunctionalized starting materials, discussed above in Chapter 1.1, represents the major disadvantage of this approach.

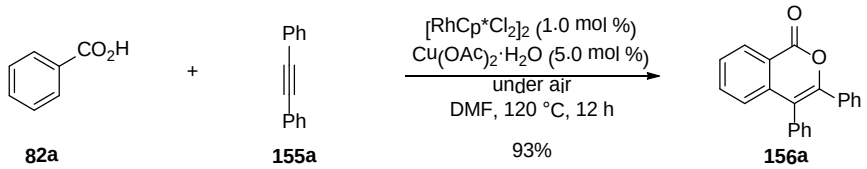


154 **155** **79**

Scheme 1.56: *Larock* indole synthesis

Along with the rapid development of various transition metal-catalyzed C−H bond functionalization methods, more attention have been drawn to apply these methodologies into synthesis of natural products and pharmaceuticals.[198-200]

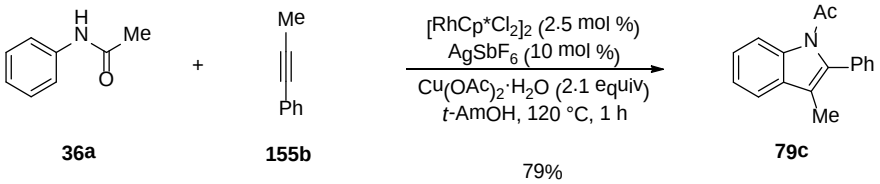
In this context, the group of *Miura* and *Satoh* reported the rhodium-catalyzed annulation of benzoic acids **82** with internal alkynes **155**, a variety of isocoumarin derivatives **156** were prepared using this method (Scheme 1.57).[160,201]



82a **155a** **156a**

Scheme 1.57: Rhodium-catalyzed oxidative annulation with benzoic acid (**82a**)

Shortly thereafter, *Fagnou* and co-workers published a rhodium-catalyzed indole synthesis through C−H/N−H bond functionalizations (Scheme 1.58).[202] Acetanilides **36** underwent insertion of internal alkynes **155** through initial C−H bond activation followed by oxidative annulation to produce substituted indoles **79**. Subsequently, heterocycle synthesis employing rhodium catalysis has been extensively studied by the groups of *Glorius*, *Fagnou*, and *Miura* and *Satoh*, among others.[157,203,204]

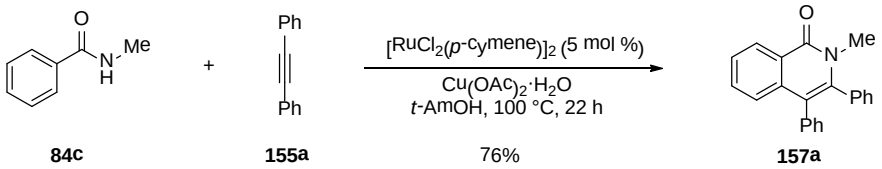


36a **155b** **79c**

Scheme 1.58: Rhodium-catalyzed indole synthesis via C−H/N−H bond functionalizations

Encouraged by their success in carboxylate-assisted ruthenium(II)-catalyzed alkylation and arylation reactions,[17,205] *Ackermann* and co-workers set out to study annulations by using less expensive ruthenium(II) catalysts.[206] Thus, in 2011, they reported on the first ruthenium(II)-catalyzed alkyne annulations by C−H/Het−H bonds functionalization (Scheme 1.59). [207] This isoquinolone **157a**

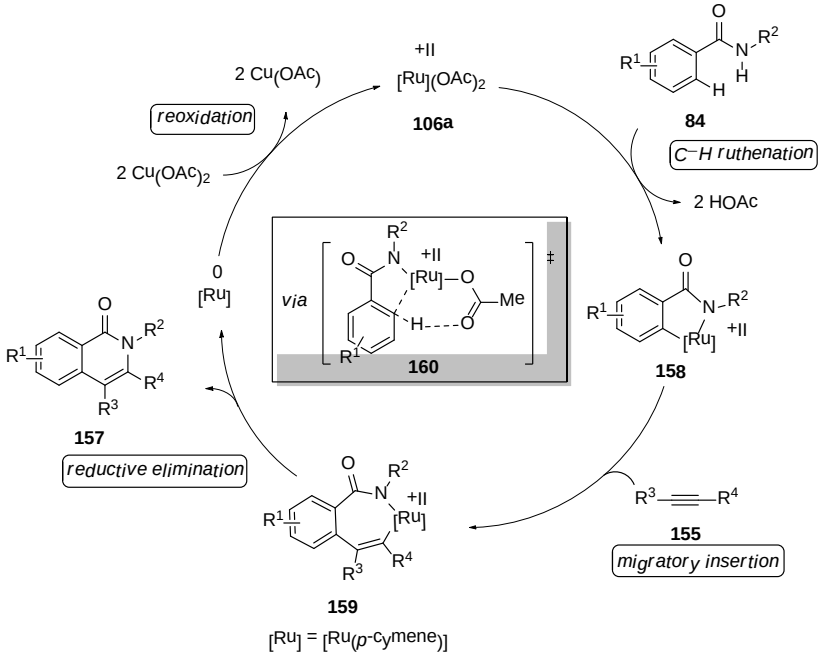
synthesis proceeded smoothly with $[RuCl_2(p\text{-cymene})]_2$ as the catalyst and stoichiometric amounts of $Cu(OAc)_2 \cdot H_2O$ as an oxidant.



84c **155a** 76% **157a**

Scheme 1.59: Ruthenium(II)-catalyzed isoquinolone synthesis via C−H/N−H bonds functionalizations

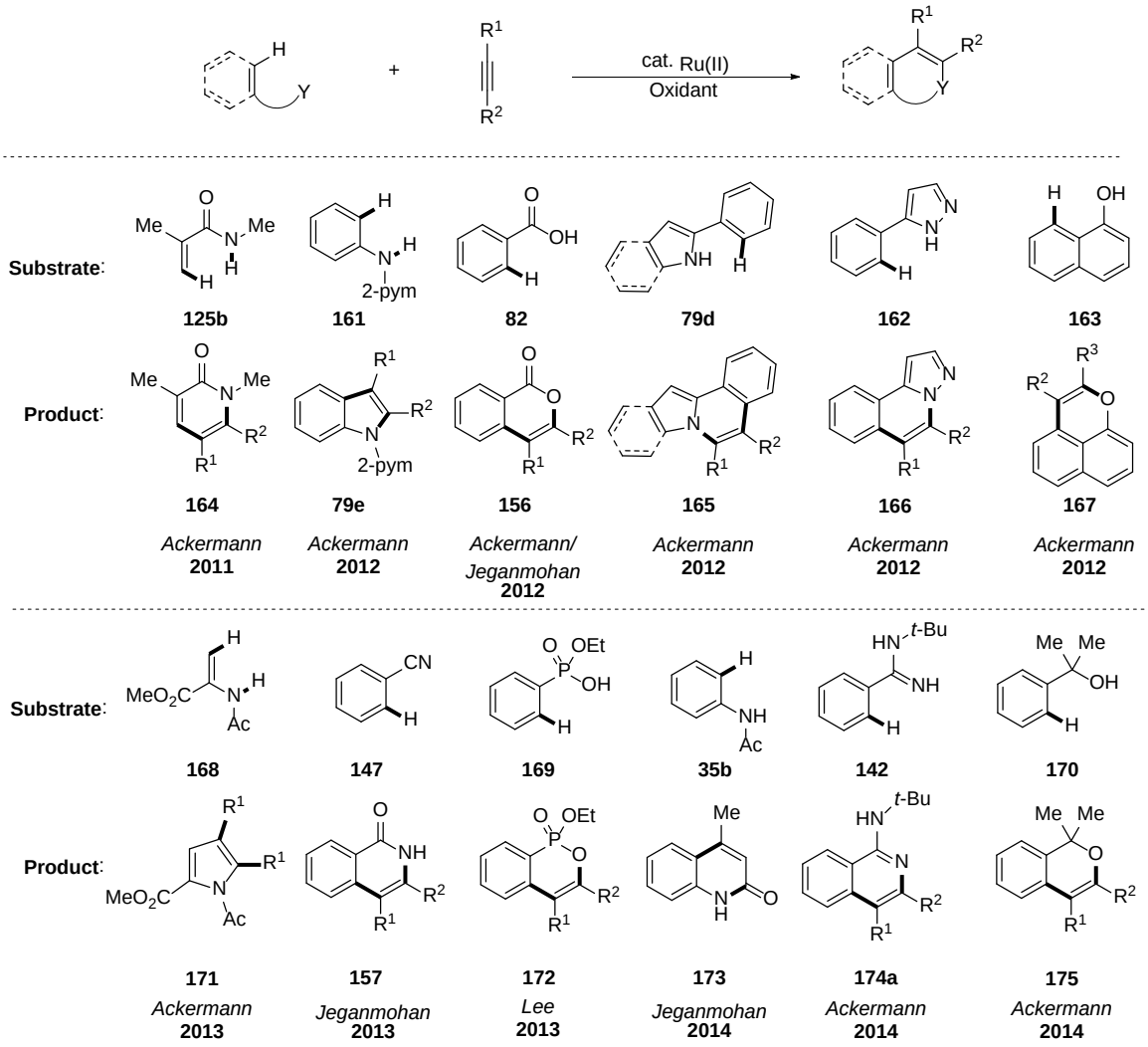
Experiments with isotopically labeled starting materials disclosed a KIE of 2.6, which indicated a kinetically relevant C−H activation step. Based on mechanistic studies, the reaction was proposed to proceed by an initial ruthenation via acetate-assisted C−H bond cleavage followed by migratory insertion of the alkyne, subsequent C−N bond-forming reductive elimination and final reoxidation to generate the active Ru(II) species (Scheme 1.60).



Scheme 1.60: Proposed catalytic cycle for ruthenium(II)-catalyzed oxidative annulation

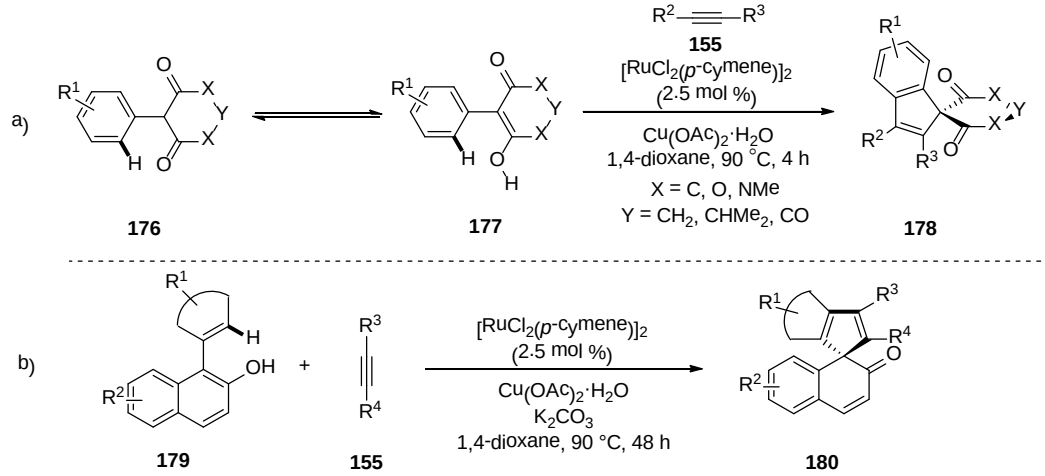
Dixneuf and Wang carried out detailed mechanistic study regarding the C−H bond ruthenation and the alkyne insertion.[208,209] The structures of isolated key intermediates were in line with the mechanism proposed in Scheme 1.60.

Encouraged by the initial success, the groups of *Ackermann* and others made efforts to extend the scope of ruthenium(II)-catalyzed oxidative alkyne annulations through C−H/Het−H bond functionalization. In this context, various substituted heterocycles such as 2-pyridones **164**,[210] indoles **79**,[211] isocumarins (**156**),[212,213] annulated pyrans (**167**),[214] isochromenes (**175**),[215] pyrroles (**171**),[216] phosphaisocoumarins **172**,[217] quinolinones **173**,[218] isoquinolones **157**[219] and isoquinolines **174a**[185,220] were prepared in the last few years. 5-Aryl-1*H*-pyrazoles **162**,[221] 2-arylpyrroles and 2-arylindoles **79**[222] also underwent smooth annulation with alkynes under ruthenium(II) catalyst (Scheme 1.61)



Scheme 1.61: Recent examples of ruthenium(II)-catalyzed oxidative annulation

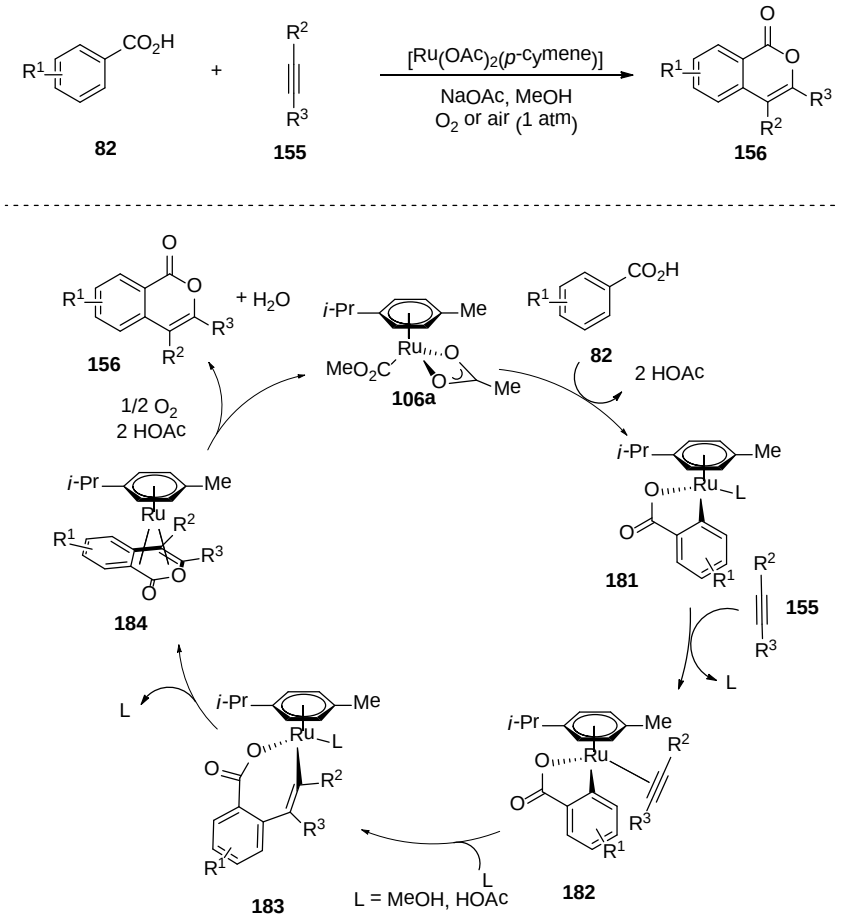
In 2012, *Lam* and co-workers developed ruthenium(II)-catalyzed oxidative alkyne annulations by 2-aryl-1,3-dicarbonyl compounds **176** involving formal functionalization of C(sp^3)–H and C(sp^2)–H bonds, thus affording products **178** containing all-carbon quaternary centers (Scheme 1.62a).[223]



Scheme 1.62: Ruthenium(II)-catalyzed oxidative annulation via C(sp^3)–H/C(sp^2)–H functionalization

The group of *Luan* also reported on a similar ruthenium(II)-catalyzed cyclization reaction of 1-aryl-2-naphthols **179**.[224] Dearomatized spirocyclic molecules bearing an all-carbon quaternary stereocenter could be obtained by this novel method with good yields and excellent site-selectivity (Scheme 1.62b).

However, due to the oxidative character of the reactions discussed above, stoichiometric amounts of external oxidants were required to regenerate the active catalyst. Very recently, *Ackermann* and co-workers developed unprecedented ruthenium(II)-catalyzed oxidative alkyne annulations with molecular oxygen as the sacrificial oxidant in the absence of any cooxidant (Scheme 1.63).[225]

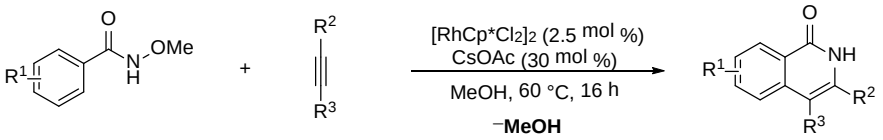


Scheme 1.63: Ruthenium(II)-catalyzed aerobic alkyne annulations and proposed catalytic cycle

This novel method prevented the use of copper or silver salts and thus generated water as the only byproduct. Moreover, a ruthenium(0) sandwich complex **184** was identified as a key intermediate of the catalytic cycle. Compound **184** was reoxidized by molecular oxygen to regenerate the active catalytic species **106a**.

Alternatively, a recently emerged strategy of using directing/oxidizing groups as internal oxidant represented itself as an important alternative in C–H functionalization.[226] *Fagnou* and co-workers reported pioneering work of using internal oxidants for alkyne annulations involving C–H/N–O bond cleavages in 2010.[227] Hydroxamic acid esters **127** were employed as substrates for the rhodium-catalyzed annulation. The only byproduct of this reaction is methanol, and the reaction

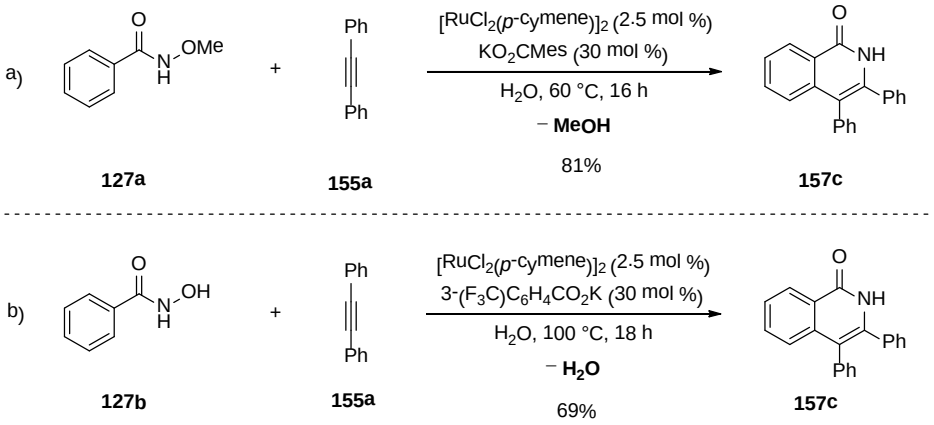
proceeded smoothly under mild conditions (Scheme 1.64).



127a **155** **157**

Scheme 1.64: Rhodium-catalyzed isoquinolone synthesis via C−H/N−O bond functionalizations

In 2011, the same strategy was independently applied in ruthenium(II)-catalyzed redox-neutral isoquinolone synthesis by the groups of *Ackermann,*[228] *Li* and *Wang.*[229] *Ackermann* and co-workers also showed that free hydroxamic acids (**127b**) were competent substrates, and the reaction proceeded smoothly in water (Scheme 1.65).[172]

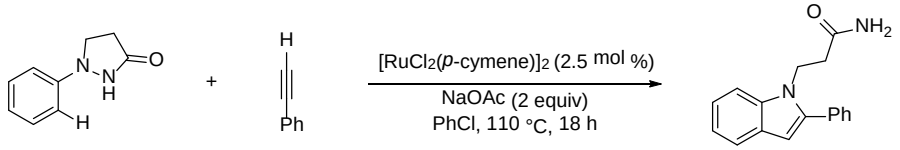


127a **155a** **157c**

127b **155a** **157c**

Scheme 1.65: Ruthenium(II)-catalyzed isoquinolone synthesis via C−H/N−O bond functionalizations

Most recently, *Huang* and co-workers reported the first ruthenium(II)-catalyzed redox-neutral annulation via N−N bond cleavage (Scheme 1.66).[230] In this case, pyrazolidin-3-one moiety in substrate **185** was demonstrated to operate as an internal oxidizing directing group. It's noteworthy that terminal alkynes, such as **155c**, which were previously mostly incompetent in ruthenium(II)-catalyzed cyclizations, reacted smoothly and delivered indole products **186** as a single regioisomer.



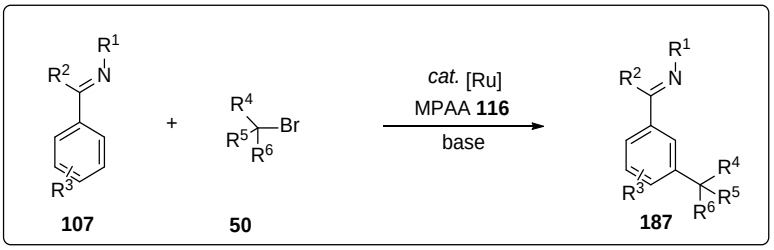
185 **155c** 83% **186**

Scheme 1.66: Ruthenium(II)-catalyzed annulation via C−H/N−N bond functionalizations

2 Objectives

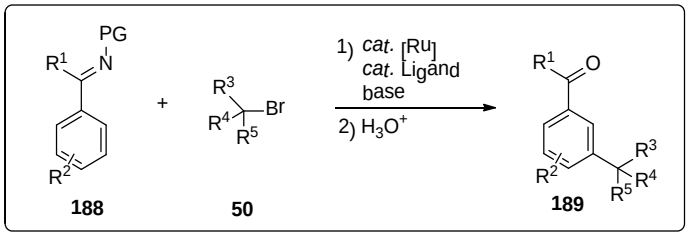
In recent years, transition metal-catalyzed C–H bond functionalizations have become an indispensable tool for chemo-, site- and enantioselective direct construction of C–C and C–Het bonds. In particular, *Ackermann* and coworkers focused on developing new strategies for C–H functionalizations employing significantly less expensive, yet highly reactive ruthenium(II) catalysts. In this context, carboxylate assistance was found to be crucial for promoting the efficiency of the C–H activation step.

Ackermann and coworkers have disclosed ruthenium(II)-catalyzed C–H alkylation of arenes with both primary and secondary alkyl halides. More importantly, direct alkylation with secondary alkyl bromides exhibited unique *meta*-selectivity. Despite the progress of employing secondary alkyl halides in traditional cross-coupling reactions, tertiary alkyl halides were less studied in either cross-coupling or C–H bond functionalization. Thus, one major emphasis of this thesis is on developing ruthenium(II)-catalyzed direct alkylation reactions with tertiary alkyl halides **50**. At the outset of this project, chelation-assisting heterocycles were employed as directing groups (**107**). Furthermore, given the significant advantages of monoprotected amino acid (MPAA) **116** as ligands in promoting palladium-catalyzed C–H bond activation, we were also interested in testing their behavior in ruthenium(II)-catalyzed direct alkylation reactions.



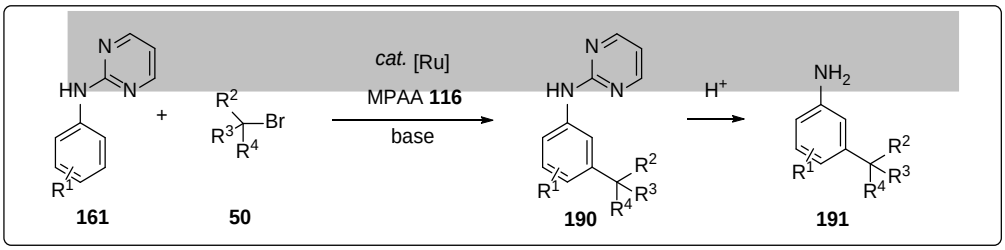
Scheme 2.1: Ruthenium(II)-catalyzed direct alkylation with tertiary alkyl halides

In addition, considering the synthetically usefulness of this novel transformation, we were interested in extending its scope to arenes bearing directing groups which can be readily removed or further functionalized. Thus, we probed ketimine derivatives **188** for ruthenium(II)-catalyzed direct alkylation with both tertiary and secondary alkyl halides **50** and **44**. Although transition metal-catalyzed *ortho*-selective C–H alkylation of ketimines was known, direct *meta*-alkylation with tertiary or secondary alkyl halides proved elusive. More importantly, simple one-pot hydrolysis could yield various *meta*-substituted ketones **189** which are indispensable intermediates in practical organic synthesis.



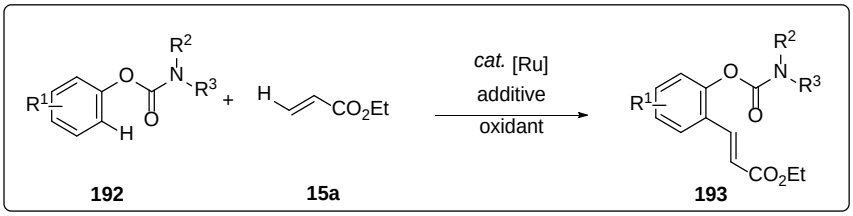
Scheme 2.2: Ruthenium(II)-catalyzed direct alkylation of ketimines **188**

Moreover, besides electron-deficient arenes, we were also interested in ruthenium(II)-catalyzed direct alkylation of the electron-rich ones. Thus, *N*-(pyrimidyl-2-yl)anilines **161** were also examined as substrates for this direct *meta*-alkylation. Tertiary, secondary as well as primary alkyl bromides were probed in this reaction. Importantly, the pyrimidyl directing group could easily be cleaved under acidic conditions to furnish a range of *meta*-alkylated anilines **191**.



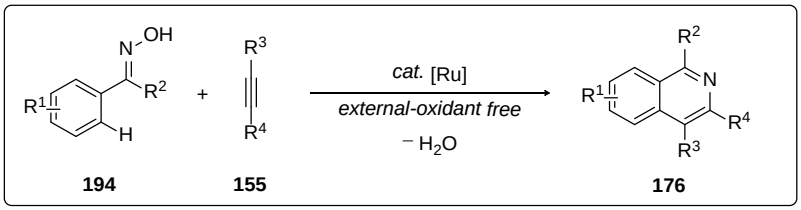
Scheme 2.3: Ruthenium(II)-catalyzed direct alkylation of *N*-(pyrimidyl-2-yl)anilines **161**

Despite the rapid development of ruthenium(II)-catalyzed Fujiwara-Moritani reactions, direct oxidative alkenylation of electron-rich arenes were underdeveloped. Consequently, we were interested in developing the first ruthenium(II)-catalyzed oxidative C–H alkenylation of phenol derivatives. Herein, we chose readily cleavable carbamates as directing groups in substrate **192** and hence facilitated the preparation of *o*-coumaric acid derivatives **193**.



Scheme 2.4: Ruthenium(II)-catalyzed oxidative C–H alkenylation of phenol carbamates **192**

Another project was to extend the scope of oximes for the ruthenium(II)-catalyzed redox-neutral alkyne annulations of alkynes **155** with oximes **194** via C–H/N–O bonds functionalization. Moreover, well-defined cationic ruthenium(II) complex was examined as a catalyst for this transformation. A variety of symmetrically as well as unsymmetrically substituted alkynes **155** were tested with this cationic ruthenium(II) catalyst.



Scheme 2.5: Ruthenium(II)-catalyzed redox-neutral alkyne annulation with oximes **194**

3 Ruthenium(II)-Catalyzed *meta*-Selective C–H Alkylations

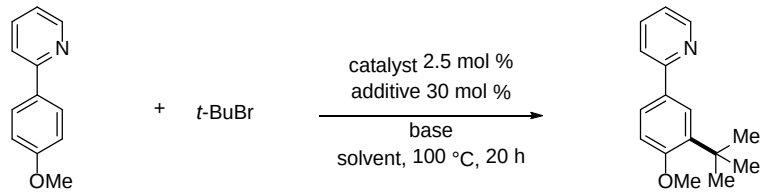
As indicated in Chapter 1.3, transition metal-catalyzed C–H alkylation with unactivated alkyl halides has emerged as an economical alternative for the construction of $C(sp^2)$–$C(sp^3)$ bonds. *Ackermann* and coworkers have demonstrated that, among a variety of transition metals, relatively cheap ruthenium(II) complexes showed excellent catalytic capability for highly site-selective direct alkylations under mild reaction conditions.[140,142] More importantly, unique *meta*-selectivity was observed when unactivated secondary alkyl halides were employed as the electrophiles (Chapter 1.2).[143] In spite of the recent success in applying secondary alkyl halides in cross-coupling and C–H functionalization,[95] unactivated tertiary alkyl halides were very rarely explored. Therefore, we set out to develop the first example of ruthenium(II)-catalyzed direct C–H alkylation with unactivated tertiary alkyl halides.

3.1 Ruthenium(II)-Catalyzed *meta*-Selective C–H Alkylations by Heterocycle Assistance with Tertiary Alkyl Bromides

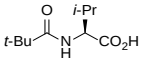
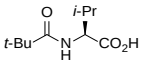
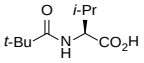
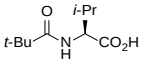
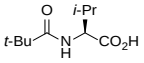
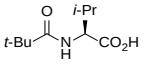
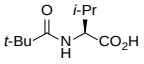
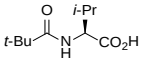
3.1.1 Optimization Studies

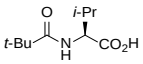
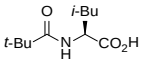
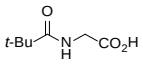
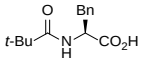
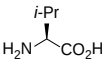
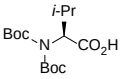
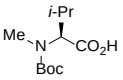
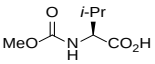
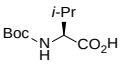
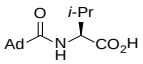
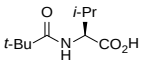
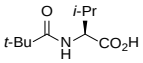
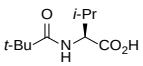
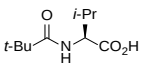
At the outset of our studies, we adopted the reaction conditions for the ruthenium(II)-catalyzed direct *meta*-alkylation with secondary alkyl bromides,[143] using 2-phenylpridine (**38b**) as the standard substrate for this challenging alkylation with *t*-butyl bromide (**50a**) (Table 3.1). To our delight, the desired *meta*-alkylated product **187ba** was obtained in 59% isolated yield (entry 1). Several other carboxylate co-catalysts also successfully delivered the target product, albeit in moderate yields (entries 2–5). While no reaction occurred in the absence of an additive (entry 6), high yield was obtained when Piv-Val-OH (**116a**) was introduced as a co-catalytic additive (entry 7). Although ruthenium(II)-amino acid complexes have been known for decades,[231,232] they have been employed as catalysts for direct C–H functionalizations only very recently.[233] Decreasing the loading of $[RuCl_2(p\text{-cymene})]_2$ to 1.0 mol % led to a slightly lower yield (entry 8). A ruthenium(II)-amino acid complex **195** was independently prepared and showed excellent catalytic activity, furnishing desired product **187ba** in even higher yield comparing to the in situ generated catalytic system (entry 9). Not surprisingly, this novel type of tertiary alkylation did not take place in the absence of ruthenium(II) catalyst or employing a Lewis acid catalyst, such as $AlCl_3$ (entries 10–11). Palladium or rhodium catalyst could not promote this transformation under otherwise identical reaction conditions (entries 12–14). Other ruthenium catalysts were also tested, whereas $[RuCl_2(PPh_3)_3]$ delivered only 10% of GC-conversion, $Ru_3(CO)_{12}$ showed no reactivity (entries 15–16). Encouraged by the excellent efficiency promoted by the Piv-Val-OH co-catalyst, we went on examining different MPAA ligands **116**. Among selected amino acids, valine derivatives proved to be optimal (entries 17–19). Unprotected valine delivered coumpound **187ba** only in low yield, thus highlighting the importance of a protecting group on the nitrogen; other *N*-protected MPAAs afforded the *meta*-alkylated product **187ba** in moderate yields (entries 20–25). Furthermore, among a variety of different solvents, 1,4-dioxane proved to be the solvent of choice (entries 26–31). Using stoichiometric quantities of acetates as bases in the absence of any co-catalyst gave product **187ba** in only unsatisfying low yields (entries 32–35).

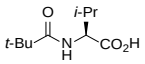
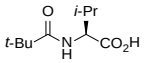
Table 3.1: Optimization for ruthenium(II)-catalyzed direct *meta*-alkylation with *t*-BuBr (**50a**)



38b **50a** **187ba**

Entry	Catalyst	Additive	Base	Solvent	Yield (%)
1	$[RuCl_2(p\text{-cymene})]_2$	$MesCO_2H$	K_2CO_3	1,4-dioxane	59
2	$[RuCl_2(p\text{-cymene})]_2$	$1\text{-}AdCO_2H$	K_2CO_3	1,4-dioxane	58
3	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	K_2CO_3	1,4-dioxane	38
4	$[RuCl_2(p\text{-cymene})]_2$	KOAc	K_2CO_3	1,4-dioxane	50
5	$[RuCl_2(p\text{-cymene})]_2$	CsOAc	K_2CO_3	1,4-dioxane	51
6	$[RuCl_2(p\text{-cymene})]_2$	---	K_2CO_3	1,4-dioxane	0
7	**$[RuCl_2(p\text{-cymene})]_2$**	 **116a**	**K_2CO_3**	**1,4-dioxane**	**76**
8	$[RuCl_2(p\text{-cymene})]_2$	 **116a**	K_2CO_3	1,4-dioxane	66[b]
9	**[RuCl(O-Val-Piv)(*p*-cymene)] 195**	**---**	**K_2CO_3**	**1,4-dioxane**	**80[c]**
10	-	 **116a**	K_2CO_3	1,4-dioxane	0
11	$AlCl_3$	 **116a**	K_2CO_3	1,4-dioxane	0
12	$Pd(OAc)_2$	 **116a**	K_2CO_3	1,4-dioxane	0
13	$[Cp^*RhCl_2]_2$	 **116a**	K_2CO_3	1,4-dioxane	0
14	$[Rh(cod)Cl]_2$	 **116a**	K_2CO_3	1,4-dioxane	0
15	$[RuCl_2(PPh_3)_3]$	 **116a**	K_2CO_3	1,4-dioxane	10[d]

16	$Ru_3(CO)_{12}$	 **116a**	K_2CO_3	1,4-dioxane	0
17	$[RuCl_2(p\text{-cymene})]_2$	 **116b**	K_2CO_3	1,4-dioxane	55
18	$[RuCl_2(p\text{-cymene})]_2$	 **116c**	K_2CO_3	1,4-dioxane	48
19	$[RuCl_2(p\text{-cymene})]_2$	 **116d**	K_2CO_3	1,4-dioxane	53
20	$[RuCl_2(p\text{-cymene})]_2$	 **116e**	K_2CO_3	1,4-dioxane	19
21	$[RuCl_2(p\text{-cymene})]_2$	 **116f**	K_2CO_3	1,4-dioxane	46
22	$[RuCl_2(p\text{-cymene})]_2$	 **116g**	K_2CO_3	1,4-dioxane	42
23	$[RuCl_2(p\text{-cymene})]_2$	 **116h**	K_2CO_3	1,4-dioxane	58
24	$[RuCl_2(p\text{-cymene})]_2$	 **116i**	K_2CO_3	1,4-dioxane	61
25	$[RuCl_2(p\text{-cymene})]_2$	 **116j**	K_2CO_3	1,4-dioxane	55
26	$[RuCl_2(p\text{-cymene})]_2$	 **116a**	K_2CO_3	DME	71
27	$[RuCl_2(p\text{-cymene})]_2$	 **116a**	K_2CO_3	*t*-AmOH	14
28	$[RuCl_2(p\text{-cymene})]_2$	 **116a**	K_2CO_3	PhMe	74
29	$[RuCl_2(p\text{-cymene})]_2$	 **116a**	K_2CO_3	H_2O	0

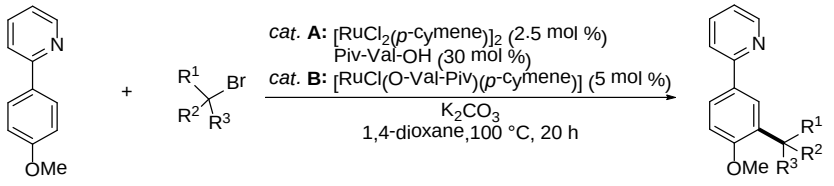
30	$[RuCl_2(p\text{-cymene})]_2$	 **116a**	K_2CO_3	diglyme	8[d]
31	$[RuCl_2(p\text{-cymene})]_2$	 **116a**	K_2CO_3	DMA	15[d]
32	$[RuCl_2(p\text{-cymene})]_2$	--	KOAc	1,4-dioxane	37
33	$[RuCl_2(p\text{-cymene})]_2$	--	NaOAc	DME	49
34	$[RuCl_2(p\text{-cymene})]_2$	--	CsOPiv	DME	41
35	$[RuCl_2(p\text{-cymene})]_2$	--	CsOPiv	1,4-dioxane	33

[a] Reaction conditions: **38b** (0.5 mmol), **50a** (1.5 mmol), catalyst (2.5 mol %), additive (30 mol %), base (1.0 mmol), solvent (2 mL), 100 °C, 20 h, under N_2; isolated yields. [b] 1.0 mol % catalyst. [c] 5.0 mol % catalyst. [d] GC-conversion.

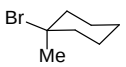
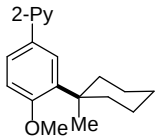
3.1.2 *meta*-C–H Alkylation with Tertiary Alkyl Bromides: Scope and Limitations

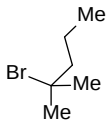
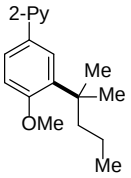
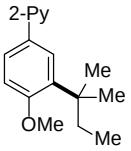
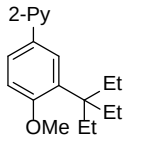
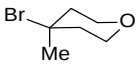
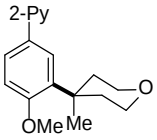
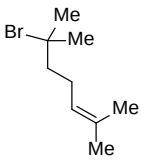
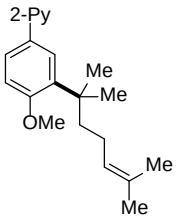
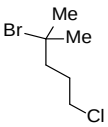
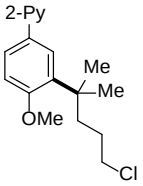
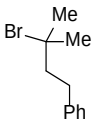
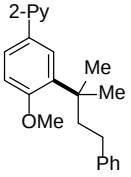
With the optimized conditions in hand, we subsequently explored the scope and limitations of this *meta*-selective alkylation. Various unactivated tertiary alkyl bromides **50** were tested with both in-situ generated ruthenium(II) catalyst and the single-component complex **195**. In most cases, these two systems delivered comparable yields (Table 3.2). Thus, 1-methylcyclohexyl bromide (**50b**) gave the alkylated product **187bb** in 78% and 75% yield, respectively (entry 1). Sterically more congested tertiary alkyl bromides also afforded desired products in moderate yields (entries 2–4). More importantly, tertiary alkyl bromides bearing functional groups, such as ether (**50f**), olefin (**50g**), chloride (**50h**) and phenyl groups (**50i** and **50j**), were well tolerated (entries 5–9). Interestingly, despite the well-established method of ruthenium(II)-catalyzed alkylation with primary alkyl chlorides, compound **187bh** was not contaminated with any primary alkylated byproduct (entry 7).

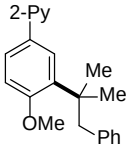
Table 3.2: Scope of direct *meta*-alkylation with tertiary alkyl bromides **50**



38b **50** **187**

Entry	Tertiary Bromide 50	Product 187	Yield (%)
1	 **50b**	 **187bb**	**A:** 78 **B:** 75

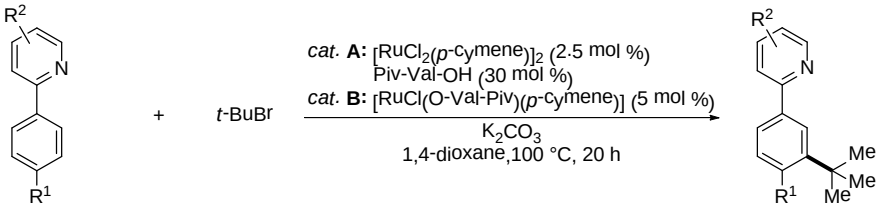
2	 **50c**	 **187bc**	**A:** 59 **B:** 50
3	 **50d**	 **187bd**	**A:** 67 **B:** 60
4	 **50e**	 **187be**	**A:** 52 **B:** 35
5	 **50f**	 **187bf**	**A:** 78 **B:** 75
6	 **50g**	 **187bg**	**A:** 61[b]
7	 **50h**	 **187bh**	**A:** 59 **B:** 59
8	 **50i**	 **187bi**	**A:** 66 **B:** 59

9			**A:** 59
	50j	**187bj**	

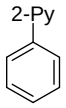
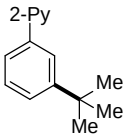
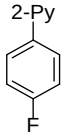
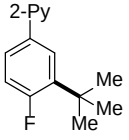
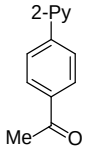
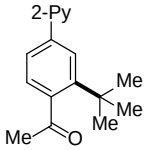
[a] Reaction conditions: cat. **A**: $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), Piv-Val-OH (30 mol %) or cat **B**: [RuCl(O-Val-Piv)(*p*-cymene)] (5.0 mol %); **38b** (0.5 mmol), **50** (1.5 mmol), K_2CO_3 (1.0 mmol), 1,4-dioxane (2 mL), 100 °C, 20 h, under N_2; isolated yields. [b] $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %).

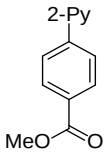
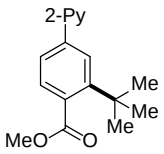
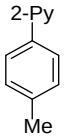
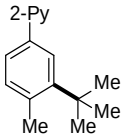
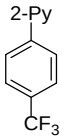
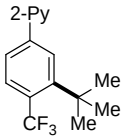
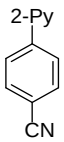
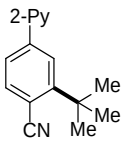
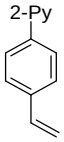
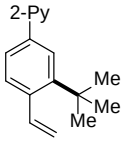
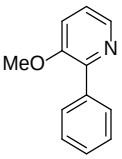
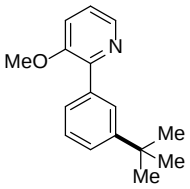
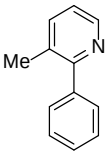
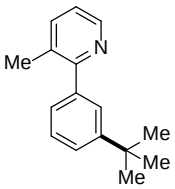
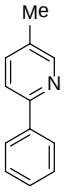
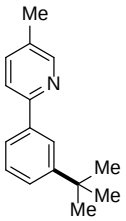
Subsequently, the influence of electron-donating and electron-withdrawing substituents on the aryl moiety upon the efficiency of the alkylation was examined (Table 3.3). Unsubstituted 2-phenylpyridine (**38a**) was smoothly converted in good yield under both conditions (entry 1). Phenylpyridines bearing electron-withdrawing fluoro (**38c**), acetyl (**38d**) and ester (**38e**) groups in the *para*-position (entries 2–4) as well as *p*-tolylpyridine **38f** (entry 5) selectively delivered *meta*-selective products in moderate to good yields. It is noteworthy that these functional groups could be valuable for further functionalization. However, surprisingly low yields were observed for electron-deficient trifluoromethyl- or cyano-substituted substrates **38g** and **38h**, respectively (entries 6 and 7). The same held true for the vinyl-containing substrate **38i** (entry 8). Substituents in the 3-, 4-, or 5- position on the pyridine moiety in substrates **38** generally did not significantly affect the reaction outcome, affording the *meta*-alkylated products in moderate to good yields (entries 9–15).

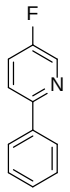
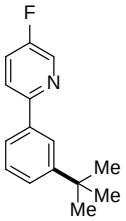
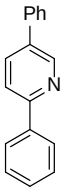
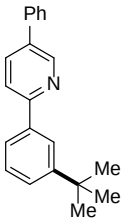
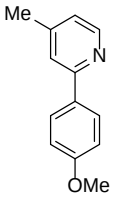
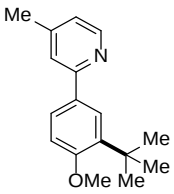
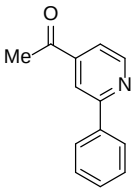
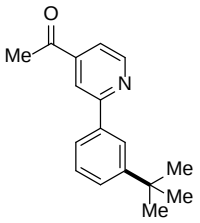
Table 3.3: Scope for *meta*-C–H alkylation of *para*-substituted 2-phenylpyridines **38**



38 **50a** **187**

Entry	Phenylpyridine 38	Product 187	Yield (%)
1			**A:** 65 **B:** 59
	38a	**187aa**	
2			**A:** 80 **B:** 81
	38c	**187ca**	
3			**A:** 58[b] **B:** 54[b]
	38d	**187da**	

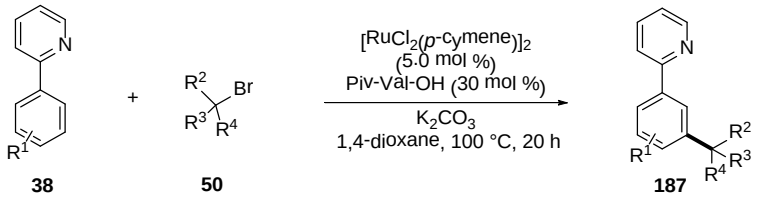
4			**A:** 51[b] **B:** 50[b]
	38e	**187ea**	
5			**A:** 45[b]
	38f	**187fa**	
6			**A:** 26
	38g	**187ga**	
7			**A:** 14
	38h	**187ha**	
8			**A:** 20
	38i	**187ia**	
9			**A:** 72 **B:** 71
	38j	**187ja**	
10			**A:** 61 **B:** 79
	38k	**187ka**	
11			**A:** 57 **B:** 65
	38l	**187la**	

12	 **38m**	 **187ma**	**A:** 56
13	 **38n**	 **187na**	**A:** 24
14	 **38o**	 **187oa**	**A:** 52 **B:** 74
15	 **38p**	 **187pa**	**A:** 48[b]

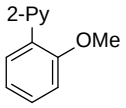
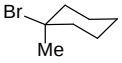
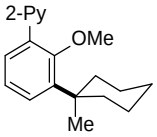
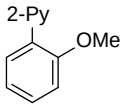
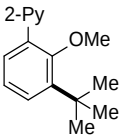
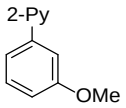
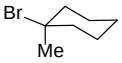
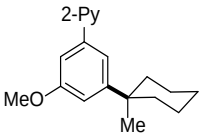
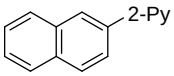
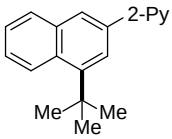
[a] Reaction conditions: cat. **A**: $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), Piv-Val-OH (30 mol %) or cat **B**: [RuCl(O-Val-Piv)(*p*-cymene)] (5.0 mol %); **38** (0.5 mmol), **50a** (1.5 mmol), K_2CO_3 (1.0 mmol), 1,4-dioxane (2 mL), 100 °C, 20 h, under N_2; isolated yields. [b] 10 mol % [Ru].

Summarizing the results of alkylations of *ortho*- and *meta*-substituted 2-phenylpyridines **38** (Table 3.4), it is particularly noteworthy that *ortho*-substituted arene **38q** furnished the products **187** being substituted exclusively at the sterically more congested *meta*-position (entries 1 and 2). *meta*-Methoxy substituted arene **38r** selectively furnished the product **187rb** alkylated in *meta*-position, with respect to both methoxy and pyridyl substituents, although with lower efficacy (entry 3). Furthermore, *meta*-selective alkylation of naphthalene derivative **38s** gave rise to 4-substituted product **187sa**, albeit in low yield (entry 4).

Table 3.4: Scope for *meta*-alkylation of *ortho*- and *meta*-substituted 2-phenylpyridines **38**

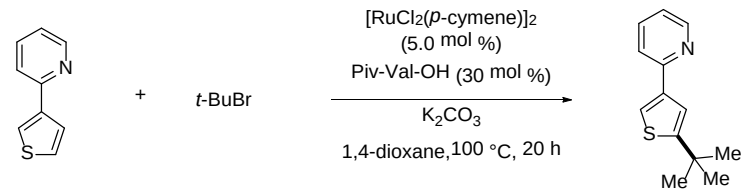


38 **50** **187**

Entry	Phenylpyridine 37	Tertiary Bromide 50	Product 187	Yield (%)
1	 **38q**	 **50b**	 **187qb**	46
2	 **38q**	*t*-BuBr **50a**	 **187qa**	41
3	 **38r**	 **50b**	 **187rb**	35
4	 **38s**	*t*-BuBr **50a**	 **187sa**	22

Reaction conditions: **38** (0.5 mmol), **50** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), Piv-Val-OH (30 mol %), K_2CO_3 (1.0 mmol), 1,4-dioxane (2 mL), 100 °C, 20 h, under N_2; isolated yields.

Taking the importance of heteroarenes as key motifs in various bioactive compounds into consideration, we were delighted to observe alkylation of substituted thiophene **38t** in a *meta*-selective fashion as well (Scheme 3.1).



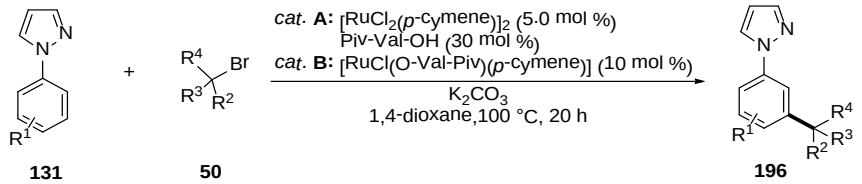
38t **50a** **187ta**

Scheme 3.1: Direct *meta*-alkylation of 2-(thiophen-3-yl)pyridine (**37t**)

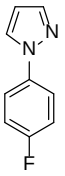
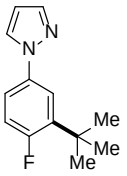
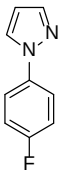
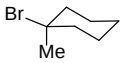
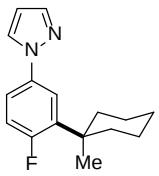
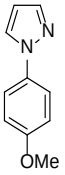
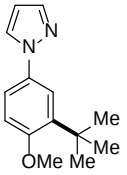
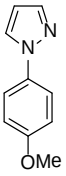
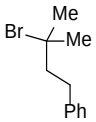
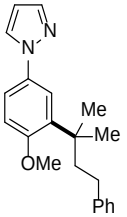
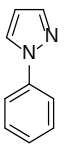
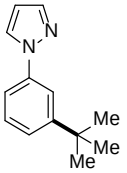
Besides pyridine, synthetically useful the pyrazole heteroarene could serve as a directing group for the ruthenium(II)-catalyzed *meta*-alkylation as well (Table 3.5). 1-Phenylpyrazole derivatives **131** bearing either electron-donating or electron-withdrawing groups could be smoothly *meta*-alkylated

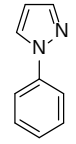
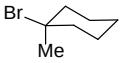
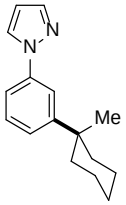
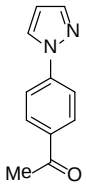
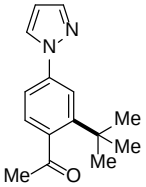
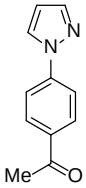
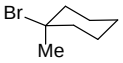
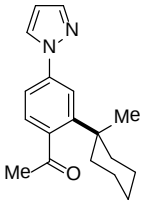
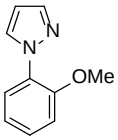
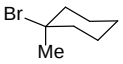
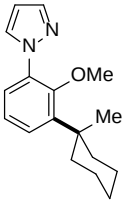
with a range of tertiary alkyl bromides (entries 1–4). However, moderate to low yields were observed when electron-neutral 1-phenylpyrazole (**131c**) (entries 5–6) or electron-deficient one **131d** (entries 7 and 9) were subjected to the optimized reaction condition. In accordance with the reactivity of *ortho*-substituted 2-phenylpyridines **38** discussed above, direct alkylation of *ortho*-substituted 1-phenylpyrazole **131e** only took place at the sterically more congested *meta*-C–H bond (entries 9).

Table 3.5: Scope for *meta*-C–H alkylation of substituted 1-phenylpyrazoles **131**



131 **50** **196**

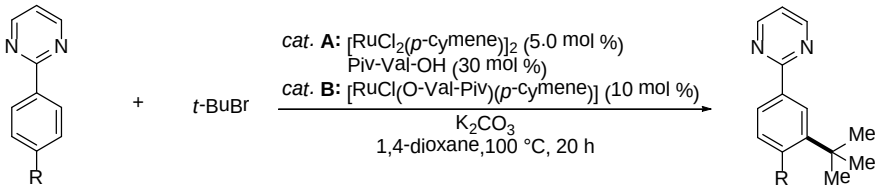
Entry	Substrate 131	Tertiary Bromide 50	Product 196	Yield (%)
1		*t*-BuBr		**A:** 72 **B:** 73
	131a	**50a**	**196aa**	
2				**A:** 67 **B:** 64
	131a	**50b**	**196ab**	
3		*t*-BuBr		**A:** 67 **B:** 63
	131b	**50a**	**196ba**	
4				**A:** 58 **B:** 54
	131b	**50i**	**196bi**	
5		*t*-BuBr		**A:** 44
	131c	**50a**	**196ca**	

6	 **131c**	 **50b**	 **196cb**	**A:** 29
7	 **131d**	*t*-BuBr **50a**	 **196da**	**A:** 38
8	 **131d**	 **50b**	 **196db**	**A:** 21
9	 **131e**	 **50b**	 **196eb**	**A:** 24

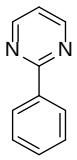
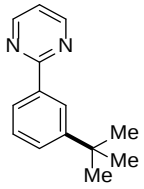
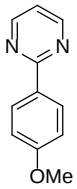
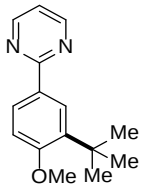
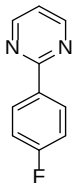
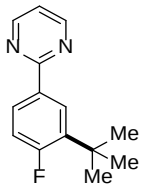
[a] Reaction conditions: **A**: $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), Piv-Val-OH (30 mol %); **B**: [RuCl(O-Val-Piv)(*p*-cymene)] (**195**) (10 mol %); **131** (0.5 mmol), **50** (1.5 mmol), K_2CO_3 (1.0 mmol), 1,4-dioxane (2 mL), 100 °C, 20 h, under N_2; isolated yields.

Moreover, 2-phenylpyrimidine derivatives **197** appeared to be suitable substrates for the ruthenium(II)-catalyzed *meta*-selective direct alkylation as well (Table 3.6). Both the in situ formed catalytic system and the ruthenium(II) complex **195** were applicable. Unsubstituted arene **197a** smoothly delivered *meta*-alkylated product **198aa** in moderate yields (entry 1). While electron-rich arene **197b** showed lower efficacy (entry 2), high yield was obtained for electron-deficient arene **197c** under catalysis with the ruthenium(II)-Piv-Val-OH complex **195** (entry 3).

Table 3.6: Direct *meta*-C–H alkylation of substituted pyrimidine **197**



197 **50a** **198**

Entry	Substrate 197	Product 198	Yield (%)
1			**A:** 50 **B:** 62
	197a	**198aa**	
2			**A:** 44 **B:** 47
	197b	**198ba**	
3			**A:** 52 **B:** 71
	197c	**198ca**	

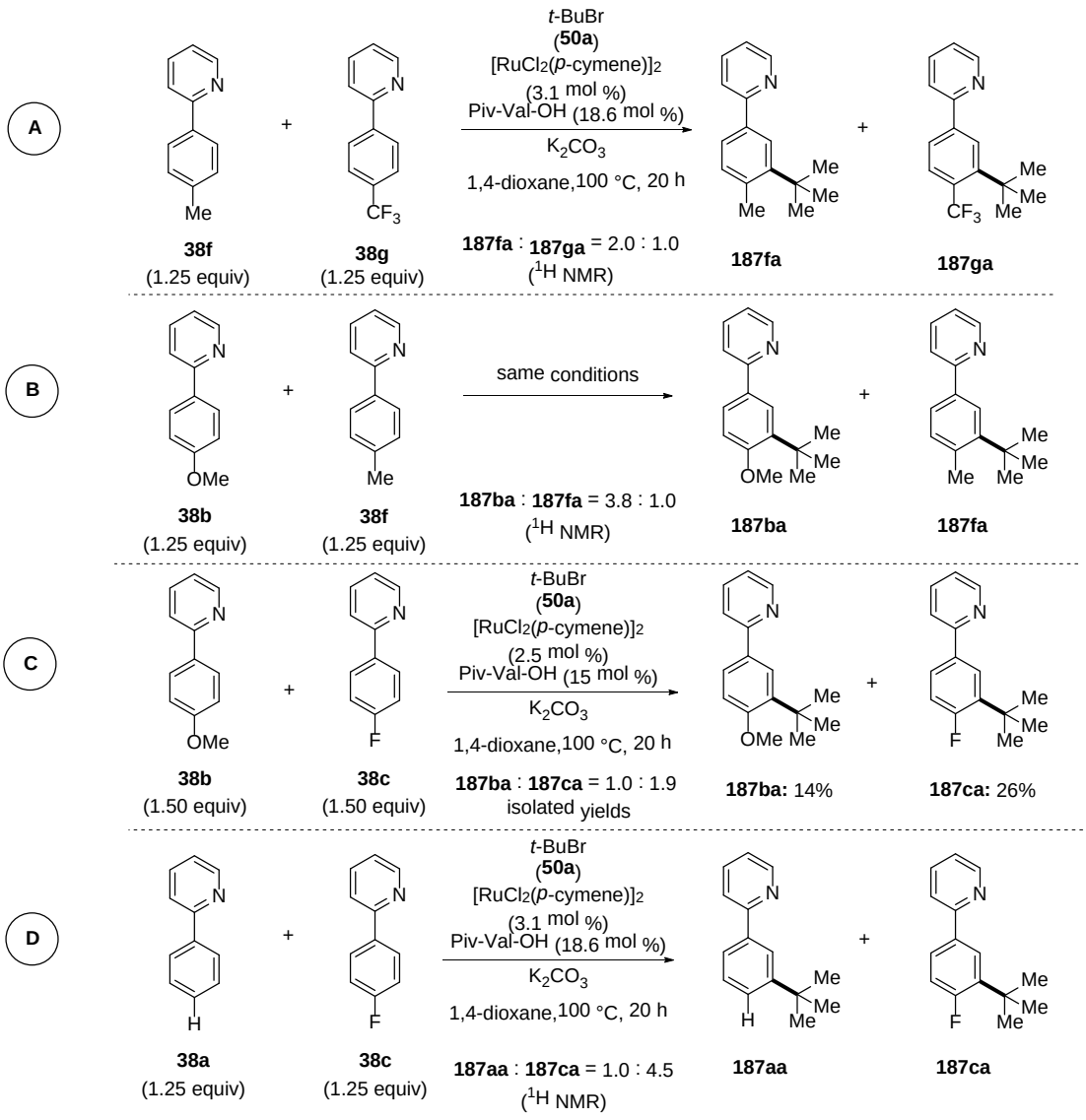
[a] Reaction conditions: cat. **A**: $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), Piv-Val-OH (30 mol %) or cat **B**: [RuCl(O-Val-Piv)(*p*-cymene)] (10 mol %); **197** (0.5 mmol), **50a** (1.5 mmol), K_2CO_3 (1.0 mmol), 1,4-dioxane (2 mL), 100 °C, 20 h, under N_2; isolated yields.

3.1.3 Mechanistic Studies

Given the unique *meta*-selectivity of our ruthenium(II)-catalyzed direct alkylation, we performed detailed mechanistic studies to delineate its mode of action. To this end, we conducted intermolecular competition experiments and experiments with isotopically labeled starting materials.

3.1.3.1 Intermolecular Competition Experiments

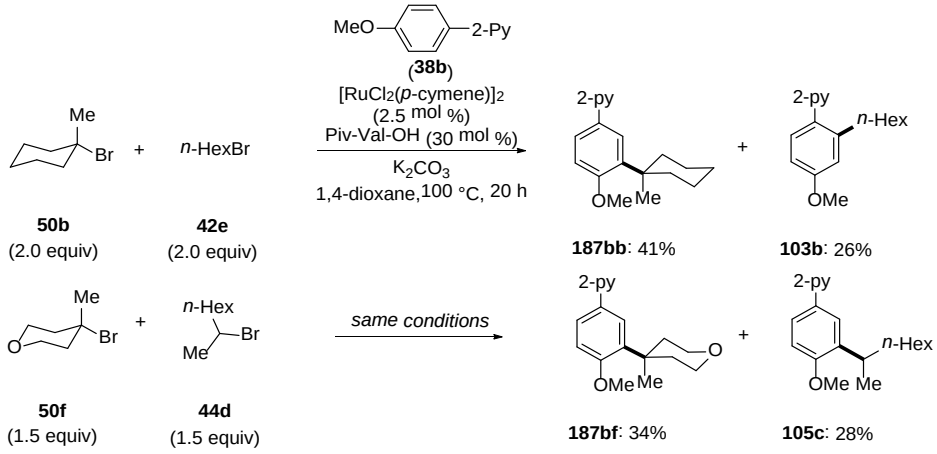
Intermolecular competition experiments between *para*-substituted 2-phenylpyridines (**38**) were performed, in which a 1.25 fold excess of both substrates was treated with bromide **50a** as the limiting reagent under otherwise identical optimized reaction conditions. The ratio of products was determined by ^{1}H-NMR after aqueous workup.



Scheme 3.2: Intermolecular competition experiments between substituted 2-phenylpyridines **38**

Experiment **A** showed electron-rich substrate **38f** to be more reactive in comparison to its trifluoromethyl-substituted analogue **38g**. Similar result could be observed in experiment **B**, in which arene **38b** with electronically more donating substituent reacted more rapidly than methyl-containing compound **38f**. Interesting results were obtained from experiments **C** and **D**. Thus, electron-deficient fluoro-substituted arene **38c** was found to be more reactive than both methoxy substituted **38b** and unsubstituted **38a**. This phenomenon could be rationalized as the result of *ortho*-orienting effect of the fluorine substituent.[234]

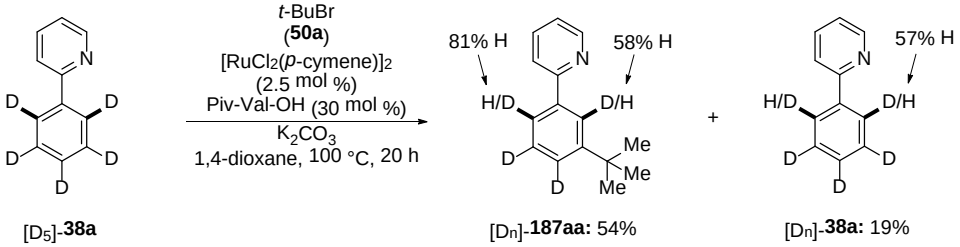
Subsequently, we performed competition experiments between tertiary alkyl bromide **50b** and primary alkyl bromide **42e** as well as between **50f** and secondary alkyl bromide **44d**. These results showed no special preference of either reaction. The reaction rates appeared to be comparable and still conserving the individual regioselectivity mode for each electrophile.



Scheme 3.3: Intermolecular competition experiments between alkyl bromides **42e**, **44d** and **50b**, **50f**

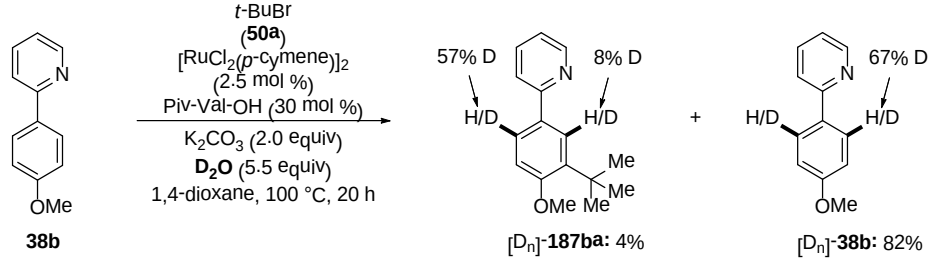
3.1.3.2 Experiments with Deuterium-Labeled Substrates

As shown in Scheme 3.4, upon alkylation of deuterated 2-phenylpyridine [D_5]-**38a** under the optimized reaction conditions, significant D/H exchanges in the *ortho*-positions of both substrate and product were observed. We found 81% and 58% hydrogen incorporation in the product [D_n]-**187aa** as well as 57% hydrogen incorporation in the recovered starting material [D_n]-**38a**. This result provided strong support for the C–H bond metalation step to proceed initially in the *ortho*-position of the arene. Moreover, the D/H-exchange caused by adventitious water in the stoichiometric base and by the acid moiety in the co-catalytic additive Piv-Val-OH indicated the *ortho* C–H bond metalation to be reversible in nature.



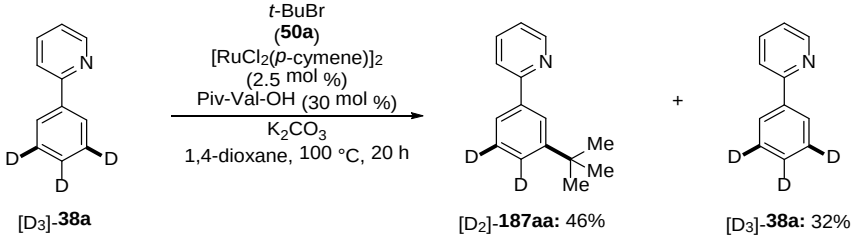
Scheme 3.4: D/H exchange during direct *meta*-alkylation of [D_5]-phenylpyridine **38a**

We also performed our standard reaction in the presence of small amounts of D_2O (Scheme 3.5). In accordance with our previously discussed reaction of [D_5]-**38a** (Scheme 3.4), a significant amount of deuterium incorporation in the *ortho*-positions of both product and recovered starting material was observed.



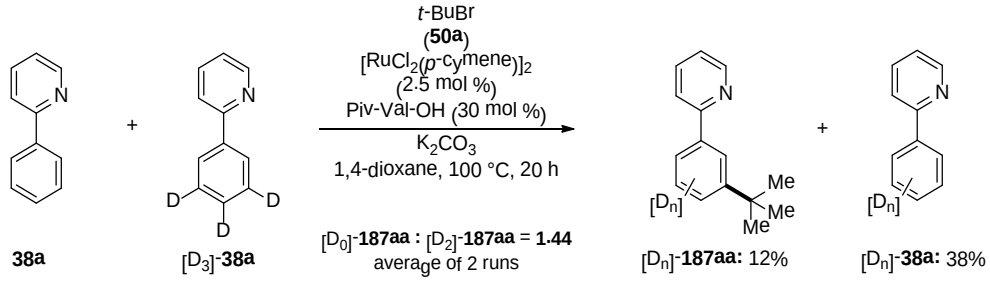
Scheme 3.5: Direct *meta*-alkylation of arene **38b** in the presence of D_2O

To probe the mechanism of the cleavage of the *meta*-C−H bond and the formation of the C−C bond, [D_3]-**38a** was also subjected to the optimized reaction conditions. The reaction smoothly delivered *meta*-alkylated product [D_2]-**187aa** in 46% isolated yield together with 32% of recovered substrate [D_3]-**38a** (Scheme 3.6). Detailed ^{1}H NMR studies showed no hydrogen incorporation in any *meta*-positions neither of the product nor of the recovered starting material, thus indicating the *meta*-C−H bond cleavage and C−C bond forming step to be irreversible.



Scheme 3.6: Direct *meta*-alkylation of (trideuteriophenyl)pyridine [D_3]-**37a**

Moreover, we performed an intermolecular competition experiment between equimolar amounts of 2-phenylpyridines **38a** and [D_3]-**38a** under the optimized reaction conditions. On the average of 2 runs, a KIE of 1.44 was established.

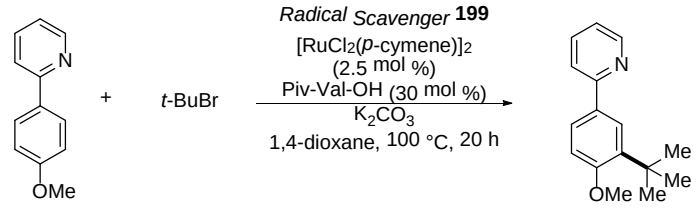


Scheme 3.7: KIE study through competition between arenes [D_0]-**37a** and [D_3]-**37a**

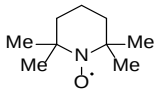
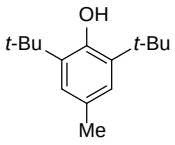
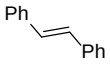
3.1.3.3 Experiments in the Presence of Radical Scavengers

In order to gain some understanding about the C−C bond formation, we performed reactions in the presence of different radical scavengers **199** to see, if any kind of alkyl radical was formed in this novel transformation (Table 3.7). Stoichiometric amounts of TEMPO (**199a**) completely inhibited the reaction. However, this observation could not finally confirm a radical mechanism. For instance, it is known that ruthenium hydride smoothly react with TEMPO to form a ruthenium-TEMPO complex.[235] On the contrary, other representative scavengers such as BHT (**199b**) and *E*-stilbene (**199d**) did not affect the reaction outcome, furnishing product **187ba** in comparable yields. When 1,1-diphenylethylene (**199c**) was added, only 9% of the *meta*-alkylated product **187ba** was obtained.

Table 3.7: C–H *meta*-alkylation in the presence of radical scavengers **199**



38b **50a** **187ba**

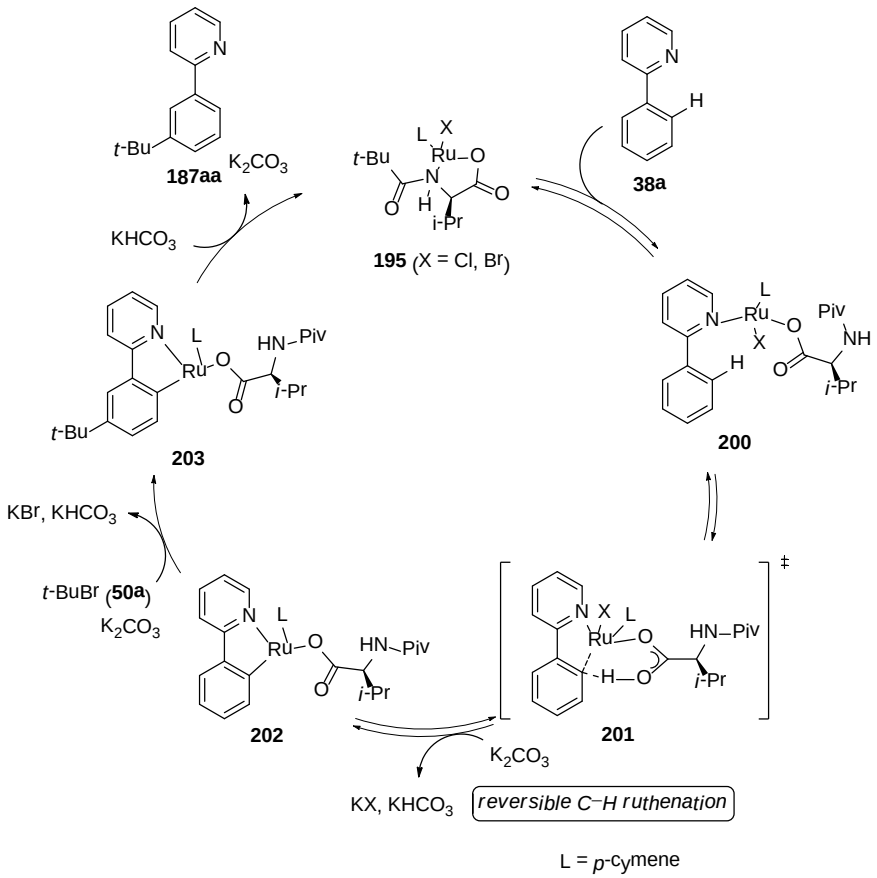
Entry	Radical Scavenger 199	Yield (%)
1	 **199a**	0
2	 **199b**	80
3	 **199c**	9
4	 **199d**	79

Reaction conditions: **38b** (0.5 mmol), **50a** (1.5 mmol), radical scavenger **199** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), Piv-Val-OH (30 mol %), K_2CO_3 (1.0 mmol), 1,4-dioxane (2 mL), 100 °C, 20 h, under N_2; isolated yields.

3.1.3.4 Proposed Catalytic Cycle

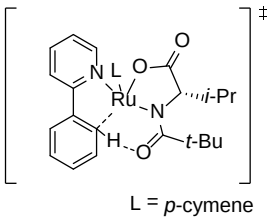
Based on the experimental studies summarized above and taken into account the studies of ruthenium(II)-catalyzed *meta*-alkylation with secondary alkyl halides[143] and ruthenium(II)-catalyzed *meta*-sulfonylation,[70] we propose a plausible catalytic cycle which is shown in Scheme 3.8.

Initially, the ruthenium(II)-MPAA complex **195** undergoes ligand exchange with substrate **38a** and is coordinated by the nitrogen atom of the pyridine directing group to form complex **200**. Subsequently, the amino acid enables the reversible cyclometalation via transition state **201**, thus forming a five-membered ruthenacycle **202**. The strong directing group effect of the Ru–C(sp^2) σ-bond introduces the irreversible *tert*-alkylation predominantly in the remote *para*-position.[73] However, the exact pathway for the C–C bond forming step is still not understood, and tertiary alkyl cation or radical could be involved as well. Finally, the proto-demetalation step delivers the *meta*-alkylated product **187aa** and regenerating the catalytically active species **195**.



Scheme 3.8: Proposed catalytic cycle for the ruthenium(II)-catalyzed direct *meta*-alkylation with bromide **50a**

Moreover, *Houk*, *Yu* and *Wu* have investigated the role of *N*-acyl amino acid in palladium-catalyzed remote C−H activation of tethered arenes.[236] Computational studies suggested the MPAA ligand not only to stabilize the monomeric palladium complex but also to serve as the internal base for proton abstraction. Hence, a similar transition state **205** for the ruthenium(II)-catalyzed *meta*-alkylation enabled by MPAA ligand could be possible.



205

Scheme 3.9: Possible transition state **205** for the ruthenium(II)-catalyzed direct *meta*-alkylation

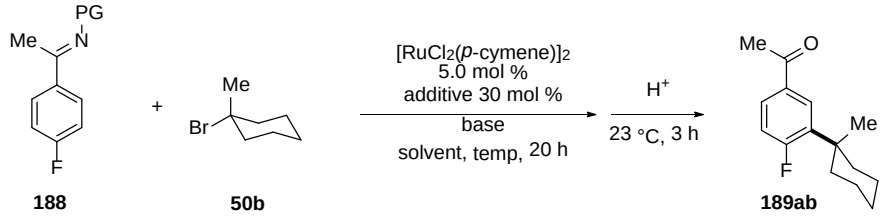
3.2 Ruthenium(II)-Catalyzed *meta*-Selective C–H Alkylations of Ketimines with Secondary and Tertiary Alkyl Bromides

Inspired by the success of our ruthenium(II)-catalyzed direct *meta*-alkylation reactions of 2-phenylpyridines **38**, 1-phenylpyrazoles **131** and 2-phenylpyrimidines **197** described above, we became intrigued to enlarge the synthetically usefulness of this unprecedented *meta*-selective tertiary alkylation by modifying the directing group from heterocycles to those which can be readily manipulated. Since the *Ackermann* group reported on the ruthenium(II)-catalyzed *ortho*-alkylation of ketimines with primary alkyl bromides and given the versatile application of ketimines,[142] we set out to develop ruthenium(II)-catalyzed direct *meta*-alkylation of ketimines **188** with both tertiary and secondary alkyl bromides.

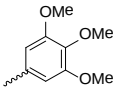
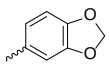
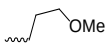
3.2.1 Optimization Studies

Preliminary studies by *N. Hoffmann* on the ruthenium(II)-catalyzed secondary alkylation of ketimines showed that ketimine **188a** bearing electron-withdrawing substituent could be *meta*-alkylated with both cyclic and acyclic secondary alkyl bromides.[237] Although only unsatisfactory low yields were obtained, it was a proof of principle that ketimines are suitable substrates for this transformation. At the outset of our studies, we subjected substituted ketimine **188aa** to our standard reaction conditions for the *meta*-alkylation of 2-phenylpyridines; the results are summarized in Table 3.8. To our delight, the desired *meta*-alkylated acetophenone **189ab** was obtained in 22% yield after one-pot hydrolysis (entry 1). Whereas $MesCO_2H$ provided only 26% NMR conversion, the desired product **189ab** was obtained in 50% yield when using 1-$AdCO_2H$ as an additive (entries 2 and 3). Decreasing the reaction temperature to 100 °C completely shut down the reaction. Moreover, elevating the reaction temperature to 140 °C led to lower yields (entries 4 and 5). Among several solvents screened, toluene and *o*-xylene could give comparable results (entries 6–9). Using Cs_2CO_3 as a base instead of K_2CO_3 could also deliver the product in comparable 49% yield. On the contrary, Na_2CO_3 and Ag_2CO_3 proved to be unsuitable bases (entries 10–12). Furthermore, stoichiometric amount of base in the absence of co-catalyst only led to unsatisfactory low yields (entries 13 and 14). Subsequently, we tested different protecting groups on the imine moiety, among which 3,4,5-trimethoxyphenyl (TMP) proved to be the most efficient one (entries 16–21). As shown in entry 18, although a high GC-conversion was determined in this transformation, only 66% NMR conversion and 52% isolated product was obtained, which indicated an unsatisfactory mass balance. Generally, a pale spot could always be observed on the baseline of the TLC analysis in these reactions. However, attempts on isolating and identifying these by-products were unsuccessful.

Table 3.8: Optimization for ruthenium(II)-catalyzed direct *meta*-alkylation of ketimines **188**



188 **50b** **189ab**

Entry	PG	Additive	Base	Solvent	Temp(°C)	Yield (%)
1	PMP (**188aa**)	Piv-Val-OH	K_2CO_3	1,4-dioxane	120	22
2	PMP	$MesCO_2H$	K_2CO_3	1,4-dioxane	120	26[b]
3	PMP	1-$AdCO_2H$	K_2CO_3	1,4-dioxane	120	50
4	PMP	1-$AdCO_2H$	K_2CO_3	1,4-dioxane	100	0
5	PMP	1-$AdCO_2H$	K_2CO_3	1,4-dioxane	140	47
6	PMP	1-$AdCO_2H$	K_2CO_3	NMP	120	0
7	PMP	1-$AdCO_2H$	K_2CO_3	*o*-xylene	120	49
8	PMP	1-$AdCO_2H$	K_2CO_3	DME	120	36
9	PMP	1-$AdCO_2H$	K_2CO_3	PhMe	120	52
10	PMP	1-$AdCO_2H$	Na_2CO_3	PhMe	120	<5
11	PMP	1-$AdCO_2H$	Cs_2CO_3	PhMe	120	49
12	PMP	1-$AdCO_2H$	Ag_2CO_3	PhMe	120	0
13	PMP	-	KOAc	PhMe	120	30[b]
14	PMP	-	NaOAc	PhMe	120	<5
15	PMP	Piv-Val-OH	K_2CO_3	PhMe	120	30[b]
16	Bn (**188ab**)	1-$AdCO_2H$	K_2CO_3	PhMe	120	30
17	 **(188a)**	**1-$AdCO_2H$**	**K_2CO_3**	**PhMe**	**120**	**58**
18		1-$AdCO_2H$	K_2CO_3	1,4-dioxane	120	87[c], 66[b], 52
19		Piv-Val-OH	K_2CO_3	PhMe	120	26[b]
20	 (**188ac**)	1-$AdCO_2H$	K_2CO_3	PhMe	120	51
21	 (**188ad**)	1-$AdCO_2H$	K_2CO_3	PhMe	120	50[b]

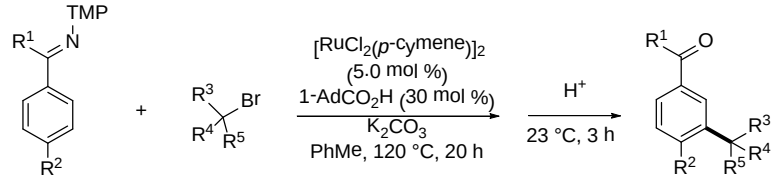
[a] Reaction conditions: **188a** (0.5 mmol), **50b** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), additive (30 mol %), base (1.0 mmol), solvent (2 mL), 20 h, under N_2; yield of isolated products. [b] NMR yield with CH_2Br_2 as internal standard. [c] GC-conversion.

3.2.2 Direct *meta*-Alkylation with Tertiary Alkyl Bromides: Scope and Limitations

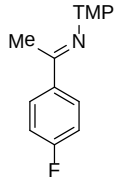
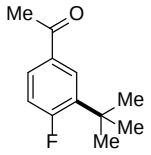
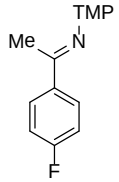
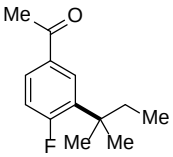
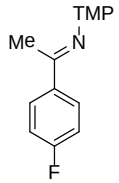
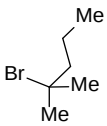
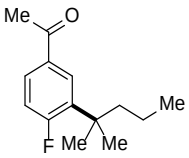
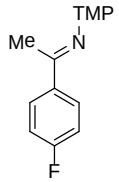
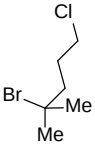
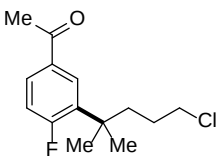
With the optimized reaction conditions in hand, we subsequently explored the scope and limitations of the *meta*-selective alkylation in terms of differently substituted ketimines **188** and tertiary alkyl

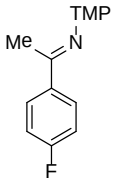
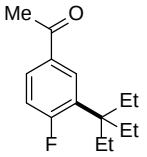
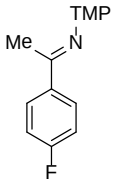
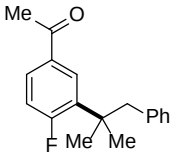
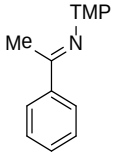
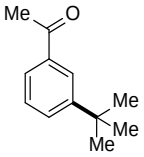
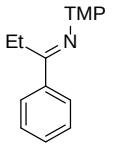
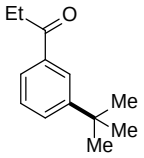
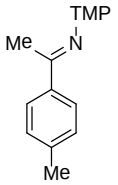
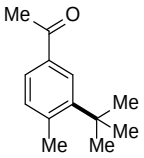
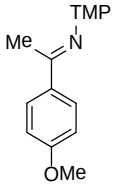
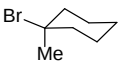
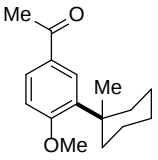
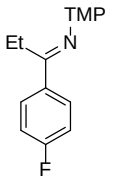
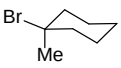
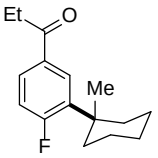
bromides **50** (Table 3.9). The parent *t*-BuBr (**50a**) smoothly delivered the desired product **189aa** in 59% yield (entry 1). Sterically more hindered tertiary alkyl bromides also afforded the corresponding products in moderate yields (entries 2–6). It should be emphasized that tertiary alkyl bromide **50h** bearing the chlorine substituent was well tolerated (entry 4). Unsubstituted ketimines were also examined under the standard reaction conditions. Thus, *meta*-alkylated acetophenone **189ba** and propiophenone **189ca** were obtained in 54% and 55% yield, respectively (entries 7 and 8). When arenes **188** bearing electron-donating groups were tested, switching solvent from toluene to 1,4-dioxane was necessary to prevent the undesired benzylation. Both alkylations afforded products **189da** and **189eb** in 47% yield (entries 9 and 10). Electron-deficient propiophenone-derived ketimine **188f** was tolerated in this transformation as well (entry 11).

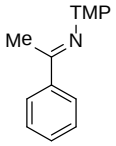
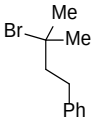
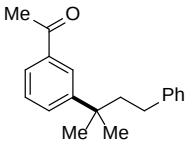
Table 3.9: Direct *meta*-alkylation of ketimines **188** with tertiary alkyl bromides **50**



188 **50** **189**

Entry	Substrate 188	Tertiary Bromide 50	Product 189	Yield (%)
1		*t*-BuBr		59
	188a	**50a**	**189aa**	
2				57
	188a	**50d**	**189ad**	
3				49
	188a	**50c**	**189ac**	
4				50
	188a	**50h**	**189ah**	

5				34
	188a	**50e**	**189ae**	
6				36
	188a	**50j**	**189aj**	
7		*t*-BuBr		54
	188b	**50a**	**189ba**	
8		*t*-BuBr		55
	188c	**50a**	**189ca**	
9		*t*-BuBr		47[b]
	188d	**50a**	**189da**	
10				47[b]
	188e	**50b**	**189eb**	
11				62
	188f	**50b**	**189fb**	

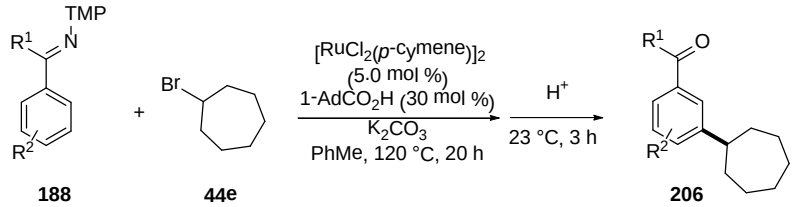
12				35
	188b	**50i**	**189bi**	

[a] Reaction conditions: **188** (0.5 mmol), **50** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), 1-$AdCO_2H$ (30 mol %), K_2CO_3 (1.0 mmol), PhMe (2 mL), 120 °C, 20 h, under N_2; yield of isolated products. [b] 1,4-dioxane (2 mL) as the solvent.

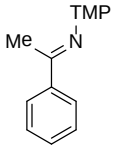
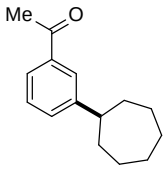
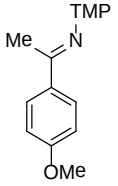
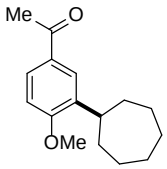
3.2.3 Direct *meta*-Alkylation with Secondary Bromides: Scope and Limitations

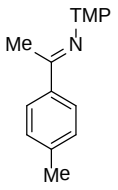
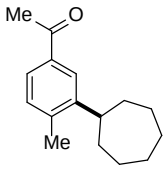
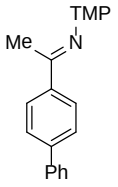
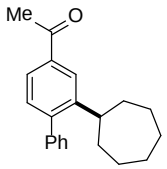
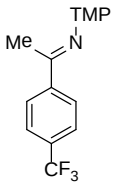
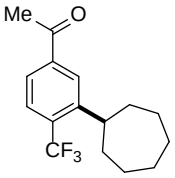
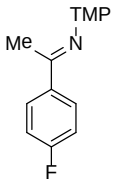
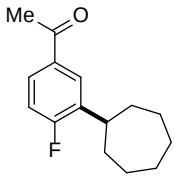
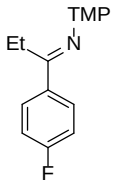
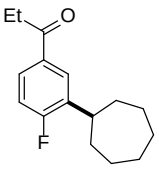
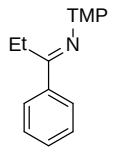
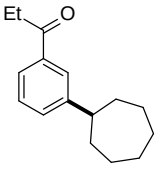
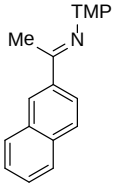
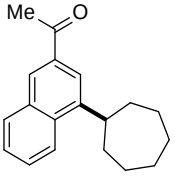
Besides tertiary alkyl bromides **50**, we were pleased to find that secondary alkyl bromides **44** could also serve as electrophiles in the *meta*-C–H alkylation reactions. Differently substituted ketimines **188** were tested under the optimized reaction conditions with bromocycloheptane (**44e**) (Table 3.10). A generally broader scope of ketimines was observed compared to the tertiary alkyl bromides **50**. Transformation of unsubstituted ketimines to the desired products **206** proceeded smoothly (entries 1 and 8). Ketimines bearing both electron-donating and electron-withdrawing groups were well tolerated and delivered *meta*-alkylated products in moderate to good yields (entries 2–7). It is worth noting that naphthalene derivative **188i** selectively furnished *meta*-substituted product **206ie** under the optimized reaction conditions (entry 9).

Table 3.10: Direct *meta*-C–H alkylation of ketimines **188** with secondary alkyl bromide **44e**



188 **44e** **206**

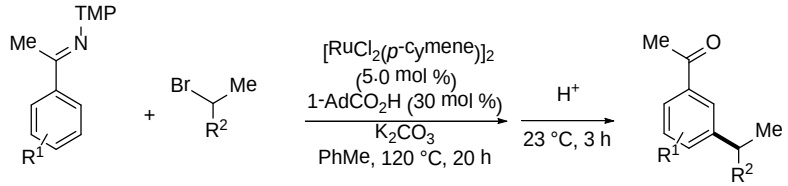
Entry	Substrate 188	Product 206	Yield (%)
1			58
	188b	**206be**	
2			53[b]
	188e	**206ee**	

3			51
	188d	**206de**	
4			60
	188g	**206ge**	
5			44
	188h	**206he**	
6			64
	188a	**206ae**	
7			62[b]
	188f	**206fe**	
8			53
	188c	**206ce**	
9			50
	188i	**206ie**	

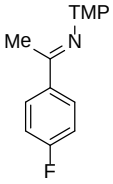
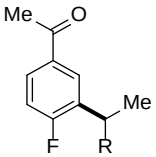
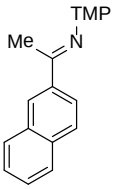
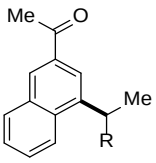
[a] Reaction conditions: **188** (0.5 mmol), **44e** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), 1-$AdCO_2H$ (30 mol %), K_2CO_3 (1.0 mmol), PhMe (2 mL), 120 °C, 20 h, under N_2; yield of isolated products. [b] 1,4-Dioxane (2 mL) as the solvent.

Subsequently, we continued to explore the scope of acyclic secondary alkyl bromides **44** (Table 3.11). In contrast to the monoalkylation of ketimine **188a** with cyclic secondary alkyl bromides **44**, the reaction with the acyclic secondary bromide **44f** led to the formation of dialkylated product in large amounts, whereas the monoalkylated product **206af** was isolated in low yield (entry 1). Unfortunately, the dialkylated products which could be observed on GC-MS analysis were difficult to isolate as pure compounds. To our delight, in the case of the 2-substituted naphthalene derivative **188i** with its single *meta*-position, products **206i** were obtained in excellent yields (entries 4–7).

Table 3.11: Direct *meta*-C–H alkylation of ketimines **188** with acyclic secondary alkyl bromides **44**

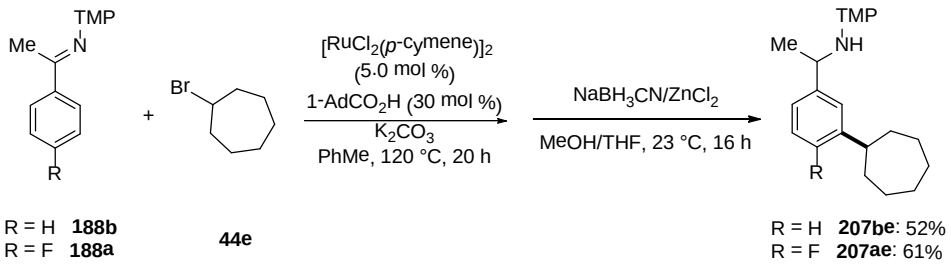


188 **44** **206**

Entry	Substrate 188	Secondary Bromide 44	Product 206	Yield (%)
1		 **44f**		**206af:** 43[b]
2		 **44g**		**206ag:** 46[b]
3	**188a**	 **44d**	**206**	**206ad:** 40[b]
4		 **44h**		**206ih:** 77
5		 **44f**		**206if:** 74
6		 **44g**		**206ig:** 77
7	**188i**	 **44d**	**206**	**206id:** 61

[a] Reaction conditions: **188** (0.5 mmol), **44** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), 1-$AdCO_2H$ (30 mol %), K_2CO_3 (1.0 mmol), PhMe (2 mL), 120 °C, 20 h, under N_2; yield of isolated products. [b] **44** (0.75 mmol).

Furthermore, given the importance of amines as structural motifs in organic synthesis, we performed a one-pot reduction of the *meta*-alkylated ketimine products **188**. Not surprisingly, both unsubstituted ketimine **188b** and *para*-fluoroacetophenone imine **188a** afforded secondary amines in good yields (Scheme 3.10).

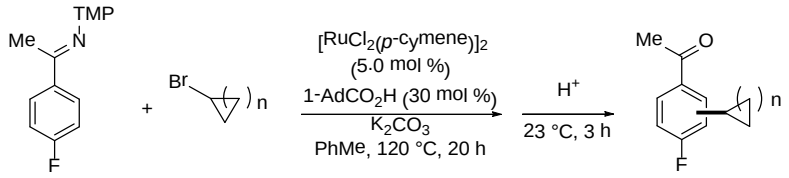


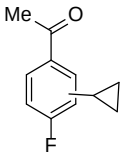
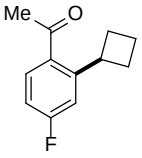
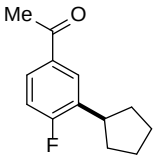
Scheme 3.10: One-pot synthesis of *meta*-alkylated secondary amines **207**

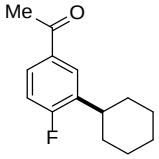
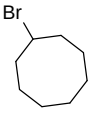
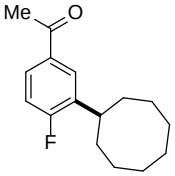
3.2.4 Direct *meta*- versus *ortho*-Alkylation with Cyclic Secondary Alkyl Bromides

Besides bromocycloheptane (**44e**), we explored the reaction scope with different cyclic secondary alkyl bromides as well (Table 3.12). Unfortunately, bromocyclopropane (**44i**) proved unsuitable for this reaction (entry 1). However, cyclic alkyl bromides with ring sizes varying from 4 to 8 could be smoothly converted and gave alkylated product **206** in moderate yields (entries 2–5). Surprisingly, ruthenium(II)-catalyzed alkylation with bromocyclobutane (**44j**) turned out to exclusively yield *ortho*-functionalized product **206aj** in 50% yield (entry 2)), as was disclosed by 2D NMR data for selected products.

Table 3.12: Direct alkylation of ketimines **188** with cyclic secondary alkyl bromides **44**



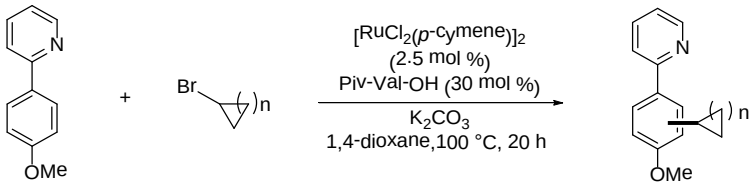
Entry	Secondary Bromide 44	Product 206	Yield (%)
1	 **44i**	 **206ai**	0
2	 **44j**	 **206aj**	50
3	 **44k**	 **206ak**	53

4			27
	44c	**206ac**	
5			60
	44l	**206al**	

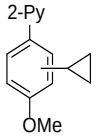
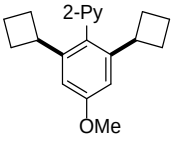
[a] Reaction conditions: **188a** (0.5 mmol), **44** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), 1-$AdCO_2H$ (30 mol %), K_2CO_3 (1.0 mmol), PhMe (2 mL), 120 °C, 20 h, under N_2; yield of isolated products.

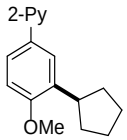
In order to test the universality of this phenomenon, we chose 2-phenylpyridine derivative **38b** for the alkylation with cyclic secondary alkyl bromides **44** under the conditions optimized for the alkylation with tertiary bromides (Table 3.13). As above, we found no product formation in the reaction with bromocyclopropane **44i** (entry 1). Furthermore, the *ortho*-selectivity pattern was observed for the alkylation with bromocyclobutane **44j**, however, in this case resulting in the dialkylation to furnish product **208bj** (entry 2). Bromocyclopentane **44k** again smoothly delivered *meta*-alkylated product **208bk** in good yield (entry 3).

Table 3.13: Direct alkylation of 2-phenylpyridine **38b** with cyclic secondary alkyl bromides **44**



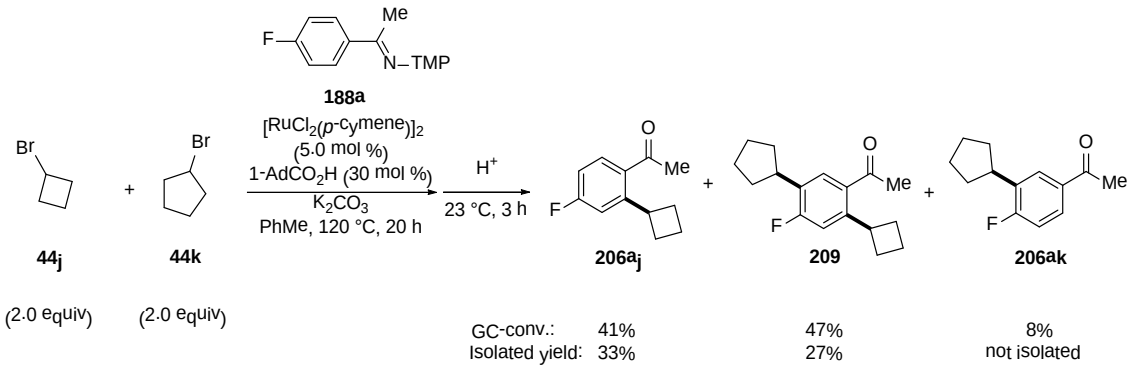
38b **44** **208**

Entry	Secondary Bromide 44	Product 208	Yield (%)
1			0
	44i	**208bi**	
2			51
	44j	**208bj**	

3	 **44k**	 **208bk**	65

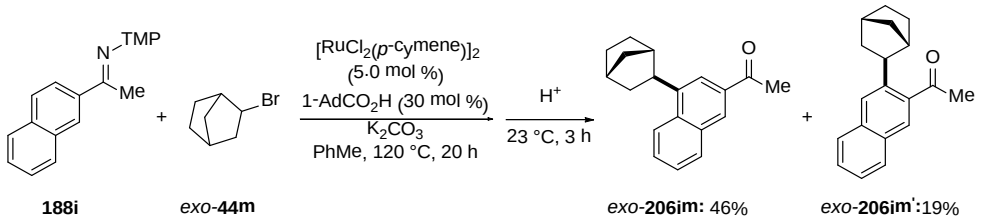
[a] Reaction conditions: **37b** (0.5 mmol), **44** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), Piv-Val-OH (30 mol %), K_2CO_3 (1.0 mmol), 1,4-dioxane (2 mL), 100 °C, 20 h, under N_2; yield of isolated products.

Intermolecular competition reaction between bromocyclobutane (**44j**) and bromocyclopentane (**44k**) was performed under the standard reaction conditions (Scheme 3.11). As expected, *ortho*-alkylated compound **206aj** was isolated as a pure product. However, we also obtained the *ortho*,*meta*-dialkylated ketone **209** which should result from either a sequential ruthenium(II)-catalyzed *ortho*-alkylation of *meta*-alkylated product **206ak** or *meta*-alkylation of *ortho*-alkylated compound **206aj**. Thus, no particular difference in reaction rates was found between these two cyclic alkyl bromides. More importantly, each alkyl bromide gave rise to the corresponding site-selectively substituted product.



Scheme 3.11: Intermolecular competition experiment between cyclic alkyl bromides **44j** and **44k**

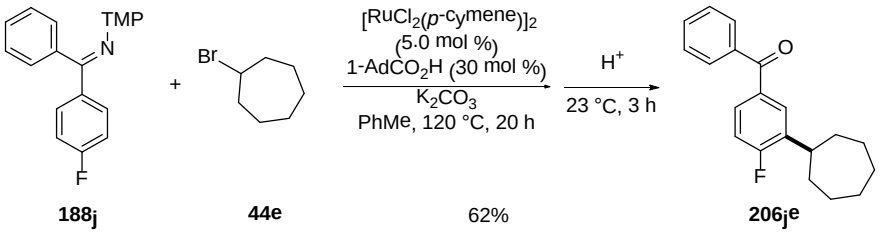
Ruthenium(II)-catalyzed direct alkylation with *exo*-bromonorbornane (**44m**) led to interesting results as well (Scheme 3.12). Both *ortho*- and *meta*-alkylated products *exo*-**206im** and *exo*-**206im'** were isolated in a ratio of 2.4 : 1 with retention of the thermodynamically more stable *exo*-configuration of the norbornyl moiety and without formation of Wagner-Meerwein-rearranged skeletons.



Scheme 3.12: Ruthenium(II)-catalyzed direct norbornylation of ketimine **188i**

3.2.5 Intramolecular Competition Experiments

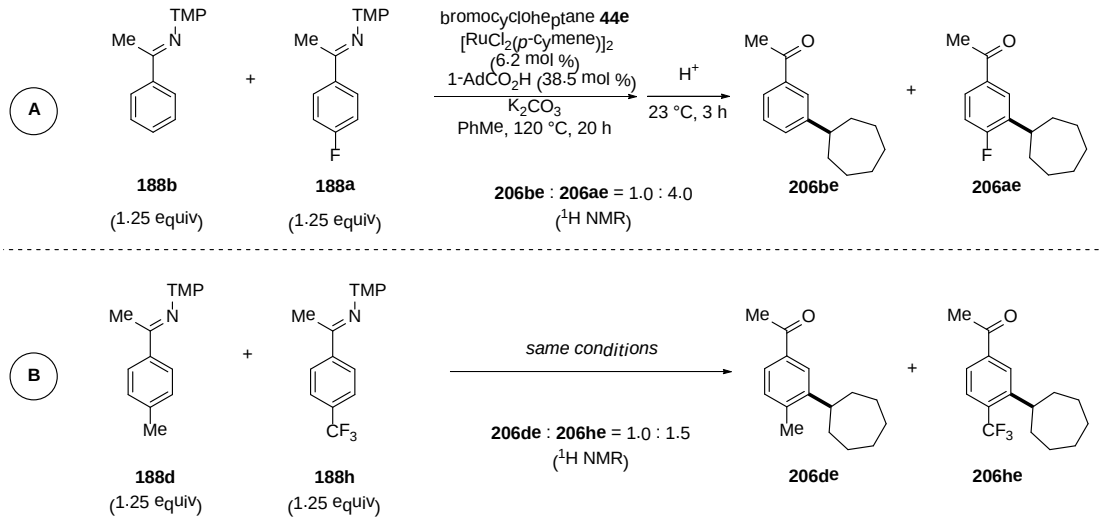
Importantly, alkylation of ketimine **188j** could be considered as an intramolecular competition reaction, the result of which showed that the arene bearing the fluorine substituent was selectively converted (Scheme 3.13).



Scheme 3.13: Intramolecular competition experiments of ketimine **188j**

3.2.6 Intermolecular Competition Experiments

Intermolecular competition experiments between substituted ketimines **188**, during which a 1.25 fold excess of both substrates **188** was treated with bromocycloheptane (**44e**) as the limiting reagent under otherwise identical reaction conditions, were performed (Scheme 3.14). The ratio of products was determined by ^{1}H NMR after aqueous workup.

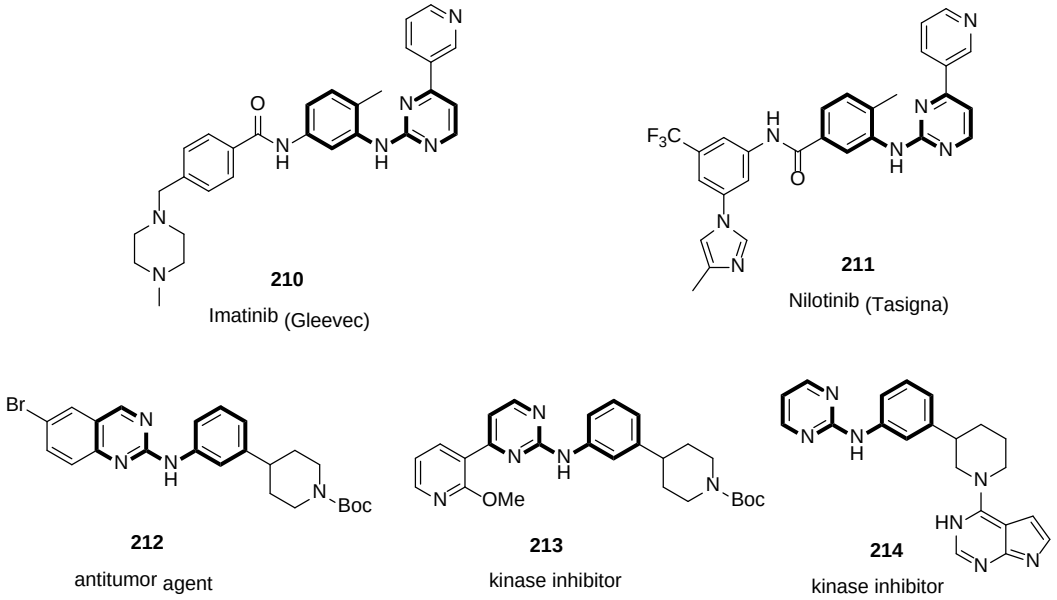


Scheme 3.14: Intermolecular competition experiments between ketimines **188**

Experiment **A** showed electron-deficient fluoro-substituted arene **188a** to be more reactive than the unsubstituted ketimine **188b**. This could be accounted for by the *ortho*-orienting effect of the fluorine substituent. However, the trifluoromethyl-bearing substrate **188h** was more reactive than the methyl substituted **188d** as well, presumably due to the increased acidity of the C–H bond in the neighboring position. This observation contrasts with the previous one made for *meta*-alkylation of 2-phenylpyridines **38** (Scheme 3.2), but in line with the effects observed in ruthenium(II)-catalyzed *ortho*-selective alkylation of ketimines with primary alkyl halides.[142]

3.3 Ruthenium(II)-Catalyzed *meta*-Selective C–H Alkylations of Aniline Derivatives with Unactivated Alkyl Bromides

N-(Pyrimidine-2-yl)anilines **161** are important structural motifs in biologically active and naturally occurring compounds and pharmacologically active substances (Scheme 3.15). Among them, Imatinib (**210**) and Nilotinib (**211**) are in the list of the top-selling drugs. Therefore, it is of particular interest to synthesize aniline derivatives via C–H bond functionalization. *Ackermann* and co-workers have reported ruthenium(II)-[211] or nickel-catalyzed[238] C–H/N–H bond functionalization of *N*-(pyrimidine-2-yl)anilines **161** where the pyrimidyl group served as a removable directing group. However, direct alkylations of arenes **161** have thus far proved elusive. Herein, we wish to extend our scope of ruthenium(II)-catalyzed direct *meta*-alkylation to *N*-(pyrimidine-2-yl)aniline derivatives **161**. More importantly, the pyrimidyl moiety can readily be cleaved, thus providing access to *meta*-alkylated aniline derivatives.

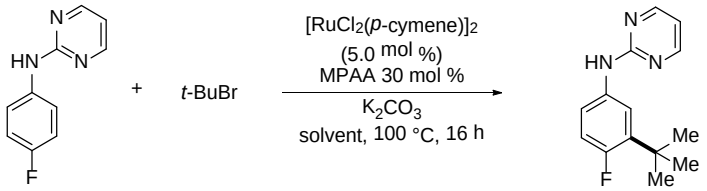


Scheme 3.15: *N*-2-Pyrimidyl anilines **161** in drugs and bioactive compounds

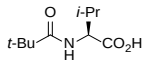
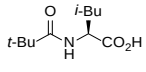
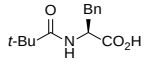
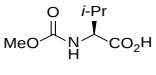
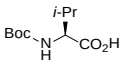
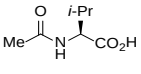
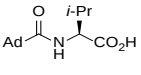
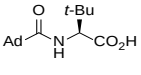
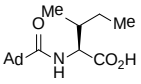
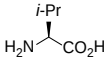
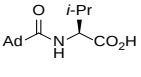
3.3.1 Optimization Studies

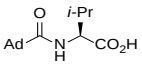
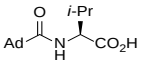
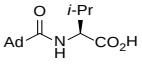
At the outset of our studies, we adopted the reaction conditions optimized for the ruthenium(II)-catalyzed *meta*-alkylation of 2-phenylpyridines **38** (Table 3.14). To our delight, the desired product **215aa** was isolated in 66% yield (entry 1). Other MPAAs as well as different *N*-protecting groups showed lower efficiency (entries 2–8). Unprotected valine (**116e**) was also capable to promote this transformation, albeit with lower efficacy (entry 9). Among a variety of solvents, 1,4-dioxane proved to be most efficient (entries 10–14). However, ^{1}H NMR only showed a mass balance of 80%, which is similar to the case of *meta*-C–H alkylation of ketimines **188**.

Table 3.14: Optimization for the direct *meta*-alkylation of *N*-(pyrimidine-2-yl)aniline **161a**



161a **50a** **215aa**

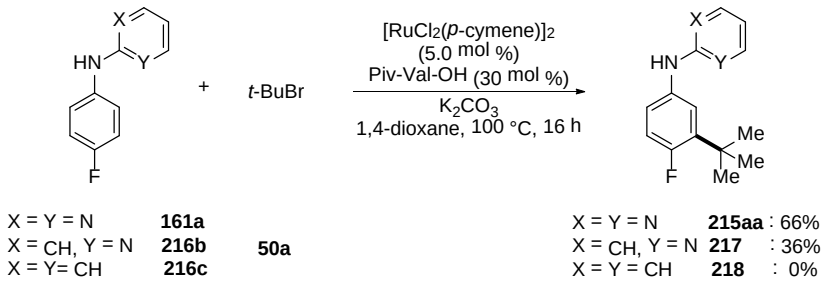
Entry	MPAA 116	Solvent	Yield (%)
1	 **116a**	1,4-dioxane	66
2	 **116b**	1,4-dioxane	58
3	 **116d**	1,4-dioxane	50
4	 **116h**	1,4-dioxane	58
5	 **116i**	1,4-dioxane	55
6	 **116m**	1,4-dioxane	47
7	 **116j**	1,4-dioxane	62
8	 **116k**	1,4-dioxane	50
9	 **116l**	1,4-dioxane	65
10	 **116e**	1,4-dioxane	35[b]
11	 **116j**	DME	61

12	 **116j**	DCE	20[b]
13	 **116j**	*t*-AmOH	34[b]
14	 **116j**	PhMe	25[b]

[a] Reaction conditions: **161a** (0.5 mmol), **50a** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), MPAA **116** (30 mol %), K_2CO_3 (1.0 mmol), solvent (2 mL), 100 °C, 16 h, under N_2; isolated yields. [b] GC-conversion.

3.3.2 Effect of Directing Groups

Furthermore, we probed the effect of the different directing group for this ruthenium(II)-catalyzed direct *meta*-alkylation (Scheme 3.16). Switching the pyrimidyl group to the pyridyl one under otherwise identical reaction conditions resulted in a 30% lower isolated yield of the product **217**, indicating pyridyl to be the less efficient directing group in this transformation. A simple phenyl substitution failed to yield any product **218**. This observation clearly showed the necessity of a chelating heteroatom in the directing group for this reaction. Moreover, this indirectly proved this reaction not to be a simple electrophilic aromatic substitution, in which the ruthenium(II) complex functioned only as a Lewis acid. Besides, electron-donating amines are well-known *ortho*- and *para*-directing groups. Thus, this mechanism could cause an alternative to *meta*-selective functionalizations reaction of aniline derivatives.



X = Y = N **161a**
X = CH, Y = N **216b** **50a**
X = Y= CH **216c**

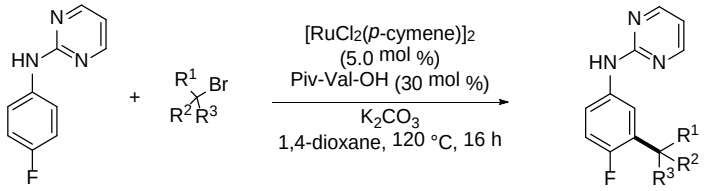
X = Y = N **215aa** : 66%
X = CH, Y = N **217** : 36%
X = Y = CH **218** : 0%

Scheme 3.16: Directing group effect in the direct *meta*-alkylation of aniline derivatives

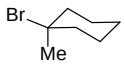
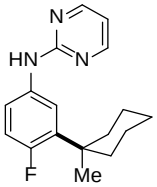
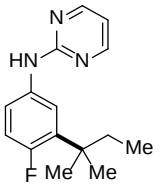
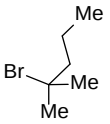
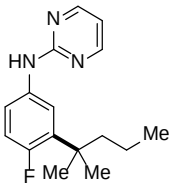
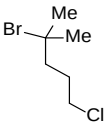
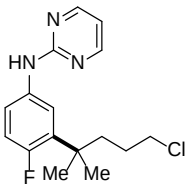
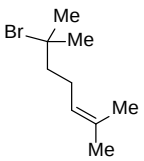
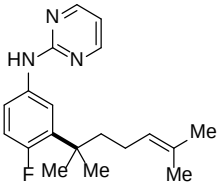
3.3.3 Direct *meta*-Alkylation with Tertiary Alkyl Bromides: Scope and Limitations

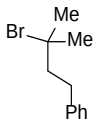
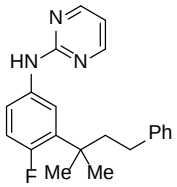
With the optimized reaction conditions in hand, we subsequently explored the scope and limitations of the *meta*-selective alkylation with a range of tertiary alkyl bromides **50** (Table 3.15). Cyclic tertiary bromide **50b** delivered the desired product **212ab** in 60% yield (entry 1). Sterically hindered tertiary alkyl bromides **50** also afforded the corresponding products in moderate yields (entries 2–3). It should be emphasized that alkyl bromide **50h** with a chlorine substituent was well tolerated (entry 4). Moreover, alkenyl- (**50g**) and phenylsubstituted bromides **50i** could smoothly be converted as well (entries 5 and 6).

Table 3.15: Scope for ruthenium(II)-catalyzed *meta*-alkylation with tertiary alkyl bromides **50**



161a **50** **215**

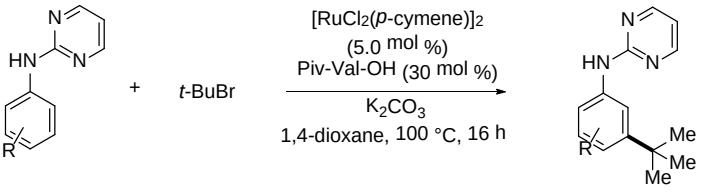
Entry	Tertiary Bromide 50	Product 215	Yield (%)
1	 **50b**	 **215ab**	60
2	 **50d**	 **215ad**	58
3	 **50c**	 **215ac**	53
4	 **50h**	 **215ah**	64
5	 **50g**	 **215ag**	57

6			55
	50i	**215ai**	

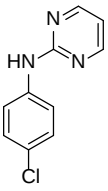
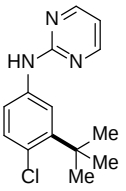
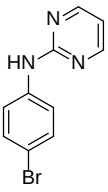
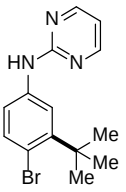
[a] Reaction conditions: **161a** (0.5 mmol), **50** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), Piv-Val-OH (30 mol %), K_2CO_3 (1.0 mmol), 1,4-dioxane (2 mL), 120 °C, 20 h, under N_2; isolated yields.

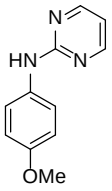
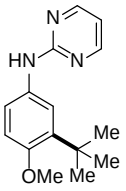
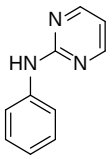
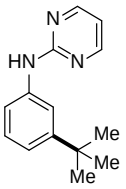
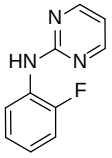
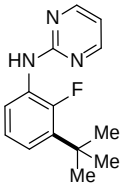
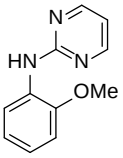
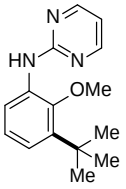
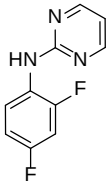
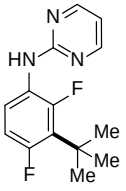
Thereafter, we explored the scope of substituted *N*-(pyrimidine-2-yl)anilines **161** for the direct *meta*-selective alkylation (Table 3.16). To our delight, arenes bearing bromine (**161b**) and chlorine (**161c**) substituents were smoothly converted, giving the *meta*-alkylated products **215ba** and **215ca** in moderate yields (entries 1 and 2). Likewise, electron-neutral as well as electron-rich arenes delivered the target compounds **215da** and **215ea** in good yields as well (entries 3 and 4). Notably, switching the ligand to Ad-Ile-OH enabled the direct *meta*-alkylation of challenging *ortho*-substituted substrates. Aniline derivate **161f** and **161g** furnished alkylation products exclusively at the sterically more congested *meta*-C–H bond (entries 5 and 6). 2,4-Substituted aniline **161h** was smoothly alkylated at the 3-position, highlighting the excellent site-selectivity of this approach (entry 7).

Table 3.16: Scope for direct *meta*-alkylation of *N*-(pyrimidine-2-yl)anilines **161**



161 **50a** **215**

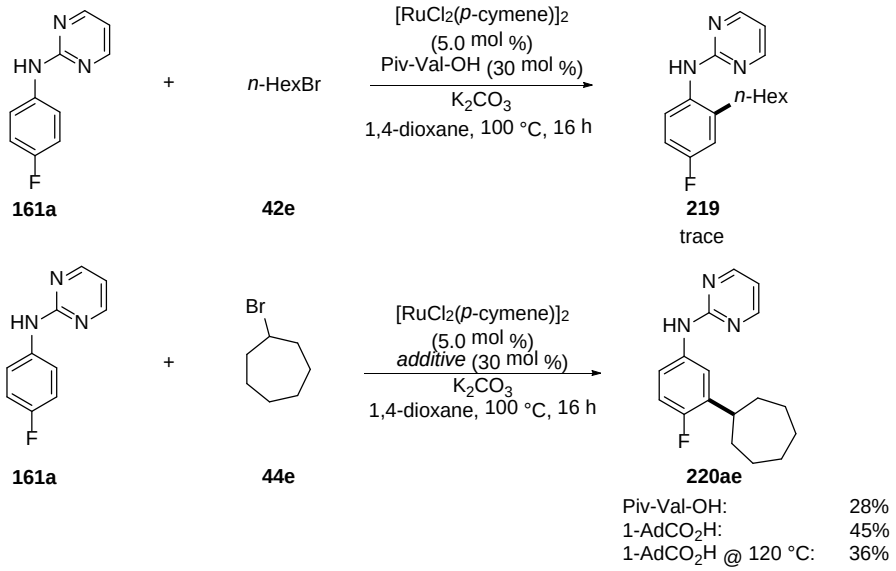
Entry	Substrate 161	Product 215	Yield (%)
1			58
	161b	**215ba**	
2			46[b]
	161c	**215ca**	

3			54
	161d	**215da**	
4			53[b]
	161e	**215ea**	
5			61[c]
	161f	**215fa**	
6			40[b,c]
	161g	**215ga**	
7			55[b,c]
	161h	**215ha**	

[a] Reaction conditions: **161** (0.5 mmol), **50a** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), Piv-Val-OH (30 mol %), K_2CO_3 (1.0 mmol), 1,4-dioxane (2 mL), 100 °C, 20 h, under N_2; isolated yields; [b] 120 °C. [c] Ad-Ile-OH instead of Piv-Val-OH.

3.3.4 Direct Alkylation with Primary and Secondary Alkyl Bromides

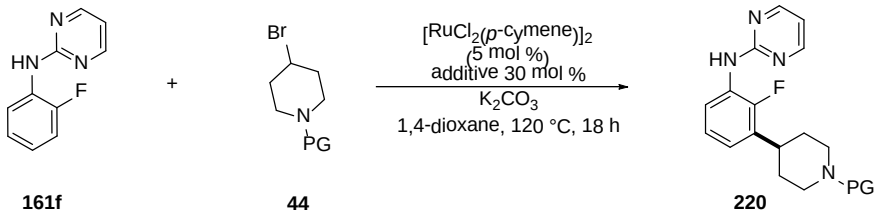
Furthermore, we probed if this optimized catalytic system could be applied for the alkylation with primary and secondary alkyl bromides (Scheme 3.17). However, only trace quantity of the product **219** was detected when 1-bromohexane (**42e**) was employed. Bromocycloheptane (**44e**) was able to deliver the desired product under standard conditions, albeit only in a unsatisfactory low yield. Replacing MPAA ligand by 1-AdCO_2H could improve the yield to 45%, unfortunately, the yield could not be further improved by raising the reaction temperature.



Scheme 3.17: Direct alkylations with primary and secondary alkyl bromides **42e** and **44e**

Given the fact that *N*-(pyrimidine-2-yl)anilines containing the piperidine moiety are important constituents in antitumor reagents and kinase inhibitors, we were interested in preparing these analogues employing our ruthenium(II)-catalyzed *meta*-selective direct alkylation strategy (Table 3.17). We chose fluoro-substituted aniline **161f** as the standard substrate, *N*-Boc-protected piperidine **44n** as the alkylating reagent. Under the optimized reaction conditions, the desired product **220** could be obtained in 32% isolated yield (entry 1). However, other carboxylates as well as MPAAs provided only low conversions (entries 2−4). Subsequently, we tested different protecting groups on the piperidine nitrogen. However, alkylation with neither pivaloyl- nor tosyl-protected piperidine **44** allowed to improve the yield (entries 5−6).

Table 3.17: Direct *meta*-alkylation with 4-bromopiperidine derivative **44**

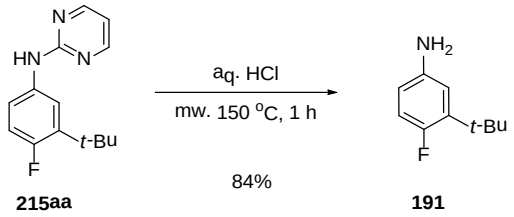


Entry	PG	Additive	Yield (%)
1	Boc (**44n**)	1-AdCO_2H	32
2	Boc (**44n**)	MesCO_2H	<5
3	Boc (**44n**)	Piv-Val-OH	<5
4	Boc (**44n**)	Ad-Ile-OH	<5
5	Piv (**44o**)	1-AdCO_2H	20
6	Ts (**44a**)	1-AdCO_2H	<5

[a] Reaction conditions: **161f** (0.25 mmol), **44** (0.75 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (5 mol %), additive (30 mol %), K_2CO_3 (0.75 mmol), 1,4-dioxane (2 mL), 120 °C, 18 h, under N_2; isolated yields.

3.3.5 Removal of the Directing Group

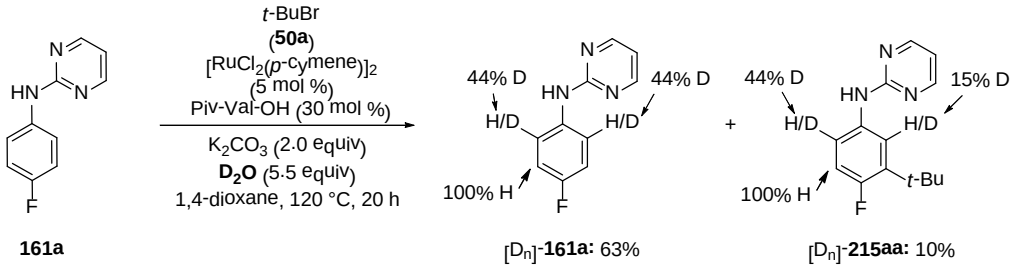
Importantly, the pyrimidyl directing group could readily be cleaved under acidic conditions, providing *meta*-alkylated aniline derivative **191** in high yield (Scheme 3.18). Thus, our new methodology offered a novel approach for the synthesis of *meta*-substituted anilines.



Scheme 3.18: Removal of the directing group

3.3.6 H/D Exchange

In order to gain insight into the reaction mechanism of the ruthenium(II)-catalyzed *meta*-selective direct alkylation of aniline derivatives **161**, we performed an experiment in the presence of D_2O under the optimized reaction conditions. As shown in Scheme 3.18, a significant H/D exchange was observed in the *ortho*-position of both the product $[D_n]$-**215aa** and the recovered starting material $[D_n]$-**161a**, thus indicating the reversible nature of the *ortho*-C−H bond metalation.



Scheme 3.19: Direct *meta*-alkylation of aniline **161a** in the presence of D_2O

Most probably, the mechanism of these *meta*-alkylation corresponds to those discussed above (Scheme 3.9).

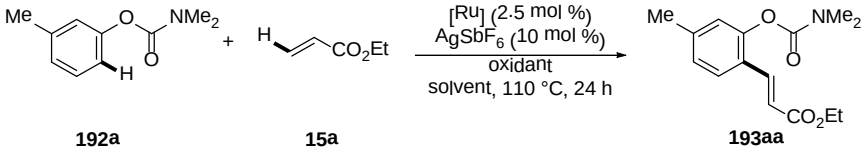
4 Ruthenium(II)-Catalyzed Oxidative C–H Alkenylation of Aryl Carbamates

As discussed above in Chapter 1.4, significant progress has been accomplished in ruthenium(II)-catalyzed environmentally benign twofold C–H bond alkenylations. In contrast, the use of air- and moisture stable ruthenium(II) complexes for challenging oxidative C–H bond alkenylations with widely accessible phenol derivatives has unfortunately proven to be elusive until recently.[178] In the course of our continuing efforts in step-economical C–H bond functionalizations, we devised reaction conditions for ruthenium(II)-catalyzed cross-dehydrogenative alkenylations of aryl carbamates bearing removable directing groups.[239-241] Importantly, aryl carbamates are key intermediates in organic synthesis, and serve as versatile organic electrophiles in transition metal catalysis.[242,243]

4.1 Optimization Studies

At the outset of our studies, we optimized reaction conditions for the oxidative alkenylation of aryl carbamate **192a** (Table 4.1). Preliminary studies with a naphthyl carbamate indicated that the desired oxidative alkenylation was not viable with CsOAc or KPF_6 as the co-catalytic additive. However, satisfactory results were gratifyingly achieved when employing 10 mol% of $AgSbF_6$. The desired olefination did not occur in the absence of the ruthenium complex $[RuCl_2(p\text{-cymene})]_2$ (entry 1). Among a set of representative solvents, DME turned out to be the optimal one (entries 2–6), and the catalytic system was found to be air-stable (entry 7). The use of a combination of $CuBr_2$ and NaOAc as terminal oxidant failed to deliver the desired product (entry 8). Notably, the cross-dehydrogenative alkenylation failed to proceed in the absence of $AgSbF_6$ as the co-catalyst (entry 9), thus being suggestive of the formation of a cationic ruthenium(II) catalyst. Yet, the preformed cationic complex $[Ru_2Cl_3(p\text{-cymene})_2][PF_6]$ bearing the PF_6^- counteranion did not deliver the desired product under otherwise identical reaction conditions (entry 10).

Table 4.1: Optimization of oxidative alkenylation with carbamate **192a**



192a **15a** **193aa**

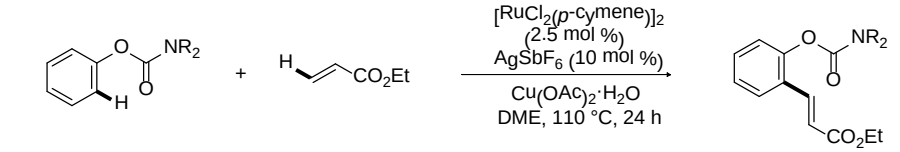
Entry	Catalyst	Oxidant	Solvent	Yield (%)
1	---	$Cu(OAc)_2 \cdot H_2O$	DME	0
2	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	DMF	0
3	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	PhMe	0
4	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	DCE	40
5	**$[RuCl_2(p\text{-cymene})]_2$**	**$Cu(OAc)_2 \cdot H_2O$**	**DME**	**84**
6	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	*t*-AmOH	48
7	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	DME	84[b]
8	$[RuCl_2(p\text{-cymene})]_2$	$CuBr_2$/NaOAc	DME	0

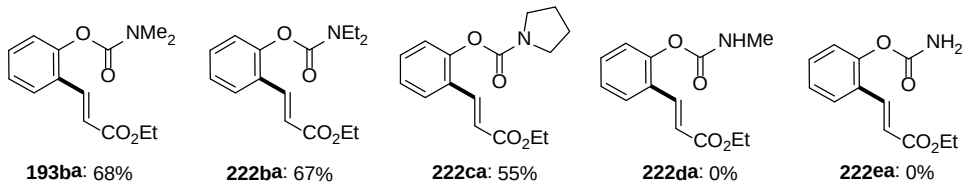
9	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2{\cdot}H_2O$	DME	0[c]
10	$[Ru_2Cl_3(p\text{-cymene})_2][PF_6]$	$Cu(OAc)_2{\cdot}H_2O$	DME	0[c]

[a] Reaction conditions: **192a** (0.5 mmol), **15a** (1.0 mmol), catalyst (2.5 mol %), oxidant (1.0 mmol), solvent (3 mL); isolated yields. [b] Under air. [c] Without $AgSbF_6$.

4.2 Effect of Directing Groups

With the optimized catalytic system in hand, we tested the influence of the *N*-substituents of the phenyl carbamates on the reaction efficacy (Scheme 4.1). Thus, *N*,*N*-dialkyl-substituted carbamates **192** and **221** furnished the desired products **193** and **222** in high yields, with atom-economical *N*,*N*-dimethyl derivative **192b** providing the best results. Mono *N*-substituted carbamate **221d** as well as *N*-unsubstituted carbamate **221e** proved to be unsuitable substrates for this oxidative alkenylation.



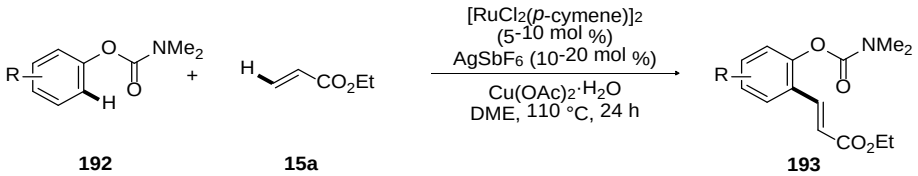


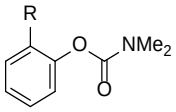
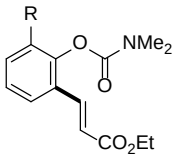
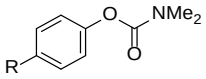
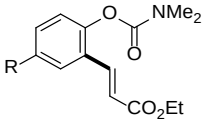
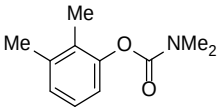
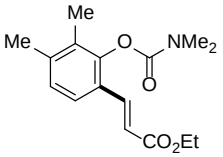
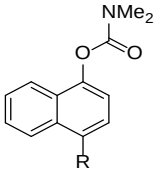
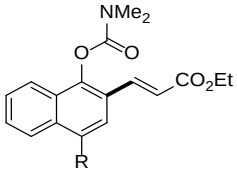
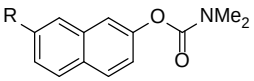
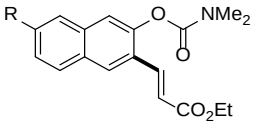
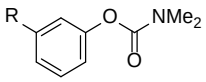
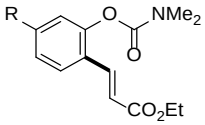
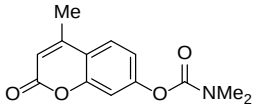
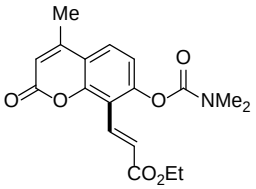
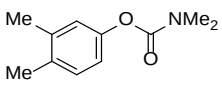
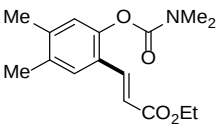
Scheme 4.1 Effect of *N*-substituents on C–H bond alkenylation of cabarmates

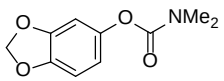
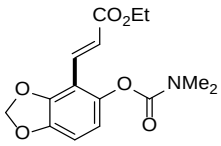
4.3 Scope and Limitations

Subsequently, we probed the scope of the optimized catalyst in the twofold C–H bond functionalizations with moisture-stable phenol derivatives **192** (Table 4.2). The cationic ruthenium(II) catalyst proved to be broadly applicable. Thus, substrates bearing *ortho*- and *para*-substituents were efficiently converted into the corresponding monoalkenylated products **193** (entries 1–13). Notably, valuable functional groups, such as aryl and alkyl fluorides (entries 5 and 11), chlorides (entries 7 and 16) or bromides (entries 12, 18 and 20), were well tolerated and therefore provide a handle for further elaborations. Furthermore, we observed that intramolecular competition experiments with *meta*-substituted substrates proceeded with high site-selectivities, furnishing alkenylated carbamates **193** as the sole products (entries 14–24).

Table 4.2: Scope of oxidative alkenylation with phenol carbamates **192**

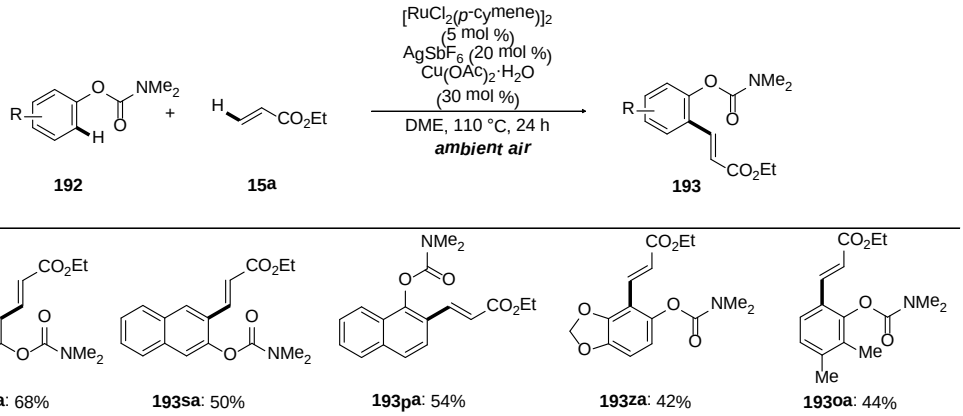


Entry	Carbamate 192		Product 193		Yield(%)
1		R = Me (**192c**)		**193ca**	70
2		R = Ph (**192d**)		**193da**	77
3		R = *i*-Pr (**192e**)		**193ea**	78
4		R = OMe (**192f**)		**193fa**	65
5		R = F (**192g**)		**193ga**	73
6		R = CF_3 (**192h**)		**193ha**	65
7		R = Cl (**192i**)		**193ia**	51
8		R = Me (**192j**)		**193ja**	56
9		R = Ph (**192k**)		**193ka**	59
10		R = OMe (**192l**)		**193la**	65
11		R = F (**192m**)		**193ma**	61
12		R = Br (**192n**)		**193na**	60
13					78
	192o		**193oa**		
14		R = H (**192p**)		**193pa**	76[b]
15		R= OMe (**192q**)		**193qa**	68[b]
16		R = Cl (**192r**)		**193ra**	75[b]
17		R = H (**192s**)		**193sa**	87[b]
18		R = Br (**192t**)		**193ta**	73[b]
19		R = Ph (**192u**)		**193ua**	97
20		R = Br (**192v**)		**193va**	59
21		R = I (**192w**)		**193wa**	53
22					59[b]
	192x		**193xa**		
23					86
	192y		**193ya**		

24			65
	192z	**193za**	

[a] Reaction conditions: **192** (0.5 mmol), **15a** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1.0 mmol), DME (3 mL), 110 °C, 24 h, under N_2; isolated yields. [b] $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %).

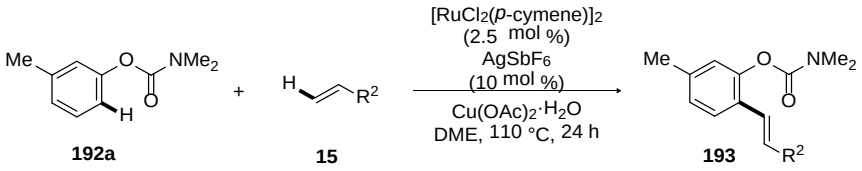
Importantly, the double C–H bond functionalization was not limited to the use of stoichiometric amounts of $Cu(OAc)_2{\cdot}H_2O$. Indeed, aerobic oxidative alkenylations proved to be viable with $Cu(OAc)_2{\cdot}H_2O$ as the cocatalyst under an atmosphere of ambient air, although in moderate yields (Scheme 4.2).



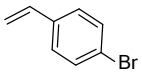
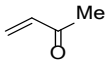
Scheme 4.2: Aerobic oxidative C–H bond alkenylations

Unfortunately, the cationic ruthenium(II) catalyst provided only rather low conversions in alkenylations with acrylonitrile (**15e**), styrene (**15c**), 4-bromostyrene (**15f**) and methyl vinyl ketone (**15g**) (Table 4.3).

Table 4.3: Oxidative alkenylations with alkene derivatives **15**



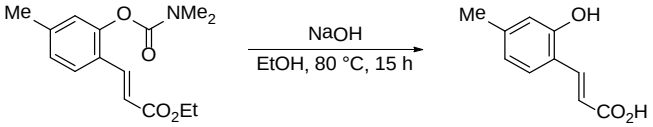
Entry	Alkene 15	Conversion (%)
1	 **15e**	<5
2	 **15c**	0

3	 **15f**	0
4	 **15g**	0

[a] Reaction Conditions: **192a** (0.5 mmol), **15** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.0 mmol), DME (3 mL), 110 °C, 24 h, under N_2; GC-conversion.

4.4 Removal of Directing Group

Importantly, compounds **193** are of great synthetic value, as the carbamate directing groups can easily be cleaved under basic conditions, thus leading to *o*-coumaric acid derivative **223** in high yield (Scheme 4.3).



193aa **223:** 74%

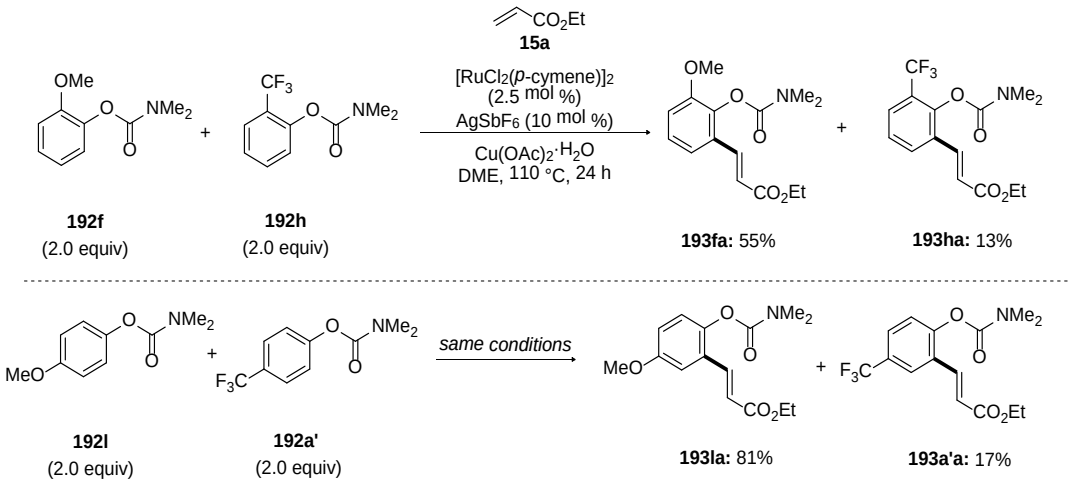
Scheme 4.3: Removal of directing group

The latter play an important role in chemistry of naturally occurring compounds. For example, as intermediates in phenylanine metabolism in enzymatic reactions catalyzed with 2-coumarate reductase.[244]

4.5 Mechanistic Studies

4.5.1 Intermolecular Competition Experiments

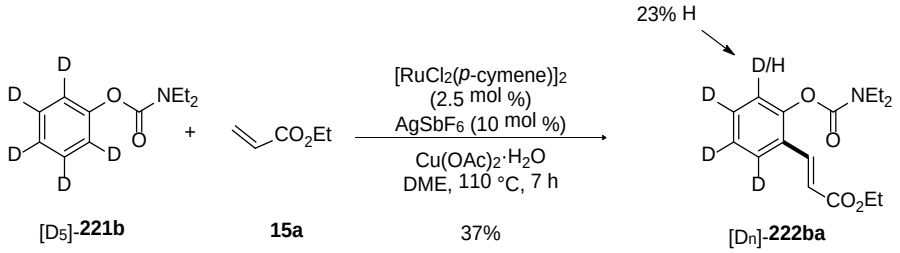
Considering the remarkable activity and high selectivity of the cationic ruthenium(II) catalyst, we became interested in probing its mode of action. To this end, we conducted intermolecular competition experiments with differently substituted arenes **192**, which revealed electron-rich substrates to be preferentially converted (Scheme 4.4). This result indicated an electrophilic activation manifold.



Scheme 4.4: Intermolecular competition experiments between carbamates **192**

4.5.2 Reaction with Isotopically Labelled Substrate

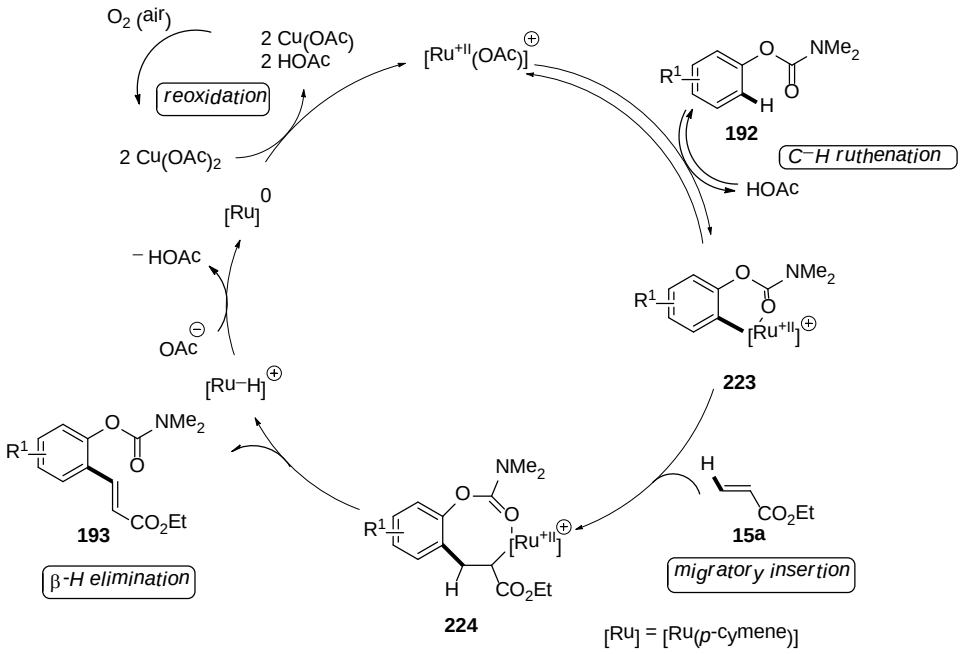
Subsequently, we performed a reaction with deuterated labeled substrate [D_5]-**221b** under the standard reaction conditions (Scheme 4.5). A significant D/H scrambling on the remaining *ortho*-position of the alkenylated product [D_5]-**222ba** was observed. This finding clearly indicated the ruthenium(II)-catalyzed oxidative alkenylation proceeded with participation of a reversible C–H bond metalation step.



Scheme 4.5: Ruthenium(II)-catalyzed oxidative alkenylation of carbamate [D_5]-**221b**

4.5.3 Proposed Catalytic Cycle

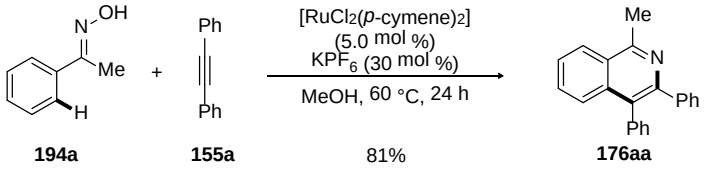
Based on these mechanistic studies as well as on our previous findings with cationic ruthenium(II) catalysts, we proposed the catalytic cycle which began with an initial base-assisted, reversible cycloruthenation (Scheme 4.6). Thereafter, migratory insertion of alkene and β-hydride elimination deliver product **191**, while reductive elimination and reoxidation by $Cu(OAc)_2 \cdot H_2O$ regenerate the active cationic catalyst.



Scheme 4.6: Proposed mechanism for ruthenium(II)-catalyzed oxidative alkenylation

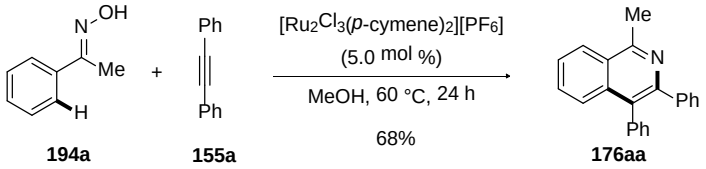
5 Cationic Ruthenium(II) Catalysts for C–H/N–O Functionalizations of Oximes

Transition metal-catalyzed annulations of alkynes that involve sequential C–H and Het–H bond cleavages have become an important tool for the regioselective synthesis of decorated heterocycles (Chapter 1.5). Since the pioneering work of *Ackermann* and coworkers which employed less expensive ruthenium(II) catalysts for the oxidative annulation of alkynes by benzamides,[207] several publications on ruthenium(II)-catalyzed oxidative annulation reactions have appeared during the last four years.[206] Unfortunately, these transformations are restricted to the use of external oxidants. Hence, developing novel methods which employ internal oxidants continues to be of importance. For example, a redox-neutral approach for the preparation of isoquinolones has been reported by dehydrogenative annulations of alkynes with free hydroxamic acids.[228] On this basis, *C. Kornhaaß* elaborated a redox-neutral annulation of alkynes with acetophenone oximes.[245]



Scheme 5.1: Redox-neutral annulation with oximes as optimized by *C. Kornhaaß*

The optimized reaction conditions employed a catalytic system consisting of $[RuCl_2(p\text{-cymene})]_2$ as the precatalyst and KPF_6 as a co-catalytic additive. Since this dehydrogenative annulation is redox-neutral in nature, no external oxidant is needed, while MeOH proved to be the solvent of choice affording the isoquinoline **176aa** in 81% yield under these conditions (Scheme 5.1). During the course of this transformation, a cationic ruthenium(II) species was most likely formed through abstraction of a chlorine atom from the precatalyst with a non-coordinating $[PF_6]^-$ anion. In order to support this concept, the presynthesized cationic complex $[Ru_2Cl_3(p\text{-cymene})_2][PF_6]$ was tested as the catalyst and furnished the desired product **176aa** in good yield as well (Scheme 5.2).

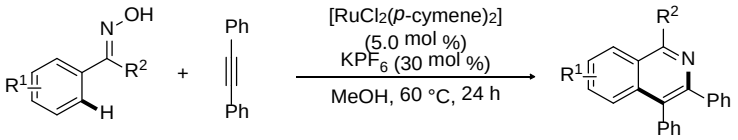


Scheme 5.2: Redox-neutral annulation using cationic ruthenium(II) complex

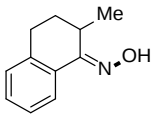
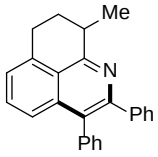
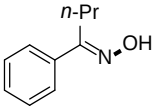
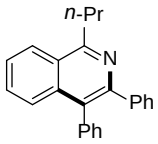
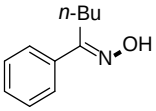
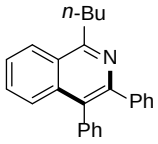
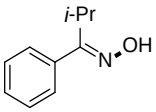
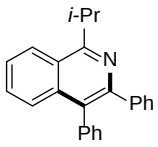
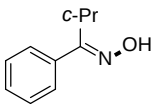
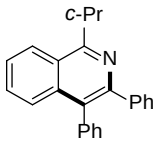
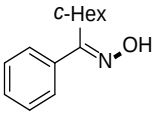
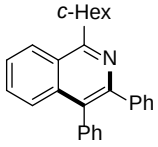
Under the optimized reaction conditions, a variety of differently substituted isoquinolines **194** bearing valuable electrophilic functional groups was chemoselectively accessed (Table 5.1). As shown in entry 1, a tetralone oxime derivative **194b** can be converted into the corresponding isoquinoline **176ba** in excellent yield. Elongation of the aliphatic chain in the oximes had no negative effect on the reaction outcome, smoothly delivering the desired products in high yields (entries 2 and 3). However, oximes containing isopropyl, cyclopropyl, cyclohexyl and benzyl groups demanded elevated reaction temperatures and additional molecular sieve to obtain high yields (entries 4–7). Oxime **194b** with a

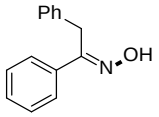
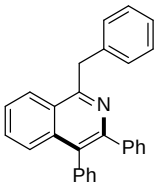
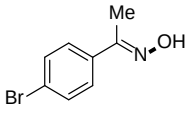
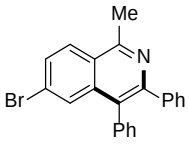
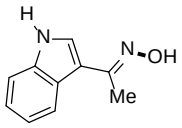
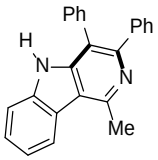
para-bromide substituent, which is valuable for post-synthetic elaboration, could also be converted in moderate yield (entry 8). In addition, indole derivative **194j** also proved to be a suitable substrate, although the reaction resulted in a lower yield (entry 9).

Table 5.1: Scope of direct annulations of diphenylacetylene (**155a**) by oxime **194**



194 **155a** **176**

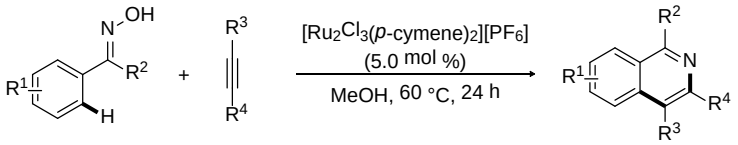
Entry	Oxime 194	Product 176	Yield (%)
1	 **194b**	 **176ba**	94
2	 **194c**	 **176ca**	89
3	 **194d**	 **176da**	85
4	 **194e**	 **176ea**	43[b]
5	 **194f**	 **176fa**	84[b]
6	 **194g**	 **176ga**	81[b]

7	 **194h**	 **176ha**	54[b]
8	 **194i**	 **176ia**	55[b]
9	 **194j**	 **176ja**	37[c]

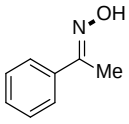
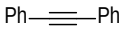
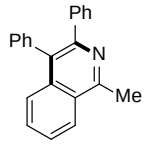
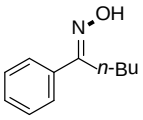
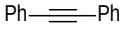
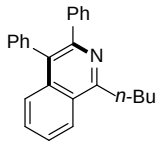
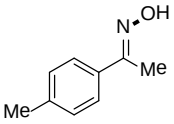
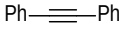
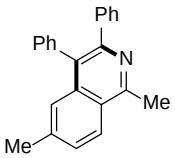
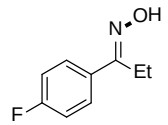
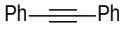
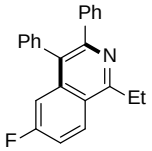
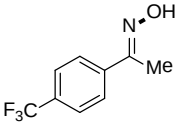
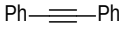
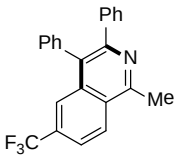
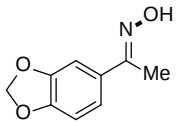
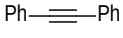
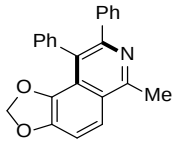
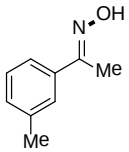
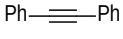
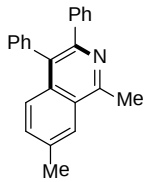
[a] Reaction conditions: **194** (0.5 mmol), **55a** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), KPF_6 (30 mol %), MeOH (2 mL), 60 °C, 24 h, under N_2; isolated yields. [b] 4 Å Mol-sieves (100 mg per 0.5 mmol **194**), 80 °C. [c] 4 Å Mol-sieves, 100 °C.

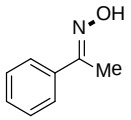
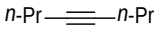
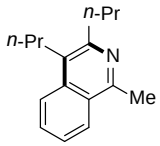
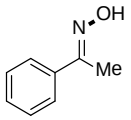
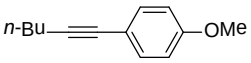
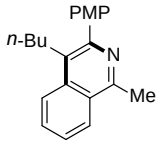
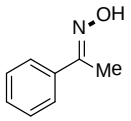
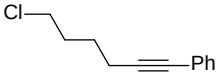
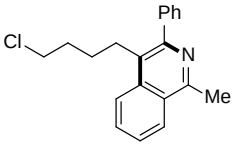
Given the remarkable efficacy of the in-situ generated ruthenium(II) catalyst, we subsequently probed the efficacy of presynthesized cationic complex $[Ru_2Cl_3(p\text{-cymene})_2][PF_6]$. Importantly, this well-defined complex displayed an activity as well as chemo-, regio- and siteselectivity being comparable to the one demonstrated by the in-situ formed catalytic system (Table 5.2, entries 1 and 2). Electron-rich methyl- (**194k**) as well as electron-deficient fluoro- (**194l**) and trifluoromethyl-containing (**194m**) oximes could all be converted to the desired isoquinolines in moderate to good yields (entries 3–5). Interestingly, when *meta*-substituted oximes were subjected to the reaction conditions, different regioselectivities were observed for the substrates with diverse electronic properties. Indeed, whereas *m*-methylacetophenone oxime (**194o**) only delivered the sterically less hindered product **176oa** (entry 7), annulation with oxime **194n** containing a fused dioxolane-moiety took place at the sterically more congested C–H bond (entry 6). This finding could be explained a secondary chelation effect caused by the oxygen atom in 3-position, which served as a secondary directing group through lone pair donation to the metal center. Such secondary directing group effect has recently been reported also for ruthenium(II)-catalyzed hydroarylation of olefins.[246] Furthermore, this cationic ruthenium(II)-catalyzed annulation was not limited to the use of diphenylacetylene. Symmetrically substituted dialkylacetylene as well as unsymmetrical alkynes bearing both alkyl and aryl substituents also furnished the target products in moderate to good yield (entries 8–10).

Table 5.2: Scope of direct annulations with well-defined cationic complex as the catalyst



194 **155** **176**

Entry	Oxime 194	Alkyne 155	Product 176	Yield (%)
1				65
	194a	**155a**	**176aa**	
2				86
	194d	**155a**	**176da**	
3				80
	194k	**155a**	**176ka**	
4				60
	194l	**155a**	**176la**	
5				47
	194m	**155a**	**176ma**	
6				86
	194n	**155a**	**176na**	
7				77
	194o	**155a**	**176oa**	

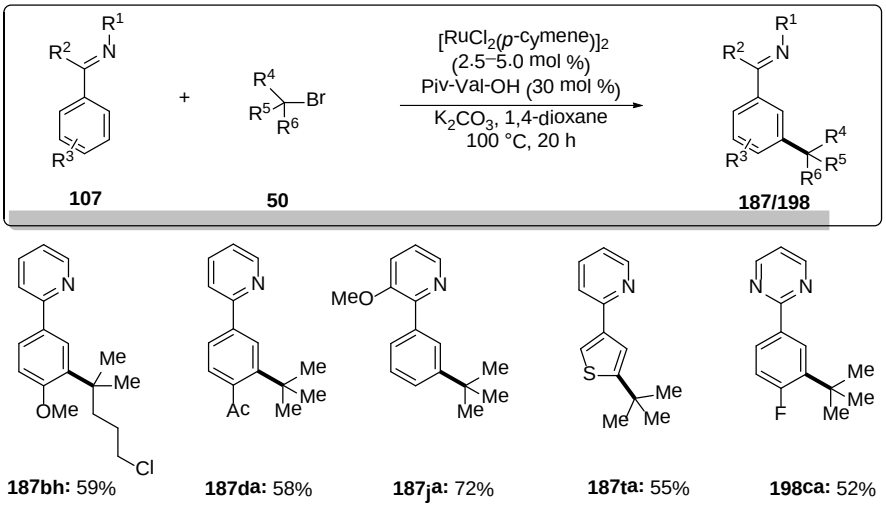
8				77
	194a	**155d**	**176ad**	
9				46
	194a	**155e**	**176ae**	
10				72
	194a	**155f**	**176af**	

[a] Reaction conditions: **192** (0.5 mmol), **155** (1.0 mmol), $[Ru_2Cl_3(p\text{-cymene})_2][PF_6]$ (5.0 mol %), MeOH (2 mL), 60 °C, 24 h, under N_2; isolated yields.

6 Summary and Outlook

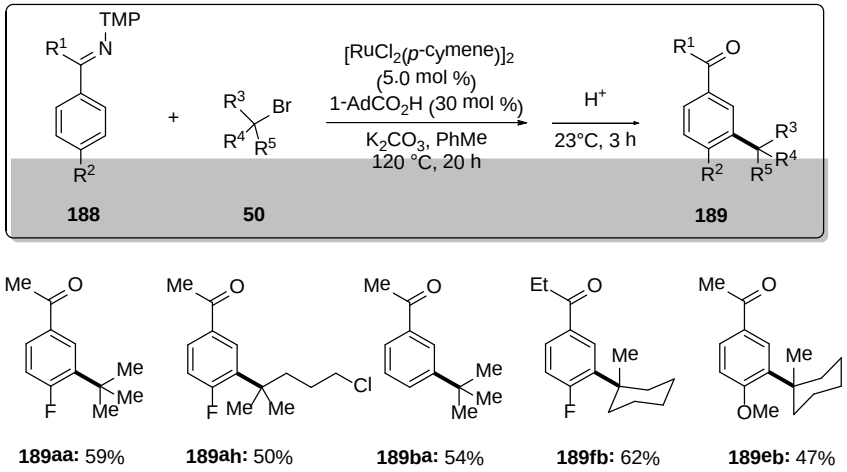
Ruthenium(II)-catalyzed C−H functionalizations have recently emerged as a reliable tool for the efficient chemo- and site-selective construction of C−C and C−Het bonds. Within this thesis, efforts have been devoted to developing new synthetic methods employing versatile ruthenium(II) catalysts.

In the first project, a novel catalytic system consisting of $[RuCl_2(p\text{-cymene})]_2$ and MPAAs as the ligands was elaborated and exhibited excellent activity and regioselectivity in unprecedented direct *meta*-alkylation with tertiary alkyl bromides **50**. A broad substrate scope of 2-phenylpyridines **187** as well as tertiary alkyl halides **50** were found under the optimized reaction conditions. Various functional groups, including chloro, ether and ester were well tolerated (Scheme 6.1). Moreover, other *N*-containing heterocycles, such as pyrimidine and pyrazole, served as competent directing groups for promoting this transformation in arenes **197** and **131**, respectively. Interestingly, heteroarenes such as thiophene **38t** could successfully be alkylated in a site-selective fashion.



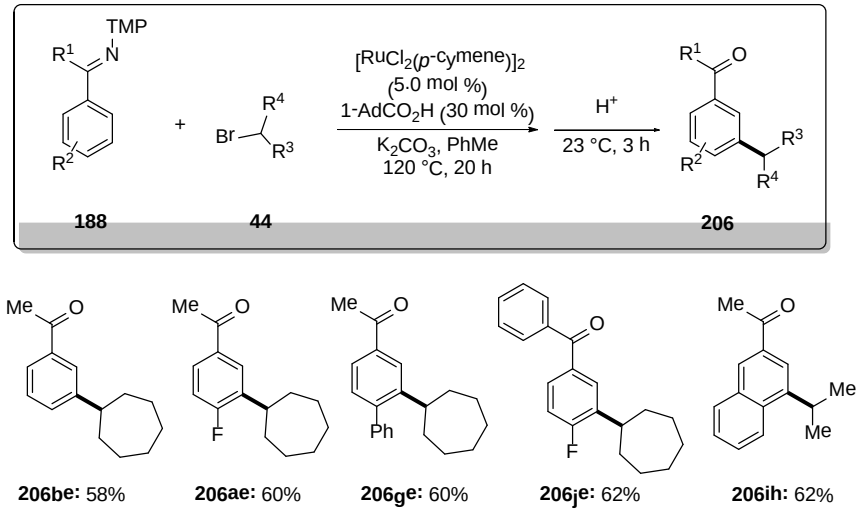
Scheme 6.1: Ruthenium(II)-catalyzed direct *meta*-alkylation with tertiary alkyl bromides **50**

Importantly, ruthenium(II) catalysis also allowed for the facile direct *meta*-alkylation of ketimines **188**. Electron-deficient ketimines **188** were favorably converted comparing to their election-rich analogues. Sterically hindered tertiary alkyl bromides **50** smoothly gave rise to the desired *meta*-alkylated products **189**. The auxiliary from the alkylated products can easily be removed within a one-pot hydrolysis, thus yielding a wide range of *meta*-functionalized aryl ketones **189** (Scheme 6.2). Futhermore, the imine double bond in the *meta*-alkylated ketimines underwent one-pot reduction, furnishing secondary amines **207** in good yields. Although the yields of these alkylations were moderate comparing to the case of heterocycle-directed reactions, compounds **189** and **207** are generally more useful building blocks in organic synthesis.



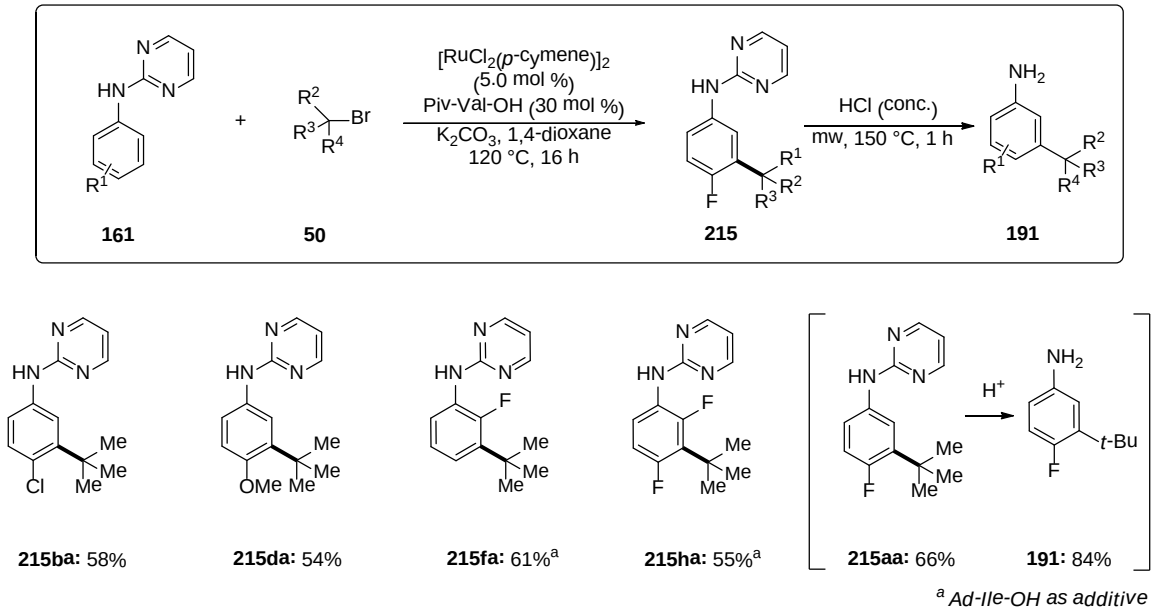
Scheme 6.2: Ruthenium(II)-catalyzed direct *meta*-alkylation of ketimines **188**

Not only tertiary alkyl bromides **50**, but also secondary alkyl bromides **44,** both cyclic and acyclic, were competent electrophiles for this novel transformation (scheme 6.3). Electron-rich as well electron-deficient ketimines **188** were smoothly converted. The intermolecular competition experiments revealed electron-deficient arenes to be preferentially alkylated.



Scheme 6.3: Ruthenium(II)-catalyzed direct *meta*-alkylation with secondary alkyl bromides **44**

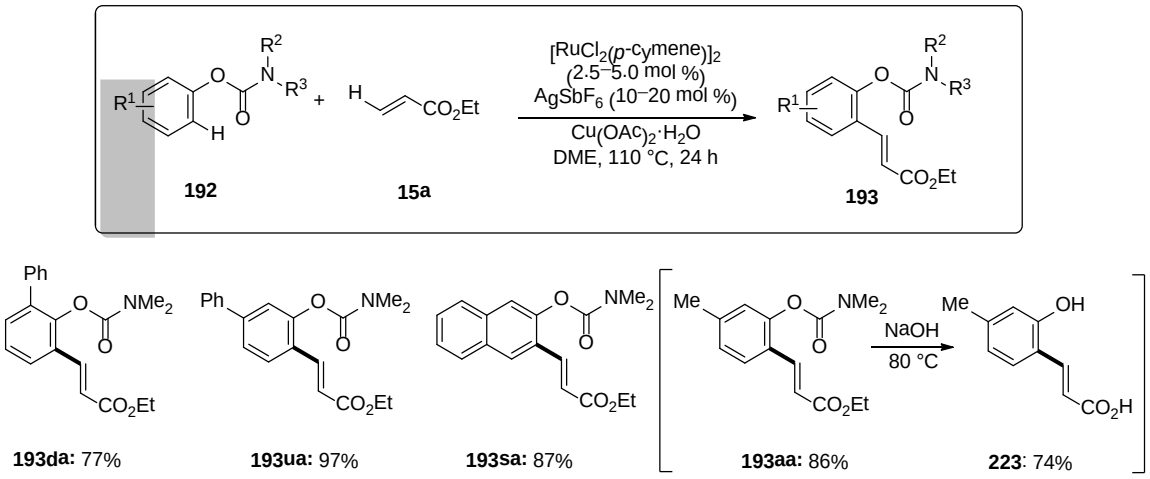
Further investigation of this approach realized the ruthenium(II)-catalyzed direct alkylation of *N*-(pyrimidyl-2-yl)anilines **161** (Scheme 6.4). Again, the ruthenium(II)-MPAA catalytic system proved to be the most efficient. The direct alkylation smoothly took place at the *meta*-position of an electron-donating directing group, which in not anticipated by classical electrophilic aromatic substation. Another important aspect of this reaction is the *N*-pyrimidyl could readily be cleaved, thus leading to *meta*-alkylated aniline **191**. Moreover, excellent site-electivity was achieved when *ortho*- or even di-substituted anilines **161** were employed, furnishing selectively the *meta*-functionalized products in good yields.



Scheme 6.4: Ruthenium(II)-catalyzed direct *meta*-alkylation of aniline derivatives **161**

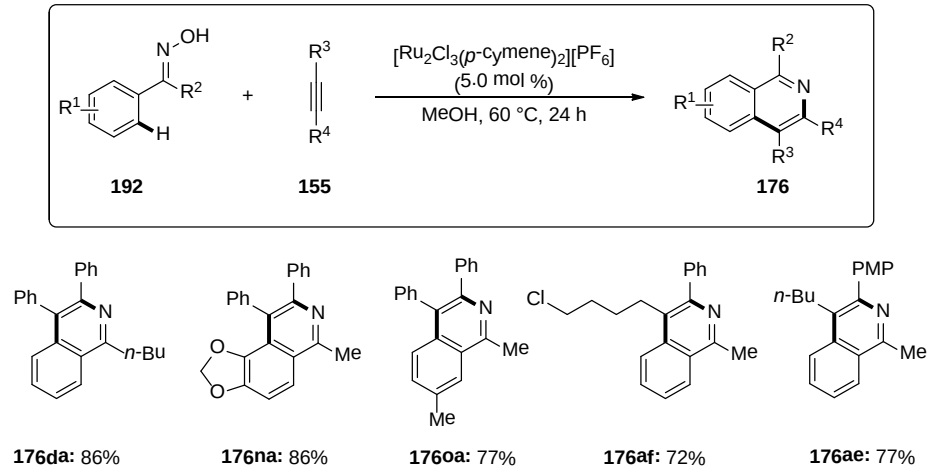
Future investigations of the ruthenium(II)-catalyzed direct *meta*-alkylation should be performed addressing three major issues. First of all, *meta*-alkylations accomplished in this thesis were realized via cyclometalation assisted by *N*-containing directing group. Extending the substrate scope to readily available, weakly-coordinating directing groups including ketones or esters is of major interest. Secondly, since research directed towards enantioselective cross-coupling of secondary alkyl halides is active nowadays, developing transition metal-catalyzed enatioselective direct alkylation reactions should be an important goal. At last, despite the preliminary understanding of the reaction mechanism, detailed explanation of how the elementary steps of activation of the tertiary halide and C–C bond formation take place remain unclear and need further elucidation. Better insight of the reaction mechanism is crucial for further development of ruthenium(II)-catalyzed *meta*-selective C–H functionalization.

Within the second project, a ruthenium(II)-catalyzed cross-dehydrogenative coupling of aryl carbamates **192** with acrylates **15a** was achieved (Scheme 6.5). The cationic ruthenium(II) catalyst enabled the highly efficient olefination of electron-rich arenes **192** with high site-selectivity. Carbamates bearing *ortho*-, *meta*-, or *para*-substitutions underwent facile alkenylation, delivering a broad range of protected phenols **193**. Importantly, the weakly-coordinating cabarmate group could easily be removed, thus providing a practical method for the preparation of *o*-coumaric acids which are important intermediates in enzymology and useful building blocks in organic synthesis.



Scheme 6.5: Ruthenium(II)-catalyzed oxidative alkenylation of carbamate **192**

The third project focused on redox-neutral annulations of alkynes **155** via ruthenium(II)-catalyzed C−H/N−O bond functionalization of oximes **194**. A well-defined cationic ruthenium(II)-catalyst allowed the synthesis of highly substituted isoquinolines **176** (Scheme 6.6). Electron-rich as well as electron-deficient oximes could be efficiently converted. Unsymmetrical aryl-alkyl-alkynes **155** bearing functional groups were regioselectively transformed to the corresponding isoquinolines.



Scheme 6.6: Well-defined ruthenium(II) complex-catalyzed alkyne annulation

However, only poor yields were obtained with terminal alkynes in most of the ruthenium(II)-catalyzed annulation reactions. Presumably this is the result of dimerization of the terminal alkyne. Interestingly, in a recent published work, this shortage was successfully overcome via ruthenium(II)-catalyzed C−H/N−N bond functionalization.[230] This offered broad implications for future developments of ruthenium(II)-catalyzed alkyne annulations for more functionalized heterocycle synthesis.

7 Experimental Section

7.1 General Remarks

Unless otherwise noticed, all reactions were performed under a N_2 atmosphere using pre-dried glassware and standard Schlenk techniques.

Solvents

All solvents for reactions involving moisture-sensitive reagents were dried, distilled and stored under inert atmosphere (Ar or N_2) according to the following standard procedures. *tert*-Amylalcohol (*t*-AmOH) was used as supplied by Merck or stirred over sodium chips for 5 h at 120 °C and distilled under ambient pressure; water (H_2O) was degassed before its use applying repeated Freeze-Pump-Thaw degassing procedure; 1,2-dichloroethane (DCE), *i*-BuOH, *N*,*N*-dimethylformamide (DMF), acetonitrile (MeCN) and dimethylacetamide (DMA) were dried over CaH_2 for 8 h, degassed and distilled under reduced pressure; dichloromethane and tetrahydrofuran (THF) were purified using a solvent purification system (SPS) from MBRAUN; *N*-methyl-2-pyrrolidone (NMP) was stirred over CaH_2 for 4 h at 150 °C and subsequently distilled under reduced pressure; methanol (MeOH) was distilled from magnesium methanolate; toluene was pre-dried over KH followed by distillation from sodium benzophenone ketyl; 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 (M. p.)

Melting points were measured using a *Stuart® Melting Point Apparatus SMP3* from BARLOWORLD SCIENTIFIC. Reported values are uncorrected.

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 or 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).

Gas Chromatograpgy (GC)

The conversion of the reactions was monitored applying coupled gas chromatography/mass spectrometry using *G1760C 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 m) were used.

High Performance Liquid Chromatography (HPLC)

Preparative and analytical separations were performed on an HPLC-System from KNAUE (*Smartline*

Pump 100, Dynamic Mixing Chamber, Injection- and Control-Valve, *Smartline UV Detector 2500*). Separation normal phase column (250 × 10 mm) from MACHEREY-NAGEL (MN) 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.

Nuclear Magnetic Resonance Spectroscopy (NMR)

Nuclear magnetic resonance (NMR) spectroscopy was performed at 300, 400 or 600 MHz (^{1}H NMR), 75 or 125 MHz (^{13}C NMR, APT) and 283 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. For characterization of the observed resonance multiplicities the following abbreviations 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 (IR)

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

Mass Spectrometry (MS)

MS (EI) and HR-MS (EI) 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, Fourier Transform Ion Cyclotron Resonance (FTICR)] mass spectrometer. The ratios of mass to charge (*m*/*z*) are indicated, intensities relative to the base peak (I = 100) are written in parentheses.

Reagents

Chemicals obtained from commercial sources with purity above 95% were used without further purification. The following compounds are known and were synthesized according to previously described methods.

2-Phenylpyridines **38**,[247] tertiary alkyl bromides **50**,[95] mono-protected amino acids **116**,[248] 2-phenylpyrimidine **197b–c**,[247] ketimines **188**,[249] *N*-(pyrimidine-2-yl)anilines **161**,[211] *N*-(4-fluorophenyl)pyridin-2-amine **216b**,[250] secondary alkyl bromides **44n–o**,[251] **44a**,[91] aryl carbamate **192**,[252] oxime **194b–j**,[253] $[Ru_2Cl_3(p\text{-cymene})_2][PF_6]$.[211]

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

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

Dr. Christoph Kornhaaß: Oximes **194a**, **194k–o**, Alkynes **155d–f**.

Dr. Nora Hofmann: Secondary alkyl bromide **44d**.

M. Sc. Svenja Warratz: [RuCl(O-Val-Piv)(*p*-cymene)] (**195**).

M. Sc. Keshav Raghuvanshi: 1-Phenylprazoles **131a–e.**

M. Sc. Sebastian Lackner: *N*-2-Pyrimidyl anilines **161d**.

M. Sc. Zhixiong Ruan: *N*-2-Pyrimidyl aniline **161h**.

M. Sc. Weiping Liu: Aryl carbamate [D_5]-**221b**.

M. Sc. Eloisa Eriko Ishikawa: Tertiary alkyl halide **50g**, 4-fluoro-N-phenylaniline (**216c**)

Dr. Nora Hofmann & Dr. Marvin Schinkel: 2-phenylpyridines **38g–38h**, **38o–38p**, **38q–38r**, [D_5]-**38a**, [D_3]-**38a,** 2-phenylpyrimidine **197a**

7.2 General Procedures

General Procedure A:
Ruthenium(II)-catalyzed direct *meta*-alkylation

Substrate **38b** (0.50 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (7.7 mg, 2.5 mol %), Piv-Val-OH (30.0 mg, 30 mol %) and K_2CO_3 (138 mg, 1.00 mmol) were placed in a pre-dried 25 mL pressure tube. The mixture was degassed and purged with N_2 for 3 times. Tertiary alkyl bromide **50a** (1.50 mmol) and 1,4-dioxane (2.0 mL) were then added, and the mixture was stirred at 100 °C for 20 h. At ambient temperature, EtOAc (15 mL) was added, and the reaction mixture was filtered through a pad of silica gel. The solvents were removed *in vacuo* and purification of the residue by column chromatography (*n*-hexane/EtOAc) yielded compound **187ba**.

In several specific cases indicated below, Piv-Val-OH was replaced by *N*-(1-adamantane-2-carbonyl)-L-isoleucine (1-Ad-Ile-OH, 44.0 mg, 30 mol %).

General Procedure B:
Ruthenium(II)-catalyzed direct *meta*-Alkylation using [RuCl(O-Val-Piv)(*p*-cymene)]

Substrate **38b** (0.50 mmol), [RuCl(O-Val-Piv)(*p*-cymene)] (11.8 mg, 5.0 mol %) and K_2CO_3 (138.0 mg, 1.00 mmol) were placed in a pre-dried 25 mL pressure tube. The mixture was degassed and purged with N_2 for 3 times. Tertiary alkyl bromide **50a** (1.50 mmol) and 1,4-dioxane (2.0 mL) were then added and the mixture was stirred at 100 °C for 20 h. At ambient temperature, EtOAc (15 mL) was added and the reaction mixture was filtered through a pad of silica gel. The solvents were removed *in vacuo* and purification of the residue by column chromatography (*n*-hexane/EtOAc) yielded compound **187ba**.

General Procedure C:
Ruthenium(II)-catalyzed direct *meta*-alkylation of ketimine 188

Ketimine **188** (0.50 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 2.5 µmol, 5.0 mol %), 1-AdCO_2H (27.8 mg, 30 mol %) and K_2CO_3 (138 mg, 1.00 mmol) were placed in a pre-dried 25 mL pressure tube. The mixture was degassed and purged with N_2 for 3 times. Tertiary alkyl bromide **50** (1.50 mmol) and PhMe (2.0 mL) were then added and the mixture was stirred at 120 °C for 20 h. At ambient temperature, 2 N HCl (3.0 mL) was added, and the resulting mixture was stirred for additional 3 hours, then extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc or *n*-pentane/Et_2O) yielded compound **189**.

General Procedure D:
Ruthenium(II)-catalyzed oxidative alkenylation of aryl carbamate 192

In a 25 ml schlenk tube, a suspension of carbamate **192** (0.50 mmol), ethyl acrylate (**15a**) (100.1 mg, 1.00 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (7.7 mg, 2.5 mol %), $AgSbF_6$ (17.2 mg, 10 mol %) and Cu(OAc)$_2$·H_2O

(200 mg, 1.00 mmol) in DME (3.0 mL) was stirred at 110 °C for 24 h under an atmosphere of N_2. At ambient temperature, EtOAc (15 mL) was added, and the mixture was filtered through a pad of silica gel. The solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc) yielded compound **193**.

General Procedure E:

Ruthenium(II)-catalyzed oxidative aerobic alkenylation of aryl carbamate 192 with cocatalytic amounts of $Cu(OAc)_2 \cdot H_2O$

In a 25 ml schlenk tube, a suspension of carbamate **192** (0.50 mmol), ethyl acrylate (**15a**) (100.1 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), $AgSbF_6$ (34.4 mg, 20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (29.7 mg, 30 mmol %) in DME (3.0 mL) was pre-stirred at ambient temperature for 10 min under N_2. Thereafter, the reaction mixture was purged with air for 10 min. Then, the reaction tube was sealed and the mixture was stirred at 110 °C for 24 h under an atmosphere of ambient air. At ambient temperature, EtOAc (15 mL) was added, and the mixture was filtered through a pad of silica gel. The solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc) yielded compound **193**.

General Procedure F:

Synthesis of isoquinoline 176 *via* ruthenium(II)-catalyzed C–H/N–O functionalizations

Oxime **194** (0.50 mmol), alkyne **155** (1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and KPF_6 (27.6 mg, 30 mol %) were placed in a pre-dried 25 mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Dry MeOH (2.0 mL) was added (and the liquid alkyne **155** was also added at this stage), and the reaction mixture was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL), was added and the solvents were removed *in vacuo*. The product **176** was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

General Procedure G:

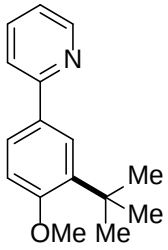
Synthesis of Isoquinoline 176 *via* well-defined cationic ruthenium(II) complex catalyzed C–H/N–O functionalizations

Oxime **194** (0.50 mmol), solid alkyne **155** (1.00 mmol), $[Ru_2Cl_3(p\text{-cymene})_2][PF_6]$ (18.0 mg, 5.0 mol %) were placed to a pre-dried 25 mL Schlenk tube. The mixture was degassed and purged with N_2 for 3 times. Dry MeOH (2.0 mL) was added (and the liquid alkyne **155** was also added at this stage), and the reaction mixture was stirred at 60 °C for 24 h. At ambient temperature, EtOAc (15 mL) was added, and the solvents were removed *in vacuo*. The product **176** was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

7.3 Analytical Data

7.3.1 Analytical Data for the Products of the Ruthenium(II)-Catalyzed Direct *meta*-Alkylation

Synthesis of 2-[3-(*tert*-Butyl)-4-methoxyphenyl]pyridine (187ba)



The general procedure **A** was followed using substrate **38b** (93 mg, 0.50 mmol) and *t*-BuBr (**50a**) (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **187ba** (91 mg, 76%) as a colorless oil.

The general procedure **B** was followed using substrate **38b** (93 mg, 0.50 mmol) and *t*-BuBr (**50a**) (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **187ba** (96 mg, 80%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 4.9 Hz, 1H), 7.97 (d, *J* = 2.3 Hz, 1H), 7.81 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.73–7.64 (m, 2H), 7.15 (ddd, *J* = 6.8, 4.9, 1.9 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 3.90 (s, 3H), 1.46 (s, 9H).

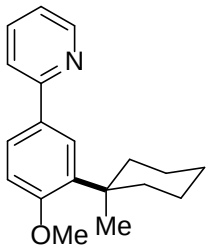
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4 (C_q), 157.8 (C_q), 149.5 (CH), 138.4 (C_q), 136.5 (CH), 131.4 (C_q), 125.7 (CH), 125.4 (CH), 121.1 (CH), 120.0 (CH), 111.6 (CH), 55.1 (CH_3), 35.0 (C_q), 29.7 (CH_3).

IR (neat): $\tilde{\nu}$ = 3077, 2954, 1586, 1463, 1270, 1091, 819, 741 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 241 (42) $[M]^+$, 226 (100), 210 (15), 167 (15).

HR-MS (EI): *m*/*z* calcd for $C_{16}H_{19}NO^+$ $[M]^+$ 241.1461, found 241.1475.

Synthesis of 2-[4-Methoxy-3-(1-methylcyclohexyl)phenyl]pyridine (187bb)



The general procedure **A** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **50b** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187bb** (110 mg, 78%) as a colorless oil.

The general procedure **B** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **50b** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187bb** (106 mg, 76%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 4.9 Hz, 1H), 8.00 (d, *J* = 2.4 Hz, 1H), 7.81 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.74–7.64 (m, 2H), 7.15 (ddd, *J* = 6.8, 4.8, 2.0 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 3.87 (s, 3H), 2.23–2.12 (m, 2H), 1.86–1.75 (m, 2H), 1.67–1.48 (m, 6H), 1.36 (s, 3H).

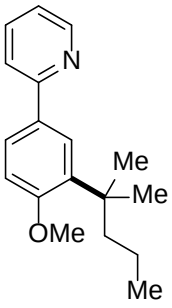
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6 (C_q), 157.9 (C_q), 149.5 (CH), 137.9 (C_q), 136.5 (CH), 131.4 (C_q), 126.4 (CH), 125.4 (CH), 121.1 (CH), 119.9 (CH), 111.9 (CH), 55.1 (CH_3), 38.3 (C_q), 36.9 (CH_2), 26.6 (CH_2), 25.1 (CH_3), 22.8 (CH_2).

IR (neat): $\tilde{\nu}$ = 3077, 2922, 1724, 1588, 1429, 1239, 1120, 1025, 856, 593 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 281 (100) $[M]^+$, 266 (75), 198 (50), 167 (28).

HR-MS (EI): *m*/*z* calcd for $C_{19}H_{22}NO^+$ $[M-H]^+$,280.1696, found 280.1705.

Synthesis of 2-[4-Methoxy-3-(2-methylpentan-2-yl)phenyl]pyridine (187bc)



The general procedure **A** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **50c** (248 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187bc** (80 mg, 59%) as a colorless oil.

The general procedure **B** was followed, using **38b** (93 mg, 0.50 mmol) and **50c** (248 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187bc** (68 mg, 50%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 4.9 Hz, 1H), 7.91 (d, *J* = 2.4 Hz, 1H), 7.82 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.73–7.64 (m, 2H), 7.15 (ddd, *J* = 6.8, 4.6, 1.8 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 3.87 (s, 3H), 1.87–1.80 (m, 2H), 1.43 (s, 6H), 1.12–0.98 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H).

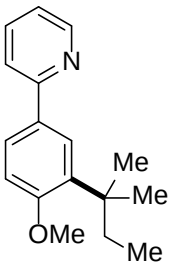
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4 (C_q), 157.8 (C_q), 149.4 (CH), 137.0 (C_q), 136.5 (CH), 131.3 (C_q), 126.5 (CH), 125.6 (CH), 121.1 (CH), 119.9 (CH), 111.5 (CH), 55.1 (CH_3), 43.4 (CH_2), 38.4 (C_q), 28.4 (CH_3), 18.5 (CH_2), 14.9 (CH_3).

IR (neat): $\tilde{\nu}$ = 3052, 2954, 1587, 1562, 1462, 1429, 1159, 1096, 1027, 779 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 269 (20) $[M]^+$, 226 (100), 198 (17), 167 (16).

HR-MS (EI): *m*/*z* calcd for $C_{18}H_{23}NO^+$ $[M]^+$ 269.1774, found 269.1784.

Synthesis of 2-[4-Methoxy-3-(*tert*-pentyl)phenyl]pyridine (187bd)



The general procedure **A** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **50d** (226 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187bd** (86 mg, 67%) as a colorless oil.

The general procedure **B** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **50d** (226 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187bd** (77 mg, 60%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 4.9 Hz, 1H), 7.91 (d, *J* = 2.3 Hz, 1H), 7.83 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.73–7.64 (m, 2H), 7.15 (ddd, *J* = 6.2, 4.8, 2.3 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 3.87 (s, 3H), 1.90 (q, *J* = 7.5 Hz, 2H), 1.42 (s, 6H), 0.67 (t, *J* = 7.5 Hz, 3H).

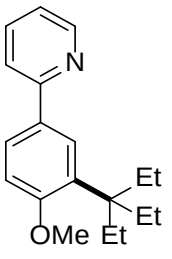
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4 (C_q), 157.8 (C_q), 149.5 (CH), 136.7 (C_q), 136.5 (CH), 131.3 (C_q), 126.7 (CH), 125.6 (CH), 121.1 (CH), 119.9 (CH), 111.4 (CH), 55.1 (CH_3), 38.7 (C_q), 33.1 (CH_2), 27.9 (CH_3), 9.6 (CH_3).

IR (neat): $\tilde{\nu}$ = 3050, 2960, 1586, 1438, 1396, 1240, 1180, 1093, 778 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 255 (27) $[M]^+$, 226 (98), 198 (18), 167 (20).

HR-MS (EI): *m*/*z* calcd for $C_{17}H_{21}NO^+$ $[M]^+$ 255.1618, found 255.1627.

Synthesis of 2-[3-(3-Ethylpentan-3-yl)-4-methoxyphenyl]pyridine (187be)



The general procedure **A** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **50e** (269 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187be** (73 mg, 52%) as a white solid.

The general procedure **B** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **50e** (269 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187be** (50 mg, 35%) as a white solid.

M. p.: 80–82 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 4.9 Hz, 1H), 7.88 (d, *J* = 2.3 Hz, 1H), 7.83 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.73–7.64 (m, 2H), 7.13 (ddd, *J* = 6.8, 4.6, 2.3 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 1.86 (q, *J* = 7.3 Hz, 6H), 0.64 (t, *J* = 7.3 Hz, 9H).

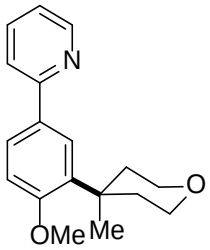
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6 (C_q), 157.9 (C_q), 149.5 (CH), 136.5 (CH), 134.8 (C_q), 131.1 (C_q), 128.3 (CH), 125.5 (CH), 121.1 (CH), 119.9 (CH), 111.5 (CH), 55.2 (CH_3), 44.6 (C_q), 26.1 (CH_2), 8.5 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2961, 2938, 2873, 1562, 1460, 1439, 1270, 1238, 1088, 816 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 283 (23) $[M]^+$, 284 (76), 212 (60), 198 (100), 167 (27).

HR-MS (EI): *m*/*z* calcd for $C_{19}H_{25}NO^+$ $[M]^+$ 283.1931, found 283.1933.

Synthesis of 2-[4-Methoxy-3-(4-methyltetrahydro-2H-pyran-4-yl)phenyl]pyridine (187bf)



The general procedure **A** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **50f** (269 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **187bf** (110 mg, 78%) as a colorless oil.

The general procedure **B** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **50f** (269 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **187bf** (106 mg, 75%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (d, *J* = 4.9 Hz, 1H), 7.92 (d, *J* = 2.3 Hz, 1H), 7.81 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.74–7.63 (m, 2H), 7.17 (ddd, *J* = 6.7, 4.8, 1.3 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 3.86–3.41 (m, 4H), 2.37–2.26 (m, 2H), 2.00–1.91 (m, 2H), 1.44 (s, 3H).

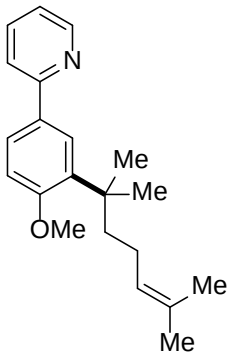
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4 (C_q), 157.6 (C_q), 149.5 (CH), 136.7 (C_q), 136.6 (CH), 131.6 (C_q), 125.9 (CH), 125.8 (CH), 121.3 (CH), 119.9 (CH), 111.9 (CH), 69.5 (CH_2), 55.1 (CH_3), 36.9 (CH_2), 35.9 (C_q), 24.1(CH_3).

IR (neat): $\tilde{\nu}$ = 3047, 2949, 1585, 1269, 1234, 1023, 779 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 283 (100) $[M]^+$, 268 (27), 210 (60), 167 (37).

HR-MS (EI): *m*/*z* calcd for $C_{18}H_{20}NO_2^+$ $[M-H]^+$ 282.1489, found 282.1503.

Synthesis of 2-[3-(2,6-Dimethylhept-5-en-2-yl)-4-methoxyphenyl]pyridine (187bg)



The general procedure **A** was followed, using substrate **38b** (93 mg, 0.50 mmol) and bromide **50g** (308 mg, 1.50 mmol) with $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), After 20 h, purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **187bg** (95 mg, 61%) as a colorless oil.

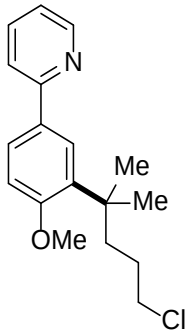
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.88 (d, *J* = 2.3 Hz, 1H), 7.80 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.71–7.61 (m, 2H), 7.13 (ddd, *J* = 7.0, 4.8, 1.5 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 5.05 (tt, *J* = 7.1, 1.4 Hz, 1H), 3.85 (s, 3H), 1.90–1.79 (m, 2H), 1.71–1.62 (m, 2H), 1.61 (d, *J* = 1.3 Hz, 3H), 1.46–1.44 (m, 3H), 1.42 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (C_q), 157.7 (C_q), 149.4 (CH), 136.5 (C_q), 136.4 (CH), 131.3 (C_q), 130.5 (C_q), 126.5 (CH), 125.6 (CH), 125.2 (CH), 121.0 (CH), 119.8 (CH), 111.3 (CH), 55.1 (CH_3), 40.9 (CH_2), 38.4 (CH_2), 28.5 (CH_3), 25.7 (CH_3), 24.2 (C_q), 17.4 (CH_3).

IR (neat): $\tilde{\nu}$ = 2962, 2911, 1587, 1463, 1270, 1180, 1026, 819 cm^{-1}.

MS (EI) *m/z* (relative intensity) 309 (12) $[M]^+$, 278 (18), 226 (100), 167 (20).
HR-MS (EI): *m/z* calcd for $C_{21}H_{27}NO^+$ $[M]^+$ 309.2087, found 309.2092.

Synthesis of 2-[3-(5-Chloro-2-methylpentan-2-yl)-4-methoxyphenyl]pyridine (187bh)

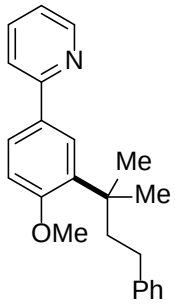


The general procedure **A** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **50h** (299 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 80:1) yielded **187bh** (90 mg, 59%) as a colorless oil.

The general procedure **B** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **50h** (299 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 80:1) yielded **187bh** (90 mg, 59%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (d, *J* = 4.9 Hz, 1H), 7.89 (d, *J* = 2.3 Hz, 1H), 7.81 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.74–7.63 (m, 2H), 7.16 (ddd, *J* = 6.9, 4.9, 1.9 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H), 3.43 (t, *J* = 6.7 Hz, 2H), 2.05–1.96 (m, 2H), 1.54–1.46 (m, 2H), 1.44 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (C_q), 157.7 (C_q), 149.5 (CH), 136.6 (CH), 136.0 (C_q), 131.5 (C_q), 126.6 (CH), 126.0 (CH), 121.2 (CH), 112.0 (CH), 111.4 (CH), 55.2 (CH_3), 46.1 (CH_2), 38.1 (C_q), 38.0 (CH_2), 28.9 (CH_2), 28.4 (CH_3).
IR (neat): $\tilde{\nu}$ = 3954, 2955, 2865, 1603, 1586, 1498, 1238, 1087, 1025, 779 cm^{-1}.
MS (EI) *m/z* (relative intensity) 305/303 (5/16) $[M^+]$, 226 (100), 198 (14), 167 (14).
HR-MS (EI): *m/z* calcd for $C_{18}H_{22}{}^{35}ClNO^+$ $[M^+]$ 303.1384, found 303.1390.

Synthesis of 2-[4-Methoxy-3-(2-methyl-4-phenylbutan-2-yl)phenyl]pyridine (187bi)

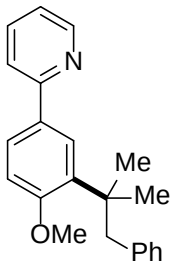


The general procedure **A** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **50i** (341 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187bi** (110 mg, 66%) as a colorless oil.

The general procedure **B** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **50i** (341 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187bi** (98 mg, 59%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 4.9 Hz, 1H), 7.96 (d, *J* = 2.3 Hz, 1H), 7.83 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.74–7.65 (m, 2H), 7.25–7.19 (m, 2H), 7.18–7.13 (m, 2H), 7.10–7.06 (m, 2H), 6.97 (d, *J* = 8.7 Hz, 1H), 3.88 (s, 3H), 2.34–2.26 (m, 2H), 2.23–2.15 (m, 2H), 1.48 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (C_q), 157.7 (C_q), 149.4 (CH), 143.6 (C_q), 136.4 (CH), 136.2 (C_q), 131.4 (C_q), 128.2 (CH), 128.1 (CH), 126.6 (CH), 125.8 (CH), 125.2 (CH), 121.1 (CH), 119.9 (CH), 111.4 (CH), 55.2 (CH_3), 43.0 (CH_2), 38.6 (C_q), 32.1 (CH_2), 28.6 (CH_3).
IR (neat): $\tilde{\nu}$ = 3024, 2960, 1586, 1462, 1429, 1270, 1237, 1069, 1026, 779 cm^{-1}.
MS (EI) *m/z* (relative intensity) 331 (40) $[M]^+$, 226 (100), 198 (15), 167 (17), 91 (20).
HR-MS (EI): *m/z* calcd for $C_{23}H_{25}NO^+$ $[M]^+$ 331.1931, found 331.1926.

Synthesis of 2-[4-Methoxy-3-(2-methyl-1-phenylpropan-2-yl)phenyl]pyridine (187bj)



The general procedure **A** was followed, using substrate **38b** (93mg, 0.50 mmol) and bromide **50j** (320 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 80:1) yielded **187bj** (93 mg, 59%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.61 (d, *J* = 4.9 Hz, 1H), 7.86 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.69–7.62 (m, 2H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.16–7.06 (m, 4H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.93–6.87 (m, 2H), 3.99 (s, 3H), 3.19 (s, 2H), 1.43 (s, 6H).

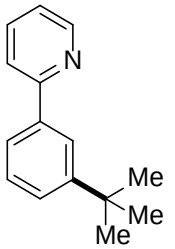
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (C_q), 157.7 (C_q), 149.4 (CH), 139.9 (C_q), 136.5 (CH), 136.4 (C_q), 131.5 (C_q), 130.3 (CH), 127.1 (CH), 126.6 (CH), 126.0 (CH), 125.5 (CH), 121.2 (CH), 120.0 (CH), 111.5 (CH), 55.2 (CH_3), 46.0 (CH_2), 39.3 (C_q), 28.0 (CH_3).

IR (neat): $\tilde{\nu}$ = 3002, 2959, 1586, 1462, 1270, 1236, 1086, 1025, 779 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 317 (5) $[M]^+$, 226 (98), 198 (13), 167 (18), 91 (17).

HR-MS (EI): *m*/*z* calcd for $C_{22}H_{23}NO^+$ $[M]^+$ 317.1774, found 317.1793.

Synthesis of 2-[3-(*tert*-Butyl)phenyl]pyridine (187aa)



The general procedure **A** was followed using substrate **37a** (78 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 80:1) yielded **187aa** (69 mg, 65%) as a colorless oil.

The general procedure **B** was followed using substrate **38a** (78 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 80:1) yielded **187aa** (62 mg, 59%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 4.9 Hz, 1H), 8.06 (t, *J* = 1.6 Hz, 1H), 7.80–7.71 (m, 3H), 7.50–7.39 (m, 2H), 7.25–7.19 (m, 1H), 1.41 (s, 9H).

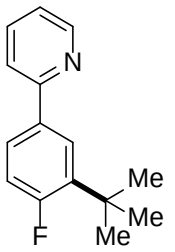
^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.0 (C_q), 151.6 (C_q), 149.6 (CH), 139.2 (C_q), 136.6 (CH), 128.4 (CH), 126.0 (CH), 124.1 (CH), 123.9 (CH), 121.9 (CH), 120.7 (CH), 34.8 (C_q), 29.7 (CH_3).

IR (neat): $\tilde{\nu}$ = 3064, 2961, 1584, 1564, 1460, 1431, 1251, 770 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 211 (34) $[M]^+$, 196 (100), 167 (18), 155 (12).

HR-MS (EI): *m*/*z* calcd for $C_{15}H_{16}N^+$ $[M-H]^+$ 210.1277, found 210.1287.

Synthesis of 2-[3-(*tert*-Butyl)-4-fluorophenyl]pyridine (187ca)



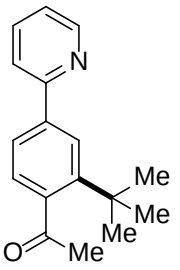
The general procedure **A** was followed using substrate **38c** (87 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 80:1) yielded **187ca** (92 mg, 80%) as a colorless oil.

The general procedure **B** was followed using substrate **38c** (87 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 80:1) yielded **187ca** (93 mg, 81%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.98 (dd, *J* = 8.1, 2.6 Hz, 1H), 7.79–7.64 (m, 3H), 7.19 (ddd, *J* = 7.4, 4.7, 1.3 Hz, 1H), 7.09 (ddd, *J* = 12.3, 8.5, 1.1 Hz, 1H), 1.43 (d, *J* = 1.0 Hz, 9H).

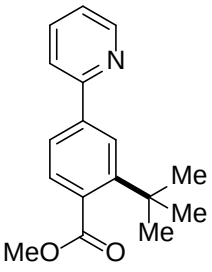
^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.7 (d, $^1J_{C\text{-}F}$ = 251 Hz, C_q), 157.1 (C_q), 149.6 (CH), 137.3 (d, $^2J_{C\text{-}F}$ = 12 Hz, C_q), 136.7 (CH), 135.1 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 126.2 (d, $^3J_{C\text{-}F}$ = 2 Hz, CH), 126.1 (d, $^3J_{C\text{-}F}$ = 5 Hz, CH), 121.8 (CH), 120.4 (CH), 116.5 (d, $^2J_{C\text{-}F}$ = 24 Hz, CH), 34.4 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 29.9 (d, $^4J_{C\text{-}F}$ = 3 Hz, CH_3).
^{19}F NMR (282 MHz, $CDCl_3$): δ = -109.4 (s).
IR (neat): $\tilde{\nu}$ = 3050, 2958, 1590, 1460, 1432, 1364, 1214, 1088, 778 cm^{-1}.
MS (EI) *m/z* (relative intensity) 229 (40) $[M]^+$, 214 (100), 186 (36), 173 (10).
HR-MS (EI): *m/z* calcd for $C_{15}H_{15}FN^+$ $[M-H]^+$ 228.1183, found 228.1191.

Synthesis of 1-[2-(*tert*-Butyl)-4-(pyridin-2-yl)phenyl]ethan-1-one (187da)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **38d** (99 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187da** (74 mg, 58%) as a white solid.
The general procedure **B** was followed using [RuCl(O-Val-Piv)(*p*-cymene)] (23.6 mg, 10.0 mol %), substrate **38d** (99 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187da** (69 mg, 54%) as a white solid.
M. p.: 84–86 °C.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 4.9 Hz, 1H), 8.12 (d, *J* = 1.6 Hz, 1H), 7.80–7.67 (m, 3H), 7.25–7.20 (m, 2H), 2.60 (s, 3H), 1.42 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.6 (C_q), 157.0 (C_q), 149.7 (CH), 147.4 (C_q), 142.4 (C_q), 140.0 (C_q), 136.7 (CH), 126.5 (CH), 126.0 (CH), 123.8 (CH), 122.3 (CH), 120.7 (CH), 36.1 (C_q), 32.5 (CH_3), 31.8 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3060, 3001, 1693, 1583, 1465, 1352, 1240, 1052, 839 cm^{-1}.
MS (EI) *m/z* (relative intensity) 253 (5) $[M]^+$, 238 (77), 220 (17), 167 (7).
HR-MS (EI): *m/z* calcd for $C_{17}H_{19}NO^+$ $[M]^+$ 253.1461, found 253.1464.

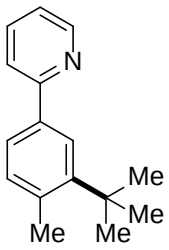
Synthesis of Methyl 2-(*tert*-Butyl)-4-(pyridin-2-yl)benzoate (187ea)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), sbustrate **38e** (107 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187ea** (68 mg, 51%) as a colorless oil.
The general procedure **B** was followed using [RuCl(O-Val-Piv)(*p*-cymene)] (23.6 mg, 10.0 mol %), substrate **38e** (107 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187ea** (67 mg, 50%) as a colorless oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 4.9 Hz, 1H), 8.14 (d, *J* = 1.7 Hz, 1H), 7.79–7.67 (m, 3H), 7.39 (d, *J* = 8.0 Hz, 1H), 6.50 (ddd, *J* = 6.8, 4.9, 1.9 Hz, 1H), 3.89 (s, 3H), 1.45 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3 (C_q), 156.9 (C_q), 149.7 (CH), 148.2 (C_q), 140.6 (C_q), 136.7 (CH), 133.0 (C_q), 129.2 (CH), 125.7 (CH), 123.8 (CH), 122.4 (CH), 120.8 (CH), 52.4 (CH_3), 36.0 (C_q), 31.3 (CH_3).
IR (neat): $\tilde{\nu}$ = 3083, 2950, 2869, 1723, 1573, 1464, 1297, 1121, 1066, 772 cm^{-1}.

MS (EI) *m/z* (relative intensity) 269 (23) $[M]^+$, 254 (64), 222 (100), 194 (37), 167 (17).
HR-MS (EI): *m/z* calcd for $C_{17}H_{19}NO_2^+$ $[M]^+$ 269.1410, found 269.1418.

Synthesis of 2-[3-(*tert*-Butyl)-4-methylphenyl]pyridine (187fa)

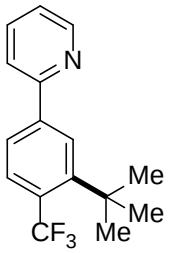


The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **38f** (85 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **187fa** (51 mg, 45%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 4.9 Hz, 1H), 8.06 (d, *J* = 1.9 Hz, 1H), 7.74–7.64 (m, 3H), 7.23–7.15 (m, 2H), 2.57 (s, 3H), 1.47 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.0 (C_q), 149.5 (CH), 148.3 (C_q), 137.3 (C_q), 136.8 (C_q), 136.6 (CH), 133.2 (CH), 124.8 (CH), 124.2 (CH), 121.6 (CH), 120.4 (CH), 36.0 (C_q), 30.8 (CH_3), 23.1 (CH_3).
IR (neat): $\tilde{\nu}$ = 2957, 2923, 2870, 1584, 1463, 1242, 1087, 776 cm^{-1}.
MS (EI) *m/z* (relative intensity) 225 (33) $[M]^+$, 210 (100), 195 (25), 183 (36).
HR-MS (EI): *m/z* calcd for $C_{16}H_{19}N^+$ $[M]^+$ 225.1512, found 225.1512.

Synthesis of 2-[3-(*tert*-Butyl)-4-(trifluoromethyl)phenyl]pyridine (187ga)

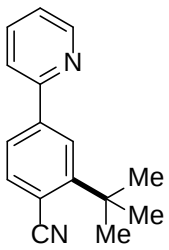


The general procedure **A** was followed, using substrate **38g** (112 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187ga** (37 mg, 26%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.71 (ddd, *J* = 4.8, 1.1, 1.1 Hz, 1H), 8.32 (s, 1H), 7.87–7.70 (m, 4H), 7.26 (ddd, *J* = 7.5, 5.2, 2.1 Hz, 1H), 1.51 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ =156.4 (C_q), 149.9 (CH), 149.7 (q, $^3J_{C\text{-}F}$ = 2 Hz, C_q), 142.1 (C_q), 136.8 (CH), 128.9 (q, $^3J_{C\text{-}F}$ = 7 Hz, CH), 128.4 (q, $^2J_{C\text{-}F}$ = 30 Hz, C_q), 127.5 (CH), 125.1 (q, $^1J_{C\text{-}F}$ = 273 Hz, C_q), 124.1 (CH), 122.7 (CH), 120.9 (CH), 36.8 (C_q), 32.0 (q, $^5J_{C\text{-}F}$ = 3 Hz, CH_3).
^{19}F NMR (282 MHz, $CDCl_3$): δ = -152.8 (s).
IR (neat): $\tilde{\nu}$ = 2961, 2875, 1587, 1560, 1436, 1238, 1106, 1034, 780 cm^{-1}.
MS (EI) *m/z* (relative intensity) 279 (52) $[M]^+$, 264 (100), 244 (83), 223 (62).
HR-MS (EI): *m/z* calcd for $C_{16}H_{16}F_3N^+$ $[M]^+$ 279.1229, found 279.1230.

Synthesis of 2-(*tert*-Butyl)-4-(pyridin-2-yl)benzonitrile (187ha)



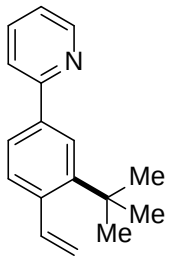
The general procedure **A** was followed using substrate **38h** (90 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187ha** (17 mg, 14%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.71 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 8.14 (d, *J* = 1.7 Hz, 1H), 7.85–7.70 (m, 4H), 7.29 (ddd, *J* = 7.2, 4.8, 1.4 Hz, 1H), 1.57 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9 (C_q), 154.2 (C_q), 150.0 (CH), 143.2 (C_q), 137.0 (CH), 136.0 (CH), 125.0 (CH), 124.4 (CH), 123.1 (CH), 121.1 (CH), 120.3 (C_q), 110.8 (C_q), 35.9 (C_q), 30.2 (CH_3).
IR (neat): $\tilde{\nu}$ = 3052, 2962, 2871, 2218, 1586, 1481, 1433, 1192, 990 cm^{-1}.
MS (EI) *m/z* (relative intensity) 236 (33) $[M]^+$, 221 (100), 193 (33), 169 (16).

HR-MS (EI): *m/z* calcd for $C_{16}H_{16}N_2^+$ $[M]^+$ 236.1308, found 236.1316.

Synthesis of 2-[3-(*tert*-Butyl)-4-vinylphenyl]pyridine (187ia)



The general procedure **A** was followed using substrate **38i** (91 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187ia** (24 mg, 20%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68 (ddd, *J* = 4.8, 1.6, 1.6 Hz, 1H), 8.04 (d, *J* = 1.9 Hz, 1H), 7.78–7.67 (m, 3H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.42 (dd, *J* = 17.1, 10.8 Hz, 1H), 7.19 (ddd, *J* = 5.9, 4.8, 2.7 Hz, 1H), 5.52 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.28 (dd, *J* = 10.8, 1.6 Hz, 1H), 1.48 (s, 9H).

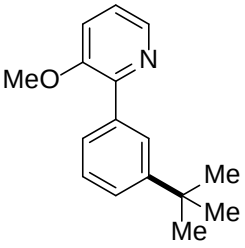
^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.7 (C_q), 149.6 (CH), 147.6 (C_q), 138.7 (CH), 138.6 (C_q), 138.4 (C_q), 136.6 (CH), 129.5 (CH), 124.5 (CH), 124.5 (CH), 121.9 (CH), 120.5 (CH), 115.36 (CH_2), 35.9 (C_q), 31.3 (CH_3).

IR (neat): $\tilde{\nu}$ = 3049, 2964, 1711, 1681, 1464, 1366, 1243, 1071, 781 cm^{-1}.

MS (EI) *m/z* (relative intensity) 237 (17) $[M]^+$, 222 (52), 206 (22), 193 (6).

HR-MS (EI): *m/z* calcd for $C_{17}H_{19}N^+$ $[M]^+$ 237.1512, found 237.1516.

Synthesis of 2-[3-(*tert*-Butyl)phenyl]-3-methoxypyridine (187ja)



The general procedure **A** was followed using substrate **38j** (93 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **187ja** (87 mg, 72%) as a colorless oil.

The general procedure **B** was followed using substrate **38j** (93 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **187ja** (86 mg, 71%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (dd, *J* = 4.6, 1.4 Hz, 1H), 7.90 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.68 (ddd, *J* = 7.2, 1.8, 1.8 Hz, 1H), 7.44–7.33 (m, 2H), 7.28–7.17 (m, 2H), 3.83 (s, 3H), 1.36 (s, 9H).

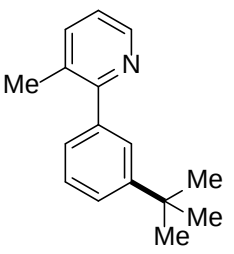
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.4 (C_q), 150.5 (C_q), 148.8 (C_q), 141.2 (CH), 137.2 (C_q), 127.5 (CH), 126.5 (CH), 126.4 (CH), 125.3 (CH), 122.6 (CH), 118.3 (CH), 55.4 (CH_3), 34.7 (C_q), 31.4 (CH_3).

IR (neat): $\tilde{\nu}$ = 3060, 2960, 1579, 1444, 1408, 1249, 1128, 1016, 801 cm^{-1}.

MS (EI) *m/z* (relative intensity) 241 (54) $[M]^+$, 226 (100), 211 (20), 185 (17).

HR-MS (EI): *m/z* calcd for $C_{16}H_{19}NO^+$ $[M]^+$ 241.1461, found 241.1458.

Synthesis of 2-[3-(*tert*-Butyl)phenyl]-3-methylpyridine (187ka)



The general procedure **A** was followed using substrate **38k** (85 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187ka** (69 mg, 61%) as a colorless oil.

The general procedure **B** was followed using substrate **38k** (85 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187ka** (89 mg, 79%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 4.6 Hz, 1H), 7.57–7.50 (m, 2H), 7.43–7.28 (m, 3H), 7.15 (dd,

J = 7.7, 4.6 Hz, 1H), 2.33 (s, 3H), 1.34 (s, 9H).

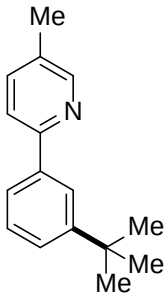
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (C_q), 150.8 (C_q), 146.8 (CH), 140.1 (C_q), 138.3(CH), 130.8 (C_q), 127.7 (CH), 126.0 (CH), 125.9 (CH), 124.8 (CH), 121.9 (CH), 34.7 (C_q), 31.3 (CH_3), 20.1 (CH_3).

IR (neat): $\tilde{\nu}$ = 3049, 2959, 1582, 1565, 1445, 1250, 1122, 787 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 225 (55) $[M]^+$, 210 (100), 194 (20), 168 (33).

HR-MS (EI): *m*/*z* calcd for $C_{16}H_{19}N^+$ $[M]^+$ 225.1512, found 225.1507.

Synthesis of 2-[3-(*tert*-Butyl)phenyl]-5-methylpyridine (187la)



The general procedure **A** was followed using substrate **38l** (85 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **187la** (64 mg, 57%) as a colorless oil.

The general procedure **B** was followed using substrate **38l** (85 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **187la** (73 mg, 65%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (dd, *J* = 1.4, 0.8 Hz, 1H), 8.00 (td, *J* = 1.9, 0.6 Hz, 1H), 7.72 (dt, *J* = 7.1, 1.9 Hz, 1H), 7.62–7.58 (m, 1H), 7.55–7.50 (m, 1H), 7.45–7.35 (m, 2H), 2.35 (s, 3H), 1.38 (s, 9H).

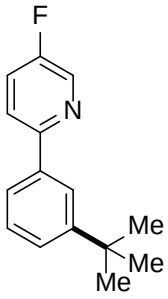
^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4 (C_q), 151.5 (C_q), 150.0 (CH), 139.2 (C_q), 137.2 (CH), 131.3 (C_q), 128.3 (CH), 125.7 (CH), 123.9 (CH), 123.7 (CH), 120.2 (CH), 34.8 (C_q), 31.4 (CH_3), 18.1 (CH_3).

IR (neat): $\tilde{\nu}$ = 3065, 2961, 2867, 1599, 1471, 1253, 999, 832 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 225 (37) $[M]^+$, 210 (100), 194 (20), 169 (17).

HR-MS (EI): *m*/*z* calcd for $C_{16}H_{19}N^+$ $[M]^+$ 225.1512, found 225.1517.

Synthesis of 2-[3-(*tert*-Butyl)phenyl]-5-fluoropyridine (187ma)



The general procedure **A** was followed using substrate **38m** (74 mg, 0.43 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **187ma** (55 mg, 56%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 3.0 Hz, 1H), 7.98 (dd, *J* = 2.0, 2.0 Hz, 1H), 7.73–7.67 (m, 2H), 7.48–7.36 (m, 3H), 1.38 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7 (d, $^1J_{C\text{-}F}$ = 257 Hz, C_q), 154.3 (d, $^4J_{C\text{-}F}$ = 4 Hz, C_q), 151.7 (C_q), 138.2 (C_q), 137.6 (d, $^2J_{C\text{-}F}$ = 24 Hz, CH), 128.5 (CH), 126.0 (CH), 124.0 (CH), 123.8 (CH), 123.4 (d, $^2J_{C\text{-}F}$ = 19 Hz, CH), 121.5 (d, $^3J_{C\text{-}F}$ = 4 Hz, CH), 34.8 (C_q), 31.4 (CH_3).

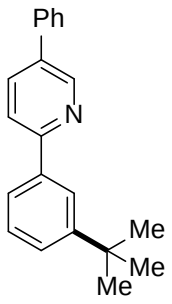
^{19}F NMR (282 MHz, $CDCl_3$): δ = −130.2 (s).

IR (neat): $\tilde{\nu}$ = 3065, 2962, 1671, 1579, 1468, 1224, 1017, 834 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 229 (38) $[M]^+$, 214 (100), 199 (23), 185 (21).

HR-MS (EI): *m*/*z* calcd for $C_{15}H_{16}FN^+$ $[M]^+$ 229.1261, found 229.1260.

Synthesis of 2-[3-(*tert*-Butyl)phenyl]-5-phenylpyridine (187na)



The general procedure **A** was followed using substrate **38n** (116 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187na** (35 mg, 24%) as a white solid.

M. p.: 133–135 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.94 (dd, *J* = 2.4, 0.8 Hz, 1H), 8.10–8.08 (m, 1H), 7.94 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.83–7.77 (m, 2H), 7.65–7.61 (m, 2H), 7.52–7.37 (m, 5H), 1.40 (s, 9H).

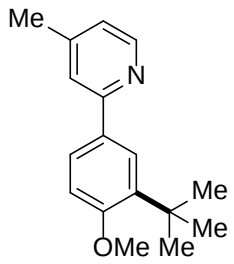
^{13}C NMR (126 MHz, $CDCl_3$) δ =156.8 (C_q), 151.7 (C_q), 148.0 (CH), 138.8 (C_q), 137.7 (C_q), 135.0 (CH), 134.7 (C_q), 129.1 (CH), 128.5 (CH), 128.0 (CH), 127.0 (CH), 126.1 (CH), 124.1 (CH), 123.9 (CH), 120.5 (CH), 34.9 (C_q), 31.4 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3409, 3058, 3020, 1590, 1472, 1249, 1077, 993, 773 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 287 (56) $[M]^+$, 272 (100), 256 (17), 231 (24).

HR-MS (EI): *m*/*z* calcd for $C_{21}H_{21}N^+$ $[M]^+$ 287.1669, found 287.1673.

Synthesis of 2-[3-(*tert*-Butyl)-4-methoxyphenyl]-4-methylpyridine (187oa)



The general procedure **A** was followed using substrate **38o** (100 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187oa** (66 mg, 52%) as a colorless oil.

The general procedure **B** was followed using substrate **38o** (100 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187oa** (95 mg, 74%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 5.0 Hz, 1H), 7.93 (d, *J* = 2.3 Hz, 1H), 7.77 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.46 (dt, *J* = 1.5, 0.8 Hz, 1H), 6.99–6.92 (m, 2H), 3.87 (s, 3H), 2.37 (s, 3H), 1.43 (s, 9H).

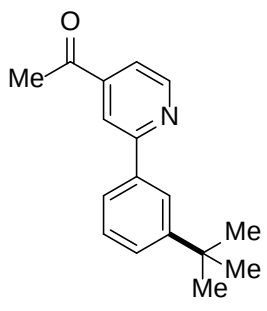
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (C_q), 157.7 (C_q), 149.2 (CH), 147.4 (C_q), 138.3 (C_q), 131.5 (C_q), 125.6 (CH), 125.4 (CH), 122.2 (CH), 120.9 (CH), 111.5 (CH), 55.1 (CH_3), 35.0 (C_q), 29.7 (CH_3), 21.2 (CH_3).

IR (neat): $\tilde{\nu}$ = 2953, 2913, 1601, 1556, 1452, 1234, 1093, 1027, 810 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 255 (41) $[M]^+$, 240 (100), 224 (18), 212 (12).

HR-MS (EI): *m*/*z* calcd for $C_{17}H_{21}NO^+$ $[M]^+$ 255.1618, found 255.1626.

Synthesis of 1-{2-[3-(*tert*-Butyl)phenyl]pyridin-4-yl}ethan-1-one (187pa)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **38p** (99 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187pa** (61 mg, 48%) as a white solid.

M. p.: 86–88 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.22 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.26 (dd, *J* = 8.4, 2.3 Hz, 1H), 8.10 (dd, *J* = 1.9, 1.9 Hz, 1H), 7.84–7.79 (m, 2H), 7.50 (ddd, *J* = 7.9, 2.1, 1.2 Hz, 1H), 7.41 (dd, *J* = 7.7, 7.7 Hz, 1H), 2.64 (s, 3H), 1.38 (s, 9H).

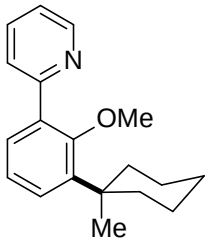
^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.5 (C_q), 161.5 (C_q), 151.9 (C_q), 150.1 (CH), 137.9 (C_q), 136.2 (CH), 130.4 (C_q), 128.6 (CH), 127.2 (CH), 124.6 (CH), 124.4 (CH), 120.3 (CH), 34.9 (C_q), 31.3 (CH_3), 26.7 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3024, 2959, 1593, 1494, 1453, 1044, 1027, 809 cm^{-1}.

MS (EI) *m/z* (relative intensity) 253 (15) $[M]^+$, 238 (45), 210 (6), 197 (6).

HR-MS (EI): *m/z* calcd for $C_{17}H_{19}NO^+$ $[M]^+$ 253.1461, found 253.1463.

Synthesis of 2-[2-Methoxy-3-(1-methylcyclohexyl)phenyl]pyridine (187qb)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **38q** (93 mg, 0.50 mmol) and bromide **50b** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187qb** (65 mg, 46%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 4.7 Hz, 1H), 7.74–7.65 (m, 2H), 7.43 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.35 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.20 (ddd, *J* = 6.5, 4.9, 2.2 Hz, 1H), 7.12 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.28 (s, 3H), 2.20–2.11 (m, 2H), 1.74–1.64 (m, 2H), 1.59–1.40 (m, 6H), 1.31 (s, 3H).

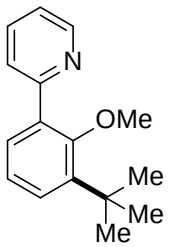
^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1 (C_q), 157.9 (C_q), 149.7 (CH), 142.0 (C_q), 136.1 (CH), 134.5 (C_q), 129.6 (CH), 128.5 (CH), 124.7 (CH), 123.5 (CH), 121.6 (CH), 61.2 (CH_3), 38.8 (C_q), 37.9 (CH_2), 27.5 (CH_3), 26.6 (CH_2), 23.0 (CH_2).

IR (neat): $\tilde{\nu}$ = 3058, 2923, 1586, 1407, 1211, 1005, 775 cm^{-1}.

MS (EI) *m/z* (relative intensity) 281 (43) $[M]^+$, 266 (90), 248 (47), 222 (36).

HR-MS (EI): *m/z* calcd for $C_{19}H_{23}NO^+$ $[M]^+$ 281.1774, found 281.1785.

Synthesis of 2-[3-(*tert*-Butyl)-2-methoxyphenyl]pyridine (187qa)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **38q** (93 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **187qa** (50 mg, 41%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 4.9 Hz, 1H), 7.76–7.66 (m, 2H), 7.44 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.34 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.21 (ddd, *J* = 6.5, 4.9, 2.2 Hz, 1H), 7.09 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.31 (s, 3H), 1.42 (s, 9H).

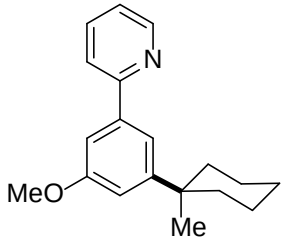
^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.8 (C_q), 157.8 (C_q), 149.7 (CH), 142.9 (C_q), 136.1 (CH), 134.1 (C_q), 129.8 (CH), 127.3 (CH), 124.6 (CH), 123.4 (CH), 121.7 (CH), 61.3 (CH_3), 35.1 (C_q), 30.8 (CH_3).

IR (neat): $\tilde{\nu}$ = 3051, 2867, 1587, 1562, 1473, 1223, 1006, 760 cm^{-1}.

MS (EI) *m/z* (relative intensity) 241 (51) $[M]^+$, 226 (83), 210 (100), 167 (32).

HR-MS (EI): *m/z* calcd for $C_{16}H_{19}NO^+$ $[M]^+$ 241.1461, found 241.1465.

Synthesis of 2-[3-Methoxy-5-(1-methylcyclohexyl)phenyl]pyridine (187rb)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **38r** (93 mg, 0.50 mmol) and bromide **50b** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 40:1) yielded **187rb** (49 mg,

35%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 4.9 Hz, 1H), 7.75–7.67 (m, 2H), 7.56 (dd, *J* = 1.6,1.6 Hz, 1H), 7.36 (dd, *J* = 2.5, 1.4 Hz, 1H), 7.20 (ddd, *J* = 6.2, 4.9, 2.3 Hz, 1H), 6.99 (dd, *J* = 2.5, 1.4 Hz, 1H), 3.88 (s, 3H), 2.08–1.99 (m, 2H), 1.64–1.40 (m, 8H), 1.22 (s, 3H).

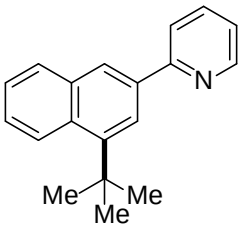
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0 (C_q), 158.0 (C_q), 152.2 (C_q), 149.5 (CH), 140.6 (C_q), 136.6 (CH), 122.0 (CH), 120.8 (CH), 117.4 (CH), 113.9 (CH), 108.2 (CH), 55.3 (CH_3), 38.2 (C_q), 38.0 (CH_2), 30.4 (CH_3), 26.3 (CH_2), 22.7 (CH_2).

IR (neat): $\tilde{\nu}$ = 2924, 2854, 1583, 1450, 1330, 1214, 1058, 781 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 281 (100) $[M]^+$, 266 (53), 252 (26), 226 (73).

HR-MS (EI): *m*/*z* calcd for $C_{19}H_{23}NO^+$ $[M]^+$ 281.1774, found 281.1773.

Synthesis of 2-[4-(*tert*-Butyl)naphthalen-2-yl]pyridine (187sa)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **38s** (103 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 40:1) yielded **187sa** (29 mg, 22%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74 (ddd, *J* = 4.8, 1.9, 1.0 Hz, 1H), 8.47 (d, *J* = 8.7 Hz, 1H), 8.29 (dd, *J* = 1.7, 0.9 Hz, 1H), 8.19 (d, *J* = 1.8 Hz, 1H), 7.97 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.86 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.77 (ddd, *J* = 7.9, 7.3, 1.8 Hz, 1H), 7.56–7.39 (m, 2H), 7.24 (ddd, *J* = 7.2, 4.8, 1.2 Hz, 1H), 1.69 (s, 9H).

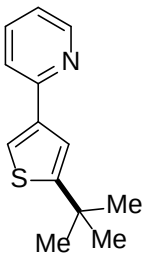
^{13}C NMR (126 MHz, $CDCl_3$) δ =157.7 (C_q), 149.6 (CH), 146.6 (C_q), 136.6 (CH), 135.6 (C_q), 135.1 (C_q), 131.7 (C_q), 130.4 (CH), 126.8 (CH), 125.7 (CH), 125.1 (CH), 124.9 (CH), 122.1 (CH), 121.9 (CH), 120.9 (CH), 36.4 (C_q), 31.9 (CH_3).

IR (neat): $\tilde{\nu}$ = 3052, 2957, 1586, 1563, 1471, 1364, 1153, 990, 781 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 261 (58) $[M]^+$, 246 (100), 231 (42), 217 (17).

HR-MS (EI): *m*/*z* calcd for $C_{19}H_{19}N^+$ $[M]^+$ 261.1512, found 261.1514

Synthesis of 2-[5-(*tert*-butyl)thiophen-3-yl]pyridine (187ta)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **38t** (81 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 40:1) yielded **187ta** (60 mg, 55%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 4.9 Hz, 1H), 7.67–7.55 (m, 3H), 7.40 (d, *J* = 1.4 Hz, 1H), 7.11 (ddd, *J* = 7.3, 4.9, 1.3 Hz, 1H), 1.41 (s, 9H).

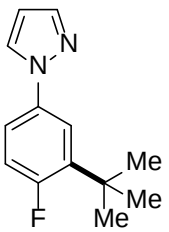
^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.5 (C_q), 153.9 (C_q), 149.4 (CH), 141.3 (C_q), 136.5 (CH), 121.5 (CH), 120.5 (CH), 120.5 (CH), 120.1 (CH), 34.6 (C_q), 34.2 (CH_3).

IR (neat): $\tilde{\nu}$ = 3085, 3060, 1768, 1704, 1586, 1483, 1244, 1064, 747 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 217 (26) $[M]^+$, 202 (100), 187 (10), 168 (8).

HR-MS (EI): *m*/*z* calcd for $C_{13}H_{15}NS^+$ $[M]^+$ 217.0920, found 217.0930.

Synthesis of 1-[3-(*tert*-Butyl)-4-fluorophenyl]-1*H*-pyrazole (196aa)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **131a** (81 mg, 0.50 mmol) and

bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **196aa** (79 mg, 72%) as a colorless oil.

The general procedure **B** was followed using [RuCl(O-Val-Piv)(*p*-cymene)] (23.6 mg, 10.0 mol %), substrate **131a** (81 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **196aa** (80mg, 73%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 1.7 Hz, 1H), 7.65 (dd, *J* = 7.1, 2.8 Hz, 1H), 7.42 (ddd, *J* = 8.8, 3.9, 2.8 Hz, 1H), 7.07 (dd, *J* = 11.8, 8.8 Hz, 1H), 6.45 (dd, *J* = 2.2, 2.2 Hz, 1H), 1.42 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.3 (d, $^1J_{C\text{-}F}$ = 247 Hz, C_q), 140.9 (CH), 138.4 (d, $^2J_{C\text{-}F}$ = 13 Hz, C_q), 136.2 (d, $^4J_{C\text{-}F}$ = 2 Hz, C_q), 127.0 (CH), 119.1 (d, $^3J_{C\text{-}F}$ = 6 Hz, CH), 118.4 (d, $^3J_{C\text{-}F}$ = 9 Hz, CH), 116.9 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 107.4 (CH), 34.5 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 29.7 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_3).

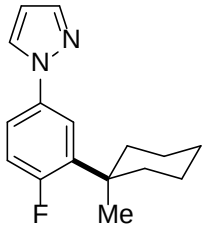
^{19}F NMR (282 MHz, $CDCl_3$): δ = −112.1 (s).

IR (neat): $\tilde{\nu}$ = 3111, 2960, 1592, 1490, 1394, 1211, 1044, 949 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 218 (55) $[M]^+$, 203 (100), 175 (60), 133 (5).

HR-MS (EI): *m*/*z* calcd for $C_{13}H_{15}FN_2^+$ $[M]^+$ 218.1214, found 218.1216.

Synthesis of 1-[4-Fluoro-3-(1-methylcyclohexyl)phenyl]-1*H*-pyrazole (196ab)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **131a** (81 mg, 0.50 mmol) and bromide **50b** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **196ab** (87 mg, 67%) as a colorless oil.

The general procedure **B** was followed using [RuCl(O-Val-Piv)(*p*-cymene)] (23.6 mg, 10.0 mol %), substrate **131a** (81 mg, 0.50 mmol) and bromide **50b** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **196ab** (83 mg, 64%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 2.4 Hz, 1H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.66 (dd, *J* = 7.1, 2.8 Hz, 1H), 7.39 (ddd, J = 8.7, 3.9, 2.8 Hz, 1H), 7.04 (dd, *J* = 12.2, 8.7 Hz, 1H), 6.43 (dd, *J* = 2.4, 1.8 Hz, 1H), 2.12–2.01 (m, 2H), 1.72–1.45(m, 8H), 1.31 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4 (d, $^1J_{C\text{-}F}$ = 248 Hz, C_q), 140.9 (CH), 137.8 (d, $^2J_{C\text{-}F}$ = 13 Hz, C_q), 136.3 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 127.0 (CH), 120.0 (d, $^3J_{C\text{-}F}$ = 6 Hz, CH), 118.2 (d, $^3J_{C\text{-}F}$ = 10 Hz, CH), 117.2 (d, $^2J_{C\text{-}F}$ = 28 Hz, CH), 107.4 (CH), 38.0 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 37.0 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_2), 26.4 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_3), 26.3 (CH_2), 22.6 (CH_2).

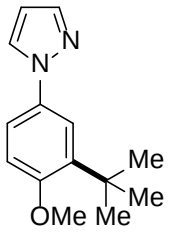
^{19}F NMR (282 MHz, $CDCl_3$): δ = –111.5 (s).

IR (neat): $\tilde{\nu}$ = 3112, 2925, 1593, 1490, 1451, 1211, 1043, 947 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 258 (100) $[M]^+$, 243 (74), 202 (49), 175 (35).

HR-MS (EI): *m*/*z* calcd for $C_{16}H_{19}FN_2^+$ $[M]^+$ 258.1527, found 258.1529.

Synthesis of 1-[3-(*tert*-Butyl)-4-methoxyphenyl]-1*H*-pyrazole (196ba)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **131b** (93 mg, 0.53 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 40:1) yielded **196ba** (82 mg, 67%) as a colorless

oil.

The general procedure **B** was followed using [RuCl(O-Val-Piv)(*p*-cymene)] (23.6 mg, 10.0 mol %), substrate **131b** (87 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 40:1) yielded **196ba** (73 mg, 63%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.68 (d, *J* = 1.7 Hz, 1H), 7.59 (d, *J* = 2.8 Hz, 1H), 7.40 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 1H), 6.41 (dd, *J* = 2.1, 2.1 Hz, 1H), 3.85 (s, 3H), 1.40 (s, 9H).

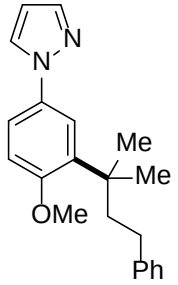
^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2 (C_q), 140.4 (CH), 139.4 (C_q), 133.5 (C_q), 127.0 (CH), 119.0 (CH), 118.2 (CH), 111.8 (CH), 106.9 (CH), 55.3 (CH_3), 35.0 (C_q), 29.5 (CH_3).

IR (neat): $\tilde{\nu}$ = 3111, 2997, 1592, 1516, 1428, 1397, 1045, 1027, 951 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 230 (63) $[M]^+$, 215 (100), 200 (32), 187 (32).

HR-MS (EI): *m*/*z* calcd for $C_{14}H_{18}N_2O^+$ $[M]^+$ 230.1414, found 230.1410.

Synthesis of 1-[4-Methoxy-3-(2-methyl-4-phenylbutan-2-yl)phenyl]-1H-pyrazole (196bi)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **131b** (87 mg, 0.50 mmol) and bromide **50i** (341 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **196bi** (93 mg, 58%) as a colorless oil.

The general procedure **B** was followed using [RuCl(O-Val-Piv)(*p*-cymene)] (23.6 mg, 10.0 mol %), substrate **131b** (87 mg, 0.50 mmol) and bromide **50i** (341 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **196bi** (87 mg, 54%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 2.4 Hz, 1H), 7.73 (d, *J* = 1.8 Hz, 1H), 7.63 (d, *J* = 2.8 Hz, 1H), 7.46 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.28–7.21 (m, 2H), 7.17–7.08 (m, 3H), 6.94 (d, *J* = 8.7 Hz, 1H), 6.47–6.45 (m, 1H), 3.88 (s, 3H), 2.34–2.26 (m, 2H), 2.23–2.16 (m, 2H), 1.48 (s, 6H).

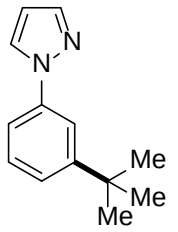
^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2 (C_q), 143.5 (C_q), 140.5 (CH), 137.4 (C_q), 133.7 (C_q), 128.3 (CH), 128.2 (CH), 127.0 (CH), 125.4 (CH), 120.2 (CH), 118.4 (CH), 111.6 (CH), 107.0 (CH), 55.4 (CH_3), 42.7 (CH_2), 38.7 (CH_2), 32.0 (C_q), 28.4 (CH_3).

IR (neat): $\tilde{\nu}$ = 3024, 2959, 1593, 1516, 1494, 1235, 1027, 809 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 320 (62) $[M]^+$, 215 (100), 187 (22), 157 (8), 91 (32).

HR-MS (EI): *m*/*z* calcd for $C_{21}H_{24}N_2O^+$ $[M]^+$ 320.1883, found 320.1882.

1-[3-(*tert*-Butyl)phenyl]-1*H*-pyrazole (196ca)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **131c** (72 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 80:1) yielded **196ca** (44 mg, 44%) as a colorless oil.

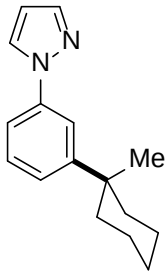
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 2.4 Hz, 1H), 7.76–7.70 (m, 2H), 7.46–7.29 (m, 3H), 6.46–6.43 (m, 1H), 1.36 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ =152.9 (C_q), 140.9 (CH), 140.1 (C_q), 128.9 (CH), 126.9 (CH), 123.6 (CH), 116.8 (CH), 116.4 (CH), 107.3 (CH), 34.9 (C_q), 31.2 (CH_3).

IR (neat): $\tilde{\nu}$ = 2962, 2866, 1608, 1588, 1488, 1405, 1333, 1198, 1043, 787 cm^{-1}.

MS (EI) *m/z* (relative intensity) 200 (26) $[M]^+$, 185 (100), 157 (13), 115 (6).
HR-MS (EI): *m/z* calcd for $C_{13}H_{16}N_2^+$ $[M]^+$ 200.1308, found 200.1319.

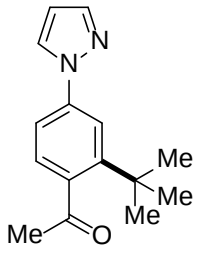
Synthesis of 1-[3-(1-Methylcyclohexyl)phenyl]-1*H*-pyrazole (196cb)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **131c** (72 mg, 0.50 mmol) and bromide **50b** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 80:1) yielded **196cb** (35 mg, 29%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 2.5, 0.6 Hz, 1H), 7.74–7.71 (m, 2H), 7.45–7.28 (m, 3H), 6.45–6.43 (m, 1H), 2.08–1.98 (m, 2H), 1.63–1.41 (m, 8H), 1.22 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ =151.8 (C_q), 140.8 (CH), 140.2 (C_q), 129.0 (CH), 126.8 (CH), 124.1 (CH), 117.3 (CH), 116.2 (CH), 107.2 (CH), 38.2 (C_q), 37.9 (CH_2), 30.4 (CH_3), 26.3 (CH_2), 22.7 (CH_2).
IR (neat): $\tilde{\nu}$ = 2925, 2856, 1605, 1518, 1466, 1332, 1192, 1043, 964 cm^{-1}.
MS (EI) *m/z* (relative intensity) 240 (100) $[M]^+$, 225 (78), 197 (37), 184 (41).
HR-MS (EI): *m/z* calcd for $C_{16}H_{20}N_2^+$ $[M]^+$ 240.1621, found 240.1623.

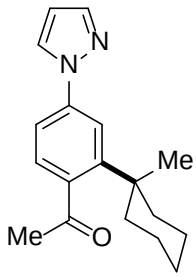
Synthesis of 1-[2-(*tert*-Butyl)-4-(1*H*-pyrazol-1-yl)phenyl]ethan-1-one (196da)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **131d** (93 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 40:1) yielded **196da** (46 mg, 38%) as a white solid.

M. p.: 68–70 °C.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (dd, *J* = 2.5, 0.7 Hz, 1H), 7.84 (d, *J* = 2.1 Hz, 1H), 7.71 (d, *J* = 1.7 Hz, 1H), 7.47 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 6.45 (dd, *J* = 2.5, 1.7 Hz, 1H), 2.58 (s, 3H), 1.40 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.8 (C_q), 149.1 (C_q), 141.3 (CH), 140.4 (C_q), 140.1 (C_q), 127.3 (CH), 126.8 (CH), 118.3 (CH), 115.7 (CH), 107.8 (CH), 36.2 (C_q), 32.4 (CH_3), 31.6 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3129, 2962, 1691, 1517, 1398, 1105, 1047, 945, 760 cm^{-1}.
MS (EI) *m/z* (relative intensity) 242 (5) $[M]^+$, 227 (100), 209 (20), 115 (8).
HR-MS (EI): *m/z* calcd for $C_{15}H_{18}N_2O^+$ $[M]^+$ 242.1414, found 242.1423.

Synthesis of 1-[2-(1-Methylcyclohexyl)-4-(1*H*-pyrazol-1-yl)phenyl]ethan-1-one (196db)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **131d** (93 mg, 0.50 mmol) and bromide **50b** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 40:1) yielded **196db** (30 mg, 21%) as a white solid.

M. p.: 92–94 °C.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 2.4 Hz, 1H), 7.85 (d, *J* = 2.1 Hz, 1H), 7.74 (d, *J* = 1.7 Hz, 1H), 7.49 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 1H), 6.48 (dd, *J* = 2.5, 1.7 Hz, 1H), 2.59 (s, 3H), 2.10–2.01 (m, 2H), 1.68–1.52 (m, 5H), 1.46–1.40 (m, 3H), 1.37 (s, 3H).

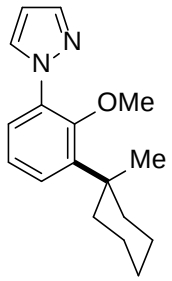
^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.9 (C_q), 147.5 (C_q), 141.3 (CH), 140.7 (C_q), 140.6 (C_q), 127.4 (CH), 126.8 (CH), 119.0 (CH), 115.7 (CH), 107.8 (CH), 39.9 (C_q), 38.4 (CH_2), 32.1 (CH_3), 29.9 (CH_3), 26.2 (CH_2), 22.8 (CH_2).

IR (ATR): 3143, 2953, 1689, 1602, 1517, 1408, 1199, 1041, 747 cm^{-1}.

MS (EI) *m/z* (relative intensity) 282 (8) $[M]^+$, 267 (100), 249 (23), 225 (18).

HR-MS (EI): *m/z* calcd for $C_{18}H_{22}N_2O^+$ $[M]^+$ 282.1727, found 282.1730.

Synthesis of 1-(2-methoxy-3-(1-methylcyclohexyl)phenyl)-1*H*-pyrazole (196eb)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **131e** (90 mg, 0.52 mmol) and bromide **50b** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **196eb** (34 mg, 24%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.71 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.37 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.32 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.10 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.45–6.43 (m, 1H), 3.15 (s, 3H), 2.17–2.07 (m, 2H), 1.69–1.44 (m, 8H), 1.29 (s, 3H).

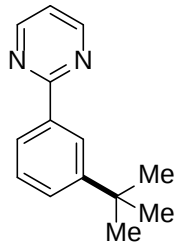
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.2 (C_q), 143.1 (C_q), 140.5 (CH), 134.6 (C_q), 131.2 (CH), 127.4 (CH), 124.8 (CH), 123.4 (CH), 106.9 (CH), 59.8 (CH_3), 38.9 (C_q), 37.7 (CH_2), 27.3 (CH_3), 26.5 (CH_2), 22.9 (CH_2).

IR (neat): $\tilde{\nu}$ = 2924, 2854, 186, 1518, 1423, 1229, 1041, 948, 790 cm^{-1}.

MS (EI) *m/z* (relative intensity) 270 (63) $[M]^+$, 255 (100), 237 (37), 187 (26).

HR-MS (EI): *m/z* calcd for $C_{17}H_{22}N_2O^+$ $[M]^+$ 270.1727, found 270.1731.

Synthesis of 2-[3-(*tert*-Butyl)phenyl]pyrimidine (198aa)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **197a** (78 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **198aa** (53 mg, 50%) as a white solid.

The general procedure **B** was followed using [RuCl(O-Val-Piv)(*p*-cymene)] (23.6 mg, 10.0 mol %), substrate **197a** (78.1 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **198aa** (65 mg, 61%) as a white solid.

M. p.:74–76 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.79 (d, *J* = 4.8 Hz, 2 H), 8.48 (dd, *J* = 1.8, 1.8 Hz, 1H), 8.24 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.52 (ddd, *J* = 7.8, 2.0, 1.2 Hz, 1H), 7.41 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.15 (dd, *J* = 4.8, 4.8 Hz, 1H), 1.40 (s, 9H).

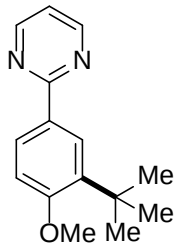
^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1 (C_q), 157.2 (CH), 151.5 (C_q), 137.3 (C_q), 128.3 (CH), 127.9 (CH), 125.4 (CH), 125.0 (CH), 118.9 (CH), 34.9 (C_q), 31.4 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3069, 3037, 1567, 1403, 1259, 1244, 781, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity) 212 (7) $[M]^+$, 197 (33), 182 (5), 169 (5).

HR-MS (EI): *m/z* calcd for $C_{14}H_{16}N_2^+$ $[M]^+$ 212.1308, found 212.1313.

Synthesis of 2-[3-(*tert*-Butyl)-4-methoxyphenyl]pyrimidine (198ba)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **197b** (93 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **198ba** (53 mg, 44%) as a colorless oil.

The general procedure **B** was followed using [RuCl(O-Val-Piv)(*p*-cymene)] (23.6 mg, 10.0 mol %), substrate **197b** (93 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **198ba** (57 mg, 47%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.73 (d, *J* = 4.8 Hz, 2H), 8.40 (d, *J* = 2.2 Hz, 1H), 8.27 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.07 (dd, *J* = 4.8, 4.8 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 3.89 (s, 3H), 1.43 (s, 9H).

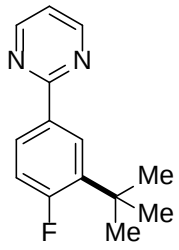
^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0 (C_q), 160.9 (C_q), 157.1 (CH), 138.2 (C_q), 129.5 (C_q), 127.5 (CH), 126.7 (CH), 118.1 (CH), 111.4 (CH), 55.1 (CH_3), 35.0 (C_q), 29.7 (CH_3).

IR (neat): $\tilde{\nu}$ = 2966, 2955, 1566, 1549, 1395, 1252, 1027, 797 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 242 (36) $[M]^+$, 227 (100), 199 (23), 169 (17).

HR-MS (EI): *m*/*z* calcd for $C_{15}H_{18}N_2O^+$ $[M]^+$ 242.1414, found 242.1423.

Synthesis of 2-[3-(*tert*-Butyl)-4-fluorophenyl]pyrimidine (198ca)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **197c** (87 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **197ca** (60 mg, 52%) as a colorless oil.

The general procedure **B** was followed using [RuCl(O-Val-Piv)(*p*-cymene)] (23.6 mg, 10.0 mol %), substrate **197c** (87 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **198ca** (82 mg, 71%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.76 (d, *J* = 4.8 Hz, 2H), 8.43 (dd, *J* = 8.3, 2.3 Hz, 1H), 8.25 (ddd, *J* = 8.5, 4.7, 2.3 Hz, 1H), 7.13 (dd, *J* = 4.8, 4.8 Hz, 1H), 7.02 (dd, *J* = 12.1, 8.5 Hz, 1H), 1.44 (d, *J* = 1.0 Hz, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0 (d, $^1J_{C\text{-}F}$ = 254 Hz, C_q), 164.3 (C_q), 157.1 (CH), 137.2 (d, $^2J_{C\text{-}F}$ = 12 Hz, C_q), 133.2 (d, $^4J_{C\text{-}F}$ = 2 Hz, C_q), 127.8 (d, $^3J_{C\text{-}F}$ = 10 Hz, CH), 127.5 (d, $^3J_{C\text{-}F}$ = 7 Hz, CH), 118.7 (CH), 116.5 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 34.4 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 29.9 (d, $^4J_{C\text{-}F}$ = 3 Hz, CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = −106.4 (s).

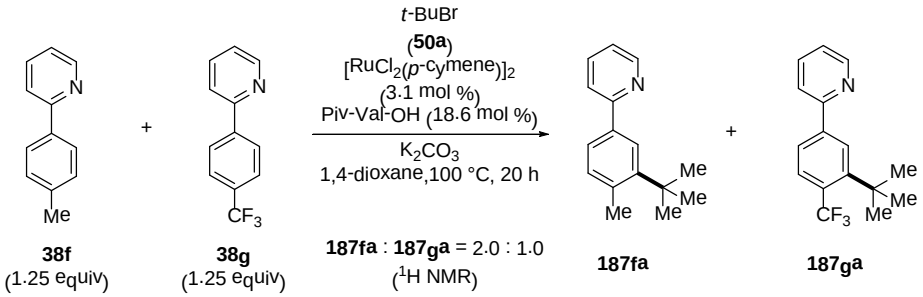
IR (neat): $\tilde{\nu}$ = 3036, 2959, 2870, 1567, 1415, 1210, 1084, 799 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 230 (28) $[M]^+$, 215 (100), 187 (48), 134 (10).

HR-MS (EI): *m*/*z* calcd for $C_{14}H_{15}FN_2^+$ $[M]^+$ 230.1214, found 230.1218.

Mechanistic Studies

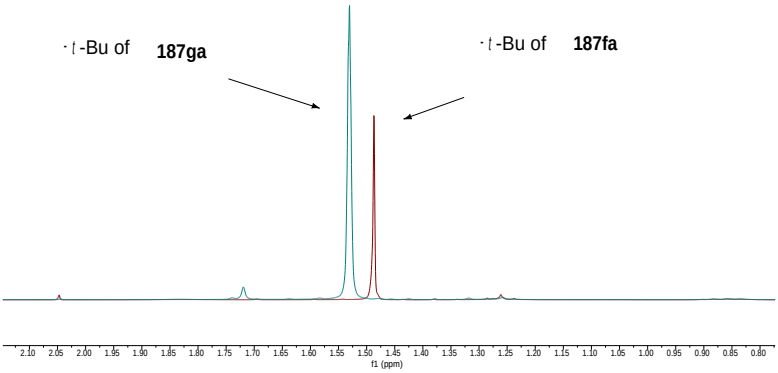
Intermolecular Competition Experiment between Substrates 38f and 38g

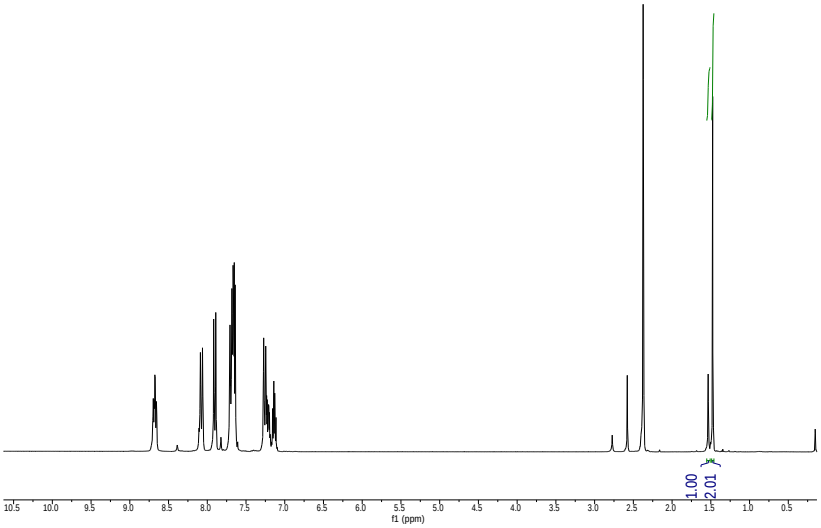


38f (1.25 equiv) + **38g** (1.25 equiv) → **187fa** : **187ga** = 2.0 : 1.0 (¹H NMR) + **187fa** + **187ga**

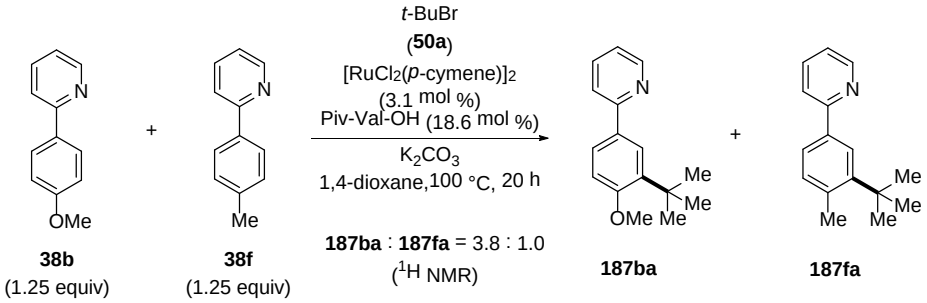
A mixture of substrates **38f** (169 mg, 1.00 mmol), **38g** (223 mg, 1.00 mmol) and bromide **50a** (110 mg, 0.80 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 3.1 mol %), Piv-Val-OH (30.0 mg, 18.6 mol %) and K_2CO_3 (276 mg, 2.00 mmol) in 1,4-dioxane (4.0 mL) was stirred at 100 °C for 20 h under an atmosphere of N_2. At ambient temperature, EtOAc (15 mL) was added, and the mixture was filtered through a pad of silica gel. The solvents were removed *in vacuo*, and the residue was purified by column chromatography (*n*-hexane/EtOAc 20:1). Careful ^{1}H NMR analysis disclosed a ratio of **187fa**/**187ga** to be 2.0 : 1.0. Their spectral data were identical to those reported above.

Standard spectra



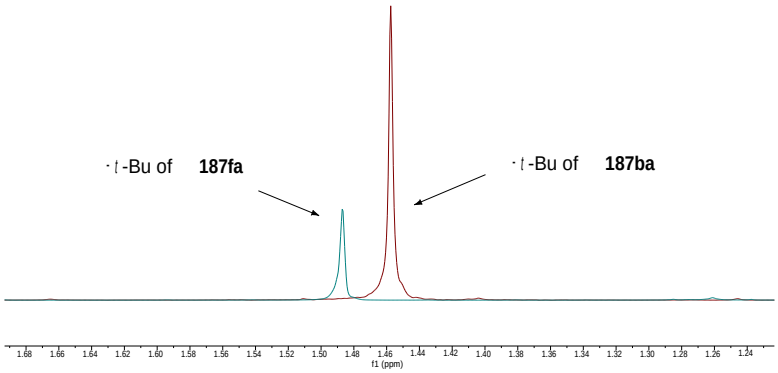


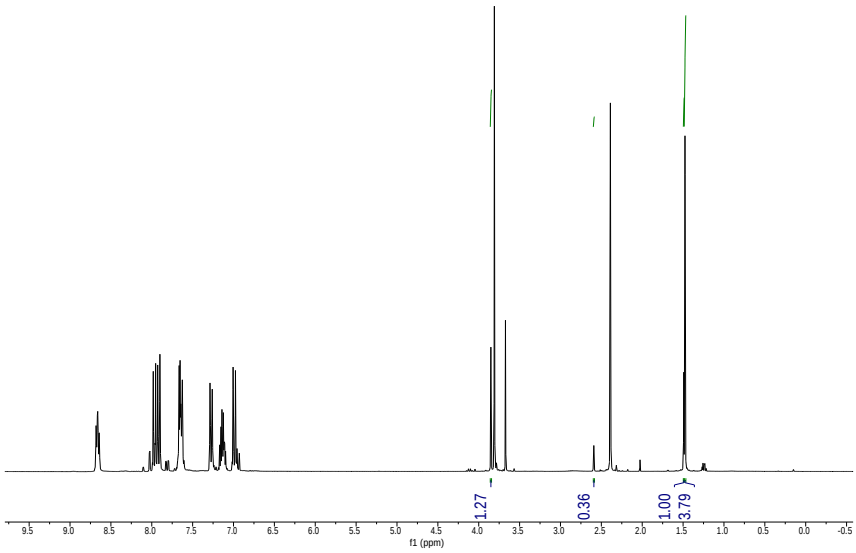
Intermolecular Competition Experiment between Substrates 38b and 38f



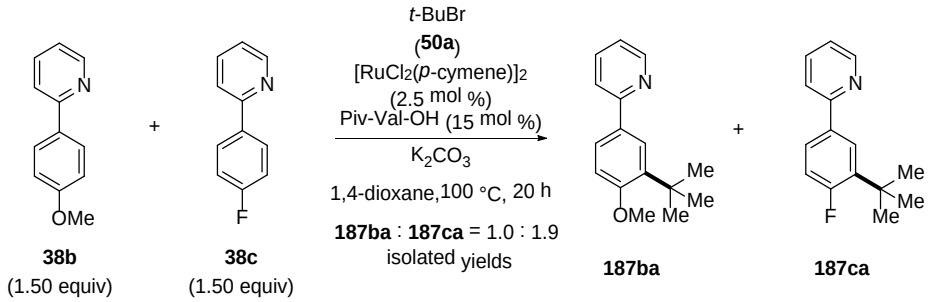
A mixture of substrates **38b** (185 mg, 1.00 mmol), **38f** (169 mg, 1.00 mmol) and bromide **50a** (110 mg, 0.80 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 3.1 mol %), Piv-Val-OH (30.0 mg, 18.6 mol %) and K_2CO_3 (276 mg, 2.00 mmol) in 1,4-dioxane (4.0 mL) was stirred at 100 °C for 20 h under an atmosphere of N_2. At ambient temperature, EtOAc (15 mL) was added, and the mixture was filtered through a pad of silica gel. The solvents were removed *in vacuo*, and the residue was purified by column chromatography (*n*-hexane/EtOAc 20:1). Careful ^{1}H NMR analysis disclosed a ratio of **187ba**/**187fa** to be 3.8 : 1.0. Their spectral data were identical to those reported above.

Standard spectra



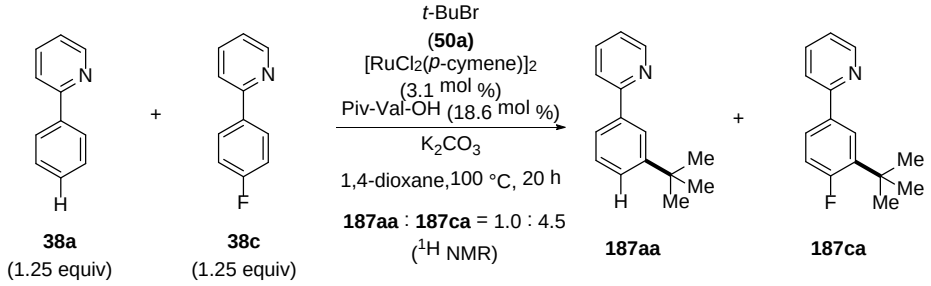


Intermolecular Competition Experiment between Substrates 38b and 38c



A mixture of substrates **38b** (278 mg, 1.50 mmol), **38c** (260 mg, 1.50 mmol) and bromide **50a** (137 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 2.5 mol %), Piv-Val-OH (30.0 mg, 15 mol %) and K_2CO_3 (276 mg, 2.00 mmol) in 1,4-dioxane (4.0 mL) was stirred at 100 °C for 20 h under an atmosphere of N_2. At ambient temperature, EtOAc (15 mL) was added, and the mixture was filtered through a pad of silica gel. The solvents were removed *in vacuo*, and purification of the residue by column chromatography (*n*-hexane/EtOAc 100:1→80:1→20:1) yielded compound **187ba** (34 mg, 14%) and **187ca** (60mg, 26%). The ratio of isolated products **187ba** to **187ca** was established to be 1.0 : 1.9. Their spectral data were identical to those reported above.

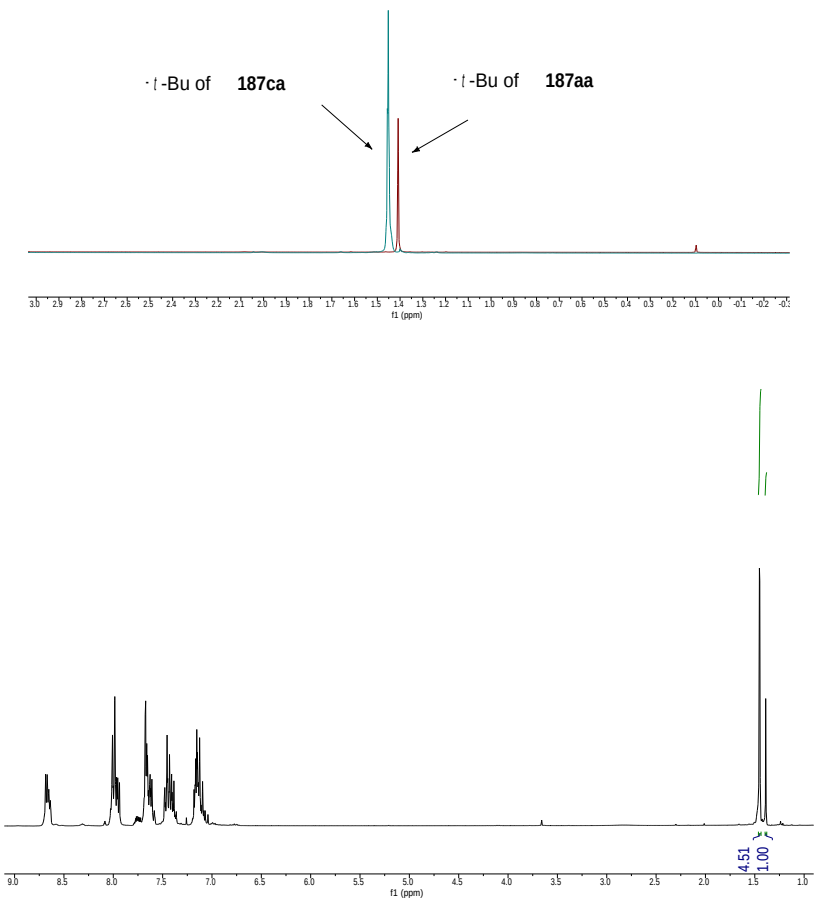
Intermolecular Competition Experiment between Substrates 38a and 38c



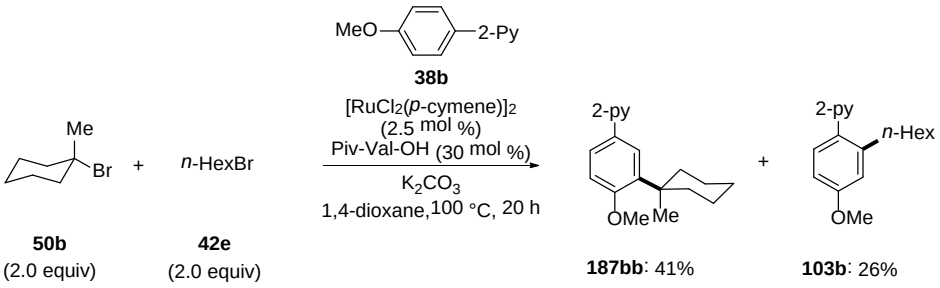
A mixture of substrates **38a** (155 mg, 1.00 mmol), **38c** (173 mg, 1.00 mmol) and bromide **50a** (110 mg, 0.80 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 2.5 mol %), Piv-Val-OH (30.0 mg, 30 mol %) and K_2CO_3 (276 mg, 2.00 mmol) in 1,4-dioxane (4.0 mL) was stirred at 100 °C for 20 h under an atmosphere of

N_2. At ambient temperature, EtOAc (15 mL) was added, and the mixture was filtered through a pad of silica gel. The solvents were removed *in vacuo*, and the residue was purified by column chromatography (*n*-hexane/EtOAc 20:1). Careful ^{1}H NMR analysis disclosed a ratio of **187aa**/**187ca** to be 1.0 : 4.5. Their spectral data were identical to those reported above.

Standard spectra



Intermolecular Competition Experiment between Tertiary Alkyl bromide 50b and Primary Alkyl Bromide 42e

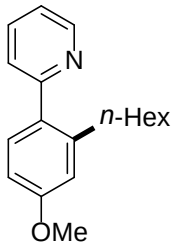


50b (2.0 equiv) **42e** (2.0 equiv) **187bb**: 41% **103b**: 26%

A mixture of substrate **38b** (93 mg, 0.50 mmol) and bromides **50b** (177 mg, 1.00 mmol) and **42e** (165 mg, 1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 2.5 mol %), Piv-Val-OH (30.0 mg, 30 mol %) and K_2CO_3 (138 mg, 1.00 mmol) in 1,4-dioxane (2.0 mL) was stirred at 100 °C for 20 h under an atmosphere of

N_2. At ambient temperature, EtOAc (15 mL) was added, and the mixture was filtered through a pad of silica gel. The solvents were removed *in vacuo*, and purification of the residue by column chromatography (*n*-hexane/EtOAc 20:1) yielded compound **187bb** (58 mg, 41%) and **103b** (35 mg, 26%) as colorless oils. The spectral data of **187bb** was identical to those reported above.

Analytical Data for 2-(2-*n*-Hexyl-4-methoxyphenyl)pyridine (103b)



^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.61 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.65 (dt, *J* = 7.7, 1.9 Hz, 1H), 7.29 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 7.15 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 6.80–6.72 (m, 2H), 3.78 (s, 3H), 2.64 (dd, *J* = 8.0, 7.8 Hz, 2H), 1.45-1.33 (m, 2H), 1.21–1.05 (m, 6H), 0.76 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1 (C_q), 159.5 (C_q), 149.0 (CH), 142.4 (C_q), 135.9 (CH), 133.2 (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), 31.5 (CH_2), 31.1 (CH_2), 29.1 (CH_2), 22.4 (CH_2), 14.0 (CH_3).

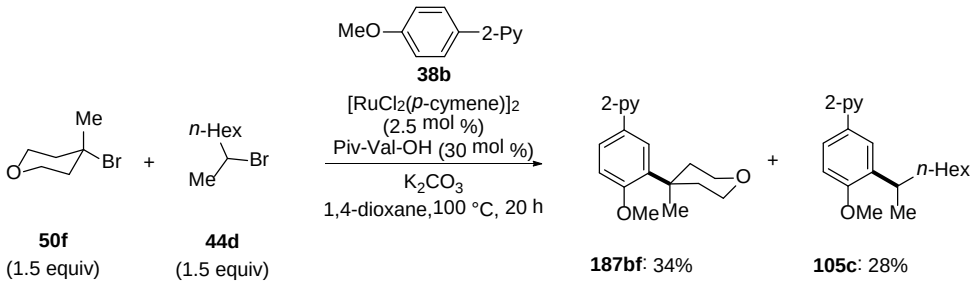
IR (neat): $\tilde{\nu}$ = 2927, 2855, 1607, 1587, 1505, 1465, 1427, 1280, 1236, 1162, 1045, 787, 749 cm^{-1}.

MS (EI) *m/z* (relative intensity) 269 (33) $[M]^+$, 226 (9), 212 (100), 197 (18), 154 (10).

HR-MS (ESI) *m/z* calcd for $C_{18}H_{24}NO^+$ $[M+H]^+$ 270.1852, found 270.1852.

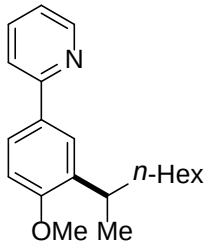
The spectral data were in accordance with those reported in the literature.[140]

Intermolecular Competition Experiment between Tertiary Alkyl Bromide 50f and Secondary Alkyl Bromide 44d



A mixture of substrate **38b** (93 mg, 0.50 mmol), bromides **50f** (134 mg, 0.75 mmol) and **44d** (145 mg, 0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 2.5 mol %), Piv-Val-OH (30.0 mg, 30 mol %) and K_2CO_3 (138 mg, 1.00 mmol) in 1,4-dioxane (2.0 mL) was stirred at 100 °C for 20 h under an atmosphere of N_2. At ambient temperature, EtOAc (15 mL) was added, and the mixture was filtered through a pad of silica gel. The solvents were removed *in vacuo*, and purification of the residue by column chromatography (*n*-hexane/EtOAc 40:1→20:1) yielded compound **187bf** (48 mg, 34%) and **105c** (42 mg, 28%) as colorless oils. The spectral data of **187bf** was identical to those reported above.

Analytical Data for 2-[4-Methoxy-3-(octan-2-yl)phenyl]pyridine (105c)



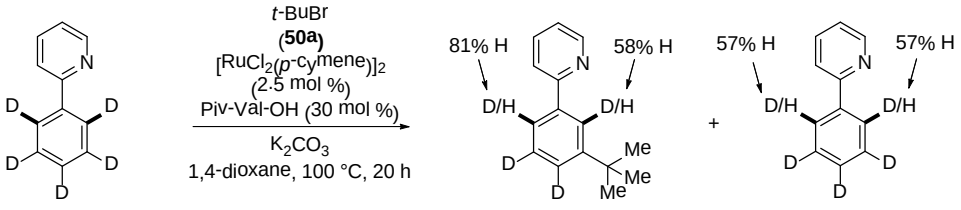
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.4, 1.4, 1.0 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.80 (dt, *J* = 8.5, 1.8 Hz, 1H), 7.75–7.63 (m, 2H), 7.19–7.11 (m, 1H), 6.94 (dd, *J* = 8.4, 1.2 Hz, 1H), 3.87 (s, 3H), 3.23 (qt, *J* = 7.1, 6.9 Hz, 1H), 1.79–1.50 (m, 2H), 1.34–1.16 (m, 11H), 0.86 (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).

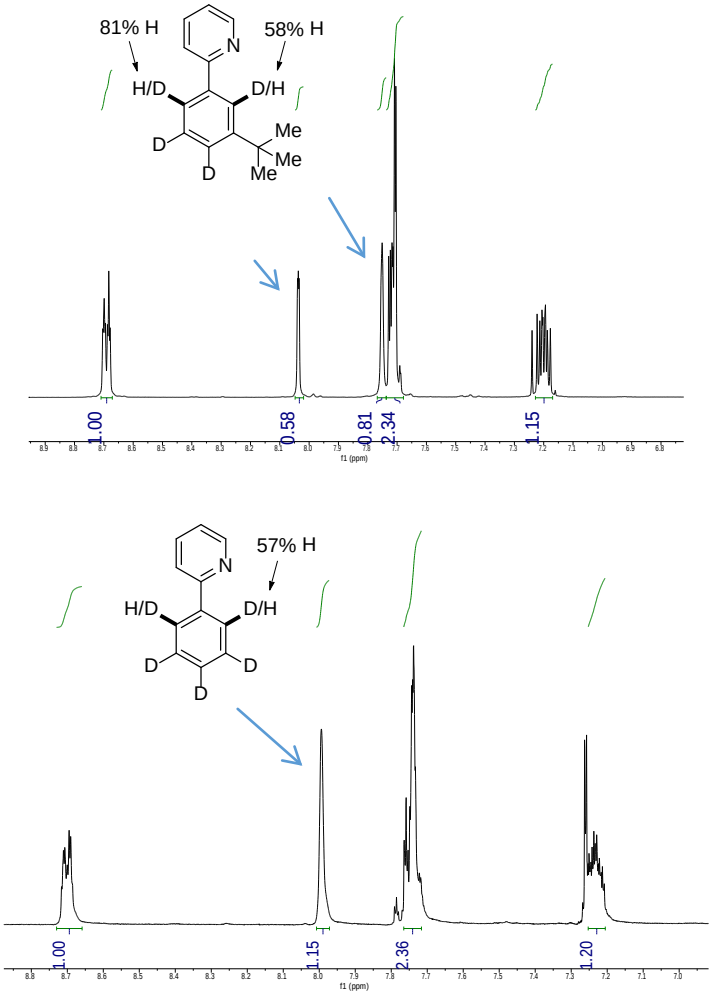
IR (neat): $\tilde{\nu}$ = 2956, 2927, 2856, 1606, 1563, 1502, 1464, 1431, 1271, 1245, 781 cm^{-1}.

MS (EI) *m/z* (relative intensity) 297 (27) $[M]^+$, 212 (100), 197 (15), 167 (30).
HR-MS (EI) m/z calculated for $C_{20}H_{27}NO^+$ $[M]^+$ 297.2087; found 297.2094.
The spectral data were in accordance with those reported in the literature.[143]

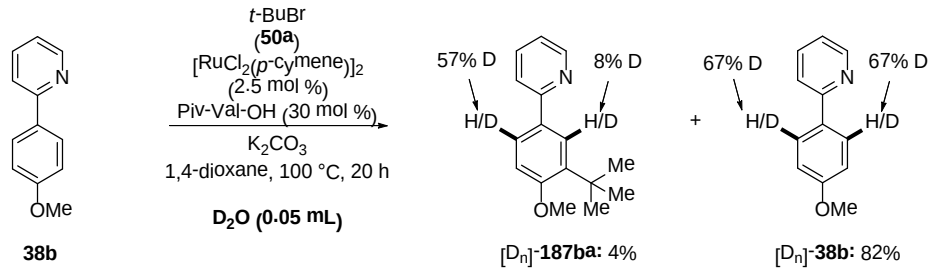
Experiment with Deuterium-Labeled 2-Phenylpyridine [D_5]-38



The general procedure **A** was followed using substrate [D_5]-**38a** (80 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 80:1) yielded [D_n]-**187aa** (57 mg, 53%) and reisolated [D_n]-**38a** (15 mg, 19%) as colorless oils.

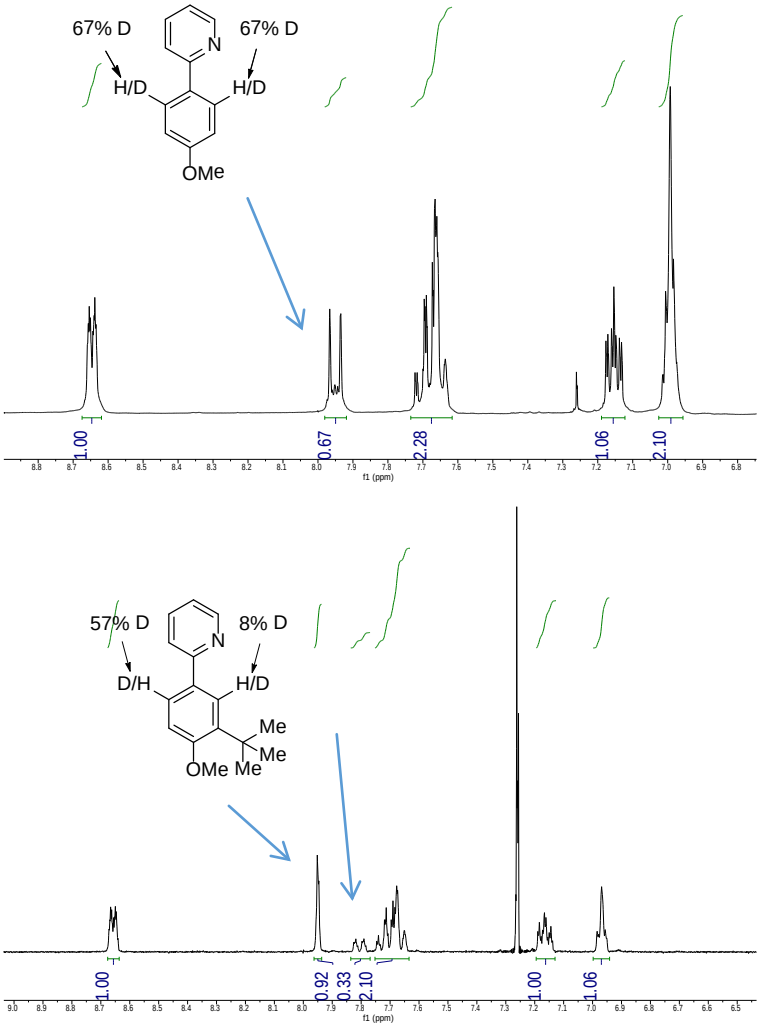


Experiment with Substrate 38b in the Presence of D_2O

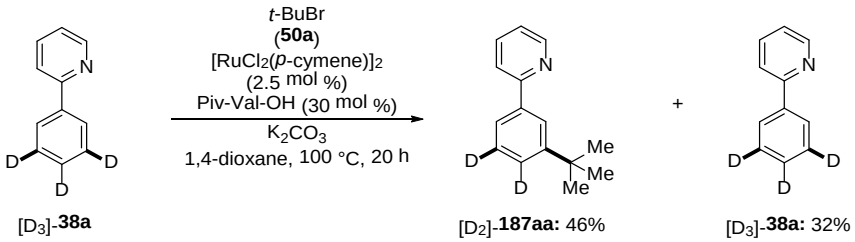


38b [D_n]-**187ba:** 4% [D_n]-**38b:** 82%

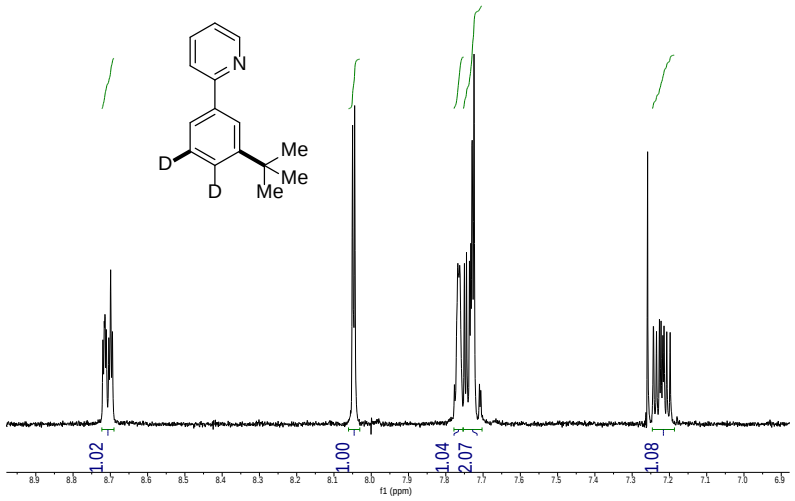
The general procedure **A** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol) in the presence of D_2O (0.05 mL). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded [D_n]-**187ba** (5 mg, 4%) and reisolated [D_n]-**38b** (76 mg, 82%) as colorless oils.



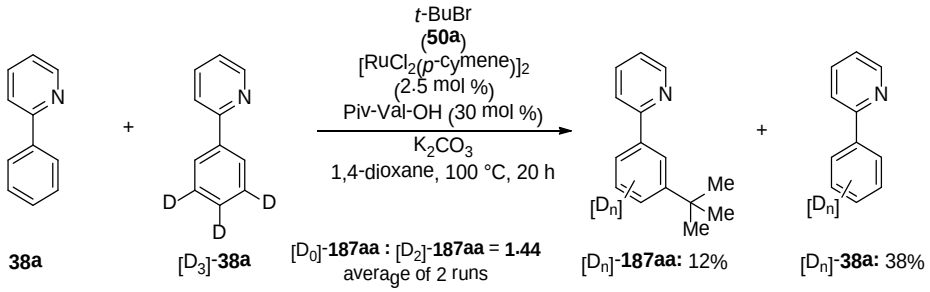
Experiment with Deuterium-Labeled Phenylpyridine [D_3]-38a



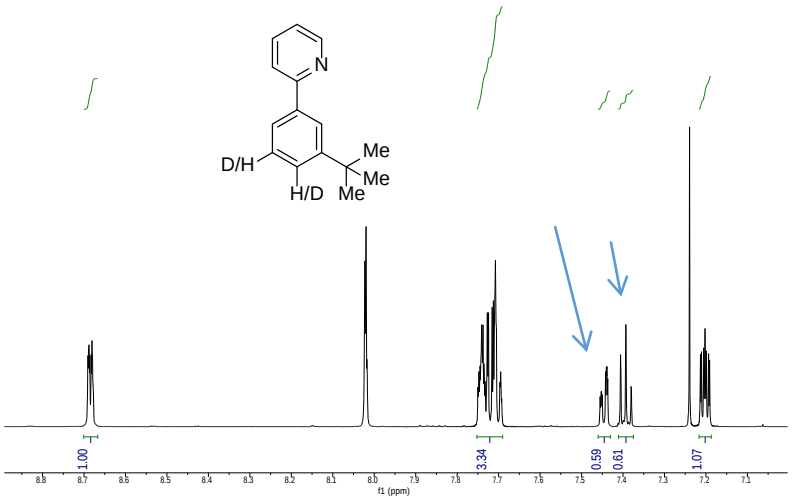
The general procedure **A** was followed using substrate [D_3]-**38a** (75 mg, 0.47 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 80:1) yielded [D_2]-**187aa** (46 mg, 46%) and reisolated [D_3]-**38a** (24 mg, 32%) as colorless oils.



Intermolecular Competition Experiment between Substrates [D_3]-38a and 38a

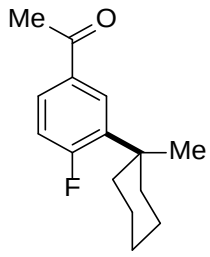


A mixture of substrates **38a** (82 mg, 0.53 mmol), [D_3]-**38a** (84 mg, 0.53 mmol) and bromide **50a** (137 mg, 1.0 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 2.5 mol %), Piv-Val-OH (60.0 mg, 30 mol %) and K_2CO_3 (276 mg, 2.00 mmol) in 1,4-dioxane (4.0 mL) was stirred at 100 °C for 20 h under an atmosphere of N_2. At ambient temperature, EtOAc (15 mL) was added, and the mixture was filtered through a pad of silica gel. The solvents were removed *in vacuo*, and purification of the residue by column chromatography (*n*-hexane/EtOAc 40:1→20:1) yielded compound [D_n]-**187aa** (27 mg, 12%) and the reisolated [D_n]-**38a** (63 mg, 38%) as colorless oils. The ratio of H/D was determined by ^{1}H NMR basing for 2 individual runs. KIE value was estimated to be 1.44.



7.3.2 Analytical Data for the Products of the Ruthenium(II)-Catalyzed Direct *meta*-Selective Alkylation of Ketimines with Tertiary Alkyl Bromides

Synthesis of 1-[4-Fluoro-3-(1-methylcyclohexyl)phenyl]ethan-1-one (189ab)



The general procedure **C** was followed using substrate **188a** (152 mg, 0.50 mmol) and bromide **50b** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **189ab** (68 mg, 58%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.77 (ddd, *J* = 8.4, 4.5, 2.3 Hz, 1H), 7.03 (dd, *J* = 12.4, 8.4 Hz, 1H), 2.57 (s, 3H), 2.11–1.99 (m, 2H), 1.72–1.52 (m, 5H), 1.48–1.37 (m, 3H), 1.28 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.0 (C_q), 165.2 (d, $^1J_{C\text{-}F}$ = 257 Hz, C_q), 136.9 (d, $^2J_{C\text{-}F}$ = 12 Hz, C_q), 133.2 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 129.1 (d, $^3J_{C\text{-}F}$ = 8 Hz, CH), 128.3 (d, $^3J_{C\text{-}F}$ = 11 Hz, CH), 116.8 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 38.0 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 37.0 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_2), 26.5 (CH_3), 26.5 (CH_3), 26.3 (CH_2), 22.6 (CH_2).

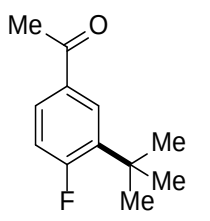
^{19}F NMR (282 MHz, $CDCl_3$): δ = –101.6 (s).

IR (neat): $\tilde{\nu}$ = 2953, 2870, 1687, 1590, 1340, 1280, 1067, 830 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 234 (24) $[M]^+$, 219 (60), 178 (35), 163 (62).

HR-MS (EI): *m*/*z* calcd for $C_{15}H_{19}FO^+$ $[M]^+$ 234.1414, found 234.1420.

Synthesis of 1-[3-(*tert*-Butyl)-4-fluorophenyl]ethan-1-one (189aa)



The general procedure **C** was followed using substrate **188a** (152 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **189aa** (57 mg, 59%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.77 (ddd, *J* = 8.4, 4.6, 2.3 Hz, 1H), 7.03 (dd, *J* = 12.0, 8.4 Hz, 1H), 2.56 (s, 3H), 1.38 (d, *J* = 1.1 Hz, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.0 (C_q), 165.1 (d, $^1J_{C\text{-}F}$ = 257 Hz, C_q), 137.5 (d, $^2J_{C\text{-}F}$ = 12 Hz, C_q), 133.1 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 128.6 (d, $^3J_{C\text{-}F}$ = 11 Hz, CH), 127.9 (d, $^3J_{C\text{-}F}$ = 7 Hz, CH), 116.4 (d, $^2J_{C\text{-}F}$ = 25 Hz, CH), 34.4 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 29.7 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_3), 26.5 (CH_3).

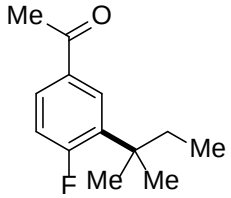
^{19}F NMR (282 MHz, $CDCl_3$): δ = –101.6 (s).

IR (neat): $\tilde{\nu}$ = 2961, 2873, 1683, 1606, 1490, 1355, 1235, 1094, 817 cm^{-1}.

MS (EI) *m/z* (relative intensity) 194 (18) $[M]^+$, 179 (100), 151 (58), 136 (10).

HR-MS (EI): *m/z* calcd for $C_{12}H_{15}FO^+$ $[M]^+$ 194.1101, found 194.1106.

Synthesis of 1-[4-Fluoro-3-(*tert*-pentyl)phenyl]ethan-1-one (189ad)



The general procedure **C** was followed using substrate **188a** (152 mg, 0.50 mmol) and bromide **50d** (227 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **189ad** (59 mg, 57%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.78 (ddd, *J* = 8.4, 4.5, 2.3 Hz, 1H), 7.02 (dd, *J* = 12.1, 8.4 Hz, 1H), 2.56 (s, 3H), 1.77 (qd, *J* = 7.5, 1.5 Hz, 2H), 1.35 (d, *J* = 1.1 Hz, 6H), 0.65 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.0 (C_q), 165.0 (d, $^1J_{C\text{-}F}$ = 257 Hz, C_q), 136.0 (d, $^2J_{C\text{-}F}$ = 12 Hz, C_q), 133.0 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 129.1 (d, $^3J_{C\text{-}F}$ = 8 Hz, CH), 128.6 (d, $^3J_{C\text{-}F}$ = 11 Hz, CH), 116.4 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 38.1 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 34.0 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_2), 27.6 (d, $^4J_{C\text{-}F}$ = 3 Hz, CH_3), 26.5 (CH_3), 9.3 (CH_3).

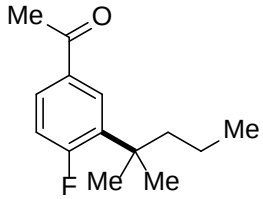
^{19}F-NMR (282 MHz, $CDCl_3$): δ = –101.6 (s).

IR (neat): $\tilde{\nu}$ = 2965, 2877, 1683, 1604, 1491, 1355, 1252, 1094, 822 cm^{-1}.

MS (EI) *m/z* (relative intensity) 208 (7) $[M]^+$, 179 (100), 151 (65), 136 (10).

HR-MS (EI): *m/z* calcd for $C_{13}H_{17}FO^+$ $[M]^+$ 208.1258, found 208.1266.

Synthesis of 1-[4-Fluoro-3-(2-methylpentan-2-yl)phenyl]ethan-1-one (189ac)



The general procedure **C** was followed using substrate **188a** (152 mg, 0.50 mmol) and bromide **50c** (248 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-pentane/ether 40:1) yielded **189ac** (55 mg, 49%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.79 (ddd, *J* = 8.4, 4.5, 2.3 Hz, 1H), 7.03 (dd, *J* = 12.1, 8.4 Hz, 1H), 2.57 (s, 3H), 1.75–1.67 (m, 2H), 1.37 (d, *J* = 1.1 Hz, 6H), 1.08–0.96 (m, 2H), 0.82 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.0 (C_q), 164.9 (d, $^1J_{C\text{-}F}$ = 257 Hz, C_q), 136.3 (d, $^2J_{C\text{-}F}$ = 12 Hz, C_q), 133.0 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 128.9 (d, $^3J_{C\text{-}F}$ = 8 Hz, CH), 128.5 (d, $^3J_{C\text{-}F}$ = 11 Hz, CH), 116.3 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 44.0 (d, $^3J_{C\text{-}F}$ = 4 Hz, C_q), 37.9 (d, $^4J_{C\text{-}F}$ = 3 Hz, CH_2), 28.0 (d, $^4J_{C\text{-}F}$ = 3 Hz, CH_3), 26.5 (CH_3), 18.3 (CH_2), 14.6 (CH_3).

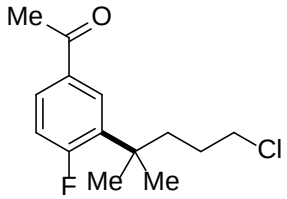
^{19}F NMR (282 MHz, $CDCl_3$): –101.6 (s).

IR (neat): $\tilde{\nu}$ = 2958, 2931, 1683, 1583, 1490, 1355, 1247, 1097, 958 cm^{-1}.

MS (EI) *m/z* (relative intensity) 222 (5) $[M]^+$, 179 (100), 151 (56), 115 (6).

HR-MS (ESI): *m/z* calcd for $C_{14}H_{20}FO^+$ $[M+H]^+$ 223.1493, found 223.1493.

Synthesis of 1-[3-(5-Chloro-2-methylpentan-2-yl)-4-fluorophenyl]ethan-1-one (189ah)



The general procedure **C** was followed using substrate **188a** (152 mg, 0.50 mmol) and bromide **50h** (299 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-pentane/ether 40:1) yielded **189ah** (64 mg, 50%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.81 (ddd, *J* =

8.4, 4.5, 2.3 Hz, 1H), 7.06 (dd, *J* = 12.1, 8.4 Hz, 1H), 3.44 (t, *J* = 6.6 Hz, 2H), 2.58 (s, 3H), 1.92–1.85 (m, 2H), 1.56–1.44 (m, 2H), 1.40 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7 (C_q), 164.7 (d, $^1J_{C\text{-}F}$ = 257 Hz, C_q), 135.3 (d, $^2J_{C\text{-}F}$ = 12 Hz, C_q), 133.1 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 128.8 (d, $^3J_{C\text{-}F}$ = 11 Hz, CH), 128.8 (d, $^3J_{C\text{-}F}$ = 8 Hz, CH), 116.5 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 45.3 (CH_2), 38.7 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_2), 37.4 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 28.5 (CH_2), 28.0 (d, $^4J_{C\text{-}F}$ = 3 Hz, CH_3), 26.4 (CH_3).

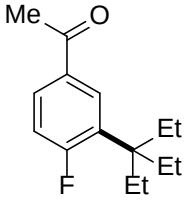
^{19}F NMR (282 MHz, $CDCl_3$): δ = –101.7 (s).

IR (neat): $\tilde{\nu}$ = 2961, 2874, 1682, 1581, 1477, 1258, 1090, 822 cm^{-1}.

MS (EI) *m/z* (relative intensity) 258/256 (1/3) $[M]^+$, 179 (100), 151 (48), 115 (5).

HR-MS (ESI): *m/z* calcd for $C_{14}H_{19}FClO^+$ $[M+H]^+$ 257.1103, found 257.1103.

Synthesis of 1-[3-(3-Ethylpentan-3-yl)-4-fluorophenyl]ethan-1-one (189ae)



The general procedure **C** was followed using substrate **188a** (152 mg, 0.50 mmol) and bromide **50e** (269 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-pentane/ether 40:1) yielded **189ae** (40 mg, 34%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.78 (ddd, *J* = 8.4, 4.5, 2.3 Hz, 1H), 7.02 (dd, *J* = 12.5, 8.4 Hz, 1H), 2.57 (s, 3H), 1.78 (qd, *J* = 7.4, 0.9 Hz, 6H), 0.64 (t, *J* = 7.4 Hz, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.9 (C_q), 164.7 (d, $^1J_{C\text{-}F}$ = 257 Hz, C_q), 134.2 (d, $^2J_{C\text{-}F}$ = 11 Hz, C_q), 132.8 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 130.5 (d, $^3J_{C\text{-}F}$ = 8 Hz, CH), 128.4 (d, $^3J_{C\text{-}F}$ = 11 Hz, CH), 116.3 (d, $^2J_{C\text{-}F}$ = 27 Hz, CH), 44.4 (d, $^3J_{C\text{-}F}$ = 4 Hz, C_q), 26.8 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_2), 26.6 (CH_3), 8.3 (CH_3).

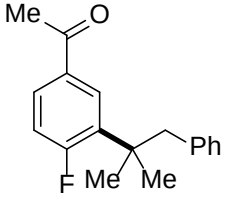
^{19}F NMR (282 MHz, $CDCl_3$): δ = –101.7 (s).

IR (neat): $\tilde{\nu}$ = 2965, 2878, 1684, 1581, 1469, 1355, 1250, 1093, 829 cm^{-1}.

MS (EI) *m/z* (relative intensity) 237 (32) $[M]^+$, 207 (52), 165 (100), 151 (77).

HR-MS (ESI): *m/z* calcd for $C_{15}H_{22}FO^+$ $[M+H]^+$ 237.1649 found 237.1649.

Synthesis of 1-[4-Fluoro-3-(2-methyl-1-phenylpropan-2-yl)phenyl]ethan-1-one (189aj)



The general procedure **C** was followed using substrate **188a** (152 mg, 0.50 mmol) and bromide **50j** (320 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-pentane/ether 40:1) yielded **189aj** (48 mg, 36%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (ddd, *J* = 8.4, 4.6, 2.3 Hz, 1H), 7.68 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.19–7.05 (m, 4H), 6.92–6.81 (m, 2H), 3.04 (s, 2H), 2.49 (s, 3H), 1.40 (d, *J* = 1.1 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7 (C_q), 164.8 (d, $^1J_{C\text{-}F}$ = 256 Hz, C_q), 138.3 (C_q), 135.6 (d, $^2J_{C\text{-}F}$ = 12 Hz, C_q), 133.1 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 130.0 (CH), 129.0 (d, $^3J_{C\text{-}F}$ = 8 Hz, CH), 128.7 (d, $^3J_{C\text{-}F}$ = 11 Hz, CH), 127.5 (CH), 125.9 (CH), 116.3 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 47.2 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_2), 38.8 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 27.6 (d, $^4J_{C\text{-}F}$ = 3 Hz, CH_3), 26.4 (CH_3).

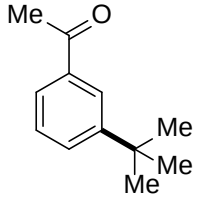
^{19}F NMR (282 MHz, $CDCl_3$): δ = –101.0 (s).

IR (neat): $\tilde{\nu}$ = 2966, 2926, 1683, 1581, 1399, 1243, 1089, 823 cm^{-1}.

MS (EI) *m/z* (relative intensity) 270 (84) $[M]^+$, 255 (58), 179 (47), 151 (14).

HR-MS (EI): *m/z* calcd for $C_{18}H_{20}FO^+$ $[M+H]^+$ 271.1493 found 271.1493.

Synthesis of 1-[(3-(*tert*-Butyl)phenyl]ethan-1-one (189ba)



The general procedure **C** was followed using substrate **188b** (143 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **189ba** (48 mg, 54%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (dd, *J* = 2.1, 1.7 Hz, 1H), 7.74 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 7.59 (ddd, *J* = 7.8, 2.1, 1.1 Hz, 1H), 7.38 (dd, *J* = 7.8, 7.8 Hz, 1H), 2.59 (s, 3H), 1.33 (s, 9H).

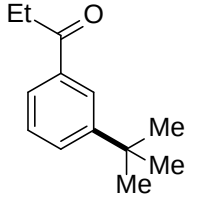
^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.5 (C_q), 151.7 (C_q), 137.0 (C_q), 130.2 (CH), 128.3 (CH), 125.8 (CH), 124.9 (CH), 34.8 (C_q), 31.2 (CH_3), 26.7 (CH_3).

IR (neat): $\tilde{\nu}$ = 2962, 2869, 1682, 1581, 1460, 1353, 1283, 967, 795 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 176 (21) $[M]^+$, 161 (100), 133 (23), 115 (8).

HR-MS (EI): *m*/*z* calcd for $C_{12}H_{16}O^+$ $[M]^+$ 176.1196, found 176.1203.

Synthesis of 1-[3-(*tert*-Butyl)phenyl]propan-1-one (189ca)



The general procedure **C** was followed using substrate **188c** (150 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-pentane/ether 40:1) yielded **189ca** (52 mg, 55%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (dd, *J* = 2.1, 2.0 Hz, 1H), 7.77 (ddd, *J* = 7.7, 2.0, 1.2 Hz, 1H), 7.59 (ddd, *J* = 7.8, 2.1, 1.2 Hz, 1H), 7.38 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.01 (q, *J* = 7.2 Hz, 2H), 1.35 (s, 9H), 1.23 (t, *J* = 7.2 Hz, 3H).

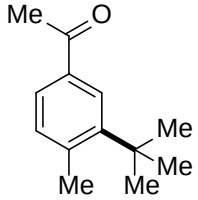
^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.1 (C_q), 151.5 (C_q), 136.7 (C_q), 129.9 (CH), 128.2 (CH), 125.3 (CH), 124.6 (CH), 34.8 (C_q), 31.9 (CH_2), 31.3 (CH_3), 8.37 (CH_3).

IR (neat): $\tilde{\nu}$ = 2963, 2872, 1685, 1581, 1459, 1364, 1209, 850 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 190 (6) $[M]^+$, 161 (100), 133 (13), 115 (10).

HR-MS (EI): *m*/*z* calcd for $C_{13}H_{19}O^+$ $[M+H]^+$ 191.1430, found 191.1436.

Synthesis of 1-[3-(*tert*-Butyl)-4-methylphenyl]ethan-1-one (189da)



The general procedure **C** was followed using substrate **188d** (150 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol) in 1,4-dioxane (2 mL). After 20 h, purification by column chromatography (*n*-pentane/ether 40:1) yielded **189da** (45 mg, 47%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 1.9 Hz, 1H), 7.65 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 2.58 (s, 3H), 2.56 (s, 3H), 1.42 (s, 9H).

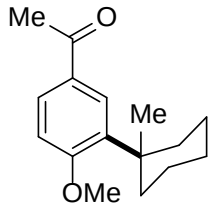
^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.1 (C_q), 148.2 (C_q), 142.3 (C_q), 134.8 (C_q), 132.8 (CH), 125.9 (CH), 125.8 (CH), 36.0 (C_q), 30.8 (CH_3), 26.6 (CH_3), 23.5 (CH_3).

IR (neat): $\tilde{\nu}$ = 2960, 2873, 1679, 1402, 1353, 1265, 1197, 1091, 816 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 190 (26) $[M]^+$, 175 (100), 147 (21), 115 (13).

HR-MS (EI): *m*/*z* calcd for $C_{13}H_{18}O^+$ $[M]^+$ 190.1352, found 190.1366.

Synthesis of 1-[4-Methoxy-3-(1-methylcyclohexyl)phenyl]ethan-1-one (189eb)



The general procedure **C** was followed using substrate **188e** (158 mg, 0.50 mmol) and bromide **50b** (266 mg, 1.50 mmol) in 1,4-dioxane (2 mL). After 20 h, purification by column chromatography (*n*-pentane/ether 40:1) yielded **189eb** (58 mg, 47%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 2.3 Hz, 1H), 7.80 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 3.86 (s, 3H), 2.54 (s, 3H), 2.13–2.03 (m, 2H), 1.77–1.65 (m, 2H), 1.60–1.30 (m, 6H), 1.27 (s, 3H).

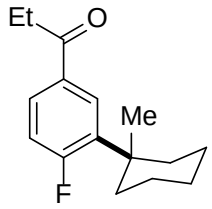
^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3 (C_q), 162.7 (C_q), 137.6 (C_q), 129.8 (C_q), 128.3 (CH), 128.3 (CH), 111.0 (CH), 55.2 (CH_3), 38.3 (C_q), 36.8 (CH_2), 26.6 (CH_2), 26.3 (CH_3), 25.1 (CH_3), 22.7 (CH_2).

IR (neat): $\tilde{\nu}$ = 2923, 2853, 1673, 1593, 1492, 1353, 1244, 1022, 812 cm^{-1}.

MS (EI) *m/z* (relative intensity) 246 (76) $[M]^+$, 231 (70), 163 (80), 115 (15).

HR-MS (EI): *m/z* calcd for $C_{16}H_{22}O_2^+$ $[M]^+$ 246.1614, found 246.1618.

Synthesis of 1-[4-Fluoro-3-(1-methylcyclohexyl)phenyl]propan-1-one (189fb)



The general procedure **C** was followed using substrate **188f** (159 mg, 0.50 mmol) and bromide **50b** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-pentane/ether 100:1) yielded **189fb** (77 mg, 62%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.78 (ddd, *J* = 8.5, 4.5, 2.3 Hz, 1H), 7.02 (dd, *J* = 12.3, 8.4 Hz, 1H), 2.96 (q, *J* = 7.2 Hz, 2H), 2.11–2.02 (m, 2H), 1.71–1.52 (m, 4H), 1.50–1.34 (m, 4H), 1.28 (d, *J* = 1.0 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.5 (C_q), 165.0 (d, $^1J_{C\text{-}F}$ = 257 Hz, C_q), 136.7 (d, $^2J_{C\text{-}F}$ = 11 Hz, C_q), 132.8 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 128.8 (d, $^3J_{C\text{-}F}$ = 8 Hz, CH), 127.7 (d, $^3J_{C\text{-}F}$ = 11 Hz, CH), 116.7 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 37.9 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 37.0 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_2), 31.6 (CH_2), 26.5 (CH_3), 26.2 (CH_2), 22.5 (CH_2), 8.2 (CH_3).

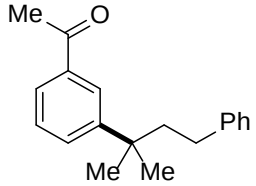
^{19}F NMR (282 MHz, $CDCl_3$): δ = –101.4 (s).

IR (neat): $\tilde{\nu}$ = 2927, 2858, 1685, 1581, 1488, 1451, 1228, 1182, 799 cm^{-1}.

MS (EI) *m/z* (relative intensity) 248 (8) $[M]^+$, 219 (100), 163 (22), 133 (12).

HR-MS (EI): *m/z* calcd for $C_{16}H_{21}FO^+$ $[M]^+$ 248.1571, found 248.1579.

Synthesis of 1-[3-(2-Methyl-4-phenylbutan-2-yl)phenyl]ethan-1-one (189bi)



The general procedure **C** was followed using substrate **188b** (143 mg, 0.50 mmol) and bromide **50i** (320 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-pentane/ether 40:1) yielded **189bi** (47 mg, 35%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04–8.01 (m, 1H), 7.83–7.78 (m, 1H), 7.65–7.60 (m, 1H), 7.48–7.42 (m, 1H), 7.28–7.06 (m, 5H), 2.64 (s, 3H), 2.40–2.32 (m, 2H), 2.01–1.94 (m, 2H), 1.43(s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.2 (C_q), 149.6 (C_q), 142.5 (C_q), 137.0 (C_q), 130.6 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 125.9 (CH), 125.5 (CH), 125.3 (CH), 46.5 (CH_2), 38.1 (C_q), 31.3 (CH_2), 28.9 (CH_3), 26.8 (CH_3).

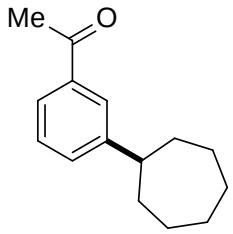
IR (neat): $\tilde{\nu}$ = 3026, 2930, 1682, 1495, 1355, 1263, 797, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity) 266 (24) $[M]^+$, 161 (100), 133 (33), 105 (25).

HR-MS (ESI): *m/z* calcd for $C_{19}H_{23}O^+$ $[M+H]^+$ 267.1743, found 267.1749.

7.3.3 Analytical Data for the Products of the Ruthenium(II)-Catalyzed Direct *meta*-Selective Alkylation with Secondary Alkyl Bromides

Synthesis of 1-(3-Cycloheptylphenyl)ethan-1-one (206be)



The general procedure **C** was followed using substrate **188b** (143 mg, 0.50 mmol) and bromide **44e** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206be** (63 mg, 58%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.72 (ddd, *J* = 7.2, 1.8, 1.8 Hz, 1H), 7.40– 7.30 (m, 2H), 2.76–2.66 (m, 1H), 2.57 (s, 3H), 1.90–1.53 (m, 12H).

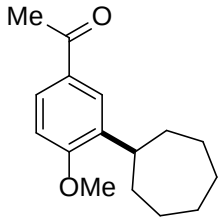
^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.2 (C_q), 150.3 (C_q), 137.1 (C_q), 131.5 (CH), 128.4 (CH), 126.3 (CH), 125.7 (CH), 47.0 (CH), 36.7 (CH_2), 27.9 (CH_2), 27.2 (CH_2), 26.7 (CH_3).

IR (neat): $\tilde{\nu}$ =3352, 2921, 2853, 1681, 1582, 1434, 1356, 1270, 793 cm^{-1}.

MS (EI) *m/z* (relative intensity) 216 (60) $[M]^+$, 201 (100), 146 (36), 131 (64).

HR-MS (EI): *m/z* calcd for $C_{15}H_{20}O^+$ $[M]^+$ 216.1514, found 216.1510.

Synthesis of 1-(3-Cycloheptyl-4-methoxyphenyl)ethan-1-one (206ee)



The general procedure **C** was followed, using substrate **188e** (158 mg, 0.50 mmol) and bromide **44e** (266 mg, 1.50 mmol) in 1,4-dioxane (2 mL). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206ee** (65 mg, 53%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 2.3 Hz, 1H), 7.76 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 3.86 (s, 3H), 3.12–3.02 (m, 1H), 2.52 (s, 3H), 1.90–1.53 (m, 12H).

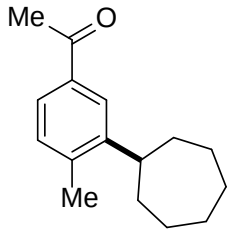
^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.1 (C_q), 160.2 (C_q), 138.2 (C_q), 130.0 (C_q), 127.9 (CH), 127.1 (CH), 109.5 (CH), 55.5 (CH_3), 38.9 (CH), 35.2 (CH_2), 27.8 (CH_2), 27.4 (CH_2), 26.2 (CH_3).

IR (neat): $\tilde{\nu}$ = 2919, 2852, 1672, 1596, 1495, 1354, 1241, 1025, 810 cm^{-1}.

MS (EI) *m/z* (relative intensity) 246 (95) $[M]^+$, 231 (100), 161 (57), 147 (26).

HR-MS (EI): *m/z* calcd for $C_{16}H_{22}O_2^+$ $[M]^+$ 246.1614, found 246.1630.

Synthesis of 1-(3-Cycloheptyl-4-methylphenyl)ethan-1-one (206de)



The general procedure **C** was followed using substrate **188d** (150 mg, 0.50 mmol) and bromide **44e** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206de** (59 mg, 51%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 1.9 Hz, 1H), 7.62 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 2.92–2.82 (m, 1H), 2.55 (s, 3H), 2.35 (s, 3H), 1.88–1.76 (m, 4H), 1.74–1.49 (m, 8H).

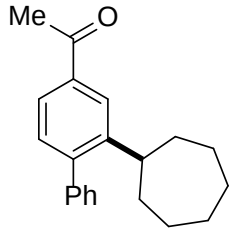
^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.1 (C_q), 148.3 (C_q), 140.4 (C_q), 135.4 (C_q), 130.2 (CH), 125.5 (CH), 125.4 (CH), 41.7 (CH), 35.9 (CH_2), 27.6 (CH_2), 27.5 (CH_2), 26.5 (CH_3), 19.7 (CH_3).

IR (neat): $\tilde{\nu}$ = 2920, 2853, 1678, 1602, 1444, 1353, 1242, 813 cm^{-1}.

MS (EI) *m/z* (relative intensity) 230 (42) $[M]^+$, 215 (100), 145 (40), 115 (18).

HR-MS (EI): *m/z* calcd for $C_{16}H_{22}O^+$ $[M]^+$ 230.1665, found 230.1673.

Synthesis of 1-(2-Cycloheptyl-[1,1'-biphenyl]-4-yl)ethan-1-one (206ge)



The general procedure **C** was followed using substrate **188g** (181 mg, 0.50 mmol) and bromide **44e** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206ge** (88 mg, 60%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 1.9 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.46–7.32 (m, 3H), 7.28–7.22 (m, 3H), 2.88–2.75 (m, 1H), 2.62 (s, 3H), 1.84–1.63 (m, 6H), 1.56–1.47 (m, 4H), 1.37–1.24 (m, 2H).

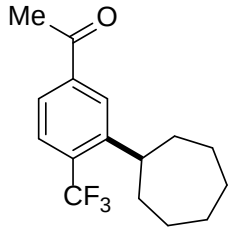
^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9 (C_q), 147.9 (C_q), 145.2 (C_q), 140.9 (C_q), 136.4 (C_q), 130.0 (CH), 128.8 (CH), 127.9 (CH), 127.1 (CH), 126.3 (CH), 125.1 (CH), 41.6 (CH), 36.8 (CH_2), 27.6 (CH_2), 27.3 (CH_2), 26.7 (CH_3).

IR (neat): $\tilde{\nu}$ = 2919, 2852, 1681, 1597, 1458, 1353, 1277, 1008, 827 cm^{-1}.

MS (EI) *m/z* (relative intensity) 292 (85) $[M]^+$, 221 (46), 165 (41), 115 (6).

HR-MS (ESI): *m/z* calcd for $C_{21}H_{25}O^+$ $[M+H]^+$ 293.1900, found 293.1905.

Synthesis of 1-(3-Cycloheptyl-4-(trifluoromethyl)phenyl)ethan-1-one (206he)



The general procedure **C** was followed using substrate **188h** (177 mg, 0.50 mmol) and bromide **44e** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206he** (62 mg, 44%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 1.8 Hz, 1H), 7.75 (ddd, *J* = 8.2, 1.8, 0.9 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 3.14–3.02 (m, 1H), 2.60 (s, 3H), 1.86–1.52 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.2 (C_q), 149.7 (q, $^3J_{C\text{-}F}$ = 2 Hz, C_q), 139.7 (C_q), 130.7 (q, $^2J_{C\text{-}F}$ = 30 Hz, C_q), 127.7 (CH), 125.9 (q, $^3J_{C\text{-}F}$ = 6 Hz, CH), 125.3 (CH), 124.1 (q, $^1J_{C\text{-}F}$ = 274 Hz, C_q), 41.7 (q, $^4J_{C\text{-}F}$ = 2 Hz, CH), 36.9 (CH_2), 27.6 (CH_2), 27.5 (CH_2), 26.8 (CH_3).

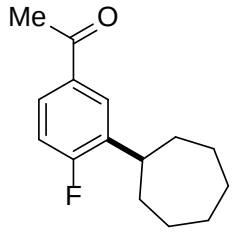
^{19}F NMR (282 MHz, $CDCl_3$): δ = –59.5 (s).

IR (neat): $\tilde{\nu}$ = 2925, 2856, 1692, 1574, 1415, 1310, 1238, 1154, 1035, 829 cm^{-1}.

MS (EI) *m/z* (relative intensity) 284 (35) $[M]^+$, 214 (55), 199 (100), 151 (23).

HR-MS (ESI): *m/z* calcd for $C_{16}H_{19}F_3NaO^+$ $[M+Na]^+$ 307.1280, found 307.1286.

Synthesis of 1-(3-Cycloheptyl-4-fluorophenyl)ethan-1-one (206ae)



The general procedure **C** was followed using substrate **188a** (152 mg, 0.50 mmol) and bromide **44e** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 80:1) yielded **206ae** (75 mg, 64%) as a colorless oil.

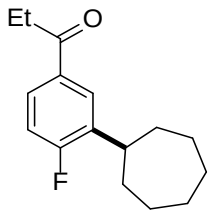
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 7.2, 2.3 Hz, 1H), 7.73 (ddd, *J* = 8.5, 4.9, 2.3 Hz, 1H), 7.02 (dd, *J* = 9.9, 8.5 Hz, 1H), 3.06–2.92 (m, 1H), 2.55 (s, 3H), 1.92–1.50 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.9 (C_q), 163.1 (d, $^1J_{C\text{-}F}$ = 253 Hz, C_q), 136.8 (d, $^2J_{C\text{-}F}$ = 16 Hz, C_q), 133.5 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 128.6 (d, $^3J_{C\text{-}F}$ = 7 Hz, CH), 127.6 (d, $^3J_{C\text{-}F}$ = 10 Hz, CH), 115.4 (d, $^2J_{C\text{-}F}$ = 24 Hz, CH), 39.5 (d, $^3J_{C\text{-}F}$ = 1 Hz, CH), 35.2 (d, $^4J_{C\text{-}F}$ = 1 Hz, CH_2), 27.7 (CH_2), 27.2 (CH_2), 26.5 (CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –111.1 (s).

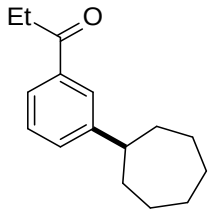
IR (neat): $\tilde{\nu}$ = 2921, 2855, 1682, 1585, 1492, 1416, 1355, 1243, 1170, 1104, 819 cm^{-1}.
MS (EI) *m/z* (relative intensity) 234 (41) $[M]^+$, 219 (100), 164 (40), 149 (70).
HR-MS (EI): *m/z* calcd for $C_{15}H_{19}FO^+$ $[M]^+$ 234.1414, found 234.1416.

Synthesis of 1-(3-Cycloheptyl-4-fluorophenyl)propan-1-one (206fe)



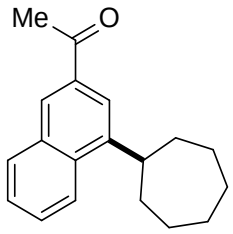
The general procedure **C** was followed using substrate **188f** (159 mg, 0.50 mmol) and bromide **44e** (266 mg, 1.50 mmol) in 1,4-dioxane (2 mL). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206fe** (77 mg, 62%) as a colorless oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.74 (ddd, *J* = 8.5, 5.0, 2.3 Hz, 1H), 7.01 (dd, *J* = 9.9, 8.5 Hz, 1H), 3.04–2.90 (m, 3H), 1.92–1.47 (m, 12H), 1.19 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.4 (C_q), 162.8 (d, $^1J_{C\text{-}F}$ = 253 Hz, C_q), 136.6 (d, $^2J_{C\text{-}F}$ = 16 Hz, C_q), 133.2 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 128.3 (d, $^3J_{C\text{-}F}$ = 7 Hz, CH), 127.3 (d, $^3J_{C\text{-}F}$ = 8 Hz, CH), 115.3 (d, $^2J_{C\text{-}F}$ = 24 Hz, CH), 39.5 (CH), 35.3 (CH_2), 31.7 (CH_2), 27.8 (CH_2), 27.3 (CH_2), 8.4 (CH_3).
^{19}F NMR (282 MHz, $CDCl_3$): δ = –111.3 (s).
IR (neat): $\tilde{\nu}$ = 2923, 2855, 1685, 1586, 1492, 1350, 1237, 1150, 797 cm^{-1}.
MS (EI) *m/z* (relative intensity) 248 (6) $[M]^+$, 219 (100), 149 (10), 109 (13).
HR-MS (ESI): *m/z* calcd for $C_{16}H_{22}FO^+$ $[M+H]^+$ 249.1649, found 249.1654.

Synthesis of 1-(3-Cycloheptylphenyl)propan-1-one (206ce)



The general procedure **C** was followed using substrate **188c** (150 mg, 0.50 mmol) and bromide **44e** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206ce** (61 mg, 53%) as a colorless oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.75 (ddd, *J* = 7.2, 1.8, 1.8 Hz, 1H), 7.40– 7.30 (m, 2H), 2.99 (q, *J* = 7.2 Hz, 2H), 2.76–2.66 (m, 1H), 1.90–1.53 (m, 12H), 1.22 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.0 (C_q), 150.3 (C_q), 137.0 (C_q), 131.3 (CH), 128.4 (CH), 126.2 (CH), 125.3 (CH), 47.0 (CH), 36.7 (CH_2), 31.8 (CH_2), 27.9 (CH_2), 27.2 (CH_2), 8.4 (CH_3).
IR (neat): $\tilde{\nu}$ = 3391, 2921, 2853, 1683, 1582, 1482, 1348, 1233, 1161, 781 cm^{-1}.
MS (EI) *m/z* (relative intensity) 230 (5) $[M]^+$, 201 (100), 179 (13), 131 (8).
HR-MS (EI): *m/z* calcd for $C_{16}H_{23}O^+$ $[M+H]^+$ 231.1743, found 231.1749.

Synthesis of 1-(4-Cycloheptylnaphthalen-2-yl)ethan-1-one (206ie)



The general procedure **C** was followed using substrate **188i** (168 mg, 0.50 mmol) and bromide **44e** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206ie** (67 mg, 50%) as a colorless oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32–8.26 (m, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 8.00–7.92 (m, 2H), 7.63 (tt, *J* = 8.3, 1.4 Hz, 1H), 7.58–7.49 (m, 1H), 3.54–3.43 (m, 1H), 2.72 (s, 3H), 2.14–1.99 (m, 2H), 1.96–1.58 (m, 10H).

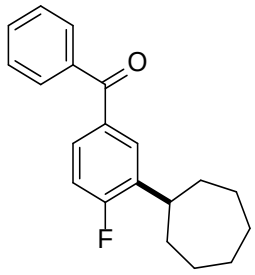
^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.2 (C_q), 146.5 (C_q), 134.0 (C_q), 133.4 (C_q), 133.0 (C_q), 130.5 (CH), 128.5 (CH), 128.1 (CH), 126.0 (CH), 123.4 (CH), 120.3 (CH), 41.2 (CH), 36.3 (CH_2), 27.9 (CH_2), 27.7 (CH_2), 26.6 (CH_3).

IR (neat): $\tilde{\nu}$ = 2919, 2852, 1674, 1457, 1397, 1260, 1194, 885 cm^{-1}.

MS (EI) *m/z* (relative intensity) 266 (100) $[M]^+$, 209 (16), 183 (28), 153 (40).

HR-MS (EI): *m/z* calcd for $C_{19}H_{22}O^+$ $[M]^+$ 266.1665, found 266.1661.

Synthesis of (3-Cycloheptyl-4-fluorophenyl)(phenyl)methanone (206je)



The general procedure **C** was followed using substrate **188j** (183 mg, 0.50 mmol) and bromide **44e** (266 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206je** (92 mg, 62%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79–7.75 (m, 3H), 7.62–7.56 (m, 2H), 7.52–7.46 (m, 2H), 7.07 (dd, *J* = 9.9, 8.4 Hz, 1H), 3.10–2.99 (m, 1H), 1.89–1.55 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.8 (C_q), 162.9 (d, $^1J_{C\text{-}F}$ = 253 Hz, C_q), 137.8 (C_q), 136.8 (d, $^2J_{C\text{-}F}$ = 16 Hz, C_q), 133.7 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 132.4 (CH), 130.5 (d, $^3J_{C\text{-}F}$ = 7 Hz, CH), 130.0 (CH), 129.8 (d, $^3J_{C\text{-}F}$ = 10 Hz, CH), 128.3 (CH), 115.2 (d, $^2J_{C\text{-}F}$ = 24 Hz, CH), 39.4 (CH), 35.2 (CH_2), 27.6 (CH_2), 27.2 (CH_2).

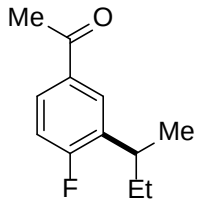
^{19}F NMR (282 MHz, $CDCl_3$): δ = –111.8 (s).

IR (neat): $\tilde{\nu}$ = 2924, 2855, 1657, 1599, 1490, 1446, 1281, 1092, 713 cm^{-1}.

MS (EI) *m/z* (relative intensity) 296 (92) $[M]^+$, 226 (68), 149 (53), 105 (100).

HR-MS (ESI): *m/z* calcd for $C_{20}H_{22}FO^+$ $[M+H]^+$ 297.1649, found 297.1654.

Synthesis of 1-[3-(*sec*-Butyl)-4-fluorophenyl]ethan-1-one (206af)



The general procedure **C** was followed using substrate **188a** (152 mg, 0.50 mmol) and bromide **44f** (103 mg, 0.75 mmol). After 20 h, purification by column chromatography (*n*-pentane/Et_2O 50:1) yielded **206af** (42 mg, 43%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 7.2, 2.3 Hz, 1H), 7.75 (ddd, *J* = 8.5, 5.0, 2.3 Hz, 1H), 7.03 (dd, *J* = 9.8, 8.5 Hz, 1H), 2.98 (dt, *J* = 7.1, 7.1 Hz, 1H), 2.55 (s, 3H), 1.69–1.58 (m, 2H), 1.24 (d, 3H, *J* = 7.2 Hz), 0.82 (t, 3H, *J* = 7.3 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7 (C_q), 163.9 (d, $^1J_{C\text{-}F}$ = 253 Hz, C_q), 134.5 (d, $^2J_{C\text{-}F}$ = 16 Hz, C_q), 133.4 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 128.6 (d, $^3J_{C\text{-}F}$ = 7 Hz, CH), 128.0 (d, $^3J_{C\text{-}F}$ = 10 Hz, CH), 115.4 (d, $^2J_{C\text{-}F}$ = 24 Hz, CH), 34.3 (d, $^3J_{C\text{-}F}$ = 1 Hz, CH), 29.8 (CH_2), 26.5 (CH_3), 20.4 (CH_3), 12.1 (CH_3).

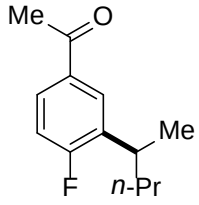
^{19}F NMR (282 MHz, $CDCl_3$): δ = –111.0 (s).

IR (neat): $\tilde{\nu}$ = 2964, 2976, 1683, 1606, 1586, 1493, 1357, 1283 ,1176, 1101, 820 cm^{-1}.

MS (EI) *m/z* (relative intensity) 194 (34) $[M]^+$, 179 (67), 165 (100), 151 (20).

HR-MS (EI): *m/z* calcd for $C_{12}H_{15}FO^+$ $[M]^+$ 194.1101, found 194.1102.

Synthesis of 1-[4-Fluoro-3-(pentan-2-yl)phenyl]ethan-1-one (206ag)



The general procedure **C** was followed using siubstrate **188a** (152 mg, 0.50 mmol) and bromide **44g** (113 mg, 0.75 mmol). After 20 h, purification by column chromatography (*n*-pentane/Et_2O 50:1) yielded **206ag** (48 mg, 46%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 7.2, 2.3 Hz, 1H), 7.75 (ddd, *J* = 8.5, 4.9, 2.3 Hz, 1H), 7.03 (dd, *J* = 9.8, 8.5 Hz, 1H), 3.08 (dt, *J* = 7.1, 7.1 Hz, 1H), 2.56 (s, 3H), 1.61–1.51 (m, 2H), 1.33–1.11 (m, 5H), 0.91–0.82 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7 (C_q), 163.8 (d, $^1J_{C\text{-}F}$ = 253 Hz, C_q), 134.8 (d, $^2J_{C\text{-}F}$ = 16 Hz, C_q), 133.5 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 128.8 (d, $^3J_{C\text{-}F}$ = 7 Hz, CH), 128.2 (d, $^3J_{C\text{-}F}$ = 10 Hz, CH), 115.5 (d, $^2J_{C\text{-}F}$ = 24 Hz, CH), 39.2 (d, $^4J_{C\text{-}F}$ = 1 Hz, CH_2), 32.4 (d, $^3J_{C\text{-}F}$ = 1 Hz, CH), 26.6 (CH_3), 20.8 (CH_3), 20.8 (CH_2), 14.0 (CH_3).

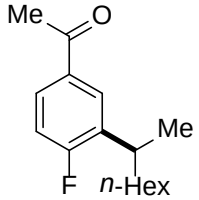
^{19}F NMR (282 MHz, $CDCl_3$): δ = –111.1(s).

IR (neat): $\tilde{\nu}$ = 2960, 2873, 1683, 1493, 1356, 1284, 1175, 1102, 820 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 208 (28) $[M]^+$, 193 (50), 165 (100), 151 (15).

HR-MS (EI): *m*/*z* calcd for $C_{13}H_{17}FO^+$ $[M]^+$ 208.1258, found 208.1264.

Synthesis of 1-[4-Fluoro-3-(octan-2-yl)phenyl]ethan-1-one (206ad)



The general procedure **C** was followed using substrate **188a** (152 mg, 0.50 mmol) and bromide **44d** (145 mg, 0.75 mmol). After 20 h, purification by column chromatography (*n*-pentane/Et_2O 40:1) yielded **206ad** (50 mg, 40%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 7.2, 2.3 Hz, 1H), 7.76 (ddd, *J* = 8.5, 4.9, 2.3 Hz, 1H), 7.04 (dd, *J* = 9.8, 8.5 Hz, 1H), 3.06 (dt, *J* = 7.1, 7.1 Hz, 1H), 2.57 (s, 3H), 1.64–1.52 (m, 2H), 1.32–1.12 (m, 11H), 0.90–0.79 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7 (C_q), 164.1 (d, $^1J_{C\text{-}F}$ = 253 Hz, C_q), 134.9 (d, $^2J_{C\text{-}F}$ = 16 Hz, C_q), 133.5 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 128.6 (d, $^3J_{C\text{-}F}$ = 7 Hz, CH), 128.0 (d, $^3J_{C\text{-}F}$ = 10 Hz, CH), 115.4 (d, $^2J_{C\text{-}F}$ = 24 Hz, CH), 37.0 (d, $^4J_{C\text{-}F}$ = 1 Hz, CH_2), 32.7 (d, $^3J_{C\text{-}F}$ = 1 Hz, CH), 31.8 (CH_2), 29.3 (CH_2), 27.6 (CH_2), 26.6 (CH_3), 22.7 (CH_2), 20.9 (CH_3), 14.1 (CH_3).

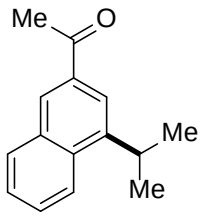
^{19}F NMR (282 MHz, $CDCl_3$): δ = –111.0(s).

IR (neat): $\tilde{\nu}$ = 2959, 2856, 1684, 1586, 1493 ,1458, 1356, 1284, 1106, 819 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 250 (23) $[M]^+$, 235 (35), 165 (100), 151 (22).

HR-MS (ESI): *m*/*z* calcd for $C_{16}H_{24}FO^+$ $[M+H]^+$ 251.1806, found 251.1811.

Synthesis of 1-(4-Isopropylnaphthalen-2-yl)ethan-1-one (206ih)



The general procedure **C** was followed using substrate **188i** (168 mg, 0.50 mmol) and bromide **44h** (185 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206ih** (82 mg, 77%) as a white solid.

M. p.: 60–62 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31–8.27 (m, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 1.7 Hz, 1H), 7.98–7.92 (m, 1H), 7.62 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 3.73 (hept, *J* = 6.9 Hz, 1H), 2.71 (s, 3H), 1.42 (d, *J* = 6.9 Hz, 6H).

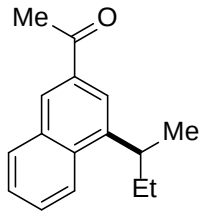
^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.2 (C_q), 145.3 (C_q), 134.0 (C_q), 133.6 (C_q), 132.9 (C_q), 130.4 (CH), 128.7 (CH), 128.2 (CH), 126.0 (CH), 123.3 (CH), 119.4 (CH), 28.7 (CH), 26.6 (CH_3), 23.4 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3063, 2960, 1671, 1397, 1271, 1229, 1194, 1142, 882 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 212 (58) $[M]^+$, 197 (100), 152 (25), 115 (8).

HR-MS (EI): *m*/*z* calcd for $C_{15}H_{16}O^+$ $[M]^+$ 212.1196, found 212.1209.

Synthesis of 1-[4-(*sec*-Butyl)naphthalen-2-yl]ethan-1-one (206if)



The general procedure **C** was followed using substrate **188i** (168 mg, 0.50 mmol) and bromide **44f** (206 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206if** (84 mg, 74%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 1.4 Hz, 1H), 8.13 (ddd, *J* = 8.5, 1.3, 0.7 Hz, 1H), 8.00–7.90 (m, 2H), 7.61 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 3.50 (dt, *J* = 6.9 Hz, 1H), 2.72 (s, 3H), 1.97–1.80 (m, 1H), 1.80–1.63 (m, 1H), 1.39 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H).

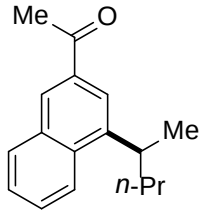
^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.2 (C_q), 144.5 (C_q), 134.1 (C_q), 134.0 (C_q), 133.0 (C_q), 130.4 (CH), 128.6 (CH), 128.1 (CH), 126.0 (CH), 123.3 (CH), 120.1 (CH), 35.5 (CH), 30.5 (CH_2), 26.6 (CH_3), 21.1 (CH_3), 12.3 (CH_3).

IR (neat): $\tilde{\nu}$ = 3056, 2961, 1674, 1622, 1425, 1396, 1278, 1174, 885 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 226 (52) $[M]^+$, 197 (100), 153 (525), 127 (10).

HR-MS (EI): *m*/*z* calcd for $C_{16}H_{18}O^+$ $[M]^+$ 226.1352, found 226.1365.

Synthesis of 1-[4-(Pentan-2-yl)naphthalen-2-yl]ethan-1-one (206ig)



The general procedure **C** was followed using substrate **188i** (168 mg, 0.50 mmol) and bromide **44g** (227 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206ig** (93 mg, 77%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (dd, *J* = 1.7, 0.8 Hz, 1H), 8.17–8.10 (m, 1H), 7.98–7.92 (m, 2H), 7.61 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 3.59 (dt, *J* = 6.9 Hz, 1H), 2.72 (s, 3H), 1.90–1.77 (m, 1H), 1.77–1.61 (m, 1H), 1.46–1.24 (m, 5H), 0.90 (t, *J* = 7.3 Hz, 3H).

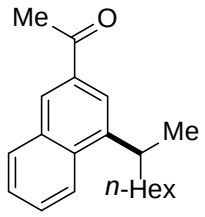
^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.2 (C_q), 144.8 (C_q), 134.0 (C_q), 134.0 (C_q), 133.4 (C_q), 130.0 (CH), 128.6 (CH), 128.1 (CH), 126.0 (CH), 123.3 (CH), 120.1 (CH), 40.0 (CH_2), 33.6 (CH), 26.6 (CH_3), 21.6 (CH_3), 20.9 (CH_2), 14.3 (CH_3).

IR (neat): $\tilde{\nu}$ = 2957, 2928, 1675, 1623, 1453, 1375, 1277, 1194, 885 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 240 (53) $[M]^+$, 197 (100), 153 (26), 127 (11).

HR-MS (EI): *m*/*z* calcd for $C_{17}H_{20}O^+$ $[M]^+$ 240.1509, found 240.1523.

Synthesis of 1-(4-(Octan-2-yl)naphthalen-2-yl)ethan-1-one (206id)

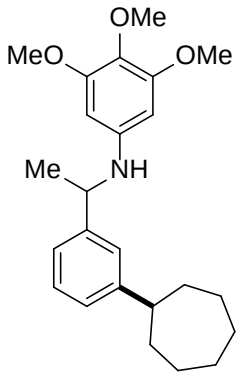


The general procedure **C** was followed using substrate **188i** (168 mg, 0.50 mmol) and bromide **44d** (290 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206id** (86 mg, 61%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31–8.27 (m, 1H), 8.17–8.10 (m, 1H), 7.99–7.92 (m, 2H), 7.61 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 3.57 (dt, *J* = 6.9 Hz, 1H), 2.72 (s, 3H), 1.91–1.75 (m, 1H), 1.75–1.63 (m, 1H), 1.39 (d, *J* = 6.9 Hz, 3H), 1.33–1.10 (m, 8H), 0.92–0.72 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.2 (C_q), 144.8 (C_q), 134.0 (C_q), 134.0 (C_q), 133.0 (C_q), 130.4 (CH), 128.6 (CH), 128.1 (CH), 126.0 (CH), 123.2 (CH), 120.1 (CH), 37.8 (CH_2), 33.9 (CH), 31.8 (CH_2), 29.5 (CH_2), 27.8 (CH_2), 26.6 (CH_3), 22.7 (CH_2), 21.6 (CH_3), 14.1 (CH_3).
IR (neat): $\tilde{\nu}$ = 2956, 2954, 1677, 1454, 1352, 1276, 1195, 885 cm^{-1}.
MS (EI) *m*/*z* (relative intensity) 282 (50) $[M]^+$, 191 (100), 153 (22), 127 (5).
HR-MS (EI): *m*/*z* calcd for $C_{20}H_{26}O^+$ $[M]^+$ 282.1978, found 282.1994.

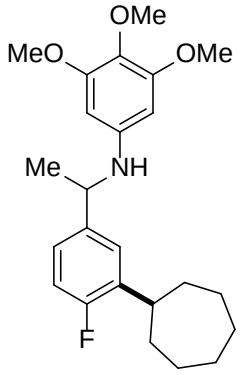
Synthesis of *N*-[1-(3-Cycloheptylphenyl)ethy]-3,4,5-trimethoxyaniline (207be)



The general procedure **C** was followed using $[RuCl_2(p\text{-cymene})]_2$ (30.6 mg, 5.0 mol %), 1-AdCO_2H (54.1 mg, 30 mol %), substrate **188b** (285.3 mg, 1.0 mmol) and bromide **44e** (531 mg, 3.0 mmol). After 20 h, a solution of $ZnCl_2$ in THF (1.7 M, 1.0 mmol), $NaBH_3CN$ (126.0 mg, 2.0 mmol) and MeOH (3 mL) were successively added to the reaction mixture at ambient temperature. The reaction mixture was stirred at ambient temperature for an additional 16 h and then distributed between 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*. Purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **207be** (200.0 mg, 52%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.19 (m, 1H), 7.19–7.14 (m, 2H), 7.05 (dt, *J* = 7.5, 1.5 Hz, 1H), 5.76 (s, 2H), 4.38 (q, *J* = 6.7 Hz, 1H), 3.71 (s, 3H), 3.67 (s, 6H), 2.68–2.61 (m, 1H), 1.90–1.84 (m, 2H), 1.83–1.72 (m, 2H), 1.72–1.52 (m, 8H), 1.50 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.4 (C_q), 150.2 (C_q), 145.1 (C_q), 144.0 (C_q), 129.7 (C_q), 128.5 (CH), 125.1 (CH), 124.3 (CH), 122.7 (CH), 91.0 (CH), 60.9 (CH), 55.6 (CH_3), 54.4 (CH_3), 47.0 (CH), 36.9 (CH_2), 36.7 (CH_2), 27.9 (CH_2), 27.9 (CH_2), 27.2 (CH_2), 27.2 (CH_2), 24.7 (CH_3).
IR (neat): $\tilde{\nu}$ = 3356, 2996, 2850, 1599, 1507, 1447, 1205, 1126, 1008, 812 cm^{-1}.
MS (EI) *m*/*z* (relative intensity) 383 (92) $[M]^+$, 201 (100), 168 (78), 119 (15).
HR-MS (EI): *m*/*z* calcd for $C_{24}H_{33}NO_3^+$ $[M]^+$ 383.2455, found 383.2469.

Synthesis of *N*-[1-(3-Cycloheptyl-4-fluorophenyl)ethyl]-3,4,5-trimethoxyaniline (207ae)



The general procedure **C** was followed using $[RuCl_2(p\text{-cymene})]_2$ (30.6 mg, 5.0 mol %), 1-AdCO_2H (54.1 mg, 30 mol %), substrate **188a** (303.3 mg, 1.0 mmol) and bromide **44e** (531 mg, 3.0 mmol). After 20 h, a solution of $ZnCl_2$ in THF (1.7 M, 1.0 mmol), $NaBH_3CN$ (126.0 mg, 2.0 mmol) and MeOH (3 mL) were successively added to the reaction mixture at ambient temperature. The reaction mixture was stirred at ambient temperature for an additional 16 h and then distributed between 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*. Purification by column chromatography (*n*-hexane/EtOAc 10:1) yielded **207ae** (245.0 mg, 61%) as a yellow solid.

M. p.: 60–62 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (dd, *J* = 7.1, 2.3 Hz, 1H), 7.11 (ddd, *J* = 8.4, 4.9, 2.3 Hz, 1H), 6.91 (dd, *J* = 10.1, 8.4 Hz, 1H), 5.73 (s, 2H), 4.36 (q, *J* = 6.6 Hz, 1H), 4.01–3.78 (m, 1H), 3.70 (s, 3H), 3.67 (s, 6H), 3.01–2.90 (m, 1H), 1.89–1.49 (m, 12H), 1.46 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8 (d, $^1J_{C\text{-}F}$ = 243 Hz, C_q), 153.5 (C_q), 144.0 (C_q), 140.8 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 136.3 (d, $^2J_{C\text{-}F}$ = 16 Hz, C_q), 129.8 (C_q), 125.4 (d, $^3J_{C\text{-}F}$ = 6 Hz, CH), 123.8 (d, $^3J_{C\text{-}F}$ = 9 Hz, CH), 115.4 (d, $^2J_{C\text{-}F}$ = 24 Hz, CH), 91.0 (CH), 61.0 (CH), 55.7 (CH_3), 53.9 (CH_3), 39.7 (d, $^3J_{C\text{-}F}$ = 1 Hz, CH), 35.5 (CH_2), 35.3 (CH_2), 27.8 (CH_2), 27.8 (CH_2), 27.3 (CH_2), 27.3 (CH_2), 24.9 (CH_3).

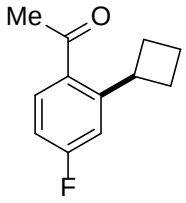
^{19}F-NMR (282 MHz, $CDCl_3$): δ = –121.7 (s).

IR (ATR): $\tilde{\nu}$ = 3378, 2921, 2851, 1607, 1507, 1411, 1232, 1008, 792 cm^{-1}.

MS (EI) *m/z* (relative intensity) 401 (85) [M$^+$], 219 (100), 168 (68), 119 (13).

HR-MS (EI): *m/z* calcd for $C_{24}H_{32}FNO_3^+$ [M]$^+$ 401.2361, found 401.2371.

Synthesis of 1-(2-Cyclobutyl-4-fluorophenyl)ethan-1-one (206aj)



The general procedure **C** was followed using substrate **188a** (152 mg, 0.50 mmol) and bromide **44j** (203 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206aj** (48 mg, 50%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (dd, *J* = 8.5, 5.8 Hz, 1H), 7.08 (ddd, *J* = 10.6, 2.6, 0.8 Hz, 1H), 6.88 (dddd, *J* = 8.5, 7.8, 2.6, 0.6 Hz, 1H), 4.13–3.93 (m, 1H), 2.51 (s, 3H), 2.39–2.23 (m, 2H), 2.07–1.88 (m, 3H), 1.85–1.69 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.7 (C_q), 164.2 (d, $^1J_{C\text{-}F}$ = 253 Hz, C_q), 149.3 (d, $^3J_{C\text{-}F}$ = 8 Hz, C_q), 134.0 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 130.9 (d, $^3J_{C\text{-}F}$ = 9 Hz, CH), 114.6 (d, $^2J_{C\text{-}F}$ = 22 Hz, CH), 112.2 (d, $^2J_{C\text{-}F}$ = 22 Hz, CH), 38.2 (d, $^4J_{C\text{-}F}$ = 1 Hz, CH), 29.8 (CH_3), 29.3 (CH_2), 18.0 (CH_2).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –108.0 (s).

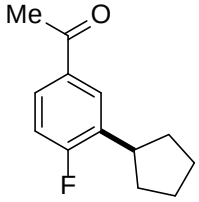
IR (neat): $\tilde{\nu}$ = 2923, 2855, 1675, 1579, 1495, 1442, 1355, 1242, 1130, 1026, 815 cm^{-1}.

MS (EI) *m/z* (relative intensity) 192 (8) [M]$^+$, 163 (100), 149 (55), 121 (20).

HR-MS (EI): *m/z* calcd for $C_{12}H_{13}FO^+$ [M]$^+$ 192.0945, found 192.0947.

The spectral data were in accordance with those reported in the literature.[118]

Synthesis of 1-(3-Cyclopentyl-4-fluorophenyl)ethan-1-one (206ak)



The general procedure **C** was followed using substrate **188a** (152 mg, 0.50 mmol) and bromide **44k** (224 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206ak** (55 mg, 53%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 7.3, 2.4 Hz, 1H), 7.73 (ddd, *J* = 8.5, 4.9, 2.4 Hz, 1H), 7.04 (dd, *J* = 9.9, 8.5 Hz, 1H), 3.31–3.17 (m, 1H), 2.57 (s, 3H), 2.14–1.97 (m, 2H), 1.87–1.76 (m, 2H), 1.73–1.57 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.6 (C_q), 164.0 (d, $^1J_{C\text{-}F}$ = 253 Hz, C_q), 133.4 (d, $^2J_{C\text{-}F}$ = 15 Hz, C_q), 133.3 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 128.5 (d, $^3J_{C\text{-}F}$ = 7 Hz, CH), 128.0 (d, $^3J_{C\text{-}F}$ = 10 Hz, CH), 115.3 (d, $^2J_{C\text{-}F}$ = 24 Hz, CH), 38.8 (d, $^3J_{C\text{-}F}$ = 1 Hz, CH), 33.1 (d, $^4J_{C\text{-}F}$ = 1 Hz, CH_2), 26.5 (CH_3), 25.4 (CH_2).

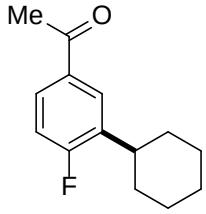
^{19}F NMR (282 MHz, $CDCl_3$): δ = –109.7 (s).

IR (neat): $\tilde{\nu}$ = 3348, 2954, 2871, 1682, 1585, 1492, 1356, 1250, 1112, 822 cm^{-1}.

MS (EI) *m/z* (relative intensity) 206 (23) [M]$^+$, 191 (100), 163 (16), 149 (20).

HR-MS (EI): *m/z* calcd for $C_{13}H_{15}FO^+$ [M]$^+$ 206.1101, found 206.1112.

Synthesis of 1-(3-Cyclohexyl-4-fluorophenyl)ethan-1-one (206ac)



The general procedure **C** was followed using substrate **188a** (152 mg, 0.50 mmol) and bromide **44c** (245 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206ac** (30 mg, 27%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.75 (ddd, *J* = 8.5, 5.0, 2.3 Hz, 1H), 7.03 (dd, *J* = 9.9, 8.5 Hz, 1H), 2.90–2.80 (m, 1H), 2.55 (s, 3H), 1.88–1.69 (m, 5H), 1.54–1.20 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7 (C_q), 163.6 (d, $^{1}J_{C\text{-}F}$ = 253 Hz, C_q), 134.9 (d, $^{2}J_{C\text{-}F}$ = 16 Hz, C_q), 133.4 (d, $^{4}J_{C\text{-}F}$ = 3 Hz, C_q), 128.3 (d, $^{3}J_{C\text{-}F}$ = 7 Hz, CH), 128.0 (d, $^{3}J_{C\text{-}F}$ = 10 Hz, CH), 115.3 (d, $^{2}J_{C\text{-}F}$ = 24 Hz, CH), 37.2 (d, $^{3}J_{C\text{-}F}$ = 2 Hz, CH), 32.9 (CH_2), 26.8 (CH_2), 26.6 (CH_3), 26.1 (CH_2).

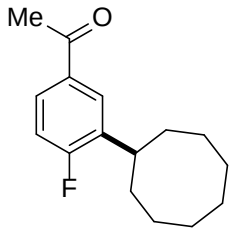
^{19}F NMR (282 MHz, $CDCl_3$): δ = –111.6 (s).

IR (neat): $\tilde{\nu}$ = 2926, 2852, 1682, 1586, 1492, 1355, 1254, 1107, 820 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 220 (23) $[M]^+$, 205 (100), 149 (23), 109 (12).

HR-MS (EI): *m*/*z* calcd for $C_{14}H_{17}FO^+$ $[M]^+$ 220.1258, found 220.1262.

1-(3-Cyclooctyl-4-fluorophenyl)ethan-1-one (206al)



The general procedure **C** was followed using substrate **188a**(152 mg, 0.50 mmol) and bromide **44l** (287 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206al** (75 mg, 60%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (dd, *J* = 7.3, 2.4 Hz, 1H), 7.75 (ddd, *J* = 8.5, 4.9, 2.4 Hz, 1H), 7.03 (dd, *J* = 9.9, 8.5 Hz, 1H), 3.18–3.06 (m, 1H), 2.57 (s, 3H), 1.83–1.76 (m, 6H), 1.70–1.56 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7 (C_q), 163.1 (d, $^{1}J_{C\text{-}F}$ = 253 Hz, C_q), 137.2 (d, $^{2}J_{C\text{-}F}$ = 16 Hz, C_q), 133.3 (d, $^{4}J_{C\text{-}F}$ = 3 Hz, C_q), 128.8 (d, $^{3}J_{C\text{-}F}$ = 7 Hz, CH), 127.8 (d, $^{3}J_{C\text{-}F}$ = 10 Hz, CH), 115.4 (d, $^{2}J_{C\text{-}F}$ = 24 Hz, CH), 37.3 (CH), 33.4 (CH_2), 26.7 (CH_2), 26.6 (CH_3), 26.4 (CH_2), 26.0 (CH_2).

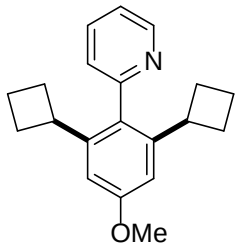
^{19}F NMR (282 MHz, $CDCl_3$): δ = –110.6 (s).

IR (neat): $\tilde{\nu}$ = 2919, 2852, 1682, 1585, 1492, 1355, 1283, 1108, 822 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 248 (47) $[M]^+$, 233 (38), 164 (69), 149 (100).

HR-MS (EI): *m*/*z* calcd for $C_{16}H_{22}FO^+$ $[M+H]^+$ 249.1649, found 249.1654.

Synthesis of 2-(2,6-Dicyclobutyl-4-methoxyphenyl)pyridine (208bj)

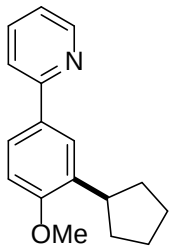


The general procedure **A** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **44j** (202 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **208bj** (75 mg, 51%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.66 (ddd, *J* = 7.7, 7.7, 1.9 Hz, 1H), 7.20 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 7.14 (ddd, *J* = 7.8,

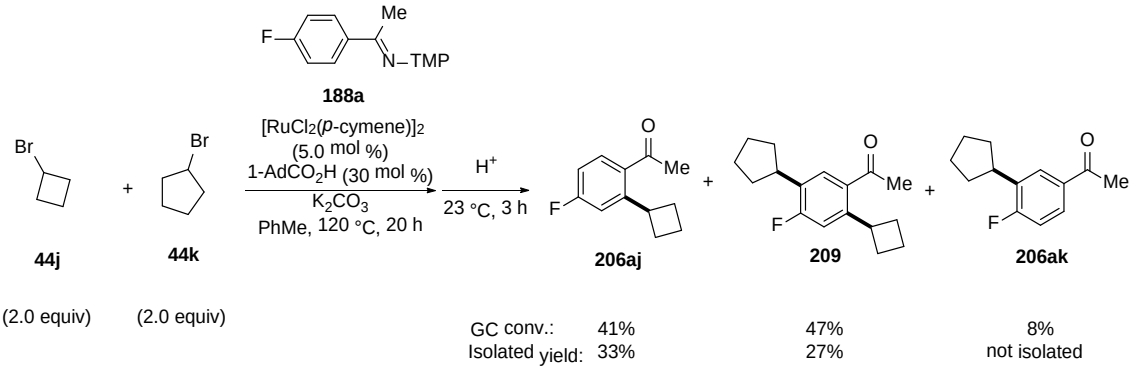
7.8, 1.1 Hz, 1H), 6.76 (s, 2H), 3.86 (s, 3H), 3.38–3.22 (m, 2H), 2.07–1.86 (m, 4H), 1.81–1.57 (m, 8H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4 (C_q), 159.3 (C_q), 149.0 (CH), 144.9 (C_q), 135.5 (CH), 131.1 (C_q), 125.4 (CH), 121.2 (CH), 109.0 (CH), 55.2 (CH_3), 38.7 (CH), 30.0 (CH_2), 29.3 (CH_2), 18.0 (CH_2).
IR (neat): $\tilde{\nu}$ = 2962, 2962, 1598, 1453, 1302, 1156, 1072, 860 cm^{-1}.
MS (EI) *m*/*z* (relative intensity) 293 (58) $[M]^+$, 264 (92), 236 (100), 192 (23).
HR-MS (EI): *m*/*z* calcd for $C_{20}H_{22}NO^+$ $[M–H]^+$ 292.1696, found 292.1704.

Synthesis of 2-(3-Cyclopentyl-4-methoxyphenyl)pyridine (208bk)



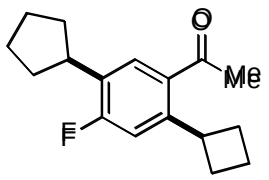
The general procedure **A** was followed using substrate **38b** (93 mg, 0.50 mmol) and bromide **44k** (224 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-hexane/EtOAc 20:1) yielded **208bk** (82 mg, 65%) as a colorless oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 4.9 Hz, 1H), 7.89 (d, *J* = 2.3 Hz, 1H), 7.77 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.72–7.59 (m, 2H), 7.13 (ddd, *J* = 6.7, 4.9, 2.1 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 3.86 (s, 3H), 3.42–3.28 (m, 1H), 2.10–1.99 (m, 2H), 1.87–1.75 (m, 2H), 1.74–1.60 (m, 4H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.3 (C_q), 157.5 (C_q), 149.3 (CH), 136.4 (CH), 134.7 (C_q), 131.6 (C_q), 125.4 (CH), 125.2 (CH), 121.1 (CH), 119.8 (CH), 110.3 (CH), 55.5 (CH_3), 39.4 (CH), 33.0 (CH_2), 25.5 (CH_2).
IR (neat): $\tilde{\nu}$ = 2950, 2867, 1587, 1462, 1242, 1122, 777, 594 cm^{-1}.
MS (EI) *m*/*z* (relative intensity) 253 (100) $[M]^+$, 212 (83), 196 (22), 167 (33).
HR-MS (EI): *m*/*z* calcd for $C_{17}H_{19}NO^+$ $[M]^+$ 253.1461, found 253.1465.

Intermolecular Competition Experiment between Secondary Alkyl Halides 44j and 44k



The general procedure **C** was followed using $[RuCl_2(p\text{-cymene})]_2$ (30.6 mg, 5.0 mol %), 1-$AdCO_2H$ (54.1 mg, 30 mol %), ketimine **188a** (304 mg, 1.0 mmol) and bromides **44j** (270 mg, 2.0 mmol), **44k** (298 mg, 2.0 mmol). After 20 h, 2 N HCl (3.0 mL) was added, and the resulting mixture was stirred at ambient temperature for additional 3 hours, then extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (*n*-hexane/EtOAc 100:1) yielded **206aj** (63 mg, 33%) and **209** (70 mg, 27%) as colorless oils. The spectral data of **206aj** were identical to those reported above.

Analytical Data for 1-(2-Cyclobutyl-5-cyclopentyl-4-fluorophenyl)ethan-1-one (209)



^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 12.0 Hz, 1H), 4.06–3.93 (m, 1H), 3.26–3.13 (m, 1H), 2.52 (s, 3H), 2.38–2.27 (m, 2H),

2.09–1.94 (m, 5H), 1.86–1.75 (m, 3H), 1.73–1.58 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.2 (C_q), 162.7 (d, $^1J_{C\text{-}F}$ = 251 Hz, C_q), 146.0 (d, $^3J_{C\text{-}F}$ = 8 Hz, C_q), 134.0 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 129.9 (d, $^2J_{C\text{-}F}$ = 15 Hz, C_q), 128.8 (d, $^3J_{C\text{-}F}$ = 7 Hz, CH), 114.4 (d, $^2J_{C\text{-}F}$ = 24 Hz, CH), 38.7 (CH), 37.8 (d, $^3J_{C\text{-}F}$ = 1 Hz, CH), 33.1 (d, $^4J_{C\text{-}F}$ = 1 Hz, CH_2), 29.9 (CH_3), 29.5 (CH_2), 29.4 (CH_2), 18.1 (CH_2).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –112.5 (s).

IR (neat): $\tilde{\nu}$ = 2940, 2853, 1584, 1460, 1232, 1120, 747, 594 cm^{-1}.

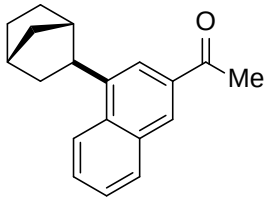
MS (EI) *m/z* (relative intensity) 260 (26) $[M]^+$, 231 (100), 217 (37), 149 (18).

HR-MS (ESI): *m/z* calcd for $C_{17}H_{22}FO^+$ $[M+H]^+$ 261.1649, found 261.1655.

Synthesis of 1-{4-(*exo*-Bicyclo[2.2.1]heptan-2-yl)naphthalen-2-yl}ethan-1-one (206im) and 1-{3-(*exo*-Bicyclo[2.2.1]heptan-2-yl)naphthalen-2-yl}ethan-1-one (206im')

The general procedure **C** was followed using substrate **188i** (168 mg, 0.50 mmol) and **44m** (263 mg, 1.50 mmol). After 20 h, purification by column chromatography (*n*-pentane/$Et_2$0 80:1) yielded **206im** (61 mg, 46%) and **206im'** (25 mg ,19%) as colorless oils.

Analytical Data:



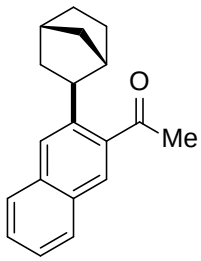
206im: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.96–7.92 (m, 2H), 7.64–7.58 (m, 1H), 7.55-7.49 (m, 1H), 3.38–3.31 (m, 1H), 2.71 (s, 3H), 2.62–2.59 (m, 1H), 2.42–2.37 (m, 1H), 2.02–1.92 (m, 1H), 1.74–1.61 (m, 4H), 1.57–1.47 (m, 1H), 1.44–1.38 (m, 1H), 1.33–1.27 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.2 (C_q), 143.7 (C_q), 134.3 (C_q), 133.8 (C_q), 133.1 (C_q), 130.3 (CH), 128.6 (CH), 128.1 (CH), 126.1 (CH), 124.3 (CH), 119.2 (CH), 43.4 (CH), 41.6 (CH), 39.4 (CH_2), 37.1 (CH), 36.6 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 26.7 (CH_3).

IR (neat): $\tilde{\nu}$ = 2950, 2938, 1670, 1623, 1353, 1275, 1277, 1094, 880 cm^{-1}.

MS (EI) *m/z* (relative intensity) 264 (100) $[M]^+$, 184 (73), 153 (64), 141 (64).

HR-MS (EI): *m/z* calcd for $C_{19}H_{20}O^+$ $[M]^+$ 264.1509, found 264.1514.



206im': ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (s, 1H), 7.80 (ddd, *J* = 8.6, 7.3, 1.2 Hz, 2H), 7.74 (s, 1H), 7.51 (ddd, *J* = 8.2, 6.9, 1.5 Hz, 1H), 7.44 (ddd, *J* = 8.2, 6.9, 1.5 Hz, 1H), 3.42–3.36 (m, 1H), 2.67 (s, 3H), 2.52–2.48 (m, 1H), 2.36–2.32 (m, 1H), 1.88–1.79 (m, 1H), 1.65–1.54 (m, 4H), 1.48–1.40 (m, 1H),1.35–1.29 (m, 1H), 1.29–1.25 (m, 1H).

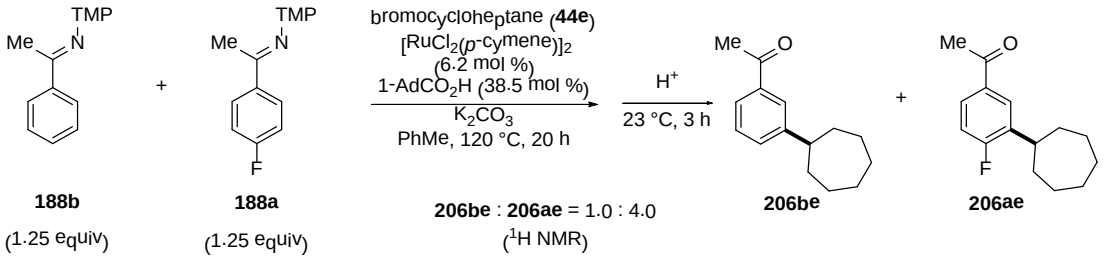
^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.2 (C_q), 142.9 (C_q), 138.1 (C_q), 134.2 (C_q), 130.4 (C_q), 138.8 (CH), 128.0 (CH), 127.6 (CH), 127.5 (CH), 125.9 (CH), 124.7 (CH), 43.5 (CH), 42.3 (CH), 39.9 (CH_2), 37.3 (CH), 36.5 (CH_2), 30.7 (CH_3), 30.4 (CH_2), 29.0 (CH_2).

IR (neat): $\tilde{\nu}$ = 2937, 2928, 1675, 1623, 1450, 1375, 1247, 1193, 775 cm^{-1}.

MS (EI) *m/z* (relative intensity) 264 (71) $[M]^+$, 195 (100), 181 (27), 152 (30).

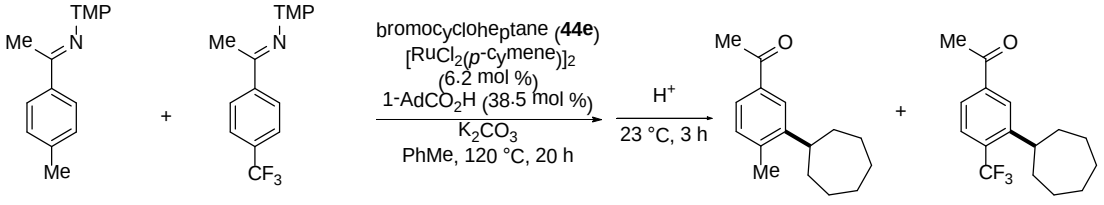
HR-MS (EI): *m/z* calcd for $C_{19}H_{20}O^+$ $[M]^+$ 264.1509, found 264.1523.

Intermolecular Competition Experiment between Ketimines 188b and 188a



The general procedure **C** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 6.2 mol %), 1-AdCO_2H (38.5 mg, 30 mol %), ketimines **188b** (143.0 mg, 0.50 mmol) and **188a** (152.0 mg, 0.50 mmol), bromide **44e** (71.0 mg, 0.4 mmol). After 20 h, HCl (3.0 mL, 2 N) was added, and the resulting mixture was stirred at ambient temperature for additional 3 h, then extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Careful ^{1}H-NMR analysis displayed a ratio of **206be**/**206ae** = 1.0 : 4.0. Their spectral data were identical to those reported above.

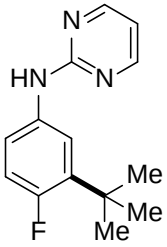
Intermolecular Competition Experiment between ketamine 188d and 188h



The general procedure **C** was followed, using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 6.2 mol %), 1-AdCO_2H (27.8 mg, 38.5 mol %), ketimines **188d** (150.0 mg, 0.50 mmol) and **188h** (177.0 mg, 0.50 mmol), bromide **44e** (71.0 mg, 0.4 mmol). After 20 h, HCl (3.0 mL, 2 N) was added, and the resulting mixture was stirred at ambient temperature for additional 3 h, then extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Careful ^{1}H NMR analysis displayed a ratio of **206de**/**206he** = 1.0 : 1.5. Their spectral data were identical to those reported above.

7.3.4 Analytical Data for the Products of the Ruthenium-Catalyzed Direct *meta*-Selective Alkylations of *N*-(Pyrimidyl-2-yl)anilines and *N*-(Pyridin-2-yl)anilines

Synthesis of *N*-[3-(*tert*-Butyl)-4-fluorophenyl]pyrimidin-2-amine (215aa)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **161a** (95 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **215aa** (81 mg, 66%) as a yellow solid.

M. p.: 129–131 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 4.8 Hz, 2H), 7.53–7.46 (m, 2H), 7.35 (dd, *J* = 7.2, 2.8 Hz, 1H), 6.96 (dd, *J* = 12.1, 8.7 Hz, 1H), 6.67 (t, *J* = 4.8 Hz, 1H), 1.37 (d, *J* = 1.0 Hz, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.3 (C_q), 158.1 (CH), 158.0 (d, $^1J_{C\text{-}F}$ = 245 Hz, C_q), 137.3 (d, $^2J_{C\text{-}F}$ = 13

Hz, C_q), 134.7 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 119.4 (d, $^3J_{C\text{-}F}$ = 6 Hz, CH), 119.2 (d, $^3J_{C\text{-}F}$ = 9 Hz, CH), 116.3 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 112.2 (CH), 34.4 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 29.9 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_3).

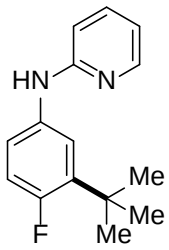
^{19}F NMR (282 MHz, $CDCl_3$): δ = –116.3 (s).

IR (ATR): $\tilde{\nu}$ = 3252, 3080, 2964, 1577, 1487, 1420, 1201, 784 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 245 (100) $[M]^+$, 230 (100), 188 (24), 160 (10).

HR-MS (EI): *m*/*z* calcd for $C_{14}H_{16}FN_3^+$ $[M]^+$ 245.1323, found 245.1331.

Synthesis of *N*-[3-(*tert*-Butyl)-4-fluorophenyl]pyridin-2-amine (217)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **213b** (94 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **217** (44 mg, 36%) as a yellow solid.

M. p.: 131–133 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.44 (ddd, *J* = 8.5, 7.2, 1.9 Hz, 1H), 7.18–7.12 (m, 2H), 6.98–6.91 (m, 1H), 6.82 (s, 1H), 6.72 (ddd, *J* = 8.5, 8.5, 0.9 Hz, 1H), 6.68 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 1.36 (d, *J* = 1.1 Hz, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.2 (d, $^1J_{C\text{-}F}$ = 246 Hz, C_q), 156.8 (C_q), 148.3 (CH), 137.9 (d, $^2J_{C\text{-}F}$ = 13 Hz, C_q), 137.7 (CH), 135.8 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 121.0 (d, $^3J_{C\text{-}F}$ = 6 Hz, CH), 120.5 (d, $^3J_{C\text{-}F}$ = 9 Hz, CH), 116.7 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 114.6 (CH), 107.5 (CH), 34.3 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 29.8 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_3).

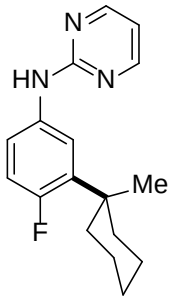
^{19}F NMR (282 MHz, $CDCl_3$): δ = –115.8 (s).

IR (ATR): $\tilde{\nu}$ = 3225, 3199, 2980, 1604, 1578, 1492, 1437, 1205, 786 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 244 (100) $[M]^+$, 229 (72), 188 (32), 100 (15).

HR-MS (EI): *m*/*z* calcd for $C_{15}H_{16}FN_2^+$ $[M–H]^+$ 243.1292, found 243.1304.

Synthesis of *N*-[4-Fluoro-3-(1-methylcyclohexyl)phenyl]pyrimidin-2-amine (215ab)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **161a** (95 mg, 0.50 mmol) and bromide **50b** (266 mg, 1.50 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **215ab** (85 mg, 60%) as a yellow solid.

M. p.: 95–97 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 4.8 Hz, 2H), 7.51–7.44 (m, 2H), 7.39 (dd, *J* = 7.2, 2.7 Hz, 1H), 6.95 (dd, *J* = 12.5, 8.7 Hz, 1H), 6.67 (t, *J* = 4.8 Hz, 1H), 2.11–1.96 (m, 2H), 1.69–1.36 (m, 8H), 1.28 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.3 (C_q), 157.9 (CH), 157.9 (d, $^1J_{C\text{-}F}$ = 244 Hz, C_q), 136.5 (d, $^2J_{C\text{-}F}$ = 12 Hz, C_q), 134.7 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 120.4 (d, $^3J_{C\text{-}F}$ = 6 Hz, CH), 118.9 (d, $^3J_{C\text{-}F}$ = 9 Hz, CH), 116.6 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 112.2 (CH), 38.0 (d, $^3J_{C\text{-}F}$ = 4 Hz, C_q), 37.2 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_2), 26.9 (CH_3), 26.4 (CH_2), 22.7 (CH_2).

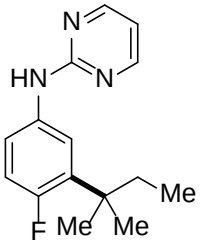
^{19}F NMR (282 MHz, $CDCl_3$): δ = –115.6 (s).

IR (ATR): $\tilde{\nu}$ = 3256, 3060, 2926, 1578, 1494, 1388, 1185, 820 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 285 (100) $[M]^+$, 270 (28), 230 (30), 202 (23).

HR-MS (EI): *m/z* calcd for $C_{17}H_{20}FN_3^+$ [M]$^+$ 285.1636, found 285.1645.

Synthesis of *N*-[4-Fluoro-3-(*tert*-pentyl)phenyl]pyrimidin-2-amine (215ad)



The general procedure **A** was followed using [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **161a** (95 mg, 0.50 mmol) and bromide **50d** (227 mg, 1.50 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **215ad** (75 mg, 58%) as a yellow solid.

M. p.: 94–96 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 4.8 Hz, 2H), 7.70 (s, 1H), 7.62–7.48 (m, 1H), 7.30 (dd, *J* = 7.2, 2.6 Hz, 1H), 6.96 (dd, *J* = 12.1, 8.7 Hz, 1H), 6.69 (t, *J* = 4.8 Hz, 1H), 1.77 (q, *J* = 7.5 Hz, 2H), 1.34 (s, 6H), 0.71 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.3 (C_q), 157.9 (CH), 157.6 (d, $^1J_{C\text{-}F}$ = 244 Hz, C_q), 135.7 (d, $^2J_{C\text{-}F}$ = 13 Hz, C_q), 134.7 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 120.4 (d, $^3J_{C\text{-}F}$ = 6 Hz, CH), 119.0 (d, $^3J_{C\text{-}F}$ = 9 Hz, CH), 116.2 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 112.2 (CH), 38.1 (d, $^3J_{C\text{-}F}$ = 4 Hz, C_q), 34.2 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_2), 27.7 (d, $^4J_{C\text{-}F}$ = 3 Hz, CH_3), 9.5 (CH_3).

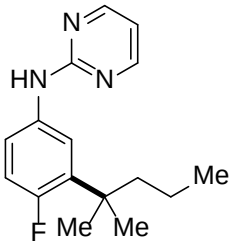
^{19}F NMR (282 MHz, $CDCl_3$): δ = –116.4 (s).

IR (ATR): $\tilde{\nu}$ = 3249, 3039, 2929, 1581, 1444, 1384, 1203, 995, 798 cm^{-1}.

MS (EI) *m/z* (relative intensity) 259 (44) [M]$^+$, 244 (12), 230 (100), 188 (13).

HR-MS (EI): *m/z* calcd for $C_{15}H_{18}FN_3^+$ [M]$^+$ 259.1479, found 259.1491.

Synthesis of *N*-[4-Fluoro-3-(2-methylpentan-2-yl)phenyl]pyrimidin-2-amine (215ac)



The general procedure **A** was followed using [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **161a** (95 mg, 0.50 mmol) and bromide **50c** (248 mg, 1.50 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **215ac** (73 mg, 53%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 4.8 Hz, 2H), 7.65 (s, 1H), 7.52 (ddd, *J* = 8.7, 4.0, 2.8 Hz, 1H), 7.29 (dd, *J* = 7.2, 2.8 Hz, 1H), 6.94 (dd, *J* = 12.1, 8.7 Hz, 1H), 6.67 (t, *J* = 4.8 Hz, 1H), 1.74–1.62 (m, 2H), 1.33 (d, *J* = 1.1 Hz, 6H), 1.15–1.00 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4 (C_q), 158.0 (CH), 157.8 (d, $^1J_{C\text{-}F}$ = 244 Hz, C_q), 136.1 (d, $^2J_{C\text{-}F}$ = 13 Hz, C_q), 134.8 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 120.3 (d, $^3J_{C\text{-}F}$ = 6 Hz, CH), 119.1 (d, $^3J_{C\text{-}F}$ = 9 Hz, CH), 116.3 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 112.2 (CH), 44.2 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_2), 37.8 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 28.2 (d, $^4J_{C\text{-}F}$ = 3 Hz, CH_3), 18.3 (CH_2), 14.7 (CH_3).

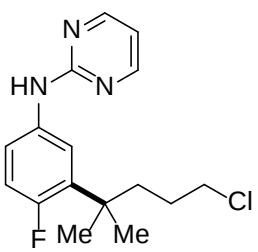
^{19}F NMR (282 MHz, $CDCl_3$): δ = –116.3 (s).

IR (neat): $\tilde{\nu}$ = 3270, 3104, 2956, 1580, 1489, 1446, 1205, 992, 783 cm^{-1}.

MS (EI) *m/z* (relative intensity) 273 (42) [M]$^+$, 230 (100), 188 (12), 160 (5).

HR-MS (EI): *m/z* calcd for $C_{16}H_{20}FN_3^+$ [M]$^+$ 273.1636, found 273.1635.

Synthesis of *N*-[3-(5-Chloro-2-methylpentan-2-yl)-4-fluorophenyl]pyrimidin-2-amine (215ah)



The general procedure **A** was followed using [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **161a** (95 mg, 0.50 mmol) and bromide **50h** (300 mg, 1.50 mmol). After 16 h, purification by

column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **215ah** (99 mg, 64%) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 4.8 Hz, 2H), 7.55–7.43 (m, 2H), 7.33 (dd, *J* = 7.2, 2.8 Hz, 1H), 6.95 (dd, *J* = 12.1, 8.7 Hz, 1H), 6.68 (t, *J* = 4.8 Hz, 1H), 3.44 (t, *J* = 6.8 Hz, 2H), 1.90–1.79 (m, 2H), 1.62–1.50 (m, 2H), 1.36 (d, *J* = 1.0 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2 (C_q), 157.9 (CH), 157.4 (d, $^1J_{C\text{-}F}$ = 245 Hz, C_q), 135.0 (d, $^2J_{C\text{-}F}$ = 13 Hz, C_q), 134.9 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 120.0 (d, $^3J_{C\text{-}F}$ = 6 Hz, CH), 119.2 (d, $^3J_{C\text{-}F}$ = 9 Hz, CH), 116.4 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 112.3 (CH), 45.6 (CH_2), 39.1 (d, $^3J_{C\text{-}F}$ = 4 Hz, C_q), 37.5 (d, $^4J_{C\text{-}F}$ = 3 Hz, CH_2), 28.8 (CH_2), 28.2 (d, $^4J_{C\text{-}F}$ = 3 Hz, CH_3).

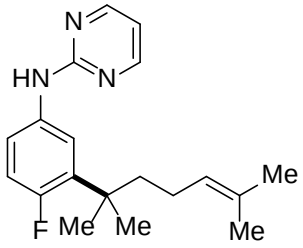
^{19}F-NMR (282 MHz, $CDCl_3$): δ = –116.6 (s).

IR (neat): $\tilde{\nu}$ = 3267, 3106, 2960, 1580, 1489, 1416, 1297, 1204, 992, 639 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 309/307 (13/38) $[M]^+$, 230 (100), 188 (14), 160 (6).

HR-MS (EI): *m*/*z* calcd for $C_{16}H_{19}{}^{35}ClFN_3{}^+$ $[M]^+$ 307.1246, found 307.1265.

Synthesis of *N*-[3-(2,6-Dimethylhept-5-en-2-yl)-4-fluorophenyl]pyrimidin-2-amine (215ag)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **161a** (94.6 mg, 0.50 mmol) and bromide **50g** (308 mg, 1.50 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **215ag** (90 mg, 57%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 4.8 Hz, 2H), 7.65–7.51 (m, 2H), 7.29 (dd, *J* = 7.2, 2.8 Hz, 1H), 6.95 (dd, *J* = 12.1, 8.7 Hz, 1H), 6.67 (t, *J* = 4.8 Hz, 1H), 5.06–5.01 (m, 1H), 1.75–1.71 (m, 4H), 1.64–1.59 (m, 3H), 1.48 (d, *J* = 1.2 Hz, 3H), 1.35 (d, *J* = 1.0 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2 (C_q), 157.9 (CH), 157.6 (d, $^1J_{C\text{-}F}$ = 244 Hz, C_q), 135.7 (d, $^2J_{C\text{-}F}$ = 13 Hz, C_q), 134.7 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 131.1 (C_q), 124.6 (CH), 120.2 (d, $^3J_{C\text{-}F}$ = 6 Hz, CH), 119.0 (d, $^3J_{C\text{-}F}$ = 9 Hz, CH), 116.3 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 112.3 (CH), 41.8 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_2), 37.8 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 28.2 (d, $^4J_{C\text{-}F}$ = 3 Hz, CH_3), 25.7 (CH_3), 24.0 (CH_2), 17.4 (CH_3).

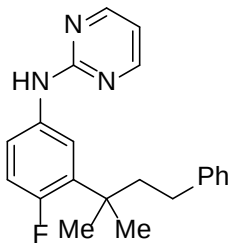
^{19}F NMR (282 MHz, $CDCl_3$): δ = –116.3 (s).

IR (neat): $\tilde{\nu}$ = 3273, 2964, 2863, 1580, 1489, 1447, 1417, 1205, 992, 783 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 313 (30) $[M]^+$, 293 (18), 231 (100), 188 (16).

HR-MS (EI): *m*/*z* calcd for $C_{19}H_{24}FN_3{}^+$ $[M]^+$ 313.1949, found 313.1967.

Synthesis of *N*-[4-Fluoro-3-(2-methyl-4-phenylbutan-2-yl)phenyl]pyrimidin-2-amine (215ai)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **161a** (95 mg, 0.50 mmol) and bromide **50i** (341 mg, 1.50 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **215ai** (93 mg, 55%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 4.8 Hz, 2H), 7.55 (ddd, *J* = 8.7, 4.0, 2.7 Hz, 1H), 7.39 (dd, *J* = 7.2, 2.8 Hz, 2H), 7.27–7.17 (m, 2H), 7.17–7.06 (m, 3H), 6.99 (dd, *J* = 12.1, 8.7 Hz, 1H), 6.68 (t, *J* = 4.8 Hz, 1H), 2.43–2.32 (m, 2H), 2.13–2.00 (m, 2H), 1.42 (d, *J* = 1.0 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2 (C_q), 157.9 (CH), 157.2 (d, $^1J_{C\text{-}F}$ = 243, C_q), 142.8 (C_q), 135.4 (d, $^2J_{C\text{-}F}$ = 13 Hz, C_q), 134.8 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 128.2 (CH), 128.1 (CH), 125.4 (CH), 120.1 (d, $^3J_{C\text{-}F}$ = 6 Hz,

CH), 119.1 (d, $^{3}J_{C\text{-}F}$ = 9 Hz, CH), 116.4 (d, $^{2}J_{C\text{-}F}$ = 24 Hz, CH), 112.3 (CH), 43.9 (d, $^{3}J_{C\text{-}F}$ = 5 Hz, C_q), 38.0 (d, $^{4}J_{C\text{-}F}$ = 3 Hz, CH_2), 31.8 (CH_2), 28.3 (d, $^{4}J_{C\text{-}F}$ = 3 Hz, CH_3).

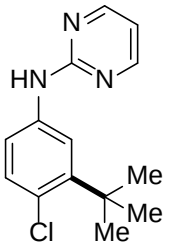
^{19}F NMR (282 MHz, $CDCl_3$): δ = –116.5 (s).

IR (neat): $\tilde{\nu}$ = 3266, 3083, 2866, 1579, 1532, 1489, 1416, 1204, 796 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 335 (56) $[M]^+$, 231 (100), 188 (16), 91 (42).

HR-MS (EI): *m*/*z* calcd for $C_{21}H_{22}FN_3^+$ $[M]^+$ 335.1792, found 335.1794.

Synthesis of *N*-[3-(*tert*-Butyl)-4-chlorophenyl]pyrimidin-2-amine (215ba)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **161b** (103 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **215ba** (76 mg, 58%) as a yellow solid.

M. p.: 110–112 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 4.7 Hz, 2H), 7.66 (s, 1H), 7.55 (dd, *J* = 8.5, 2.7 Hz, 1H), 7.52 (d, *J* = 2.7 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 6.70 (t, *J* = 4.7 Hz, 1H), 1.47 (s, 9H).

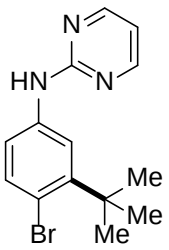
^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.0 (C_q), 157.9 (CH), 146.8 (C_q), 137.8 (C_q), 132.0 (CH), 127.0 (C_q), 119.1 (CH), 118.3 (CH), 112.5 (CH), 36.16 (C_q), 29.6 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3235, 3164, 2962, 1603, 1566, 1526, 1441, 1273, 1034, 796 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 263/261 (33/100) $[M]^+$, 248/246 (23/73), 207/205 (9/28), 117 (5/15).

HR-MS (EI): *m*/*z* calcd for $C_{14}H_{16}{}^{35}ClN_3$ $[M]^+$ 261.10327, found 261.1023.

Synthesis of *N*-[4-Bromo-3-(*tert*-butyl)phenyl]pyrimidin-2-amine (215ca)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **161c** (125 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **215ca** (70 mg, 46%) as a yellow solid.

M. p.: 103–105 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 4.8 Hz, 2H), 7.75 (s, 1H), 7.58 (dd, *J* = 2.5 Hz, 1H), 7.56–7.45 (m, 2H), 6.73 (t, *J* = 4.8 Hz, 1H), 1.52 (s, 9H).

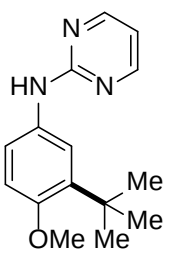
^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.0 (C_q), 158.0 (CH), 148.2 (C_q), 138.5 (C_q), 135.9 (CH), 119.4 (CH), 118.6 (CH), 115.2 (C_q), 112.6 (CH), 36.6 (C_q), 29.6 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3243, 3079, 2903, 1574, 1521, 1407, 1232, 1012, 794 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 307/305 (100/100) $[M]^+$, 292/290 (44/44), 210 (68), 170 (30).

HR-MS (EI): *m*/*z* calcd for $C_{14}H_{16}{}^{79}BrN_3^+$ $[M]^+$ 305.0522, found 305.0519.

Synthesis of *N*-[3-(*tert*-Butyl)-4-methoxyphenyl]pyrimidin-2-amine (215da)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **161d** (101 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 16 h, purification by column

chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **215da** (70 mg, 54%) as a yellow solid.

M. p.: 134–136 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 4.7 Hz, 2H), 7.51 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.35–7.25 (m, 2H), 6.88 (d, *J* = 8.6 Hz, 1H), 6.64 (t, *J* = 4.7 Hz, 1H), 3.83 (s, 3H), 1.38 (s, 9H).

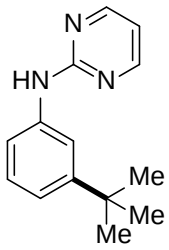
^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.7 (C_q), 157.9 (CH), 154.8 (C_q), 138.7 (C_q), 131.5 (C_q), 120.2 (CH), 119.6 (CH), 112.0 (CH), 111.7 (CH), 55.4 (CH_3), 34.9 (C_q), 29.7 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3255, 3175, 2955, 1604, 1583, 1497, 1275, 1030, 807 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 257 (100) $[M]^+$, 242 (95), 227 (25), 214 (15).

HR-MS (EI): *m*/*z* calcd for $C_{15}H_{19}N_3O^+$ 257.1523, found 257.1529.

Synthesis of *N*-[3-(*tert*-Butyl)phenyl]pyrimidin-2-amine (215ea)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **161e** (86 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **215ea** (60 mg, 53%) as a yellow solid.

M. p.: 72–74 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 4.8 Hz, 2H), 7.61–7.50 (m, 3H), 7.29 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 6.69 (t, *J* = 4.8 Hz, 1H), 1.34 (s, 9H).

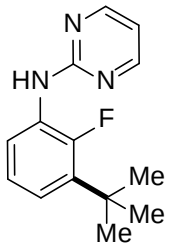
^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.3 (C_q), 157.8 (CH), 151.9 (C_q), 138.9 (C_q), 128.4 (CH), 119.9 (CH), 117.0 (CH), 117.0 (CH), 112.2 (CH), 34.7 (C_q), 31.4 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3254, 3100, 2960, 1608, 1575, 1429, 1358, 1253, 780 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 227 (80) $[M]^+$, 212 (100), 170 (25), 142 (7).

HR-MS (EI): *m*/*z* calcd for $C_{14}H_{17}N_3^+$ $[M]^+$ 227.1417, found 227.1417.

Synthesis of *N*-[3-(*tert*-Butyl)-2-fluorophenyl]pyrimidin-2-amine (215fa)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Ad-Ile-OH (44.0 mg, 30 mol %), substrate **161f** (95 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **215fa** (75 mg, 61%) as a white solid.

M. p.: 102–104 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 4.8 Hz, 2H), 8.26 (ddd, *J* = 7.8, 7.8, 1.7 Hz, 1H), 7.49 (s, 1H), 7.05 (ddd, *J* = 8.0, 8.0, 1.1 Hz, 1H), 6.94 (ddd, *J* = 7.8, 7.8, 1.7 Hz, 1H), 6.72 (t, *J* = 4.8 Hz, 1H), 1.38 (d, *J* = 1.1 Hz, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.9 (C_q), 157.8 (CH), 151.8 (d, $^1J_{C\text{-}F}$ = 245 Hz, C_q), 136.5 (d, $^2J_{C\text{-}F}$ = 11 Hz, C_q), 128.2 (d, $^2J_{C\text{-}F}$ = 12 Hz, C_q), 123.2 (d, $^3J_{C\text{-}F}$ = 4 Hz, CH), 120.1 (d, $^3J_{C\text{-}F}$ = 6 Hz, CH), 118.8 (CH), 112.7 (CH), 34.4 (d, $^3J_{C\text{-}F}$ = 2 Hz, C_q), 30.0 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_3).

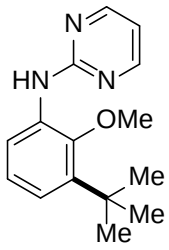
^{19}F NMR (282 MHz, $CDCl_3$): δ = –129.1 (s).

IR (ATR): $\tilde{\nu}$ = 3264, 3090, 2965, 1574, 1535, 1410, 1200, 997, 783 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 245 (100) $[M]^+$, 230 (95), 210 (55), 188 (77).

HR-MS (EI): *m*/*z* calcd for $C_{14}H_{16}FN_3^+$ $[M]^+$ 245.1323, found 245.1322.

Synthesis of *N*-[3-(*tert*-Butyl)-2-methoxyphenyl]pyrimidin-2-amine (215ga)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Ad-Ile-OH (44.0 mg, 30 mol %), substrate **161g** (101 mg, 0.50 mmol) and

bromide **50a** (206 mg, 1.50 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **215ga** (52 mg, 40%) as a white solid.

M. p.: 144–146 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 4.8 Hz, 2H), 8.07 (dd, *J* = 6.1, 3.5 Hz, 1H), 7.45 (s, 1H), 7.12–7.01 (m, 2H), 6.70 (t, *J* = 4.8 Hz, 1H), 3.80 (s, 3H), 1.41 (s, 9H).

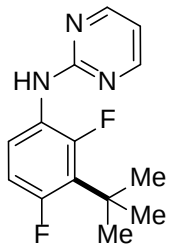
^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.4 (C_q), 158.1 (CH), 150.0 (C_q), 142.7 (C_q), 133.0 (C_q), 123.5 (CH), 121.5 (CH), 120.2 (CH), 112.4 (CH), 60.8 (CH_3), 35.0 (C_q), 30.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3240, 3077, 2958, 1599, 1528, 1420, 1270, 995, 797 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 257 (18) $[M]^+$, 242 (12), 226 (100), 210 (20).

HR-MS (EI): *m*/*z* calcd for $C_{15}H_{19}N_3O^+$ $[M]^+$ 257.1523, found 257.1527.

Synthesis of *N*-[3-(*tert*-Butyl)-2,4-difluorophenyl]pyrimidin-2-amine (215ha)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Ad-Ile-OH (44.0 mg, 30 mol %), substrate **161h** (104 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **215ha** (72 mg, 55%) as a white solid.

M. p.: 102–104 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 4.8 Hz, 2H), 8.13 (ddd, *J* = 9.1, 9.1, 5.4, 1H), 7.28 (s, 1H), 6.80 (ddd, *J* = 12.5, 9.1, 2.1 Hz, 1H), 6.71 (t, *J* = 4.8 Hz, 1H), 1.46 (dd, *J* = 2.3, 2.3 Hz, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.0 (C_q), 157.8 (CH), 156.5 (dd, $^1J_{C\text{-}F}$ = 245, $^3J_{C\text{-}F}$ = 10 Hz, C_q), 152.0 (dd, $^1J_{C\text{-}F}$ = 245, $^3J_{C\text{-}F}$ = 10 Hz, C_q), 124.7 (dd, $^2J_{C\text{-}F}$ = 13, $^4J_{C\text{-}F}$ = 2 Hz, C_q), 124.1 (dd, $^2J_{C\text{-}F}$ = 16, $^2J_{C\text{-}F}$ = 14 Hz, C_q), 119.0 (dd, $^3J_{C\text{-}F}$ = 11, $^3J_{C\text{-}F}$ = 2 Hz, CH), 112.8 (CH), 111.5 (dd, $^2J_{C\text{-}F}$ = 27, $^4J_{C\text{-}F}$ = 3 Hz, CH), 36.0 (dd, $^3J_{C\text{-}F}$ =3, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 31.1 (dd, $^4J_{C\text{-}F}$ =6, $^4J_{C\text{-}F}$ = 6 Hz, CH_3).

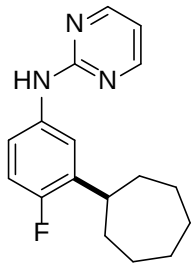
^{19}F NMR (282 MHz, $CDCl_3$): δ = –113.6 (s), –123.7 (s).

IR (ATR): $\tilde{\nu}$ = 3256, 3196, 3000, 1582, 1471, 1408, 1241, 1001, 785 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 263 (87) $[M]^+$, 248 (100), 228 (37), 206 (32).

HR-MS (EI): *m*/*z* calcd for $C_{14}H_{15}F_2N_3^+$ $[M]^+$ 263.1229, found 263.1226.

Synthesis of *N*-(3-Cycloheptyl-4-fluorophenyl)pyrimidin-2-amine (220ae)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **161a** (95 mg, 0.50 mmol) and bromide **44e** (266 mg, 1.50 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 10:1:0.1) yielded **220ae** (40 mg, 28%) as a yellow solid.

M. p.: 121–123 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 4.8 Hz, 2H), 7.79 (bs, 1H), 7.45 (ddd, *J* = 8.8, 4.4, 2.8 Hz, 1H), 7.33 (dd, *J* = 6.5, 2.8 Hz, 1H), 6.96 (dd, *J* = 9.8, 8.8 Hz, 1H), 6.68 (t, *J* = 4.8 Hz, 1H), 2.99 (tt, *J* = 10.3, 3.4 Hz, 1H), 1.96–1.89 (m, 2H), 1.85–1.76 (m, 2H), 1.73–1.53 (m, 8H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.3 (C_q), 157.9 (CH), 155.9 (C_q, $^1J_{C\text{-}F}$ = 240 Hz), 136.5 (C_q, $^2J_{C\text{-}F}$ = 16 Hz), 135.1 (C_q, $^4J_{C\text{-}F}$ = 3 Hz), 119.8 (CH, $^3J_{C\text{-}F}$ = 5 Hz), 118.7 (CH, $^3J_{C\text{-}F}$ = 8 Hz), 115.3 (CH, $^2J_{C\text{-}F}$ = 24 Hz), 112.1 (CH), 39.6 (CH), 35.3 (CH_2), 27.9 (CH_2), 27.3 (CH_2).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –125.6 (s).

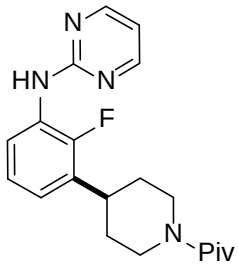
IR (ATR): $\tilde{\nu}$ = 2920, 2853, 1583, 1537, 1487, 1450, 1244, 1198, 796, 554 cm^{-1}.

MS (EI) *m/z* (relative intensity) 285 (100) $[M]^+$, 216 (47), 188 (18).

HR-MS (EI) *m/z* calcd. For $C_{17}H_{20}FN_3^+$ $[M]^+$ 285.1636, found 285.1643.

Synthesis of

1-{4-[2-Fluoro-3-(pyrimidin-2-ylamino)phenyl]piperidin-1-yl}-2,2-dimethylpropan-1-one (220fo)



The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 5.0 mol %), 1-$AdCO_2H$ (13.5 mg, 30 mol %), substrate **161f** (47 mg, 0.25 mmol) and bromide **44o** (186 mg, 0.75 mmol). After 16 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 5:1:0.1) yielded **212fo** (18 mg, 20%) as a yellow solid.

M. p.: 165–167 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 4.8 Hz, 2H), 8.29 (ddd, *J* = 8.1, 8.1, 1.5 Hz, 1H), 7.32 (s, 1H), 7.08 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H), 6.85–6.80 (m, 1H), 6.75 (t, *J* = 4.8 Hz, 1H), 4.61–4.52 (m, 2H), 3.20–3.07 (m, 1H), 2.94–2.82 (m, 2H), 1.91–1.82 (m, 2H), 1.71–1.62 (m, 2H), 1.30 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.2 (C_q), 159.9 (CH), 158.0 (C_q), 150.2 (d, $^1J_{C\text{-}F}$ = 242 Hz, C_q), 131.5 (d, $^2J_{C\text{-}F}$ = 13 Hz, C_q), 127.8 (d, $^2J_{C\text{-}F}$ = 11 Hz, C_q), 124.0 (d, $^3J_{C\text{-}F}$ = 4 Hz, CH), 120.2 (d, $^3J_{C\text{-}F}$ = 4 Hz, CH), 118.7 (CH), 113.1 (CH), 45.8 (CH_2), 38.7 (CH_2), 35.8 (d, $^3J_{C\text{-}F}$ = 3 Hz, CH), 32.1 (C_q), 28.5 (CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –138.0 (s).

IR (ATR): $\tilde{\nu}$ = 3247, 2977, 2911, 1600, 1574, 1428, 1296, 1188, 971, 795 cm^{-1}.

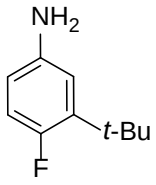
MS (EI) *m/z* (relative intensity) 356 (29) $[M]^+$, 299 (100), 216 (77), 188 (34).

HR-MS (ESI): *m/z* calcd for $C_{20}H_{26}FN_4O^+$ $[M+H]^+$ 357.2085, found 357.2091.

Removal of Directing Group

meta-Alkylated product **215aa** (61.3 mg, 0.25 mmol) was dissolved in concentrated HCl (1 mL) in a microwave vial. The vial was heated up to 150 °C for 1 h in microwave. The reaction mixture was allowed to cool to ambient temperature and poured into to EtOAc (15 mL), then saturated $NaHCO_3$ solution was added until the pH was adjusted to 7. Aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* affording **191** (35 mg, 84%) as a yellow oil.

Analytical Data for 3-(*tert*-Butyl)-4-fluoroaniline (191)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (ddd, *J* = 12.2, 8.5, 0.3 Hz, 1H), 6.59 (dd, *J* = 7.0, 2.9 Hz, 1H), 6.45 (ddd, *J* = 8.5, 3.7, 2.9 Hz, 1H), 3.47 (bs, 2H), 1.32 (d, *J* = 1.0 Hz, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6 (d, $^1J_{C\text{-}F}$ = 244 Hz, C_q), 141.8 (d, $^4J_{C\text{-}F}$ = 2 Hz, C_q), 137.6 (d, $^2J_{C\text{-}F}$ = 13 Hz, C_q), 116.5 (d, $^2J_{C\text{-}F}$ = 26 Hz, CH), 114.0 (d, $^3J_{C\text{-}F}$ = 6 Hz, CH), 113.4 (d, $^3J_{C\text{-}F}$ = 6 Hz, CH), 34.1 (d, $^3J_{C\text{-}F}$ = 3 Hz, C_q), 29.8 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH_3).

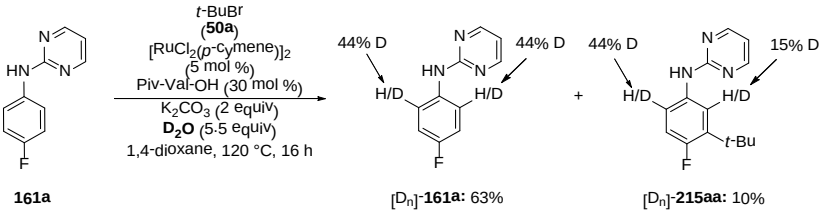
^{19}F NMR (282 MHz, $CDCl_3$): δ = –122.9 (s).

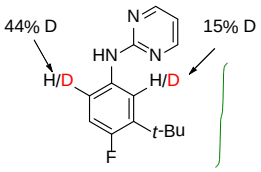
IR (neat): $\tilde{\nu}$ = 3335, 2958, 2871, 1670, 1492, 1364, 1203, 865 cm^{-1}.

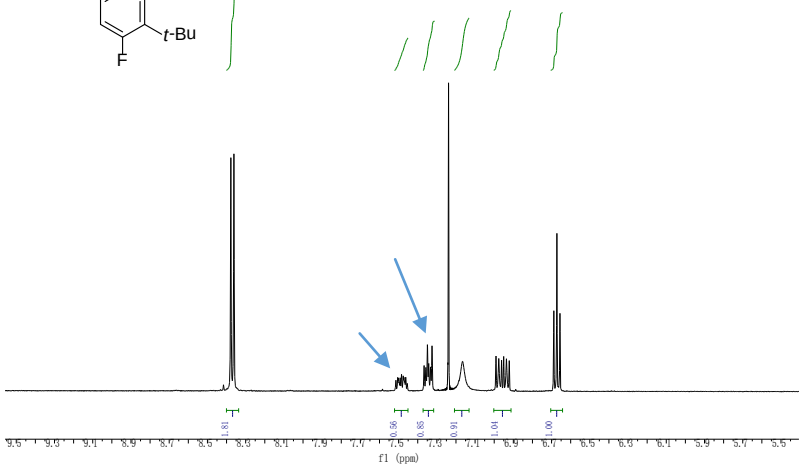
MS (EI) *m/z* (relative intensity) 167 (55) $[M]^+$, 152 (100), 124 (70), 109 (20).
HR-MS (EI): *m/z* calcd for $C_{10}H_{14}FN^+$ $[M]^+$ 167.1105, found 167.1111.

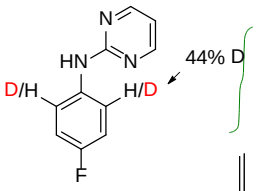
Experiment with Substrate 161a in the Presence of D_2O

The general procedure **A** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), Piv-Val-OH (30.0 mg, 30 mol %), substrate **161a** (95 mg, 0.50 mmol) and bromide **50a** (206 mg, 1.50 mmol) and D_2O (0.05 mL). After 20 h, purification by column chromatography (*n*-hexane/EtOAc/Et_3N 5:1:0.1) yielded $[D_n]$-**215aa** (12 mg, 10%) and reisolated $[D_n]$-**161a** (60 mg, 63%) as white solids.



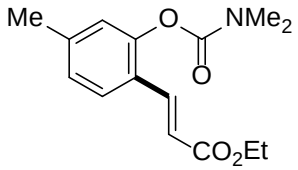






7.3.5 Analytical Data for the Products of Ruthenium(II)-Catalyzed Oxidative Alkenylation of Aryl Carbamates

Synthesis of Ethyl (*E*)-3-{2-[(*N,N*-Dimethylcarbamoyl)oxy)]}-4-methylphenyl}acrylate (193aa)



The general procedure **D** was followed using substrate **192a** (90 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193aa** (117 mg, 84%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 16.1 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.94 (s, 1H), 6.34 (d, *J* = 16.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.11 (s, 3H), 2.97 (s, 3H), 2.30 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

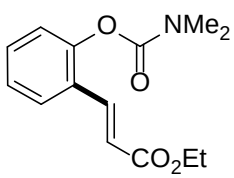
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (C_q), 154.2 (C_q), 149.9 (C_q), 141.7 (C_q), 138.1 (CH), 126.9 (CH), 126.5 (CH), 124.3 (C_q), 123.7 (CH), 118.5 (CH), 60.2 (CH_2), 36.6 (CH_3), 36.3 (CH_3), 21.2 (CH_3), 14.1 (CH_3).

IR (neat): $\tilde{\nu}$ = 2934, 1708, 1632, 1381, 1149, 884, 619 cm^{-1}.

MS (EI) *m/z* (relative intensity) 277 (5) $[M]^+$, 189 (25), 132 (5), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{15}H_{19}NO_4^+$ $[M]^+$ 277.1309, found 277.1316.

Synthesis of Ethyl (*E*)-3-{2-[(*N,N*-Dimethylcarbamoyl)oxy]phenyl}acrylate (193ba)



The general procedure **D** was followed using substrate **192b** (83 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193ba** (89 mg, 68%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 16.1 Hz, 1H), 7.58 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.35 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.21–7.12 (m, 2H), 6.41 (d, *J* = 16.1 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.14 (s, 3H), 2.99 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (C_q), 154.2 (C_q), 150.0 (C_q), 138.2 (CH), 130.9 (CH), 127.2 (CH), 127.2 (C_q), 125.6 (CH), 123.3 (CH), 119.7 (CH), 60.4 (CH_2), 36.8 (CH_3), 36.4 (CH_3), 14.2 (CH_3).

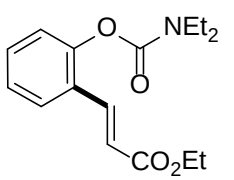
IR (neat): $\tilde{\nu}$ = 2938, 1708, 1635, 1149, 1094, 754 cm^{-1}.

MS (EI) *m/z* (relative intensity) 263 (5) $[M]^+$, 175 (25), 118 (6), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{14}H_{17}NO_4^+$ $[M]^+$ 263.1152, found 263.1159.

The spectral data were in accordance with those reported in the literature.[254]

Synthesis of Ethyl (*E*)-3-{2-[(*N,N*-Diethylcarbamoyl)oxy]phenyl}acrylate (222ba)



The general procedure **D** was followed using substrate **221b** (97 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **222ba** (98 mg, 67%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 16.1 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.35 (ddd, *J* = 7.8, 7.8, 1.7 Hz, 1H), 7.21–7.13 (m, 2H), 6.40 (d, *J* = 16.1 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.49 (q, *J* = 7.1 Hz, 2H), 3.37 (q, *J* = 7.1 Hz, 2H), 1.33–1.25 (m, 6H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7 (C_q), 153.5 (C_q), 150.1 (C_q), 138.2 (CH), 130.9 (CH), 127.3 (C_q), 127.1 (CH), 125.5 (CH), 123.3 (CH), 119.6 (CH), 60.4 (CH_2), 42.3 (CH_2), 41.9 (CH_2), 14.2 (CH_3), 14.2

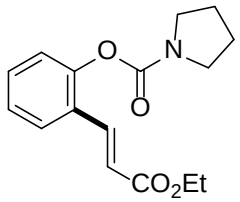
(CH_3), 13.2 (CH_3).

IR (neat): $\tilde{\nu}$ = 2978, 1708, 1636, 1148, 1038, 881 cm^{-1}.

MS (EI) *m/z* (relative intensity) 291 (5) $[M]^+$, 175 (10), 118 (10), 100 (100), 72 (55), 44 (15).

HR-MS (ESI): *m/z* calcd for $C_{16}H_{21}NNaO_4^+$ $[M+Na]^+$ 314.1363, found 314.1367.

Synthesis of (*E*)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenyl Pyrrolidine-1-carboxylate (222ca)



The general procedure **D** was followed using substrate **221c** (96 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **222ca** (79 mg, 55%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 16.1 Hz, 1H), 7.58 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.34 (ddd, *J* = 7.8, 7.8, 1.7 Hz, 1H), 7.21–7.13 (m, 2H), 6.40 (d, *J* = 16.1 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.61 (t, *J* = 6.7 Hz, 2H), 3,46 (t, *J* = 6.7 Hz, 2H), 2.01–1.83 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H).

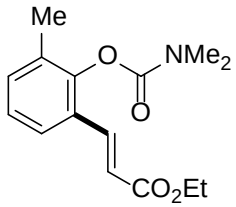
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (C_q), 152.3 (C_q), 149.9 (C_q), 138.4 (CH), 130.9 (CH), 127.1 (C_q), 127.1 (CH), 125.4 (CH), 123.3 (CH), 119.5 (CH), 60.4 (CH_2), 46.5 (CH_2), 46.4 (CH_2), 25.7 (CH_2), 24.8 (CH_2), 14.2 (CH_3).

IR (neat): $\tilde{\nu}$ = 2978, 1708, 1635, 1392, 1170, 757 cm^{-1}.

MS (EI) *m/z* (relative intensity) 289 (5) $[M]^+$, 175 (13), 118 (14), 98 (100), 55 (50), 43 (44).

HR-MS (ESI): *m/z* calcd for $C_{16}H_{19}NNaO_4^+$ $[M+H]^+$ 312.1206, found 312.1207.

Synthesis of Ethyl (*E*)-3-{2-[(*N,N*-Dimethylcarbamoyl)oxy]-3-methylphenyl}acrylate (193ca)



The general procedure **D** was followed using substrate **192c** (90 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193ca** (97 mg, 70%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 16.1 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H) , 7.10 (dd, *J* = 7.6, 8.0 Hz, 1H), 6.38 (d, *J* = 16.1 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.17 (s, 3H), 3.00 (s, 3H), 2.18 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

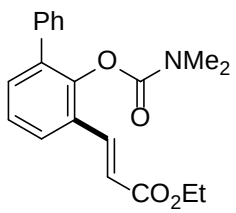
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (C_q), 153.7 (C_q), 148.8 (C_q), 138.6 (CH), 132.7 (CH), 131.9 (C_q), 127.9 (C_q), 125.7 (CH), 124.8 (CH), 119.7 (CH), 60.3 (CH_2), 36.8 (CH_3), 36.4 (CH_3), 16.1 (CH_3), 14.2 (CH_3).

IR (neat): $\tilde{\nu}$ = 2934, 1708, 1635, 1463, 1149, 1035, 847 cm^{-1}.

MS (EI) *m/z* (relative intensity) 277 (5) $[M]^+$, 189 (25), 160 (6), 131 (6), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{15}H_{19}NO_4^+$ $[M]^+$ 277.1309, found 277.1316.

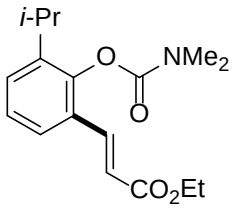
Synthesis of Ethyl (*E*)-3-{2-[(*N,N*-Dimethylcarbamoyl)oxy]-[1,1'-biphenyl]-3-yl}acrylate (193da)



The general procedure **D** was followed using **192d** (121 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193da** (130 mg, 77%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 16.1 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.41–7.25 (m, 7H), 6.47 (d, *J* = 16.1 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.90 (s, 3H), 2.77 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6 (C_q), 153.6 (C_q), 147.3 (C_q), 138.5 (CH), 137.3 (C_q), 136.4 (C_q), 132.3 (CH), 128.8 (CH), 128.7 (C_q), 127.9 (CH), 127.4 (CH), 126.3 (CH), 125.9 (CH), 120.0 (CH), 60.3 (CH_2), 36.5 (CH_3), 36.2 (CH_3), 14.2 (CH_3).
IR (neat): $\tilde{\nu}$ = 2934, 1709, 1635, 1429, 1382, 1148, 841 cm^{-1}.
MS (EI) *m/z* (relative intensity) 339 (5) $[M]^+$, 251 (25), 194 (10), 165 (10), 72 (100).
HR-MS (EI): *m/z* calcd for $C_{20}H_{21}NO_4^+$ $[M]^+$ 339.1465, found 339.1468.

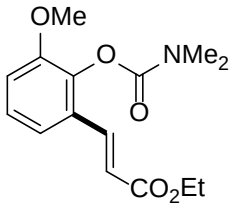
Synthesis of Ethyl (*E*)-3-{2-[(*N,N*-Dimethylcarbamoyl)oxy]-3-isopropylphenyl}acrylate (193ea)



The general procedure A was followed using substrate **192e** (104 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193ea** (119 mg, 78%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 16.0 Hz, 1H), 7.44 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.31 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.18 (dd, *J* = 7.8, 7.7 Hz, 1H), 6.38 (d, *J* = 16.0 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.09 (s, 3H), 3.07–2.95 (m, 1H), 3.01 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H). 1.20 (d, *J* = 6.9 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2 (C_q), 154.7 (C_q), 148.0 (C_q), 142.4 (C_q), 139.4 (CH), 128.7 (CH), 128.6 (C_q), 126.5 (CH), 125.1 (CH), 120.1 (CH), 60.8 (CH_2), 37.3 (CH_3), 36.9 (CH_3), 27.8 (CH_3), 23.4 (CH), 14.7 (CH_3).
IR (neat): $\tilde{\nu}$ = 2979, 1708, 1636, 1392, 1170, 1056, 911, 757 cm^{-1}.
MS (EI) *m/z* (relative intensity) 305 (5) $[M]^+$ 217 (15), 72 (100).
HR-MS (ESI): *m/z* calcd for $C_{17}H_{23}NNaO_4^+$ $[M+Na]^+$ 328.1519, found 328.1521.

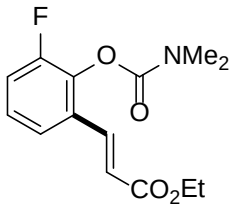
Synthesis of Ethyl (*E*)-3-{2-[(*N,N*-Dimethylcarbamoyl)oxy]-3-methoxyphenyl}acrylate (193fa)



The general procedure **D** was followed using substrate **192f** (98 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193fa** (96 mg, 65%) as a white solid.

M. p.: 99–101 °C.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 16.1 Hz, 1H), 7.16 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.11 (dd, *J* = 7.6, 8.0 Hz, 1H), 6.91 (dd, *J* = 7.6, 2.0 Hz, 1H), 6.40 (d, *J* = 16.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 3.12 (s, 3H), 2.97 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6 (C_q), 153.9 (C_q), 152.1 (C_q), 139.5 (C_q), 138.2 (CH), 128.7 (C_q), 125.9 (CH), 120.0 (CH), 118.5 (CH), 113.4 (CH), 60.3 (CH_2), 56.0 (CH_3), 36.7 (CH_3), 36.5 (CH_3), 14.1 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2984, 1715, 1634, 1580, 1181, 1059, 781 cm^{-1}.
MS (EI) *m/z* (relative intensity) 293 (5) $[M]^+$, 205 (12), 176 (5), 148 (5), 105 (5), 72 (100).
HR-MS (EI): *m/z* calcd for $C_{15}H_{19}NO_5^+$ $[M]^+$ 293.1258, found 293.1253.

Synthesis of Ethyl (*E*)-3-[2-(*N,N*-Dimethylcarbamoyloxy)-3-fluorophenyl]acrylate (193ga)



The general procedure **D** was followed using substrate **192g** (92 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column

chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193ga** (102 mg, 73%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 16.2 Hz, 1H), 7.37–7.32 (m, 1H), 7.17–7.10 (m, 2H), 6.42 (d, *J* = 16.2 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.14 (s, 3H), 3.00 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4 (C_q), 155.1 (d, $^1J_{C\text{-}F}$ = 250 Hz, C_q), 153.1 (C_q), 138.8 (d, $^2J_{C\text{-}F}$ = 13 Hz, C_q), 137.1 (d, $^4J_{C\text{-}F}$ = 3 Hz, CH), 130.0 (C_q), 126.2 (d, $^3J_{C\text{-}F}$ = 8 Hz, CH), 122.4 (d, $^4J_{C\text{-}F}$ = 3 Hz, CH), 121.0 (CH), 117.6 (d, $^2J_{C\text{-}F}$ = 19 Hz, CH), 60.5 (CH_2), 36.9 (CH_3), 36.5 (CH_3), 14.2 (CH_3).

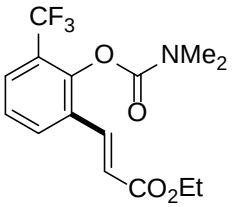
^{19}F NMR (282 MHz, $CDCl_3$): δ = –(128.1–128.2) (m).

IR (neat): $\tilde{\nu}$ = 2938, 1709, 1639, 1584, 1259, 1145, 845 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 281 (5) $[M]^+$, 193 (18), 164 (5), 136 (5), 107 (5), 72 (100).

HR-MS (EI): *m*/*z* calcd for $C_{14}H_{16}FNO_4^+$ $[M]^+$ 281.1058, found 281.1060.

Synthesis of Ethyl (*E*)-3-{2-[(*N,N*-Dimethylcarbamoyl)oxy]-3-[trifluoromethyl]phenyl}acrylate (193ha)



The general procedure **D** was followed using substrate **192h** (117 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193ha** (107 mg, 65%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 16.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.13 (s, 3H), 2.98 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2 (C_q), 153.3 (C_q), 147.6 (q, $^4J_{C\text{-}F}$ = 2 Hz, C_q), 136.8 (CH), 130.7 (CH), 130.7 (C_q), 128.0 (q, $^3J_{C\text{-}F}$ = 5 Hz, CH), 125.9 (CH), 124.5 (q, $^2J_{C\text{-}F}$ = 31 Hz, C_q), 122.8 (q, $^1J_{C\text{-}F}$ = 272 Hz, C_q), 121.4 (CH), 60.3 (CH_2), 36.5 (CH_3), 36.2 (CH_3), 14.2 (CH_3).

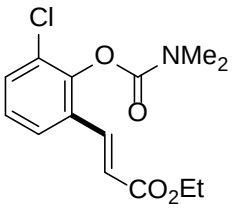
^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.1 (s).

IR (neat): $\tilde{\nu}$ = 2940, 1713, 1640, 1443, 1329, 1127, 1034, 979, 848 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 331 (5) $[M]^+$, 243 (20), 186 (5), 72 (100).

HR-MS (ESI): *m*/*z* calcd for $C_{15}H_{16}F_3NNaO_4^+$ $[M]^+$ 354.0924, found 354.0924.

Synthesis of Ethyl (*E*)-3-{3-Chloro-2-[(*N,N*-Dimethylcarbamoyl)oxy]phenyl}acrylate (193ia)



The general procedure **D** was followed using substrate **192i** (100 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193ia** (76 mg, 51%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 16.1 Hz, 1H), 7.48 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.40 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.13 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.41 (d, *J* = 16.1 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.17 (s, 3H), 3.00 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

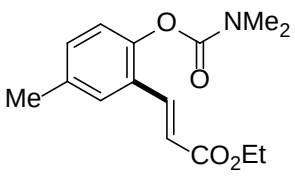
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4 (C_q), 153.0 (C_q), 146.4 (C_q), 137.6 (CH), 131.3 (CH), 130.2 (C_q), 128.7 (C_q), 126.4 (CH), 125.6 (CH), 121.1 (CH), 60.5 (CH_2), 36.9 (CH_3), 36.5 (CH_3), 14.2 (CH_3).

IR (neat): $\tilde{\nu}$ = 2938, 1709, 1637, 1567, 1438, 1148, 842 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 299/297 (2/5) $[M]^+$, 211/209 (4/12), 154/152 (3/8), 89 (8), 72 (100).

HR-MS (EI): *m*/*z* calcd for $C_{14}H_{16}{}^{35}ClNO_4^+$ $[M]^+$ 297.0762, found 297.0761.

Synthesis of Ethyl (*E*)-3-{2-[(*N,N*-Dimethylcarbamoyl)oxy]-5-methylphenyl}acrylate (193ja)



The general procedure **D** was followed using substrate **192j** (90 mg,

0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193ja** (77 mg, 56%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 16.1 Hz, 1H), 7.38 (d, *J* = 1.9 Hz, 1H), 7.15 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.39 (d, *J* = 16.1 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.13 (s, 3H), 2.99 (s, 3H), 2.30 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

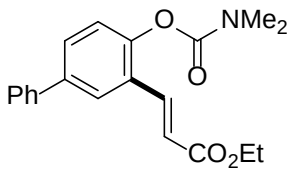
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (C_q), 154.4 (C_q), 147.9 (C_q), 138.4 (CH), 135.1 (C_q), 131.7 (CH), 127.5 (CH), 126.8 (C_q), 123.0 (CH), 119.4 (CH), 60.3 (CH_2), 36.7 (CH_3), 36.4 (CH_3), 20.8 (CH_3), 14.2 (CH_3).

IR (neat): $\tilde{\nu}$ = 2984, 1707, 1607, 1497, 1158, 1035, 1035, 978, 855 cm^{-1}.

MS (EI) *m/z* (relative intensity) 277 (3) $[M]^+$, 189 (25), 132 (6), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{15}H_{19}NO_4^+$ $[M]^+$ 277.1309, found 277.1316.

Synthesis of Ethyl (*E*)-3-{4-[(*N,N*-Dimethylcarbamoyl)oxy]-[1,1'-biphenyl]-3-yl}acrylate (193ka)



The general procedure **D** was followed using substrate **192k** (121 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193ka** (100 mg, 59%) as a white solid.

M. p.: 112–114 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 16.1 Hz, 1H), 7.79 (d, *J* = 2.2 Hz, 1H), 7.59–7.52 (m, 3H), 7.46–7.39 (m, 2H), 7.37–7.31 (m, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 6.51 (d, *J* = 16.1 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.17 (s, 3H), 3.03 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

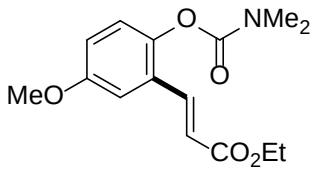
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7 (C_q), 154.2 (C_q), 149.4 (C_q), 139.8 (C_q), 138.8 (C_q), 138.2 (CH), 129.7 (CH), 128.7 (CH), 127.5 (CH), 127.4 (C_q), 127.0 (CH), 125.8 (CH), 123.6 (CH), 120.0 (CH), 60.4 (CH_2), 36.8 (CH_3), 36.4 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2927, 1720, 1700, 1477, 1386, 1154, 996, 756, 693 cm^{-1}.

MS (EI) *m/z* (relative intensity) 339 (8) $[M^+]$, 251 (15), 194 (8), 165 (8), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{20}H_{21}NO_4^+$ $[M^+]$ 339.1465, found 339.1476.

Synthesis of Ethyl (*E*)-3-{2-[(*N,N*-Dimethylcarbamoyl)oxy]-5-methoxyphenyl}acrylate (193la)



The general procedure **D** was followed using substrate **192l** (98 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193la** (95 mg, 65%) as a white solid.

M. p.: 52–54 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 16.1 Hz, 1H), 7.06 (d, *J* = 2.9 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 1H), 6.90 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.38 (d, *J* = 16.1 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 3.14 (s, 3H), 2.99 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).

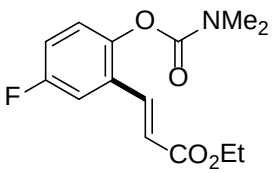
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7 (C_q), 156.9 (C_q), 154.7 (C_q), 143.9 (C_q), 138.3 (CH), 127.9 (C_q), 124.3 (CH), 119.9 (CH), 117.1 (CH), 111.1 (CH), 60.5 (CH_2), 55.6 (CH_3), 36.8 (CH_3), 36.4 (CH_3), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2984, 1707, 1607, 1497, 1385, 1158, 1035, 855 cm^{-1}.

MS (EI) *m/z* (relative intensity) 293 (10) $[M^+]$, 205 (20), 176 (8), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{15}H_{19}NO_5^+$ $[M^+]$ 293.1258, found 293.1254.

Synthesis of Ethyl (*E*)-3-{2-[(*N,N*-Dimethylcarbamoyl)oxy]-5-fluorophenyl}acrylate (193ma)



The general procedure **D** was followed using substrate **192m** (90 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193ma** (84 mg, 61 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (dd, *J* = 16.1, 1.5 Hz, 1H), 7.25 (dd, *J* = 9.1, 2.9 Hz, 1H), 7.12–6.99 (m, 2H), 6.37 (d, *J* = 16.1 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.13 (s, 3H), 2.99 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4 (C_q), 159.7 (d, $^1J_{C\text{-}F}$ = 248 Hz, C_q), 154.1 (C_q), 145.9 (d, $^4J_{C\text{-}F}$ = 3 Hz, C_q), 137.1 (d, $^4J_{C\text{-}F}$ = 2 Hz, CH), 128.8 (d, $^3J_{C\text{-}F}$ = 9 Hz, C_q), 124.8 (d, $^3J_{C\text{-}F}$ = 9 Hz, CH), 120.9 (CH), 117.6 (d, $^2J_{C\text{-}F}$ = 25 Hz, CH), 113.0 (d, $^2J_{C\text{-}F}$ = 25 Hz, CH), 60.6 (CH_2), 36.8 (CH_3), 36.4 (CH_3), 14.2 (CH_3).

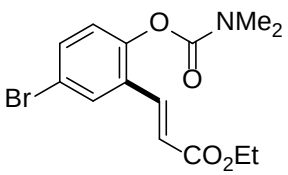
^{19}F NMR (282 MHz, $CDCl_3$): δ = –(116.6–116.7) (m).

IR (neat): $\tilde{\nu}$ = 2938, 1709, 1637, 1483, 1385, 1145, 1033, 865, 751 cm^{-1}.

MS (EI) *m/z* (relative intensity) 281 (5) $[M]^+$, 193 (8), 164 (5), 136 (5), 107 (5), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{14}H_{16}FNO_4^+$ $[M]^+$ 281.1058, found 281.1073.

Synthesis of Ethyl (*E*)-3-{5-Bromo-2-[(*N,N*-dimethylcarbamoyl)oxy]phenyl}acrylate (193na)



The general procedure **D** was followed using substrate **192n** (122 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193na** (103 mg, 60%) as a white solid.

M. p.: 107–109 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 16.1 Hz, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.42 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.38 (d, *J* = 16.1 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.11 (s, 3H), 2.97 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H).

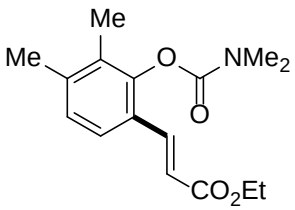
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3 (C_q), 153.7 (C_q), 148.9 (C_q), 136.7 (CH), 133.5 (CH), 129.8 (CH), 129.2 (C_q), 125.0 (CH), 120.9 (CH), 118.6 (C_q), 60.6 (CH_2), 36.8 (CH_3), 36.4 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2932, 1699, 1474, 1384, 1215, 1107, 973, 855 cm^{-1}.

MS (EI) *m/z* (relative intensity) 343/341 (5/5) $[M]^+$, 255/253 (15/15), 198/196 (5/5), 89 (6), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{14}H_{16}{}^{79}BrNO_4^+$ $[M]^+$ 341.0257, found 341.0265.

Synthesis of Ethyl (*E*)-3-{2-[(*N,N*-Dimethylcarbamoyl)oxy]-3,4-dimethylphenyl}acrylate (193oa)



The general procedure **D** was followed using substrate **192o** (97 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193oa** (114 mg, 78%) as a white solid.

The general procedure **E** was followed using substrate **192o** (97 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193oa** (64 mg, 44%) as a white solid.

M. p.: 63–65 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 16.1 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.35 (d, *J* = 16.1 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.18 (s, 3H), 3.00 (s, 3H), 2.26 (s, 3H), 2.06 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9 (C_q), 154.0 (C_q), 148.5 (C_q), 140.7 (C_q), 138.9 (CH), 130.3 (C_q),

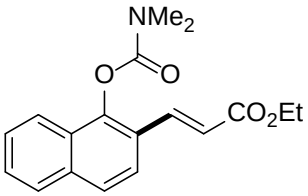
127.3 (CH), 125.4 (C_q), 123.9 (CH), 118.5 (CH), 60.2 (CH_2), 36.8 (CH_3), 36.4 (CH_3), 20.2 (CH_3), 14.2 (CH_3), 12.4 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2926, 1704, 1631, 1453, 1313, 1156, 978, 862 cm^{-1}.

MS (EI) *m/z* (relative intensity) 291 (5) $[M]^+$, 203 (15), 174 (5), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{16}H_{21}NO_4^+$ $[M]^+$ 291.1465, found 291.1472.

Synthesis of Ethyl (*E*)-3-{1-[(*N,N*-Dimethylcarbamoyl)oxy]naphthalen-2-yl}acrylate (193pa)



The general procedure **D** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), $AgSbF_6$ (34.4 mg, 20 mol %), substrate **192p** (108 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193pa** (119 mg, 76%) as a white solid.

The general procedure **E** was followed using substrate **192p** (108 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193pa** (82 mg, 54%) as a white solid.

M. p.: 86–88 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 16.1 Hz, 1H), 7.89–7.80 (m, 2H), 7.74–7.66 (m, 2H), 7.56–7.48 (m, 2H), 6.54 (d, *J* = 16.1 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.35 (s, 3H), 3.09 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H).

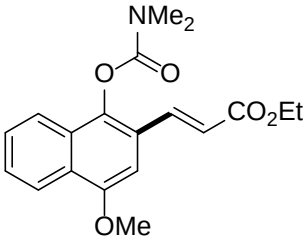
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9 (C_q), 154.3 (C_q), 146.7 (C_q), 138.1 (CH), 135.3 (C_q), 128.0 (CH), 127.4 (CH), 127.1 (CH), 126.1 (CH), 124.0 (C_q), 124.0 (C_q), 122.8 (CH), 122.2 (CH), 119.9 (CH), 60.5 (CH_2), 37.0 (CH_3), 36.7 (CH_3), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2962, 1712, 1631, 1441, 1393, 1294, 1032, 872, 751 cm^{-1}.

MS (EI) *m/z* (relative intensity) 313 (5) $[M]^+$, 225 (12), 196 (8), 168 (10), 139 (10), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{18}H_{19}NO_4^+$ $[M]^+$ 313.1309, found 313.1317.

Synthesis of Ethyl (*E*)-3-{1-[(*N,N*-Dimethylcarbamoyl)oxy]-4-methoxynaphthalen-2-yl} acrylate (193qa)



The general procedure **D** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), $AgSbF_6$ (34.4 mg, 20 mol %), substrate **192q** (123 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193qa** (116 mg, 68%) as a yellow solid.

M. p.: 131–133 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23–8.18 (m, 1H), 7.95 (d, *J* = 16.0 Hz, 1H), 7.80–7.75 (m, 1H), 7.55–7.45 (m, 2H), 6.89 (s, 1H), 6.49 (d, *J* = 16.0 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.98 (s, 3H), 3.31 (s, 3H), 3.06 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H).

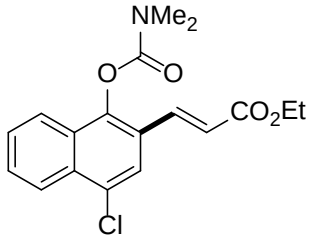
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (C_q), 154.6 (C_q), 153.2 (C_q), 140.7 (C_q), 138.4 (CH), 128.5 (C_q), 127.5 (CH), 127.5 (C_q), 126.8 (CH), 123.5 (C_q), 122.4 (CH), 122.0 (CH), 119.3 (CH), 99.5 (CH), 60.5 (CH_2), 55.5 (CH_3), 37.0 (CH_3), 36.7 (CH_3), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2937, 1717, 1702, 1633, 1511, 1446, 1288, 1088, 820 cm^{-1}.

MS (EI) *m/z* (relative intensity) 343 (10) $[M]^+$, 255 (5), 226 (8), 198 (5), 183 (10), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{19}H_{21}NO_5^+$ $[M]^+$ 343.1414, found 343.1415.

Synthesis of Ethyl (*E*)-3-{4-Chloro-1-[(*N,N*-Dimethylcarbamoyl)oxy]naphthalen-2-yl}acrylate (193ra)



The general procedure **D** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), $AgSbF_6$ (34.4 mg, 20 mol %), substrate **192r** (123 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193ra** (128 mg, 75%) as a yellow solid.

M. p.: 127–129 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.6 Hz, 1H), 7.87 (d, *J* = 16.0 Hz, 1H), 7.88–7.84 (m, 1H), 7.77 (s, 1H), 7.65–7.54 (m, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.33 (s, 3H), 3.06 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H).

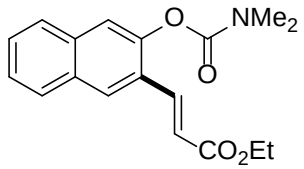
^{13}C NMR (75 MHz, $CDCl_3$): δ= 166.6 (C_q), 154.1 (C_q), 145.6 (C_q), 136.9 (CH), 132.2 (C_q), 129.9 (C_q), 129.0 (C_q), 128.4 (CH), 127.8 (CH), 125.0 (CH), 124.4 (C_q), 122.9 (CH), 122.7 (CH), 120.7 (CH), 60.6 (CH_2), 37.0 (CH_3), 36.7 (CH_3), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2976, 1728, 1704, 1593, 1453, 1393, 1255, 1088, 754 cm^{-1}.

MS (EI) *m/z* (relative intensity) 349/347 (5) $[M]^+$, 261/259 (2/5), 232/230 (2/5), 139 (10), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{18}H_{18}{}^{35}ClNO_4{}^+$ $[M]^+$ 347.0919, found 347.0920.

Synthesis of Ethyl (*E*)-3-{3-[(*N,N*-Dimethylcarbamoyl)oxy]naphthalen-2-yl}acrylate (193sa)



The general procedure **D** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), $AgSbF_6$ (34.4 mg, 20 mol %), substrate **192s** (108 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193sa** (137 mg, 87%) as a white solid.

The general procedure **E** was followed using substrate **192s** (108 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193sa** (78 mg, 50%) as a white solid.

M. p.: 82–84 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (s, 1H), 7.92 (d, *J* = 16.1 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.60 (s, 1H), 7.49–7.38 (m, 2H), 6.57 (d, *J* = 16.1 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.19 (s, 3H), 3.03 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H).

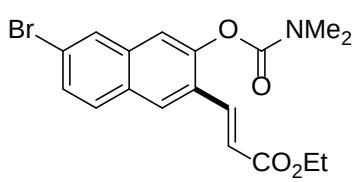
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7 (C_q), 154.4 (C_q), 147.2 (C_q), 138.9 (CH), 134.4 (C_q), 130.9 (C_q), 128.1 (CH), 128.0 (CH), 127.4 (CH), 127.3 (CH), 127.0 (C_q), 126.0 (CH), 120.2 (CH), 120.2 (CH), 60.4 (CH_2), 36.8 (CH_3), 36.5 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2987, 1711, 1638, 1440, 1270, 1157, 979, 860, 734 cm^{-1}.

MS (EI) *m/z* (relative intensity) 313 (10) $[M]^+$, 225 (20), 196 (8), 168 (10), 139 (10), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{18}H_{19}NO_4{}^+$ $[M]^+$ 313.1309, found 313.1318.

Synthesis of Ethyl (*E*)-3-{6-Bromo-3-[(*N,N*-dimethylcarbamoyl)oxy]naphthalen-2-yl}acrylate (193ta)



The general procedure **D** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), $AgSbF_6$ (34.4 mg, 20 mol %), substrate **192t**

(147 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193ta** (143 mg, 73%) as a white solid.

M. p.: 120–122 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (s, 1H), 7.92 (s, 1H), 7.86 (d, *J* = 16.0 Hz, 1H), 7.59–7.53 (m, 2H), 7.49 (d, *J* = 8.7 Hz, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.18 (s, 3H), 3.03 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H).

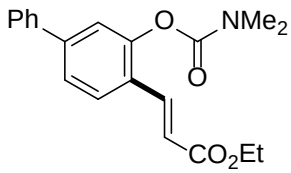
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5 (C_q), 154.1 (C_q), 147.5 (C_q), 138.3 (CH), 132.7 (C_q), 131.9 (C_q), 130.6 (CH), 130.0 (CH), 128.9 (CH), 128.0 (C_q), 126.8 (CH), 121.0 (CH), 120.2 (CH), 119.8 (C_q), 60.5 (CH_2), 36.9 (CH_3), 36.5 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2927, 1730, 1633, 1481, 1362, 1161, 1052, 884 cm^{-1}.

MS (EI) *m/z* (relative intensity) 393/391 (5/5) $[M]^+$, 303 (10), 276/274 (5/5), 248/246 (8/8), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{18}H_{18}{}^{79}BrNO_4{}^+$ $[M]^+$ 391.0414, found 391.0411.

Synthesis of Ethyl (*E*)-3-{3-[(*N,N*-Dimethylcarbamoyl)oxy]-[1,1'-biphenyl]-4-yl}acrylate (193ua)



The general procedure **D** was followed using substrate **192u** (121 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193ua** (165 mg, 97%) as a white solid.

The general procedure **E** was followed using substrate **192u** (121 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193ua** (116 mg, 68%) as a white solid.

M. p.: 110–112 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 16.0 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.60–7.56 (m, 2H), 7.47–7.37 (m, 4H), 7.36–7.30 (m, 1H), 6.46 (d, *J* = 16.0 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.18 (s, 3H), 3.03 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H).

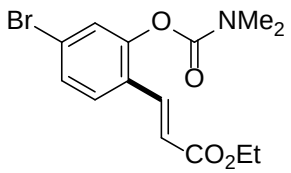
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (C_q), 154.2 (C_q), 150.4 (C_q), 144.0 (C_q), 139.3 (C_q), 137.9 (CH), 128.8 (CH), 128.0 (CH), 127.6 (CH), 127.0 (CH), 126.0 (C_q), 124.3 (CH), 121.8 (CH), 119.4 (CH), 60.4 (CH_2), 36.8 (CH_3), 36.5 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2982, 1631, 1610, 1483, 1383, 1157, 893, 762 cm^{-1}.

MS (EI) *m/z* (relative intensity) 339 (5) $[M]^+$, 251 (20), 194 (8), 165 (10),72 (100).

HR-MS (EI): *m/z* calcd for $C_{20}H_{21}NO_4{}^+$ $[M]^+$ 339.1465, found 339.1470.

Synthesis of Ethyl (*E*)-3-{4-Bromo-2-[(*N,N*-dimethylcarbamoyl)oxy]phenyl}acrylate (193va)



The general procedure **D** was followed using substrate **192v** (122 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193va** (101 mg, 59%) as a white solid.

M. p.: 68–70 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 16.1 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.35–7.28 (m, 2H), 6.38 (d, *J* = 16.1 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.11 (s, 3H), 2.98 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H).

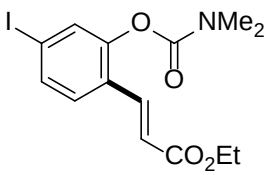
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5 (C_q), 153.6 (C_q), 150.2 (C_q), 137.1 (CH), 128.9 (CH), 128.1 (CH), 126.7 (CH), 126.3 (C_q), 123.9 (C_q), 120.1 (CH), 60.5 (CH_2), 36.8 (CH_3), 36.4 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2939, 1713, 1636, 1590, 1370, 1146, 1032, 889, 815 cm^{-1}.

MS (EI) *m/z* (relative intensity) 343/341 (5) $[M]^+$, 255/253 (15/15), 198/196 (5/5), 89 (8), 72 (100).

HR-MS (EI): *m*/*z* calcd for $C_{14}H_{16}{}^{79}BrNO_4{}^+$ [M]$^+$ 341.0257, found 341.0278.

Synthesis of Ethyl (*E*)-3-{2-[(*N*,*N*-Dimethylcarbamoyl)oxy]-4-iodophenyl}acrylate (193wa)



The general procedure **D** was followed using substrate **192w** (146 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193wa** (104 mg, 53%) as a yellow solid.

M. p.: 84–86 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 16.1 Hz, 1H), 7.53–7.49 (m, 2H), 7.28 (d, *J* = 8.9 Hz, 1H), 6.40 (d, *J* = 16.1 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.11 (s, 3H), 2.99 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

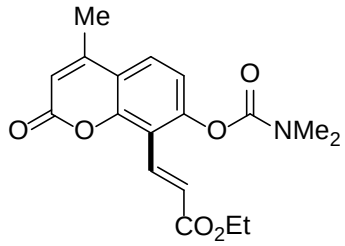
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5 (C_q), 153.7 (C_q), 149.9 (C_q), 137.3 (CH), 134.8 (CH), 132.5 (CH), 128.2 (CH), 127.0 (C_q), 120.2 (CH), 95.5 (C_q), 60.5 (CH_2), 36.8 (CH_3), 36.5 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2938, 1707, 1636, 1477, 1370, 1147, 1032, 868 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 389 (5) [M]$^+$, 301 (20), 243 (5), 72 (100).

HR-MS (EI): *m*/*z* calcd for $C_{14}H_{16}INO_4{}^+$ [M]$^+$ 389.0119, found 389.0117.

Synthesis of Ethyl (*E*)-3-{7-[(*N*,*N*-Dimethylcarbamoyl)oxy]-4-methyl-2-oxo-2*H*-chromen-8-yl}acrylate (193xa)



The general procedure **D** was followed using $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), $AgSbF_6$ (34.4 mg, 20 mol %), substrate **192x** (117 mg, 0.47 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193xa** (96 mg, 59%) as a yellow solid.

M. p.: 201–203 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 16.5 Hz, 1H), 7.58 (d, *J* = 8.9 Hz, 1H), 7.16 (d, *J* = 8.9 Hz, 1H), 6.95 (d, *J* = 16.5 Hz, 1H), 6.27 (d, *J* = 1.2 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.17 (s, 3H), 3.02 (s, 3H), 2.42 (d, *J* = 1.2 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H).

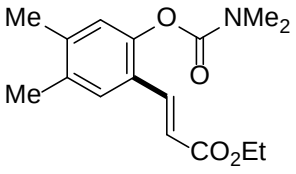
^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3 (C_q), 159.7 (C_q), 153.4 (C_q), 152.7 (C_q), 152.6 (C_q), 152.2 (C_q), 132.2 (CH), 125.5 (CH), 125.5 (CH), 119.3 (CH), 117.6 (C_q), 116.6 (C_q), 114.3 (CH), 60.7 (CH_2), 37.0 (CH_3), 36.6 (CH_3), 19.0 (CH_3), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2980, 1726, 1703, 1629, 1382, 1296, 1152, 1032, 869 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 345 (5) [M]$^+$, 257 (10), 228 (5), 172 (5), 72 (100), 43 (7).

HR-MS (EI): *m*/*z* calcd for $C_{18}H_{19}NO_6{}^+$ [M]$^+$ 345.1207, found 345.1208.

Synthesis of Ethyl (*E*)-3-{2-[(*N*,*N*-Dimethylcarbamoyl)oxy]-4,5-dimethylphenyl}acrylate (193ya)



The general procedure **D** was followed using substrate **192y** (97 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193ya** (126 mg, 87%) as a white solid.

M. p.: 86–88 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 16.1 Hz, 1H), 7.35 (s, 1H), 6.91 (s, 1H), 6.36 (d, *J* = 16.1 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.14 (s, 3H), 3.00 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1 (C_q), 154.6 (C_q), 148.1 (C_q), 140.5 (C_q), 138.4 (CH), 134.1 (C_q),

128.0 (CH), 124.4 (C_q), 124.2 (CH), 118.4 (CH), 60.3 (CH_2), 36.8 (CH_3), 36.5 (CH_3), 19.9 (CH_3), 19.2 (CH_3), 14.3 (CH_3).

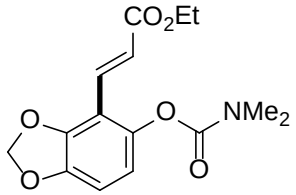
IR (ATR): $\tilde{\nu}$ = 2937, 1702, 1630, 1498, 1452, 1154, 1029, 991, 875 cm^{-1}.

MS (EI) *m/z* (relative intensity) 291 (5) $[M]^+$, 203 (30), 174 (5), 146 (6), 72 (100).

HR-MS (EI): *m/z* calcd for $C_{16}H_{21}NO_4^+$ $[M]^+$ 291.1471, found 291.1482.

The spectral data were in accordance with those reported in the literature.[254]

Synthesis of Ethyl (*E*)-3-{5-[(*N,N*-Dimethylcarbamoyl)oxy]benzo[*d*][1,3]dioxol-4-yl}acrylate (193za)



The general procedure **D** was followed using substrate **192z** (105 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193za** (100 mg, 65%) as a white solid.

The general procedure **E** was followed using substrate **192z** (105 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **193za** (65 mg, 42%) as a white solid.

M. p.: 115–117 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 16.1 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 16.1 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.05 (s, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.13 (s, 3H), 2.98 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3 (C_q), 154.7 (C_q), 147.0 (C_q), 145.2 (C_q), 144.2 (C_q), 133.4 (CH), 122.7 (CH), 115.3 (CH), 112.3 (C_q), 108.9 (CH), 102.2 (CH_2), 60.4 (CH_2), 36.9 (CH_3), 36.5 (CH_3), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2909, 1714, 1633, 1457, 1304, 1201, 1162, 977, 862 cm^{-1}.

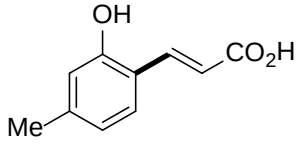
MS (EI) *m/z* (relative intensity) 307 (5) $[M]^+$, 219 (5), 190 (8), 72 (100), 43 (7).

HR-MS (EI): *m/z* calcd for $C_{15}H_{17}NO_6^+$ $[M]^+$ 307.1050, found 307.1059.

Deprotection of Carbamate 193aa

To a solution of the carbamate **193aa** (170 mg, 0.61 mmol) in EtOH (5 mL) was added NaOH (245 mg, 6.13 mmol). The reaction mixture was stirred at 80 °C for 15 h. At ambient temperature, EtOH was evaporated under reduced pressure, the residue was diluted with H_2O (20 mL), and the excess of NaOH was neutralized at 0 °C using a solution of HCl (5 mL, 2 N). The aqueous solution was extracted with Et_2O (3 × 20 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was washed with CH_2Cl_2 to afford **223** (80 mg, 74%) as a yellow solid.

Analytical Data for (*E*)-3-(2-Hydroxy-4-methylphenyl)acrylic acid (223)



M. p.: 191–193 °C.

^{1}H NMR (300 MHz, d^6-DMSO): δ = 12.04 (s_{br}, 1H), 10.00 (s, 1H), 7.78 (d, *J* = 16.1 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 6.71 (s, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.43 (d, *J* = 16.1 Hz, 1H), 2.23 (s, 3H).

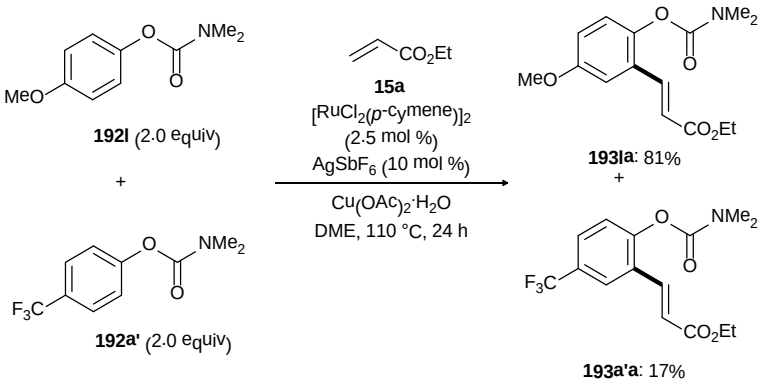
^{13}C NMR (75 MHz, DMSO): δ = 168.0 (C_q), 156.4 (C_q), 141.4 (C_q), 139.5 (CH), 128.5 (CH), 120.3 (CH), 118.2 (C_q), 117.0 (CH), 116.4 (CH), 21.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2925, 1660, 1601, 1421, 1298, 1259, 1205, 986, 854 cm^{-1}.

MS (EI) *m/z* (relative intensity) 178 (35) $[M]^+$, 160 (47), 132 (100), 104 (32), 77 (30), 43 (18).

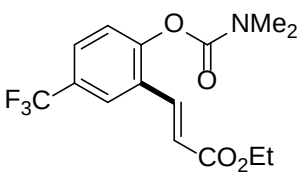
HR-MS (EI): *m/z* calcd for $C_{10}H_{10}O_3^+$ [M]$^+$ 178.0624, found 178.0634.

Intermolecular Competition Experiment with Carbamates 192l and 192a'



A mixture of substrates **192l** (195 mg, 1.00 mmol), **192a'** (233 mg, 1.00 mmol), ethyl acrylate (**15a**) (50 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 2.5 mol %), $AgSbF_6$ (17.2 mg, 10 mol %) and $Cu(OAc)_2 \cdot H_2O$ (200 mg, 1.00 mmol) in DME (3.0 mL) was stirred at 110 °C for 24 h under an atmosphere of N_2. At ambient temperature, EtOAc (15 mL) was added, and the mixture was filtered through a pad of silica gel. The solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **193la** (119 mg, 81%) as a white solid and **193a'a** (28 mg, 17%) as a white solid. The spectral data of **193la** were identical to those reported above.

Analytical Data for Ethyl (*E*)-3-{2-[(*N,N*-Dimethylcarbamoyl)oxy]-5-(trifluoromethyl)phenyl}acrylate (193a'a)



M. p.: 107–109 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 1.9 Hz, 1H), 7.80 (d, *J* = 16.3 Hz, 1H), 7.59 (dd, *J* = 8.6 Hz, 1.9 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.48 (d, *J* = 16.3 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.15 (s, 3H), 3.01 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3 (C_q), 153.5 (C_q), 152.3 (C_q), 136.8 (CH), 127.9 (q, $^2J_{C\text{-}F}$ = 33 Hz, C_q), 127.9 (C_q), 127.5 (q, $^3J_{C\text{-}F}$ = 4 Hz, CH), 124.5 (q, $^3J_{C\text{-}F}$ = 4 Hz, CH), 124.0 (CH), 123.6 (q, $^1J_{C\text{-}F}$ = 272 Hz, C_q), 121.6 (CH), 60.8 (CH_2), 36.9 (CH_3), 36.5 (CH_3), 14.2 (CH_3).

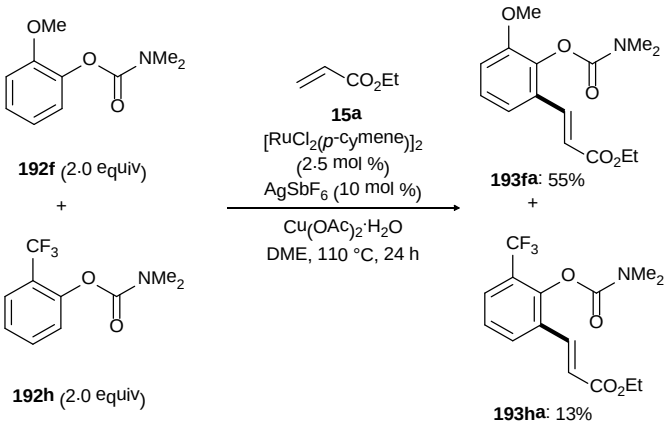
^{19}F-NMR (282 MHz, $CDCl_3$): δ = –62.5 (s).

IR (ATR): $\tilde{\nu}$ = 2943, 1702, 1486, 1334, 1110, 1008, 858, 858 cm^{-1}.

MS (EI) *m/z* (relative intensity) 331 (5) [M]$^+$, 243 (18), 186 (8), 72 (100).

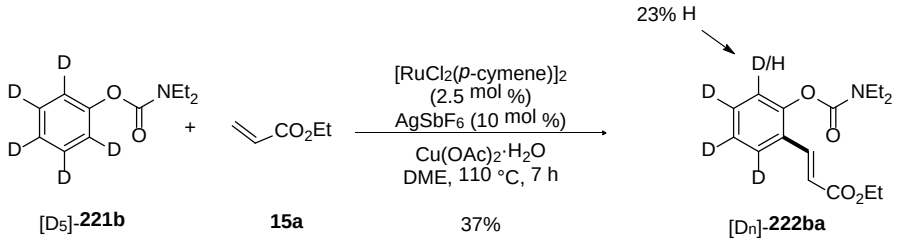
HR-MS (ESI): *m/z* calcd for $C_{15}H_{16}F_3NNaO_4^+$ [M+Na]$^+$ 354.0924, found 354.0924.

Intermolecular Competition Experiment with Carbamates 192f and 192h



A mixture of substrates **192f** (195 mg, 1.00 mmol), **192h** (233 mg, 1.00 mmol), ethyl acrylate (**15a**) (50 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 2.5 mol %), $AgSbF_6$ (17.2 mg, 10 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (200 mg, 1.00 mmol) in DME (3.0 mL) was stirred at 110 °C for 24 h under an atmosphere of N_2. At ambient temperature, EtOAc (15 mL) was added, and the mixture was filtered through a pad of silica gel. The solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **193fa** (81 mg, 55%) as a white solid and **193ha** (21 mg, 13%) as a colorless oil. Their spectral data were identical to those reported above.

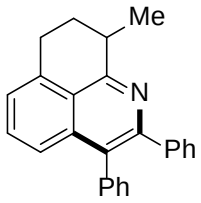
Experiment with Deuterium-Labeled Substrate [D_5]-221b



The general procedure **D** was followed using substrate [D_5]-**221b** (99 mg, 0.50 mmol) and ethyl acrylate (**15a**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded [Dn]-**222ba** (55 mg, 37%) as a colorless oil.

7.3.6 Analytical Data for the Products of Ruthenium(II)-Catalyzed Isoquinoline Synthesis

Synthesis of 9-Methyl-2,3-diphenyl-8,9-dihydro-7*H*-benzo[*de*]quinoline (176ba)



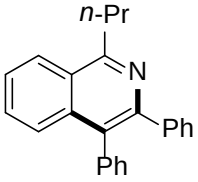
The representative procedure **F** was followed using substrate **194b** (88 mg, 0.50 mmol) and diphenylacetylene (**155a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 40/1) yielded **176ba** (157 mg, 94%) as a yellow solid.

M. p.: 145–147 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.46 (m, 2H), 7.45–7.28 (m, 7H), 7.25–7.12 (m, 4H), 3.54–3.41 (m, 1H), 3.36–3.24 (m, 1H), 3.23–3.11 (m, 1H), 2.43–2.31 (m, 1H), 2.12–1.99 (m, 1H), 1.63–1.56 (m, 3H).

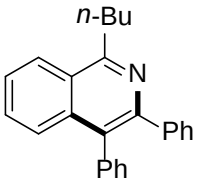
^{13}C NMR (75 MHz, $C_2D_2Cl_4$, 100 °C): δ = 162.0 (C_q), 148.7 (C_q), 141.3 (C_q), 138.0 (C_q), 138.0 (C_q), 136.2 (C_q), 131.2 (CH), 130.3 (CH), 129.3 (CH), 128.4 (C_q), 127.9 (CH), 127.0 (CH), 126.7 (CH), 126.4 (CH), 124.3 (CH), 123.3 (CH), 123.0 (C_q), 37.4 (CH), 30.8 (CH_2), 27.8 (CH_2), 19.6 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2929, 1604, 1577, 1442, 1377, 1306, 1178, 1071, 1023, 767, 699 cm^{-1}.
MS (EI) *m*/*z* (relative intensity) 335 (91) $[M]^+$, 334 (100), 320 (50), 241 (8), 43 (13).
HR-MS (EI): *m*/*z* calcd for $C_{25}H_{20}N^+$ $[M–H]^+$ 334.1590, found 334.1608.
The spectral data were in accordance with those reported in the literature.[255]

Synthesis of 3,4-Diphenyl-1-*n*-propylisoquinoline (176ca)



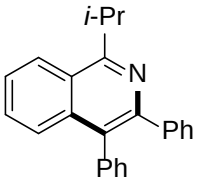
The representative procedure **F** was followed using substrate **194c** (82 mg, 0.50 mmol) and diphenylacetylene (**155a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded **176ca** (144 mg, 89%) as a yellow solid.
M. p.: 118–120 °C.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23–8.14 (m, 1H), 7.64–7.56 (m, 1H), 7.54–7.45 (m, 2H), 7.37–7.22 (m, 5H), 7.20–7.05 (m, 5H), 3.32 (t, *J* = 7.7 Hz, 2H), 1.95 (dt, *J* = 7.7, 7.3 Hz 2H), 1.08 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3 (C_q), 149.3 (C_q), 141.1 (C_q), 137.8 (C_q), 136.3 (C_q), 131.4 (CH), 130.3 (CH), 129.6 (CH), 128.9 (C_q), 128.2 (CH), 127.5 (CH), 127.5 (CH), 127.1 (CH), 126.9 (CH), 126.3 (CH), 125.6 (C_q), 125.2 (CH), 37.7 (CH_2), 23.2 (CH_2), 14.5 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3063, 2962, 1612, 1568, 1550, 1444, 1385, 1087, 1031, 757, 697 cm^{-1}.
MS (EI) *m*/*z* (relative intensity) 323 (22) $[M]^+$, 295 (100), 308 (16), 252 (7).
HR-MS (EI): *m*/*z* calcd for $C_{24}H_{20}N^+$ $[M–H]^+$ 322.1590, found 322.1607.

Synthesis of 1-*n*-Butyl-3,4-diphenylisoquinoline (176da)



The representative procedure **F** was followed using substrate **194d** (89 mg, 0.50 mmol) and diphenylacetylene (**155a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 40/1) yielded **176da** (151 mg, 89%) as a yellow solid.
The representative procedure **G** was followed using substrate **194d** (89 mg, 0.50 mmol) and diphenylacetylene (**155a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 40/1) yielded **176da** (144 mg, 85%) as a yellow solid.
M. p.: 78–80 °C.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27–8.21 (m, 1H), 7.69–7.64 (m, 1H), 7.60–7.54 (m, 2H), 7.40–7.31 (m, 5H), 7.26–7.15 (m, 5H), 3.42 (t, *J* = 8.0 Hz, 2H), 2.02–1.90 (m, 2H), 1.58 (dt, *J* = 7.7, 7.3 Hz, 2H), 1.04 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5 (C_q), 149.3 (C_q), 141.1 (C_q), 137.7 (C_q), 136.3 (C_q), 131.4 (CH), 130.3 (CH), 129.6 (CH), 128.8 (C_q), 128.2 (CH), 127.5 (CH), 127.5 (CH), 127.0 (CH), 126.8 (CH), 126.3 (CH), 125.4 (C_q), 125.2 (CH), 35.5 (CH_2), 32.1 (CH_2), 23.1 (CH_2), 14.1 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3061, 2958, 2876, 1611, 1504, 1442, 1382, 1337, 1172, 1073, 763, 697 cm^{-1}.
MS (EI) *m*/*z* (relative intensity) 337 (6) $[M]^+$, 308 (10), 295 (100), 252 (6).
HR-MS (EI): *m*/*z* calcd for $C_{25}H_{22}N^+$ $[M–H]^+$ 336.1747, found 336.1747.

Synthesis of 1-Isopropyl-3,4-diphenylisoquinoline (176ea)



The representative procedure **F** was followed using substrate **194e** (82 mg, 0.50

mmol), diphenylacetylene (**155a**) (178 mg, 1.00 mmol) and molecular sieves 4 Å (100 mg). Purification by column chromatography (*n*-hexane/EtOAc: 400/1) yielded **176ea** (70 mg, 43%) as a yellow solid.

M.p.: 140–142 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32–8.24 (m, 1H), 7.68–7.62 (m, 1H), 7.58–7.51 (m, 2H), 7.47–7.39 (m, 2H), 7.39–7.31 (m, 3H), 7.28–7.20 (m, 2H), 7.20–7.13 (m, 3H), 4.02 (dt, *J* = 6.7, 6.7 Hz, 1H), 1.52 (d, *J* = 6.7 Hz, 6H).

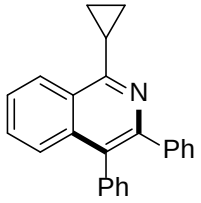
^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8 (C_q), 148.4 (C_q), 141.2 (C_q), 138.0 (C_q), 136.4 (C_q), 131.3 (CH), 130.5 (CH), 129.3 (CH), 128.3 (C_q), 128.2 (CH), 127.3 (CH), 127.0 (CH), 126.8 (CH), 126.4 (CH), 126.2 (CH), 124.69 (C_q), 124.43 (CH), 31.4 (CH), 22.34 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3073, 2969, 1551, 1446, 1381, 1258, 1104, 1007, 866 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 322 (100) $[M]^+$, 295 (86), 252 (13), 176 (8).

HR-MS (EI): *m*/*z* calcd for $C_{24}H_{20}N^+$ $[M–H]^+$ 322.1590, found 322.1596.

Synthesis of 1-Cyclopropyl-3,4-diphenylisoquinoline (176fa)



The representative procedure **F** was followed using substrate **194f** (81 mg, 0.50 mmol), diphenylacetylene (**155a**) (178 mg, 1.00 mmol) and molecular sieves 4 Å (100 mg). Purification by column chromatography (*n*-hexane/EtOAc: 200/1) yielded **176fa** (135 mg, 84%) as a yellow solid.

M. p.: 148–150 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.50 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.69–7.62 (m, 1H), 7.62–7.51 (m, 2H), 7.42–7.27 (m, 5H), 7.27–7.21 (m, 2H), 7.20–7.08 (m, 3H), 2.89–2.74 (m, 1H), 1.44–1.32 (m, 2H), 1.18–1.05 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6 (C_q), 148.7 (C_q), 141.2 (C_q), 138.0 (C_q), 136.1 (C_q), 131.4 (CH), 130.4 (CH), 129.6 (CH), 128.2 (CH), 128.0 (C_q), 127.3 (CH), 127.0 (CH), 126.8 (CH), 126.3 (CH), 126.3 (C_q), 126.2 (CH), 124.8 (CH), 13.6 (CH), 9.4 (CH_2).

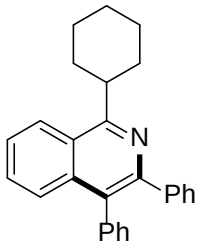
IR (ATR): $\tilde{\nu}$ = 3055, 1611, 1568, 1547, 1444, 1410, 1318, 1261, 1075, 1014, 767, 694 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 321 (68) $[M]^+$, 320 (100), 278 (5), 243 (8), 152 (5), 43 (13).

HR-MS (EI): *m*/*z* calcd for $C_{24}H_{18}N^+$ $[M–H]^+$ 320.1434, found 320.1438.

The spectral data were in accordance with those reported in the literature.[256]

Synthesis of 1-Cyclohexyl-3,4-diphenylisoquinoline (176ga)



The representative procedure **F** was followed using substrate **194g** (102 mg, 0.50 mmol), diphenylacetylene (**155a**) (178 mg, 1.00 mmol) and molecular sieves 4 Å (100 mg). Purification by column chromatography (*n*-hexane/EtOAc: 200/1) yielded **176ga** (147 mg, 81%) as a yellow solid.

M. p.: 158–160 °C.

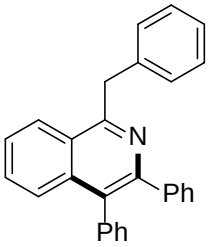
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31–8.25 (m, 1H), 7.68–7.62 (m, 1H), 7.58–7.49 (m, 2H), 7.46–7.40 (m, 2H), 7.38–7.32 (m, 3H), 7.26–7.20 (m, 2H), 7.20–7.14 (m, 2H), 3.68–3.57 (m, 1H), 2.12–1.75 (m, 7H), 1.64–1.31 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.4 (C_q), 148.6 (C_q), 141.3 (C_q), 138.1 (C_q), 136.5 (C_q), 131.4 (CH), 130.6 (CH), 129.3 (CH), 128.25 (CH), 128.23 (C_q), 127.4 (CH), 127.0 (CH), 126.8 (CH), 126.5 (CH), 126.2 (CH), 124.7 (C_q), 124.5 (CH), 41.8 (CH), 32.5 (CH_2), 26.9 (CH_2), 26.3 (CH_2).

IR (ATR): $\tilde{\nu}$ = 2924, 2850, 1670, 1612, 1551, 1504, 1446, 1373, 1334, 1260, 1029, 758, 696 cm^{-1}.

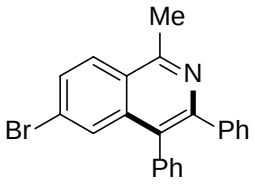
MS (EI) *m*/*z* (relative intensity) 362 (50) $[M]^+$, 334 (13), 308 (100), 295 (50), 280 (8), 43 (6).
HR-MS (EI^+): *m*/*z* calcd for $C_{27}H_{24}N^+$ $[M–H]^+$ 362.1903, found 362.1903.
The spectral data were in accordance with those reported in the literature.[256]

Synthesis of 1-Benzyl-3,4-diphenylisoquinoline (176ha)



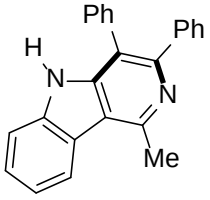
The representative procedure **F** was followed using substrate **194h** (106 mg, 0.50 mmol), diphenylacetylene (**155a**) (178 mg, 1.00 mmol) and molecular sieves 4 Å (100 mg). Purification by column chromatography (*n*-hexane/EtOAc: 100/1) yielded **176ha** (100 mg, 54%) as a yellow solid.
M. p.: 118–120 °C.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26–8,19 (m, 1H), 7.69–7.62 (m, 1H), 7.56–7.46 (m, 2H), 7.46–7.39 (m, 4H), 7.39–7.14 (m, 11H), 4.79 (s, 2H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1 (C_q), 149.4 (C_q), 140.9 (C_q), 139.7 (C_q), 137.5 (C_q), 136.7 (C_q), 131.3 (CH), 130.4 (CH), 129.7 (CH), 129.6 (C_q), 129.0 (C_q), 128.7 (CH), 128.4 (CH), 128.2 (CH), 127.6 (CH), 127.2 (CH), 127.0 (CH), 126.6 (CH), 126.4 (CH), 126.2 (CH), 125.7 (CH), 42.4 (CH_2).
IR (ATR): $\tilde{\nu}$ = 3024, 1616, 1576, 1554, 1521, 1493, 1490, 1473, 1440, 1376, 1072, 754, 697 cm^{-1}.
MS (EI) *m*/*z* (relative intensity) 370 (100) $[M]^+$, 293 (7), 265 (6), 91 (5), 43 (13).
HR-MS (EI^+): *m*/*z* calcd for $C_{28}H_{20}N^+$ $[M–H]^+$ 370.1590, found 370.1584.

Synthesis of 6-Bromo-1-methyl-3,4-diphenylisoquinoline (176ia)



The representative procedure **F** was followed using substrate **194i** (107 mg, 0.50 mmol), diphenylacetylene (**155a**) (178 mg, 1.00 mmol) and molecular sieves 4 Å (100 mg). Purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **176ia** (102 mg, 55%) as a yellow solid.
M. p.: 193–195 °C.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.9 Hz, 1H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.67 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.39–7.30 (m, 5H), 7.23–7.14 (m, 5H), 3.06 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.6 (C_q), 150.5 (C_q), 140.5 (C_q), 137.3 (C_q), 136.7 (C_q), 131.2 (CH), 130.0 (CH), 129.9 (CH), 128.3 (CH), 128.3 (CH), 128.2 (C_q), 127.6 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 125.0 (C_q), 124.5 (C_q), 22.8 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3064, 1597, 1561, 1481, 1445, 1386, 1329, 1259, 1071, 1029, 751, 697 cm^{-1}.
MS (EI) *m*/*z* (relative intensity) 375/373 (100/100) $[M]^+$, 293 (26), 252 (28), 189 (15), 43 (56).
HR-MS (ESI): *m*/*z* calcd for $C_{22}H_{17}{}^{79}BrN^+$ $[M+H]^+$ 374.0539, found 374.0538.
The spectral data were in accordance with those reported in the literature.[257]

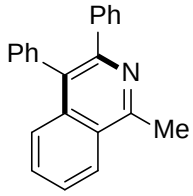
Synthesis of 1-Methyl-3,4-diphenyl-5*H*-pyrido[4,3-*b*]indole (176ja)



The representative procedure **F** was followed using substrate **194j** (87 mg, 0.50 mmol) diphenylacetylene (**155a**) (178 mg, 1.00 mmol) and molecular sieves 4 Å (100 mg). Purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **176ja** (62 mg, 37%) as a yellow solid.
M. p.: 182–184 °C.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.47 (s, 1H), 8.18 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.50–7.26 (m, 10H), 7.22–7.13 (m, 3H), 3.13 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.9 (C_q), 151.5 (C_q), 143.8 (C_q), 140.4 (C_q), 139.5 (C_q), 136.1 (C_q), 130.3 (CH), 130.2 (CH), 129.0 (CH), 127.6 (CH), 127.4 (CH), 127.1 (CH), 126.0 (CH), 122.6 (C_q), 122.3 (CH), 120.8 (CH), 116.9 (C_q), 116.82 (C_q), 110.81 (CH), 23.8 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3640, 3050, 1594, 1492, 1405, 1234, 1118, 1020, 793 cm^{-1}.
MS (EI) *m/z* (relative intensity) 334 (30) $[M]^+$, 291 (5), 167 (8), 77 (2).
HR-MS (EI): *m/z* calcd for $C_{24}H_{19}N_2^+$ $[M+H]^+$ 335.1543, found 335.1541.

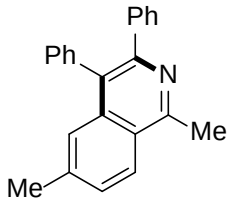
Synthesis of 1-Methyl-3,4-diphenylisoquinoline (176aa)



The representative procedure **G** was followed using substrate **194a** (68 mg, 0.50 mmol) diphenylacetylene (**155a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **176aa** (96 mg, 65%) as a yellow solid.
M. p.: 152–155 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23–8.20 (m, 1H), 7.71–7.67 (m, 1H), 7.63–7.57 (m, 2H), 7.44–7.32 (m, 5H), 7.29–7.17 (m, 5H), 3.11 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7 (C_q), 149.4 (C_q), 141.0 (C_q), 137.6 (C_q), 136.0 (C_q), 131.4 (CH), 130.2 (CH), 129.9 (CH), 129.1 (C_q), 128.1 (CH), 127.6 (CH), 127.1 (CH), 126.9 (CH), 126.5 (CH), 126.2 (CH), 126.1 (C_q), 125.5 (CH), 22.7 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3025, 1567, 1389, 1334, 1072, 1026, 765, 695, 612, 563, 496 cm^{-1}.
MS (EI) *m/z* (relative intensity) 295 (50) $[M]^+$, 294 (100), 278 (5), 252 (17), 177 (15), 43 (14).
HR-MS (EI): *m/z* calcd for $C_{22}H_{17}N^+$ $[M]^+$ 295.1356, found 295.1348.
The spectral data were in accordance with those reported in the literature.[255]

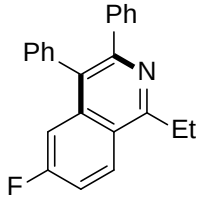
Synthesis of 1,6-Dimethyl-3,4-diphenylisoquinoline (176ka)



The representative procedure **G** was followed using substrate **194k** (75 mg, 0.50 mmol) and diphenylacetylene (**155a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **176ka** (124 mg, 80%) as a white solid.
M. p.: 160–163 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 9.2 Hz, 1H), 7.44–7.39 (m, 2H), 7.39–7.30 (m, 5H), 7.25–7.14 (m, 5H), 3.05 (s, 3H), 2.43 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.3 (C_q), 149.5 (C_q), 141.1 (C_q), 140.1 (C_q), 137.7 (C_q), 136.2 (C_q), 131.4 (CH), 130.2 (CH), 128.7 (C_q), 128.6 (CH), 128.1 (CH), 127.5 (CH), 127.0 (CH), 126.8 (CH), 125.4 (CH), 125.0 (CH), 124.5 (C_q), 22.6 (CH_3), 22.1 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3062, 1495, 1444, 1385, 1336, 1071, 1029, 813, 767, 755, 696, 614 cm^{-1}.
MS (EI) *m/z* (relative intensity) 309 (40) $[M]^+$, 308 (100), 293 (5), 265 (5), 252 (12), 43 (4).
HR-MS (ESI): *m/z* calcd for $C_{23}H_{20}N^+$ $[M+H]^+$ 310.1590, found 310.1592.
The spectral data were in accordance with those reported in the literature.[255]

Synthesis of 1-Ethyl-6-fluoro-3,4-diphenylisoquinoline (176la)



The representative procedure **G** was followed using substrate **194l** (83 mg, 0.50 mmol) and diphenyl acetylene (**155a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 15/1→12/1) yielded **176la** (98 mg, 60%) as a white solid.

M. p.: 141–142 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (dd, J = 9.2, 5.7 Hz, 1H), 7.45– 7.10 (m, 12H), 3.42 (q, J = 7.5 Hz, 2H), 1.53 (t, J = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0 (d, $^1J_{C–F}$ = 245 Hz, C_q), 162.0 (C_q), 150.7 (C_q), 140.8 (C_q), 138.4 (d, $^3J_{C–F}$ = 10 Hz, C_q), 137.3 (C_q), 131.2 (CH), 130.3 (CH), 128.7 (d, $^4J_{C–F}$ = 5 Hz, C_q), 128.4 (CH), 128.2 (d, $^3J_{C–F}$ = 10 Hz, CH), 127.6 (CH), 127.3 (CH), 127.1 (CH), 122.5 (d, $^4J_{C–F}$ = 1 Hz, C_q), 116.6 (d, $^2J_{C–F}$ = 25 Hz, CH), 110.0 (d, $^2J_{C–F}$ = 22 Hz, CH), 28.9 (CH_2), 13.9 (CH_3).

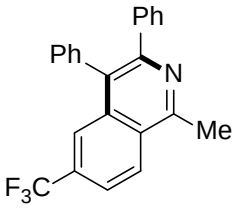
^{19}F NMR (282 MHz, $CDCl_3$): δ = –107.9 (s).

IR (ATR): $\tilde{\nu}$ = 2973, 1619, 1573, 1447, 1386, 1182, 1072, 876, 788, 753, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity) 327 (53) $[M]^+$, 326 (100), 311 (12), 298 (10), 98 (10), 57 (10).

HR-MS (ESI): *m/z* calcd for $C_{23}H_{19}FN^+$ $[M+H]^+$ 328.1496, found 328.1498.

Synthesis of 6-(Trifluoromethyl)-1-methyl-3,4-diphenylisoquinoline (176ma)



The representative procedure **G** was followed using substrate **194m** (102 mg, 0.50 mmol) and diphenylacetylene (**155a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **176ma** (86 mg, 47%) as an orange solid.

M. p.: 109–114 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (d, J = 8.8 Hz, 1H), 7.96 (d, J = 1.8 Hz, 1H), 7.75 (dd, J = 8.8, 1.8 Hz, 1H), 7.40–7.33 (m, 5H), 7.23–7.16 (m, 5H), 3.10 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.8 (C_q), 150.9 (C_q), 140.4 (C_q), 136.5 (C_q), 135.4 (C_q), 131.5 (q, $^2J_{C–F}$ = 32 Hz, Cq), 131.2 (CH), 130.2 (CH), 129.7 (C_q), 128.5 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 127.0 (C_q), 126.8 (CH), 123.9 (q, $^3J_{C–F}$ = 5 Hz, CH), 123.8 (d, $^1J_{C–F}$ = 272 Hz, C_q), 122.2 (q, $^3J_{C–F}$ = 3 Hz, CH), 22.8 (CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.9 (s).

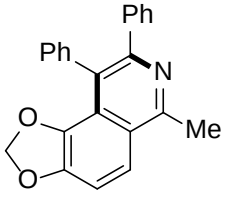
IR (ATR): $\tilde{\nu}$ = 2958, 1555, 1336, 1305, 1257, 1176, 1155, 1134, 1082, 909, 769, 696, 618 cm^{-1}.

MS (EI) *m/z* (relative intensity) 363 (50) $[M]^+$, 362 (100), 252 (8), 146 (5), 43 (5).

HR-MS (EI): *m/z* calcd for $C_{23}H1_6F_3N^+$ $[M]^+$ 363.1229, found 363.1219.

The spectral data were in accordance with those reported in the literature.[257]

Synthesis of 5,6-(Methylenedioxy)-1-methyl-3,4-diphenylisoquinoline (176na)



The representative procedure **G** was followed using substrate **194n** (90 mg, 0.50 mmol) and diphenylacetylene (**155a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **176na** (146 mg, 86%) as a white solid.

M. p.: 251–254 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.8 Hz, 1H), 7.37–7.06 (m, 11H), 5.83 (s, 2H), 2.99 (s, 3H).

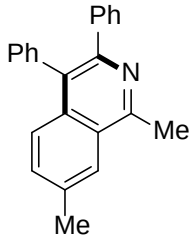
^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7 (C_q), 150.2 (C_q), 147.6 (C_q), 141.7 (C_q), 140.8 (C_q), 138.4 (C_q), 131.1 (CH), 130.2 (CH), 127.5 (CH), 127.0 (CH), 126.8 (CH), 126.7 (CH), 124.8 (C_q), 123.2 (C_q), 122.5 (C_q), 120.9 (CH), 110.8 (CH), 101.4 (CH_2), 23.4 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2899, 1626, 1549, 1512, 1432, 1383, 1353, 1279, 1209, 1119, 1049, 794 cm^{-1}.

MS (EI) *m/z* (relative intensity) 339 (100) $[M]^+$, 338 (98), 310 (18), 292 (14), 176 (5).

HR-MS (EI): *m/z* calcd for $C_{23}H_{17}NO_2^+$ $[M]^+$ 339.1254, found 339.1252.

Synthesis of 1,7-Dimethyl-3,4-diphenylisoquinoline (176oa)



The representative procedure **G** was followed using substrate **194o** (75 mg, 0.50 mmol) and diphenylacetylene (**155a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **176oa** (119 mg, 77%) as a pale orange solid.

M. p.: 134–139 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (dq, *J* = 1.8, 0.9 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.45–7.30 (m, 6H), 7.26–7.14 (m, 5H), 3.06 (s, 3H), 2.57 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.9 (C_q), 148.6 (C_q), 141.0 (C_q), 137.7 (C_q), 136.3 (C_q), 134.1 (C_q), 132.0 (CH), 131.3 (CH), 130.2 (CH), 129.0 (C_q), 128.1 (CH), 127.5 (CH), 127.0 (CH), 126.7 (CH), 126.2 (C_q), 126.0 (CH), 124.4 (CH), 22.7 (CH3), 21.8 (CH_3).

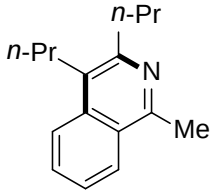
IR (ATR): $\tilde{\nu}$ = 3023, 2914, 1551, 1504, 1442, 1386, 1321, 1073, 1027, 831 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 309 (65) $[M]^+$, 293 (8), 265 (5), 252 (15), 146 (5), 100 (100).

HR-MS (ESI): *m*/*z* calcd for $C_{23}H_{20}N^+$ $[M+H]^+$ 310.1590, found 310.1592.

The spectral data were in accordance with those reported in the literature.[258]

Synthesis of 1-Methyl-3,4-di-*n*-propylisoquinoline (176ad)



The representative procedure **G** was followed using substrate **194a** (68 mg, 0.50 mmol) and oct-4-yne (**155d**) (110 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **176ad** (87 mg, 77%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.94 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.3 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.47 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 3.01–2.92 (m, 2H), 2.92–2.84 (m, 2H), 2.89 (s, 3H), 1.84–1.72 (m, 2H), 1.71–1.58 (m, 2H), 1.07 (t, *J* = 6.7 Hz, 3H), 1.03 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6 (C_q), 151.7 (C_q), 135.4 (C_q), 129.3 (CH), 126.1 (C_q), 126.1 (CH), 126.0 (C_q), 125.2 (CH), 123.5 (CH), 37.4 (CH_2), 29.8 (CH_2), 24.2 (CH_2), 23.8 (CH_2), 22.4 (CH_3), 14.6 (CH_3), 14.4 (CH_3).

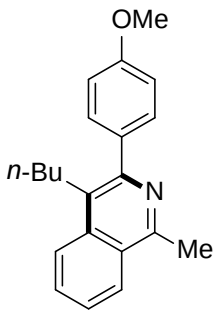
IR (neat): $\tilde{\nu}$ = 2957, 2870, 1617, 1568, 1454, 1391, 1333, 1027, 754, 614 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 227 (40) $[M]^+$, 212 (80), 198 (100), 184 (50), 171 (55), 128 (23), 115 (16).

HR-MS (EI): *m*/*z* calcd for $C_{16}H_{21}N^+$ $[M]^+$ 227.1669, found 227.1674.

The spectral data were in accordance with those reported in the literature.[255]

Synthesis of 4-*n*-Butyl-3-(4-methoxyphenyl)-1-methylisoquinoline (176ae)



The **r**epresentative procedure **G** was followed using substrate **194a** (68 mg, 0.50 mmol) and 1-(*p*-tolyl)-1-hexyne (**155e**) (172 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **176ae** (70 mg, 46%) as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (dd, *J* = 8.6, 0.9 Hz, 1H), 8.04 (dt, *J* = 8.6, 0.9

Hz, 1H), 7.70 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.56 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 3.03–2.91 (m, 2H), 2.95 (s, 3H), 2.41 (s, 3H), 1.70–1.56 (m, 2H), 1.34 (dt, *J* = 7.3, 7.3 Hz, 2H), 0.86 (t, *J* = 7.3 Hz, 3H).

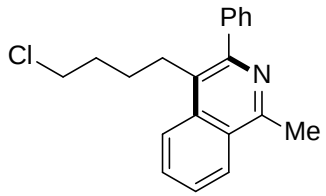
^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6 (C_q), 150.9 (C_q), 139.0 (C_q), 136.9 (C_q), 135.4 (C_q), 129.6 (CH), 129.1 (CH), 128.7 (CH), 127.2 (C_q), 126.5 (C_q), 126.2 (CH), 126.0 (CH), 124.2 (CH), 33.4 (CH_2), 28.3 (CH_2), 23.0 (CH_2), 22.5 (CH_3), 21.2 (CH_3), 13.8 (CH_3).

IR (neat): $\tilde{\nu}$ = 2955, 2923, 2869, 1614, 1563, 1513, 1438, 1391, 1333, 1026, 825, 755 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 289 (50) $[M]^+$, 260 (70), 246 (100), 231 (30), 216 (8).

HR-MS (EI): *m*/*z* calcd for $C_{21}H_{23}NO^+$ $[M]^+$ 305.1774, found 305.1771.

Synthesis of 4-(4-Chloro-*n*-butyl)-1-methyl-3-phenylisoquinoline (176af)



The representative procedure **G** was followed using substrate **194a** (68 mg, 0.50 mmol) and 6-chloro-1-phenylhexyne (**155f**) (193 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 12/1) yielded **176af** (112 mg, 72%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (ddd, *J* = 8.4, 1.3, 0.8 Hz, 1H), 8.04 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.73 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.59 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.53–7.34 (m, 5H), 3.42 (t, *J* = 6.2 Hz, 2H), 3.03–2.95 (m, 2H), 2.97 (s, 3H), 1.86–1.68 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.1 (C_q), 151.1 (C_q), 141.6 (C_q), 135.2 (C_q), 129.9 (CH), 129.2 (CH), 128.2 (CH), 127.5 (CH), 126.6 (C_q), 126.4 (C_q), 126.3 (CH), 126.2 (CH), 124.0 (CH), 44.4 (CH_2), 32.3 (CH_2), 28.1 (CH_2), 27.5 (CH_2), 22.5 (CH_3).

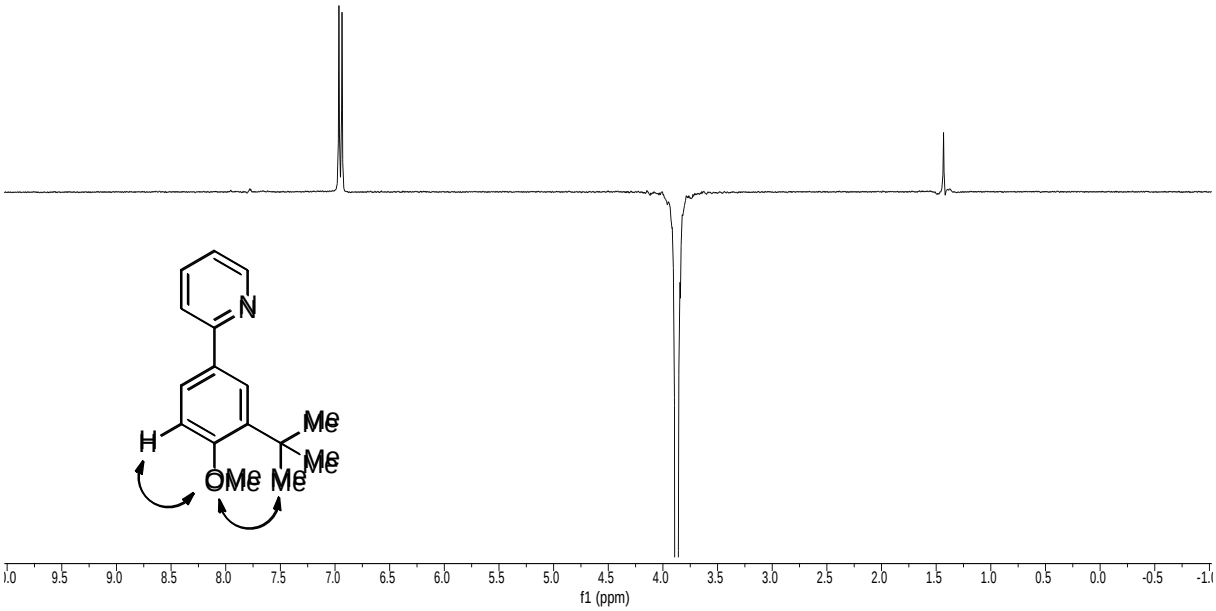
IR (neat): $\tilde{\nu}$ = 2953, 1614, 1561, 1504, 1437, 1391, 1331, 1027, 756 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 311/309 (14/41) $[M]^+$, 246 (95), 232 (100), 217 (16), 202 (6), 189 (6).

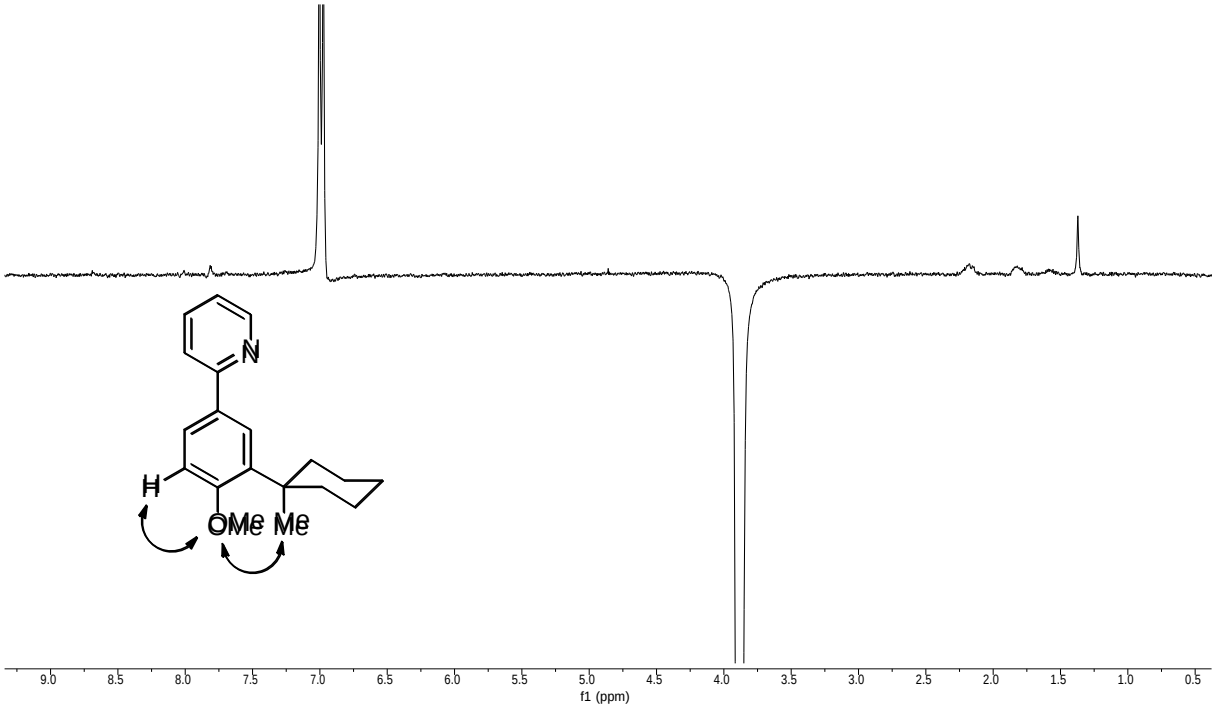
HR-MS (EI): *m*/*z* calcd for $C_{20}H_{20}{}^{35}ClN^+$ $[M]^+$ 309.1279, found 309.1297.

7.3.7 Selected NMR Spectra

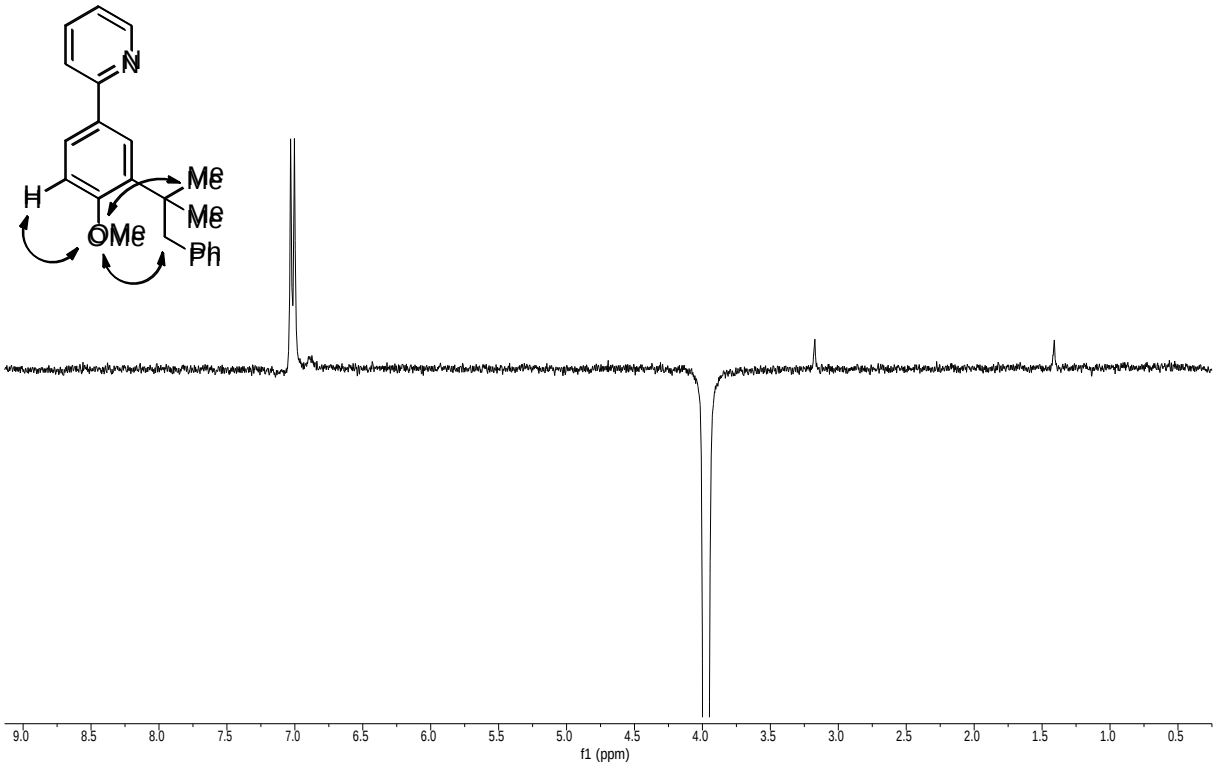
nOe 187ba



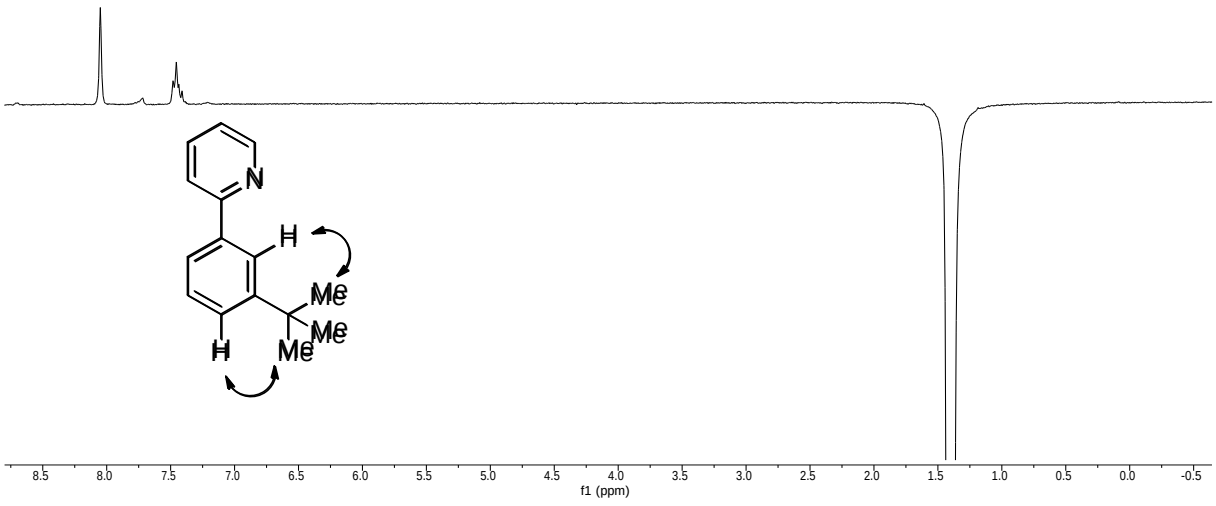
nOe 187bb



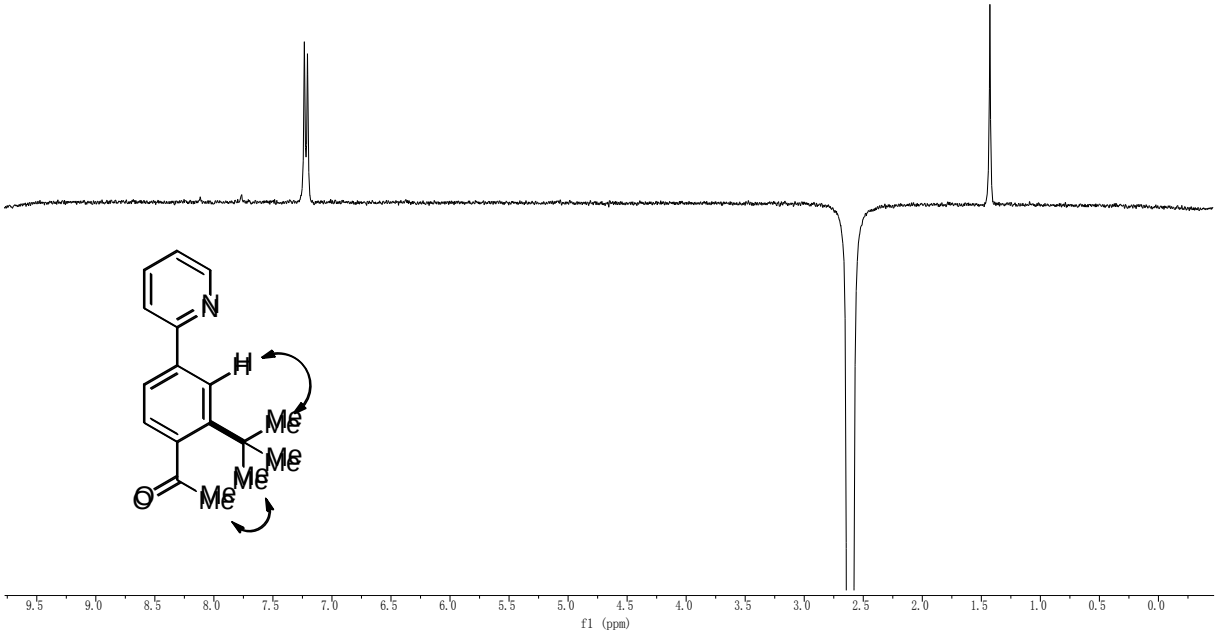
nOe 187bj


N
H
OMe
Me
Me
Ph
9.0
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
f1 (ppm)

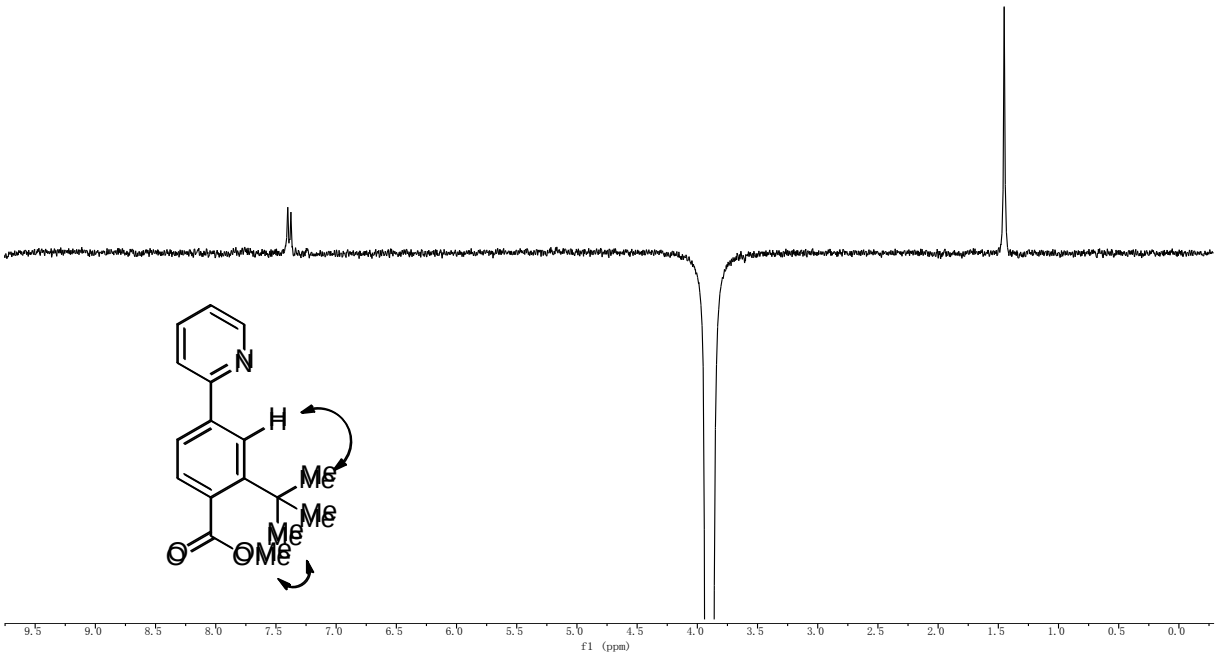
nOe 187aa


N
H
Me
Me
H
Me
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
-0.5
f1 (ppm)

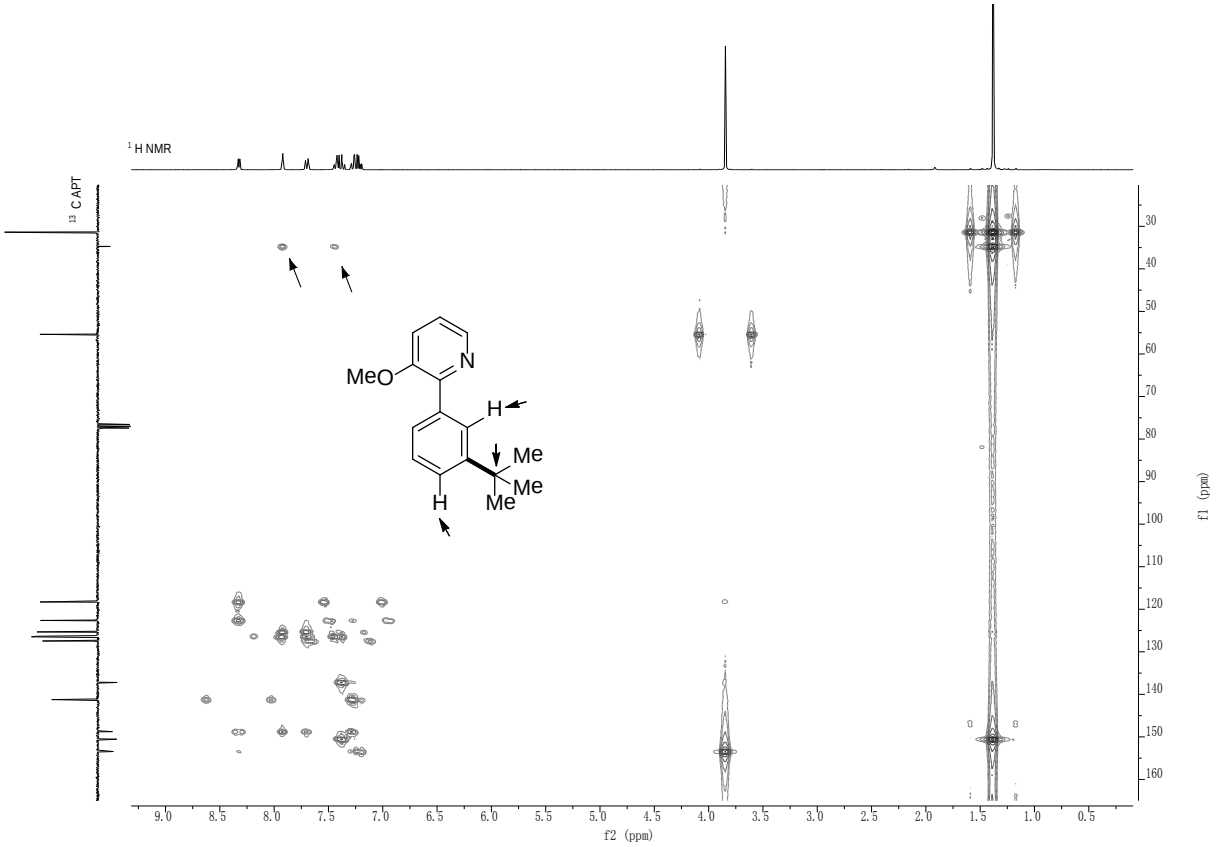
nOe 187da



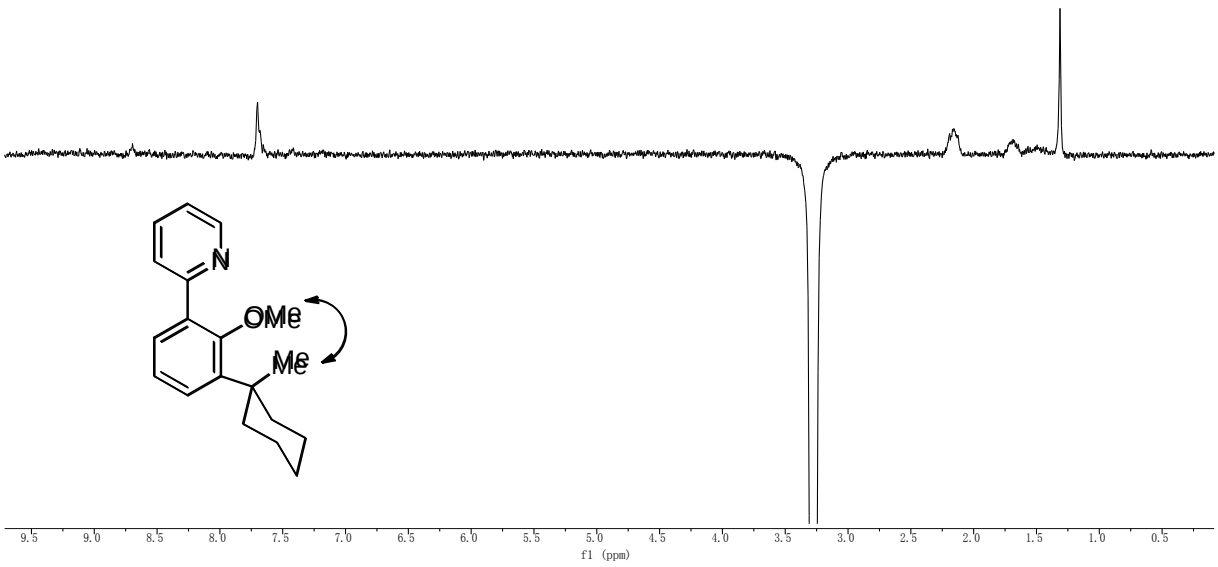
nOe 187ea



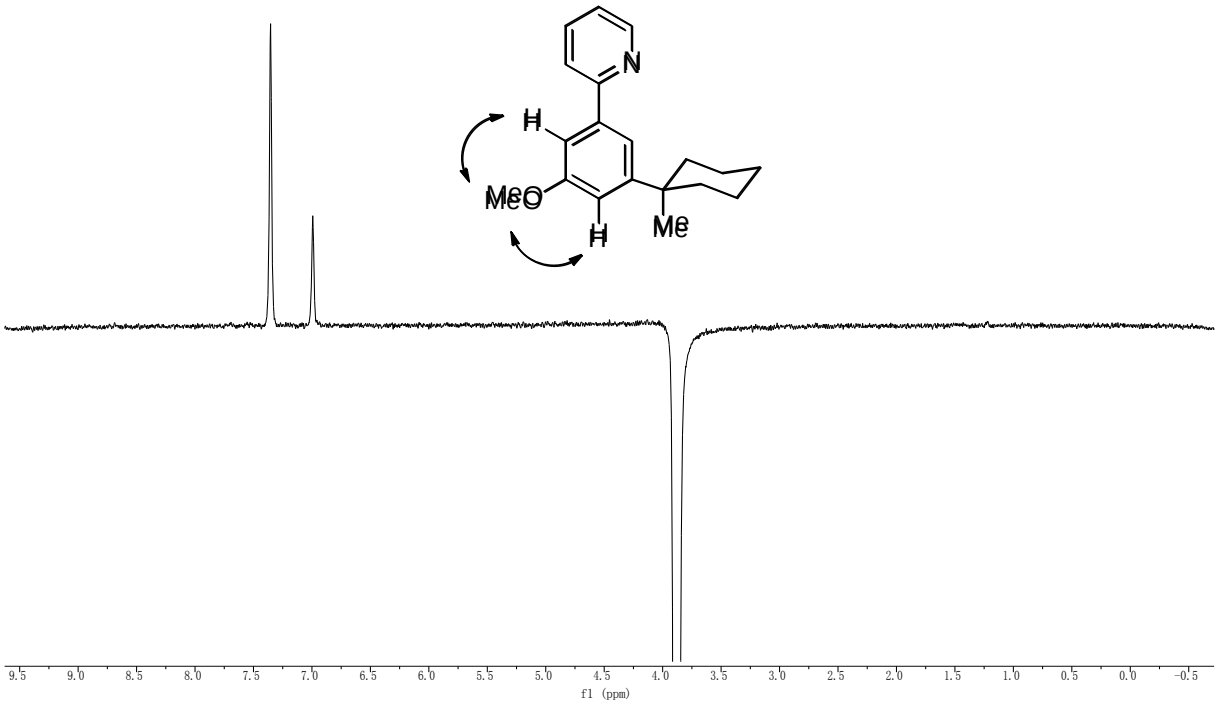
HMBC 187ja



nOe 187qb



nOe 187rb



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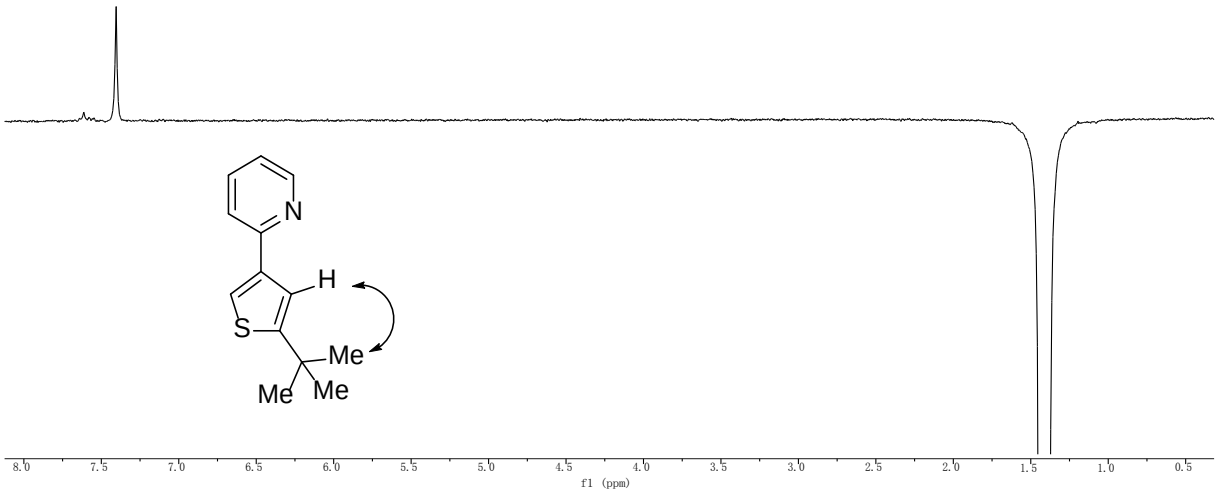

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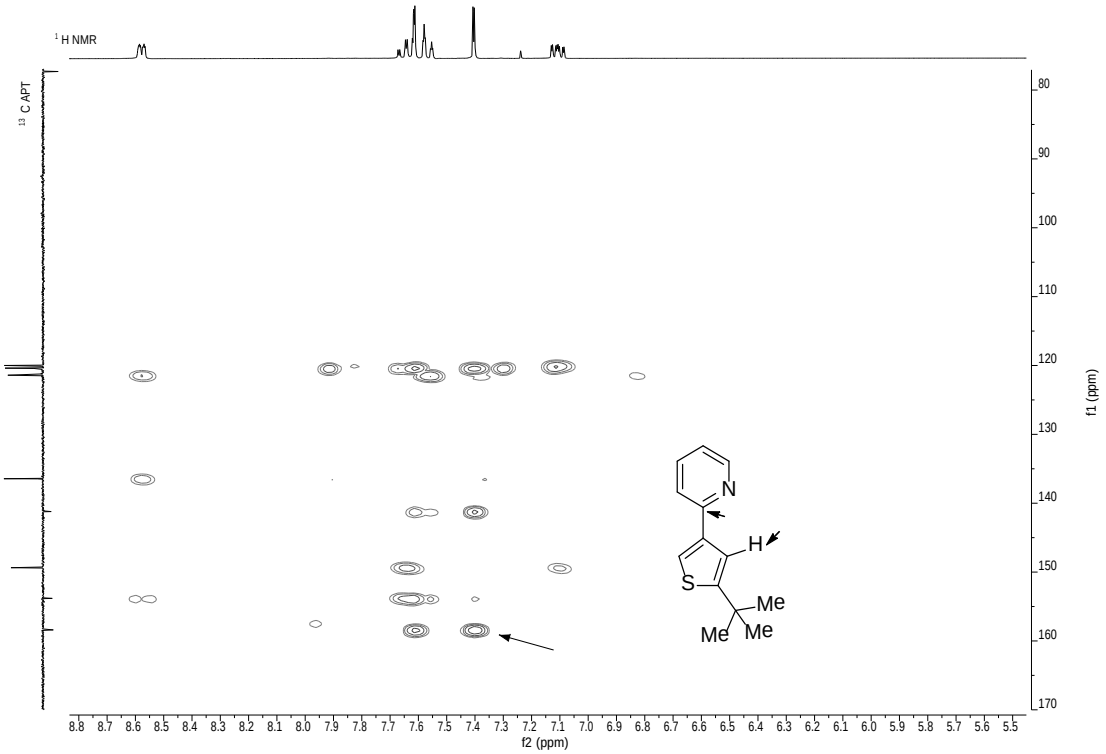

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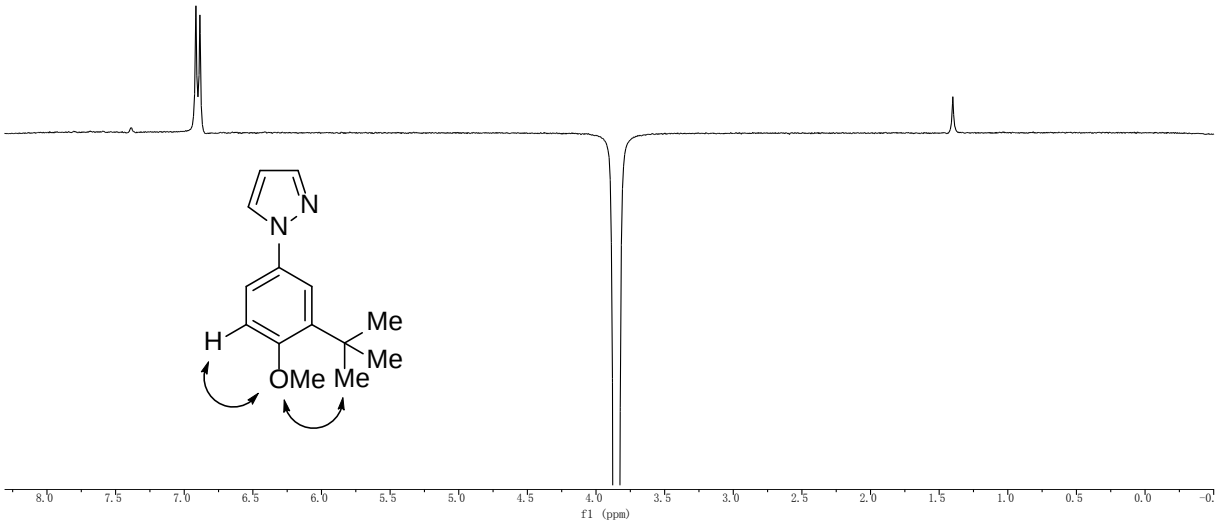

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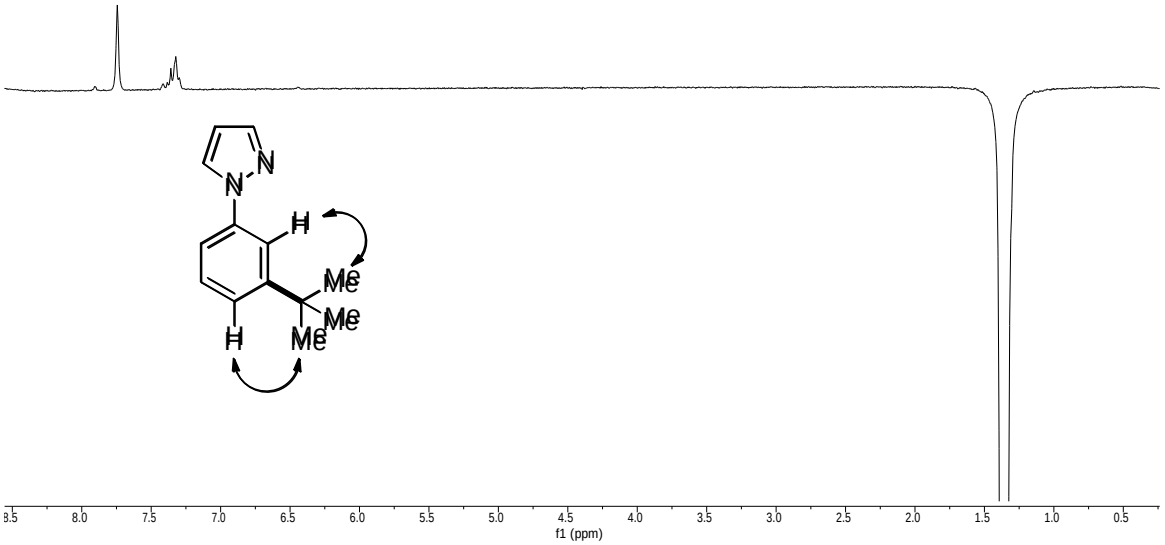

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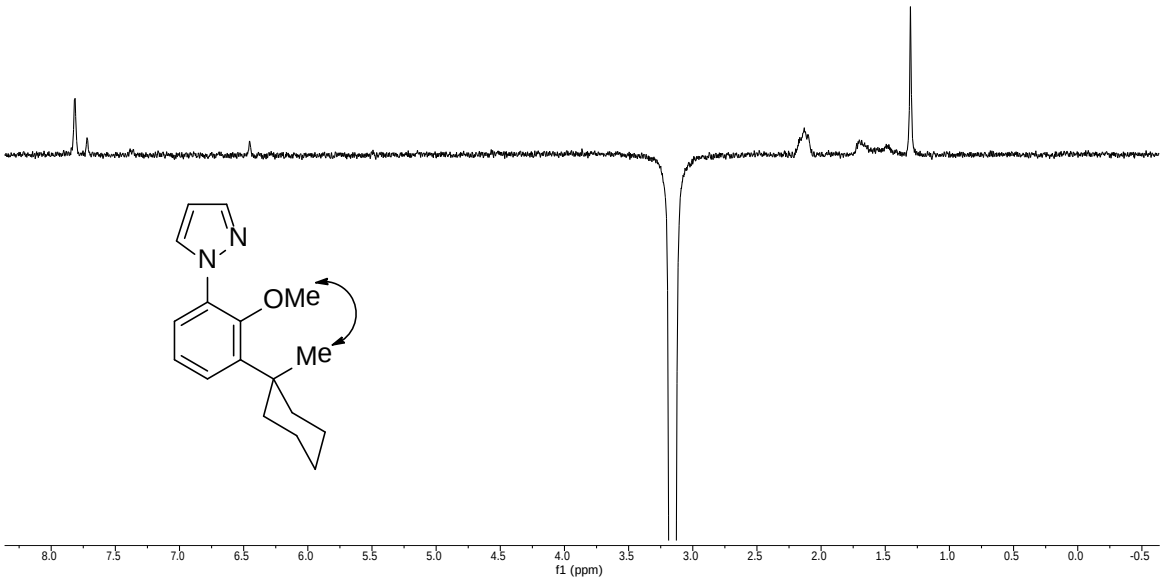

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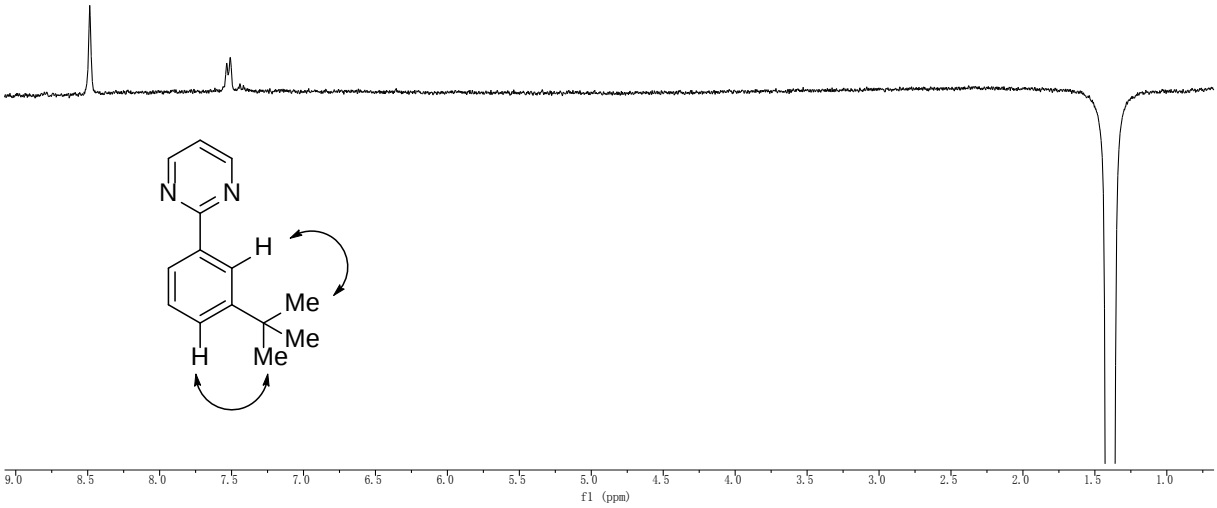

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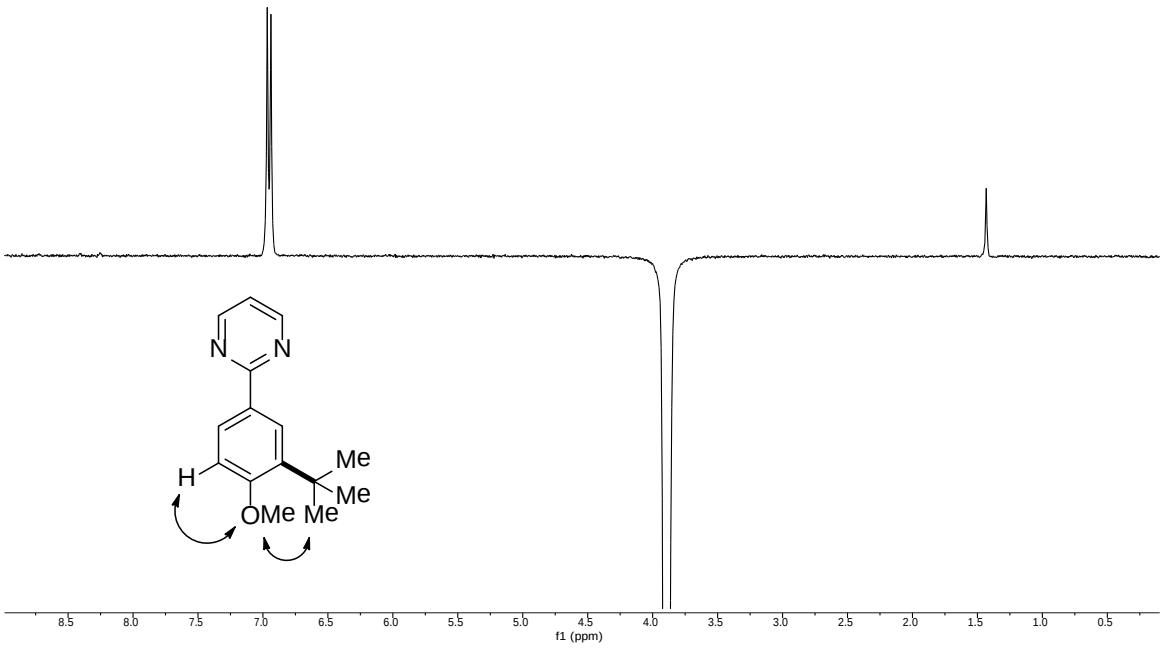

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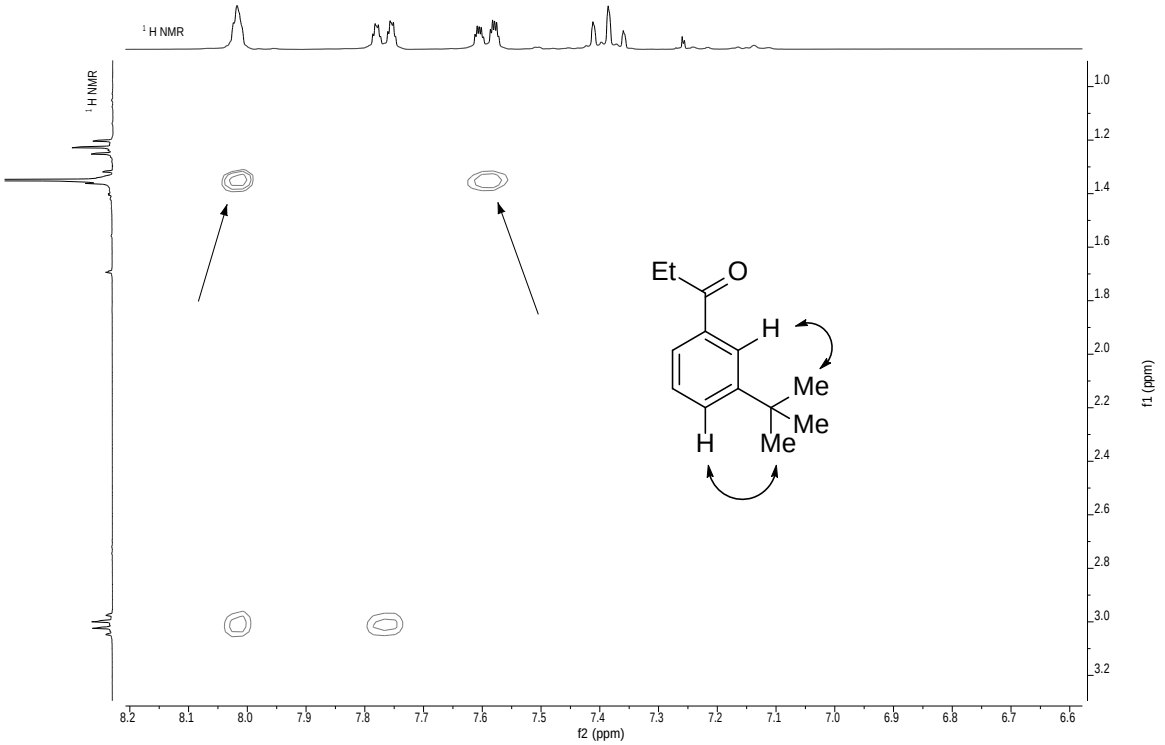

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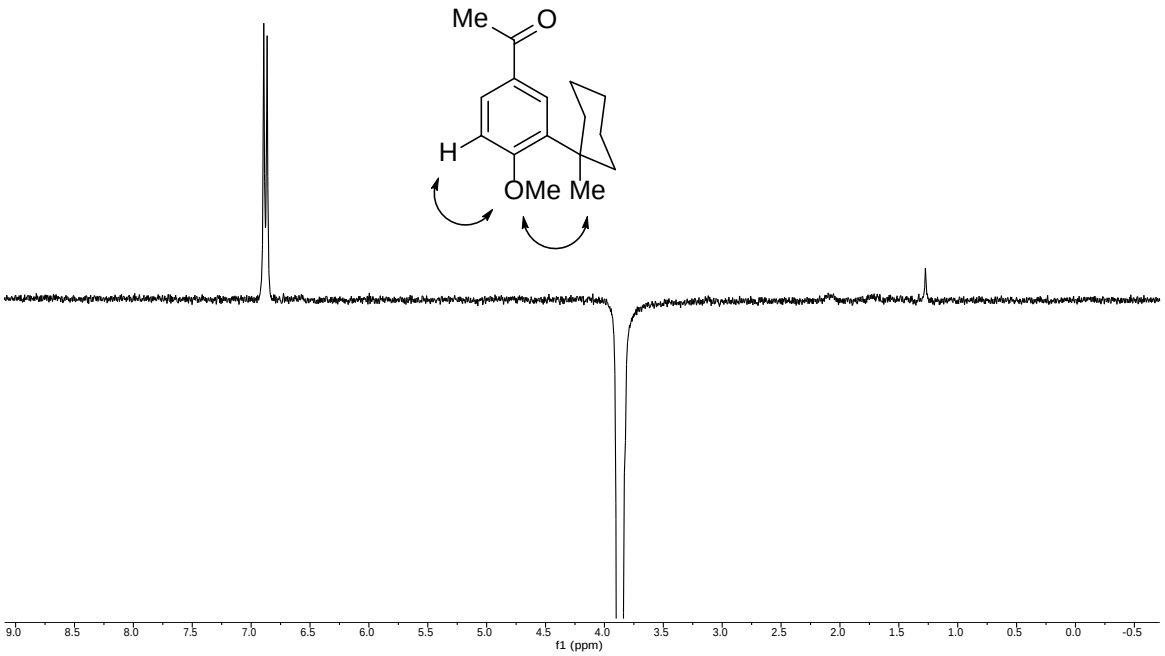

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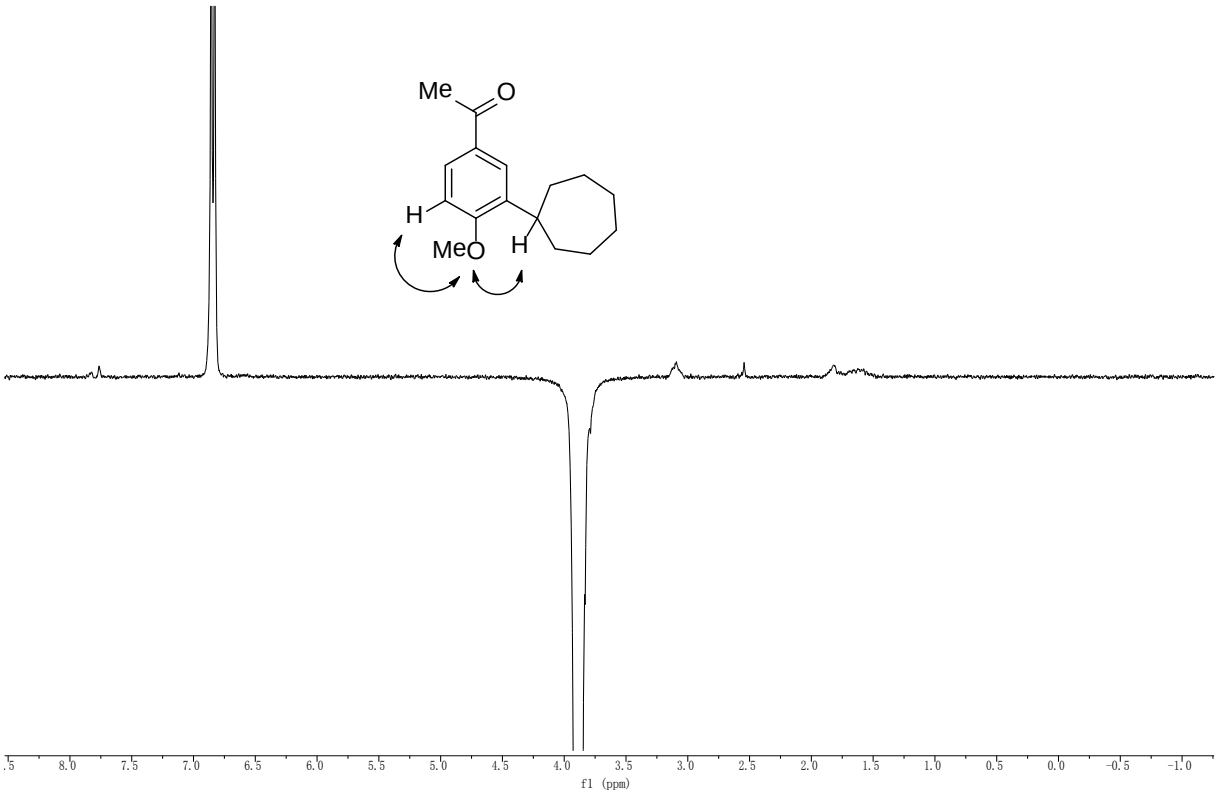

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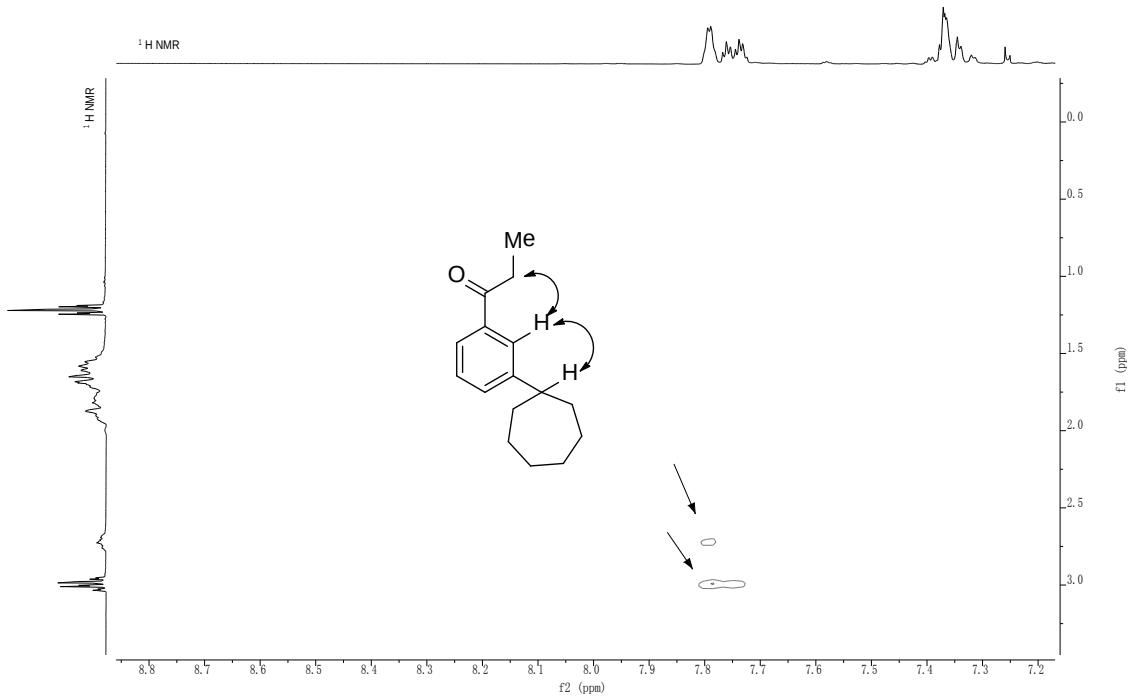

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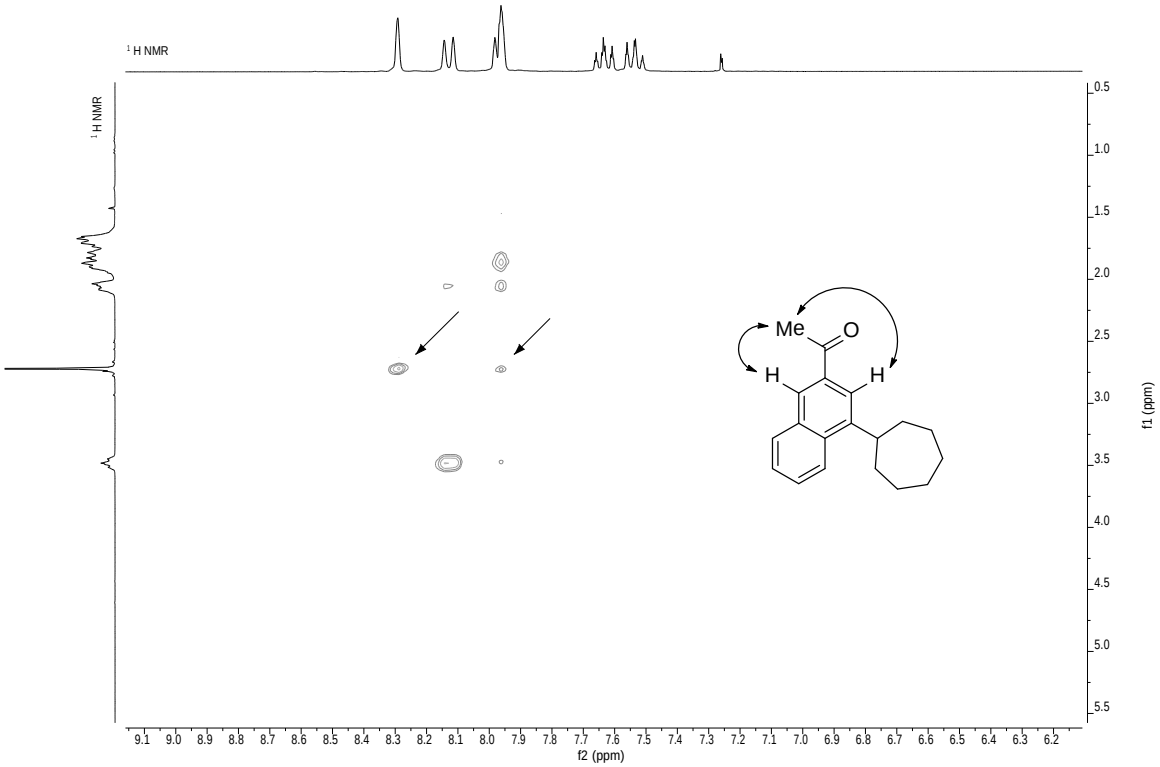

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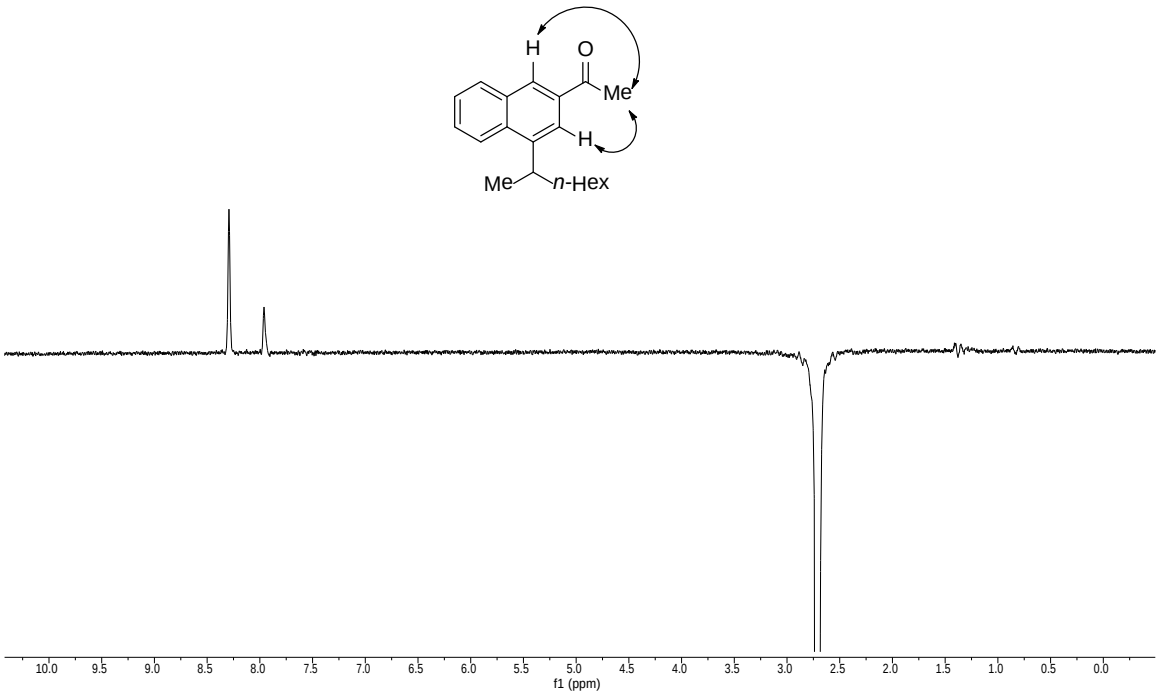

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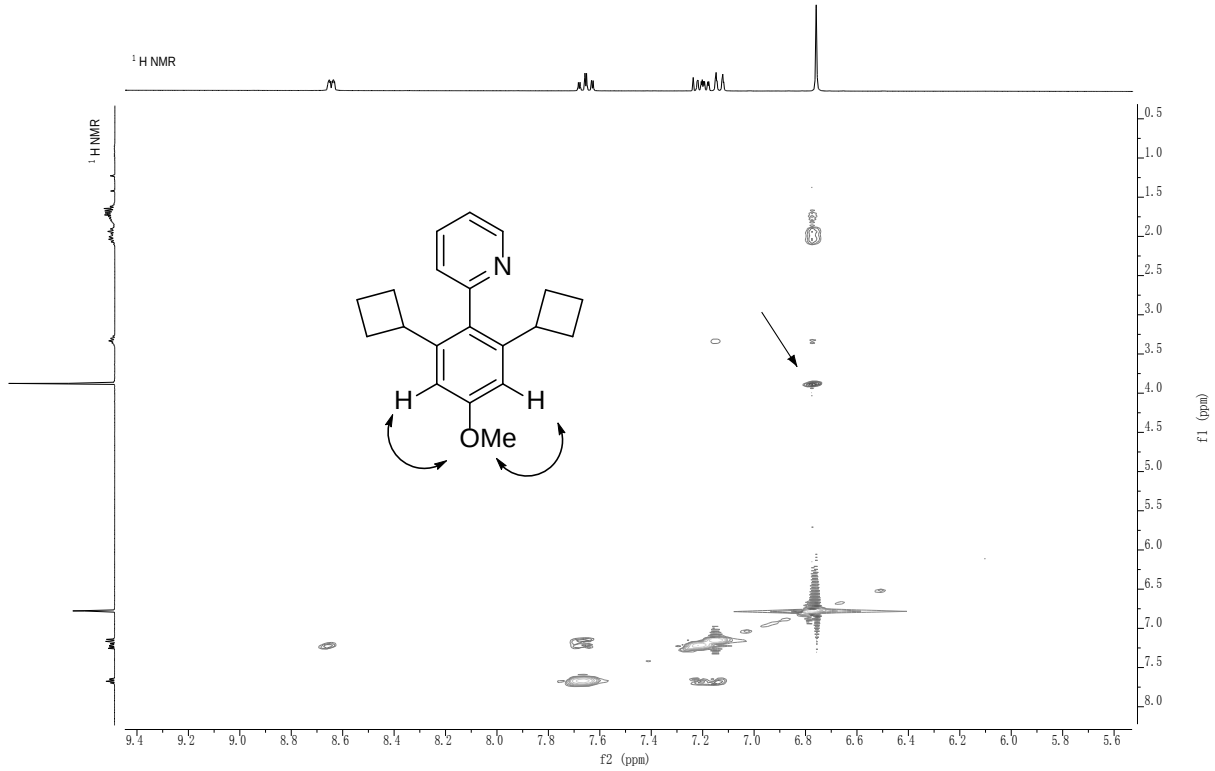

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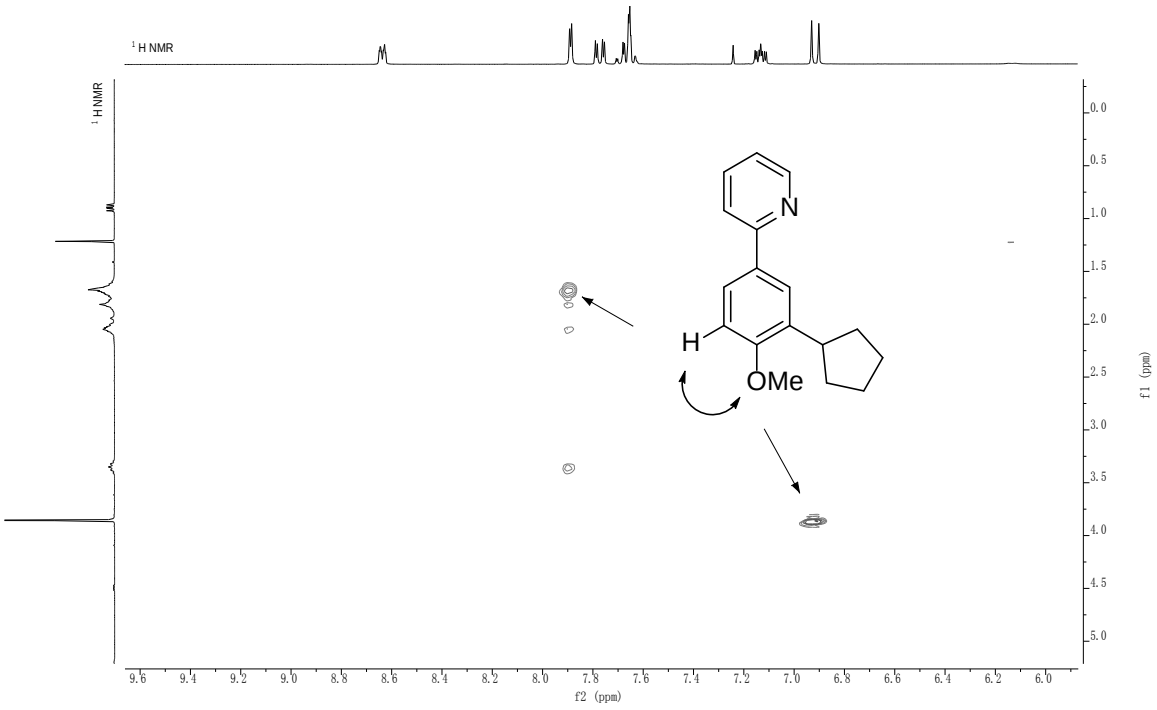

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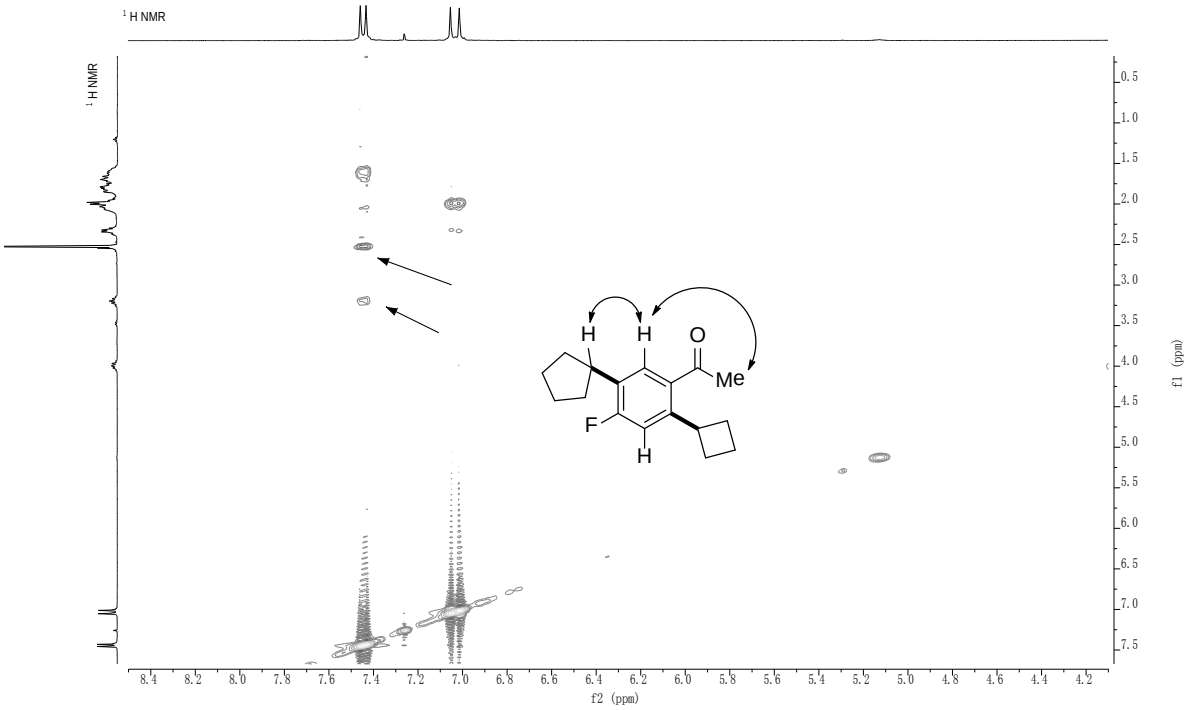

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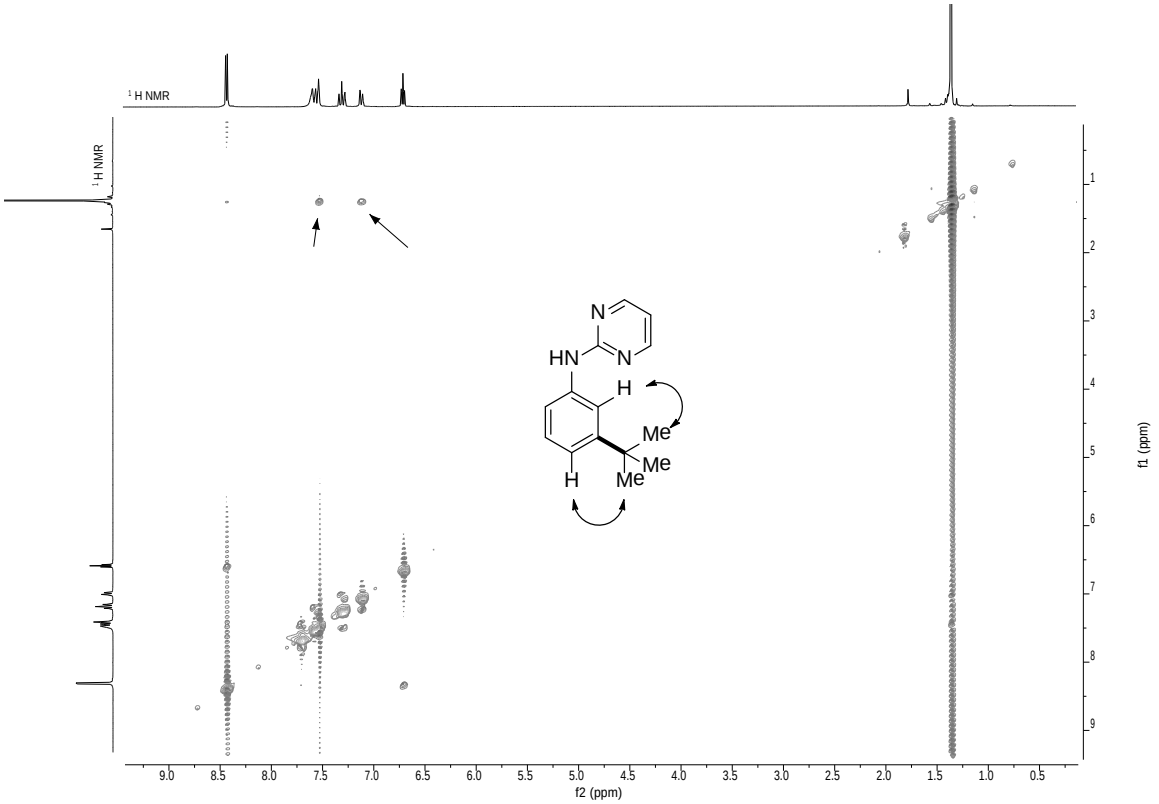

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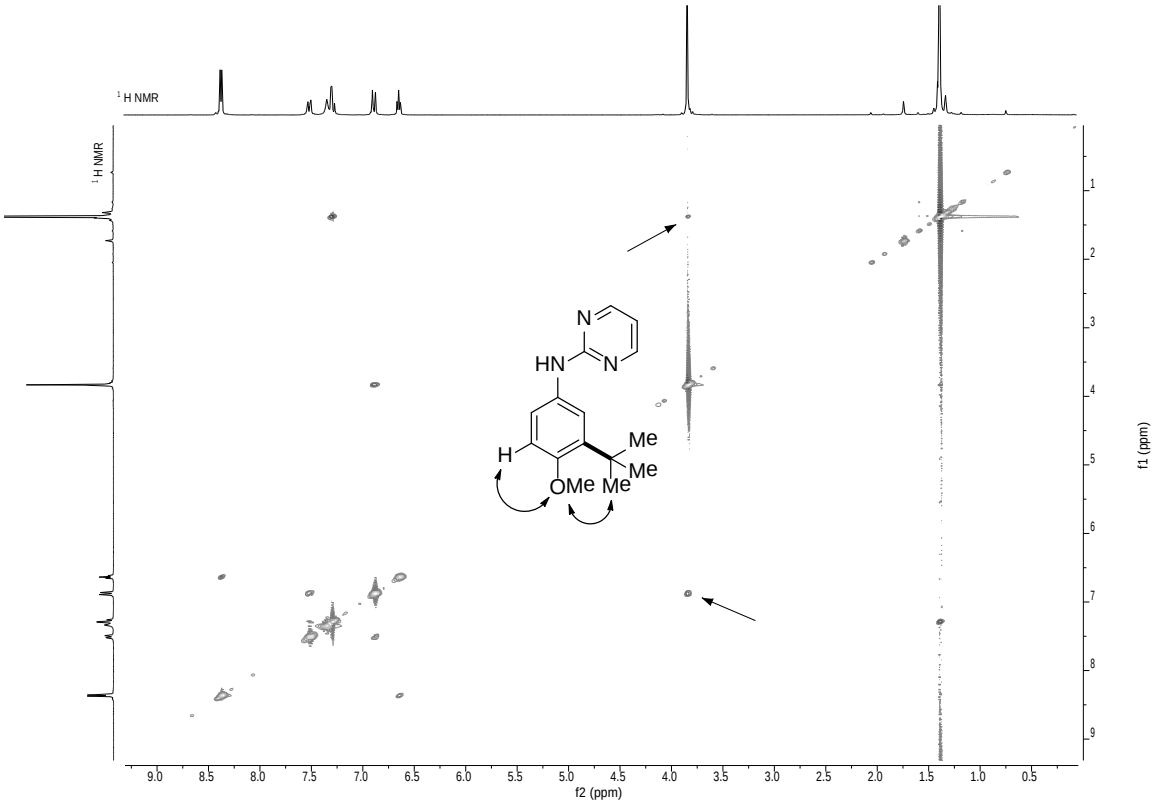

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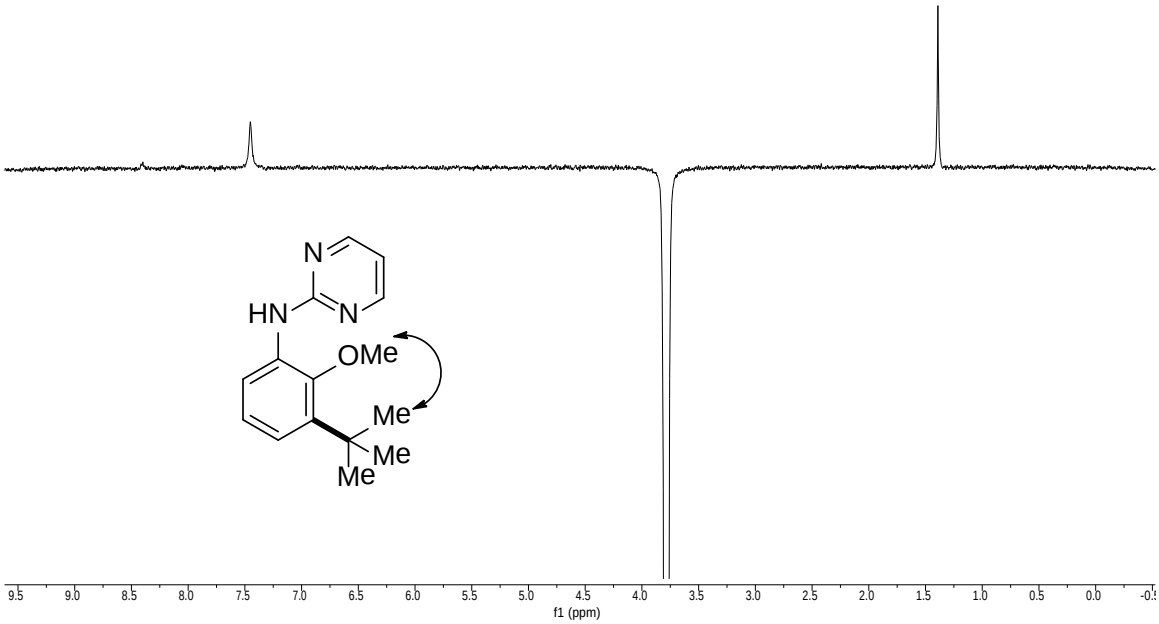
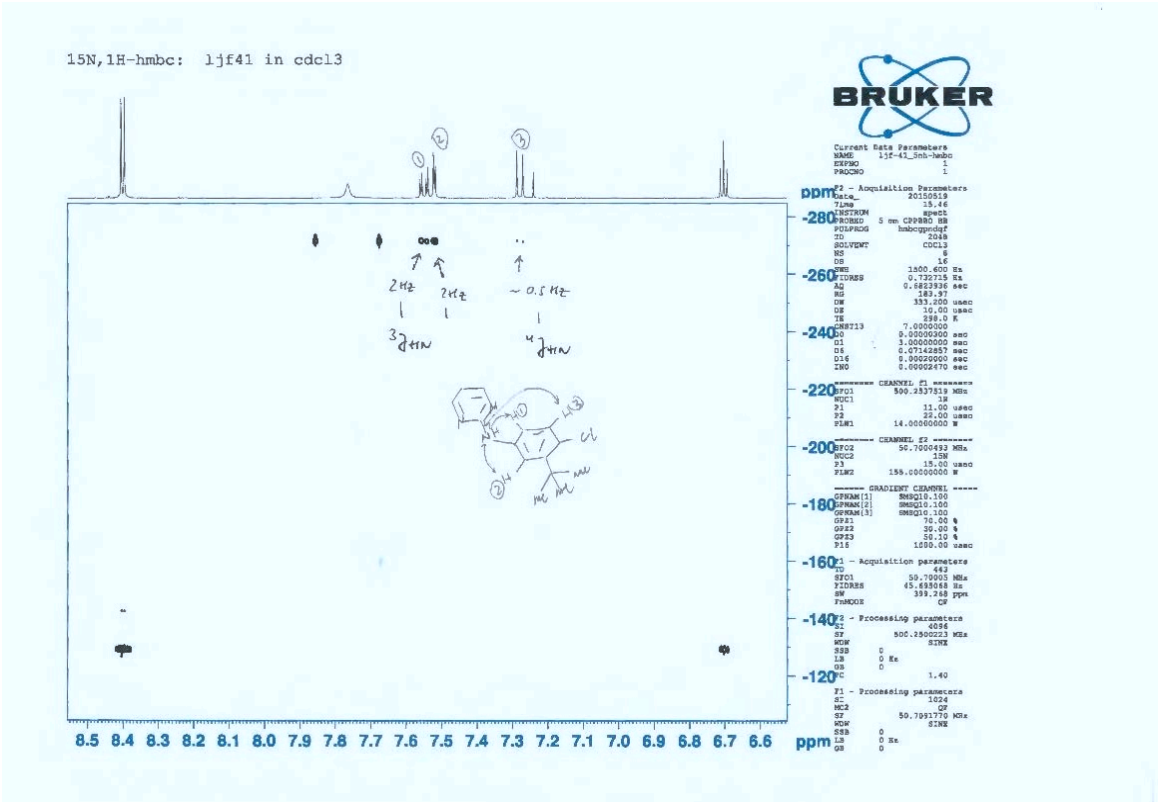


^{15}N,^{1}H-HMBC **215ba**



8 List of Abbreviations

Å	Ångström
Ac	acetyl
Ad	adamantyl
Alk	alkyl
Am	amyl
AMLA	ambiphilic metal-ligand activation
aq.	aqueous
Ar	aryl
APT	attached proton test
atm	atmospheric pressure
ATR	attenuated total reflectance
BDMAEE	bis(2-dimethylaminoethyl)ether
BHT	2,6-di-*tert*-butyl-4-methylphenol
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BQ	benzoquinoline
Bu	butyl
Bz	benzoyl
c-	cyclo
CDC	cross-dehydrogenative coupling
calc.	calculated
cat.	catalytic
CMD	concerted-metalation-deprotonation
cod	1,5-cyclooctadien
conv.	conversion
Cp*	cyclopentadienyl
Cy	cyclohexyl
δ	chemical shift
d	doublet
DCE	1,2-dichloroethane
dd	doublet of doublet
DFT	density functional theory
DG	directing group
Diglyme	bis(2-methoxyethyl)ether
DMA	*N,N*-dimethylacetamide
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DoM	directed *ortho* metalation
dppbz	1,2-bis(diphenylphosphino)benzene

dpph	2,2-diphenyl-1-picrylhydrazyl
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dt	doublet of triplet
E	electrophile
Ed.	edition
EI	electron ionization
equiv	equivalent
ESI	electronspray ionization
Et	ethyl
FG	functional group
g	gram
GC	gas chromatography
h	hour
Hal	halogen
Het	hetero(aryl)
Hept	heptyl
Hex	hexyl
HPLC	high performance liquid chromatography
HR-MS	high resolution mass spectrometry
Hz	Hertz
i	*iso*
IES	internal electrophilic substitution
Ile	isoleucine
IR	infrared spectroscopy
J	coupling constant
KIE	kinetic isotope effect
L	ligand
Leu	leucine
m	meta
m	multiplet
M	molar
$[M]^+$	molecular ion peak
Me	methyl
Mes	mesityl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mmol	millimol
M. p.	melting point
MPAA	monoprotected amino acid
MPV	membrane pump vacuum
MS	mass spectrometry

m/z	mass-to-charge ratio
n	*normal*
NHC	*N*-heterocyclic carbene
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance
NXS	*N*-halosuccinimides
o	*ortho*
oct	octane
OPV	oil pump vacuum
p	*para*
pent	pentyl
PEPPSI	[1,3-bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II)dichloride
Ph	phenyl
PMP	*para*-methoxyphenyl
Piv	pivaloyl
ppm	parts per million
Pr	propyl
Py	pyridyl
PyBOX	pyridine bis(oxazoline)
PyDipSi	pyridyldiisopropylsilyl
pym	pyrimidyl
q	quartet
R	rest
rac	*racemic*
ref.	reference
s	singlet
sat.	saturated
sec	*secondary*
S_E^{Ar}	electrophilic aromatic substitution
SET	single electron transfer
SPO	secondary phosphine oxides
SPS	solvent purification system
t	*tert*
t	triplet
T	temperature
TEMPO	2,2,6,6-tetramethylpiperidin-1-yloxy
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	trimethoxyphenyl
TM	transition metal
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl

TS	transition state
$\tilde{\nu}$	absorption
Val	valin
wt%	weight by volume
X	(pseudo)halide

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Publications

1. J. Li, L. Ackermann. "*Ruthenium(II)-Catalyzed meta-Selective C–H Alkylation of Aromatic Imines with Secondary and Tertiary Alkyl Halides*" Manuscript in Preparation.
2. J. Li, S. Warratz, D. Zell, S. De Sarkar, L. Ackermann. "*Tertiary Alkyl Halides for meta-Selective C–H Alkylation*" Manuscript in Preparation.
3. J. Li, C. Kornhaaß, L. Ackermann. *"Ruthenium-catalyzed Oxidative C–H Alkenylation of Aryl Carbamates" Chem. Commun.* **2012**, *48*, 11343-11345.
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5. J. Li, J. Meng, X. Huang, Y. Cheng. "*A highly selective fluorescent sensor for Hg^{2+} based on the water-soluble poly(p-phenyleneethynylene)*" *Polymer* **2010**, *51*, 3425-3430.