Nickel-Catalyzed Secondary Alkylations and Fluoroalkylations *via* C–H Activation

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Erklärung

Ich versichere, dass ich die vorliegende Dissertation in der Zeit von

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Institut für Organische und Biomolekulare Chemie

Der Georg-August-Universität zu Göttingen

Auf Anregung und unter Anleitung von

Herrn Prof. Dr. Lutz Ackermann

Selbstständig durchgeführt und keine anderen als die angegebenen

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Für meine Eltern

Da steh ich nun, ich armer Tor!

Und bin so klug als wie zuvor.

– Faust I, Vers 354ff

Johann Wolfgang von Goethe

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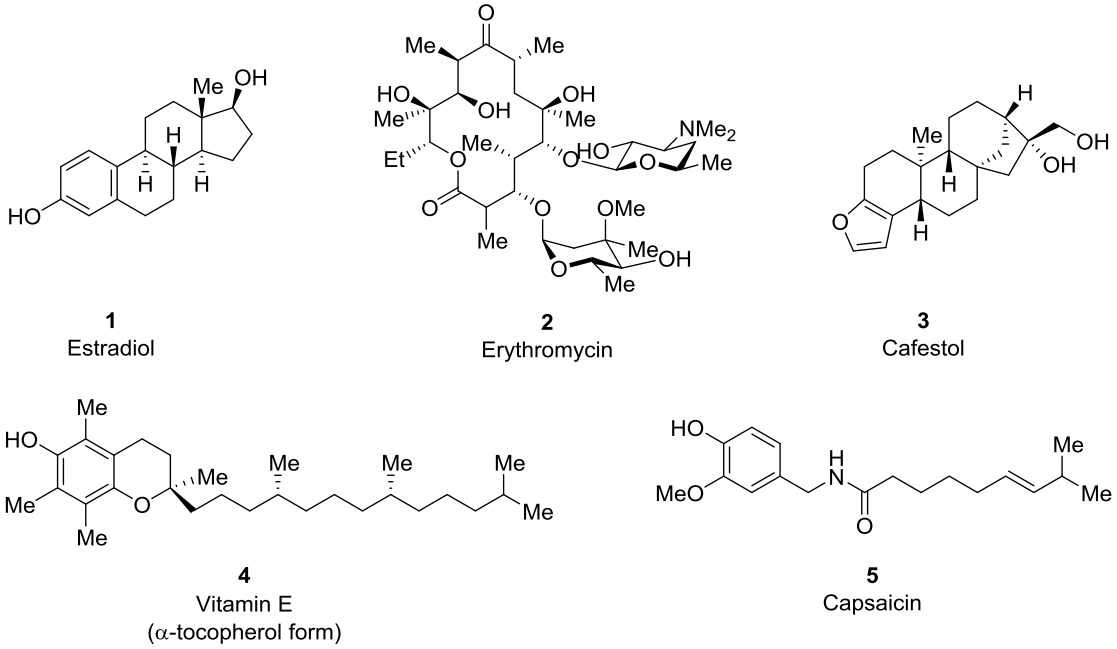
1 Introduction

1.1 Alkyl Groups in Natural Products and Pharmaceuticals

Compounds bearing alkyl groups have received significant attention in various fields of organic chemistry. This is due to their abundance in natural compounds, such as steroids, alkaloids, polyketides, lipids, as well as in the side-chain of peptides (Scheme 1).[1] Estradiol (**1**), for example, is not only relevant for regulation of the ovarian cycle, but is also, along with other estrogenes, linked to breast and ovarian cancer growth. Erythromycin (**2**) and derivatives thereof have shown anti-biotic activity. Vitamin E (**4**) inactivates reactive oxygen species, in order to avoid cell damages, such as oxidation of unsaturated membrane lipids.

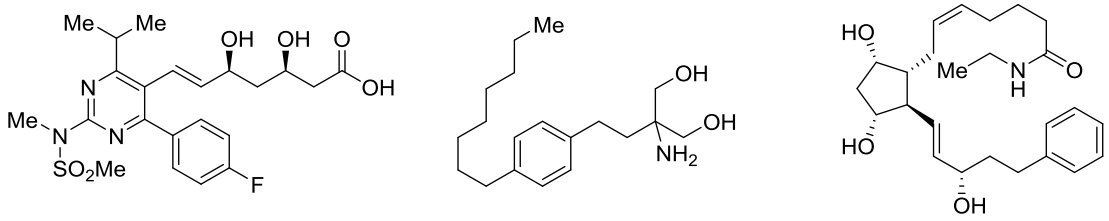


Scheme 1: Selection of natural compounds containing aliphatic groups.

Therefore, aliphatic chains and cycles with various substitution patterns and functional groups can be commonly found in a wide range of top-selling drugs and pharmaceuticals (Scheme 2).[2]

[1] (a) Berg, J. M.; Tymoczko, J. L.; Stryer, L. *Biochemistry*, 7th int. ed., E. H. Freeman and Company, New York, 2012. (b) Leeper, F. J.; Vederas, J. C. *Biosynthesis: Polyketides and Vitamins*, Springer Verlag, Berlin, 2000. (c) Kibwage, I. O.; Hoogmartens, J.; Roets, E.; Vanderhaeghe, H.; Verbist, L.; Dubost, M.; Pascal, C.; Petitjean, P.; Levol, G. *Antimicrob Agents Chemother.* **1985**, *28*, 630–633. (d) Kittakoop, P.; Mahidol, C.; Ruchirawat, S. *Curr Top. Med. Chem.* **14,** *2*, 239–252. (e) Ricketts M. L.; Boekschoten M. V.; Kreeft A. J.; Hooiveld G. J.; Moen C. J.; Müller M.; Frants R. R.; Kasanmoentalib S.; Post S. M.; Princen H. M.; Porter J. G.; Katan M. B.; Hofker M. H.; Moore D. D. *Mol. Endocrin.* **2007**, *21* , 1603–1616.

[2] (a) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Ed.* **2010**, *87*, 1348–1349. (b) Aggarwal, R. K.; Showkathali, R. *Expert Opin. Pharmacother.* **2013**, *14*, 1–13. (c) Sanford, M. *Drugs* **2014**, 74, 1411–1433. (d) Chen, M.-J.; Cheng, C.-Y.; Chen, Y.-C.; Chou, C.-K.; Hsu, W.-M. *J. Ocul. Pharmacol. Ther.* **2006**, *22*, 188–193.



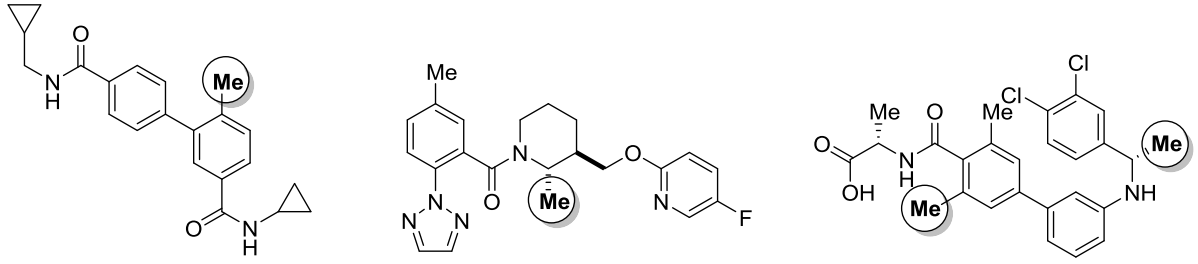
6
Rosuvastatin
anti-LDL-C

7
Fingolimod
anti-RRMS

8
Bimatoprost
anti-glaucoma

Scheme 2: Selection of marketed drugs containing aliphatic moieties.

One particularly noteworthy effect of alkyl groups within medicinal chemistry is the so-called "magic methyl" effect. .[3]Usually, when a methyl group is added to a compound, an increase of biological potency of up to tenfold can be expected. This can usually be attributed to hydrophobic and desolvation effects. However, in some cases, the potency increase can be as high as two orders of magnitude, which is then labeled as the aforementioned "magic methyl" effect (Scheme 3). Such an extreme effect usually occurs, when the introduction of the methyl group causes the unbound compound to assume a shape complementary to the bound form in the target's active site. Thus, the conformational change to achieve binding in the active site is minimised.



9
208-fold boost
p38α MAP38 kinase inhibitor

10
480-fold boost
Orexin-1/-2 antagonist

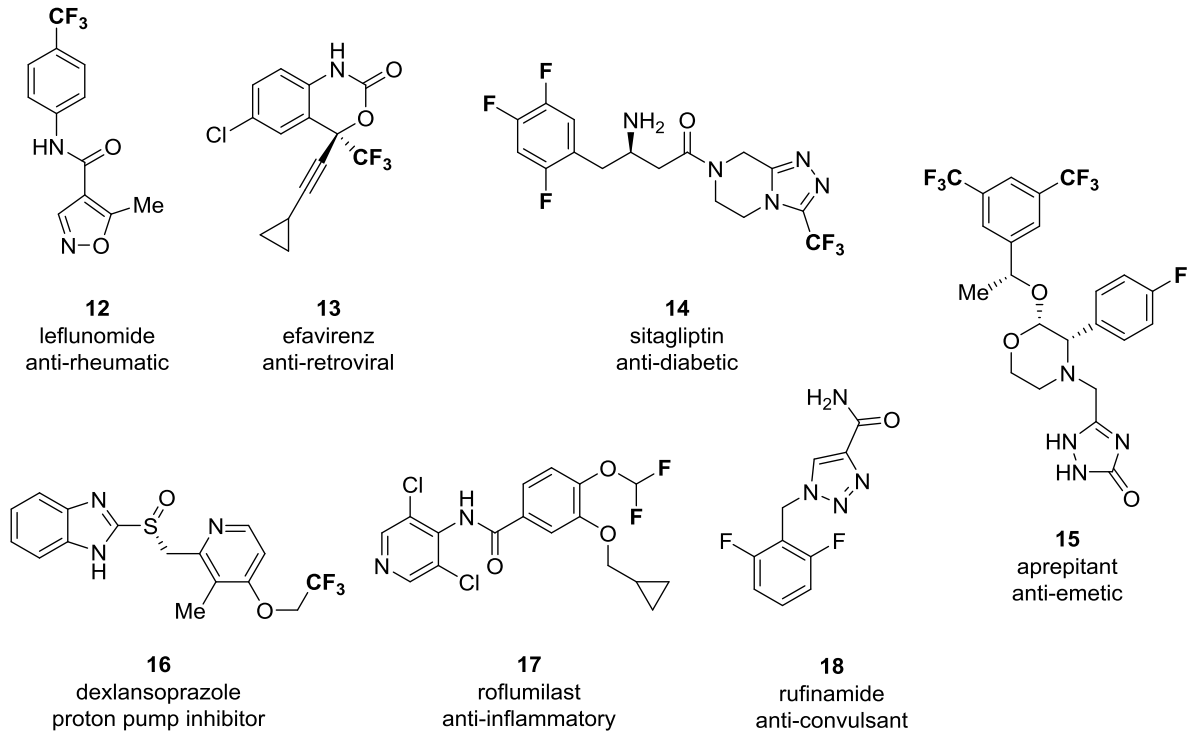
11
2135-fold boost
$S1P_1$ antagonist

Scheme 3: Boost in potency by introduction of a methyl group.

In addition to this effect there is also a particular interest within pharmaceutical research for developing fluorinated analogues of bioactive compounds. Such compounds may show significantly altered chemical reactivity, but it has also been shown that the introduction of fluorine atoms into biologically active molecules has a profound and complex impact on their metabolic behaviour. Special interest has been given in medicinal chemistry to the introduction of trifluoromethyl groups. However, fluorinated, marketed drugs are still rather

[3] Schönherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256–12267, and references cited therein.

scarce, as suitable methodologies for the introduction of fluorinated groups are still being developed.[4] A selection of fluorine-containing, marketed drugs is shown in Scheme 4.[5]



Scheme 4: Selection of fluorine-containing, marketed drugs.

1.2 Alkylations through traditional Cross-Coupling Reactions

As mentioned in the previous chapter, C–C bond forming reactions for the synthesis of alkylated scaffolds have always been of highest importance within organic synthesis. In the last few decades focus has been particularly on transition metal-catalyzed cross-coupling reactions. Early examples for cross-coupling reactions include the Glaser coupling[6] and the Ullman coupling[7] (Scheme 5). These reactions, however, apart from being limited to aryl and

[4] Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Acena, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2014**, *167*, 37–54.

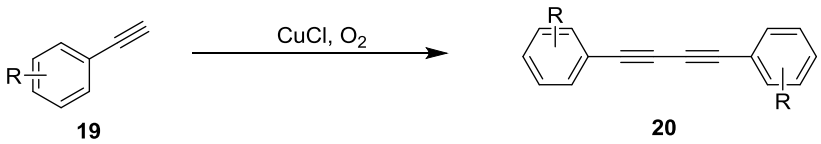
[5] (a) Sanders, S.; Harsidangkul, V. *Am. J. Med. Sci.* **2002**, *323*, 190–193. (b) Cespedes, M. S.; Aberg, J. A. *Drug Saf.* **2006**, *29*, 865–874. (c) Gadsby, R. *Clin. Med. Ther.* **2009**, *1*, 53–62. (d) Hargreaves, R.; Ferreira, J. C. A.; Hughes, D.; Brands, J.; Hale, J.; Mattson, B.; Mills, S. *Ann. N. Y. Acad. Sci.* **2011**, *1222*, 40–48. (e) Behm, B. W.; Peura, D. A. *Expert Rev. Gastroenterol. Hepatol.* **2011**, *5*, 439–445. (f) Field, S. K. Expert *Opin. Investig. Drugs* **2008**, *17*, 811–818. (g) Hakimian, S.; Cheng-Hakimian, A.; Anderson, G. D.; Miller, J. W. *Expert Opin. Pharmacother.* **2007**, *8*, 1931–1940.

[6] Glaser, C. *Justus Liebigs Ann. Chem.* **1870**, *154*, 137–171.

[7] (a) Ullman, F.; Bielecki, J. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174–2185.; A review: (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.

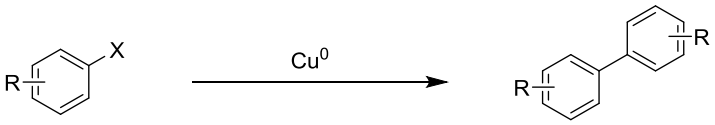
alkyne moieties, could originally only proceed by utilisation of stoichiometric amounts of transition metals.

(a) Glaser coupling



19 20

(b) Ullman coupling

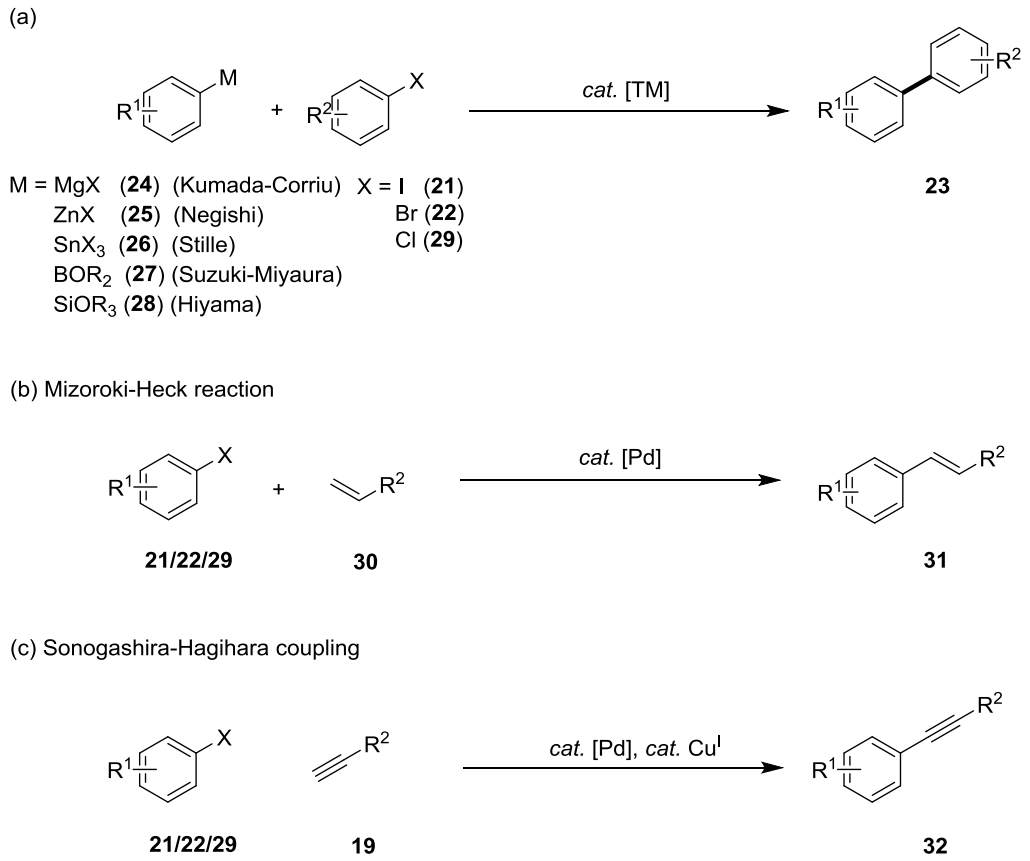


X = I (**21**), Br (**22**) **23**

Scheme 5: General reaction equation for (a) the Glaser coupling and (b) the Ullman coupling.

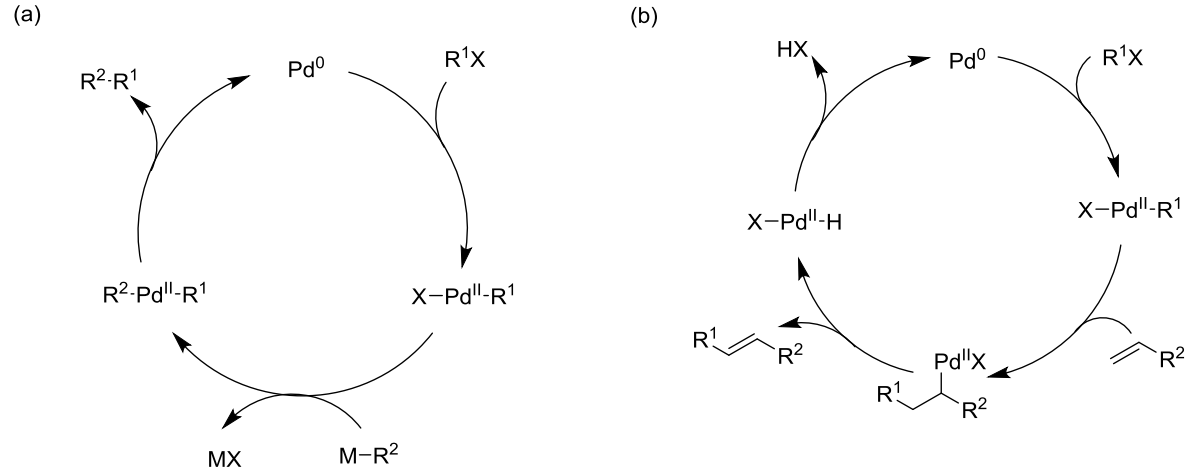
The first step towards catalyzed reactions was first achieved by Job in the early 1920s.[8] He found that a solution of phenyl magnesium bromide does not react with ethylene gas, unless anhydrous nickel dichloride is introduced. Furthermore, he showed that the uptake of ethylene gas in the reaction is solely dependent on the amount of Grignard reagent and not on the amount of nickel dichloride. Although this yielded a mixture of ethylbenzene, styrene, biphenyl and other hydrocarbons, Job thus proved that nickel dichloride could be used for such reactions in catalytic quantities. Two decades later, Kharasch conducted investigations on the cobalt-catalyzed C–C bond formation of aryl Grignard reagents with both aryl bromides and vinyl bromides to yield the corresponding biphenyls and styrenes.[9] Significant advancements in this type of reaction were achieved in the 1970s with the extension of cross-coupling reactions towards the use of palladium- and nickel-catalysis. The most commonly employed catalytic cross-coupling reactions include the Kumada-Corriu coupling, Negishi coupling, Suzuki-Miyaura coupling, Migita-Kosugi-Stille coupling, Hiyama coupling, Mizoroki-Heck reaction and Sonogashira-Hagihara coupling (Scheme 6).[10] The importance of these advancements were significant enough so that in 2010 professors Akira Suzuki, Ei-ichi Negishi and Richard Frederick Heck were honoured with the Nobel prize in Chemistry for their contributions to the field of palladium-catalyzed cross-coupling chemistry.[11]

[8] Job, A.; Reich, R. *C. R. Hebd. Seances Acad. Sci.* **1924**, *179*, 330–332.
[9] (a) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316–2320. (b) Kharasch, M. S.; Fuchs, C. F. *J. Am. Chem. Soc.* **1943**, *65*, 504–507.
[10] Selected review: Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085.
[11] http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010 (accessed December 6th, 2015).



Scheme 6: General equations for transition metal catalysed cross couplings reactions.

The widely accepted catalytic cycle for most of cross-coupling reactions consist of an oxidative addition of the organic halide to the catalyst, transmetalation with an organometallic reagent, followed by a reductive elimination (Scheme 7a). In the case of the Mizoroki-Heck reaction, the oxidative addition is followed by a *syn*-addition to the olefin, *syn*-β-hydride elimination and reductive elimination (Scheme 7b).[12]



Scheme 7: Catalytic cycles for (a) cross coupling and (b) Heck reactions.

[12] Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Inc., London, 2005.

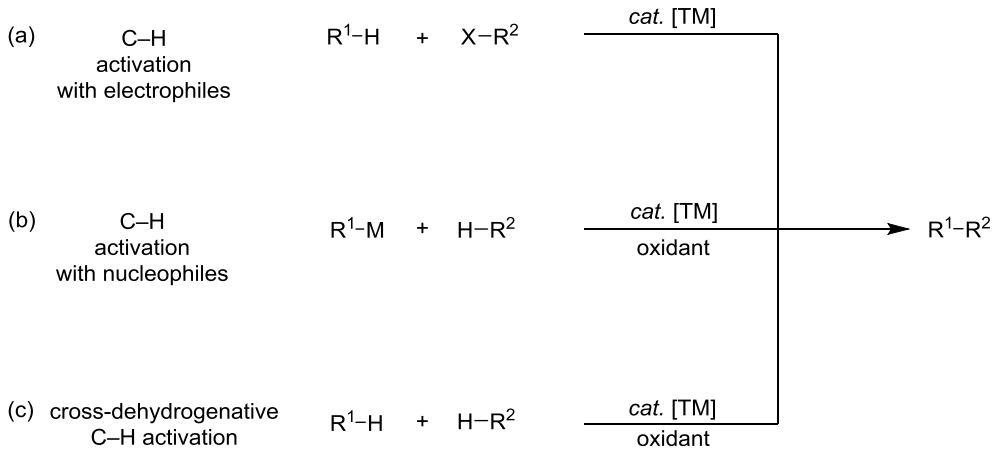
Initially, these transformations were limited to the coupling of sp^2- or sp-hybridized-carbon centres, with the exception of the nickel-catalysed Kumada-Corriu coupling. The corresponding alkylation coupling reactions proved more challenging due to the tendency of the alkylated intermediates to undergo β-hydride elimination, thus forming undesired olefinic side products.[13] In subsequent years, many new protocols for alkylation coupling reactions have been developed.[14] These cross-coupling reactions have found numerous applications in total synthesis,[15] as well as in industrial settings.[16]

1.3 Transition-metal catalyzed C–H functionalization

Despite the enormous advances achieved by the previously discussed cross-coupling reactions, limitations still need to be addressed. For traditional cross-coupling reactions organic halides, as well as a organometallic reagents, are required. Therefore pre-functionalisation of substrates was necessary. These pre-functionalisation steps, along with the cross-coupling itself, are each accompanied with the generation of stoichiometric amounts of by-products and metal waste.

Due to spiralling costs and dwindling resources sustainability has become a major focus in both industry and society in general.[17] Nonetheless, the goal of more efficient, atom-economical strategies were already pointed out in the early 1990s by Barry Trost.[18] Among possible solutions were the development of C–H functionalisation reactions *via* organometallic C–H bond activation. These type of reactions can be divided into three categories (Scheme 8).[19]

[13] Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866–4877.
[14] (a) Tollefson, E. J.; Hanna, L. E.; Jarvo, E. R. *Acc. Chem. Res.* **2015**, *48,* 2344–235. (b) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587–9652. (c) Netherton, M. R.; Fu, G. C*. Adv. Synth. Catal.* **2004**, *346*, 1525–1532.
[15] (a) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745–2759. (b) Majumdar, K. C.; Sinha, B. *Synthesis* **2013**, *45*, 1271–1299. (c) Sasaki, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 856–871.
[16] (a) Xu, S.; Kim, E. H.; Wei, A.; Negishi, E. *Sci. Technol. Adv. Mater.* **2014**, *15*, 044201. (b) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710. (c) Dumrath, A.; Lübbe, C.;Beller, M. Palladium-Catalyzed Cross-Coupling Reactions – Industrial Applications, in Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Developments, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2013. (d) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027–3043.
[17] Sheldon, R. A. *Chem. Soc. Rev.* **2012**, *41*, 1437–1451.
[18] Trost, B. M. *Science* **1991**, *254*, 1471–1477.
[19] Ackermann, L; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826.



Scheme 8: Comparison of C–H functionalisation strategies.

Friedel-Crafts-alkylation represents an early example of the synthesis of alkylated arenes (Scheme 9).[20]

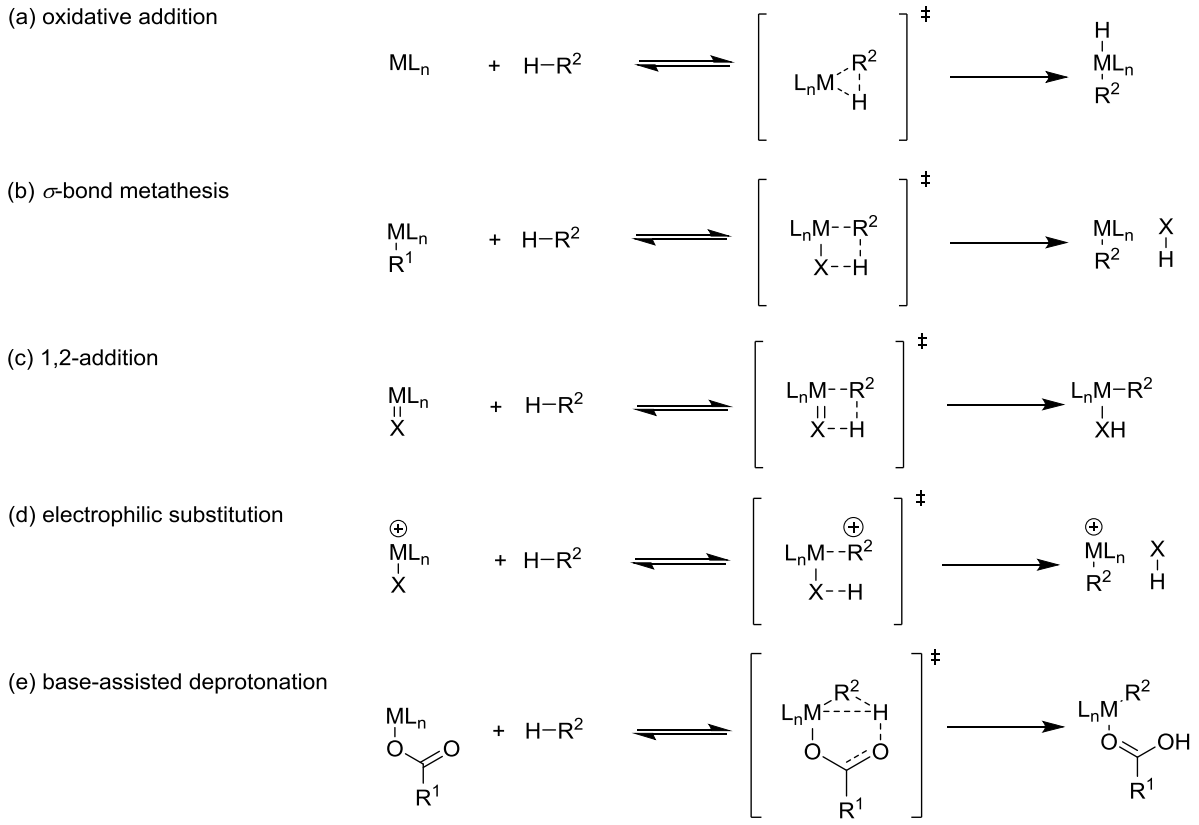
Scheme 9: General equation for the Friedel-Crafts-Alkylation.

It is, however, not considered as C–H activation, because C–H activations rely on organometallic intermediates. The term C–H activation is commonly applied to reactions, in which the active metal catalyst performs a direct C–H metalation.[21] For these C–H metalations, five mechanistic scenarios have so far been widely accepted (Scheme 10).[22]

[20] Bandini, M.; Umani-Ronchi, A. *Catalytic Asymmetric Friedel-Crafts Alkylations*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2009.

[21] (a) Sezen, B.; Sames, D. What is C–H bond activation, in Handbook of C—H transformations, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2005. (b) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879–2932.

[22] (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. (b) Balcells, D.; Clot, E.; Eisenstein, E. *Chem. Rev.* **2010**, *110*, 749–823. (c) Boutlada, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820–5831.

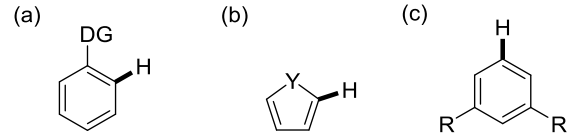


Scheme 10: Mechanistic pathways for C–H activation.

The oxidative addition mechanism usually occurs in the case of electron-rich, low-valent late-transition metal catalysts, such as iridium, platinum and ruthenium. For the *σ*–bond metathesis pathway early transition metals and lanthanoids are typically employed. Somewhat similar mechanistically is the 1,2 addition, where a heteroatom is a hydrogen acceptor, is implemented by early or mid transition metals. For electrophilic substitution processes the metal catalyst reacts as a Lewis acid, most commonly with a hydroxy or alkoxy ligand.[22b] The base-assisted deprotonation, for example, uses secondary phsphine oxides or carboxylates, acting as an internal base. This pathway has been called either concerted metalation-deprotonation pathway or ambiphilic metal ligand activation.[22a] The latter two mechanistic pathways have also been investigated and illuminated in detail through DFT studies.[22a,c]

Selectivity is of key importance in C–H activation chemistry. The organic compounds of interest possess many C–H bonds of comparable dissociation energy and therefore achieving chemo- and regioselectivity is challenging. In order to differentiate between various chemically similar C–H bonds several strategies have been developed. These include differentiation through assistance of a Lewis-basic directing group within the substrate, differently electronically activated C–H bonds and sterical bulk in combination with catalyst control (Scheme 11).[23]

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



Scheme 11: Strategies for site-selectivity in C–H functionalisation *via* (a) lewis-basic directing group (b) electronic bias and (c) steric bulk with catalyst based control.

Considering these various approaches a wide variety of catalytic C–H functionalisation reactions have been developed with transition metals employed including, for example, ruthenium, [24] rhodium, [25] palladium, [26] manganese, [27] iron, [28] cobalt [29] and nickel. [30] The transformations facilitated by these catalysts include alkenylations (Scheme 12a+b) and arylations (Scheme 12c).[31] One of the earliest examples for an alkenylation reaction is the Fujiwara-Moritani reaction (Scheme 12a).[32] However, in this case the arene (**36**) was required in large excess. Further development took advantage of directing groups to give rise to a variety of protocols for such transformations (Scheme 12b).[33] Remarkably, using an

[24] Seminal works:(a) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc*. **1986**, *108*, 2728–2735. (b) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529–531. ;for recent reviews see: (a) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281–295. (b) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461–1479. (c) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, 886–896. (d) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879–5918. (f) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010***, 292*, 211–229*.*

[25] (a) Ye, B.; Cramer, N. *Acc. Chem. Res.* **2015**, *48*, 1308–1318. (b) Song, G.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651–3678. (c) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212–11222. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655.

[26] (a) Qiu, G.; Wu, *J. Org. Chem. Front.* **2015**, *2*, 169–178. (b) Engle, K. M.; Yu, J.-Q. *J. Org. Chem.* **2013**, *78*, 8927–8955. (c) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761. (d) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292.

[27] (a) Liu, W.; Ackermann, L. *ACS Catal.* **2016**, *6*, 3743–3752 (b) Liu, W.; Zell, D.; John, M.; Ackermann, L. *Angew. Chem. Int.* **2015**, *54*, 4092–4096. (c) Liu, W.; Bang, J.; Zhang, Y.; Ackermann, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 14137–14140. (d) Liu, W.; Groves, J. T. *Acc. Chem. Res.* **2015**, *48*, 1727–1735. (e) Wang, C. *Synlett* **2013**, *24*, 1606–1613.

[28] (a) Mihovilovic, M. D.; Schnürch, M. *ChemCatChem* **2014**, *6*, 2194–2196. (b) Sun, X.; Li, J.; Huang, X.; Sun, C. *Curr. Inorg. Chem.* **2012**, *2*, 64–85. (c) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061–6067.

[29] (a) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 498–525 (b) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208–1219. (c) Ackermann, L. *J. Org. Chem.* **2014**, *79*, 8948–8954. (d) Yoshikai, N. *J. Synth. Org. Chem.* **2014**, *72*, 1198–1206.

[30] (a) Castro, L. C. M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 410–421. (b) Johnson, S. A. *Dalton Trans.* **2015**, *44*, 10905–10913.

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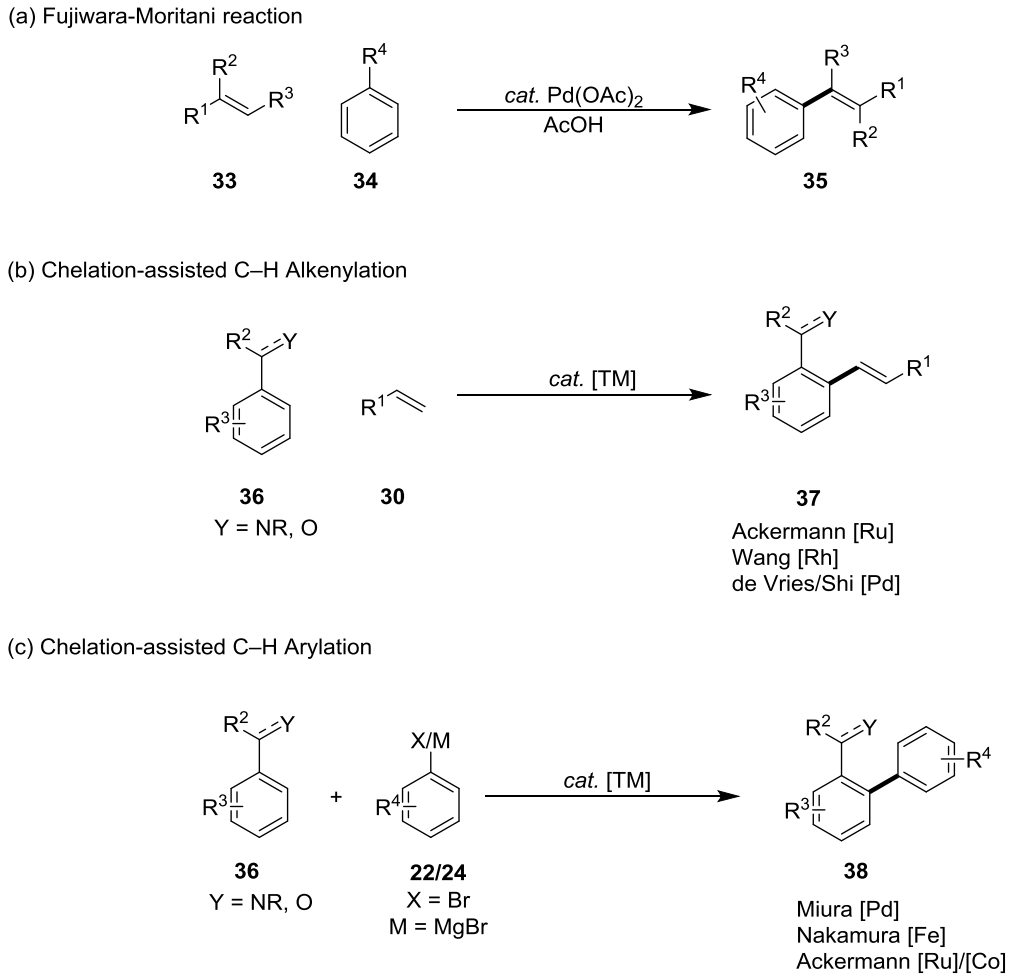
[32] (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119–1122. (b) Fujiawara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169.

[33] Selected examples: (a) Wang, Y.; Li, C.; Li, Y.; Yin, F.; Wang, X.-S*. Adv. Synth. Catal.* **2013**, *355*, 1724–1728. (b) Ackermann, L.; Wang, L.; Wolfram, R. ; Lygin, A. V. *Org. Lett.* **2012**, *14*, 728–731. (c) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129,* 7666–7673. (b) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587.

appropriate directing group, alkenylation could also be achieved with *meta*-selectivity with regard to the directing group.[34]



Scheme 12: (a) Fujiwara-Moritani reaction and (b) selected examples of directed C–H olefination and (c) arylation.

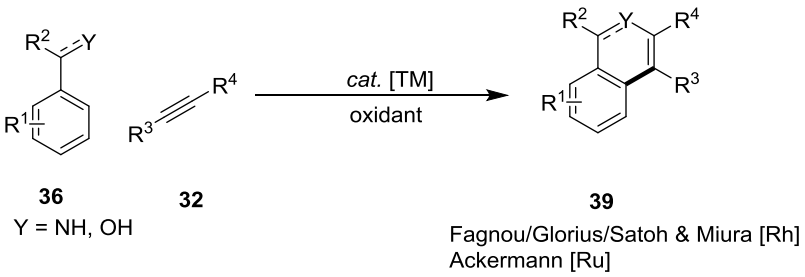
A broad range of heterocycles have been accessed using C–H functionalisation *via* oxidative annulation reactions (Scheme 13). The stoichiometric oxidant in these reactions can either be another metal, such as copper,[35] internal oxidants in the form of hetero-hetero-bonds[36]

[34] (a) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. *Nature* **2015**, *519*, 334–338. (b) Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215–220. (c) Leow, D.; Li, G.; Mei, T.-S.; Yu, J-Q. *Nature* **2012**, *486*, 518–522.

[35] (a) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*,281–295. (b) Pham, M. V.; Ye, B.; Cramer, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 10610–10614. (c) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212–11222. (d) Pham, M. V.; Ye, B.; Cramer, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 10610–10614. (e) Song, G.; Chen, D.; Pan, C.-L.; Crabtree, R. H.; Li, X. *J. Org. Chem.* **2010**, *75*, 7487–7490. (f) Su, Y.; Zhao, M.; Han, K.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5462–5465. (g) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565–10569. (h) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050–12051. (i) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1707–1409.

[36] (a) Koornhaaß, C.; Kuper, C.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1619–1624. (b) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449–6457. (c) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548–6551. (d) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908–6909.

or, ideally, aerial oxygen.[37] Apart from the relatively common annulation reactions towards six-membered heterocycles, it should be noted that the synthesis of compounds with other ring sizes through C–H functionalisation have also been achieved.[38]



Scheme 13: General examples for oxidative annulations through C–H functionalisation.

For direct C–H alkylations two approaches have been very common. One is the hydroarylation of olefins (Scheme 14a).[24b,39] The use of electrophilic alkyl halides directly has also been demonstrated (Scheme 14b).[13,40]

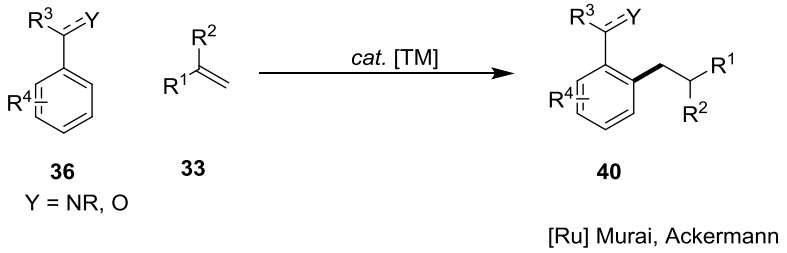
[37] (a) Warratz, S.; Koornhaaß, C.; Cajaraville, A.; Niepötter, B.; Stalke, D. Ackermann, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 5513–5517. (b) Liegault, B.; Fagnou, K. *Organometallics* **2008**, *27*, 4841–4843. (c) Liegault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *72*, 5022—5028. (d) Stahl, S. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3400–3420.

[38] (a) Burns, D. J.; Lam, H. W. *Angew. Chem. Int. Ed.* **2014**, *53*, 9931–9935.(b) Seoane, A.; Casanova, N.; Quiñones, N.; Mascareñas, J. L.; Gulías, M. *J. Am. Chem. Soc.* **2014**, *136*, 834–837. (c) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326–18339. (d) Rakshit, S. Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 8585–9587. (e) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc* **2008**, *130*, 16474–16475.

[39] (a) Schinkel, M.; Marek, I.; Ackermann, L. *Angew. Chem Int. Ed.* **2013**, *52*, 3977–3980. (b) Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Lett.* **2008**, *10*, 3409–3412. (c) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826–834.

[40] Selected examples: (a) Graczyk, K.; Haven, T.; Ackermann, L. *Chem. Eur. J.* **2015**, *21*, 8812–8815. (b) Zhu, R.-Y-; He, J.; Wang, X.-C.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 13194–13197. (c) Fruchey, E. R.; Monks, B. M.; Cook, S. P. *J. Am. Chem. Soc.* **2014**, *136*, 13130–13133. (d) Ilies, L.; Matsubara, T.; Ichikawa, S.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 13126–13129. (e) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 9279–9282. (f) Punji, B.; Song, W.; Shevchenko, G. A.; Ackermann, L. *Chem Eur. J.* **2013**, *19*, 10605–10610. (g) Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875–1877. (h) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6045–6048.

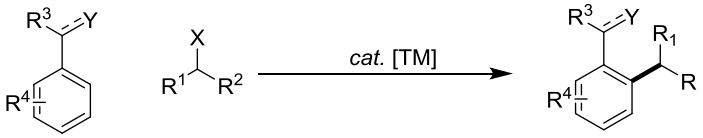
(a) Alkylation *via* Alkene Hydroarylation



36 Y = NR, O **33** **40**

[Ru] Murai, Ackermann

(b) Alkylation with Alkyl Halides



36 Y = NR, O **41** X = Cl, Br **42**

[Ru] Ackermann
[Co] Yoshikai, Ackermann
[Fe] Nakamura, Ackermann, Cook

Scheme 14: Strategies for direct alkylations *via* C–H functionalisation.

Beyond these C–C bond forming reactions it should be noted that C–X bond forming reactions have been thoroughly investigated, as well. These include C–H aminations,[41] oxygenations,[42] halogenations[43] and thiolations.[44]

Given this plethora of procedures, C–H functionalisation reactions have become viable for implementation within the total synthesis of natural products. This is demonstrated in the synthesis of dragmacidin F (**45**) and hydratoaustamide (**48**) (Scheme 15).[45]

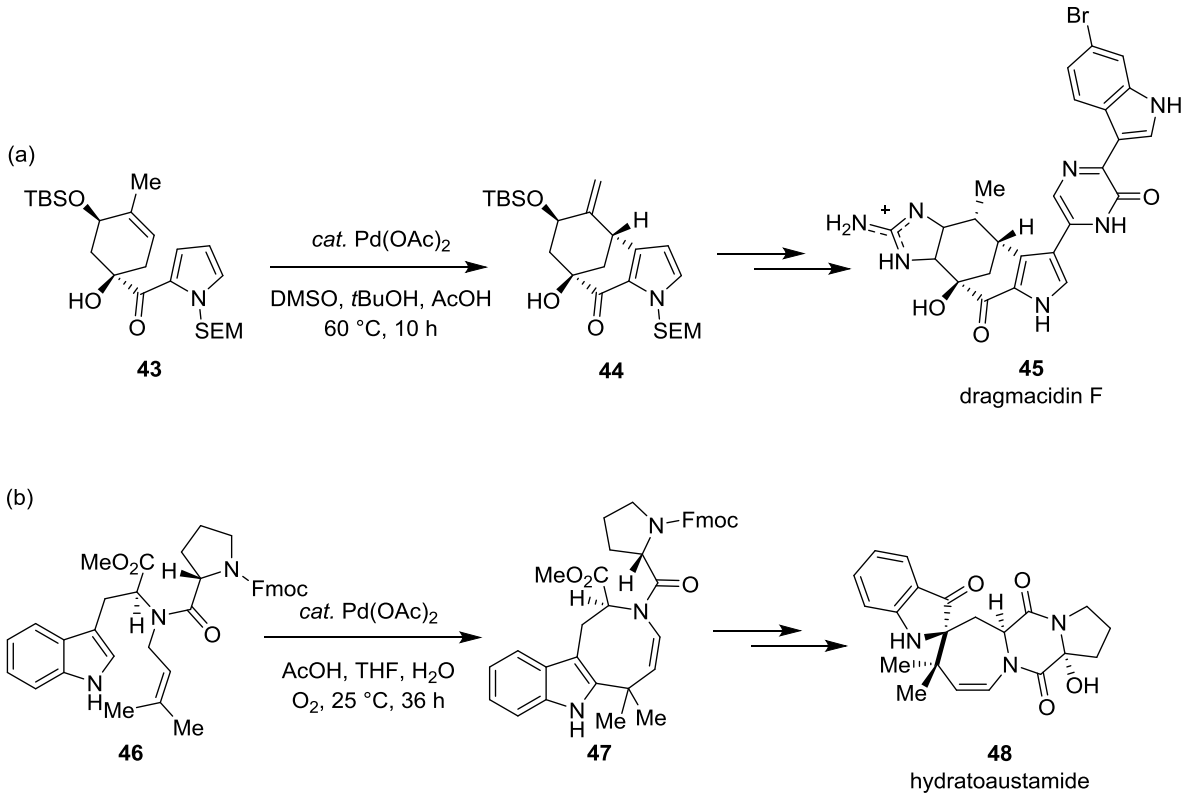
[41] Selected examples: (a) Minovilovic, M. D.; Schnürch, M. *ChemCatChem* **2014**, *6*, 2194–2196. (b) Gephart, R. T.; Warren, T. H. *Organometallics* **2012**, *31*, 7728–7752.

[42] Selected examples: (a) Yang, W.; Chen, H.; Li, J.; Li, C.; Wu, W.; Jiang, H. *Chem. Commun.* **2015**, *51*, 9575–9578. (b) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 29–39. (c) Gary, J. B.; Cook, A. K.; Sanford, M. S. *ACS Catal.* **2013**, *3*, 700–703. (d) Gulevich, A. V.; Melkonyan, F. S.; Sarkar, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2012**, *134*, 5528–5531.

[43] Selected examples: (a) Miao, J.; Yang, K.; Kurek, M.; Ge, H. *Org. Lett.* **2015**, *17*, 3738–3741. (b) Wang, L.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 1083–1085. (c) Wang, X.-C.; Hu, Y.; Bonacorsi, S.; Hong, Y.; Burrell, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 10326–10329. (c) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142–15143.

[44] Selected examples: (a) Vásques-Céspedes, S.; Ferry, A.; Candish, L.; Glorius, F. *Angew. Chem. Int. Ed.* **2015**, *54*, 5772–5776. (b) Zhou, A.-X.; Liu, X.-Y.; Yang, K.; Zhao, S.-C.; Liang, Y.-M. *Org. Biomol. Chem.* **2011**, *9*, 5456–5462.

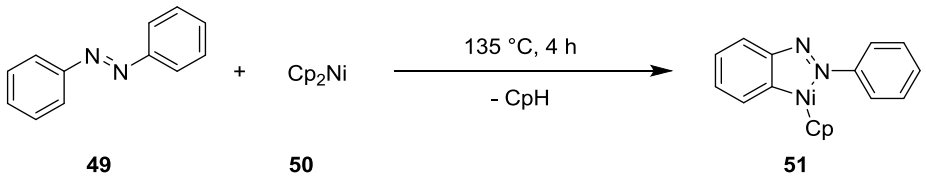
[45] (a) Gark, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 9552–9553. (b) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904–7905.



Scheme 15: Total syntheses with C–H functionalization steps shown.

1.4 Nickel-catalyzed C–H functionalization

As highlighted a wide array of C–H functionalisation reactions are possible with a range of transition metals[24–30] and nickel has been featured relatively early. Indeed, in 1963 a stoichiometric direct C–H nickelation of azobenzene was reported by Dubeck and Kleiman (Scheme 16).[46]

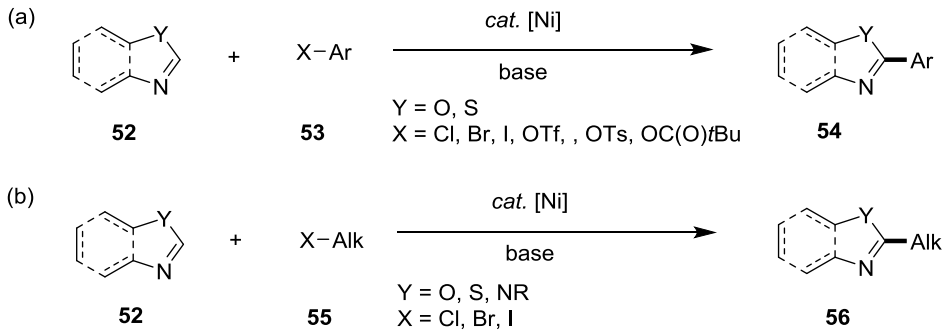


Scheme 16: Nickel-mediated C–H activation of azobenzene.

Early examples of such catalytic reactions were investigated by the groups of Miura, Hu and Ackermann.[47,48] These reports originally focused on C–H functionalisation of electronically-biased azoles and included arylation[47] and alkylation[48] reactions as depicted in Scheme 17.

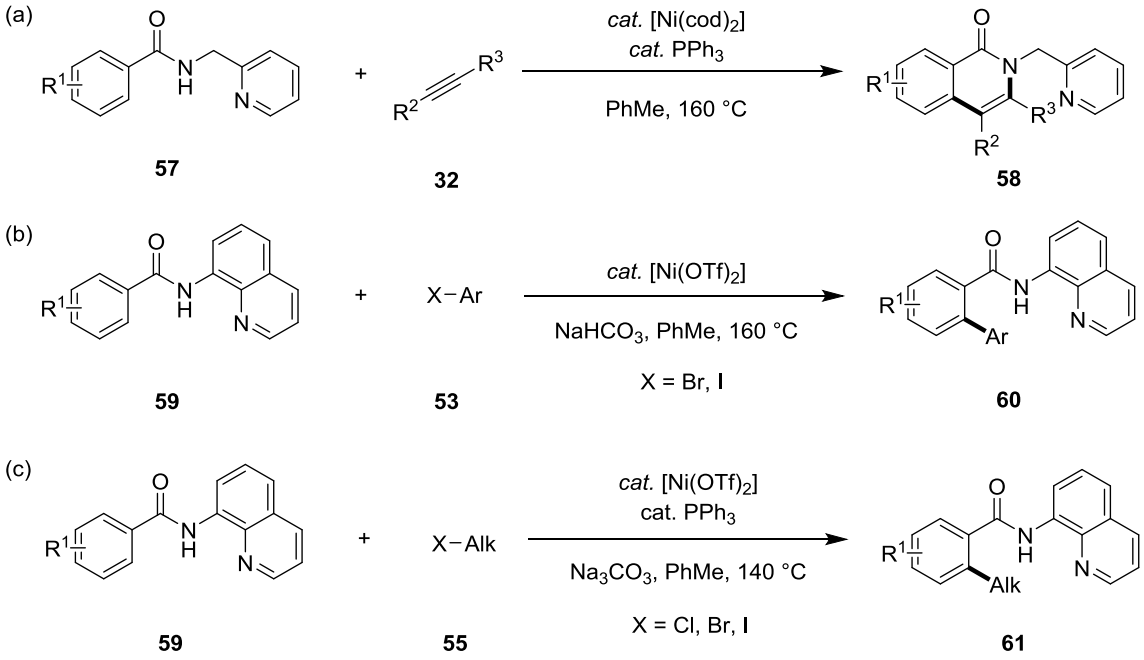
[46] Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544–1545.

[47] (a) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169–172. (b) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737–1740. (c) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733–1736. (d) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 201–204.



Scheme 17: Nickel-catalyzed C–H (a) arylation and (b) alkylation of azoles.

The utilisation of a Lewis-basic directing group for site-selective nickel-catalyzed C–H functionalization was achieved after the conception of bidentate auxiliaries was introduced by the group of Daugulis for palladium-catalysed C–H functionalisations.[49] They found that otherwise inert C–H bonds, could be functionalised, if a bidentate directing group was employed. Based on these findings the group of Chatani developed corresponding nickel-catalysed annulation,[50] arylation[51] and primary alkylation[52] reactions (Scheme 18).



Scheme 18: Nickel-catalyzed direct C–H (a) annulation, (b) arylation and (c) primary alkylation under bidentate assistance.

Taking advantage of this enhanced reactivities towards C–H bonds it was recently rendered possible to activate C(sp^3)-C–H bonds in a similar fashion (Scheme 19).[53]

---

[48] (a) Ackermann, L.; Punji, B.; Song, W. *Adv. Synth. Catal.* **2011**, *353*, 3325–3329. (b) Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem. Int. Ed.* **2010**, *49*, 3061–3064.

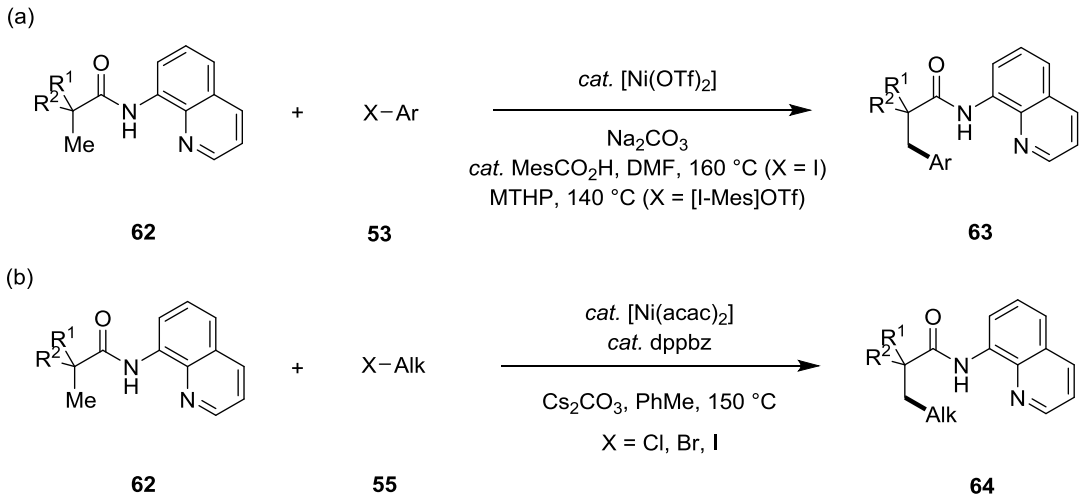
[49] Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053–1064.

[50] Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952–14955.

[51] Yokota, A.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014**, *79*, 11922–11932.

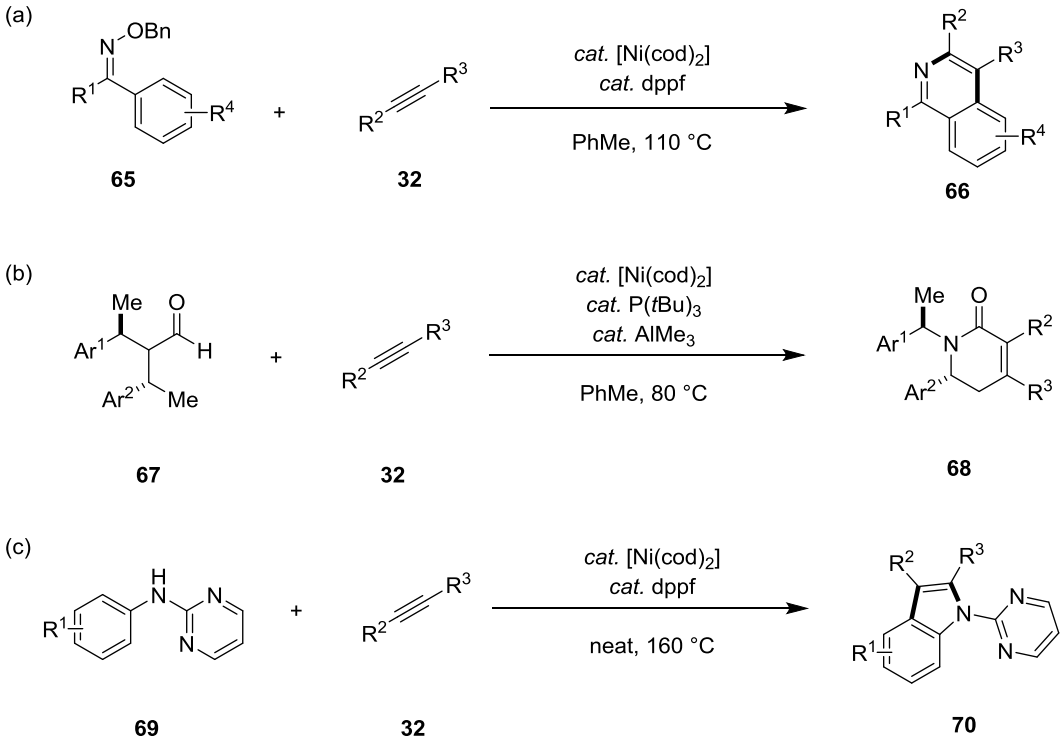
[52] Aihara, N.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308–5311.

[53] (a) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898–901. (b) Iyanaga, M.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014**, *79*, 11933–11939. (c) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, *136*, 1789–1792.



Scheme 19: Examples of C(sp^3)-C–H functionalisation through Nickel-catalysis.

The bidentate approach has remained most commonly used within directed nickel-catalyzed C–H functionalization. However, monodentate strategies have been less prevalent. One instance is the nickel-catalysed oxidative annulation of oximes developed by Matsubara (Scheme 20a).[54] Another are two annulation reactions reported by Hiyama[55] and Ackermann[56] respectively (Scheme 20b and c).



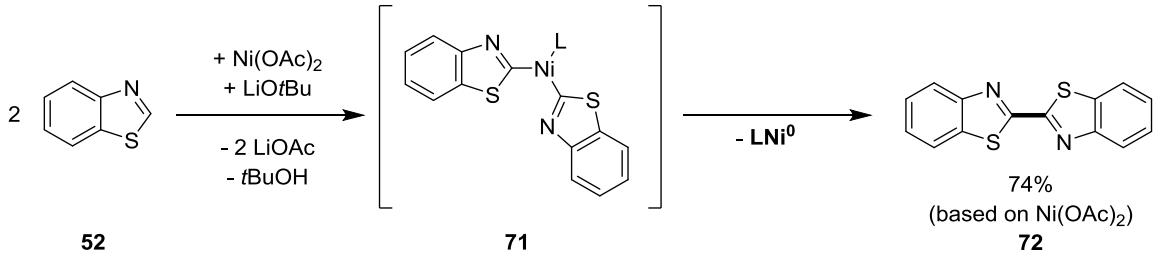
Scheme 20: Nickel-catalyzed C–H functionalisations with monodentate auxiliaries.

[54] Yoshida, Y.; Kurahashi, T.; Matsubara, S. *Chem. Lett.* **2011**, *40*, 1140–1142.
[55] Nakao, Y.; Morita, E.; Idei, H.; Hiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 3264–3267.
[56] Song, W.; Ackermann, L. *Chem. Commun.* **2013**, *49*, 6638–6640.

In addition, just as for other transition metals, protocols for the formation of C–X bonds through C–H bond functionalisation with nickel catalysts have recently been developed. These include borylation,[57] sulfonylation,[58] thiolation,[59] amination[60] and oxygenation reactions,[61] although the latter example still being a nickel-mediated process. New heterogenous nickel-catalysts, such as the reusable, metal organic framework $Ni_2(BDC)_2(DABCO)$, have emerged, as well.[62]

Nickel catalysis usually follows the previously mentioned modes for C–H activation (*vide supra* Scheme 10).[22] Oxidative addition pathways are often thought to be operative. However, the oxidation manifold has generally been unclear. In nickel-catalyzed alkylation chemistry three sets of probable oxidation states need to be considered for 2-electron changes, these being Ni(0)/Ni(II), Ni(I)/Ni(III) and Ni(II)/Ni(IV).

A typical example involving a catalytic cycle proposed for Ni(0)/Ni(II) intermediates involves the reaction of azoles.[63] In some cases the homocoupled azole **71** has been isolated, through which a Ni(0) species is proposed to be generated (Scheme 21).

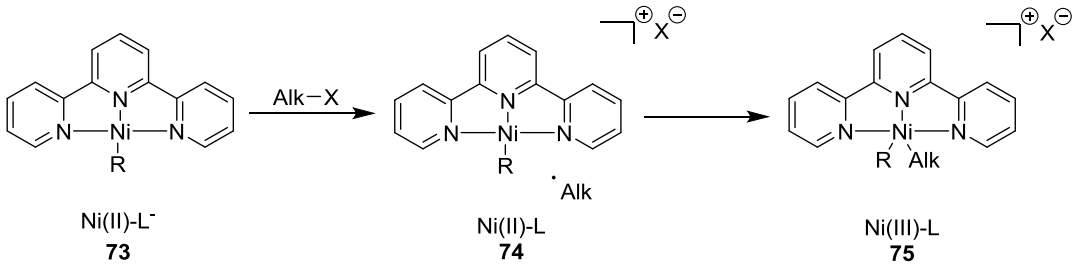


Scheme 21: Pathway for generation of nickel(0) species in the direct C–H arylation of azoles.

The Ni(I)/Ni(III) manifold is commonly invoked within alkylation reactions.[64] However, such conclusions are largely based on analogy to traditional cross coupling reactions, where isolated organonickel complexes were used for studies of the oxidative addition of unactivated alkyl halides. It has been established that the oxidative addition occurs through a single-electron-transfer, in which the alkyl halide is first bound to the nickel center and then a free organic radical is generated. Next, a rebound of the free organic radical occurs to form the new nickel-carbon bond. The initial Ni(I) species is often assumed to be only seemingly in this oxidation state, as the ligand may become redox-active. This however is mostly presumed for pyridine- and imin-based ligands (Scheme 22). Additional EPR

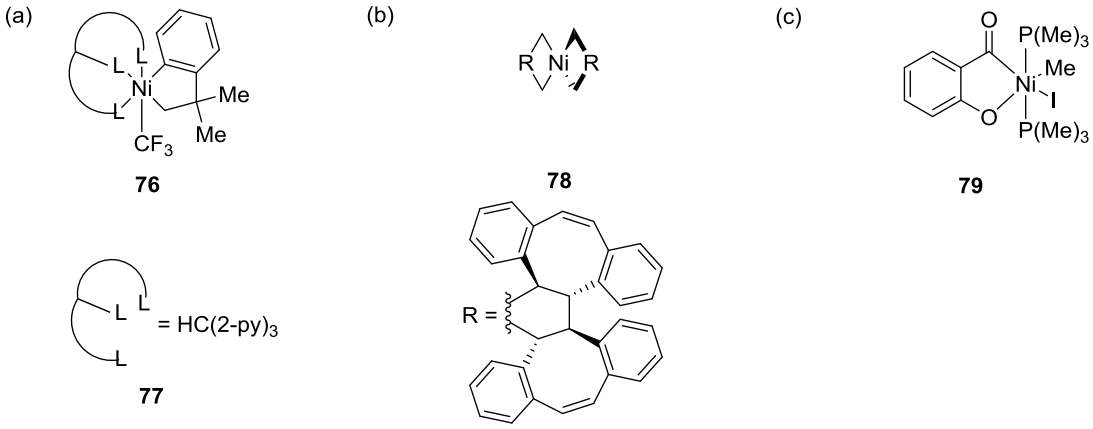
[57] Furukawa, T.; Tobisu, M.; Chatani, N. *Chem. Commun.* **2015**, *51*, 6508–6511.
[58] Yokota, A.; Chatani, N. *Chem. Lett.* **2015**, *44*, 902–904.
[59] (a) Zhu, J.; Chen, Y.; Lin, F.; Wang, B.; Chen, Z.; Liu, L. *Org. Biomol. Chem.* **2015**, *13*, 3711–3720. (b) Lin, C.; Yu, W.; Yao, J.; Wang, B.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 1340–1343.
[60] Yan, Q.; Chen, Z.; Yu, W.; Yin, H.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 2482–2485.
[61] Pattanayak, P.; Pratihar, J. L.; Patra, D.; Burrows, A.; Mohan, M.; Chattopadhyay *Eur. J. Inorg. Chem.* **2007**, 4263–4271.
[62] Phan, N. T. S.; Nguyen, C. K.; Nguyen, T. T.; Truong, T. *Catal. Sci. Technol.* **2014**, *4*, 369–377.
[63] Yamamoto, T.; Muto, K.; Komiyama, M.; Canivet, J.; Yamaguchi, J.; Itami, K. *Chem. Eur. J.* **2011**, *17*, 10113–10122.
[64] Hu, X. *Chem. Sci.* **2011**, *2*, 1867–1886, and references cited therein.

measurements conducted by Fu *et al.* confirmed the generation and importance nickel(I) intermediates.[65]



Scheme 22: Proposed intermediates for oxidative addition involving Ni(I)/Ni(III) oxidation states.

Furthermore, it could be considered that a Ni(IV) species could still be generated in these reactions, as a handful of Ni(IV)-alkyl-complexes have been isolated.[66] In case of complex **73** this was achieved by C–H functionalization (Scheme 23). However, these are typically formed under strongly oxidizing reaction conditions.



Scheme 23: Selected examples of nickel(IV)-alkyl-complexes.

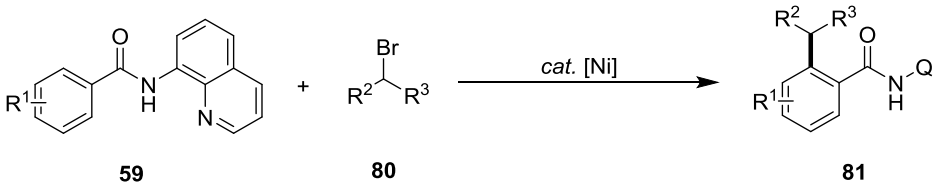
[65] Schley, N. D.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 16588–16593.

[66] (a) Camasso, N. M.; Sanford, M. S. *Science* **2015**, *347*, 1218–1220. (b) Carnes, M.; Buccella, D.; Chen, J. Y.-C.; Ramirez, A. P.; Turro, N. J.; Nuckolls, C.; Steigerwald, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 290–294. (c) Klein, H-F.; Bickelhaupt, A.; Lemke, M.; Sun, H.; Brand, A.; Jung, T.; Röhr, C.; Flörke, U.; Haupt, H.-J. *Organometallics* **1997**, *16*, 668–676.

2 Objectives

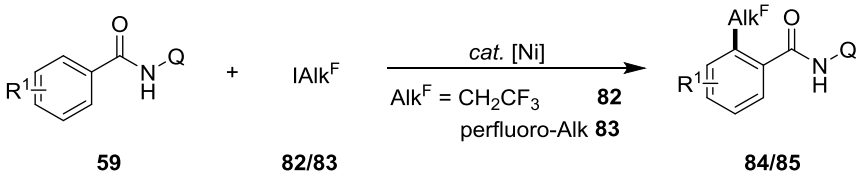
Efficient and selective alkylation and fluoroalkylation reactions are of key importance for numerous applied areas. Ongoing research within the group of Prof. Ackermann and the groups of others have developed a limited number of direct C–H alkylations with various transition metals.[13,40,48,52,53]

At the outset of this thesis, a novel direct secondary alkylation, as well as trifluoroethylation, of benzamides under bidentate assistance was developed by the co-worker Dr. Weifeng Song.[67] Based on this further expansion of the utilized secondary alkyl halides **80** was to be investigated (Scheme 24).



Scheme 24: Nickel-catalyzed bidentate-assisted secondary C–H alkylation.

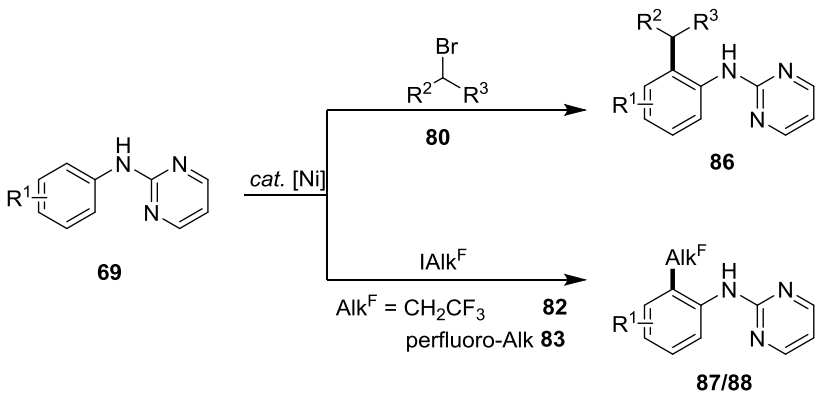
Additionally, the applicability of the direct trifluoroethylation and perfluoroalkylation of variously decorated arenes was to be probed (Scheme 25). Furthermore, more detailed studies to elucidate the details of the mechanism for these catalytic reactions was to be carried out.



Scheme 25: Nickel-catalysed bidentate-assisted fluoroalkylation.

A noticeable disadvantage of these bidentate auxiliaries, however, is their relative large size, which effectively lowers their atom economy for possible applications within industry and total synthesis.[49] Therefore, the development of simpler or biologically useful directing groups is of high interest. Based on previous findings for the efficient nickel-catalyzed synthesis of indoles from 2-pyrimidyl-anilines, the possibility to apply this useful directing group to the nickel-catalyzed alkylation and fluoroalkylation transformations was to be investigated. If successful, detailed mechanistic studies, particularly regarding the type of nickelacycle, were to be carried out. Further development of additional directing groups derived from the 2-pyrimidyl-anilines was also to be attempted (Scheme 26).

[67] Song, W. Cobalt- and Nickel- Catalyzed Functionalization of Unactivated C–Hal, C–O and C–H bonds. PhD Thesis, Georg-August-University, Göttingen, 2014.

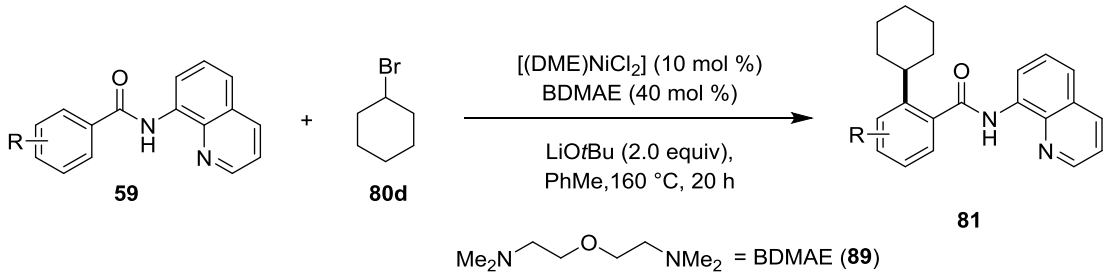


Scheme 26: Nickel-catalysed secondary C–H alkylations and fluoroalkylations of 2-pyrimidyl-anilines 69.

3 Results and Discussion

3.1 Direct C–H secondary Alkylation under Bidentate Assistance

As indicated in the introduction, direct C–H alkylations with unreactive alkyl halides **80** are of high relevance. In this context a nickel-catalyzed secondary alkylation of benzamides **59** with bidentate auxiliaries, a catalytic system has been previously developed by our co-worker Dr. Weifeng Song (Scheme 27).[67]

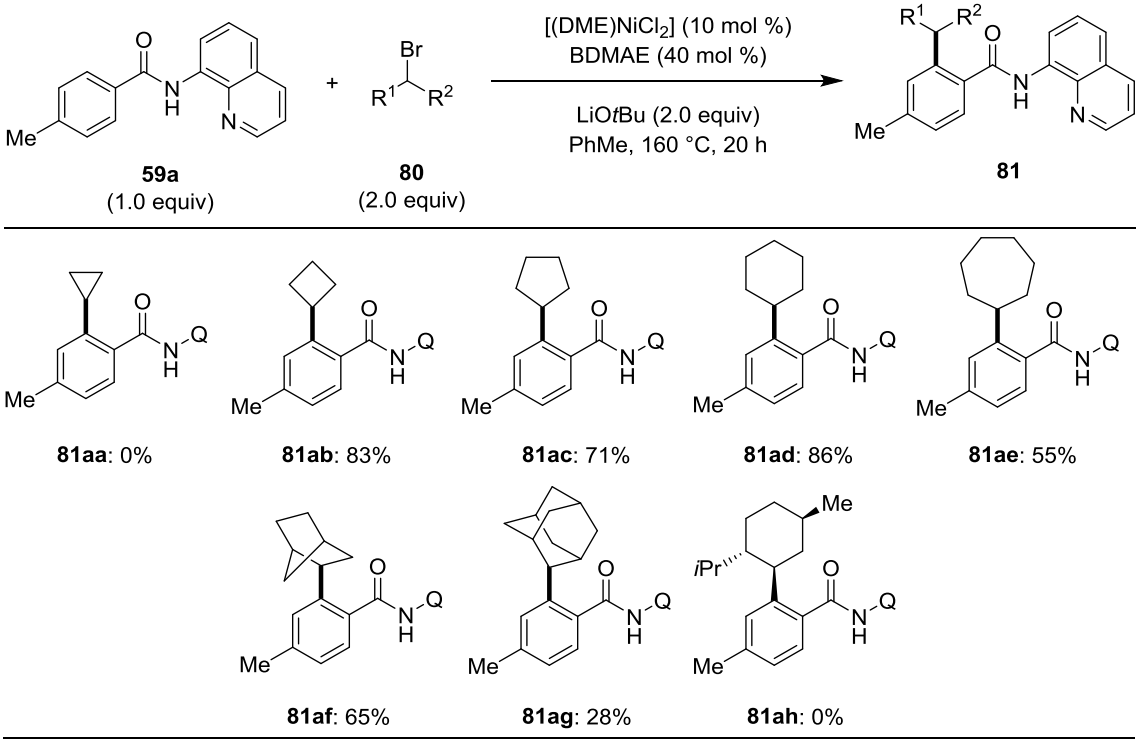


Scheme 27: System for nickel-catalyzed secondary alkylation of benzamides 59.

Mechanistic studies conducted by Dr. Weifeng Song revealed a reversible C–H metalation with the C–H acidity being of relevance.

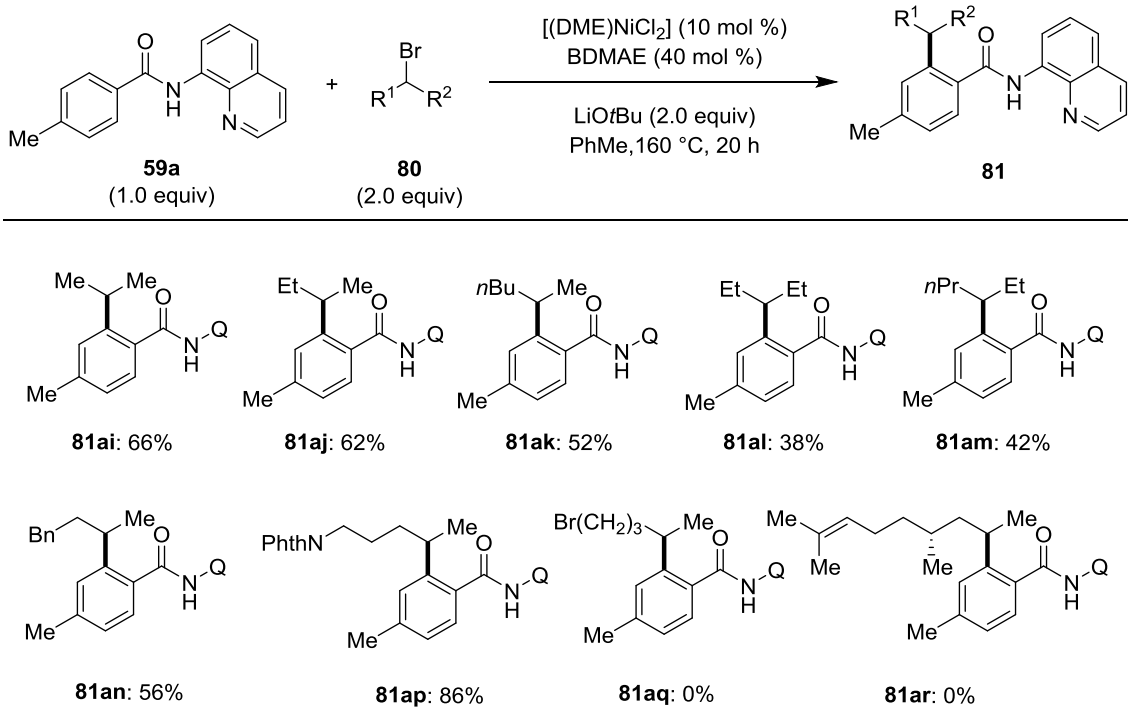
3.1.1 Scope and Limitations

Initially, cyclic alkyl bromides **80** were investigated (Scheme 28). Apart from cyclopropyl bromide **80a**, a wide range of alkyl halides with various ring sizes was well tolerated. It is also noteworthy that *exo*-bromo norbornane **80f** furnished the corresponding alkylated benzamide **81af** with retention of configuration. Only in the case of the bulkier 2-bromo adamantine **80g** did the conversion drop significantly.



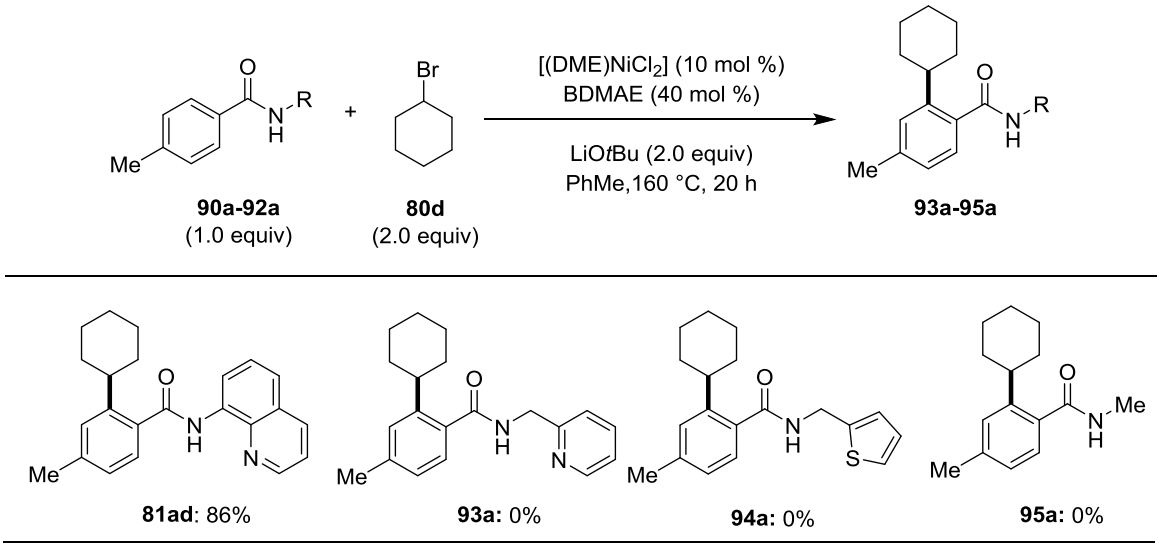
Scheme 28: Scope of secondary C–H alkylation of benzamide 59a with cyclic alkyl bromides 80.

For acyclic alkyl bromides **80** moderate yields were generally be obtained (Scheme 29). However, the trend of decreasing yields with increasing sterical demand of the alkyl chain was observed. In regards to functional groups, a protected amine in substrate **80p** was well tolerated. Additional halides or unsaturated bonds, however, were not feasible.



Scheme 29: Scope of secondary C–H alkylation of benzamide 59a with acyclic bromides 80.

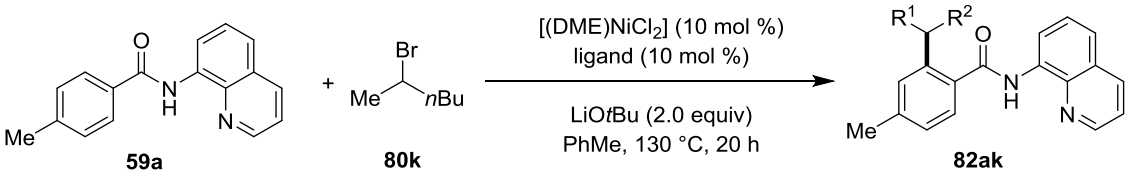
As the use of bidentate auxiliaries has proven to be impeccable, further possible variations of this basic principle were investigated (Scheme 30). These, however, proved to be incompatible with the optimized procedure.

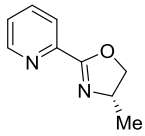
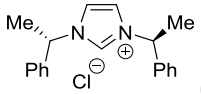


Scheme 30: Scope of alternative auxiliaries 90a–92a.

In an effort to achieve an enantioselective process a small selection of chiral ligands were probed next (Table 1). An enantiomeric excess could, however, not be observed. Based on previous protocols and findings from asymmetric nickel-catalysed cross-coupling reactions it can be reasoned that at temperatures significantly exceeding ambient temperature only low, if any, enantiomeric excess can be expected.[68] Therefore, no further studies were conducted.

Table 1: Screening of ligands for asymmetric C–H alkylation.[a]

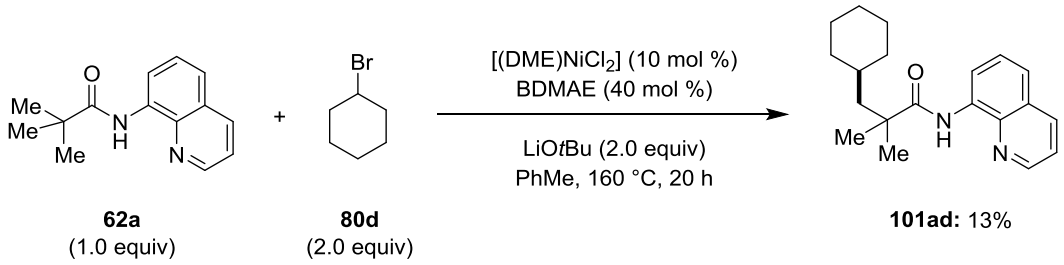


Entry	ligand	Yield [%]	ee [%]
1	(-)-pseudoephedrin (**96**)	3	0
2	(*L*)-valinol (**97**)	2	0
3	 (**98**)	(trace)	n. d.
4	 (**99**)	(trace)	n. d.
5	(*R*)-BINOL (**100**)	56	0

[a] Reactions conditions: **59a** (1.0 mmol), **80k** (2.0 mmol), LiO*t*Bu (2.0 mmol), ligand, PhMe (2 mL), 130 °C, 20 h, yields of isolated products.

[68] Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 5520–5524.

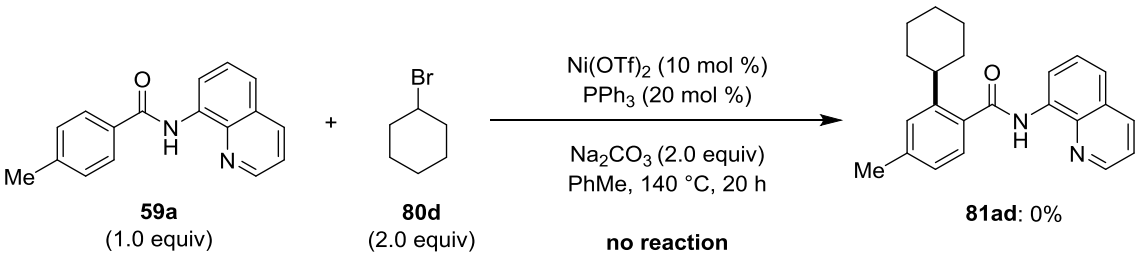
In addition to the direct C(sp^2)–H alkylation, the applicability of the optimized system towards C(sp^3)–H alkylation was preliminarily tested. Although the yield was low, it could be shown that the reaction was in principle feasible (Scheme 31).



Scheme 31: Direct C(sp^3)–H alkylation of amide 62a with 80d.

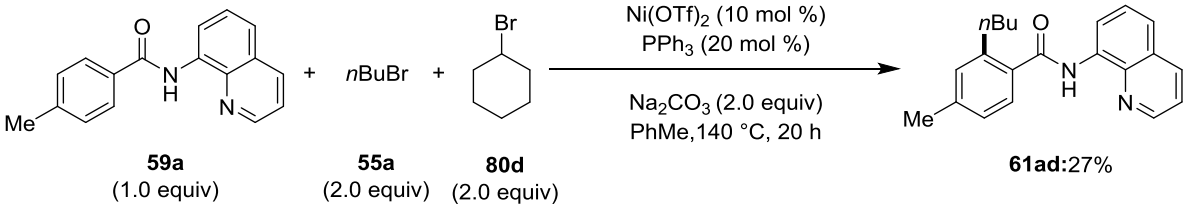
3.2.2 Mechanistic Studies

As to the reaction mechanism it could be shown that the conditions for primary alkylation, previously reported by Chatani *et al*,[52] were completely ineffective for challenging secondary C–H alkylation (Scheme 32).



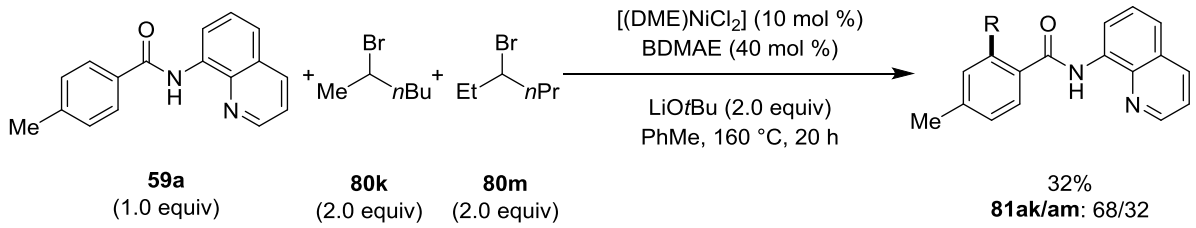
Scheme 32: Secondary C–H alkylation under conditions for primary alkylation.

Additionally, it was found that the reaction conditions for primary alkylation and the procedure for secondary alkylation were fully chemo-selective (Scheme 33).



Scheme 33: Competition experiment between primary and secondary alkyl halide.

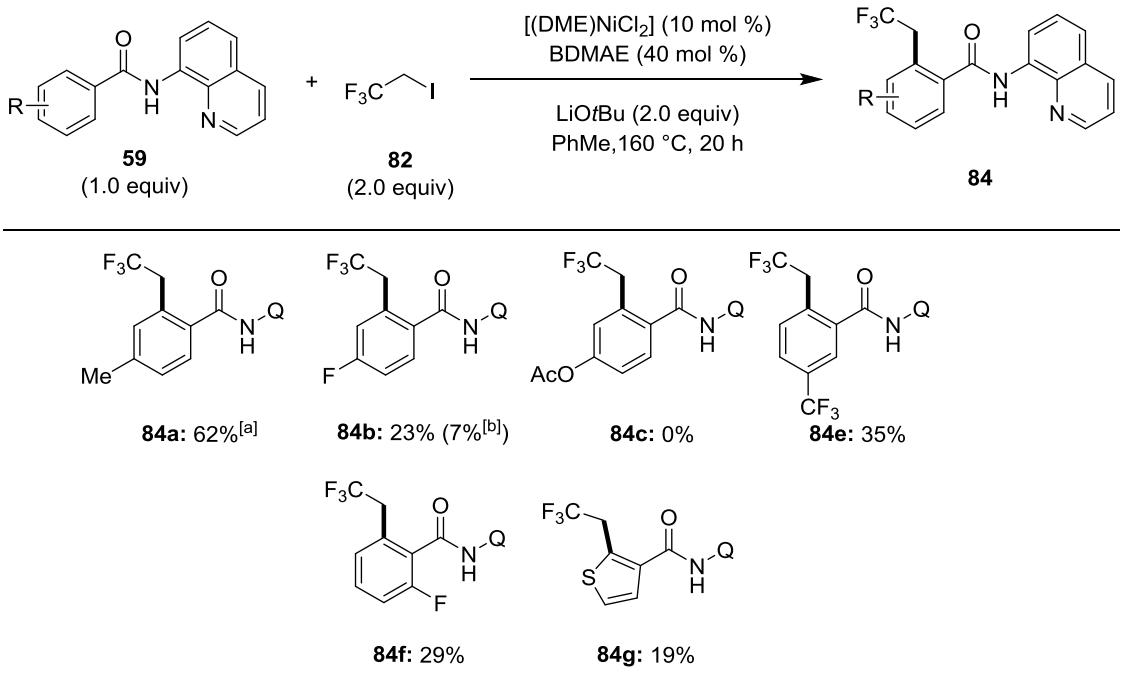
A competition experiment between 2-bromo hexane **80k** and 3-bromo hexane **80m** revealed that less sterically bulky substrates were significantly favoured (Scheme 34).



Scheme 34: Competition experiment between 2-bromo and 3-bromo hexane.

3.2 Direct C–H Trifluoroethylation under Bidentate Assistance

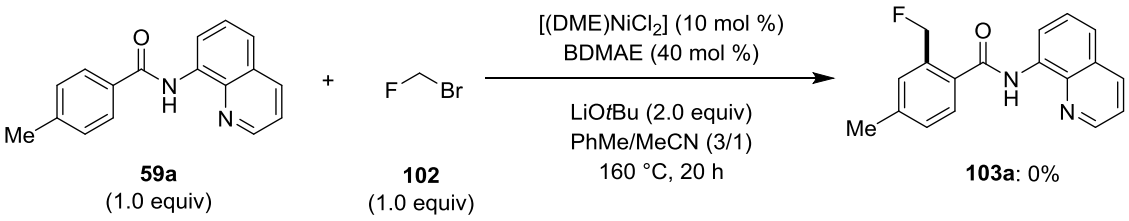
Fluorinated compounds have a significant role in medicinal chemistry (*vide supra*). Therefore, based on the catalytic system for direct secondary alkylations it was found that the first trifluoroethylation using trifluoroethyl iodide **82** was accessable by the nickel catalyst. Without further optimisation a representative set of substrates **59** were tested (Scheme 35). While the yields were rather moderate, the feasibility of this novel transformation could be shown as a proof of concept study.



[a] Performed by Dr. Weifeng Song. [b] Yield of the bis-trifluoroethylated product.

Scheme 35: Scope of Trifluoroethylation for benzamides 59.

Furthermore, based on a recently reported cross coupling transformation, [69] the related direct fluoromethylation was investigated as well (Scheme 36). However, without any optimization this attempt did not yield the desired product **101a**.

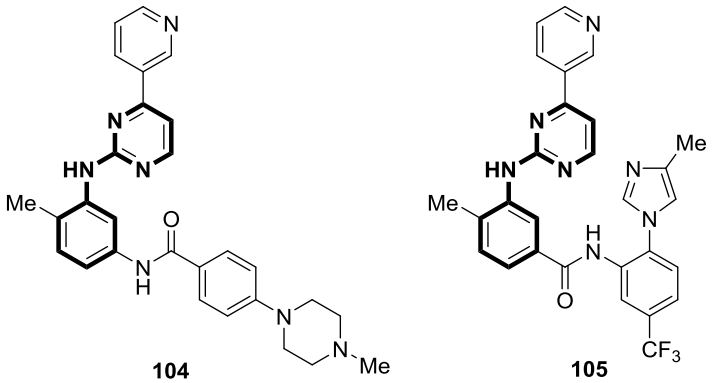


Scheme 36: Attempted fluoromethylation of benzamide 59a.

[69] An, L.; Xiao, Y.-L.; Min, Q.-Q.; Zhang, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 9079–9083.

3.3 Direct Secondary C–H Alkylation of *N*-Pyrimidyl-Anilines

Mono-dentate directing groups are severely underrepresented within nickel-catalysed C–H activation (*vide supra*). Therefore, based on the previously reported nickel-catalysed synthesis of indoles,[56] a direct C–H alkylation reaction utilising *N*-(2-pyrimidyl)-anilines **69** was envisioned. These are particularly interesting targets for alkylation reactions, as various important pharmaceuticals contain the 2-amino-pyrimidine motif.[70] Two examples of such drugs are Gleevec **104** and Tasigna **105**, both of which marketed by Novartis (Scheme 37).[71]



Scheme 37: Selected examples for marketed pharmaceuticals containing *N*-(2-pyrimidyl)-anilines.

3.3.1 Synthesis of Starting Materials

For the aniline substrates **69** an additional pathway for their synthesis was developed. Based on the known literature, usually three synthetic pathways are used. First, transition metal-catalyzed amination reactions, most commonly using palladium or copper as the transition metal, can be utilised.[72] This option can be rendered impractical, however, as trace amounts of the used transition metal need to be fully removed. This is typically achieved by distillation, which is often problematic due to the very high boiling point of these types of anilines **69**. Second, an acid-catalyzed aromatic substitution can be achieved by using 2-chloro-pyrimidine **106**.[73] This methodology, however, often gives low yields when employing

[70] (a) Kumar, S.; Deep, A.; Narasimhan, B. *Cent. Nerv. Syst. Agents Med. Chem.* **2015**, 15, 5–10. (b) Kaur, R.; Kaur, P.; Sharma, S.; Singh, G.; Mehndiratta, S.; Bedi, P. M. S.; Nepali, K. *Recent Pat. Anticancer Drug Discov.* **2015**, *10*, 23–71. (c) Dongre, R. S.; Bhat, A. R.; Meshram, J. S. *Am. J. PharmTech Res.* **2014**, *4*, 138–155. (d) Rawat, B.; Rawat, D. S. *Med. Res. Rev.* **2013**, *33*, 693–764. (d) Selvam, T. P.; James, C. R.; Dniandev, P. V.; Valzita, S. K. *Res. in Phar.* **2012**, *2*, 1–9. (e) Weisberg, E.; Manley, P.; Mestan, J.; Cowan-Jacob, S.; Ray, A.; Griffin, J. *Br. J. Cancer* **2006**, *94*, 1765–1769.

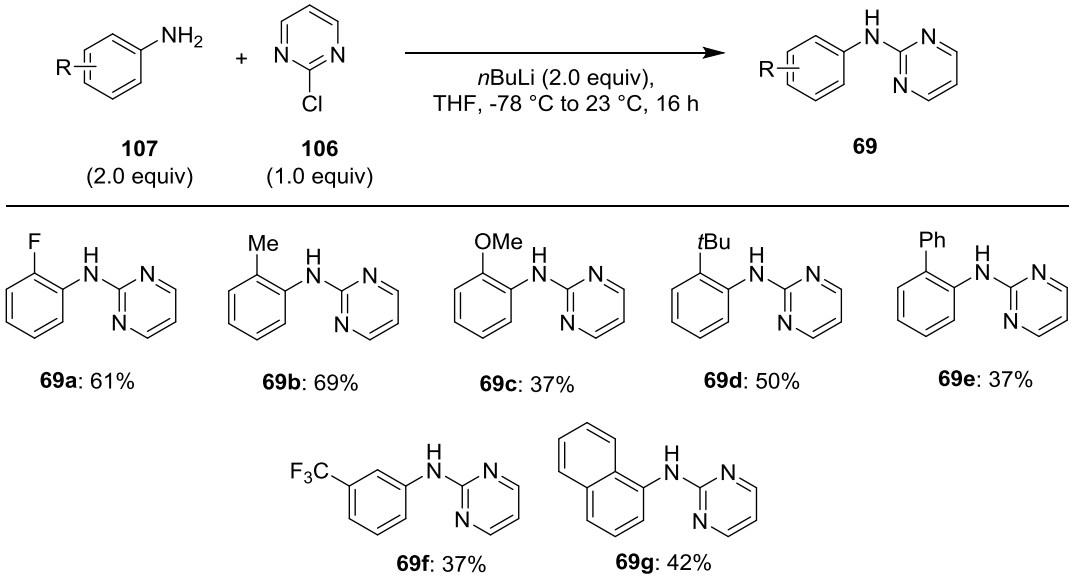
[71] (a) Breccia, M.; Alimena, G *Leuk. Res.* **2010***, 34,* 129–134. (b) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Ed.* **2010**, *87*, 1348–1349.

[72] (a) Yin, J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481–3484. (b) Liu, Y.; Bai, Y.; Zhang, J.; Li, Y.; Jiao, J.; Qi, X. *Eur. J. Org. Chem.* **2007**, 6084–6088.

[73] Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764–767.

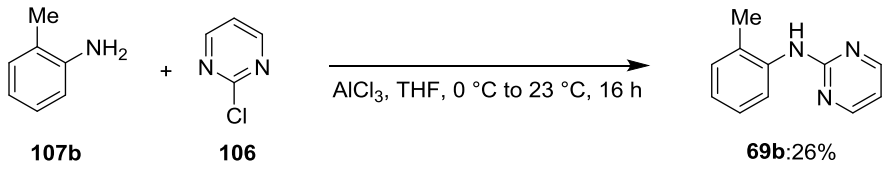
anilines, which are electron-deficient or contain sterically demanding substituents in the *ortho*-position. The typically employed protic solvent can also react with the 2-chloro-pyrimidine **106** to give undesired side products. Last, a three-step synthesis *via* a guanidinium moiety reacting with a corresponding Michael acceptor is also possible.[74] This approach, however, involves three steps with typically moderate yields. Also the scope of the substitution pattern in the 6-position of the pyrimidine is very narrow.

Hence, a more generally applicable methodology was needed and developed. Thus the nucleophilic aromatic substitution was employed without further optimisation (Scheme 38). Although the yields were generally rather moderate, otherwise unreactive anilines, such as 1-naphthylamine (**107g**), could be used here as well.



Scheme 38: Scope of basic synthesis of 2-pyrimidyl anilines 69.

A Lewis acid-mediated method was also tested, in which the typically protic solvents or co-solvents were avoided (Scheme 39). Possibly due to the high reactivity of aluminium chloride the yields were low.



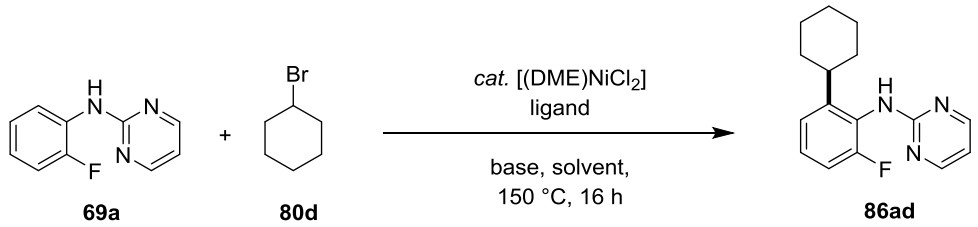
Scheme 39: Lewis acid-mediated synthesis of 2-pyrimidyl aniline 69b.

[74] Wang, S.; Meades, C.; Wood, G.; Osnowski, A.; Anderson, S.; Yuill, R.; Thomas, M.; Mezna, M.; Jackson, W.; Midgley, C.; Griffiths, G.; Fleming, I.; Green, S.; McNae, I.; Wu, S.-Y.; McInees, C.; Zheleva, D.; Walkinshaw, M. D.; Fischer, P. M. *J. Med. Chem.* **2004**, *47*, 1662–1675.

3.3.2 Optimisation Studies

At the outset of our studies, an initial test without additional ligand was performed and already furnished a low yield of desired product **83ad** (Table 2, entry 1). Adding the previously established ligand BDMAE or TMEDA significantly improved the performance (Table 2, entries 2—3). Secondary amines were also found to be suitable ligands for this transformation (Table 2, entries 4—6, 9—10). Among these, secondary amine D*t*BEDA proved to be ideal, allowing a lowering of the catalyst loading to 2.5 mol % (Table 2, entries 6—8). Surprisingly, 12-crown-4 facilitated the reaction as well (Table 2 , entry 12). While nickel complexes with related crown ether moieties are known,[75] it is unclear what type of coordination to nickel ions can occur during these type of reactions. Additionally, employing both, D*t*BEDA and 12-crown-4, together gives an intermediary yield (Table 2, entry 13). This may indicate a separate and possibly conflicting mode of action. Variation of the base showed that LiO*t*Bu was the best choice. Changing the metal cation lead to a severe decrease in conversion (Table 2, entries 13—16). Conversely, a change towards weaker lithium bases also gave no conversion. This may indicate that either certain solubility properties are crucial or that the lithium cation itself may be involved in the catalytic reaction. The latter case might be possible, if the lithium precoordinates to the directing group, effectively changing its electronic properties. Such cases have been studied for cesium bases in palladium-catalyzed C–H functionalisation.[76] Only lithium bases were therefore used in further studies. Additional lowering of the catalyst loading lead to trace conversion (Table 2, entries 18—19). Without catalyst no conversion towards the desired product was observed (Table 2, entry 20).

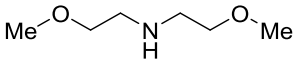
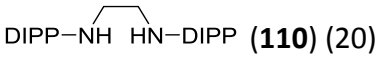
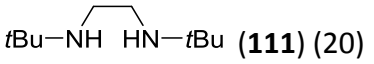
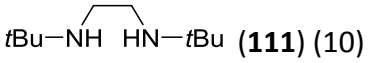
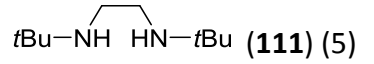
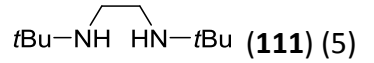
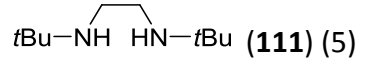
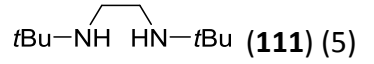
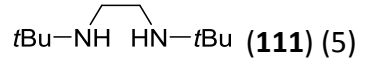
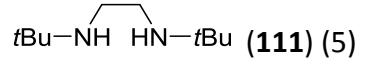
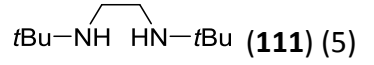
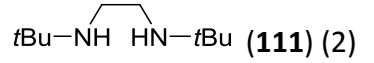
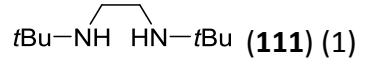
Table 2: Optimisation studies for secondary alkylation of anilines.[a]

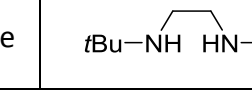


69a **80d** **86ad**

entry	Ni [mol %]	solvent	ligand (mol %)	base	yield [%]
1	10	PhMe	–	LiO*t*Bu	24
2	10	PhMe	BDMAE (**86**) (40)	LiO*t*Bu	94 (86[b])

[75] (a) Korybut-Daszkiewicz, B.; Taraszewska, J.; Zieba, K.; Makal, A.; Wozniak, K. *Eur. J. Inorg. Chem.* **2004**, 3335–3344. (b) Jarrin, J.; Dawans, F.; Robert, F.; Jeannin, Y. *Polyhedron* **1982**, *1*, 409–412.
[76] Musaev, D. G.; Figg, T. M.; Kaledin, A. L. *Chem. Soc. Rev.* **2014**, *43*, 5009–5031.

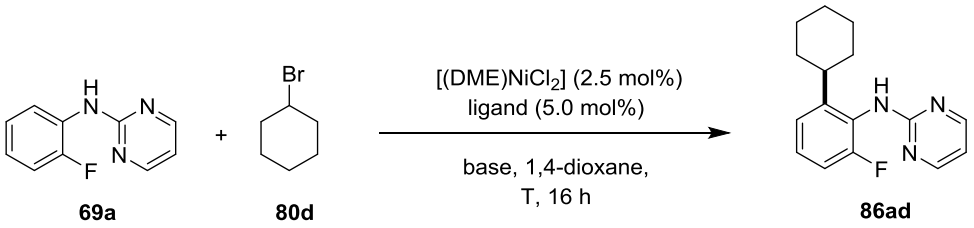
3	10	PhMe	TMEDA (**108**) (40)	LiO*t*Bu	55
4	2.5	PhMe	 (**109**) (40)	LiO*t*Bu	39
5	10	PhMe	 (**110**) (20)	LiO*t*Bu	15
6	10	PhMe	 (**111**) (20)	LiO*t*Bu	97
7	5	PhMe	 (**111**) (10)	LiO*t*Bu	96
8	2.5	PhMe	 (**111**) (5)	LiO*t*Bu	81
9	2.5	PhMe	HN*i*Pr$_2$ (**112**) (10)	LiO*t*Bu	24
10	2.5	PhMe	TMP (**113**) (10)	LiO*t*Bu	15
11	2.5	1,4-dioxane	 (**111**) (5)	LiO*t*Bu	97 (95[b])
12	2.5	1,4-dioxane	12-crown-4 (**114**) (5)	LiO*t*Bu	73
13	2.5	1,4-dioxane	12-crown-4 (**114**) (5) +  (**111**) (5)	LiO*t*Bu	91
14	2.5	1,4-dioxane	 (**111**) (5)	NaO*t*Bu	2
15	2.5	1,4-dioxane	 (**111**) (5)	KO*t*Bu	4
16	2.5	1,4-dioxane	 (**111**) (5)	Mg(O*t*Bu)$_2$	0
17	2.5	1,4-dioxane	 (**111**) (5)	Li_3PO_4	0
18	1	1,4-dioxane	 (**111**) (2)	LiO*t*Bu	2
19	0.5	1,4-dioxane	 (**111**) (1)	LiO*t*Bu	1

20	0	1,4-dioxane	 (**111**) (5)	LiO*t*Bu	0

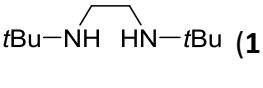
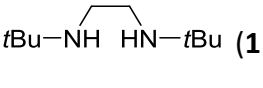
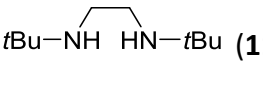
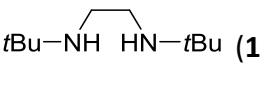
[a] Reaction conditions: **69a** (1.0 mmol), **80d** (2.0 mmol), base (2.0 mmol), [(DME)$NiCl_2$], ligand, solvent (2 mL), 150 °C, 16 h, yields based on crude ^{19}F-NMR with C_6F_6 as internal standard. [b] Isolated yield.

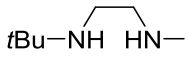
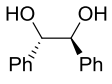
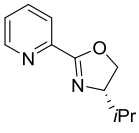
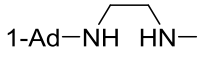
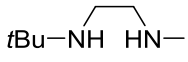
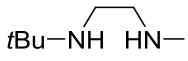
The catalytic system utilising D*t*BEDA as the ligand appeared to perform best at reaction temperatures lowered to 100-120 °C with 80 °C only giving low conversion (Table 3, entries 1—3). At these reduced reaction temperatures weaker lithium bases were still not viable for this transformation. Additional ligands consisting of bis-alcohols, oxazolines and primary amines gave no product formation (Table 3, entries 6, 8—9). *N*-heterocyclic carbene IPr, however, gave a moderate yield (Table 3, entry 7). Replacing the *tert*-butyl in D*t*BEDA with an adamantyl moiety significantly decreased the yield (Table 3, entry 10). The previously reported system for primary alkylations with bidentate auxiliaries proved to be ineffective, as well (Table 3, entry 12). Palladium dichloride was tested as the catalyst in order to exclude the possibility of catalytically active trace amount of palladium (Table 3, entry 13). Under these conditions neither the desired product nor other side-products were detected.

Table 3: Optimisation of reaction temperature, base and ligand.[a]



69a **80d** **86ad**

entry	T [°C]	ligand	base	yield [%]
1	120	 (**111**)	LiO*t*Bu	96
2	100	 (**111**)	LiO*t*Bu	98
3	80	 (**111**)	LiO*t*Bu	9
4	100	 (**111**)	Li_3PO_4	0

5	100	 (**111**)	Li_2CO_3	0
6	100	 (**115**)	LiO*t*Bu	0
7	100	IPr*HCl (**116**)	LiO*t*Bu	66
8	100	 (**117**)	LiO*t*Bu	0
9	100	Ethylene diamine (**118**)	LiO*t*Bu	0
10	100	 (**119**)	LiO*t*Bu	18
11	100	 (**111**)	LiO*t*Bu	99[b]
12	100	PPh_3 (**120**)	LiO*t*Bu	5[c]
13	100	 (**111**)	LiO*t*Bu	0[d]

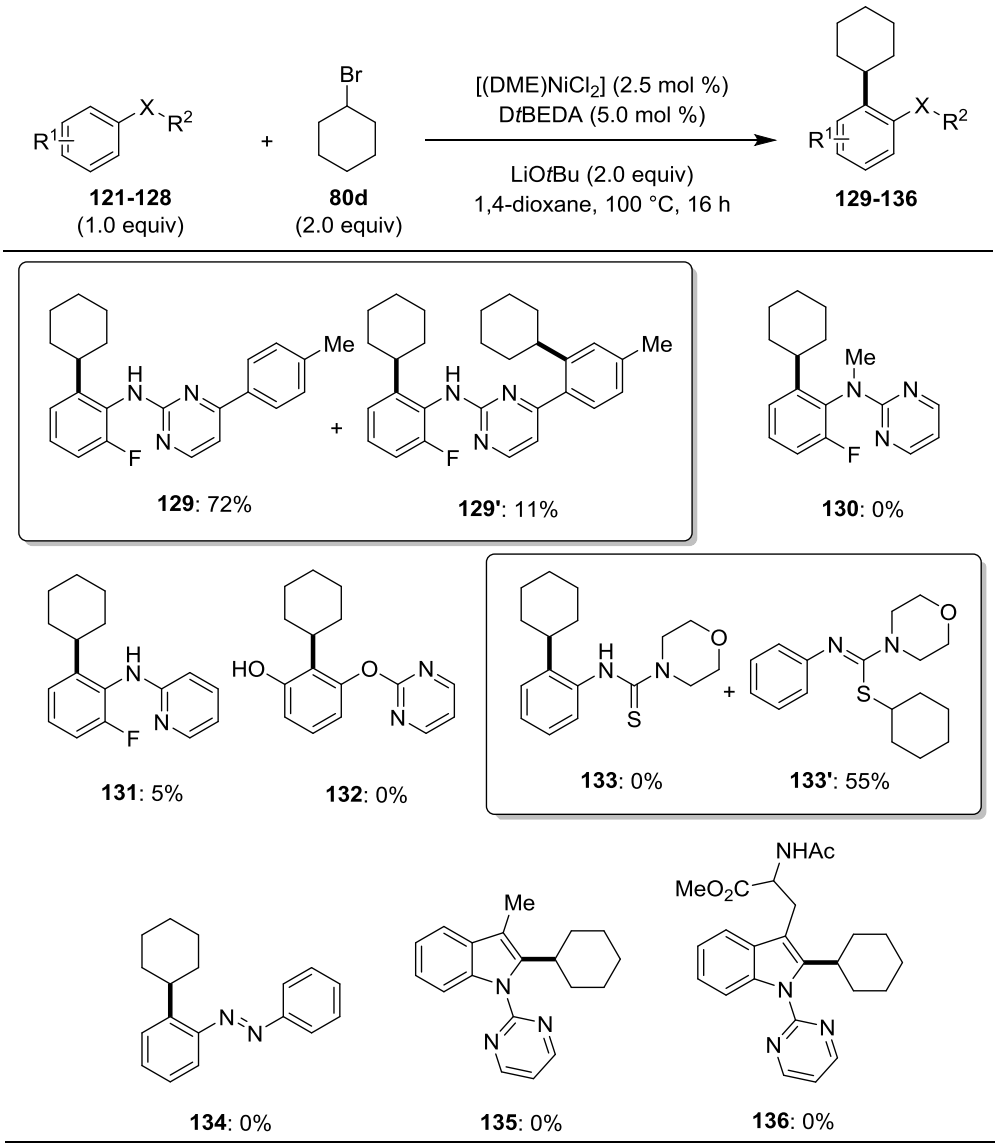
[a] Reaction conditions: **69a** (1.0 mmol), **80d** (2.0 mmol), LiO*t*Bu (2.0 mmol), [(DME)$NiCl_2$] (2.5 mol %), ligand (5.0 mol %), 1,4-dioxane (2 mL), 16 h, yields based on crude ^{19}F-NMR with C_6F_6 as internal standard. [b] [$NiCl_2(H_2O)_6$]. [c] $Ni(OTf)_2$. [d] $PdCl_2$.

3.3.3 Scope of C–H Alkylation of anilines

Due to the novelty of the employed directing group different variations of the basic pattern were examined with the optimised conditions (Scheme 40). Adding an arene substituent on the pyrimidine moiety did not significantly inhibit the reaction to product **129**. However, a sideproduct **129'** was observed. This observation clearly showed that alternative arrangements of 2-amino-pyrimidines can serve as directing groups as well. Replacing the acidic N-H- with a N-Me moiety as in compound **130** completely shut down the reaction. A change of the pyrimidine-moiety to pyridine substrate **123** caused a significant decrease in

conversion, thereby giving product **131** in trace amounts only. Spatially separating the acidic proton and the directing pyrimidyl group by using *O*-(2-pyrimidyl)-resorcinol **124** led to no conversion. Further, a simpler thiourea-derivative **125** did not give the desired product **133**, but instead the S-alkylated product **133'**.

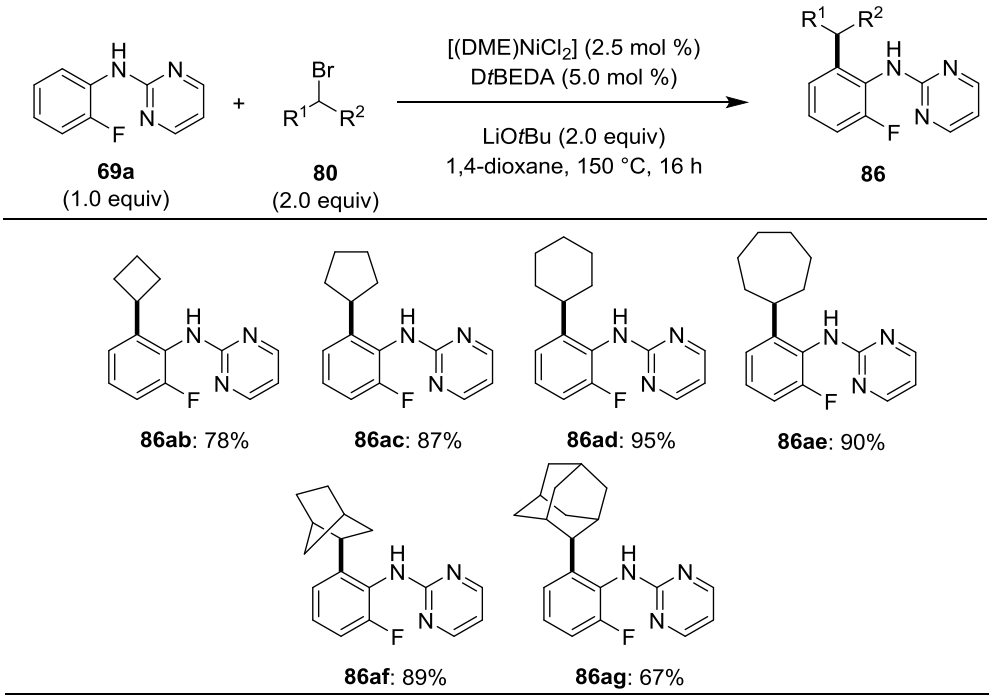
Additionally, the catalytic system proved ineffective for *N*-(2-pyrimidyl)-indole derivatives, which have been previously employed in various C–H functionalisations.[77] Azobenzene **126**, which was used by Dubeck and Kleimann very early for the synthesis of the corresponding nickelacycle, was not viable to synthesise **134**.[46]



Scheme 40: Scope of C–H alkylations with different directing groups.

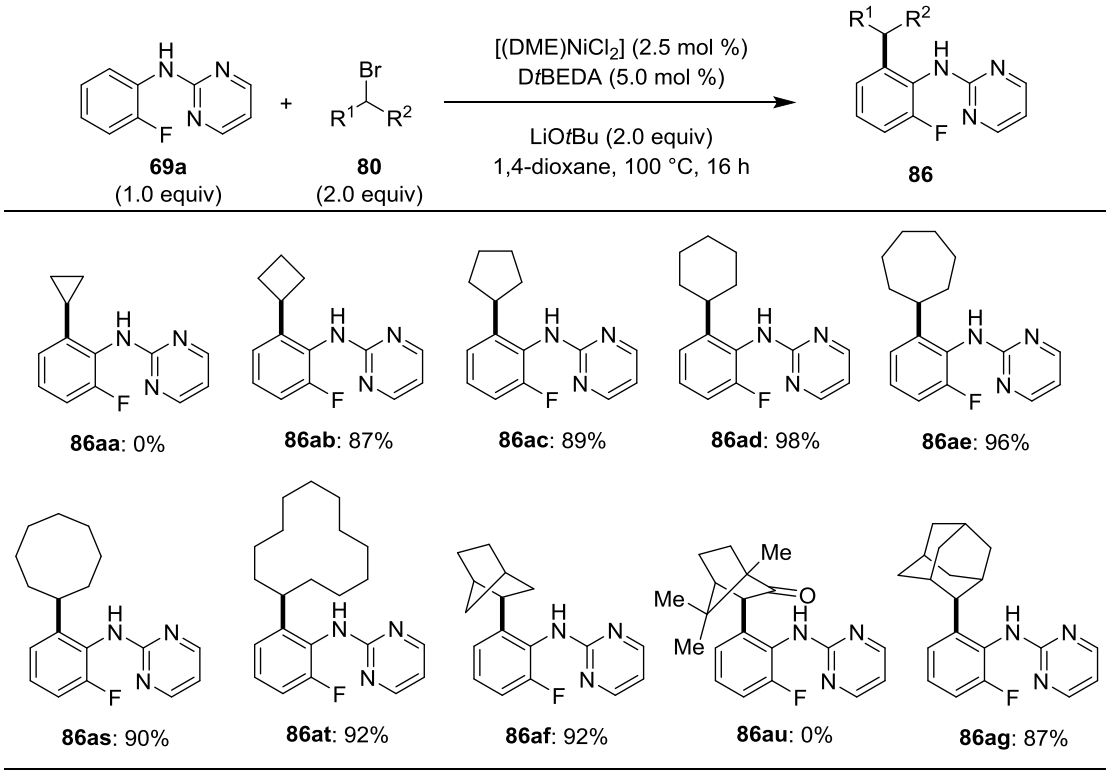
[77] Selected examples: (a) Sauermann, N.; Gonzalez, M. J.; Ackermann, L. *Org. Lett.* **2015**, *17*, 5316–5319. (b) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Eur. J. Org. Chem.* **2013**, *19*, 9142–9146. (c) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2011**, *13*, 3332–3335.

With the optimised system at hand, a variety of cyclic alkyl bromides **80** were tested. This was initially done at a reaction temperature of 150 °C (Scheme 41), as increased temperature usually provided improved efficacy for less reactive halides **80**.



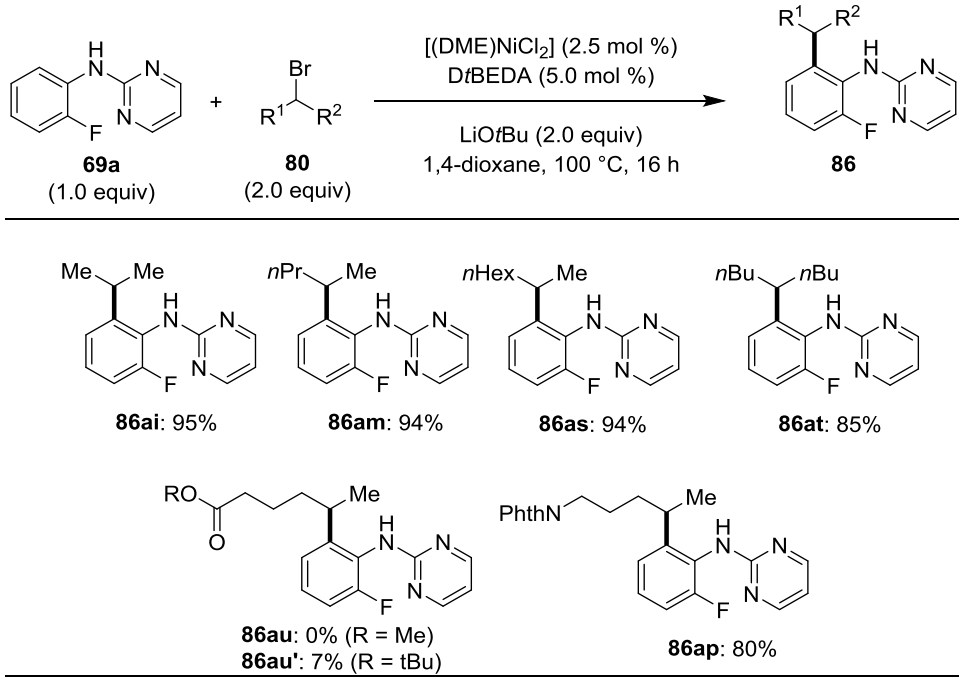
Scheme 41: Scope of C–H alkylation of aniline 69a with cyclic alkyl bromides 80 at 150 °C.

During further investigation it was found, however, that at reduced reaction temperatures the yields for corresponding cyclic alkyl bromides **80** was either identical or even better (Scheme 42). Under these reaction conditions a wide range of cyclic alkyl bromides **80** was well tolerated, with the exception of cyclopropyl bromide **80a**. Of particular interest was the use of *exo*-bromo norbornane **80f**, which reacted under retention of configuration to give product **86af**. The related *exo*-2-bromo-camphor **80u** on, however, was unreactive, presumably due to the additional keto group. In addition, the bulky 2-bromo adamantane gave **86ag** in excellent yields, as well.



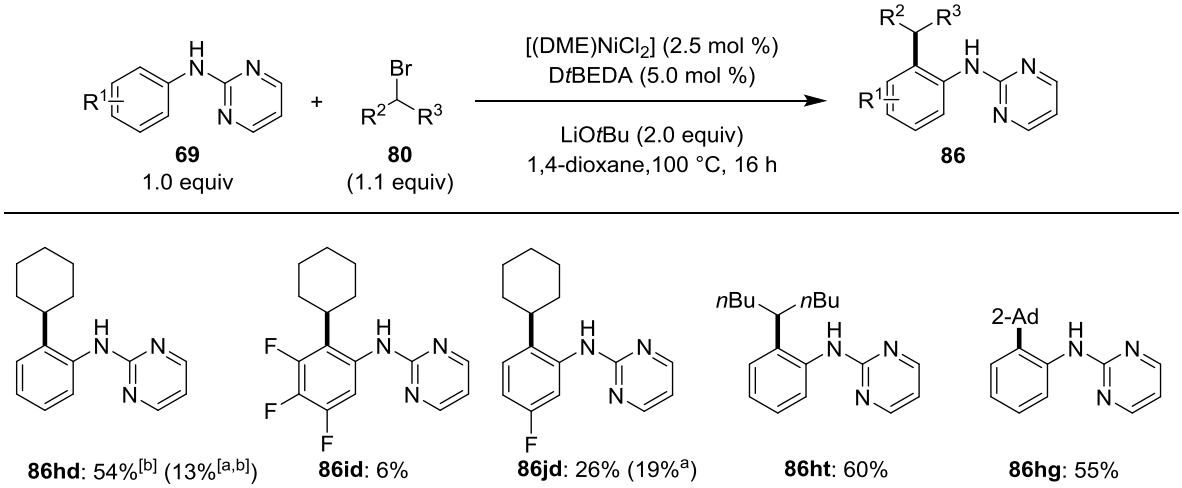
Scheme 42: Scope for C–H alkylation of aniline 69a with cyclic alkyl bromides 80 at 100 °C.

The catalytic system was not limited to cyclic alkyl bromides **80**. Acyclic bromides **80** were also viable substrates (Scheme 43). Alkyl chains containing phthalimide moieties gave excellent yields as well. Esters within the alkyl chain however only led to poor yields of transesterified product **86au'**. This is presumably caused by the formation and side reactions of the corresponding ester enolate.



Scheme 43: Scope for C–H alkylation aniline 69a with acyclic alkyl bromides 80 at 100 °C.

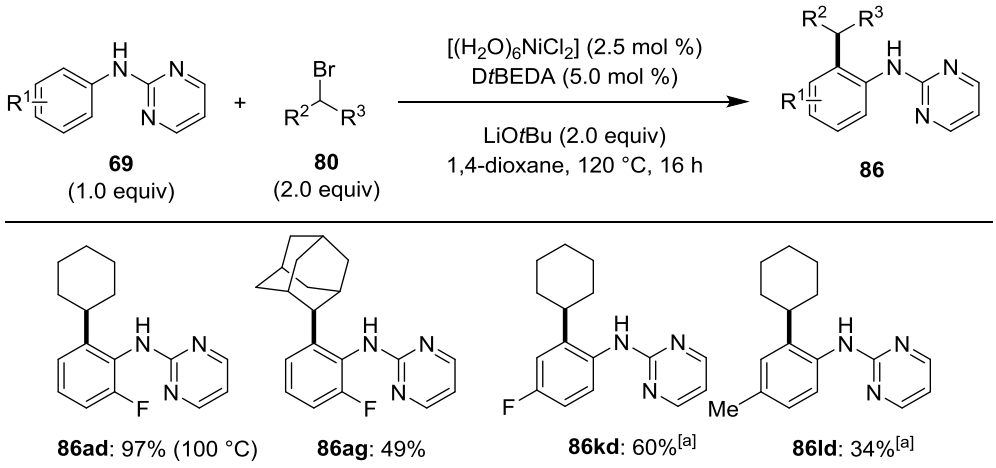
Additionally, several differently decorated arenes **69** were investigated (Scheme 44). With substrates **69h-j**, in which the *ortho*-position is unsubstituted, good selectivity for the mono-alkylated products with moderate yields can be achieved by lowering the amount of alkyl bromide **80** to 1.1 equivalents. For substrates **69i-j** bearing a fluoro-substituent in the *meta*-position yields decreased significantly. This might be attributed to either additional coordination of the fluoro-group towards the nickel-catalyst or potential C–F activation by the nickel-catalyst.



[a] yield of bis-alkylated product. [b] 3.5 mmol scale.

Scheme 44: Scope for C–H alkylation of anilines 69 with alkyl bromides 80 at 120 °C.

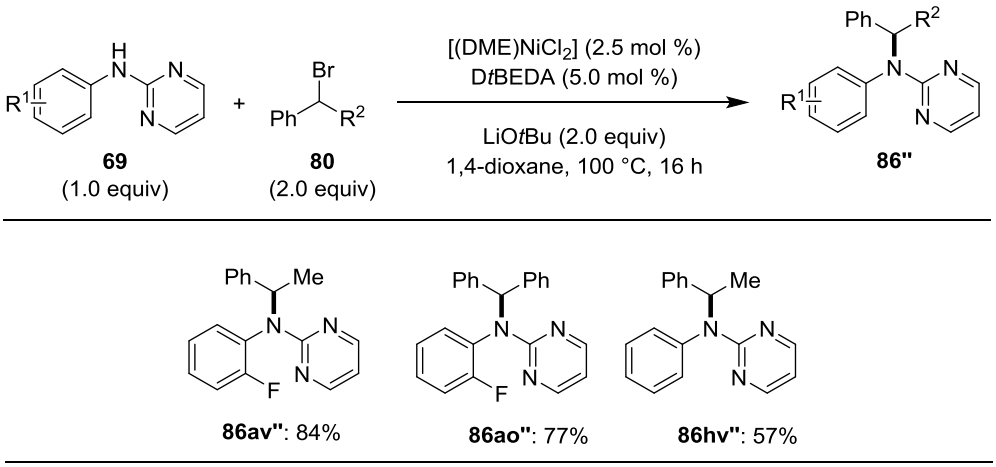
It was shown during the previous optimisation studies (Table 3, entry 11), that the bench-stable Nickel dichloride hexahydrate appeared to be an efficient catalyst also. Therefore, a small selection of substrates was tested for these conditions (Scheme 45). It was found that for most substrates the conversion was lower, yet still acceptable.



[a] 1.1 equiv of **80d** used.

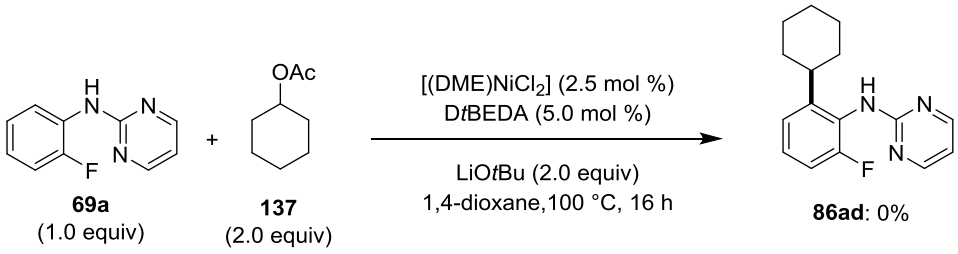
Scheme 45: Scope for C–H secondary alkylation with $[NiCl_2(H_2O)_6]$ as the catalyst.

In case of benzylic bromides **80o/v** a change in chemo-selectivity to *N*-alkylation was observed (Scheme 46).



Scheme 46: *N*-Benzylation with alkyl bromides 80v/o.

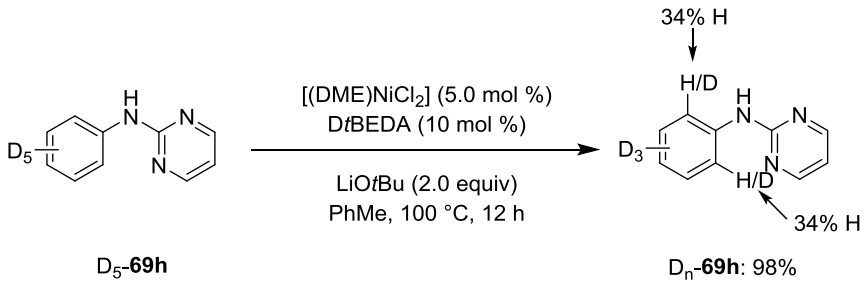
In addition to alkyl halides the more easily accessible cyclohexyl acetate (**137**) was probed (Scheme 47). However, the current catalytic system proved inefficient for this type of substrates.



Scheme 47: Attempted C–H alkylation of aniline 68a with cyclohexyl acetate (137).

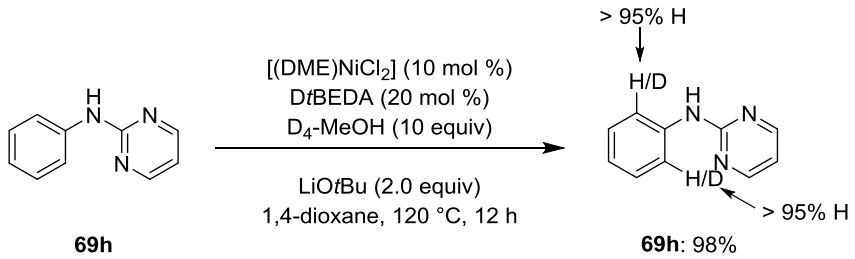
3.3.4 Mechanistic Studies

Intrigued by this unusual, new transformation a variety of mechanistic studies was conducted. First, isotopically labelled substrate D_5-**69h** was subjected to the reaction conditions with only the standard ligand D*t*BEDA as a proton source, giving significant H/D-exchange (Scheme 48).This result shows that in the absence of alkyl halides **80** the C–H metalation is facile.



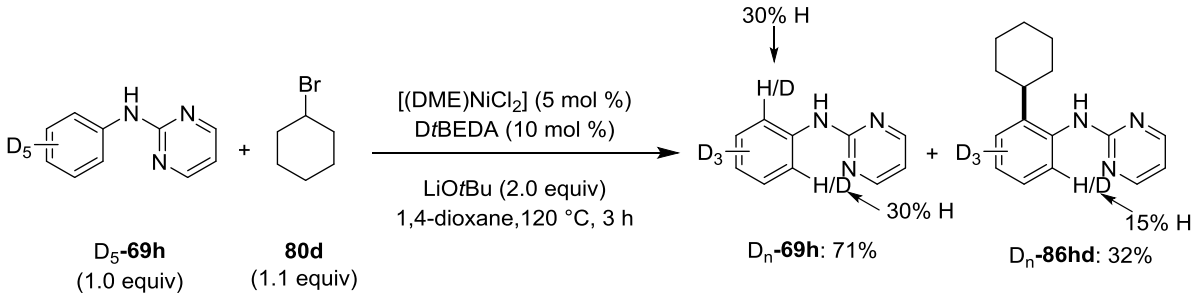
Scheme 48: H/D-exchange for substrate D_5-69d with D*t*BEDA as proton source.

The reverse process, using **69h** in the presence of D_4-methanol led to no H/D-exchange (Scheme 49). This, however, may be attributed to the significantly more acidic deuterium donor, thus changing the reaction conditions greatly, thus making them incompatible with the catalytic system.



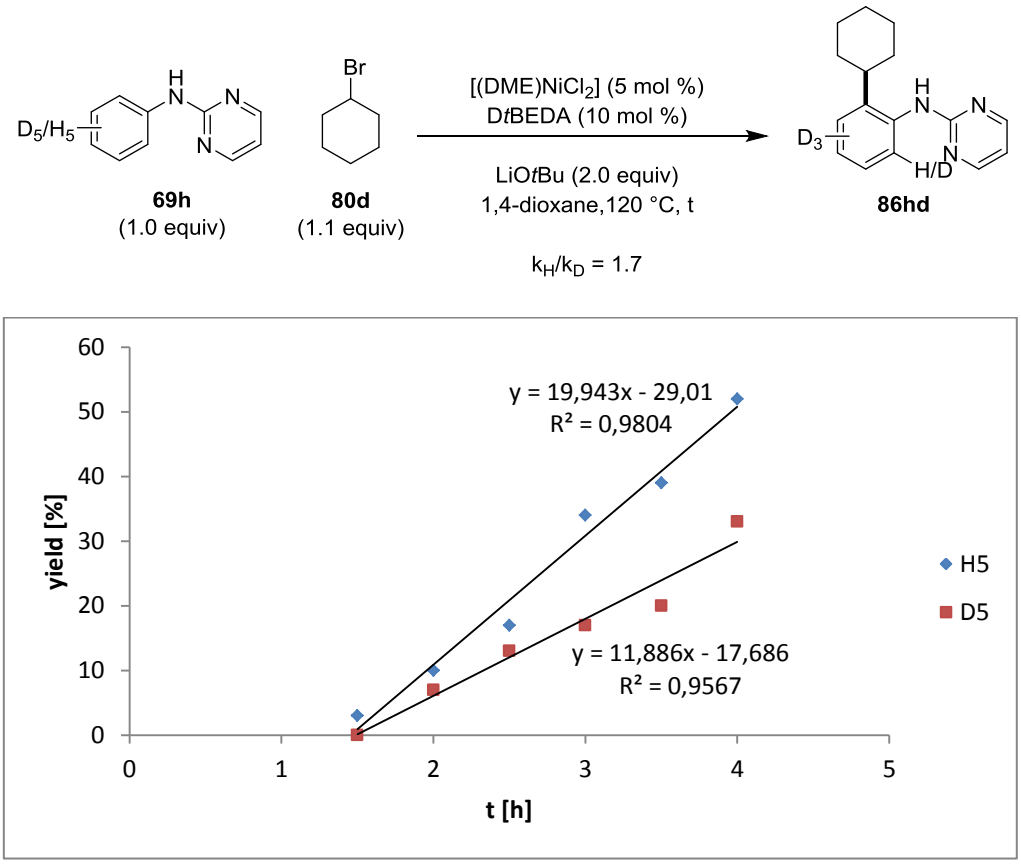
Scheme 49: Attempted H/D-exchange for 69h with D_4-MeOH as deuterium source.

The reaction of labelled substrate D_5-**69h** with alkyl halide **80d** showed significant H/D scrambling (Scheme 50). Considering these findings it can be assumed that the C–H-metalation is reversible.



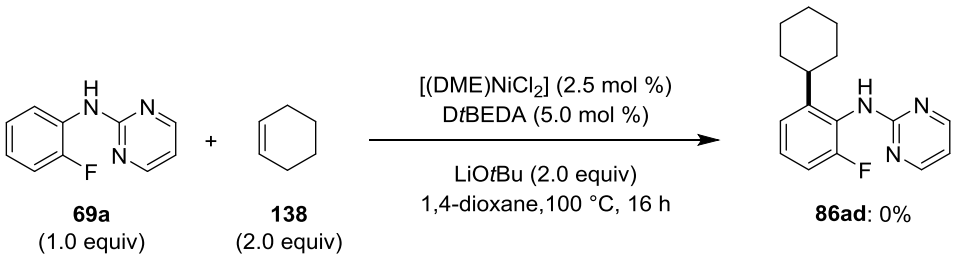
Scheme 50: H/D-exchange under standard reaction conditions.

Independent experiments with substrates **69h** and D_5-**69h** with alkylation **80d** revealed a kinetic isotope effect (KIE) of k_H/k_D = 1.7 (Scheme 51). A kinetic isotope effect (KIE) of this magnitude might indicate that the C–H metalation is not the rate determining step.



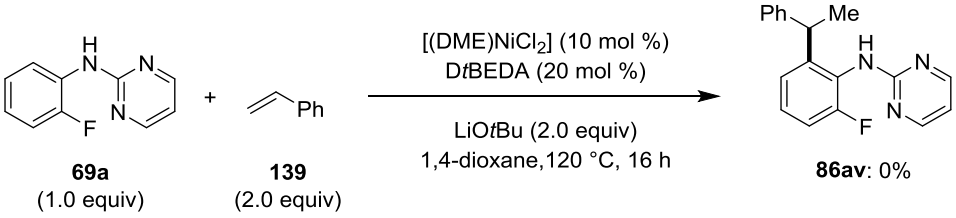
Scheme 51: Kinetic isotope effect studies.

Considering that the alkyl halides **80** may undergo elimination to the corresponding olefins, the actual alkylation agent should be identified. For this the standard reaction was attempted with cyclohexene **138** under otherwise identical reaction conditions (Scheme 52).



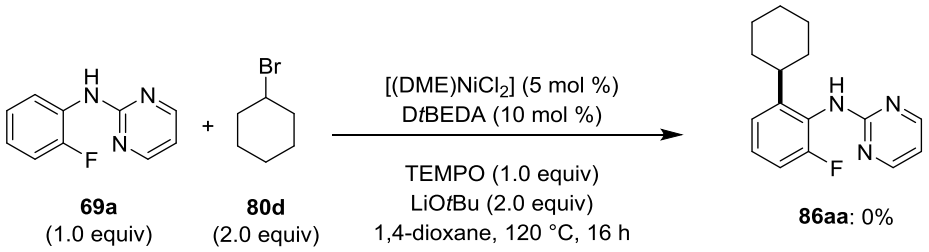
Scheme 52: Attempted alkylation of substrate 69a with cyclohexene 138.

Likewise, the more reactive styrene **139** (Scheme 53) did not yield any alkylated products. It can therefore be concluded that the alkyl halides **80** are the active alkylating agents.



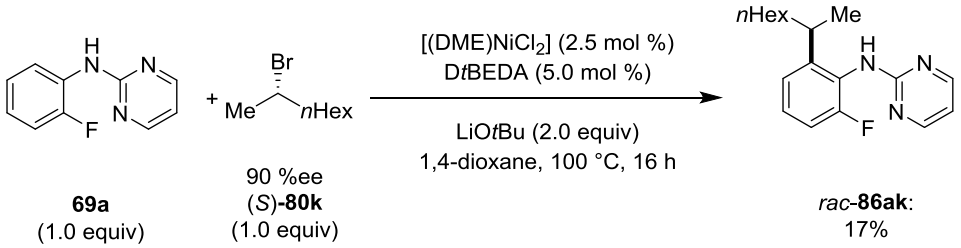
Scheme 53: Attempted alkylation of substrate 69a with styrene 139.

To probe the mode of the alkyl bromide activation a reaction was performed in the presence of the radical scavenger TEMPO (Scheme 54). This led to a shutdown of the catalytic reactivity, indicating formation of radical intermediates.



Scheme 54: Standard reaction in presence of radical scavenger TEMPO.[78]

The enantiopure alkyl halide (*S*)-**80k** lead to full racemization in the product **86ak**, further indicating a planar, radical intermediate (Scheme 55).

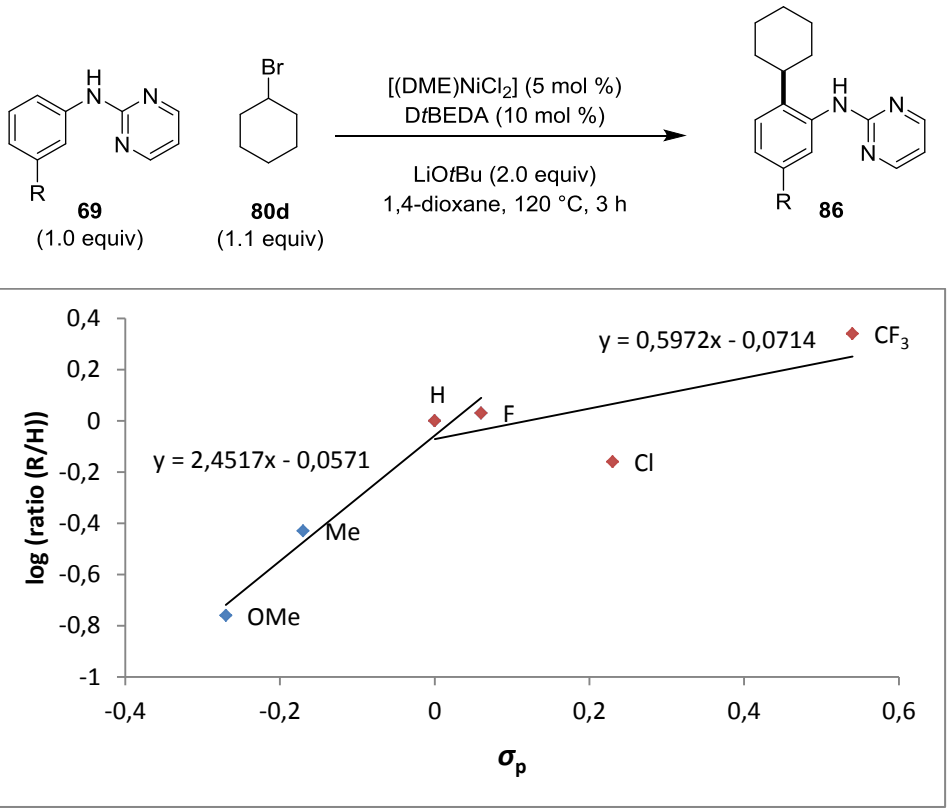


Scheme 55: Standard reaction with enantiopure *(S)*-2-bromo-octane ((*S*)-80k).

In order to elucidate electronic effects on the C–H alkylation, a Hammett plot was done (Scheme 56). Here, a clear positive inclination towards high sigma-values was observed, albeit a possibly unusual change in steepness at values near 0. This result can indicate for the reductive elimination to be rate determining. A few additional factors, however, should be taken into account. The most basic fact is that the Hammott correlation was developed for reactions that undergo a clean reaction not creating side-products, while also using substrates whose substituents do not cause secondary effects on the reaction kinetics.[79] These criteria may not fully apply in the case given here. For one, substrates containing C–F and C–Cl bonds may, to some degree, undergo side reactions involving these bonds. This may influence the rate of the corresponding reaction. Another secondary effect to be regarded here is the acidity of the N-H group. This moiety has previously been shown to be vital. The acidity should increase towards more positive sigma-values. Therefore, if said acidity may become relevant for the rate of the reaction, it may explain the observed change in inclination. Thus, for a more clear answer a significantly larger set of data points or a separate correlation between acidity and reaction rate will be required.

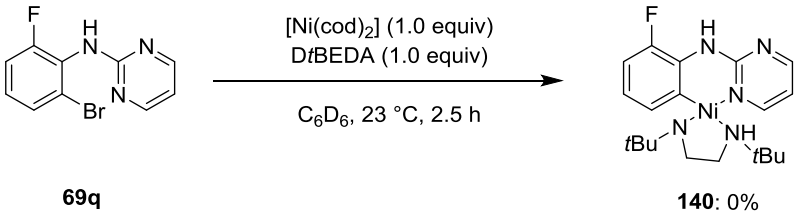
[78] Experiment performed by Zhixiong Ruan.

[79] (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195. (b) Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96–103.



Scheme 56: Hammett plot for C–H secondary alkylation of anilines 69.

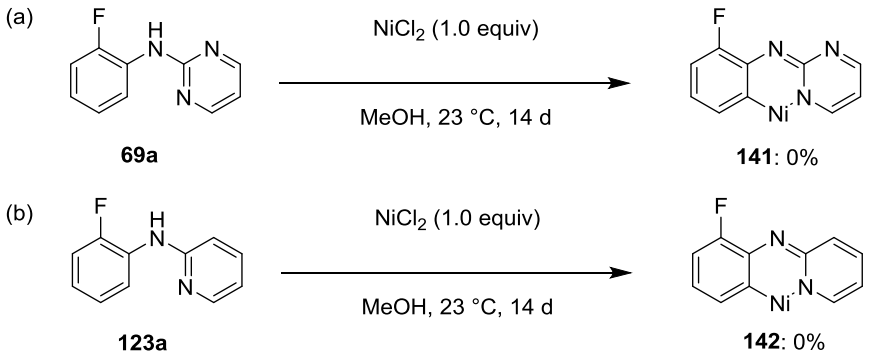
Considering the novelty of the employed directing group, studies regarding the nickelacycle were conducted. The assumed cycle is six-membered based on previous findings for palladium,[80] ruthenium[81] and gold complexes.[82] Initially an oxidative addition of Ni(0) with *ortho*-Bromo-substrate **69q** was attempted (Scheme 57). While the crude analysis indicated formation of traces of several new compounds, the assumed nickelacycle **140** could not be identified *via* crude NMR analysis or isolated.



Scheme 57: Attempted synthesis of nickelacycle 140 through oxidative addition.

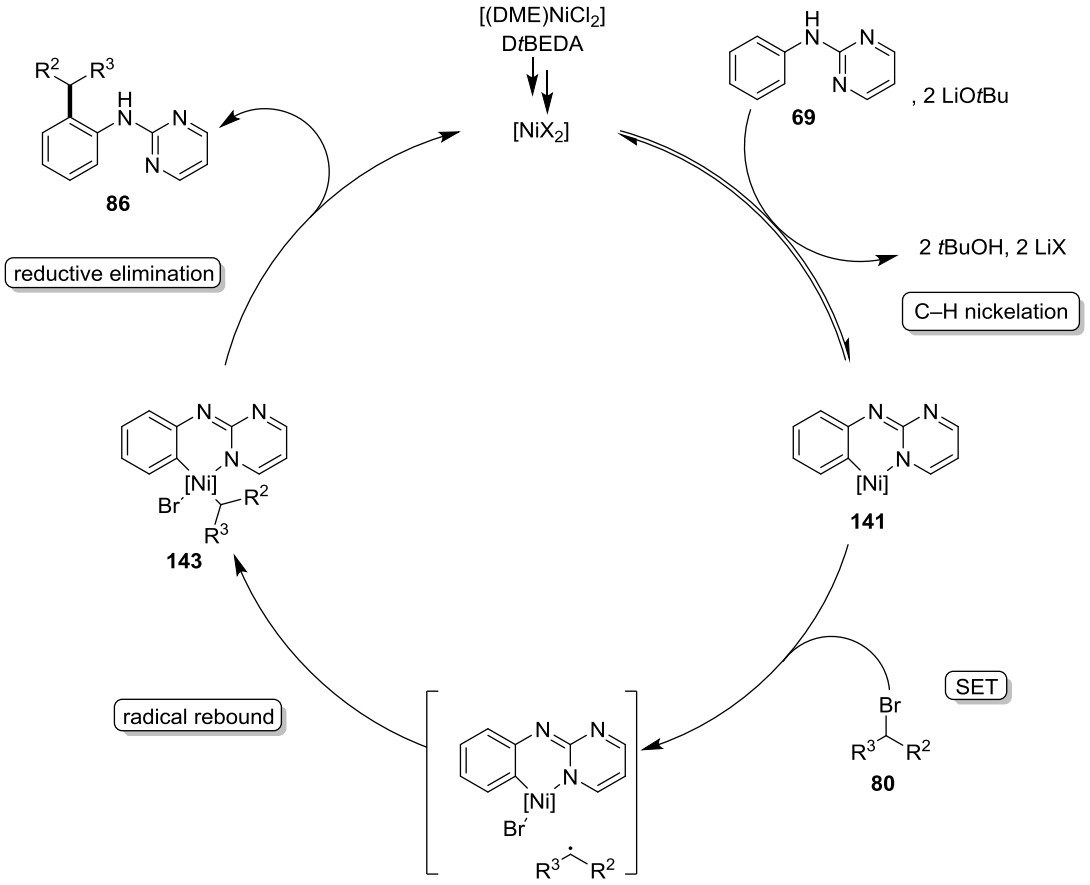
Another approach was simply applying the reported procedure for the palladacycle (Scheme 58). Crude NMR analysis indicated only simple coordination of the lewis basic nitrogen of the directing group to the nickel ion.

[80] Nonoyama, M. *Transition Met. Chem.* **1982**, *7*, 281–284.
[81] Nonoyama, M. *Polyhedron* **1985**, *4*, 765–768.
[82] Nonoyama, M.; Nakajima, K.; Nonoyama, K. *Polyhedron* **1997**, *16*, 4039–4044.



Scheme 58: Attempted formation of nickelacycle through C–H metalation.

Based on our mechanistic studies a catalytic cycle can be proposed (Scheme 59). The catalytic cycle is initiated by deprotonation of substrate **69**, followed by C–H-metallation by the nickel catalyst. Based on the mechanisms previously discussed (Scheme 10) and the electron-rich nature of the aniline substrates used, it can be considered for a intramolecular electrophilic substitution (IES) mechanism to be most probable. However, a ambiphilic metal ligand activation (AMLA) pathway should also be considered. The following oxidative addition occurs in two steps through an SET-pathway. In this the bromide reacts first with the metal centre, followed by a rebound of the organic radical to generate nickel species **140**. Last, reductive elimination leads to the desired product **86** and regeneration of the nickel catalyst.



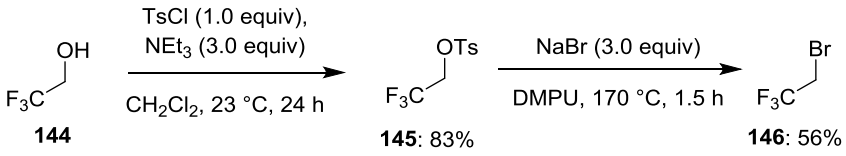
Scheme 59: Proposed catalytic cycle for the direct secondary alkylation of anilines 69.

3.4 Direct C–H Fluoroalkylation of *N*-Pyrimidyl-Anilines

Introducing fluorine or fluorine-containing functional groups into organic compounds is crucial within medicinal chemistry. In connection with the importance of the 2-amino-pyrimidine moiety in anti-cancer drugs, trifluoroethylation was attempted with the *N*-(2-pyrimidyl)-aniline substrate **69** as well.

3.4.1 Synthesis of Starting Materials

For substrate **146** a novel synthesis was developed. This became necessary due to the only reported procedures either requiring expensive reagents or special autoclave techniques.[83] Therefore, derived from these procedures, a synthesis starting from commercially available trifluoroethanol **144** was devised (Scheme 60). After tosylation of the alcohol to give trifluoroethyltosylate **145**, substitution with sodium bromide at high temperatures gave the desired reagent **146**.



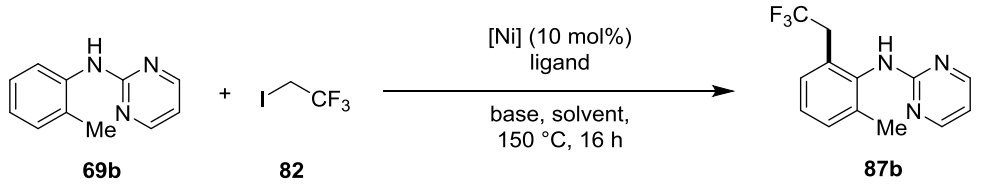
Scheme 60: Synthesis of trifluoroethyl bromide 146.

3.4.2 Optimisation Studies

At the outset, the envisioned C–H trifluoroethylation for standard substrate **69b** and commercially available trifluoroethyl iodide **82** were tested without ligand and these conditions furnished minor amounts of the desired product **87b** (Table 4, entry 1). Employing the BDMAE ligand, which has previously been used for the analogous trifluoroethylation reaction under bidentate assistance, a significant improvement was observed (Table 4, entry 2). Lowering the reaction temperature reduced the conversion notably (Table 4, entries 3—5). Similar to previous finding, use of weaker bases completely shut down the efficacy of the catalytic system (Table 4, entries 6—10).

[83] (a) Mathey, F. **2001**, Molybdenum(VI) Fluoride. e-EROS Encyclopedia of Reagents for Organic Synthesis. (b) Kashutina, E. V.; Lavrent'ev, A. N. *Zhurnal Obshchei Khimii* **2000**, *70*, 1814.

Table 4: Screening of solvents and bases for C–H trifluoroethylation of aniline 69b.[a]

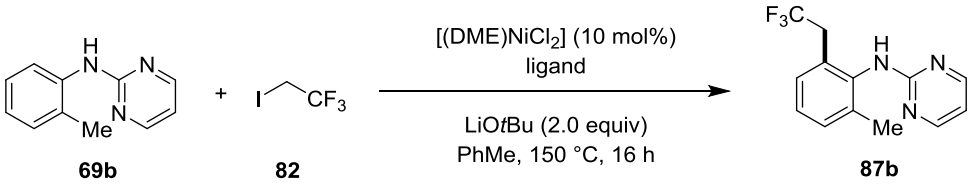


entry	[Ni]	ligand [mol %]	solvent	base	yield [%]
1	[(DME)$NiCl_2$]	–	PhMe	LiO*t*Bu	<10
2	[(DME)$NiCl_2$]	BDMAE (**89**) (40)	PhMe	LiO*t*Bu	83
3	[(DME)$NiCl_2$]	BDMAE (**89**) (40)	PhMe	LiO*t*Bu	– (<30[b,c])
4	[(DME)$NiCl_2$]	BDMAE (**89**) (40)	PhH	LiO*t*Bu	53[c]
5	[(DME)$NiCl_2$]	BDMAE (**89**) (40)	PhMe	LiO*t*Bu	69[d]
6	[(DME)$NiCl_2$]	BDMAE (**89**) (40)	PhMe/*t*BuOH (19:1)	Na_2CO_3	0
7	[(DME)$NiCl_2$]	BDMAE (**89**) (40)	PhMe/*t*BuOH (19:1)	Li_2CO_3	0
8	[(DME)$NiCl_2$]	BDMAE (**89**) (40)	PhMe	Na_2CO_3/LiBr (1.0)	0
9	[(diglyme)$NiBr_2$]	BDMAE (**89**) (40)	PhMe	Na_2CO_3	0
10	[(diglyme)$NiBr_2$]	BDMAE (**89**) (40)	PhMe	NaOAc	0

[a] Reactions conditions: **69b** (1.0 mmol), **82** (2.0 mmol), base (2.0 mmol), [Ni] (10 mol %), ligand (40 mol %), solvent (2 mL), 150 °C, 16 h, yields based on crude ^{19}F-NMR with C_6F_6 as internal standard. [b] Isolated yield. [c] 120 °C. [d] 130 °C.

Further screening of ligands revealed that other tertiary amines **108** or pyridine **147** derivatives are not viable for this transformation (Table 5, entries 1 and 2). Similarily, phosphine-, carbene- and phenol-ligands performed poorly (Table 5, entries 3—6).

Table 5: Screening of ligands for the trifluoroethylation of aniline 69b.[a]



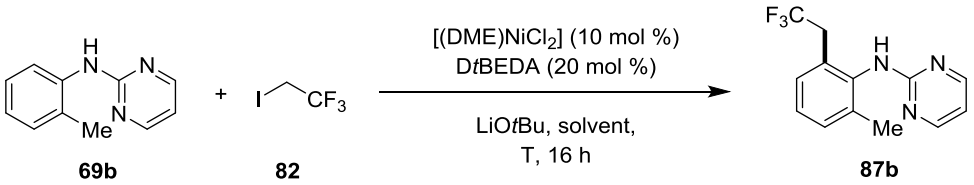
69b **82** **87b**

entry	ligand [mol %]	yield [%]
1	BDMAE (**89**) (40)	83
2	TMEDA (**108**) (40)	14
3	2,2'-bipyridine (**147**) (10)	11
4	(*R*)-BINOL (**100**) (10)	<5
5	PPh_3 (**120**) (40)	<10
6	XantPhos (**148**) (20)	21
7	IPr*HCl (**116**) (10)	<5
8	LiCp* (**149**) (10)	<5

[a] Reactions conditions: **69b** (1.0 mmol), **82** (2.0 mmol), LiO*t*Bu (2.0 mmol), PhMe (2 mL), 150 °C, 16 h, yields based on crude ^{19}F-NMR with C_6F_6 as internal standard. [b] Isolated yield.

Considering the high efficacy of the D*t*BEDA ligand in the secondary alkylation of anilines **69**, this system was also tested for the C–H trifluoroethylation (Table 6). Initially, only moderate yields were achieved, however at significantly lower reaction temperatures (Table 6, entries 1—3). Changing the solvent to arenes gave either lower or, at best, identical yields (Table 6, entries 4—7). When a wider variety of ether solvents was tested, 2-methyl-tetrahydrofuran was found to be optimal (Table 6, entries 10—16).

Table 6: Solvent effect for C–H trifluoroethylation with D*t*BEDA ligand.[a]



69b **82** **87b**

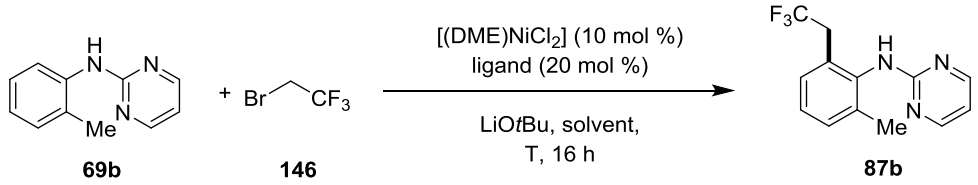
entry	T [°C]	solvent	yield [%]
1	140	1,4-dioxane	38
2	120	1,4-dioxane	44
3	100	1,4-dioxane	26
4	120	PhMe	19
5	120	Ph*t*Bu	26
6	120	PhCl	43
7	120	$PhCF_3$	18
8	120	1,4-dioxane	11[b]
9	120	1,4-dioxane	3[c]

10	120	DME	14
11	120	$(n\text{Bu})_2O$	0
12	120	THF	39
13	120	PhOMe	15
14	120	Ph_2O	9
15	120	CPME	4
16	120	2-Me-THF	47

[a] Reactions conditions: **69b** (1.0 mmol), **82** (2.0 mmol), LiO*t*Bu (2.0 mmol), solvent (2 mL), 150 °C, 16 h, yields based on crude ^{19}F-NMR with C_6F_6 as internal standard. [b] LiBr (2.0 equiv). [c] DMEDA (20 mol %) as ligand.

Further investigation revealed that trifluoroethyl bromide (**146**) appeared to be a more effective reagent (Table 7, entry 1). Further screening of reaction temperature and concentration showed that at 120 °C and at lower concentrations optimal results were achieved (Table 7, entries 4—7). With no nickel catalyst or palladium dichloride as the catalyst no conversion was observed (Table 7, entries 12—13). Re-evaluating the previous conditions with BDMAE at 150 °C with trifluoroethyl bromide (**143**) showed improved conversion, as well (Table 7, entry 14).

Table 7: C–H trifluoroethylation with trifluoroethyl bromide (146).[a]



69b **146** **87b**

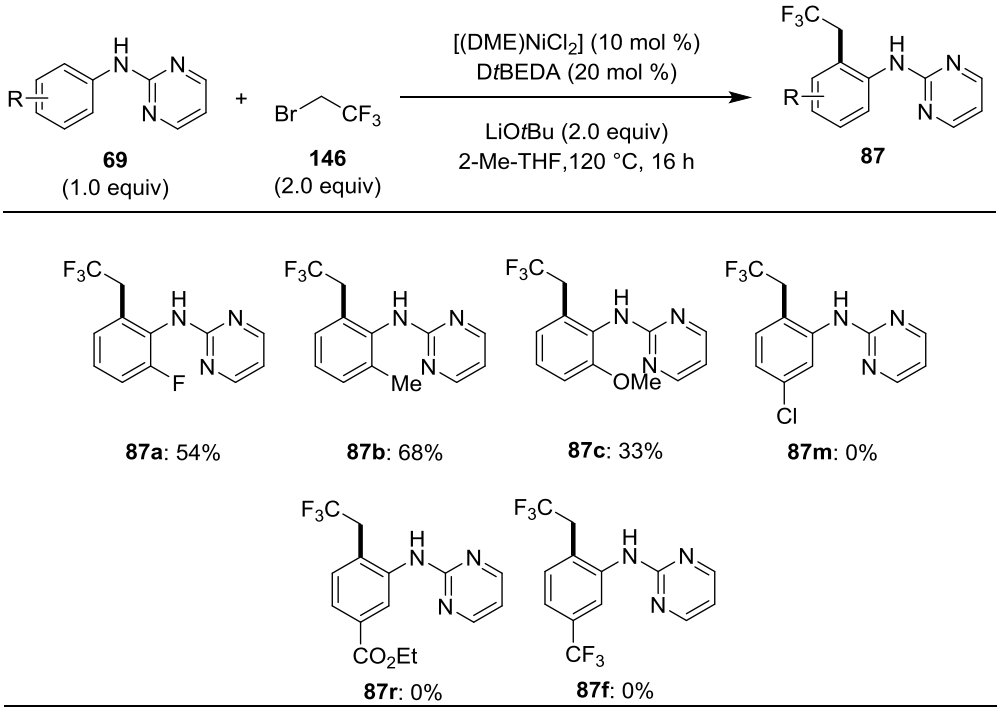
entry	ligand	T [°C]	solvent [M]	yield [%]
1	D*t*BEDA	120	2-Me-THF (0.5)	55
2	D*t*BEDA	135	2-Me-THF (0.5)	25
3	(*R*)-BINOL (10 mol%)	120	2-Me-THF (0.5)	14
4	D*t*BEDA	100	2-Me-THF (0.5)	35
5	D*t*BEDA	100	2-Me-THF (0.25)	45
6	D*t*BEDA	120	2-Me-THF (1.0)	27
7	D*t*BEDA	120	2-Me-THF (0.25)	67 (64[b])
8	D*t*BEDA	120	2-Me-THF (0.5)	61[c]
9	D*t*BEDA	120	2-Me-THF/*n*Octane (1:1) (0.5)	12

10	D*t*BEDA	120	2-Me-THF (0.25)	76 (68[b,c])
11	–	120	2-Me-THF (0.5)	38
12	D*t*BEDA	120	2-Me-THF (0.5)	0[d]
13	D*t*BEDA	120	2-Me-THF (0.5)	0[e]
14	BDMAE	150	PhMe (0.5)	78[f] (66[b])

[a] Reactions conditions: **69b** (1 mmol), **146** (2 mmol), LiO*t*Bu (2 mmol), solvent, 150 °C, 16 h, yields based on crude ^{19}F-NMR with C_6F_6 as internal standard. [b] isolated yield. [c] **146** (3 equiv). [d] No catalyst. [e] $PdCl_2$ as catalyst. [f] ligand (40 mol %).

3.4.3 Scope of Trifluoroethylation

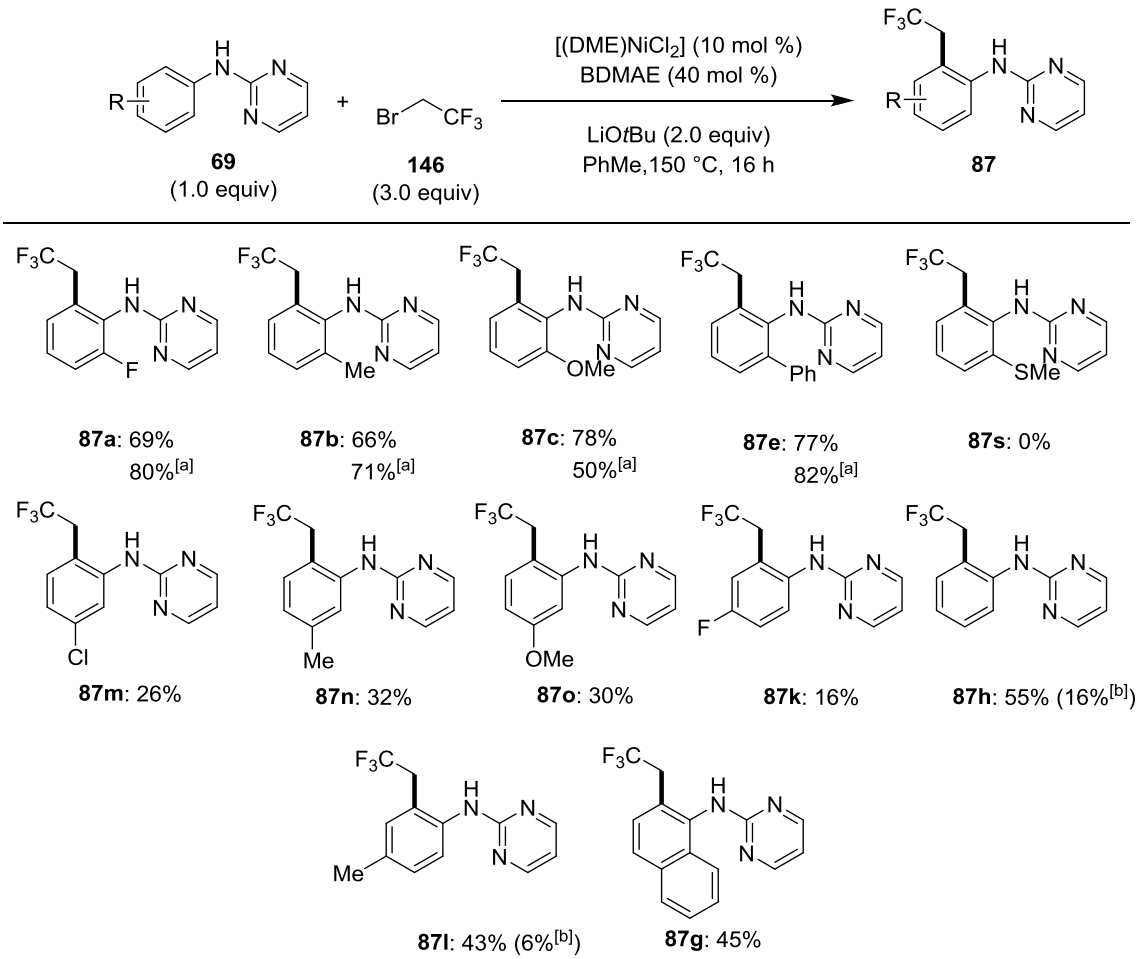
Initially, the catalytic system utilising D*t*BEDA as the ligand was probed, specifically for functional group tolerance (Scheme 61). However, both electron-rich and -deficient substrates gave only low to moderate yields. Chloro- and ester-substituents furnished no desired products **87o** and **87r**.



Scheme 61: Scope for trifluoroethylation with D*t*BEDA as ligand.

Therefore, the study of substrates was continued with the BDMAE ligand system at 150 °C (Scheme 62). Both electron-deficient and –rich *ortho*-substituents were tolerated with moderate to high yields. *meta*-Substituted substrates **69l-n**, however, gave low conversion with site-selectivity favoring the sterically less hindered position. Unsubstituted or electron-

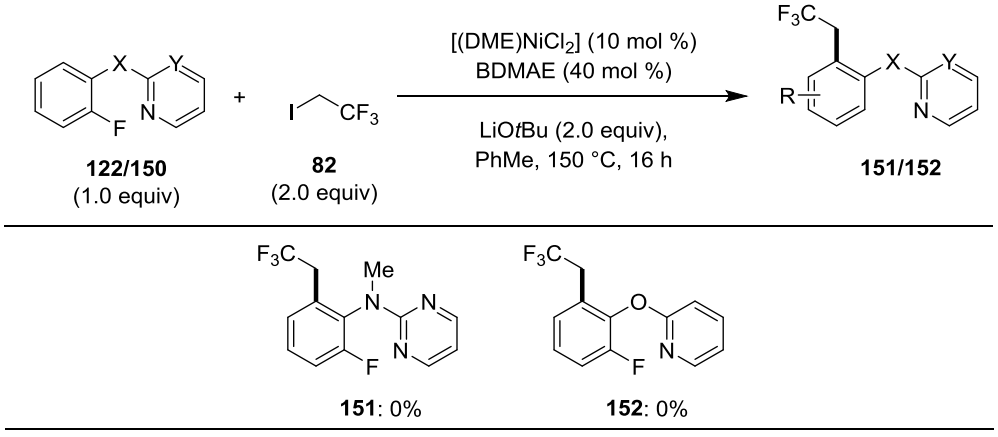
rich *para*-substituted substrates **69h/k-l** gave moderate yields. For these substrates the selectivity was mainly towards the *mono*-trifluoroethylated products **87h/k-l**, with either none or only small amounts of bis-trifluoroethylated products **87h'** and **87l'** being isolated.



[a] ICH_2CF_3 **82** (2 equiv) used. [b] Bis-trifluoroethylated product.

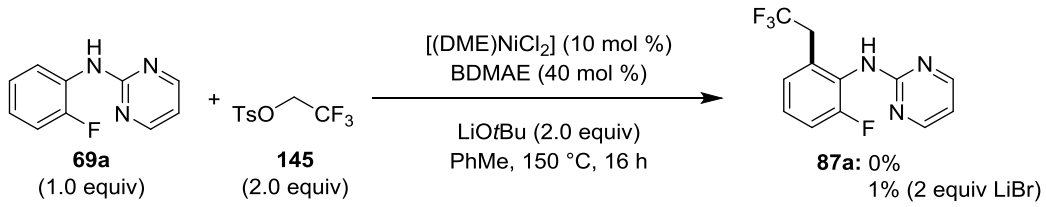
Scheme 62: Scope for C–H trifluoroethylation with BDMAE as ligand.

Identically to the secondary alkylation of anilines, the reaction does not proceed if the acidic N-H group is removed (Scheme 63).



Scheme 63: Screening of directing groups for trifluoroethylation.

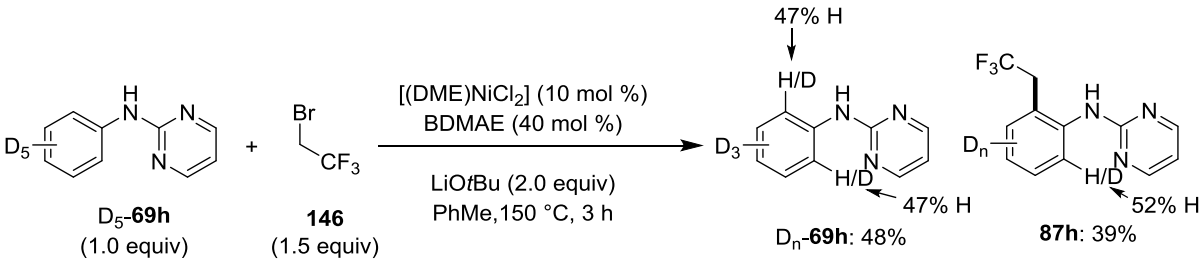
While trifluoroethyl bromide **146** was identified as an effective reagent, it also contains possible drawbacks. One issue is the relatively high volatility of the reagent with a boiling point of 28 °C. Additionally, the reagent is currently not commercially available and only few syntheses have been reported. Therefore, the viability of the more easily accessible and non-volatile tosylate derivative **145** was tested (Scheme 64). Albeit formation of only trace amounts with lithium bromide as additive, it could be shown that trifluoroethyl toslyate may be used for this type of transformation.



Scheme 64: Attempted C–H trifluoroethylation utilising trifluoroethyl tosylate (145).

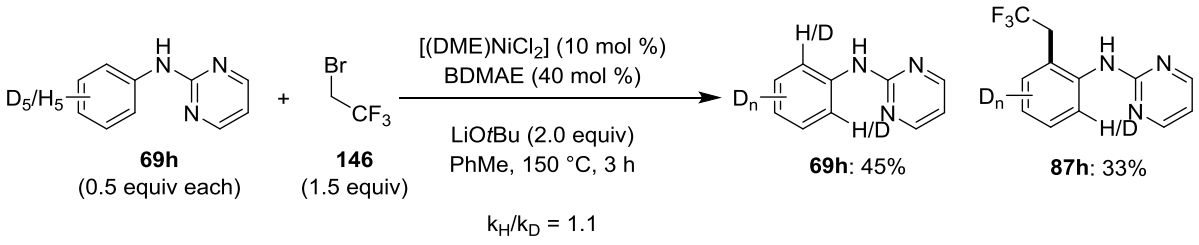
3.4.4 Mechanistic Studies

Due to the novelty of this type of transformation several mechanistic experiments were conducted. In an H/D-exchange-experiment full scrambling was found, indicating a facile C–H-metallation (Scheme 65).



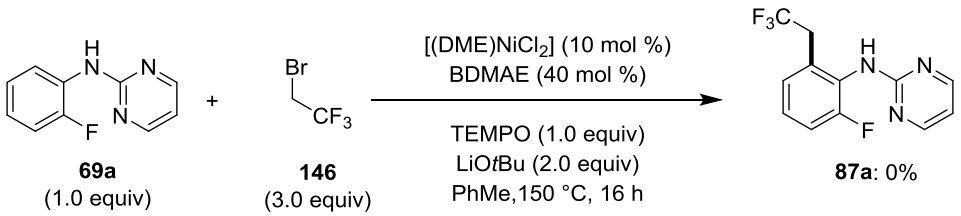
Scheme 65: H/D-exchange experiment for C-H trifluoroethylation.

Further, a direct competition between **69h** and D_5-**69h** revealed a KIE of k_H/k_D = 1.1 (Scheme 66), indicating the C–H-metallation not to being rate determining.



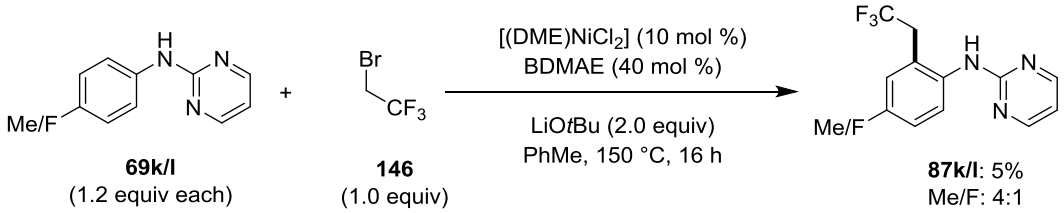
Scheme 66: Kinetic isotope effect.

The reaction was shut down by the addition of one equivalent of the radical scavenger TEMPO (Scheme 67). The formation of radical intermediates can therefore be assumed.



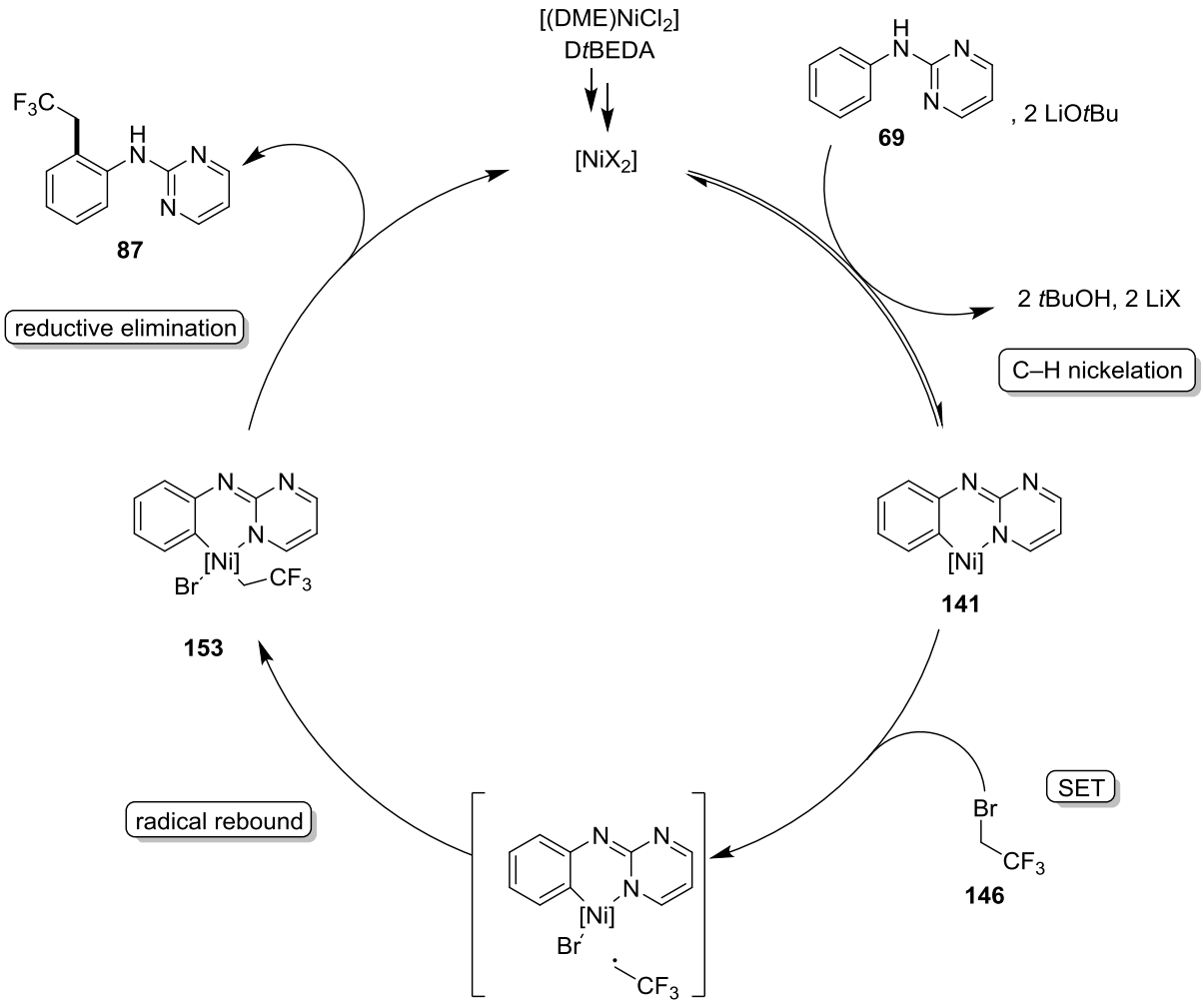
Scheme 67: Attempted trifluoroethylation with TEMPO.

A competition experiment between electron-rich and -deficient substrates revealed the electron-richer substrate to react preferentially (Scheme 68). This may point towards the oxidative addition being rate determining.



Scheme 68: Competition experiment for trifluoroethylation under standard conditions.

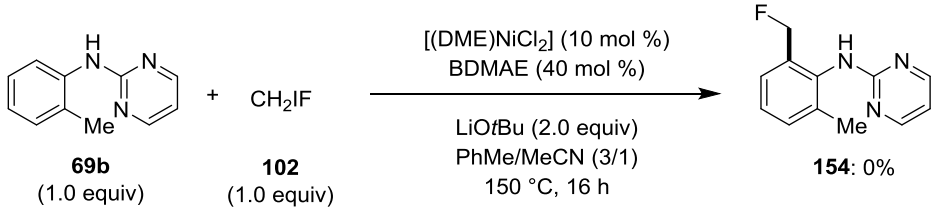
Based on these findings a plausible catalytic cycle is proposed in Scheme 69. After the initial, facile C–H nickelation, the oxidative addition occurs through a SET-type pathway. This is followed by the reductive elimination to give the desired product and regenerate the active catalyst.



Scheme 69: Proposed catalytic cycle for the C-H trifluoroethylation.

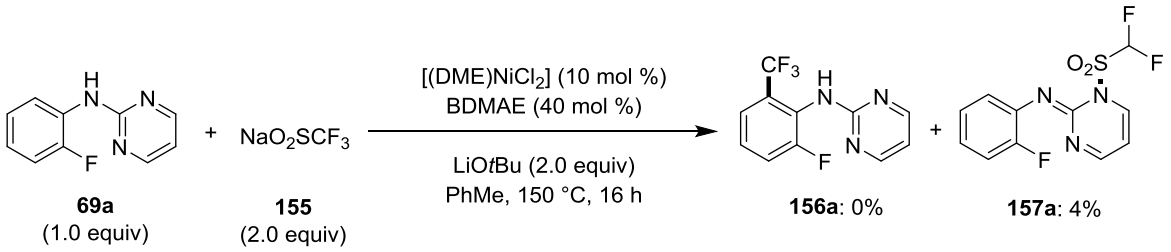
3.4.5 Further Fluoroalkylations

Based on the novelty of the trifluoroethylation, further variations of fluoroalkylation reactions were probed. These were particularly focused on fluoroalkylation reagents containing alpha-fluoro-groups. Based on a previous report of nickel-catalysed cross coupling with iodofluoromethane (**102**),[69] an analogous reaction was tested (Scheme 70). This, however, did not lead to the desired product **154**.



Scheme 70: Attempted C–H fluoromethylation of aniline 69b.

Additionally, the Langlois' reagent (**155**) was tested for a direct trifluoromethylation (Scheme 71). This led only to a low conversion to side-product **153a**.

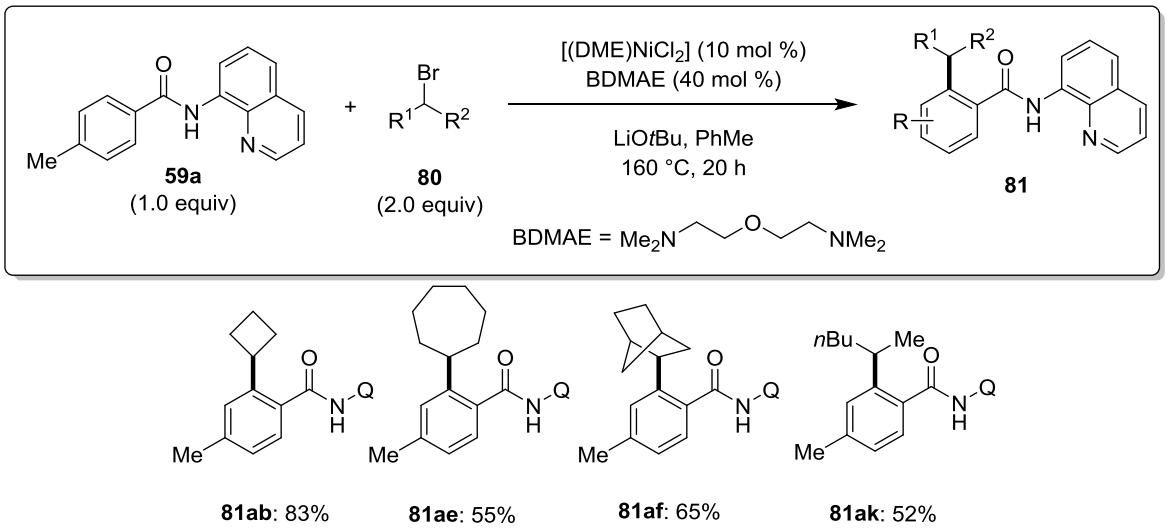


Scheme 71: Attempted trifluoromethylation of aniline 69a utilising Langlois' reagent.

4 Summary and Outlook

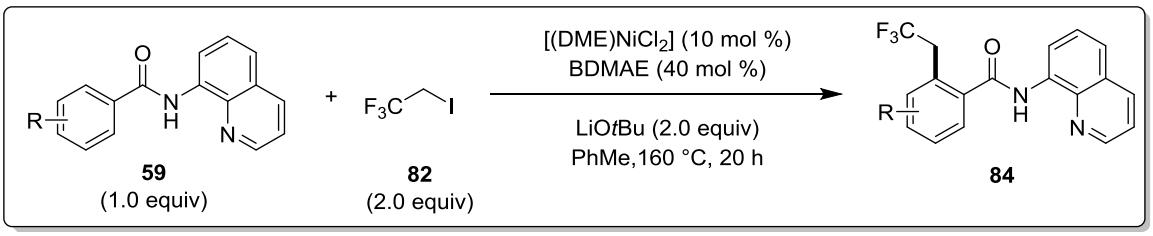
The focus within this thesis was on the development of atom- and step- economic nickel-catalyzed alkylation reactions utilising challenging, unactivated alkyl halides with β-hydrogens or β-fluorines.

In the first part, a protocol for the direct C–H secondary alkylation under bidentate assistance was devised for a variety of alkyl bromides **80** (Scheme 72).[84] This was achieved using [(DME)$NiCl_2$] as the catalyst with BDMAE as a commercially available ligand. A series of products **81** were obtained in good to excellent yields.



Scheme 72: C–H Secondary alkylation of benzamides under bidentate assistance.

Second, investigations on the first trifluoroethylation were conducted (Scheme 73).[84] Albeit in low to moderate yields, the corresponding trifluoroethylated benzamides **84** were made accessible.

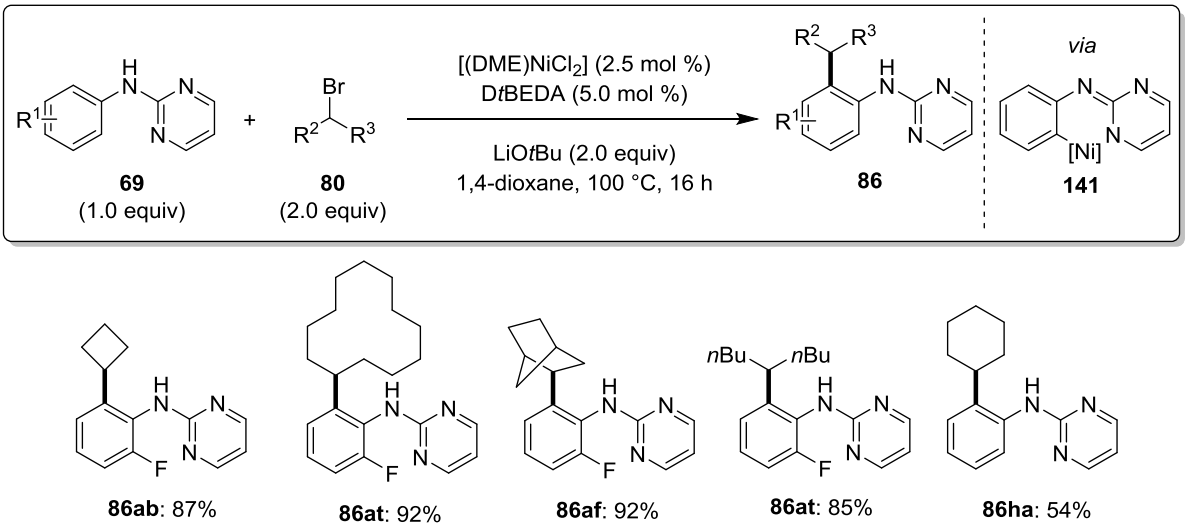


Scheme 73: C–H trifluoroethylation of benzamides 59 under bidentate assistance.

The research was then focused on utilising simpler and biologically relevant directing groups for direct C–H secondary alkylation. For this a simple catalytic system consisting of

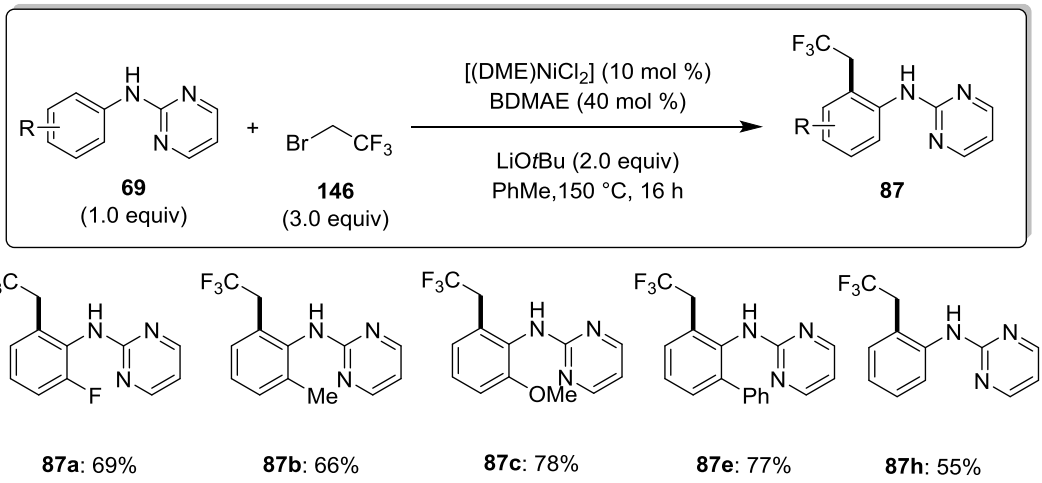
[84] Song, W.; Lackner, S.; Ackermann, L. *Angew. Chemie Int. Ed.* **2014**, *53*, 2477–2480.

[(DME)$NiCl_2$] and ligand D*t*BEDA was developed (Scheme 74).[85] The system showed broad applicability of substrates. Mechanistic studies revealed a reversible C–H nickelation and a formal oxidative addition through an SET-type pathway. The involved nickelacycle is presumed to be an unusual 6-membered metallacycle **141**.



Scheme 74: C–H Secondary alkylation of aniline derivatives 69.

Finally, the C–H trifluoroethylation was applied to aniline derivatives **69**. The protocol was amenable to a variety of substrates **69**. Mechanistic studies revealed a reversible C–H nickelation to be operative. The oxidative addition was proposed to occur *via* a SET-type pathway.



Scheme 75: C–H Trifluoroethylation of aniline derivatives 69.

[85] Ruan, Z.; Lackner, S.; Ackermann, L. *Angew. Chem. Int. Ed.* **2016**, *55*, 3153–3157.

Further research should focus on enabling tertiary alkylation and fluoroalkylations for the established substrates. The latter case being of particular interest, as novel palladium-catalyzed C–H trifluoroethylation reactions have been reported after publication of results presented herein.[86] New development of additional monodentate directing groups for nickel-catalysed C–H functionalisation based on the 2-amino-pyrimidine moiety is also of importance. Moreover, if a catalytic system with higher efficacy at lower temperatures can be found, direct C–H alkylation reactions in an enantioselective fashion may become feasible.

[86] (a) Toth, B. L.; Kovacs, S.; Salyi, G.; Novak, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 1988–1992. (b) Zhang, H.; Chen, P.; Liu, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 10174–10178.

5 Experimental

5.1 General Remarks

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

Solvents

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

solvent	drying method
CH_2Cl_2	was purified using an solvent purification system (SPS) from MBRAUN.
N,N-Dimethylformamide	was dried over CaH_2 for 8 h, degassed and distilled under reduced pressure.
N-Methyl-2-pyrrolidone	was stirred for 4 h at 150 °C over CaH_2 and subsequently distilled under reduced pressure.
Methanol	was stirred over Mg chips for 3 h at 65 °C prior to distillation.
Tetrahydrofuran	was purified using an SPS solvent purification system from MBRAUN.
Toluene	was either predried over KH followed by distillation from sodium benzophenone ketyl or purified using a solvent purification system from MBRAUN.
1,4-Dioxane	was dried by distillation from sodium benzophenone ketyl.
*n*Octane	was dried by addition of predried 4Å molecular sieve.
Diphenylether	was dried by addition of predried 4Å molecular sieve.
Chlorobenzene	was dried by addition of predried 4Å molecular sieve.

tert-Butylbenzene	was dried by addition of predried 4Å molecular sieve.
Trifluoromethylbenzene	was dried by addition of predried 4Å molecular sieve.
Anisole	was dried by stirring over Na at 135 °C prior to disitillation at 1 mbar.
Dimethoxyethane	was dried by distillation from sodium benzophenone ketyl.
Di-(*n*-butyl)-ether	was dried by distillation from sodium benzophenone ketyl.
CPME	was dried by stirring over sodium at 120 °C prior to disitillation.
tert-Butanol	was dried by distillation from sodium.
2-Methyl-tetrahydrofuran	was dried by distillation from sodium.

Vacuum

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

Melting Points

Melting points were measured using a Stuart® Melting Point Apparatus SMP3 from BARLOWORLD SCIENTIFIC. Reported values are not corrected.

Chromatography

Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60F-plate (MACHEREY-NAGEL) with 254 nm fluorescent indicator from MERCK. Plates were either visualized under ultraviolet light or developed by treatment with a potassium permanganate or a cerium ammonium molybdate solution followed by careful warming with a heat gun. Chromatographic purification of products was accomplished by flash column chromatography on MERCK silica gel, grade 60 (40–63 µm and 63–200 µm, 70–230 mesh ASTM).

High Performance Liquid Chromatography

Preparative and analytical separations were performed on an HPLC-System from Agilent. Separation column ChiralPak IC (4.6 × 250 mm) from DAICEL CHEM. IND. (LTD) was used.

Organic solvents of HPLC grade were employed. All samples were filtered through Polytetrafluorethylen Filter from ROTH (Ø 25 mm, 0.2 µm) or VWR (Ø 13 mm, 0.2 µm) prior to separation.

Gas Chromatography

Monitoring of reaction processes via coupled gas chromatography-mass spectrometry was performed using G1800C GCDplus with mass detector HP 5971, 5890 Series II with mass detector HP 5972 from HEWLETT-PACKARD and 7890A GC-System with mass detector 5975C (Triplex-Axis-Detector) from AGILENT TECHNOLOGIES. HP-5MS columns (30 m × 0.25 mm, film 0.25 µm) were used.

Gel permeation chromatography

Preparative and analytical separations were performed on an GPC-System from Japan Analytical Industry, Co. Separation column JAIGEL-1HH was used. HPLC grade chloroform stabilized with 0.6% ethanol was 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.

Infrared Spectroscopy

Infrared spectra were recorded using a BRUKER Alpha-P ATR spectrometer. Liquid samples were measured as film and solid samples neat. Analysis of the spectral data was carried out using OPUS 6. Absorption is given in wave numbers (cm^{-1}). Spectra were recorded in the range from 4000 to 400 cm^{-1}.

Mass Spectrometry

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

Nuclear Magnetic Resonance Spectroscopy (NMR)

Nuclear magnetic resonance (NMR) spectra were recorded at 300 or 600 MHz (1H NMR), 75 or 125 MHz (13C NMR and APT) and 282 MHz (19F NMR) on VARIAN Unity-300, AMX 300, Inova-500 and Inova-600 instruments. Chemical shifts are reported as *δ*-values in ppm relative to the residual proton peak or the carbon peak of the deuterated solvent.

	^{1}H NMR	^{13}C NMR
$CDCl_3$	7.26 ppm	77.2 ppm
DMSO-d_6	2.54 ppm	40.5 ppm
benzene-d_6	7.16 ppm	128.1 ppm

For characterization of the observed resonance multiplicities the following abbrevations were applied: s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), hept (heptet), m (multiplet) or analogous representations. The coupling constants J are reported in Hertz (Hz). Analysis of the recorded spectra were carried out using MestReNova 10.0 software.

Optical Rotatory Power

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

Reagents

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

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

(3-bromobutyl)benzene (**80n**),[87] 2-(4-Bromopentyl)isoindoline-1,3-dione (**80p**),[88] (*6S*)-8-Bromo-2,6-dimethylnon-2-ene (**80r**),[87] 4-Methyl-*N*-(pyridin-2-ylmethyl)benzamide (**80a**),[89] 4-methyl-*N*-(thiophen-2-ylmethyl)benzamide (**95a**),[89] (*L*)-Valinol (**97**),[90] (S)-4-Methyl-2-(pyridin-2-yl)-4,5-dihydrooxazole (**98**),[91] *N*-(Quinolin-8-yl)pivalamide (**62a**),[92] *N*-(2-pyrimidyl)-anilines

[87] Gonzalez-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360–5361.
[88] Bothmann, H.; Roncarati, R.; Bettinetti, L.; Quinn, J.; Varrone, M.; Valacchi, M.; Nencini, A.; Micco, I.; Ghiron, C.; Haydar, S. PCT Int. Appl. **2007**, WO 2007098826 A2 Sep 07, 2007.
[89] Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 6898–6899.
[90] Hsiao, Y.; Hegedus, L. S. *J. Org. Chem* **1997**, *62*, 3586–3591.
[91] Binder, J. T.; Cordier, C. J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 17003–17006.

(**69h/i/j/q**),[93] cyclododecylbromide (**80t**),[94] methyl 5-bromohexanoate (**80u**),[95] (*S*)-2-bromooctane ((*S*)-**80k**),[96] *N*-(2-fluorophenyl)pyridin-2-amine (**123**),[97] 2,4-dichloropyrimidine (**157**),[98] *N*-Phenylmorpholine-4-carbothioamide (**125**),[99] *N*-methyl-*N*-phenylpyrimidin-2-amine (**122**),[100] cyclohexylacetate (**137**),[101] *N*-(phenyl-d_5)pyrimidin-2-amine (D_5-**69h**),[102] 2,2,2-trifluoroethyl 4-methylbenzenesulfonate (**145**).[103]

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

Dr. Weifeng Song: *N*-(quinolin-8-yl)benzamides (**59a-g**),

Dr. Jie Li: *N*-Methylbenzamide (**92a**), 1,3-Bis((S)-1-phenylethyl)-1H-imidazol-3-ium chloride (**99**)

Dr. Xu Tian: (*S*)-4-Isopropyl-2-(pyridin-2-yl)-4,5-dihydrooxazole (**117**)

M. Sc. Zhixiong Ruan: *N*-(2-Pyrimidyl)-anilines (**69l-p/r**)

M. Sc. Marc Moselage: 3-Methyl-1-(pyrimidin-2-yl)-1*H*-indole (**127**), 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (dry)

M. Sc. Alexandra Schischko: Methyl *N*′-acetyl-1-(pyrimidin-2-yl)tryptophanate (**128**)

M. Sc. Thomas Müller: *N*-(2-Pyrimidyl)-anilines (**69s**)

5.3 General Procedures

General Procedure A

To solution of aniline **107** (2.0 equiv) in dry THF (1.5 mL/mmol) was added *n*-butyllithium (2.0 equiv) under stirring at -78 °C. The reaction was stirred for 15 min at ambient temperature, cooled to -78 °C and 2-chloropyrimidin (**106**) was slowly added as a suspension

[92] Zhu, L.; Qiu, R.; Cao, X.; Xiao, S.; Xu, X.; Au, C.-T.; Yin, S.-F. *Org. Lett.* **2015**, *17*, 5528–5531.
[93] Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764–767.
[94] Masson, E.; Leroux, F. *Helvetica Chimica Acta* **2005**, *88*, 1375–1386.
[95] Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. *J. Am. Chem. Soc.* **2014**, *136*, 14389–14392.
[96] Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 9523–9526.
[97] Qian, G.; Liu, B.; Tan, Q.; Zhang, S.; Xu, B. *Eur. J. Org. Chem.* **2014**, *22*, 4837–4843.
[98] Whittaker, N.; Jones, T. S. G. *J. Chem. Soc.* **1951**, 1565–1570.
[99] Biswas, K.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 4946–4949.
[100] Johansson Seechurn, C. C. C.; Parisel, S. L.; Colacot, T. J. *J. Org. Chem.* **2011**, *76*, 7918–7932.
[101] Ranu, B. C., Dey, S. S.; Hajra, A. *Green Chemistry* **2003**, *5*, 44–46.
[102] Liu, Y.; Bai, Y.; Zhang, J.; Li, Y.; Jiao, J.; Qi, X. *Eur. J. Org. Chem.* **2007**, 6084–6088.
[103] Li, L.; Huang, M.; Liu, C.; Xiao, J.-C.; Chen, Q.-Y.; Guo, Y.; Zhao, Z.-G. *Org. Lett.* **2015**, *17*, 4714–4717.

in THF (0.5 mL). The reaction mixture was slowly warmed to ambient temperature and stirred for 16 h. The reaction was stopped by addition of saturated, aqueous Na_2CO_3 solution. After extraction with EtOAc, the organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography, followed by recrystallization from hot toluene to yield **69**.

General Procedure B:

To a mixture of benzamide **59** (0.50 mmol), alkylbromide **80** (1.00 mmol), [(DME)$NiCl_2$] (11 mg, 10.0 mol %), BDMAE (32 mg, 40 mol %) and Li*O*tBu (80 mg, 1.00 mmol) was added PhMe (1.0 mL). Thereafter, the reaction mixture was stirred under Ar at 160 °C for 20 h. After cooling to ambient temperature, the crude product was purified by column chromatography on silica gel to yield product **81**.

General Procedure C:

To a mixture of benzamide **59** (0.50 mmol), trifluoroethyl iodide (**82**) (1.00 mmol), [(DME)$NiCl_2$] (11 mg, 10.0 mol %), BDMAE (32 mg, 40 mol %) and Li*O*tBu (80 mg, 1.00 mmol) was added dry PhMe (1.0 mL). Thereafter, the reaction mixture was stirred under Ar at 160 °C for 20 h.After cooling to ambient temperature, the crude product was purified by column chromatography on silica gel to yield product **84**.

General Procedure D1

Anilines **69** (1.0 mmol), [(DME)$NiCl_2$] (5.5 mg, 2.5 mol %) and Li*O*tBu (160 mg, 2.0 mmol) were placed in a 25 mL Schlenk tube. The tube was evacuated and purged with Ar three times. D*t*BEDA (11.0 µL, 5.0 mol %), alkyl bromides **80** (2.0 mmol) and 1,4-dioxane (2.0 mL) were then added, and the mixture was stirred at 100 °C for 16 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, concentrated under reduced pressure and purified by flash column chromatography on silica gel to afford the product **86**.

General Procedure D2

Anilines **69** (1.0 mmol), [(DME)$NiCl_2$] (11 mg, 5.0 mol %) and Li*O*tBu (160 mg, 2.0 mmol) were placed in a 25 mL Schlenk tube. The tube was evacuated and purged with Ar three times. D*t*BEDA (22.0 µL, 10 mol %), alkyl bromides **80** (2.0 mmol) and 1,4-dioxane (2.0 mL) were then added, and the mixture was stirred at 120 °C for 16 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, concentrated under reduced pressure and purified by flash column chromatography on silica gel to afford the products **86**.

General Procedure D3

Anilines **69** (1.0 mmol), $[NiCl_2(H_2O)_6]$ (6 mg, 2.5 mol %) and Li*O*tBu (160 mg, 2.0 mmol) were placed in a 25 mL Schlenk tube. The tube was evacuated and purged with Ar three times. D*t*BEDA (11.0 µL, 10 mol %), alkyl bromides **80** (2.0 mmol) and 1,4-dioxane (2.0 mL) were then added, and the mixture was stirred at 120 °C for 16 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, concentrated under reduced pressure and purified by flash column chromatography on silica gel to afford the products **86**.

General Procedure E1

Anilines **69** (1.0 mmol), $[(DME)NiCl_2]$ (22 mg, 10 mol %) and Li*O*tBu (160 mg, 2.0 mmol) were placed in a 25 mL sealed tube. The tube was evacuated and purged with Ar three times. D*t*BEDA (42.0 µL, 20 mol %) and 2-Me-THF (2.0 mL) were then added. The reaction was cooled to -78 °C, trifluoroethylbromide (**146**) (489 mg, 3.0 mmol) was added and the mixture was stirred at 120 °C for 16 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, the mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel to afford the products **87**.

General Procedure E2

Anilines **69** (1.0 mmol), $[(DME)NiCl_2]$ (22 mg, 10 mol %) and Li*O*tBu (160 mg, 2.0 mmol) were placed in a 25 mL sealed tube. The tube was evacuated and purged with Ar three times. BDMAE (76.0 µL, 40 mol %) and PhMe (2.0 mL) were then added. The reaction was cooled to -78 °C, trifluoroethylbromide (**146**) (489 mg, 3.0 mmol) was added and the mixture was stirred at 150 °C for 16 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, the mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel to afford the products **87**.

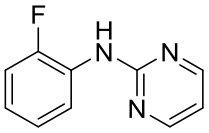
General Procedure E3

Anilines **69** (1.0 mmol), $[(DME)NiCl_2]$ (22 mg, 10 mol %) and Li*O*tBu (160 mg, 2.0 mmol) were placed in a 25 mL sealed tube. The tube was evacuated and purged with Ar three times. BDMAE (76.0 µL, 40 mol %), trifluoroethyliodide (**82**) (420 mg, 2.0 mmol) and PhMe (2.0 mL) were then added, and the mixture was stirred at 100 °C for 16 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, the mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel to afford the products **87**.

5.4 Experimental and Analytical Data

5.4.1 Analytical Data for Substrates

Synthesis of *N*-(2-fluorophenyl)pyrimidin-2-amine (69a)



The general procedure **A** was followed using **107a** (6.83 g, 61.5 mmol) and **106** (3.44 g, 30.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 95:5) and recrystallisation **69a** (3.47 g, 61%) was obtained as a white solid. Analytical data was identical to that previously reported.[104]

M.p.: 114-115 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 4.8 Hz, 2H), 8.43 (ddd, *J* = 8.5, 8.3, 1.7 Hz, 1H), 7.59 (s, 1H), 7.19 – 7.06 (m, 2H), 6.98 (dddd, *J* = 8.3, 7.3, 5.1, 1.7 Hz, 1H), 6.76 (t, *J* = 4.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.9 (C_q), 158.0 (CH), 152.8 (C_q, d, $^{1}J_{C-F}$ = 240.3 Hz), 128.0 (C_q, d, $^{2}J_{C-F}$ = 9.9 Hz), 124.3 (CH, d, $^{4}J_{C-F}$ = 3.3 Hz), 122.6 (CH, d, $^{3}J_{C-F}$ = 7.8 Hz), 121.0 (CH), 114.9 (CH, d, $^{2}J_{C-F}$ = 19.3 Hz), 113.1 (CH).

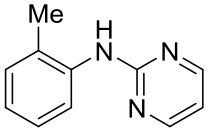
^{19}F NMR (283 MHz, $CDCl_3$): δ = -130.91 – -131.03 (m).

IR (neat): $\tilde{\nu}$ = 3231, 3165, 3005, 1576, 1440, 1409, 1251, 1179, 754, 640 cm^{-1}.

MS (ESI): *m/z* (relative intensity) 381 (24), 190 (100) [M+H$^+$], 170 (13).

HR-MS (ESI): m/z calcd for $C_{10}H_9FN_3$ [M+H$^+$] 190.0780, found 190.0777.

Synthesis of *N*-(*o*-Tolyl)pyrimidin-2-amine (69b)



Under basic conditions:

The general procedure **A** was followed using **107b** (6.59 g, 61.50 mmol) and **106** (3.44 g, 30.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 95:5) and

[104] Shaw, J. W.; Grayson, D. H.; Rozas, I. *ARKIVOC* **2014**, *2*, 161–174.

recrystallisation **69b** (3.81 g, 69%) was obtained as a white solid. Analytical data was identical to that previously reported.[93]

Under acidic conditions:

A Schlenk flask was charged with $AlCl_3$ (4.00 g, 30 mmol) and evacuated and purged with Ar three times. THF (30 mL), aniline **107b** and **106** (3.44 g, 30 mmol) were added successively at 0 °C. The reaction was stirred for 48 h at ambient temperature. The reaction was stopped with H_2O (20 mL), basified with K_2CO_3 and extracted with EtOAc (100 mL). The organic phase was washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. After purification by column chromatography (*n*-hexane/EtOAc 95:5) **69b** (1.42 g, 26%) was obtained as a white solid. Analytical data was identical to that previously reported.

M.p.: 88-89 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 4.8 Hz, 2H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.29 – 7.20 (m, 2H), 7.10 – 7.01 (m, 2H), 6.69 (t, *J* = 4.8 Hz, 1H), 2.32 (s, 3H).

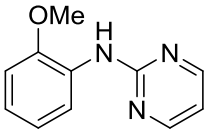
^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.8 (C_q), 158.2 (CH), 137.3 (C_q), 130.7 (CH), 129.6 (C_q), 126.8 (CH), 124.3 (CH), 122.6 (CH), 112.4 (CH), 18.2 (CH_3).

IR (neat): $\tilde{\nu}$ = 3228, 3031, 2927, 1579, 1441, 1406, 1187, 797, 751, 719 cm^{-1}.

MS (ESI): *m/z* (relative intensity) 208 (6), 186 (100) [$M+H^+$], 170 (4).

HR-MS (ESI): m/z calcd for $C_{11}H_{11}N_3$ [$M+H^+$] 186.1031, found 186.1030.

Synthesis of *N*-(2-methoxyphenyl)pyrimidin-2-amine (69c)



The general procedure **A** was followed using **107c** (4.93 g, 40.0 mmol) and **106** (2.29 g, 20.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 85:15) and recrystallisation **69c** (1.45 g, 37%) was obtained as a white solid. Analytical data was identical to that previously reported.[104]

M.p.: 119–120 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.53 – 8.48 (m, 1H), 8.43 (d, *J* = 4.8 Hz, 2H), 7.78 (s, 1H), 7.04 – 6.95 (m, 2H), 6.92 – 6.87 (m, 1H), 6.70 (t, *J* = 4.8 Hz, 1H), 3.90 (s, 3H).

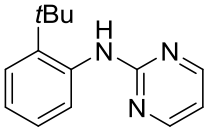
^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2 (C_q), 158.0 (CH), 148.0 (C_q), 129.3 (C_q), 121.9 (CH), 121.0 (CH), 118.6 (CH), 112.5 (CH), 110.1 (CH), 55.8 (CH_3).

IR (neat): $\tilde{\nu}$ = 3382, 2998, 2836, 1569, 1520, 1432, 1405, 1241, 721, 566 cm^{-1}.

MS (ESI): *m/z* (relative intensity) 224 (12), 202 (100) [M+H$^+$], 187 (7), 170 (18).

HR-MS (ESI): m/z calcd for $C_{11}H_{11}N_3O$ [M+H$^+$] 202.0980, found 202.0979.

Synthesis of *N*-[2-*(tert*-Butyl)phenyl]pyrimidin-2-amine (69d)



The general procedure **A** was followed using **107d** (2.98 g, 20.0 mmol) and **106** (1.14 g, 10.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 95:5) and recrystallisation **69d** (1.12 g, 50%) was obtained as a white solid.

M.p.: 95-96 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 4.8 Hz, 2H), 7.58 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.45 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.27 (ddd, *J* = 7.5, 7.5, 1.6 Hz, 1H), 7.17 (ddd, *J* = 7.5, 7.5, 1.6 Hz, 1H), 6.89 (br s, 1H), 6.64 (t, *J* = 4.8 Hz, 1H), 1.44 (s, 9H).

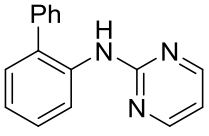
^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5 (C_q), 158.4 (CH), 143.8 (C_q), 136.9 (C_q), 128.4 (CH), 127.0 (CH), 126.9 (CH), 125.9 (CH), 112.1 (CH), 35.0 (C_q), 30.8 (CH_3).

IR (neat): $\tilde{\nu}$ = 3211, 3004, 2958, 2936, 1570, 1440, 1407, 1257, 1088, 773 cm^{-1}.

MS (ESI): *m/z* (relative intensity) 250 (23), 228 (100) [M+H$^+$], 172 (57).

HR-MS (ESI): m/z calcd for $C_{14}H_{18}N_3$ [M+H$^+$] 228.15004, found 228.1498.

Synthesis of *N*-([1,1'-Biphenyl]-2-yl)pyrimidin-2-amine (69e)



The general procedure **A** was followed using **107e** (3.48 g, 20.5 mmol) and **106** (1.14 g, 10.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 9:1) and recrystallisation **69e** (0.91 g, 37%) was obtained as a white solid. Analytical data was identical to that previously reported.

M.p.: 165–166 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40 (dd, *J* = 8.1, 0.9 Hz, 1H), 8.38 (d, *J* = 4.8 Hz, 2H), 7.50 – 7.35 (m, 6H), 7.27 (d, *J* = 8.3, 1.6 Hz, 1H), 7.13 (dd, *J* = 7.5, 7.5, 1.2 Hz, 1H), 7.08 (br s, 1H), 6.69 (t, *J* = 4.8 Hz, 1H).

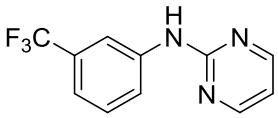
^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.3 (C_q), 158.1 (CH), 138.8 (C_q), 136.4 (C_q), 130.5 (C_q), 129.6 (CH), 129.2 (CH), 128.3 (CH), 127.9 (CH), 123.0 (CH), 120.6 (CH), 112.7 (CH).

IR (neat): $\tilde{\nu}$ = 3268, 3225, 3018, 1575, 1519, 1433, 1407, 1267, 738, 698 cm^{-1}.

MS (ESI): *m/z* (relative intensity) 381 (5), 270 (7), 248 (100) [M+H$^+$], 195 (1), 178 (3).

HR-MS (ESI): m/z calcd for $C_{16}H_{14}N_3$ [M+H$^+$] 248.1187, found 248.1185.

Synthesis of *N*-[3-(Trifluoromethyl)phenyl]pyrimidin-2-amine (69f)



The general procedure **A** was followed using **107f** (13.2 g, 82. 0 mmol) and **106** (5.58 g, 40.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 9:1) and recrystallisation **69f** (3.54 g, 37%) was obtained as a white solid.

M.p.: 123-124 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 4.8 Hz, 2H), 8.20 (br s, 1H), 8.02 (s, 1H), 7.79 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.43 (dd, *J* = 8.4, 7.7 Hz, 1H), 7.29 (ddd, *J* = 7.7, 1.5, 0.8 Hz, 1H), 6.79 (t, *J* = 4.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.9 (C_q), 158.0 (CH), 140.2 (C_q), 131.3 (C_q, q, $^2J_{C-F}$ = 32.4 Hz), 129.4 (CH), 124.2 (C_q, q, $^1J_{C-F}$ = 272.6 Hz), 122.3 (CH, q, $^4J_{C-F}$ = 1.2 Hz), 119.0 (CH, q, $^3J_{C-F}$ = 3.7 Hz), 116.0 (CH, q, $^3J_{C-F}$ = 3.9 Hz), 113.3 (CH).

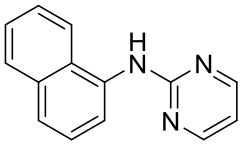
^{19}F NMR (283 MHz, $CDCl_3$): δ = -62.68 (s).

IR (neat): $\tilde{\nu}$ = 3294, 3119, 1580, 1318, 1152, 1102, 1072, 872, 792, 765 cm^{-1}.

MS (ESI): *m/z* (relative intensity) 381 (22), 240 (100) [M+H$^+$], 220 (10), 185 (3).

HR-MS (ESI): m/z calcd for $C_{11}H_8F_3N_3$ [M+H$^+$] 240.0748, found 240.0745.

Synthesis of *N*-(Naphthalen-2-yl)pyrimidin-2-amine (69g)



The general procedure **A** was followed using **107g** (2.94 g, 20.5 mmol) and **106** (1.14 g, 10.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 9:1) and recrystallisation **69g** (0.93 g, 42%) was obtained as a white solid. Analytical data was identical to that previously reported.[93]

M.p.: 147-148 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (br s, 1H), 8.32 (d, *J* = 4.8 Hz, 2H), 8.16 – 8.09 (m, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.95 – 7.86 (m, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.45 (m, 3H), 6.63 (t, *J* = 4.8 Hz, 1H).

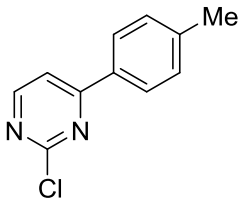
^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.6 (C_q), 158.2 (CH), 134.5 (2∗C_q), 128.6 (CH), 128.3 (C_q), 126.0 (CH), 126.0 (CH), 125.9 (CH), 125.1 (CH), 121.9 (CH), 120.6 (CH), 112.2 (CH).

IR (neat): $\tilde{\nu}$ = 3230, 3045, 2914, 1572, 1529, 1443, 1392, 1271, 777, 511 cm^{-1}.

MS (ESI): *m/z* (relative intensity) 244 (8), 222 (100) [$M+H^+$].

HR-MS (ESI): m/z calcd for $C_{14}H_{11}N_3$ [$M+H^+$] 222.1031, found 222.1024.

Synthesis of 2-Chloro-4-(*p*-tolyl)pyrimidine (160)



Following the reported procedure,[105] 2,4-dichloropyrimidine (2.2 g, 15 mmol) and *p*-tolylboronic acid (1.4 g, 10 mmol) were reacted. After purification by flash column chromatography (*n*-hexane/EtOAc 96:4) and Kugelrohr distilliation (1 mbar, 170 °C) **160** (1.4 g, 69%) was obtained as a white solid.

M.p.: 102-103 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 5.3 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 5.3 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3 (CH), 161.9 (C_q), 159.7 (C_q), 142.7 (CH), 132.4 (C_q), 130.0 (CH), 127.5 (CH), 114.9 (CH), 21.7 (CH_3).

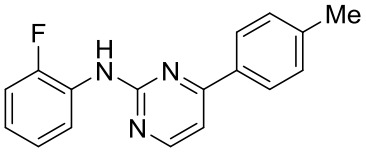
[105] Peng, Z.-H.; Journet, M.; Humphrey, G. *Org. Lett.* **2008**, *8*, 395–398.

IR (neat): ṽ = 1566, 1532, 1424, 1346, 1176, 1066, 817, 770, 687, 483 cm^{-1}.

MS (ESI): *m/z* (relative intensity) 227 (7), 205 (100) [M+H^+], 177 (4), 149 (5), 117 (46), 103 (14).

HR-MS (ESI): m/z calcd for $C_{11}H_{10}ClN_2$ [M+H^+] 205.0532, found 205.0531.

Synthesis of *N*-(2-Fluorophenyl)-4-(*p*-tolyl)pyrimidin-2-amine (121)



A round-bottom flask was charged with 2-chloro-4-(p-tolyl)pyrimidine (**160**) (819 mg, 4.0 mmol), 1,4-dioxane (12 mL), 2-fluoroaniline (0.58 mL, 6.0 mmol) and trifluoroacetic acid (3.06 mL, 40 mmol). The reaction was stirred at 80 °C for 16 h. The reaction was cooled to ambient temperature, solvents evaporated *in vacuo*, residue basified with K_2CO_3 and extracted with EtOAc threefold. The organic phases were dried over Na_2SO_4 and evaporated *in vacuo*. After purification by flash column chromatography (*n*-hexane/EtOAc 9:1) **121** (703 mg, 63%) was obtained as a white solid.

M.p.: 120-121 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.63 (ddd, *J* = 8.4, 8.2, 1.5 Hz, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 2H), 7.52 (s, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.20 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.17 (d, *J* = 5.2 Hz, 1H), 7.13 (ddd, *J* = 11.4, 8.2, 1.3 Hz, 1H), 7.02 – 6.96 (m, 1H), 2.44 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.1 (C_q), 160.1 (C_q), 158.5 (CH), 152.5 (C_q, d, $^1J_{C-F}$ = 242.8 Hz), 141.3 (C_q), 134.3 (C_q), 129.7 (CH), 128.5 (C_q, d, $^2J_{C-F}$ = 10.1 Hz), 127.2 (CH), 124.4 (CH, d, $^4J_{C-F}$ = 3.1 Hz), 122.1 (CH, d, $^3J_{C-F}$ = 7.0 Hz), 120.7 (CH), 114.8 (CH, d, $^2J_{C-F}$ = 18.7 Hz), 108.7 (CH), 21.6 (CH_3).

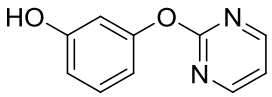
^{19}F NMR (283 MHz, $CDCl_3$): δ = -131.55 (ddd, *J* = 9.7, 7.2, 4.0 Hz).

IR (neat): $\tilde{\nu}$ = 3264, 3015, 1537, 1438, 1410, 1254, 1181, 809, 748, 509 cm^{-1}.

MS (EI): *m/z* (relative intensity) 279 (37) [M^+], 260 (100), 138 (4), 115 (8), 91 (5).

HR-MS (EI): m/z calcd for $C_{17}H_{14}FN_3$ [M^+] 279.1172, found 279.1165.

Synthesis of 3-(Pyrimidin-2-yloxy)phenol (124)



A round-bottom flask was charged with THF (40 mL), resorcinol (11.0 g, 100 mmol), 2-chloropyrimidine (**106**) (2.29 g, 20 mmol) and K_2CO_3 (5.52 g, 40 mmol). The reaction was stirred at 50 °C for 36 h. The crude reaction mixture was filtered through a paper filter, washed with EtOAc and solvent evaporated *in vacuo*. After purification by flash column chromatography (*n*-hexane/EtOAc 1:2) **124** (382 mg , 10%) was isolated as a pale brown solid.

M.p.: 205-206 °C

^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.61 (s, 1H), 8.63 (d, J = 4.8 Hz, 2H), 7.23 (t, J = 4.8 Hz, 1H), 7.20 (dd, J = 8.1, 8.1 Hz, 1H), 6.66 (ddd, J = 8.1, 2.3, 0.8 Hz, 1H), 6.59 (ddd, J = 8.1, 2.3, 0.8 Hz, 1H), 6.56 (dd, J = 2.2, 2.2 Hz, 1H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.5 (C_q), 159.7 (CH), 158.3 (C_q), 153.6 (C_q), 129.8 (CH), 116.7 (CH), 112.1 (CH), 111.8 (CH), 108.6 (CH).

IR (neat): $\tilde{\nu}$ = 3204, 2963, 2925, 1579, 1410, 1246, 1136, 1074, 787, 638 cm^{-1}.

MS (EI): *m/z* (relative intensity) 188 (100) [M$^+$], 160 (32), 146 (10), 133 (11), 117 (38), 93 (15).

HR-MS (EI): m/z calcd for $C_{10}H_7N_2O_2$ [M$^+$] 188.0586, found 188.0587.

Synthesis of Trifluoroethylbromide (146)

A round-bottom flask was charged with DMPU (50 mL), 2,2,2-trifluoroethyl 4-methylbenzenesulfonate (**145**) (50.8 g, 200 mmol) and NaBr (61.7 g, 600 mmol). A distillation bridge with a two-necked collection flask was attached to the round flask and the reaction was stirred at 170 °C for 1.5 h. The pure product **146** (18.3 g, 56%) distilled directly into the collection flask. The analytical data was identical to that reported in the literature.[106]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.67 (q, J = 9.0 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 123.2 (C_q, q, $^1J_{C-F}$ = 274.7 Hz), 26.0 (CH_2, q, $^2J_{C-F}$ = 37.7 Hz).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -68.76 (t, J = 9.0 Hz).

[106] Sigma-Aldrich Co. , http://www.sigmaaldrich.com/spectra/fnmr/FNMR003857.PDF, (accessed 22nd of April 2016)

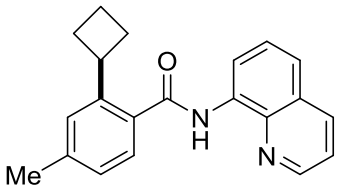
IR (neat): $\tilde{\nu}$ = 3051, 2991, 1431, 1310, 1263, 1235, 1125, 1065, 719, 629 cm^{-1}.

MS (EI): *m/z* (relative intensity) 162 (100) [M^+], 143 (22), 123 (11), 93 (26), 83 (95), 79 (10), 64 (39).

HR-MS (ESI): [not available]

5.4.2 Analytical Data for C–H Secondary Alkylation of Benzamides 59

Synthesis of 2-Cyclobutyl-4-methyl-*N*-(quinolin-8-yl)benzamide (81ab)



The general procedure **B** was followed using **59a** (131 mg, 0.50 mmol) and **80b** (67.5 mg, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 96:4) **81ab** (132 mg, 83%) was obtained as a white solid.

M.p.: 136-137 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.10 (s, 1H), 8.94 (d, J = 7.5 Hz, 1H), 8.76 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.18 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.54 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.27 (s, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 4.09 (pent, *J* = 8.9 Hz, 1H), 2.44 (s, 3H), 2.41–2.35(m, 2H), 2.23–2.15(m, 2H), 2.00–1.90 (m, 1H), 1.81–1.74 (m, 1H).

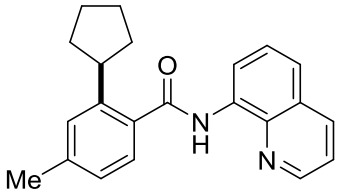
^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.8 (C_q), 148.3 (CH), 144.3 (C_q), 140.4 (C_q), 138.7 (C_q), 136.5 (CH), 135.0 (C_q), 133.4 (C_q), 128.2 (C_q), 127.9 (CH), 127.6 (CH), 127.4 (CH), 126.6 (CH), 121.8 (CH), 121.8 (CH), 116.6 (CH), 38.0 (CH), 30.0 (CH_2), 21.7 (CH_3), 18.4 (CH_2).

IR (ATR): $\tilde{\nu}$ = 3350, 2970, 2860, 1668, 1517, 1481, 1324, 1258, 827, 678, 598 cm^{-1}.

MS (EI): *m/z* (relative intensity) 316 (46) [M+], 287 (14), 172 (86), 157 (77), 145 (100), 115 (40), 91 (20), 43 (14).

HR-MS (EI): *m/z* calcd for $C_{21}H_{20}N_2O$ [M^+] 316.1576, found 316.1583.

Synthesis of 2-Cyclopentyl-4-methyl-*N*-(quinolin-8-yl)benzamide (81ac)



The general procedure **B** was followed using **59a** (262 mg, 1.00 mmol) and **80c** (298 mg, 2.00 mmol). After purification by column chromatography (n-hexane/EtOAc 97:3) **81ac** (235 mg, 71%) was obtained as a white solid.

M.p.: 121-122 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.13 (s, 1H), 8.95 (d, *J* = 7.8 Hz, 1H), 8.76 (dd, J = 4.2, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.55 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.26 (s, 1H), 7.10 (ddd, *J* = 7.6, 1.6, 0.8 Hz, 1H), 3.54 (tt, J = 9.2, 7.3 Hz, 1H), 2.41 (s, 3H), 2.21–2.14 (m, 2H), 1.83–1.78 (m, 2H), 1.70–1.61 (m, 4H).

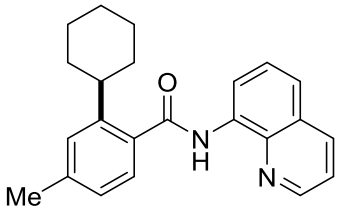
^{13}C NMR (126 MHz, CDCl3): δ = 169.2 (C_q), 148.3 (CH), 145.1 (C_q), 140.4 (C_q), 138.7 (C_q), 136.5 (CH), 135.0 (C_q), 134.7 (C_q), 128.2 (C_q), 127.7 (CH), 127.6 (CH), 127.2 (CH), 126.6 (CH), 121.8 (CH), 121.7 (CH), 116.7 (CH), 42.0 (CH), 35.6 (CH_2), 26.1 (CH_2), 21.8 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3352, 2955, 2865, 1667, 1515, 1480, 1322, 825, 761, 593 cm^{-1}.

MS (EI): *m/z* (relative intensity) 330 (35) [M^+], 186 (100), 169 (55), 158 (86), 143 (48), 129 (22), 115 (30), 105 (15), 91 (16).

HR-MS (ESI): *m/z* calcd for $C_{22}H_{23}N_2O$ [$M+H^+$] 331.1805, found 331.1804.

Synthesis of 2-Cyclohexyl-4-methyl-*N*-(quinolin-8-yl)benzamide (81ad)



The general procedure **B** was followed using **59a** (131 mg, 0.50 mmol) and **80d** (163 mg, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 20:1) **81ad** (148 mg, 86%) was obtained as a white solid.

M.p.: 177–178 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.12 (s, 1H), 8.94 (dd, *J* = 7.3, 1.1 Hz, 1H), 8.73 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.63–7.47 (m, 3H), 7.42 (dd, *J* = 8.3, 4.3 Hz, 1H),

7.23 (s, 1H), 7.09 (dd, *J* = 7.8, 1.1 Hz, 1H), 3.14 (tt, *J* = 11.7, 3.3 Hz, 1H), 2.40 (s, 3H),1.99 (d, *J* = 12.8 Hz, 2H), 1.83–1.70 (m, 2H), 1.67–1.15 (m, 6H).

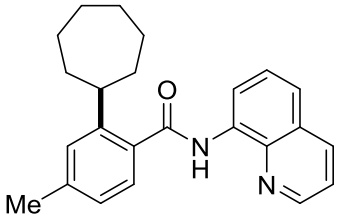
^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8 (C_q), 148.1 (CH), 146.1 (C_q), 140.2 (C_q), 138.5 (C_q), 136.3 (CH), 134.9 (C_q), 133.7(C_q), 128.0 (C_q), 127.7 (CH), 127.4 (CH), 127.3 (CH), 126.5 (CH), 121.6 (CH), 121.6 (CH), 116.4 (CH), 40.3 (CH), 34.7 (CH_2), 26.7 (CH_2), 26.1 (CH_2), 21.6 (CH_3).

IR (neat): $\tilde{\nu}$ = 3339, 2935, 2849, 1665, 1609, 1264, 828, 691 cm^{-1}.

MS (EI): *m/z* (relative intensity) 344 (43) [M^+], 200 (100), 183 (83), 144 (79), 105 (35), 43 (20).

HR-MS (EI): *m/z* calcd for $C_{23}H_{24}N_2O$ [M^+] 344.1889, found 344.1888.

Synthesis of 2-Cycloheptyl-4-methyl-*N*-(quinolin-8-yl)benzamide (81ae)



The general procedure **B** was followed using **59a** (262 mg, 1.00 mmol) and **80e** (354 mg, 2.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 97:3) **81ae** (196 mg, 55%) was obtained as a white solid.

M.p.: 157-158 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.12 (s, 1H), 8.96 (d, *J* = 7.5 Hz, 1H), 8.75 (dd, *J* = 4.3, 1.5 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.55 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.22 (s, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 3.26 (tt, *J* = 10.4, 3.4 Hz, 1H), 2.40 (s, 3H), 2.07–2.01 (m, 2H), 1.78–1.67 (m, 4H), 1.65–1.59 (m, 2H), 1.58–1.48 (m, 4H).

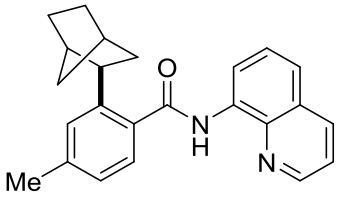
^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.0 (C_q), 148.4 (C_q), 148.3 (CH), 140.5 (C_q), 138.7 (C_q), 136.5 (CH), 135.1 (C_q), 133.2 (C_q), 128.2 (C_q), 128.1 (CH), 127.6 (CH), 127.3 (CH), 126.5 (CH), 121.7 (CH), 121.7 (CH), 116.7 (CH), 42.5 (CH), 37.2 (CH_2), 28.0 (CH_2), 27.5 (CH_2), 21.8 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3342, 2920, 2858, 1667, 1518, 1478, 1257, 1133, 829, 689, 576 cm^{-1}.

MS (EI): *m/z* (relative intensity) 358 (43) [M^+], 214 (100), 196 (44), 171 (46), 155 (52), 144 (75), 130 (30), 105 (26), 91 (16).

HR-MS (EI): *m/z* calcd for $C_{24}H_{26}N_2O$ [M^+] 358.2045, found 358.2055.

Synthesis of 2-(*exo*-norborn-2-yl)-4-methyl-*N*-(quinolin-8-yl)benzamide (81af)



The general procedure **B** was followed using **59a** (262 mg, 1.00 mmol) and **80f** (350 mg, 2.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 97:3) **81af** (231 mg, 65%) was obtained as a white solid.

M.p.: 158-160 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.11 (s, 1H), 8.95 (d, *J* = 7.6 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.55 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.25 (s, 1H), 7.11–7.08 (m, 1H), 3.30 (dd, *J* = 8.8, 6.0 Hz, 1H), 2.51 (d, *J* = 3.2 Hz, 1H), 2.42 (s, 3H), 2.30 (d, *J* = 4.2 Hz, 1H), 1.84 (ddd, *J* = 11.9, 9.1, 2.3 Hz, 1H), 1.68–1.62 (m, 2H), 1.53–1.47 (m, 2H), 1.31 (ddd, J = 10.6, 6.9, 2.4 Hz, 1H), 1.26–1.23 (m, 1H), 1.21–1.17 (m, 1H).

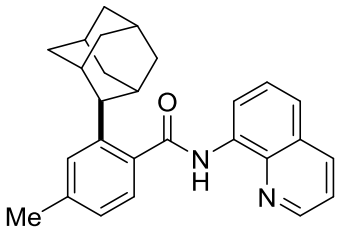
^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.3 (C_q), 148.2 (CH), 145.9 (C_q), 140.1 (C_q), 138.6 (C_q), 136.6 (CH), 135.0 (C_q), 134.6 (C_q), 128.2 (C_q), 127.7 (CH), 127.5 (CH), 127.1 (CH), 126.2 (CH), 121.8 (CH), 121.7 (CH), 116.8 (CH), 43.7 (CH), 42.8 (CH), 40.3 (CH_2), 37.1 (CH), 36.9 (CH_2), 30.7 (CH_2), 28.8 (CH_2), 21.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3335, 2950, 2869, 1672, 1517, 1478, 1324, 826, 688, 596 cm^{-1}.

MS (EI): *m/z* (relative intensity) 356 (29) [M^+], 212 (100), 184 (32), 171 (25), 144 (31), 115 (24), 67 (26).

HR-MS (EI): *m/z* calcd for $C_{24}H_{24}N_2O$ [M^+] 356.1889, found 356.1890.

Synthesis of 2-(2-Adamantyl)-4-methyl-*N*-(quinolin-8-yl)benzamide (81ag)



The general procedure **B** was followed using **59a** (262 mg, 1.00 mmol) and **80g** (430 mg, 2.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 96:4) **81ag** (104 mg, 28%) was obtained as a white solid.

M.p.: 169–170 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.16 (s, 1H), 8.91 (d, *J* = 7.4 Hz, 1H), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.59 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.55 (d, *J* = 5.2 Hz, 1H), 7.54 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.40 (s, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 3.92 (s, 1H), 2.43 (s, 3H), 2.30 (s, 2H), 1.95 (d, *J* = 12.6 Hz, 2H), 1.90 (s, 1H), 1.87 (s, 2H), 1.85 – 1.81 (m, 3H), 1.70 (s, 2H), 1.59 (d, *J* = 12.7 Hz, 2H).

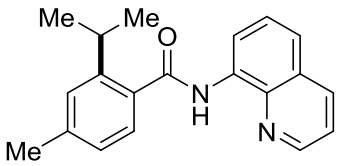
^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7 (C_q), 148.3 (CH), 144.0 (C_q), 139.8 (C_q), 138.7 (C_q), 136.5 (CH), 135.2 (C_q), 134.3 (C_q), 129.1 (CH), 128.5 (CH), 128.2 (C_q), 127.7 (CH), 126.2 (CH), 121.8 (CH), 121.7 (CH), 116.6 (CH), 44.8 (CH), 39.9 (CH_2), 38.0 (CH_2), 32.7 (CH_2), 32.6 (CH), 28.0 (CH), 27.8 (CH), 22.0 (CH_3).

IR (neat): $\tilde{\nu}$ = 3342, 2901, 2848, 1672, 1517, 1480, 1384, 1324, 826, 791 cm^{-1}.

MS (EI): *m/z* (relative intensity) 396 (23) [M^+], 252 (100), 234 (9), 195 (20), 181 (9), 144 (761).

HR-MS (EI): m/z calcd for $C_{27}H_{28}N_2O$ [M^+] 396.2202, found 396.2212.

Synthesis of 2-*iso*-Propyl-4-methyl-*N*-(quinolin-8-yl)benzamide (81ai)



The general procedure **B** was followed using **59a** (262 mg, 1.00 mmol) and **80i** (163 mg, 2.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 97:3) **81ai** (200 mg, 66%) was obtained as a white solid.

M.p.: 118-119 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.14 (s, 1H), 8.95 (d, *J* = 7.5 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.55 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.26 (s, 1H), 7.12 (dd, *J* = 7.9, 0.8 Hz, 1H), 3.54 (hept, *J* = 6.9 Hz, 1H), 2.42 (s, 3H), 1.31 (d, *J* = 6.9 Hz, 6H).

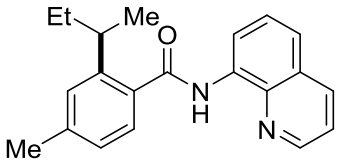
^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.0 (C_q), 148.3 (CH), 147.4 (C_q), 140.5 (C_q), 138.7 (C_q), 136.5 (CH), 135.0 (C_q), 133.8 (C_q), 128.1 (C_q), 127.6 (CH), 127.2 (CH), 127.1 (CH), 126.7 (CH), 121.9 (CH), 121.8 (CH), 116.6 (CH), 30.0 (CH), 24.5 (CH_3), 21.8 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3338, 2966, 1674, 1518, 1325, 825, 686, 599 cm^{-1}.

MS (EI): *m/z* (relative intensity) 304 (36) [M^+], 160 (100), 145 (67), 128 (25), 117 (21), 105 (16), 91 (19).

HR-MS (EI): *m/z* calcd for $C_{20}H_{20}N_2O$ [M^+] 304.1576, found 304.1570.

Synthesis of 2-(*sec*-Butyl)-4-methyl-*N*-(quinolin-8-yl)benzamide (81aj)



The general procedure **B** was followed using **59a** (131 mg, 0.50 mmol) and **80j** (137 mg, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 20:1) **81aj** (98 mg, 62%) was obtained as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.10 (s, 1H), 8.94 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.73 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.61–7.51 (m, 2H), 7.49 (d, *J* = 7.9 Hz, 1H),7.42 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.19 (s, 1H), 7.10 (ddd, *J* = 7.9, 1.7, 0.7 Hz, 1H), 3.24 (tq, *J* = 7.2, 6.9 Hz, 1H), 2.40 (s, 3H), 1.77–1.55 (m, 2H), 1.29 (d, *J* = 6.7 Hz, 3H), 0.83 (t, *J* = 7.0 Hz, 3H).

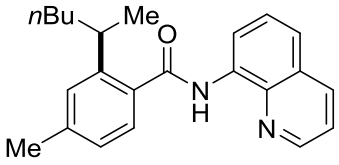
^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9 (C_q), 148.2 (CH), 146.0 (C_q), 140.2 (C_q), 138.5(C_q), 136.3 (CH), 134.9 (C_q), 134.4 (C_q), 127.9 (C_q), 127.4 (CH), 127.2 (CH), 127.0 (CH),126.5 (CH), 121.6 (CH), 121.5 (CH), 116.4 (CH), 36.8 (CH), 31.1 (CH_2), 22.3 (CH_3), 21.6 (CH_3), 12.3 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3350, 2960, 2871, 1671, 1422, 1260, 919, 789 cm^{-1}.

MS (EI): *m/z* (relative intensity) 318 (55) [M^+], 159 (100), 142 (46), 91 (27), 43 (8).

HR-MS (EI): *m/z* calcd for $C_{21}H_{22}N_2O$ [M^+] 318.1732, found 318.1730.

Synthesis of 2-(Hexan-2-yl)-4-methyl-*N*-(quinolin-8-yl)benzamide (81ak)



The general procedure **B** was followed using **59a** (262 mg, 1.00 mmol) and **80ak** (330 mg, 2.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 96:4) **81ak** (181 mg, 52%) was obtained as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 10.10 (s, 1H), 8.94 (d, *J* = 7.3 Hz, 1H), 8.75 (dd, *J* = 3.9, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.64 – 7.51 (m, 2H), 7.51 – 7.41 (m, 2H), 7.21 (s, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 3.40 – 3.21 (m, 1H), 2.42 (s, 3H), 1.74 – 1.56 (m, 2H), 1.32 – 1.17 (m, 6H), 0.87 – 0.74 (m, 4H).

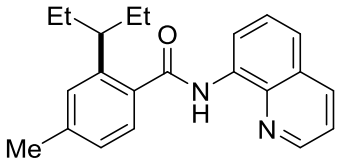
^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1 (C_q), 148.4 (CH), 146.4 (CH), 140.4 (C_q), 138.7 (C_q), 136.4 (C_q), 135.0 (CH), 134.5 (CH), 128.1 (CH), 127.6 (C_q), 127.4 (C_q), 127.2 (C_q), 126.6 (CH), 121.8 (CH), 121.8 (CH), 116.7 (CH), 61.2 (CH), 38.3 (CH_2), 35.4 (CH_3), 30.2 (CH_2), 23.0 (CH_2), 21.8 (CH_3), 14.1 (CH_3).

IR (neat): $\tilde{\nu}$ = 3350, 2958, 2926, 2858, 1676, 1521, 1482, 1325, 1261, 825 cm^{-1}.

MS (ESI): *m/z* (relative intensity) 715 (64), 369 (100), 347 (76) [M+H$^+$], 236 (8), 203 (20).

HR-MS (ESI): m/z calcd for $C_{23}H_{27}N_2O$ [M+H$^+$] 347.2123, found 347.2115.

Synthesis of 4-Methyl-2-(pentan-3-yl)-*N*-(quinolin-8-yl)benzamide (81al)



The general procedure **B** was followed using **59a** (262 mg, 1.00 mmol) and **80l** (302 mg, 2.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 97:3) **81al** (126 mg, 38%) was obtained as a white solid.

M.p.: 80–81 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.07 (s, 1H), 8.94 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.15 (s, 1H), 7.11 (ddd, *J* = 7.7, 1.7, 0.6 Hz, 1H), 3.06 (tt, *J* = 8.8, 5.9 Hz, 1H), 2.42 (s, 3H), 1.80 – 1.60 (m, 4H), 0.83 (t, *J* = 7.4 Hz, 6H).

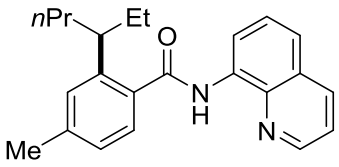
^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2 (C_q), 148.3 (CH), 144.3 (C_q), 140.2 (C_q), 138.7 (C_q), 136.4 (CH), 135.8 (C_q), 135.1 (C_q), 128.1 (C_q), 127.6 (CH), 127.5 (CH), 127.0 (CH), 126.7 (CH), 121.7 (CH), 121.7 (CH), 116.6 (CH), 44.1 (CH), 29.6 (CH_2), 21.8 (CH_3), 12.3 (CH_3).

IR (neat): $\tilde{\nu}$ = 3342, 2959, 2923, 2854, 1667, 1519, 1481, 1383, 1325, 781 cm^{-1}.

MS (EI): *m/z* (relative intensity) 332 (46) [M$^+$], 208 (28), 189 (57), 173 (100), 144 (65), 130 (36).

HR-MS (EI): m/z calcd for $C_{22}H_{24}N_2O$ [M$^+$] 332.1889, found 332.1880.

Synthesis of 2-(Hexan-3-yl)-4-methyl-*N*-(quinolin-8-yl)benzamide (81am)



The general procedure **B** was followed using **59a** (262 mg, 1.00 mmol) and **80m** (330 mg, 2.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 96:4) **81am** (147 mg, 42%) was obtained as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.06 (s, 1H), 8.94 (d, *J* = 7.7 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.17 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.59 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.16 (s, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 3.13 (ddd, *J* = 14.6, 8.7, 6.0 Hz, 1H), 2.41 (s, 3H), 1.74 – 1.57 (m, 3H), 1.34 – 1.23 (m, 2H), 1.23 – 1.12 (m, 1H), 0.85 – 0.78 (m, 6H).

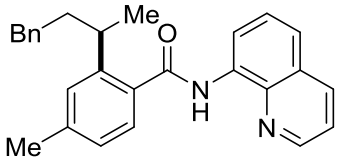
^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0 (C_q), 148.2 (CH), 144.5 (C_q), 140.1 (C_q), 138.7 (C_q), 136.3 (CH), 135.6 (C_q), 135.0 (C_q), 128.1 (C_q), 127.5 (CH), 127.4 (CH), 126.9 (CH), 126.6 (CH), 121.7 (CH), 121.7 (CH), 116.6 (CH), 42.5 (CH), 39.4 (CH_2), 30.1 (CH_2), 21.9 (CH_3), 21.1 (CH_2), 14.6 (CH_3), 12.4 (CH_3).

IR (neat): $\tilde{\nu}$ = 3352, 2958, 2928, 2870, 1677, 1521, 1482, 1385, 1325, 825 cm^{-1}.

MS (ESI): *m/z* (relative intensity) 715 (52), 369 (100), 347 (68) [M+H$^+$], 236 (8), 203 (20).

HR-MS (ESI): m/z calcd for $C_{23}H_{27}N_2O$ [M+H$^+$] 347.2123, found 347.2119.

Synthesis of 4-Methyl-2-(4-phenylbutan-2-yl)-*N*-(quinolin-8-yl)benzamide (81an)



The general procedure **B** was followed using **59a** (262 mg, 1.00 mmol) and **80n** (426 mg, 2.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 97:3) **81an** (224 mg, 56%) was obtained as a viscous oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.15 (s, 1H), 8.96 (d, *J* = 7.5 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.19 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.57 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.17–7.09 (m, 5H), 7.07–7.03 (m, 1H), 3.45 (tq, *J* = 6.9, 6.9 Hz, 1H), 2.65 (ddd, *J* = 13.7, 11.0, 5.5 Hz, 1H), 2.52 (ddd, *J* = 13.7, 11.0, 5.5 Hz, 1H), 2.45 (s, 3H), 2.10–2.03 (m, 1H), 1.98–1.90 (m, 1H), 1.40 (d, *J* = 6.8 Hz, 3H).

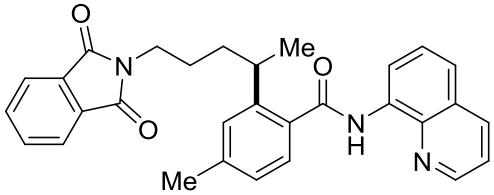
^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.9 (C_q), 148.3 (CH), 145.8 (C_q), 142.7 (C_q), 140.5 (C_q), 138.7 (C_q), 136.4 (CH), 134.9 (C_q), 134.5 (C_q), 128.4 (CH), 128.2 (CH), 128.1 (C_q), 127.5 (CH), 127.4 (CH), 127.2 (CH), 126.9 (CH), 125.6 (CH), 121.8 (CH), 121.7 (CH), 116.6 (CH), 40.2 (CH_3), 35.2 (CH), 34.2 (CH_3), 23.0 (CH_2), 21.8 (CH_2).

IR (ATR): $\tilde{\nu}$ = 3350, 3025, 2923, 1672, 1517, 1454, 1260, 824, 696, 594 cm^{-1}.

MS (EI): *m/z* (relative intensity) 394 (11) [M^+], 303 (76), 159 (100), 145 (36), 117 (15), 91 (76).

HR-MS (ESI): *m/z* calcd for $C_{27}H_{27}N_2O$ [$M+H^+$] 395.2123, found 395.2120.

Synthesis of 2-[5-(1,3-Dioxoisoindolin-2-yl)pentan-2-yl]-4-methyl-*N*-(quinolin-8-yl)benzamide (81ap)



The general procedure **B** was followed using **59a** (262 mg, 1.00 mmol) and **80p** (592 mg, 2.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 80:20) **81ap** (178 mg, 37%) was obtained as a white solid.

M.p.: 136–137 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.09 (s, 1H), 8.90 (d, *J* = 6.8 Hz, 1H), 8.70 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.77 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.66 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.57 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.52 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.18 (s, 1H), 7.10 (ddd, *J* = 7.8, 1.6, 0.6 Hz, 1H), 3.67 – 3.57 (m, 2H), 3.37 (tq, *J* = 7.0, 6.9 Hz, 1H), 2.39 (s, 3H), 1.80 – 1.68 (m, 2H), 1.68 – 1.62 (m, 1H), 1.59 – 1.51 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 3H).

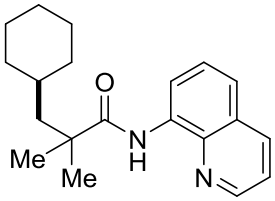
^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6 (C_q), 168.3 (C_q), 148.2 (CH), 145.5 (C_q), 140.5 (C_q), 138.6 (C_q), 136.3 (CH), 134.9 (C_q), 134.3 (C_q), 133.8 (CH), 132.2 (C_q), 128.0 (C_q), 127.5 (CH), 127.3 (CH), 127.1 (CH), 126.8 (CH), 123.1 (CH), 121.7 (CH), 121.6 (CH), 116.6 (CH), 38.4 (CH_2), 35.6 (CH_2), 35.1 (CH), 27.2 (CH_2), 23.1 (CH_3), 21.8 (CH_3).

IR (neat): $\tilde{\nu}$ = 3354, 2930, 2861, 1704, 1668, 1521, 1482, 1394, 1049, 717 cm^{-1}.

MS (EI): *m/z* (relative intensity) 477 (34) [M^+], 333 (39), 315 (32), 186 (20), 169 (66), 160 (100), 130 (46).

HR-MS (ESI): m/z calcd for $C_{31}H_{29}N_3O_3$ [$M+H^+$] 478.2131, found 478.2125.

Synthesis of 3-Cyclohexyl-2,2-dimethyl-*N*-(quinolin-8-yl)propanamide (101ad)



The general procedure **B** was followed using **62a** (228 mg, 1.00 mmol) and **80d** (326 mg, 2.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 2:1) followed by GPC **101ad** (41 mg, 13%) was obtained as a brown oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.25 (s, 1H), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.78 (dd, *J* = 7.6, 1.3 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.53 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.48 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 1.72 – 1.66 (m, 4H), 1.61 – 1.52 (m, 3H), 1.47 – 1.41 (m, 1H), 1.40 (s, 6H), 1.16 (ttt, *J* = 12.6, 12.6, 3.2 Hz, 2H), 1.06 (ttt, *J* = 12.6, 12.6, 3.2 Hz, 1H), 0.96 (ttd, *J* = 12.9, 12.9, 3.2 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.0 (C_q), 148.2 (CH), 138.9 (C_q), 136.3 (CH), 134.8 (C_q), 128.0 (C_q), 127.6 (CH), 121.6 (CH), 121.2 (CH), 116.3 (CH), 49.2 (CH), 43.6 (C_q), 35.0 (CH_2), 34.8 (CH_2), 26.7 (CH_3), 26.6 (CH_2), 26.5 (CH_2).

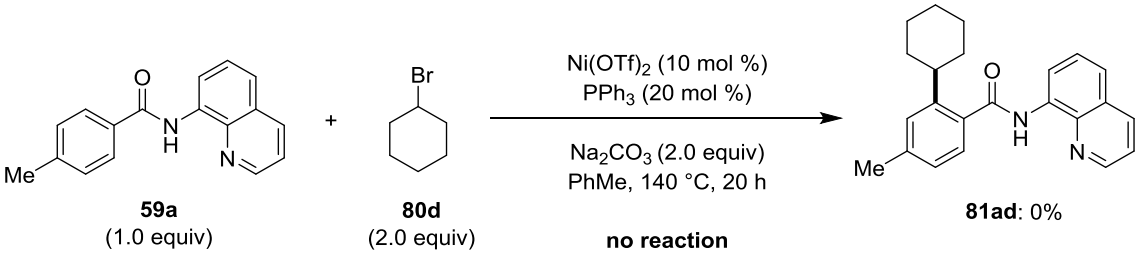
IR (neat): $\tilde{\nu}$ = 3365, 2920, 2849, 1678, 1521, 1485, 1382, 1324, 1131, 790, 678 cm^{-1}.

MS (EI): *m/z* (relative intensity) 310 (4) [M^+], 253 (3), 214 (36), 171 (100), 144 (52), 116 (7).

HR-MS (EI): m/z calcd for $C_{20}H_{26}N_2O$ [M^+] 310.2045, found 310.2044.

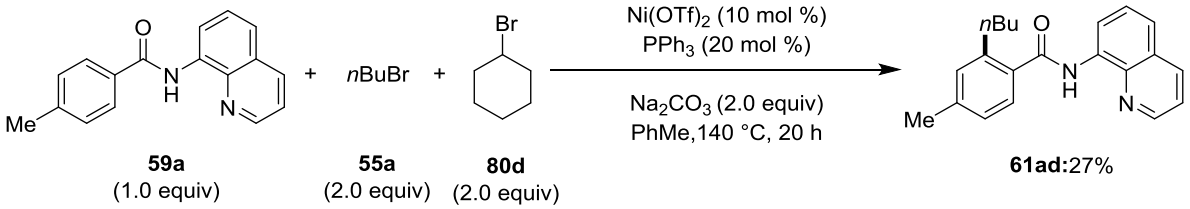
Mechanistic studies

Reaction of 59a under primary alkylation conditions



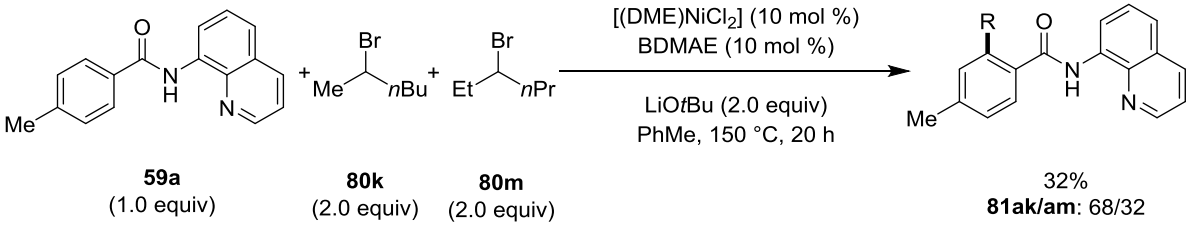
Following the reported procedure,[52] **59a** (262 mg, 1.0 mmol) was reacted with **80d** (326 mg, 2.0 mmol). At ambient temperature, CH_2Cl_2 (2.0 mL) was added. No conversion was observed through ^1H NMR spectroscopic analysis of the crude reaction mixture.

Intermolecular Competition Experiment between 59a and 80d



Benzamide **59a** (262 mg, 1.0 mmol), [Ni(OTf)$_2$] (37 mg, 10 mol %), PPh_3 (53 mg, 20 mol %) and Na_2CO_3 (212 mg, 2.0 mmol) were placed in a 25 mL sealed tube. The tube was evacuated and purged with Ar for three times. *n*-Butyl bromide (**55a**) (274 mg, 2.0 mmol), cyclohexyl bromide (**80d**) (326 mg, 2.0 mmol) and toluene (2.0 mL) were then added, and the mixture was stirred at 140 °C for 16 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, and the reaction mixture was transferred into a round-bottom flask with CH_2Cl_2 and concentrated under reduced pressure. Analysis of the crude reaction mixture by GCMS gave 27% of **60ad** as the sole product.

Intermolecular Competition Experiment between 80k and 80m

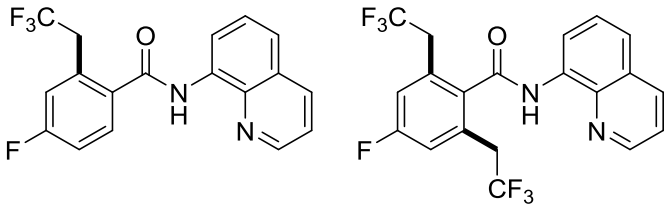


Benzamide **59a** (262 mg, 1.0 mmol), [(DME)NiCl$_2$] (22 mg, 10 mol %) and Li*O*t*Bu* (160 mg, 2.0 mmol) were placed in a 25 mL sealed tube. The tube was evacuated and purged with Ar for three times. BDMAE (76 µL, 40 mol %), 2-bromo-octane (**80k**) (386 mg, 2.0 mmol), 3-bromo-octane (**80m**) (386 mg, 2.0 mmol) and PhMe (2.0 mL) were then added, and the mixture was stirred at 150 °C for 20 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, and the reaction mixture was transferred into a round-bottom flask with CH_2Cl_2 and concentrated under reduced pressure. After purification by column chromatography (*n*-

hexane/EtOAc 97:3) **81ak/am** (55 mg, 32%) was isolated as a mixture. The ratio of products was determined by ^{1}H NMR spectroscopy.

5.4.3 Analytical Data for C–H Trifluoroethylation of benzamides 59

Synthesis of 4-Fluoro-*N*-(quinolin-8-yl)-2-(2,2,2-trifluoroethyl)benzamide (84b) and 4-Fluoro-*N*-(quinolin-8-yl)-2,6-bis(2,2,2-trifluoroethyl)benzamide (84b')



The general procedure **C** was followed using **59b** (133 mg, 0.50 mmol) and **82** (210 mg, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 2:1), followed by GPC, **84b** (41 mg, 23%) and **84b'** (16 mg, 7%) were obtained as yellow solids.

84b:

M.p.: 95–96 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.30 (s, 1H), 8.88 (dd, J = 7.1, 1.4 Hz, 1H), 8.79 (dd, J = 4.2, 1.7 Hz, 1H), 8.19 (dd, J = 8.3, 1.6 Hz, 1H), 7.83 – 7.78 (m, 1H), 7.62 – 7.59 (m, 1H), 7.58 (dd, J = 8.3, 1.8 Hz, 1H), 7.47 (dd, J = 8.2, 4.2 Hz, 1H), 7.21 – 7.18 (m, 2H), 3.97 (q, J = 10.8 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4 (C_q), 163.4 (C_q, d, $^{1}J_{C–F}$ = 252.3 Hz), 148.4 (CH), 138.6 (C_q), 136.5 (CH), 134.5 (C_q), 133.8 (C_q, d, $^{4}J_{C–F}$ = 3.5 Hz), 132.6 (C_q, dq, $^{3}J_{C–F}$ = 8.3, 2.9 Hz), 129.8 (CH, d, $^{3}J_{C–F}$ = 9.2 Hz), 128.1 (C_q), 127.4 (CH), 125.7 (C_q, q, $^{1}J_{C–F}$ = 276.4 Hz), 122.3 (CH), 121.9 (CH), 119.7 (CH, d, $^{2}J_{C–F}$ = 21.9 Hz), 116.8 (CH), 115.5 (CH, d, $^{2}J_{C–F}$ = 20.6 Hz), 36.4 (CH_2, q, $^{2}J_{C–F}$ = 30.7 Hz).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -64.95 (t, J = 10.8 Hz), -108.36 – -109.18 (m).

IR (neat): $\tilde{\nu}$ = 3326, 1663, 1527, 1485, 1251, 1142, 1067, 915, 788, 593 cm^{-1}.

MS (EI): *m/z* (relative intensity) 348 (99) [M^+], 205 (100), 185 (98), 171 (15), 157 (25), 144 (71), 127 (35).

HR-MS (EI): m/z calcd for $C_{18}H_{12}F_4N_2O$ [M^+] 348.0886, found 348.0879.

84b':

M.p.: 181–182 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.14 (s, 1H), 8.91 (dd, J = 6.3, 2.6 Hz, 1H), 8.75 (dd, J = 4.2, 1.6 Hz, 1H), 8.20 (dd, J = 8.3, 1.6 Hz, 1H), 7.63 – 7.61 (m, 2H), 7.47 (dd, J = 8.3, 4.2 Hz, 1H), 7.22 (d, J = 8.9 Hz, 2H), 3.60 (q, J = 9.1 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.4 (C_q), 163.2 (C_q, d, $^1J_{C–F}$ = 249.1 Hz), 148.5 (CH), 138.5 (C_q), 136.6 (C_q, d, $^4J_{C–F}$ = 3.6 Hz), 136.2 (CH), 133.5 (C_q), 130.4 (C_q, dq, $^3J_{C–F}$ = 8.3, 2.8 Hz), 127.9 (C_q), 127.1 (CH), 125.1 (C_q, q, $^1J_{C–F}$ = 276.8 Hz), 122.8 (CH), 121.8 (CH), 118.1 (CH, d, $^2J_{C–F}$ = 22.8 Hz), 117.1 (CH), 37.6 (CH_2, q, $^2J_{C–F}$ = 29.5 Hz).

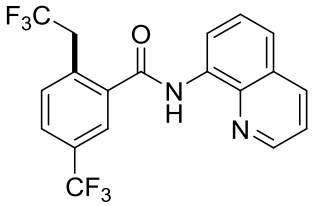
^{19}F NMR (283 MHz, $CDCl_3$): δ = -64.60 (t, J = 10.4 Hz), -109.92 (t, J = 8.9 Hz).

IR (neat): $\tilde{\nu}$ = 3356, 2924, 1666, 1527, 1486, 1280, 1243, 1124, 1085, 788 cm^{-1}.

MS (EI): *m/z* (relative intensity) 430 (10) [M^+], 287 (100), 267 (8), 247 (5), 144 (11).

HR-MS (EI): m/z calcd for $C_{20}H_{13}F_7N_2O$ [M^+] 430.0916, found 430.0922.

Synthesis of *N*-(Quinolin-8-yl)-2-(2,2,2-trifluoroethyl)-5-(trifluoromethyl)benzamide (84e)



The general procedure **C** was followed using **59e** (158 mg, 0.50 mmol) and **82** (210 mg, 1.00 mmol). After purification by column chromatography (*n*-hexane/DCM 2:1) **84e** (70 mg, 35%) was obtained as a white solid.

M.p.: 115–116 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.34 (s, 1H), 8.88 (dd, J = 5.1, 3.7 Hz, 1H), 8.81 (dd, J = 4.2, 1.6 Hz, 1H), 8.21 (dd, J = 8.3, 1.6 Hz, 1H), 8.01 (s, 1H), 7.78 (dd, J = 7.9, 1.4 Hz, 1H), 7.64 – 7.60 (m, 3H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 3.99 (q, J = 10.7 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1 (C_q), 148.7 (CH), 138.7 (C_q), 138.6 (C_q), 136.6 (CH), 134.3 (C_q), 133.5 (C_q), 133.2 (CH), 131.1 (C_q, q, $^2J_{C-F}$ = 33.6 Hz), 128.2 (C_q), 127.4 (CH), 127.3 (CH, q, $^3J_{C-F}$ = 3.4 Hz), 125.6 (C_q, q, $^1J_{C-F}$ = 277.3 Hz), 124.5 (CH, q, $^3J_{C-F}$ = 3.6 Hz), 123.6 (C_q, q, $^1J_{C-F}$ = 270.8 Hz), 122.6 (CH),122.0 (CH), 117.1 (CH), 36.5 (CH_2, q, $^2J_{C-F}$ = 30.0 Hz).

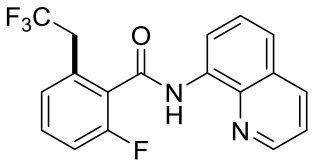
^{19}F NMR (283 MHz, $CDCl_3$): δ = -62.79 (s), -64.83 (t, J = 10.7 Hz).

IR (neat): $\tilde{\nu}$ = 3336, 1676, 1527, 1485, 1326, 1257, 1114, 1069, 785, 669 cm^{-1}.

MS (EI): *m/z* (relative intensity) 398 (86) [M^+], 255 (40), 235 (79), 207 (34), 171 (57), 144 (100), 130 (15).

HR-MS (EI): m/z calcd for $C_{19}H_{12}F_6N_2O$ [M^+] 398.0854, found 398.0853.

Synthesis of 2-Fluoro-*N*-(quinolin-8-yl)-6-(2,2,2-trifluoroethyl)benzamide (84f)



The general procedure **C** was followed using **59f** (133 mg, 0.50 mmol) and **82** (210 mg, 1.00 mmol). After purification by column chromatography (*n*-hexane/DCM 2:1) **84f** (51 mg, 29%) was obtained as a white solid.

M.p.: 155–156 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.32 (s, 1H), 8.93 (dd, J = 6.9, 1.9 Hz, 1H), 8.79 (dd, J = 4.2, 1.6 Hz, 1H), 8.18 (dd, J = 8.3, 1.6 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.49 – 7.44 (m, 2H), 7.27 (d, J = 7.5 Hz, 1H), 7.23 (dd, J = 8.9, 8.7 Hz, 1H), 3.82 (q, J = 10.7 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.6 (C_q), 159.7 (C_q, d, $^1J_{C-F}$ = 248.3 Hz), 148.6 (CH), 138.7 (C_q), 136.5 (CH), 134.3 (C_q), 131.5 (CH, d, $^3J_{C-F}$ = 8.3 Hz), 131.4 (C_q, d, $^3J_{C-F}$ = 5.7 Hz), 128.1 (C_q), 127.9 (CH, d, $^4J_{C-F}$ = 2.7 Hz), 127.9 (CH), 126.4 (C_q, d, $^2J_{C-F}$ = 17.3 Hz), 125.7 (C_q, q, $^1J_{C-F}$ = 275.7 Hz), 122.5 (CH), 121.9 (CH), 117.1 (CH), 116.3 (CH, d, $^2J_{C-F}$ = 22.5 Hz), 36.6 (CH_2, qd, $^{2,4}J_{C-F}$ = 30.7, 2.2 Hz).

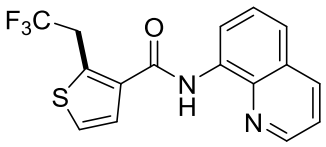
^{19}F NMR (283 MHz, $CDCl_3$): δ = -65.00 (t, J = 10.9 Hz), -113.53 (ddd, J = 9.5, 5.7, 1.0 Hz).

IR (neat): $\tilde{\nu}$ = 3343, 1672, 1526, 1486, 1262, 1099, 1061, 910, 784, 686 cm^{-1}.

MS (EI): *m/z* (relative intensity) 348 (81) [M^+], 261 (10), 205 (76), 185 (100), 171 (33), 144 (75), 127 (19).

HR-MS (EI): m/z calcd for $C_{18}H_{12}F_4N_2O$ [M^+] 348.0886, found 348.0884.

Synthesis of *N*-(Quinolin-8-yl)-2-(2,2,2-trifluoroethyl)thiophene-3-carboxamide (84g)



The general procedure **C** was followed using **59g** (127 mg, 0.50 mmol) and **82** (210 mg, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc 2:1) followed by GPC **84g** (33 mg, 19%) was obtained as a yellow solid.

M.p.: 128–129 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.48 (s, 1H), 8.86 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.83 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.18 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.60 – 7.54 (m, 3H), 7.48 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.41 (d, *J* = 5.3 Hz, 1H), 4.32 (q, *J* = 10.5 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.9 (C_q), 148.4 (CH), 138.7 (C_q), 136.70 (C_q, q, $^3J_{C–F}$ = 3.6 Hz), 136.5 (CH), 135.6 (C_q), 134.4 (C_q), 128.1 (C_q), 127.5 (CH), 126.3 (CH), 125.7 (CH), 125.1 (C_q, q, $^1J_{C–F}$ = 275.8 Hz), 122.0 (CH), 121.8 (CH), 116.7 (CH), 32.9 (CH_2, q, $^2J_{C–F}$ = 32.3 Hz).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -65.70 (t, *J* = 10.5 Hz).

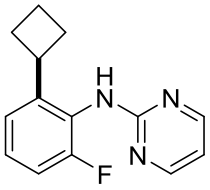
IR (neat): $\tilde{\nu}$ = 3363, 3096, 1661, 1540, 1524, 1355, 1248, 1137, 789, 654 cm^{-1}.

MS (EI): *m/z* (relative intensity) 336 (42) [M^+], 296 (17), 193 (39), 173 (41), 144 (100), 115 (9).

HR-MS (EI): m/z calcd for $C_{16}H_{11}F_3N_2OS$ [M^+] 336.0544, found 336.0546.

5.4.4 Analytical Data for C–H Secondary Alkylation of *N*-(2-Pyrimidyl)anilines 69

Synthesis of *N*-(2-Cyclobutyl-6-fluorophenyl)pyrimidin-2-amine (86ab)



The general procedure **D1** was followed using substrate **69a** (95 mg, 0.5 mmol), bromide **80b** (135 mg, 1.0 mmol), [(DME)$NiCl_2$] (2.8 mg, 2.5 mol %) and D*t*BEDA (5.5 µL, 5.0 mol %) at 100 °C. Isolation by column chromatography (*n*-hexane/EtOAc: 9/1) yielded **86ab** (108 mg, 89%) as a white solid.

M.p.: 121–122 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 4.8 Hz, 2H), 7.24 (ddd, *J* = 8.0, 8.0, 5.6 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.01 (ddd, *J* = 9.3, 7.8, 0.8 Hz, 1H), 6.94 (s, 1H), 6.65 (t, *J* = 4.8 Hz, 1H), 3.70 (p, *J* = 8.9 Hz, 1H), 2.31–2.23 (m, 2H), 2.16–2.08 (m, 2H), 1.99–1.89 (m, 1H), 1.85–1.75 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.6 (C_q), 158.6 (C_q, $^1J_{C\text{-}F}$ = 247.6 Hz), 158.3 (CH), 145.4 (C_q), 127.5 (CH, $^3J_{C\text{-}F}$ = 8.6 Hz), 123.9 (C_q, $^2J_{C\text{-}F}$ = 12.8 Hz), 122.2 (CH, $^4J_{C\text{-}F}$ = 3.0 Hz), 113.6 (CH, d, $^2J_{C\text{-}F}$ = 20.9 Hz), 112.2 (CH), 37.0 (CH, $^4J_{C\text{-}F}$ = 2.4 Hz), 29.3 (CH_2), 18.6 (CH_2).

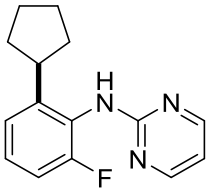
^{19}F NMR (283 MHz, $CDCl_3$): δ = -120.6 (dd, *J* = 9.6, 5.5 Hz).

IR (neat): $\tilde{\nu}$ = 3328, 2974, 2934, 1582, 1471, 1446, 1268, 782, 644, 496 cm^{-1}.

MS (EI): *m/z* (relative intensity) 243 (54) [M^+], 214 (80), 196 (100), 188 (35), 148(9), 135 (10), 107 (11).

HR-MS (EI): *m/z* calcd for $C_{14}H_{14}FN_3$ [M^+] 243.1172, found 243.1166.

Synthesis of *N*-(2-Cyclopentyl-6-fluorophenyl)pyrimidin-2-amine (86ac)



The general procedure **D1** was followed using substrate **69a** (189 mg, 1.0 mmol) and bromide **80c** (298 mg, 2.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 9/1) yielded **86ac** (230 mg, 90%) as a white solid.

M.p.: 117–118 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 4.8 Hz, 2H), 7.23 (ddd, *J* = 8.0, 8.0, 5.6 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.99 (ddd, *J* = 9.5, 8.0, 1.4 Hz, 1H), 6.95 (s, 1H), 6.65 (t, *J* = 4.8 Hz, 1H), 3.27 (p, *J* = 8.3 Hz, 1H), 2.05–1.98 (m, 2H), 1.82–1.74 (m, 2H), 1.66–1.53 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.0 (C_q), 158.9 (C_q, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 158.4 (CH), 146.8 (C_q), 128.0 (CH, $^{3}J_{C\text{-}F}$ = 9.0 Hz), 124.5 (C_q, $^{2}J_{C\text{-}F}$ = 12.6 Hz), 122.0 (CH, d, $^{4}J_{C\text{-}F}$ = 3.4 Hz), 113.3 (CH, $^{2}J_{C\text{-}F}$ = 20.3 Hz), 112.2 (CH), 40.5 (CH, $^{4}J_{C\text{-}F}$ = 2.3 Hz), 34.2 (CH_2), 25.8 (CH_2).

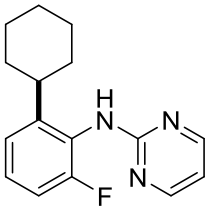
^{19}F NMR (283 MHz, $CDCl_3$): δ = -119.3 (dd, *J* = 9.5, 5.5 Hz).

IR (neat): $\tilde{\nu}$ = 3216, 2953, 2865, 1578, 1444, 1405, 1247, 789, 641 cm^{-1}.

MS (EI): *m/z* (relative intensity) 257 (51) [M^+], 241 (25), 188 (100), 107 (12).

HR-MS (EI): *m/z* calcd for $C_{15}H_{16}FN_3$ [M^+] 257.1328, found 257.1320.

Synthesis of *N*-(2-Cyclohexyl-6-fluorophenyl)pyrimidin-2-amine (86ad)



The general procedure **D1** was followed using substrate **69a** (189 mg, 1.0 mmol) and bromide **80d** (246 µL, 2.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **86ad** (270 mg, 98%) as a yellow solid.

The general procedure **D3** was followed using substrate **69a** (189 mg, 1.0 mmol) and bromide **80d** (246 µL, 2.0 mmol) at 100 °C. Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **86ad** (264 mg, 97%) as a yellow solid.

M.p.: 93–94 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 4.8 Hz, 2H), 7.21 (ddd, *J* = 8.0, 8.0, 4.0 Hz, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 6.97 (ddd, *J* = 9.6, 8.2, 1.3 Hz, 1H), 6.85 (s, 1H), 6.63 (t, *J* = 4.8 Hz, 1H), 2.85–2.78 (m, 1H), 1.83–1.73 (m, 4H), 1.72–1.65 (m, 1H), 1.43–1.33 (m, 2H), 1.33–1.15 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.9 (C_q), 158.6 (C_q, $^1J_{C\text{-}F}$ = 248.0 Hz), 158.2 (CH), 147.5 (C_q), 127.8 (CH, $^3J_{C\text{-}F}$ = 8.6 Hz), 123.6 (C_q, $^2J_{C\text{-}F}$ = 12.4 Hz), 122.0 (CH, $^4J_{C\text{-}F}$ = 3.3 Hz), 113.2 (CH, $^2J_{C\text{-}F}$ = 20.8 Hz), 112.1 (CH), 38.8 (CH, $^4J_{C\text{-}F}$ = 2.1 Hz), 33.7 (CH_2), 26.8 (CH_2), 26.1 (CH_2).

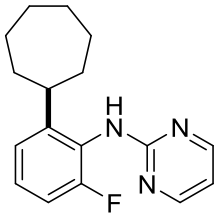
^{19}F NMR (282 MHz, $CDCl_3$) δ = -118.83 (dd, *J* = 9.8, 5.4 Hz).

IR (neat): $\tilde{\nu}$ = 3224, 2935, 2851, 1582, 1523, 1446, 1413, 1256, 958, 776, 641 cm^{-1}.

MS (EI) *m/z* (relative intensity) 271 (60) [M^+], 188 (100), 170 (5).

HR-MS (EI) *m/z* calcd for $C_{16}H_{18}FN_3$ [M^+] 271.1485, found 271.1486.

Synthesis of *N*-(2-Cycloheptyl-6-fluorophenyl)pyrimidin-2-amine (86ae)



The general procedure **D1** was followed using substrate **69a** (189 mg, 1.0 mmol) and bromide **80e** (354 mg, 2.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 9/1) yielded **86ae** (273 mg, 96%) as a white solid.

M.p.: 103–104 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 4.8 Hz, 2H), 7.48 (s, 1H), 7.22 (ddd, *J* = 8.2, 8.2, 5.6 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 6.98 (ddd, *J* = 9.6, 8.2, 1.4 Hz, 1H), 6.62 (t, *J* = 4.8 Hz, 1H), 3.02 (tt, *J* = 10.6, 3.4 Hz, 1H), 1.90–1.83 (m, 2H), 1.77–1.70 (m, 2H), 1.66–1.59 (m, 4H), 1.58–1.51 (m, 2H), 1.46–1.37 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.1 (C_q), 158.8 (C_q, $^1J_{C\text{-}F}$ = 249.9 Hz), 158.3 (CH), 149.8 (C_q), 128.0 (CH, $^3J_{C\text{-}F}$ = 8.8 Hz), 123.3 (C_q, $^2J_{C\text{-}F}$ = 12.5 Hz), 122.2 (CH, $^4J_{C\text{-}F}$ = 3.0 Hz), 113.0 (CH, $^2J_{C\text{-}F}$ = 21.1 Hz), 112.0 (CH), 40.8 (CH, $^4J_{C\text{-}F}$ = 2.1 Hz), 36.0 (CH_2), 27.9 (CH_2), 27.5 (CH_2).

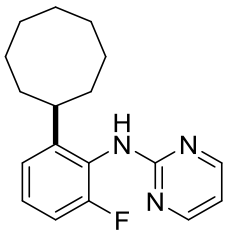
^{19}F NMR (283 MHz, $CDCl_3$): δ = -119.0 (ddd, *J* = 9.4, 5.5, 1.0 Hz).

IR (neat): $\tilde{\nu}$ = 3227, 2923, 2850, 1580, 1527, 1446, 1408, 1261, 970, 784 cm^{-1}.

MS (EI): *m/z* (relative intensity) 285 (58) [M^+], 242 (24), 228 (34), 201 (15), 188 (100), 148 (15), 94 (12), 43 (31).

HR-MS (EI): *m/z* calcd for $C_{17}H_{20}FN_3$ [M^+] 285.1641, found 285.1641.

Synthesis of *N*-(2-Cyclooctyl-6-fluorophenyl)pyrimidin-2-amine (86as)



The general procedure **D1** was followed using substrate **69a** (189 mg, 1.0 mmol) and bromide **80s** (382 mg, 2.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 9/1) yielded **86as** (270 mg, 90%) as a white solid.

M.p.: 111–112 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 4.8 Hz, 2H), 7.22 (ddd, *J* = 8.0, 8.0, 5.6 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.97 (ddd, *J* = 9.5, 8.2, 1.3 Hz, 1H), 6.71 (s, 1H), 6.65 (t, *J* = 4.8 Hz, 1H), 3.10 (tt, *J* = 9.6, 3.4 Hz, 1H), 1.81–1.75 (m, 2H), 1.74–1.67 (m, 4H), 1.62–1.56 (m, 1H), 1.55–1.51 (m, 4H), 1.50–1.44 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.0 (C_q), 158.8 (C_q, $^1J_{C\text{-}F}$ = 247.7 Hz), 158.4 (CH), 150.5 (C_q), 128.1 (CH, $^3J_{C\text{-}F}$ = 8.7 Hz), 123.2 (C_q, $^2J_{C\text{-}F}$ = 12.3 Hz), 122.7 (CH, $^4J_{C\text{-}F}$ = 3.5 Hz), 113.1 (CH, $^2J_{C\text{-}F}$ = 20.3 Hz), 112.2 (CH), 38.3 (CH, d, $^4J_{C\text{-}F}$ = 1.9 Hz), 34.3 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.3 (CH_2).

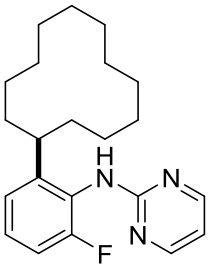
^{19}F NMR (283 MHz, $CDCl_3$): δ = -119.2 (ddd, *J* = 9.4, 5.5, 1.1 Hz).

IR (neat): $\tilde{\nu}$ = 3225, 2915, 2844, 1580, 1445, 1409, 1266, 785, 641cm^{-1}.

MS (EI): *m/z* (relative intensity) 299 (63) [M+], 242 (31), 228 (46), 214 (39), 188 (100), 148 (15), 94 (11).

HR-MS (EI): *m/z* calcd for $C_{18}H_{22}FN_3$ [M^+] 299.1798, found 299.1798.

Synthesis of *N*-(2-Cyclododecyl-6-fluorophenyl)pyrimidin-2-amine (86at)



The general procedure **D1** was followed using substrate **69a** (189 mg, 1.0 mmol) and bromide **80t** (494 mg, 2.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 85/15) yielded **86at** (330 mg, 93%) as a white solid.

M.p.: 166–167 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 4.8 Hz, 2H), 7.25 (ddd, *J* = 8.0, 8.0, 5.6 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 7.00 (ddd, *J* = 9.3, 8.1, 1.0 Hz, 1H), 6.70 (s, 1H), 6.63 (t, *J* = 4.8 Hz, 1H), 3.16 (tt, *J* = 6.6, 6.6 Hz, 1H), 1.79–1.71 (m, 2H), 1.48–1.42 (m, 2H), 1.39–1.29 (m, 6H), 1.29–1.16 (m, 10H), 1.16–1.07 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.1 (C_q), 159.0 (C_q, $^{1}J_{C\text{-}F}$ = 247.0 Hz), 158.4 (CH), 148.4 (C_q), 128.2 (CH, $^{3}J_{C\text{-}F}$ = 8.7 Hz), 124.5 (C_q, $^{2}J_{C\text{-}F}$ = 12.5 Hz), 122.9 (CH, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 113.2 (CH, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 112.1 (CH), 33.4 (CH, $J_{C\text{-}F}$ = 1.9 Hz), 31.4 (CH_2), 24.1 (CH_2), 24.0 (CH_2), 23.2 (CH_2), 23.0 (CH_2), 22.8 (CH_2).

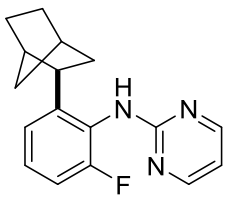
^{19}F NMR (283 MHz, $CDCl_3$): δ = -119.7 (dd, *J* = 9.5, 5.7 Hz).

IR (neat): $\tilde{\nu}$ = 3218, 2930, 2844, 1595, 1450, 1415, 796, 643, 511 cm^{-1}.

MS (EI): *m/z* (relative intensity) 355 (100) [M^+], 242 (21), 228 (35), 214 (40), 201 (39), 188 (98), 148 (12), 55 (21).

HR-MS (EI): *m/z* calcd for $C_{22}H_{30}FN_3$ [M^+] 355.2424, found 355.2419.

Synthesis of *N*-(2-*exo*-Norbornyl-6-fluorophenyl)pyrimidin-2-amine (86af)



The general procedure **D1** was followed using substrate **69a** (189 mg, 1.0 mmol) and *exo*-norbornyl bromide (**80f**) (350 mg, 2.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 85/15) yielded **86af** (260 mg, 92%) as a white solid.

M.p.: 128–129 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 4.8 Hz, 2H), 7.21 (ddd, *J* = 8.1, 8.1, 5.6 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 6.99 (ddd, *J* = 9.5, 8.2, 1.3 Hz, 1H), 6.94 (s, 1H), 6.64 (t, *J* = 4.8 Hz, 1H), 2.92 (dd, *J* = 8.9, 5.8 Hz, 1H), 2.41 (d, *J* = 3.0 Hz, 1H), 2.30 (s, 1H), 1.76 (ddd, *J* = 11.7, 9.1, 2.2 Hz, 1H), 1.59–1.52 (m, 3H), 1.51–1.45 (m, 1H), 1.28–1.18 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.7 (C_q), 159.2 (C_q, $^{1}J_{C\text{-}F}$ = 248.6 Hz), 158.3 (CH), 147.1 (C_q), 127.6 (CH, $^{3}J_{C\text{-}F}$ = 8.6 Hz), 124.4 (C_q, $^{2}J_{C\text{-}F}$ = 12.3 Hz), 121.3 (CH, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 113.3 (CH, $^{2}J_{C\text{-}F}$ = 20.7 Hz), 112.1 (CH), 42.7 (CH, $^{4}J_{C\text{-}F}$ = 2.2 Hz), 41.4 (CH_2), 39.3 (CH), 37.0 (CH), 36.6 (CH_2), 30.5 (CH_2), 28.9 (CH_2).

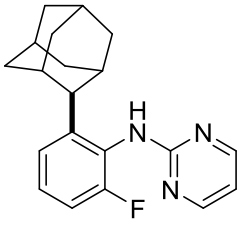
^{19}F NMR (283 MHz, $CDCl_3$): δ = -118.2 (dd, *J* = 9.4, 5.5 Hz).

IR (neat): $\tilde{\nu}$ = 3217, 2950, 2867, 1582, 1524, 1410, 1262, 933, 784, 641cm^{-1}.

MS (EI): *m/z* (relative intensity) 283 (86) [M^+], 254 (84), 214 (37), 201 (45), 188 (100), 148 (20).

HR-MS (EI): *m/z* calcd for $C_{17}H_{18}FN_3$ [M^+] 283.1485, found 283.1487.

Synthesis of *N*-(2-Adamantyl-6-fluorophenyl)pyrimidin-2-amine (86ag)



The general procedure **D1** was followed using substrate **69a** (189 mg, 1.0 mmol) and bromide **80g** (430 mg, 2.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 85/15) yielded **86ag** (284 mg, 87%) as a yellow solid.

The general procedure **D3** was followed using substrate **69a** (189 mg, 1.0 mmol) and bromide **80g** (430 mg, 2.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 85/15) yielded **86ag** (159 mg, 49%) as a yellow solid.

M.p.: 169–170 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32 (dd, *J* = 4.8, 0.6 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.24 (ddd, *J* = 8.0, 8.0, 5.4 Hz, 1H), 7.03 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.84 (s, 1H), 6.64 (td, *J* = 4.8, 0.6 Hz, 1H), 3.27 (s, 1H), 2.23 (s, 2H), 2.07–2.02 (m, 2H), 1.93–1.81 (m, 6H), 1.75 (s, 2H), 1.63 (d, *J* = 12.2 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.6 (C_q), 159.2 (C_q, $^{1}J_{C\text{-}F}$ = 247.9 Hz), 158.3 (CH), 145.3 (C_q), 127.3 (CH, d, $^{3}J_{C\text{-}F}$ = 8.7 Hz), 125.0 (C_q, $^{2}J_{C\text{-}F}$ = 12.2 Hz), 123.3 (CH, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 113.6 (CH, $^{2}J_{C\text{-}F}$ = 20.3 Hz), 112.1 (CH), 45.6 (CH, $^{4}J_{C\text{-}F}$ = 2.0 Hz), 40.3 (CH), 38.0 (CH_2), 32.8 (CH), 32.0 (CH), 28.1 (CH_2), 27.7 (CH_2).

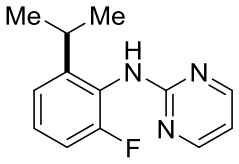
^{19}F NMR (283 MHz, $CDCl_3$): δ = -118.3 (dd, *J* = 9.4, 5.6 Hz).

IR (neat): $\tilde{\nu}$ = 3210, 2897, 2849, 1584, 1445, 1411, 995, 789, 641, 492 cm^{-1}.

MS (EI): *m/z* (relative intensity) 323 (66) [M^+], 295 (100), 266 (10), 201 (16), 188 (76), 170 (9).

HR-MS (EI): *m/z* calcd for $C_{20}H_{22}FN_3$ [M^+] 323.1798, found 323.1808.

Synthesis of *N*-(2-Fluoro-6-isopropylphenyl)pyrimidin-2-amine (86ai)



The general procedure **D1** was followed using substrate **69a** (189 mg, 1.0 mmol) and bromide **80i** (246 mg, 2.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 85/15) yielded **86ai** (219 mg, 95%) as a white solid.

M.p.: 131–132 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 4.8 Hz, 2H), 7.26 (ddd, *J* = 8.1, 8.1, 5.6 Hz, 1H), 7.17–7.12 (m, 2H), 7.00 (ddd, *J* = 9.5, 8.2, 1.3 Hz, 1H), 6.64 (t, *J* = 4.8 Hz, 1H), 3.26 (hept, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.1 (C_q), 158.9 (C_q, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 158.4 (CH), 148.8 (C_q), 128.1 (CH, $^{3}J_{C\text{-}F}$ = 8.5 Hz), 123.8 (C_q, $^{2}J_{C\text{-}F}$ = 12.7 Hz), 121.4 (CH, $^{4}J_{C\text{-}F}$ = 3.4 Hz), 113.4 (CH, $^{2}J_{C\text{-}F}$ = 20.8 Hz), 112.2 (CH), 28.6 (CH, $^{4}J_{C\text{-}F}$ = 2.3 Hz), 23.4 (CH_3).

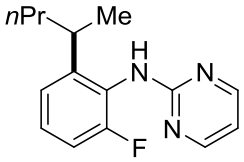
^{19}F NMR (283 MHz, $CDCl_3$): δ = -119.3 (dd, *J* = 9.6, 5.4 Hz).

IR (neat): $\tilde{\nu}$ = 3217, 2969, 2928, 1575, 1445, 1410, 1245, 954, 787, 638 cm^{-1}.

MS (EI): *m/z* (relative intensity) 231 (43) [M^+], 215 (22), 196 (10), 188 (100), 170 (6).

HR-MS (EI): *m/z* calcd for $C_{13}H_{14}FN_3$ [M^+] 231.1172, found 231.1171.

Synthesis of *N*-[2-Fluoro-6-(pentan-2-yl)phenyl]pyrimidin-2-amine (86am)



The general procedure **D1** was followed using substrate **69a** (189 mg, 1.0 mmol) and bromide **80m** (302 mg, 2.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 85/15) yielded **86am** (245 mg, 94%) as a white solid.

M.p.: 122–123 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 4.8 Hz, 2H), 7.25 (ddd, *J* = 8.0, 8.0, 5.4 Hz, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 6.99 (ddd, *J* = 9.5, 8.2, 1.4 Hz, 1H), 6.97 (s, 1H), 6.64 (t, *J* = 4.8 Hz, 1H), 3.09 (qt, *J* = 7.1, 7.1 Hz, 1H), 1.59–1.54 (m, 1H), 1.53–1.46 (m, 1H), 1.27–1.20 (m, 1H), 1.19 (d, *J* = 7.1 Hz, 3H), 1.17–1.10 (m, 1H), 0.79 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.0 (C_q), 158.9 (C_q, $^{1}J_{C\text{-}F}$ = 247.3 Hz), 158.3 (CH), 148.2 (C_q), 128.1 (CH, $^{3}J_{C\text{-}F}$ = 8.4 Hz), 124.2 (C_q, $^{2}J_{C\text{-}F}$ =12.7 Hz), 121.9 (CH, $^{4}J_{C\text{-}F}$ =3.5 Hz), 113.3 (CH, $^{2}J_{C\text{-}F}$ =20.8 Hz), 112.2 (CH), 40.3 (CH_2), 33.5 (CH, $^{4}J_{C\text{-}F}$ =2.1 Hz), 21.6 (CH_3), 20.9 (CH_2), 14.2 (CH_3).

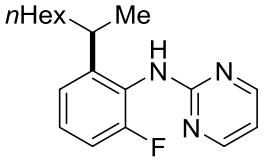
^{19}F NMR (283 MHz, $CDCl_3$): δ = -119.2 (dd, *J* = 9.4, 5.5 Hz).

IR (neat): $\tilde{\nu}$ = 3211, 2963, 2864, 1582, 1527, 1446, 1267, 957, 786, 641cm^{-1}.

MS (EI): *m/z* (relative intensity) 259 (22) [M^+], 240 (8), 230 (100), 217 (13), 202 (15), 188 (40).

HR-MS (EI): *m/z* calcd for $C_{15}H_{18}FN_3$ [M^+] 259.1485, found 259.1480.

Synthesis of *N*-[2-Fluoro-6-(octan-2-yl)phenyl]pyrimidin-2-amine (86as)



The general procedure **D1** was followed using substrate **69a** (189 mg, 1.0 mmol) and bromide **80s** (386 mg, 2.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 85/15) yielded **86as** (284 mg, 94%) as a white solid.

M.p.: 85–86 °C

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 4.8 Hz, 2H), 7.27–7.23 (m, 2H), 7.10 (d, *J* = 7.9 Hz, 1H), 7.00 (ddd, *J* = 9.5, 8.2, 1.3 Hz, 1H), 6.63 (t, *J* = 4.8 Hz, 1H), 3.08 (qt, *J* = 7.0, 7.0 Hz, 1H), 1.61–1.53 (m, 1H), 1.54–1.46 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.21–1.07 (m, 8H), 0.82 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.1 (C_q), 158.9 (C_q, $^1J_{C\text{-}F}$ = 247.7 Hz), 158.3 (CH), 148.2 (C_q), 128.1 (CH, $^3J_{C\text{-}F}$ = 8.7 Hz), 124.3 (C_q, $^2J_{C\text{-}F}$ = 12.8 Hz), 121.9 (CH, $^4J_{C\text{-}F}$ = 3.4 Hz), 113.2 (CH, $^2J_{C\text{-}F}$ = 21.0 Hz), 112.1 (CH), 38.1 (CH_2), 33.8 (CH, $^4J_{C\text{-}F}$ = 2.3 Hz), 31.8 (CH_2), 29.5 (CH_2), 27.7 (CH_2), 22.7 (CH_2), 21.7 (CH_3), 14.2 (CH_3).

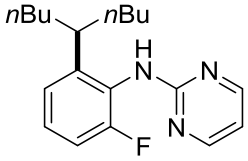
^{19}F NMR (283 MHz, $CDCl_3$) δ = -119.1 (dd, *J* = 9.4, 5.4 Hz).

IR (neat): $\tilde{\nu}$ = 3202, 2921, 2855, 1580, 1518, 1448, 1414, 943, 787, 640 cm^{-1}.

MS (EI): *m/z* (relative intensity) 301 (65) [M^+], 230 (100), 217 (40), 202 (41), 188 (93), 146 (15).

HR-MS (EI): *m/z* calcd for $C_{15}H_{18}FN_3$ [M^+] 301.1954, found 301.1960.

Synthesis of *N*-[2-Fluoro-6-(nonan-5-yl)phenyl]pyrimidin-2-amine (86at)



The general procedure **D1** was followed using substrate **69a** (189 mg, 1.0 mmol) and bromide **80t** (414 mg, 2.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/2) yielded **86at** (270 mg, 85%) as a yellow solid.

M.p.: 77–78 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 4.8 Hz, 2H), 7.24 (dd, *J* = 8.1, 5.5 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 6.99 (dd, *J* = 7.5, 9.2 Hz, 1H), 6.81 (br s, 1H), 6.62 (t, *J* = 4.8 Hz, 1H), 2.96 (tt, *J* = 8.6, 5.9 Hz, 1H), 1.65–1.57 (m, 2H), 1.57–1.50 (m, 2H), 1.24–1.02 (m, 8H), 0.77 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.8 (C_q), 158.9 (C_q, $^{1}J_{C\text{-}F}$ = 248.7 Hz), 158.1 (CH), 146.8 (C_q), 127.9 (CH, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 124.8 (C_q, $^{2}J_{C\text{-}F}$ = 12.7 Hz), 122.1 (CH, $^{4}J_{C\text{-}F}$ = 3.9 Hz), 113.0 (CH, $^{2}J_{C\text{-}F}$ = 21.4 Hz), 111.8 (CH), 39.3 (CH), 36.2 (CH_2), 29.8 (CH_2), 22.8 (CH_2), 13.9 (CH_3).

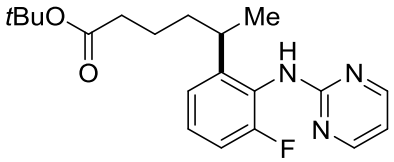
^{19}F NMR (283 MHz, $CDCl_3$): δ = -118.5 (dd, *J* = 9.57, 5.59 Hz).

IR (neat): $\tilde{\nu}$ = 3211, 2951, 2921, 1591, 1521, 1413, 1258, 912, 797, 617 cm^{-1}.

MS (EI): *m/z* (relative intensity) 315 (53) [M^+], 272 (100), 259 (31), 244 (40), 216 (24), 202 (31), 188 (53).

HR-MS (EI): m/z calcd for $C_{19}H_{26}FN_3$ [M^+] 315.2111, found 315.2117.

Synthesis of *tert*-Butyl-5-[3-fluoro-2-(pyrimidin-2-ylamino)phenyl]hexanoate (86au')



The general procedure **D1** was followed using **69a** (189 mg, 1.00 mmol) and **80u** (418 mg, 2.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 90:10) side product **86au'** (24 mg, 7%) was obtained as a white solid.

86au':

M.p.: 118–119 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 4.8 Hz, 2H), 7.28 – 7.23 (m, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.99 (ddd, *J* = 9.5, 8.2, 1.3 Hz, 1H), 6.66 (t, *J* = 4.8 Hz, 1H), 6.54 (s, 1H), 3.08 (tq, *J* = 6.9, 6.9 Hz, 1H), 2.12 (t, *J* = 7.3 Hz, 2H), 1.65 – 1.47 (m, 3H), 1.45 – 1.42 (m, 1H), 1.41 (s, 9H), 1.20 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9 (Cq), 161.9 (Cq), 158.8 (C_q, d, $^1J_{C–F}$ = 247.0 Hz), 158.3 (CH), 147.6 (C_q), 128.2 (CH, d, $^3J_{C–F}$ = 8.6 Hz), 124.2 (C_q, d, $^2J_{C–F}$ = 13.2 Hz), 121.8 (CH, d, $^4J_{C–F}$ = 3.5 Hz), 113.4 (CH, d, $^2J_{C–F}$ = 20.6 Hz), 112.3 (CH), 80.2 (C_q), 37.3 (CH_2), 35.7 (CH_2), 33.7 (CH, d, $^4J_{C–F}$ = 2.1 Hz), 28.3 (CH_3), 23.4 (CH_2), 21.8 (CH_3).

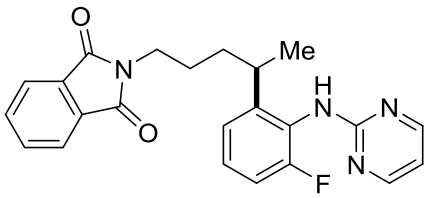
^{19}F NMR (283 MHz, $CDCl_3$): δ = -119.12 (dd, *J* = 9.5, 5.7 Hz).

IR (neat): $\tilde{\nu}$ = 3198, 2977, 2927, 2865, 1719, 1581, 1446, 1392, 1154, 787 cm^{-1}.

MS (EI): *m/z* (relative intensity) 359 (19) [M^+], 303 (12), 286 (25), 230 (33), 217 (23), 188 (100).

HR-MS (ESI): m/z calcd for $C_{20}H_{27}FN_3O_2$ [M+H^+] 360.2087, found 360.2084.

Synthesis of 2-{4-[3-fluoro-2-(pyrimidin-2-ylamino)phenyl]pentyl}isoindoline-1,3-dione (86ap)



The general procedure **D1** was followed using **69a** (189 mg, 1.0 mmol) and **80p** (592 mg, 2.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 2:1) **86ap** (324 mg, 80%) was obtained as a white solid.

M.p.: 61–62 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 4.8 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.67 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.23 (td, *J* = 8.0, 5.6 Hz, 1H), 7.12 (s, 1H), 7.07 (d, *J* = 7.9 Hz, 1H), 6.97 (dd, *J* = 8.9, 8.7 Hz, 1H), 6.61 (t, *J* = 4.8 Hz, 1H), 3.64 (dt, *J* = 14.3, 7.3 Hz, 1H), 3.56 (dt, *J* = 14.3, 7.3 Hz, 1H), 3.17 (tq, *J* = 6.9, 6.7 Hz, 1H), 1.67 – 1.51 (m, 4H), 1.20 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4 (C_q), 162.0 (C_q), 158.8 (C_q, d, $^1J_{C–F}$ = 247.3 Hz), 158.2 (CH), 147.5 (C_q), 133.9 (CH), 132.1 (C_q), 128.2 (CH, d, $^3J_{C–F}$ = 9.1 Hz), 124.5 (C_q, d, $^2J_{C–F}$ = 11.2 Hz), 123.2 (CH), 121.8 (CH, d, $^4J_{C–F}$ = 3.4 Hz), 113.4 (CH, d, $^2J_{C–F}$ = 21.5 Hz), 112.1 (CH), 37.9 (CH_2), 34.9 (CH_2), 32.9 (CH, d, $^4J_{C–F}$ = 1.4 Hz), 26.7 (CH_2), 21.9 (CH_3).

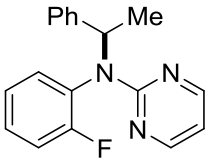
^{19}F NMR (283 MHz, $CDCl_3$): δ = -119.16 (dd, *J* = 9.4, 5.6 Hz).

IR (neat): $\tilde{\nu}$ = 3342, 3216, 2960, 2931, 1704, 1581, 1444, 1394, 788, 717 cm^{-1}.

MS (EI): *m/z* (relative intensity) 404 (25) [M$^+$], 244 (12), 230 (42), 217 (18), 188 (100), 160 (20).

HR-MS (EI): m/z calcd for $C_{23}H_{21}FN_4O_2$ [M$^+$] 404.1649, found 404.1647.

Synthesis of *N*-(2-Fluorophenyl)-*N*-(1-phenylethyl)pyrimidin-2-amine (86av'')



The general procedure **D1** was followed using substrate **69a** (189 mg, 1.0 mmol) and bromide **80v** (370 mg, 2.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 95/5) yielded **86av''** (246 mg, 84%) as a white solid.

M.p.: 96–97 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 4.7 Hz, 2H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.27 – 7.19 (m, 5H), 7.06 (t, *J* = 8.8 Hz, 1H), 6.97 (dd, *J* = 6.8, 6.8 Hz, 1H), 6.68 (bs, 1H), 6.57 (t, *J* = 4.7 Hz, 1H), 6.48 (q, *J* = 6.5 Hz, 1H), 1.53 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.7 (C_q), 160.0 (C_q, d, $^1J_{C\text{-}F}$ = 247.9 Hz), 157.8 (CH), 142.2 (C_q) 131.8 (CH, $^4J_{C\text{-}F}$ = 1.6 Hz), 128.8 (CH, d, $^3J_{C\text{-}F}$ = 7.5 Hz), 128.1 (CH), 128.0 (C_q), 127.8 (CH), 127.2 (CH), 124.0 (CH, d, $^3J_{C\text{-}F}$ = 4.9 Hz), 116.0 (CH, d, $^2J_{C\text{-}F}$ = 23.5 Hz), 111.1 (CH), 54.2 (CH), 17.0 (CH_3).

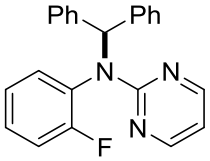
^{19}F NMR (283 MHz, $CDCl_3$): δ = -117.2 (bs).

IR (neat): $\tilde{\nu}$ = 3088, 2982, 2936, 1578, 1495, 1433, 1067, 798, 750, 593 cm^{-1}.

MS (EI) m/z (relative intensity) 293 (43) [M$^+$], 214 (9), 189 (28), 170 (100), 136 (4), 105 (45).

HR-MS (EI) m/z calcd for $C_{18}H_{16}FN_3$ [M$^+$] 293.1328, found 293.1332.

Synthesis of *N*-Benzhydryl-*N*-(2-fluorophenyl)pyrimidin-2-amine (86ao'')



The general procedure **D1** was followed using substrate **69** (189 mg, 1.0 mmol) and bromide **80o** (494 mg, 2.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 9/1) yielded **86ao''** (275 mg, 77%) as a yellow solid.

M.p.: 180–181 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (d, J = 4.8 Hz, 2H), 7.40 (s, 1H), 7.39 – 7.29 (m, 1H), 7.26 – 7.15 (m, 10H), 7.14 – 7.03 (m, 1H), 6.93 (ddd, J = 7.7, 7.7, 1.4 Hz, 1H), 6.82 (dd, J = 9.9, 8.1 Hz, 1H), 6.61 (t, J = 4.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.8 (C_q), 159.4 (C_q, d, $J_{C\text{-}F}$ = 247.7 Hz), 157.8 (CH), 140.8 (C_q), 130.8 (CH, d, $J_{C\text{-}F}$ = 1.5 Hz), 129.6 (C_q, d, $J_{C\text{-}F}$ = 12.6 Hz), 129.4 (CH), 128.5 (CH, d, $J_{C\text{-}F}$ = 7.2 Hz), 128.5 (CH), 127.8 (CH), 127.5 (C_q), 127.0 (CH), 126.5 (CH), 123.9 (CH), 111.6 (CH), 66.5 (CH).

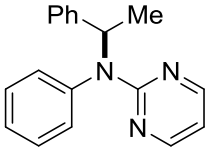
^{19}F NMR (283 MHz, $CDCl_3$): δ = -116.0 (ddd, J = 10.2, 7.6, 5.0 Hz).

IR (neat): $\tilde{\nu}$ = 3290, 3056, 2922, 1582, 1523, 1430, 1292, 1201, 1025, 736 cm^{-1}.

MS (EI) m/z (relative intensity) 355 (51) [M+], 276 (6), 185 (9), 167 (100), 152 (19).

HR-MS (EI) m/z calcd for $C_{23}H_{18}FN_3$ [M^+] 355.1485, found 355.1479.

Synthesis of *N*-Phenyl-*N*-(1-phenylethyl)pyrimidin-2-amine (86hv'')



The general procedure **D1** was followed using **69a** (128 mg, 0.75 mmol) and **80v** (153 mg, 1.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc 9:1) **86hv''** (118 mg, 57%) was obtained as a white solid.

M.p.: 92–93 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.30 (d, J = 4.8 Hz, 2H), 7.30 – 7.19 (m, 8H), 6.84 – 6.79 (m, 2H), 6.54 – 6.47 (m, 2H), 1.51 (d, J = 7.2 Hz, 3H).

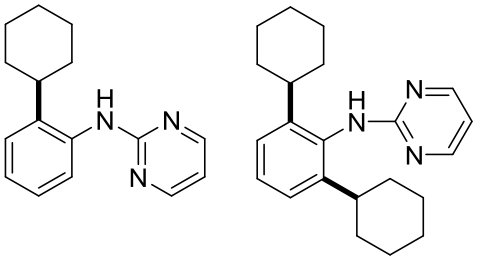
^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.3 (C_q), 157.7 (CH), 142.2 (C_q), 140.1 (C_q), 130.7 (CH), 128.8 (CH), 127.9 (CH), 127.8 (CH), 127.1 (CH), 127.0 (CH), 110.5 (CH), 53.7 (CH), 17.7 (CH_3).

IR (neat): $\tilde{\nu}$ = 2978, 2931, 1597, 1547, 1431, 1064, 962, 795, 698, 589 cm^{-1}.

MS (EI): *m/z* (relative intensity) 275 (38) [M^+], 260 (10), 196 (11), 170 (100), 105 (36), 77 (31).

HR-MS (ESI): m/z calcd for $C_{18}H_{18}N_3$ [$M+H^+$] 276.1501, found 276.1500.

Synthesis of *N*-(2-Cyclohexylphenyl)pyrimidin-2-amine (86hd) and *N*-(2,6-Dicyclohexylphenyl)pyrimidin-2-amine (86hd')



The general procedure **D2** was followed using **69h** (599 mg, 3.5 mmol) and **80d** (628 mg, 3.85 mmol). After purification by column chromatography (*n*-hexane/EtOAc 95:15) **86hd** (362 mg, 54%) and **86hd'** (150 mg, 13%) were obtained as a white solids.

86hd:

M.p.: 93–94 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 4.8 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.31 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.23 (ddd, *J* = 7.8, 7.7, 1.5 Hz, 1H), 7.16 (ddd, *J* = 7.8, 7.7, 1.2 Hz, 1H), 6.98 (s, 1H), 6.66 (t, *J* = 4.8 Hz, 1H), 2.76 (tt, *J* = 11.8, 3.0 Hz, 1H), 1.88 – 1.80 (m, 4H), 1.75 (d, *J* = 12.8 Hz, 1H), 1.49 – 1.33 (m, 4H), 1.27 (dtt, *J* = 12.9, 12.7, 3.4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.2 (C_q), 158.0 (CH), 140.1 (C_q), 135.5 (C_q), 126.4 (CH), 126.1 (CH), 125.1 (CH), 124.4 (CH), 112.0 (CH), 38.6 (CH), 33.6 (CH_2), 27.0 (CH_2), 26.3 (CH_2).

IR (neat): $\tilde{\nu}$ = 3224, 2922, 2848, 1571, 1516, 1442, 1402, 1253, 799, 752 cm^{-1}.

MS (EI): *m/z* (relative intensity) 253 (23) [M^+], 237 (8), 210 (6), 196 (12), 170 (100), 93 (9).

HR-MS (EI): m/z calcd for $C_{16}H_{19}N_3$ [M^+] 253.1579, found 253.1586.

86hd'

M.p.: 205–206 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 4.8 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 2H), 6.85 (s, 1H), 6.57 (t, *J* = 4.8 Hz, 1H), 2.77 (t, *J* = 11.7 Hz, 2H), 1.84 – 1.68 (m, 5H), 1.45 – 1.12 (m, 5H).

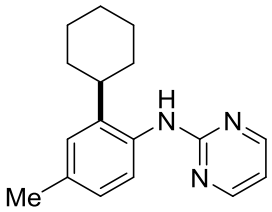
^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8 (C_q), 158.3 (CH), 146.0 (C_q), 132.9 (C_q), 128.0 (CH), 124.4 (CH), 111.2 (CH), 39.7 (CH), 34.2 (CH_2), 27.2 (CH_2), 26.4 (CH_2).

IR (neat): $\tilde{\nu}$ = 3222, 2921, 2847, 1601, 1578, 1527, 1445, 1412, 777 cm^{-1}.

MS (EI): *m/z* (relative intensity) 335 (4) [M^+], 280 (2), 252 (100), 208 (3), 196 (6).

HR-MS (EI): m/z calcd for $C_{22}H_{29}N_3$ [M^+] 335.2361, found 335.2348.

Synthesis of *N*-(2-Cyclohexyl-4-methylphenyl)pyrimidin-2-amine (86ld)



The general procedure **D3** was followed using **69l** (185 mg, 1.0 mmol) and **80d** (179 mg, 1.1 mmol). After purification by column chromatography (*n*-hexane/EtOAc 95:5) **86ld** (92 mg, 34%) was obtained as a white solid.

M.p.: 122–123 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 4.8 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.11 (s, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.83 (s, 1H), 6.63 (t, *J* = 4.8 Hz, 1H), 2.73 (tt, *J* = 11.9, 2.7 Hz, 1H), 2.34 (s, 3H), 1.81 (d, *J* = 10.9 Hz, 4H), 1.76 – 1.71 (m, 1H), 1.47 – 1.40 (m, 2H), 1.39 – 1.30 (m, 2H), 1.30 – 1.21 (m, 1H).

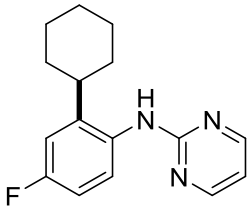
^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.8 (C_q), 158.2 (CH), 141.2 (C_q), 135.3 (C_q), 132.9 (C_q), 127.3 (CH), 127.0 (CH), 125.5 (CH), 111.9 (CH), 38.8 (CH), 33.9 (CH_2), 27.2 (CH_2), 26.5 (CH_2), 21.5 (CH_3).

IR (neat): $\tilde{\nu}$ = 3223, 2927, 2848, 1597, 1520, 1447, 1410, 797, 639 cm^{-1}.

MS (EI): *m/z* (relative intensity) 267 (18) [M^+], 251 (5), 210 (6), 184 (100), 144 (3), 107 (8).

HR-MS (EI): m/z calcd for $C_{17}H_{21}N_3$ [M^+] 267.1735, found 267.1731.

Synthesis of *N*-(2-Cyclohexyl-4-fluorophenyl)pyrimidin-2-amine (86kd)



The general procedure **D3** was followed using **69k** (189 mg, 1.0 mmol) and **80d** (179 mg, 1.1 mmol). After purification by column chromatography (*n*-hexane/EtOAc 95:5) **86kd** (162 mg, 60%) was obtained as a white solid.

M.p.: 119–120 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32 (d, J = 4.8 Hz, 2H), 7.54 (dd, J = 8.8, 5.6 Hz, 1H), 6.98 (dd, J = 10.2, 3.0 Hz, 1H), 6.89 (td, J = 8.3, 3.0 Hz, 1H), 6.83 (s, 1H), 6.64 (t, J = 4.8 Hz, 1H), 2.72 (t, J = 10.3 Hz, 1H), 1.84 – 1.76 (m, 4H), 1.75 – 1.69 (m, 1H), 1.40 – 1.18 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.6 (C_q), 160.5 (C_q, $^{1}J_{C–F}$ = 243.2 Hz), 158.2 (CH), 144.1 (C_q, $^{3}J_{C–F}$ = 6.6 Hz), 131.5 (C_q, $^{4}J_{C–F}$ = 2.2 Hz), 127.2 (C_q, $^{3}J_{C–F}$ = 7.8 Hz), 113.4 (CH, $^{2}J_{C–F}$ = 22.4 Hz), 113.0 (CH, $^{2}J_{C–F}$ = 21.5 Hz), 112.2 (CH), 39.0 (CH, $^{4}J_{C–F}$ = 1.5 Hz), 33.7 (CH_2), 27.0 (CH_2), 26.3 (CH_2).

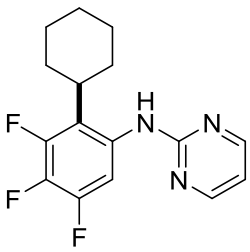
^{19}F NMR (376 MHz, $CDCl_3$): δ = -116.51 (ddd, J = 10.2, 5.6, 1.5 Hz).

IR (neat): $\tilde{\nu}$ = 3232, 2924, 2850, 1575, 1518, 1445, 1403, 1259, 1191, 799 cm^{-1}.

MS (EI): *m/z* (relative intensity) 271 (24) [M^+], 255 (8), 243 (5), 214 (11), 201 (6), 188 (100), 161 (6).

HR-MS (EI): m/z calcd for $C_{16}H_{18}FN_3$ [M^+] 271.1485, found 271.1496.

Synthesis of *N*-(2-Cyclohexyl-3,4,5-trifluorophenyl)pyrimidin-2-amine (86id)



The general procedure **D2** was followed using **69i** (225 mg, 1.0 mmol) and **80d** (179 mg, 1.1 mmol). After purification by column chromatography (*n*-hexane/EtOAc 9:1) **86id** (19 mg, 6%) was obtained as a white solid.

M.p.: 92–93 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 4.7 Hz, 2H), 7.45 (ddd, *J* = 11.6, 7.0, 2.0 Hz, 1H), 6.88 (s, 1H), 6.75 (t, *J* = 4.7 Hz, 1H), 2.80 (t, *J* = 12.2 Hz, 1H), 1.89 – 1.79 (m, 4H), 1.76 – 1.70 (m, 3H), 1.32 – 1.24 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.8 (C_q), 158.3 (CH), 125.4 (C_q, J_{C-F} = 10.9, 3.9, 1.2 Hz), 113.1 (CH), 108.8 (CH, J_{C-F} = 20.2, 3.0 Hz), 38.0 (CH), 31.0 (CH_2, J_{C-F} = 3.6 Hz), 27.2 (CH_2), 26.0 (CH_2). [4 C_q not observed]

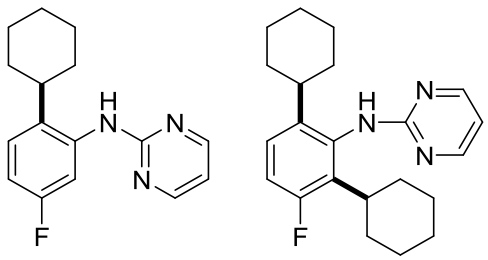
^{19}F NMR (283 MHz, $CDCl_3$): δ = -135.47 (d, *J* = 20.0 Hz), -138.02 (ddd, *J* = 21.8, 11.8, 6.3 Hz), -164.35 (ddd, *J* = 21.2, 21.0 7.1 Hz).

IR (neat): $\tilde{\nu}$ = 3225, 2937, 2848, 1585, 1505, 1443, 1409, 1117, 939, 625 cm^{-1}.

MS (EI): *m/z* (relative intensity) 307 (18) [M^+], 291 (4), 250 (8), 237 (5), 224 (100), 161 (8).

HR-MS (EI): m/z calcd for $C_{16}H_{16}F_3N_3$ [M^+] 307.1296, found 307.1289.

Synthesis of *N*-(2-Cyclohexyl-5-fluorophenyl)pyrimidin-2-amine (86jd) and *N*-(2,6-Dicyclohexyl-3-fluorophenyl)pyrimidin-2-amine (86jd')



The general procedure **D2** was followed using **69j** (95 mg, 0.5 mmol) and **80d** (90 mg, 0.55 mmol). After purification by column chromatography (*n*-hexane/EtOAc 95:5) **86jd** (33 mg, 26%) was obtained as a clear oil and **86jd'** (63 mg, 18%) was obtained as a white solid.

86la:

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 4.8 Hz, 2H), 7.84 (dd, *J* = 11.3, 2.7 Hz, 1H), 7.20 (dd, *J* = 8.7, 6.5 Hz, 1H), 6.98 (s, 1H), 6.80 (ddd, *J* = 8.3, 8.3, 2.7 Hz, 1H), 6.74 (t, *J* = 4.8 Hz, 1H), 2.66 (t, *J* = 9.0 Hz, 1H), 1.88 – 1.83 (m, 4H), 1.77 (dd, *J* = 13.3, 3.4 Hz, 1H), 1.45 – 1.39 (m, 4H), 1.31 – 1.24 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.0 (C_q, $^1J_{C-F}$ = 241.6 Hz), 160.5 (C_q), 158.2 (CH), 137.1 (C_q, $^3J_{C-F}$ = 10.1 Hz), 133.5 (C_q, $^4J_{C-F}$ = 3.4 Hz), 127.3 (CH, $^3J_{C-F}$ = 9.3 Hz), 112.9 (CH), 110.7 (CH, $^2J_{C-F}$ = 21.4 Hz), 109.5 (CH, $^2J_{C-F}$ = 25.1 Hz), 38.4 (CH), 33.9 (CH_2), 27.2 (CH_2), 26.4 (CH_2).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -116.08 (ddd, *J* = 11.8,, 11.0, 7.2 Hz).

IR (neat): $\tilde{\nu}$ = 3444, 2924, 2851, 1577, 1519, 1445, 1401, 1161, 992, 797 cm^{-1}.

MS (EI): *m/z* (relative intensity) 271 (48) [M$^+$], 255 (11), 242 (9), 228 (10), 214 (23), 201 (12), 188 (100), 161 (27).

HR-MS (EI): m/z calcd for $C_{16}H_{18}FN_3$ [M$^+$] 271.1485, found 271.1490.

86la'

M.p.: 210–211 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32 (s, 2H), 7.13 (dd, *J* = 8.7, 5.9 Hz, 1H), 6.98 (dd, *J* = 11.0, 8.8 Hz, 1H), 6.62 (t, *J* = 4.8 Hz, 1H), 6.47 (s, 1H), 2.80 (t, *J* = 12.2 Hz, 1H), 2.70 (t, *J* = 11.4 Hz, 1H), 1.89 – 1.63 (m, 12H), 1.39 – 1.11 (m, 7H), 1.06 – 0.94 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.7 (C_q), 160.6 (C_q, $^1J_{C-F}$ = 241.5 Hz), 158.4 (CH), 141.8 (C_q, $^4J_{C-F}$ = 2.9 Hz), 134.3 (C_q, $^3J_{C-F}$ = 7.7 Hz), 132.9 (C_q, $^2J_{C-F}$ = 13.2 Hz), 125.1 (CH, $^3J_{C-F}$ = 10.2 Hz), 115.8 (CH, $^2J_{C-F}$ = 23.5 Hz), 111.7 (CH), 39.5 (CH), 39.2 (CH), 34.3 (CH_2), 30.9 (CH_2), 27.3 (CH_2), 27.2 (CH_2), 26.4 (CH_2), 26.2 (CH_2).

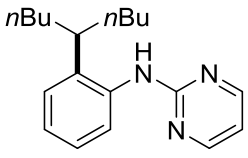
^{19}F NMR (283 MHz, $CDCl_3$): δ = -115.62 (d, *J* = 6.3 Hz).

IR (neat): $\tilde{\nu}$ = 3217, 2919, 2848, 1579, 1446, 1260, 1226, 1042, 811, 641 cm^{-1}.

MS (EI): *m/z* (relative intensity) 353 (5) [M$^+$], 298 (2), 270 (100), 226 (3), 214 (6), 200 (5).

HR-MS (EI): m/z calcd for $C_{22}H_{28}FN_3$ [M$^+$] 353.2267, found 353.2280.

Synthesis of *N*-[2-(Nonan-5-yl)phenyl]pyrimidin-2-amine (86ht)



The general procedure **D2** was followed using **69h** (128 mg, 0.75 mmol) and **80t** (171 mg, 0.83 mmol). After purification by column chromatography (*n*-hexane/EtOAc 9:1) **86ht** (134 mg, 60%) was obtained as a white solid.

M.p.: 68–69 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 4.8 Hz, 2H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.23 – 7.13 (m, 3H), 6.76 (s, 1H), 6.63 (t, *J* = 4.8 Hz, 1H), 2.84 (tt, *J* = 8.7, 5.8 Hz, 1H), 1.67 – 1.49 (m, 4H), 1.25 – 1.04 (m, 8H), 0.76 (t, *J* = 7.1 Hz, 6H).

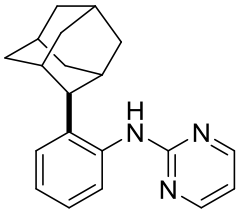
^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5 (C_q), 158.4 (CH), 139.7 (C_q), 136.7 (C_q), 127.1 (CH), 126.2 (CH), 125.6 (CH), 125.2 (CH), 112.2 (CH), 39.2 (CH), 36.3 (CH_2), 29.9 (CH_2), 23.0 (CH_2), 14.1 (CH_3).

IR (neat): $\tilde{\nu}$ = 3205, 2922, 2855, 1591, 1521, 1447, 1355, 995, 800, 641 cm^{-1}.

MS (EI): *m/z* (relative intensity) 297 (63) [M^+], 254 (92), 240 (63), 226 (44), 196 (27), 184 (66), 170 (100).

HR-MS (EI): m/z calcd for $C_{19}H_{27}N_3$ [M^+] 297.2205, found 297.2196.

Synthesis of *N*-[2-(2-Adamantyll)phenyl]pyrimidin-2-amine (86hg)



The general procedure **D2** was followed using **69h** (128 mg, 0.75 mmol) and **80g** (177 mg, 0.83 mmol). After purification by column chromatography (*n*-hexane/EtOAc 95:5) **86hg** (126 mg, 55%) was obtained as a white solid.

M.p.: 130–131 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 4.8 Hz, 2H), 7.87 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.14 (ddd, *J* = 7.9, 7.8, 1.3 Hz, 1H), 6.79 (s, 1H), 6.67 (t, *J* = 4.8 Hz, 1H), 3.16 (s, 1H), 2.27 (s, 2H), 2.09 (s, 1H), 2.05 (s, 1H), 2.01 – 1.93 (m, 4H), 1.92 – 1.87 (m, 1H), 1.78 (s, 2H), 1.67 (s, 1H), 1.63 (s, 2H).

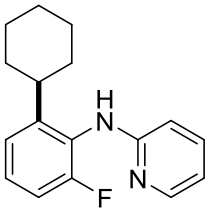
^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.8 (C_q), 158.2 (CH), 137.0 (C_q), 136.8 (C_q), 127.6 (CH), 126.2 (CH), 124.1 (CH), 123.8 (CH), 112.2 (CH), 45.2 (CH), 40.2 (CH_2), 37.9 (CH_2), 32.7 (CH_2), 31.5 (CH), 28.0 (CH), 27.5 (CH).

IR (neat): $\tilde{\nu}$ = 3224, 2899, 2845, 1579, 1519, 1443, 1407, 993, 798, 641 cm^{-1}.

MS (EI): *m/z* (relative intensity) 305 (53) [M^+], 289 (28), 277 (100), 248 (8), 208 (10), 184 (16), 170 (90).

HR-MS (EI): m/z calcd for $C_{20}H_{23}N_3$ [M^+] 305.1892, found 305.1879.

Synthesis of *N*-(2-Cyclohexyl-6-fluorophenyl)pyridin-2-amine (131)



The general procedure **D2** was followed using **123** (94 mg, 0.5 mmol) and **80d** (163 mg, 1.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 2:1), followed by GPC, **131** (6 mg, 5%) was obtained as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (s, 1H), 7.42 (ddd, *J* = 8.0, 7.7, 1.7 Hz, 1H), 7.25 – 7.18 (m, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 6.99 (ddd, *J* = 9.6, 8.0, 1.5 Hz, 1H), 6.70 – 6.65 (m, 1H), 6.24 (d, *J* = 6.8 Hz, 1H), 6.14 (s, 1H), 2.91 – 2.79 (m, 1H), 1.85 – 1.66 (m, 5H), 1.48 – 1.22 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.8 (C_q, $^1J_{C–F}$ = 246.6 Hz), 157.9 (C_q), 148.1 (CH), 147.9 (C_q), 137.9 (CH), 127.5 (CH, $^3J_{C–F}$ = 9.1 Hz), 124.8 (C_q, $^2J_{C–F}$ = 12.2 Hz), 122.4 (CH, $^4J_{C–F}$ = 3.5 Hz), 114.6 (CH), 113.6 (CH, $^2J_{C–F}$ = 20.7 Hz), 106.7 (CH), 38.9 (CH, $^4J_{C–F}$ = 2.2 Hz), 34.1 (CH_2), 27.0 (CH_2), 26.3 (CH_2).

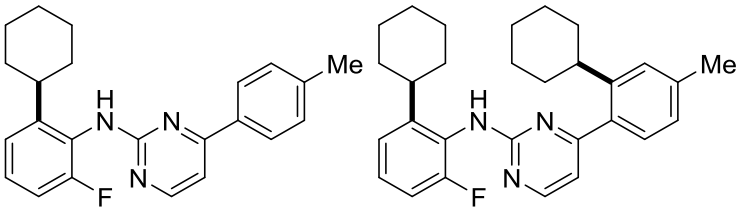
^{19}F NMR (283 MHz, $CDCl_3$): δ = -119.06 (ddd, *J* = 9.7, 5.5, 1.8 Hz).

IR (neat): $\tilde{\nu}$ = 3206, 2926, 2852, 1599, 1523, 1446, 1325, 1259, 958, 770 cm^{-1}.

MS (ESI): *m/z* (relative intensity) 271 (100) [M^+], 236 (9), 201 (1), 159 (3), 130 (2).

HR-MS (ESI): m/z calcd for $C_{17}H_{20}FN_2$ [M^+] 271.1610, found 271.1606.

Synthesis of *N*-(2-Cyclohexyl-6-fluorophenyl)-4-(*p*-tolyl)pyrimidin-2-amine (129) and 4-(2-Cyclohexyl-4-methylphenyl)-*N*-(2-cyclohexyl-6-fluorophenyl)pyrimidin-2-amine (129')



The general procedure **D1** was followed using **121** (279 mg, 1.0 mmol) and **80d** (326 mg, 2.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 95:5) **129** (262 mg, 72%) and **129'** (50 mg, 11%) were obtained as white solids.

129:

M.p.: 70–71 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 5.2 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.26 – 7.22 (m, 3H), 7.12 (d, *J* = 7.9 Hz, 1H), 7.08 (d, *J* = 5.3 Hz, 1H), 7.00 (ddd, *J* = 9.6, 8.1, 1.4 Hz, 1H), 6.57 (s, 1H), 2.89 (tt, *J* = 11.9, 3.2 Hz, 1H), 2.40 (s, 3H), 1.86 – 1.80 (m, 2H), 1.80 – 1.74 (m, 2H), 1.73 – 1.67 (m, 1H), 1.45 – 1.36 (m, 2H), 1.35 – 1.21 (m, 3H).

^{13}C NMR (76 MHz, $CDCl_3$): δ = 165.2 (C_q), 162.1 (C_q), 158.9 (C_q, $^1J_{C-F}$ = 246.3 Hz), 158.7 (CH), 147.7 (C_q), 141.1 (C_q), 134.5 (C_q), 129.6 (CH), 127.7 (CH, $^1J_{C-F}$ = 8.8 Hz), 127.1 (CH), 124.2 (C_q, $^1J_{C-F}$ = 12.5 Hz), 122.0 (CH, $^1J_{C-F}$ = 3.7 Hz), 113.3 (CH, $^1J_{C-F}$ = 20.7 Hz), 108.0 (CH), 39.0 (CH, $^1J_{C-F}$ = 2.4 Hz), 33.9 (CH_2), 26.9 (CH_2), 26.3 (CH_2), 21.6 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -118.69 (dd, *J* = 9.6, 5.5 Hz).

IR (neat): $\tilde{\nu}$ = 3219, 2923, 2850, 1575, 1549, 1443, 1280, 958, 801, 702 cm^{-1}.

MS (EI): *m/z* (relative intensity) 361 (63) [M^+], 342 (14), 304 (13), 278 (100), 251 (14), 237 (12), 184 (16).

HR-MS (EI): m/z calcd for $C_{23}H_{24}FN_3$ [M^+] 361.1954, found 361.1966.

129'

M.p.: 162–163 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 5.0 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.20 – 7.17 (m, 1H), 7.15 (s, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 6.8 Hz, 1H), 6.95 (dd, *J* = 8.9, 8.7 Hz, 1H), 6.72 (d, *J* = 5.0 Hz, 1H), 6.49 (s, 1H), 2.89 – 2.80 (m, 2H), 2.35 (s, 3H), 1.81 – 1.62 (m, 10H), 1.43 – 1.16 (m, 10H).

^{13}C NMR (76 MHz, $CDCl_3$): δ = 169.2 (C_q), 161.6 (C_q), 158.9 (C_q, $^1J_{C-F}$ = 247.3 Hz), 158.0 (CH), 147.5 (C_q), 145.8 (C_q), 139.1 (C_q), 135.2 (C_q), 129.3 (CH), 127.7 (CH, $^3J_{C-F}$ = 8.2 Hz), 127.5 (CH),

126.5 (CH), 124.0 (C_q, $^2J_{C-F}$ = 11.7 Hz), 122.0 (C_q, $^3J_{C-F}$ = 3.6 Hz), 113.3 (CH, $^2J_{C-F}$ = 20.2 Hz), 112.7 (CH), 39.8 (CH), 39.1 (CH, $^4J_{C-F}$ = 2.3 Hz), 34.6 (CH_2), 33.8 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 21.6 (CH_3).

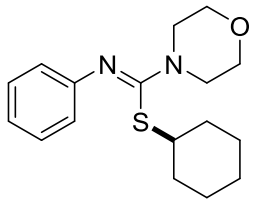
^{19}F NMR (283 MHz, $CDCl_3$): δ = -118.56 (dd, *J* = 9.7, 5.5 Hz).

IR (neat): $\tilde{\nu}$ = 3219, 2921, 2849, 1576, 1556, 1415, 961, 783, 708, 648 cm^{-1}.

MS (EI): *m/z* (relative intensity) 443 (100) [M^+], 400 (6), 388 (6), 360 (67), 319 (6), 226 (15), 208 (6).

HR-MS (EI): m/z calcd for $C_{29}H_{34}FN_3$ [M^+] 443.2737, found 443.2723.

Synthesis of Cyclohexyl-*N*-phenylmorpholine-4-carbimidothioate (133')



The general procedure **D1** was followed using **125** (222 mg, 1.0 mmol) and **80d** (326 mg, 2.0 mmol). After purification by column chromatography (n-hexane/EtOAc 3:1) **133'** (169 mg, 55%) was obtained as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.25 – 7.21 (m, 2H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 7.4 Hz, 2H), 3.73 – 3.70 (m, 4H), 3.66 – 3.63 (m, 4H), 2.55 (tt, *J* = 10.7, 3.6 Hz, 1H), 1.74 – 1.68 (m, 2H), 1.65 – 1.57 (m, 3H), 1.52 – 1.45 (m, 1H), 1.20 – 1.00 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.7 (C_q), 150.0 (C_q), 128.6 (CH), 122.3 (CH), 121.6 (CH), 67.0 (CH_2), 49.0 (CH_2), 45.1 (CH), 33.7 (CH_2), 26.1 (CH_2), 25.7 (CH_2).

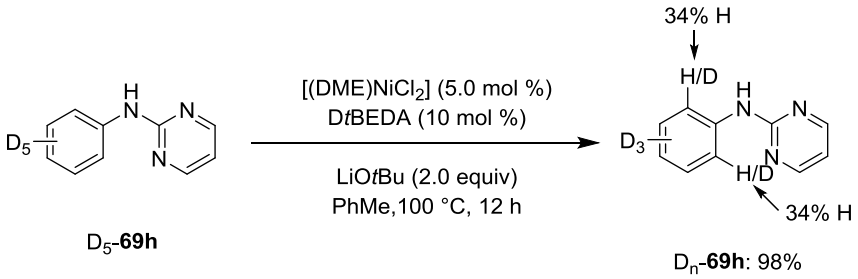
IR (neat): $\tilde{\nu}$ = 2926, 2851, 1577, 1447, 1194, 1111, 1022, 853, 763, 694 cm^{-1}.

MS (ESI): m/z (relative intensity) 327 (6), 305 (100) [M+H^+], 271 (3), 236 (11), 169 (3).

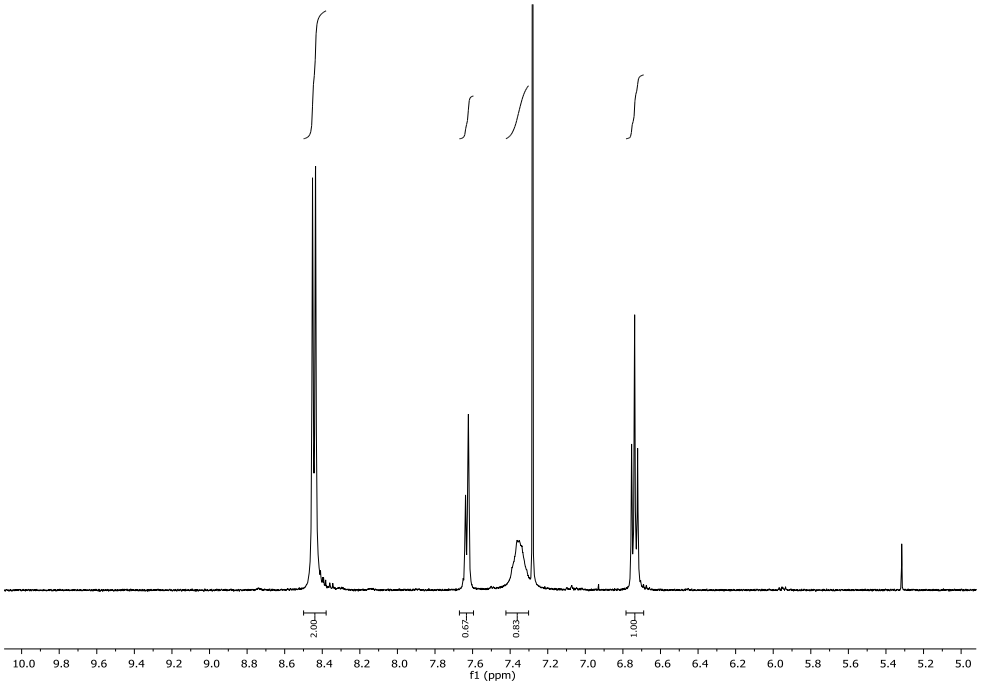
HR-MS (ESI): m/z calcd for $C_{17}H_{25}N_2OS$ [M+H^+] 305.1687, found 305.1685.

<u>Mechanistic studies</u>

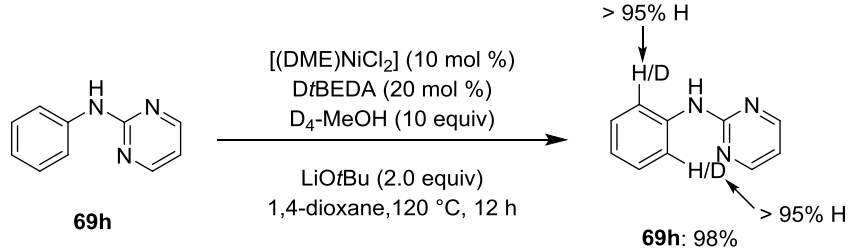
H/D exchange experiments with [D]$_5$-69h as the substrate:



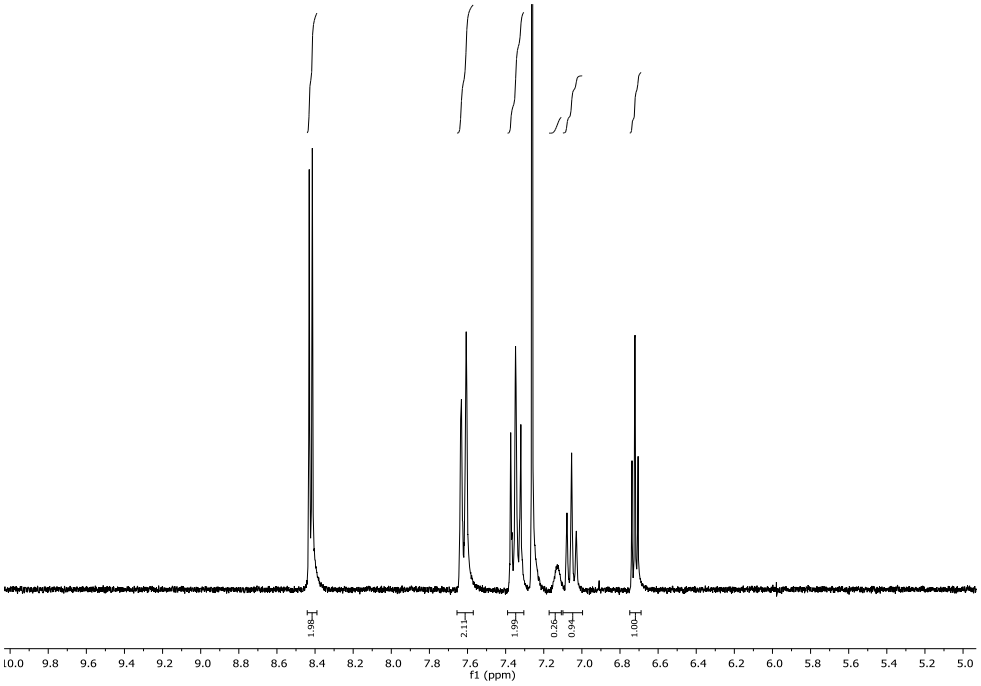
Following the general procedure **D1** [D]$_5$-**69h** (38 mg, 0.22 mmol) was reacted without alkyl halide **80**. After 12 h, the reaction was cooled to 0 °C, filtered through a silica pad and concentrated *in vacuo*, giving [D]$_n$-**69h** (36 mg, 98%).



H/D exchange experiments with 69h as the substrate:

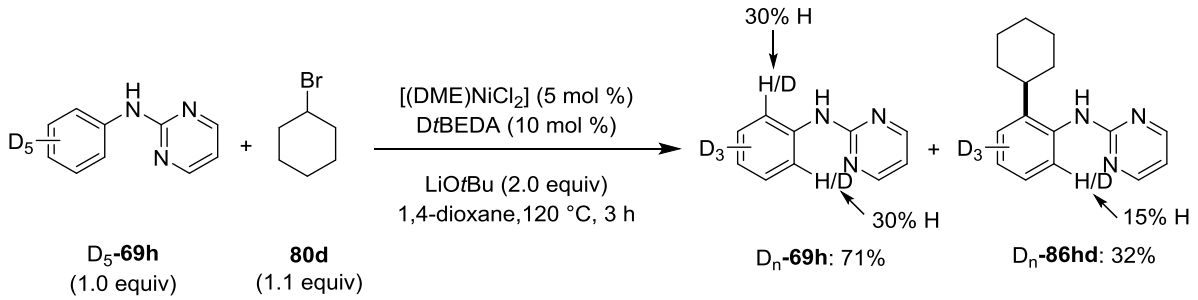


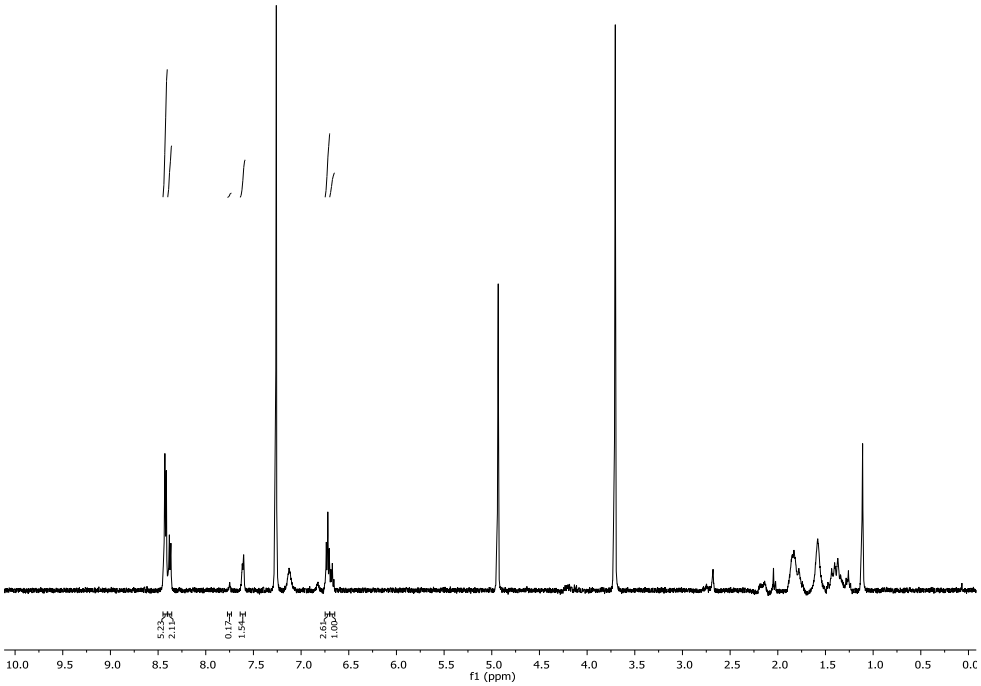
Following the general procedure **D1** **69h** (86 mg, 0.5 mmol) was reacted with D_4-MeOH (0.2 mL, 5.0 mmol). After 12 h, the reaction was cooled to 0 °C, filtered through a silica pad and concentrated *in vacuo*, giving $[D]_n$-**69h** (86 mg, 98%).



H/D exchange experiments with $[D]_5$-69h and 80d as the substrates:

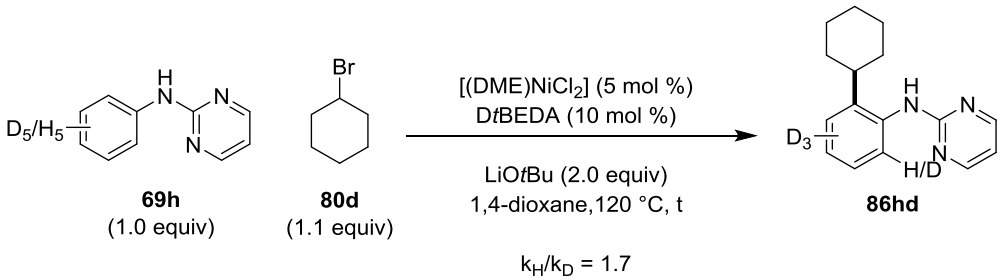
Following the general procedure **D2** $[D]_5$-**69h** (88 mg, 0.5 mmol) was reacted with **80d** (90 mg, 0.55 mmol). After 3.5 h, the reaction was cooled with an ice bath, filtered through a silica pad and concentrated *in vacuo*. The residue was analyzed by ^{1}H NMR spectroscopy. Yields of products were determined using CH_2Br_2 (49.5 mg, 0.28 mmol) as the internal standard.





KIE experiments with 69h and [D]$_5$-69h as the substrates

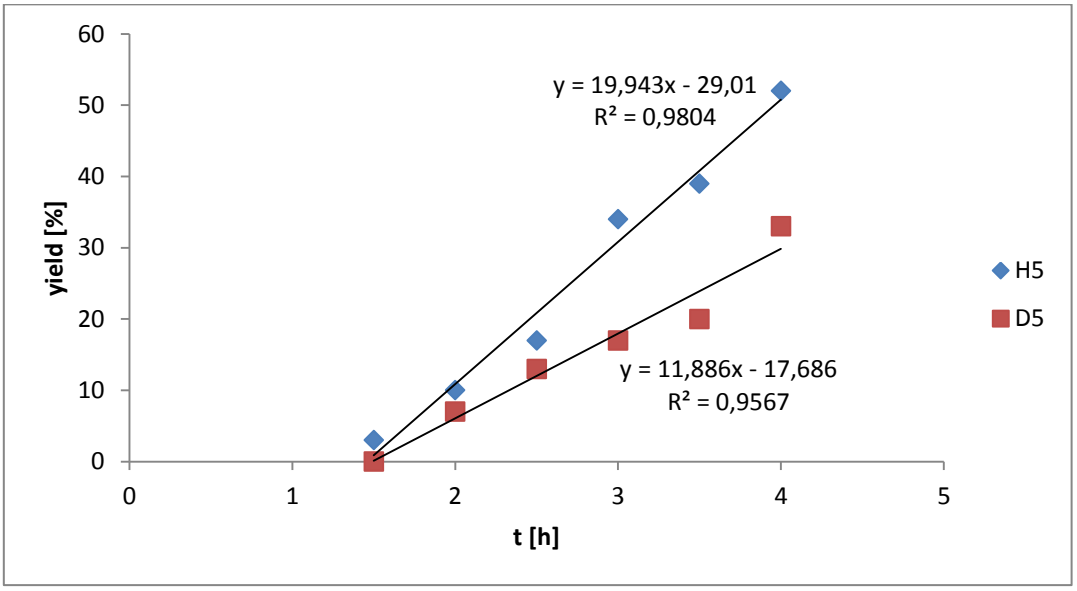
Parallel independent reactions with **69h** and [D]$_5$-**69h** were performed for different reaction times. Following general procedure **D1 69h** (86 mg, 0.5 mmol) or [D]$_5$-**69h** (88 mg, 0.5 mmol) were reacted with **80d** (90 mg, 0.55 mmol). After the reaction times indicated below, each reaction was cooled with an ice bath, filtered through a silica pad and concentrated *in vacuo*. The residue was analyzed by ^{1}H NMR spectroscopy. Yields of products were determined using CH_2Br_2 (49.5 mg, 0.28 mmol) as internal standard. For each reaction time the average of two reactions was obtained.



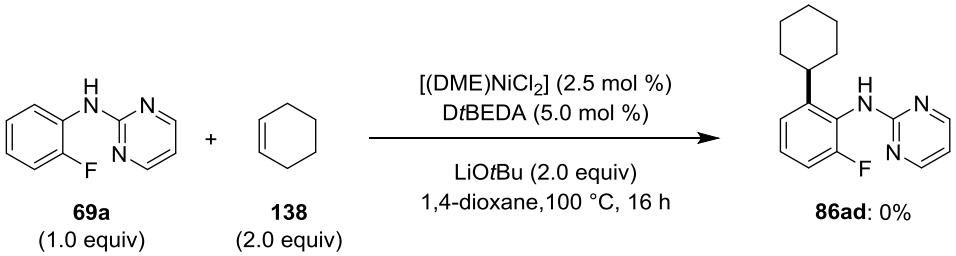
69h (1.0 equiv) **80d** (1.1 equiv) **86hd**

k_H/k_D = 1.7

t [h]	1.5	2.0	2.5	3.0	3.5	4.0
86hd	3	10	17	34	39	53
[D]$_n$-**86hd**	0	7	13	17	20	33

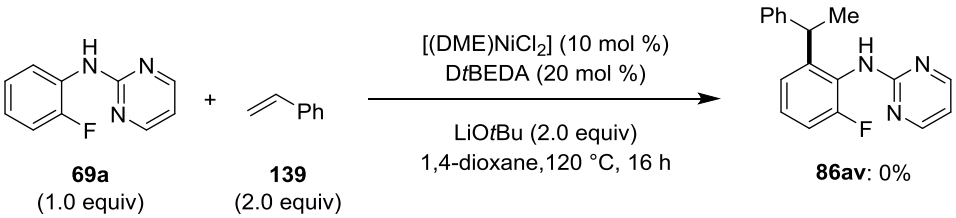


Reaction of aniline 69a with cyclohexene 138



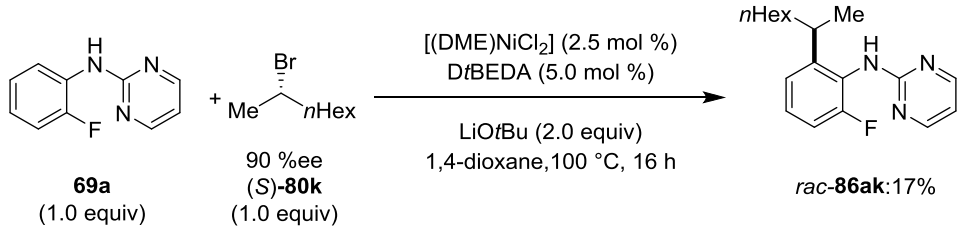
Following the general procedure **D1 69a** (189 mg, 1.0 mmol) was reacted with **138** (164 mg, 2.0 mmol). After cooling to ambient temperature, CH_2Cl_2 (2.0 mL) was added. No conversion was observed through ^{19}F NMR analysis of the crude reaction mixture.

Reaction of aniline 69a with styrene 139

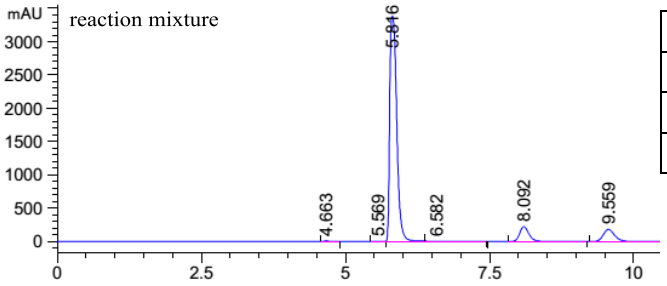


Following the general procedure **D1 69a** (189 mg, 1.0 mmol) was reacted with **139** (208 mg, 2.0 mmol). After cooling to ambient temperature, CH_2Cl_2 (2.0 mL) was added. No conversion was observed through ^{19}F NMR analysis of the crude reaction mixture.

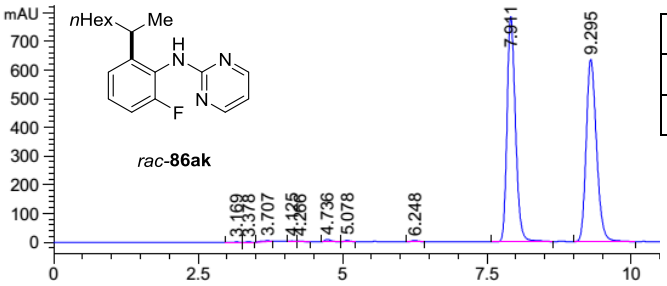
Reaction of aniline 69a with (*S*)-2-Bromooctane (80k)



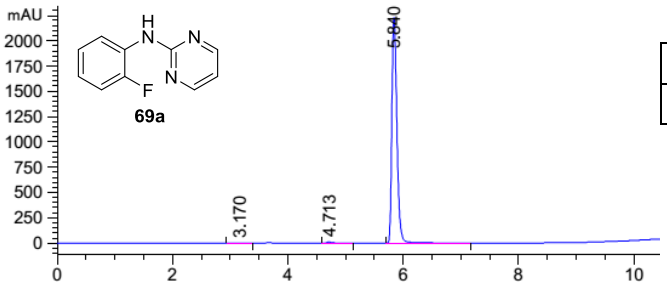
The general procedure **D2** was followed using substrate **69a** (189 mg, 1.0 mmol) and (S)-2-Bromooctane **(*S*)-80k** (193 mg, 1.0 mmol). Isolation by filtration through a silica pad (*n*-hexane/EtOAc: 85/15) yielded the mixture of **69a** and **86ak** as a white solid. Analysis by HPLC showed **86ak** to be racemic.



retention time	area	area %
5.81	28300	85.2
8.09	2452	7.4
9.56	2445	7.4



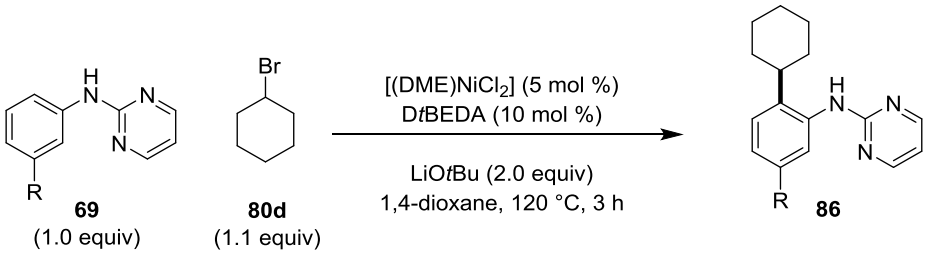
retention time	area	area %
7.91	7921	50.1
9.30	7894	49.9



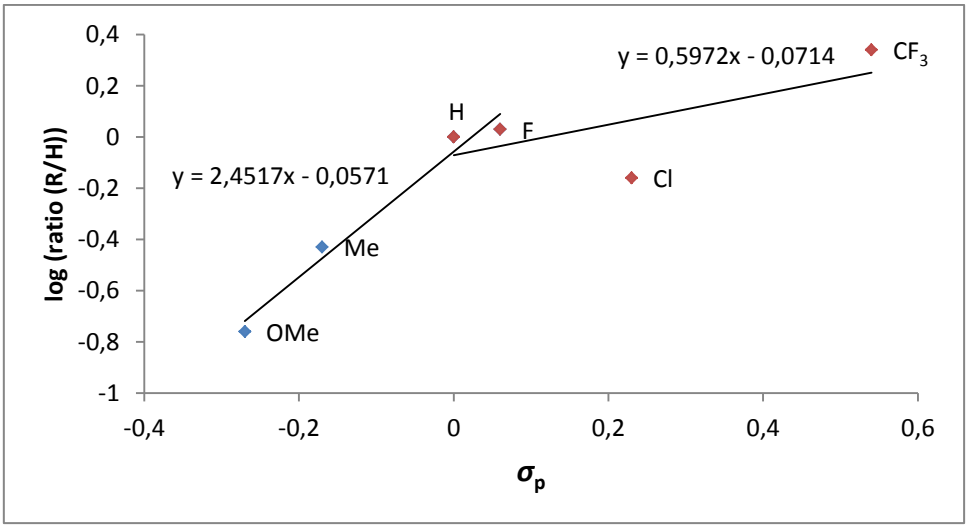
retention time	area	area %
5.84	13400	100

Hammett plot correlation for anilines 69

The general procedure **D2** was followed using anilines **69** (0.50 mmol) and cyclohexylbromide (**80d**) (90 mg, 0.55 mmol). After 3 h, the reaction mixture was cooled in an ice bath. The crude mixture was filtered through a celite pad and concentrated *in vacuo*. The residue was analyzed by ^{1}H NMR spectroscopy. Yields of products were determined using CH_2Br_2 (49.5 mg, 0.28 mmol) as the internal standard. For each substrate the average of two reactions was obtained.

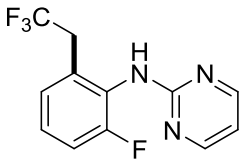


R	P	σ_p	Log (ratio (R/H)
OMe	6	- 0.27	-0.76
Me	13	- 0.17	-0.43
H	35	0.00	0
F	37	0.06	0.03
Cl	24	0.23	-0.16
CF_3	76	0.54	0.34



5.4.5 Analytical Data for C–H Fluoroalkylation of *N*-(2-Pyrimidyl)anilines 69

Synthesis of *N*-[2-Fluoro-6-(2,2,2-trifluoroethyl)phenyl]pyrimidin-2-amine (87a)



The general procedure **E1** was followed using **69a** (189 mg, 1.0 mmol) and **146** (489 mg, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87a** (147 mg, 54%) was obtained as a white solid.

The general procedure **E2** was followed using **69a** (189 mg, 1.0 mmol) and **146** (489 mg, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87a** (188 mg, 69%) was obtained as a white solid.

The general procedure **E3** was followed using **69a** (189 mg, 1.0 mmol) and **82** (420 mg, 2.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87a** (218 mg, 80%) was obtained as a white solid.

M.p.: 105–106 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 4.8 Hz, 2H), 7.30 (ddd, *J* = 8.3, 7.8, 5.4 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.17 (ddd, *J* = 9.6, 8.3, 1.4 Hz, 1H), 6.88 (s, 1H), 6.71 (t, *J* = 4.8 Hz, 1H), 3.52 (q, *J* = 10.7 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.4 (C_q), 159.0 (C_q, d, $^{1}J_{C–F}$ = 247.6 Hz), 158.3 (CH), 130.8 (C_q, q, $^{3}J_{C–F}$ = 2.7 Hz), 128.1 (CH, d, $^{3}J_{C–F}$ = 7.4 Hz), 126.8 (CH, q, $^{3}J_{C–F}$ = 2.7 Hz), 126.4 (C_q, q, $^{2}J_{C–F}$ = 13.0 Hz), 125.9 (C_q, q, $^{1}J_{C–F}$ = 277.1 Hz), 116.3 (CH, d, $^{2}J_{C–F}$ = 20.9 Hz), 112.9 (CH), 36.1 (CH_2, qd, $^{2,4}J_{C–F}$ = 30.4, 2.6 Hz).

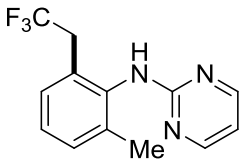
^{19}F NMR (283 MHz, $CDCl_3$): δ = -64.99 (t, *J* = 10.7 Hz), -117.63 (dd, *J* = 9.6, 5.0 Hz).

IR (neat): $\tilde{\nu}$ = 3234, 2963, 2921, 1576, 1449, 1407, 1258, 1096, 787, 638 cm^{-1}.

MS (EI): *m/z* (relative intensity) 271 (12) [M^+], 252 (27), 232 (17), 201 (8), 188 (100), 182 (3).

HR-MS (EI): m/z calcd for $C_{12}H_9F_4N_3$ [M^+] 271.0733, found 271.0743.

Synthesis of *N*-[2-Methyl-6-(2,2,2-trifluoroethyl)phenyl]pyrimidin-2-amine (87b)



The general procedure **E1** was followed using **69b** (185 mg, 1.0 mmol) and **146** (489 mg, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87b** (181 mg, 68%) was obtained as a pale brown solid.

The general procedure **E2** was followed using **69b** (185 mg, 1.0 mmol) and **146** (489 mg, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87b** (184 mg, 69%) was obtained as a pale brown solid.

The general procedure **E3** was followed using **69b** (185 mg, 1.0 mmol) and **82** (420 mg, 2.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87b** (190 mg, 71%) was obtained as a pale brown solid.

M.p.: 104–105 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32 (t, *J* = 4.8 Hz, 2H), 7.31 – 7.27 (m, 2H), 7.26 – 7.23 (m, 1H), 7.09 (s, 1H), 6.63 (t, *J* = 4.8 Hz, 1H), 3.45 (q, *J* = 10.3 Hz, 2H), 2.24 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.5 (C_q), 158.5 (CH), 137.7 (C_q), 136.4 (C_q), 131.0 (CH), 129.3 (CH), 129.1 (C_q, q, $^{3}J_{C-F}$ = 2.2 Hz), 127.6 (CH), 126.2 (C_q, q, $^{1}J_{C-F}$ = 277.6 Hz), 112.0 (CH), 36.5 (CH_2, q, $^{2}J_{C-F}$ = 29.4 Hz), 18.93 (CH_3).

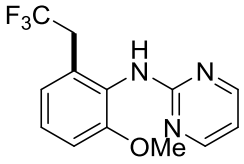
^{19}F NMR (283 MHz, $CDCl_3$): δ = -65.09 (t, *J* = 10.3 Hz).

IR (neat): $\tilde{\nu}$ = 3193, 2971, 2921, 1577, 1446, 1358, 1258, 1128, 791,639 cm^{-1}.

MS (EI): *m/z* (relative intensity) 267 (34) [M^{+}], 252 (38), 232 (18), 197 (7), 184 (100).

HR-MS (EI): m/z calcd for $C_{13}H_{12}F_3N_3$ [M^{+}] 267.0983, found 267.0993.

Synthesis of *N*-[2-Methoxy-6-(2,2,2-trifluoroethyl)phenyl]pyrimidin-2-amine (87c)



The general procedure **E1** was followed using **69c** (201 mg, 1.0 mmol) and **146** (489 mg, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87c** (94 mg, 33%) was obtained as a white solid.

The general procedure **E2** was followed using **69c** (201 mg, 1.0 mmol) and **146** (489 mg, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87c** (226 mg, 78%) was obtained as a white solid.

The general procedure **E3** was followed using **69c** (201 mg, 1.0 mmol) and **82** (420 mg, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87c** (140 mg, 50%) was obtained as a white solid.

M.p.: 118–119 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.33 (d, J = 4.8 Hz, 2H), 7.29 – 7.26 (m, 1H), 7.06 (d, J = 7.8 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.71 (s, 1H), 6.66 (t, J = 4.8 Hz, 1H), 3.78 (s, 3H), 3.49 (q, J = 11.0 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.0 (C_q), 158.3 (CH), 155.4 (C_q), 140.5 (C_q) 130.2 (C_q, q, $^{3}J_{C–F}$ = 2.6 Hz), 127.6 (CH), 126.2 (C_q, q, $^{1}J_{C–F}$ = 275.4 Hz), 122.8 (CH), 112.4 (CH), 111.2 (CH), 55.9 (CH_3), 36.2 (CH_2, q, $^{2}J_{C–F}$ = 29.9 Hz).

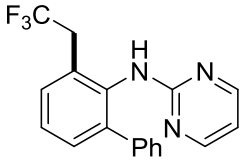
^{19}F NMR (283 MHz, $CDCl_3$): δ = -64.60 (t, J = 10.9 Hz).

IR (neat): $\tilde{\nu}$ = 3212, 3009, 2938, 2841, 1580, 1450, 1410, 1262, 1105, 795 cm^{-1}.

MS (EI): *m/z* (relative intensity) 283 (4) [M^+], 260 (52), 252 (100), 232 (54), 200 (32), 182 (25).

HR-MS (ESI): m/z calcd for $C_{13}H_{13}F_3N_3O$ [$M+H^+$] 284.1013, found 284.1007.

Synthesis of *N*-[3-(2,2,2-trifluoroethyl)-[1,1'-biphenyl]-2-yl]pyrimidin-2-amine (87e)



The general procedure **E2** was followed using **69e** (247 mg, 1.0 mmol) and **146** (489 mg, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87e** (257 mg, 77%) was obtained as a white solid.

The general procedure **E3** was followed using **69e** (247 mg, 1.0 mmol) and **82** (420 mg, 2.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87e** (270 mg, 82%) was obtained as a white solid.

M.p.: 159–160 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.21 (d, J = 4.8 Hz, 2H), 7.49 – 7.47 (m, 1H), 7.41 – 7.39 (m, 2H), 7.29 – 7.23 (m, 5H), 6.78 (s, 1H), 6.55 (t, J = 4.8 Hz, 1H), 3.51 (q, J = 10.9 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.5 (C_q), 158.2 (CH), 140.9 (C_q), 139.4 (C_q), 135.3 (C_q), 130.9 (CH), 130.6 (CH), 129.7 (C_q, q, $^{3}J_{C–F}$ = 2.8 Hz), 128.9 (CH), 128.2 (CH), 127.4 (CH), 127.4 (CH), 126.2 (C_q, q, $^{1}J_{C–F}$ = 276.9 Hz), 112.0 (CH), 36.5 (CH_2, q, $^{2}J_{C–F}$ = 27.8 Hz).

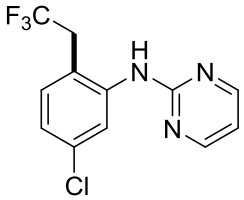
^{19}F NMR (283 MHz, $CDCl_3$): δ = -64.62 (t, J = 10.9 Hz).

IR (neat): $\tilde{\nu}$ = 3194, 3026, 2916, 1578, 1442, 1410, 1244, 1109, 1066, 759 cm^{-1}.

MS (EI): *m/z* (relative intensity) 329 (23) [M^+], 289 (6), 259 (9), 246 (100), 232 (10), 182 (5).

HR-MS (EI): m/z calcd for $C_{18}H_{14}F_3N_3$ [M^+] 329.1140, found 329.1138.

Synthesis of *N*-[5-Chloro-2-(2,2,2-trifluoroethyl)phenyl]pyrimidin-2-amine (87m)



The general procedure **E2** was followed using **69m** (206 mg, 1.0 mmol) and **146** (489 mg, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87m** (75 mg, 26%) was obtained as a white solid.

M.p.: 104–105 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 4.8 Hz, 2H), 7.89 (d, *J* = 2.2 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.17 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.01 (s, 1H), 6.77 (t, *J* = 4.8 Hz, 1H), 3.45 (q, *J* = 10.7 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.5 (C_q), 158.3 (CH), 139.2 (C_q), 134.8 (C_q), 132.9 (CH), 125.9 (C_q, q, $^{1}J_{C–F}$ = 275.1 Hz), 125.3 (CH), 125.2 (CH), 121.8 (C_q, q, $^{3}J_{C–F}$ = 2.6 Hz), 113.4 (CH), 36.0 (CH_2, q, $^{2}J_{C–F}$ = 30.7 Hz).

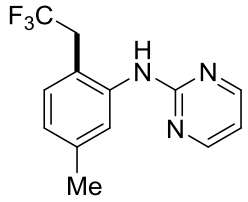
^{19}F NMR (283 MHz, $CDCl_3$): δ = -65.05 (t, *J* = 10.7 Hz).

IR (neat): $\tilde{\nu}$ = 3237, 3085, 1571, 1445, 1357, 1229, 1122, 1068, 798, 633 cm^{-1}.

MS (EI): *m/z* (relative intensity) 287 (10) [M^+], 266 (3), 247 (10), 217 (7), 204 (100), 182 (3).

HR-MS (EI): m/z calcd for $C_{12}H_9ClF_3N_3$ [M^+] 287.0437, found 287.0442.

Synthesis of *N*-[5-Methyl-2-(2,2,2-trifluoroethyl)phenyl]pyrimidin-2-amine (87n)



The general procedure **E2** was followed using **69n** (185 mg, 1.0 mmol) and **146** (489 mg, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87n** (85 mg, 32%) was obtained as a white solid.

M.p.: 99–100 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 4.8 Hz, 2H), 7.46 (s, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.06 – 7.02 (m, 2H), 6.69 (t, *J* = 4.8 Hz, 1H), 3.44 (q, *J* = 10.9 Hz, 2H), 2.37 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.2 (C_q), 158.3 (CH), 139.2 (C_q), 137.7 (C_q), 131.7 (CH), 126.9 (CH), 126.9 (CH), 126.2 (C_q, q, $^{1}J_{C–F}$ = 278.7 Hz), 122.1 (C_q, q, $^{3}J_{C–F}$ = 2.7 Hz), 112.5 (CH), 36.0 (CH_2, q, $^{2}J_{C–F}$ = 27.9 Hz), 21.5 (CH_3).

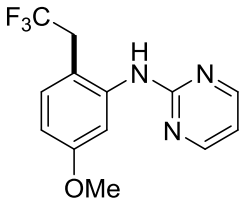
^{19}F NMR (283 MHz, $CDCl_3$): δ = -65.19 (t, *J* = 10.9 Hz).

IR (neat): $\tilde{\nu}$ = 3239, 3010, 1576, 1527, 1448, 1411, 1244, 1136, 1070, 789 cm^{-1}.

MS (EI): *m/z* (relative intensity) 267 (7) [M^+], 246 (2), 227 (4), 197 (4), 184 (100), 148 (2).

HR-MS (EI): m/z calcd for $C_{13}H_{12}F_3N_3$ [M^+] 267.0983, found 267.0984.

Synthesis of *N*-[5-Methoxy-2-(2,2,2-trifluoroethyl)phenyl]pyrimidin-2-amine (87o)



The general procedure **E2** was followed using **69o** (201 mg, 1.0 mmol) and **146** (489 mg, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87o** (85 mg, 30%) was obtained as a brown solid.

M.p.: 88–89 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.41 (d, J = 4.8 Hz, 2H), 7.38 (d, J = 2.7 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 6.89 (s, 1H), 6.79 – 6.70 (m, 2H), 3.82 (s, 3H), 3.41 (q, J = 10.9 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.1 (Cq), 160.0 (Cq), 158.2 (CH), 139.0 (Cq), 132.6 (CH), 126.2 (C_q, q, $^1J_{C–F}$ = 277.1 Hz), 116.2 (Cq), 112.8 (CH), 111.3 (CH), 111.2 (CH), 55.5 (CH_3), 35.7 (CH_2, q, $^2J_{C–F}$ = 29.3 Hz).

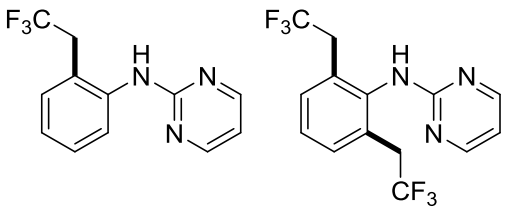
^{19}F NMR (283 MHz, $CDCl_3$): δ = -65.42 (t, J = 10.8 Hz).

IR (neat): $\tilde{\nu}$ = 3227, 3095, 3009, 1575, 1443, 1401, 1257, 1119, 1059, 798 cm^{-1}.

MS (ESI): *m/z* (relative intensity) 306 (22), 284 (100) [M+H^+], 257 (2), 227 (4), 159 (2).

HR-MS (ESI): m/z calcd for $C_{13}H_{13}F_3N_3O$ [M+H^+] 284.1010, found 284.1006.

Synthesis of *N*-[2-(2,2,2-trifluoroethyl)phenyl]pyrimidin-2-amine (87h) and *N*-[2,6-bis(2,2,2-trifluoroethyl)phenyl]pyrimidin-2-amine (87h')



The general procedure **E2** was followed using **69h** (171 mg, 1.0 mmol) and **146** (489 mg, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87h** (138 mg, 55%) and **87h'** (54 mg, 16%) were obtained as white solids.

87h

M.p.: 123–124 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 4.8 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.22 (dd, *J* = 7.6, 7.6, 1.1 Hz, 1H), 7.05 (s, 1H), 6.71 (t, *J* = 4.8 Hz, 1H), 3.49 (q, *J* = 10.8 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.1 (C_q), 158.3 (CH), 138.0 (C_q), 132.0 (CH), 129.2 (CH), 126.2 (CH), 126.1 (C_q, q, $^1J_{C–F}$ = 276.3 Hz), 125.8 (CH), 124.8 (C_q, q, $^3J_{C–F}$ = 2.3 Hz), 112.8 (CH), 36.3 (CH_2, q, $^2J_{C–F}$ = 29.6 Hz).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -65.02 (t, *J* = 10.8 Hz).

IR (neat): $\tilde{\nu}$ = 3251, 1580, 1518, 1444, 1356, 1245, 1135, 1068, 756, 653 cm^{-1}.

MS (EI): *m/z* (relative intensity) 253 (8) [M^+], 232 (3), 213 (5), 183 (4), 170 (100), 168 (3).

HR-MS (EI): m/z calcd for $C_{12}H_{10}F_3N_3$ [M^+] 253.0827, found 253.0826.

87h'

M.p.: 142–143 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 4.7 Hz, 2H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 6.93 (s, 1H), 6.68 (t, *J* = 4.7 Hz, 1H), 3.42 (br s, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.3 (C_q), 158.7 (CH), 137.3 (C_q), 131.9 (CH), 130.5 (C_q, q, $^3J_{C–F}$ = 2.5 Hz), 128.1 (CH), 125.9 (C_q, q, $^1J_{C–F}$ = 277.1 Hz), 112.5 (CH), 36.6 (CH_2, q, $^2J_{C–F}$ = 30.5 Hz).

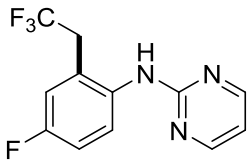
^{19}F NMR (283 MHz, $CDCl_3$): δ = -65.01 (t, *J* = 10.7 Hz).

IR (neat): $\tilde{\nu}$ = 3206, 2927, 1580, 1449, 1354, 1252, 1128, 1062, 777, 600 cm^{-1}.

MS (EI): *m/z* (relative intensity) 335 (13) [M^+], 295 (4), 275 (6), 265 (6), 252 (100), 232 (44), 226 (4), 182 (8).

HR-MS (EI): m/z calcd for $C_{14}H_{11}F_6N_3$ [M^+] 335.0857, found 335.0851.

Synthesis of *N*-[4-Fluoro-2-(2,2,2-trifluoroethyl)phenyl]pyrimidin-2-amine (87k)



The general procedure **E2** was followed using **69k** (189 mg, 1.0 mmol) and **146** (489 mg, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87k** (43 mg, 16%) was obtained as a white solid.

M.p.: 101–102 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.35 (d, J = 4.8 Hz, 2H), 7.56 (dd, J = 8.5, 5.3 Hz, 1H), 7.12 – 7.08 (m, 2H), 6.89 (s, 1H), 6.71 (t, J = 4.8 Hz, 1H), 3.46 (q, J = 10.7 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.3 (C_q), 160.2 (C_q, d, $^{1}J_{C–F}$ = 245.7 Hz), 158.3 (CH), 134.0 (C_q, d, $^{4}J_{C–F}$ = 2.9 Hz), 128.8 (CH, d, $^{3}J_{C–F}$ = 9.2 Hz), 127.8 (C_q, dq, $^{3,3}J_{C–F}$ = 7.8, 2.6 Hz), 125.9 (C_q, q, $^{1}J_{C–F}$ = 277.1 Hz), 118.3 (CH, d, $^{2}J_{C–F}$ = 24.0 Hz), 116.3 (CH, d, $^{2}J_{C–F}$ = 21.3 Hz), 112.8 (CH), 36.3 (CH_2, qd, $^{2,4}J_{C–F}$ = 30.3, 1.3 Hz).

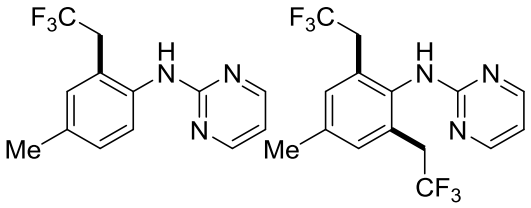
^{19}F NMR (283 MHz, $CDCl_3$): δ = -64.98 (t, J = 10.7 Hz), -115.71 (ddd, J = 8.4, 8.4, 5.3 Hz).

IR (neat): $\tilde{\nu}$ = 3206, 2928, 1581, 1412, 1255, 1209, 1129, 1070, 802, 541 cm^{-1}.

MS (EI): *m/z* (relative intensity) 271 (13) [M^+], 250 (4), 231 (9), 201 (5), 188 (100), 178 (2), 100 (2).

HR-MS (EI): m/z calcd for $C_{12}H_9F_4N_3$ [M^+] 271.0733, found 271.0735.

Synthesis of *N*-[4-Methyl-2-(2,2,2-trifluoroethyl)phenyl]pyrimidin-2-amine (87l) and *N*-[4-Methyl-2,6-bis(2,2,2-trifluoroethyl)phenyl]pyrimidin-2-amine (87l')



The general procedure **E2** was followed using **69l** (185 mg, 1.0 mmol) and **146** (326 mg, 2.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87l** (114 mg, 43%) and **87l'** (19 mg, 6%) were obtained as white solids.

87l:

M.p.: 114–115 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 4.8 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.21 – 7.18 (m, 2H), 6.99 (s, 1H), 6.67 (t, *J* = 4.8 Hz, 1H), 3.44 (q, *J* = 10.9 Hz, 2H), 2.36 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.5 (C_q), 158.3 (CH), 136.0 (C_q), 135.3 (C_q), 132.4 (CH), 130.0 (CH), 126.9 (CH), 126.2 (C_q, q, $^1J_{C–F}$ = 276.3 Hz), 125.4 (C_q, q, $^3J_{C–F}$ = 2.5 Hz), 112.4 (CH), 36.2 (CH_2, q, $^2J_{C–F}$ = 29.8 Hz), 21.2 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -65.03 (t, *J* = 10.9 Hz).

IR (neat): $\tilde{\nu}$ = 3292, 1581, 1513, 1445, 1399, 1245, 1124, 1069, 795, 608 cm^{-1}.

MS (EI): *m/z* (relative intensity) 267 (9) [M^+], 246 (3), 227 (4), 197 (3), 184 (100), 148 (2).

HR-MS (EI): m/z calcd for $C_{13}H_{12}F_3N_3$ [M^+] 267.0983, found 267.0980.

87l':

M.p.: 126–127 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 4.8 Hz, 2H), 7.26 (s, 2H), 7.10 (s, 1H), 6.65 (t, *J* = 4.8 Hz, 1H), 3.37 (br s, 4H), 2.39 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.4 (C_q), 158.7 (CH), 138.1 (C_q), 134.6 (C_q), 132.6 (CH), 130.1 (C_q, q, $^3J_{C–F}$ = 1.9 Hz), 126.0 (C_q, q, $^1J_{C–F}$ = 276.5 Hz), 112.4 (CH), 36.5 (CH_2, q, $^2J_{C–F}$ = 29.9 Hz), 21.3 (CH_3).

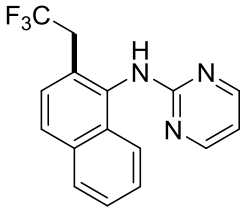
^{19}F NMR (283 MHz, $CDCl_3$): δ = -64.99 (t, *J* = 10.8 Hz).

IR (neat): $\tilde{\nu}$ = 3223, 2922, 1585, 1517, 1256, 1234, 1139, 1079, 801, 639 cm^{-1}.

MS (EI): *m/z* (relative intensity) 349 (5) [M^+], 309 (2), 279 (2), 266 (100), 246 (11), 196 (3).

HR-MS (EI): m/z calcd for $C_{15}H_{13}F_6N_3$ [M^+] 349.1014, found 349.1019.

Synthesis of *N*-[2-(2,2,2-trifluoroethyl)naphthalen-1-yl]pyrimidin-2-amine (87g)



The general procedure **E2** was followed using **69g** (221 mg, 1.0 mmol) and **146** (489 mg, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc 3:1), followed by GPC purification, **87g** (135 mg, 45%) was obtained as a white solid.

M.p.: 149–150 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.26 (d, J = 4.8 Hz, 2H), 8.03 (d, J = 8.4 Hz, 1H), 7.93 (s, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.55 – 7.48 (m, 2H), 6.61 (t, J = 4.8 Hz, 1H), 3.66 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.3 (C_q), 158.5 (CH), 134.4 (C_q), 134.1 (C_q), 131.7 (C_q), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.0 (CH), 126.7 (C_q, q, $^{3}J_{C–F}$ = 2.2 Hz), 126.6 (CH), 126.3 (C_q, q, $^{1}J_{C–F}$ = 277.1 Hz), 123.6 (CH), 112.1 (CH), 36.7 (CH_2, q, $^{2}J_{C–F}$ = 30.2 Hz).

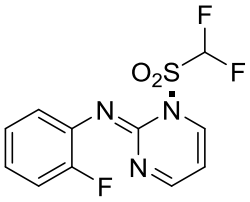
^{19}F NMR (283 MHz, $CDCl_3$): δ = -64.59 (t, J = 10.8 Hz).

IR (neat): $\tilde{\nu}$ = 3206, 3008, 2929, 1589, 1448, 1265, 1140, 1064, 812, 516 cm^{-1}.

MS (EI): *m/z* (relative intensity) 303 (17) [M^+], 282 (2), 263 (9), 232 (5), 220 (100), 192 (2).

HR-MS (EI): m/z calcd for $C_{16}H_{12}F_3N_3$ [M^+] 303.0983, found 303.0974.

Synthesis of 1-[(Difluoromethyl)sulfonyl]-*N*-(2-fluorophenyl)pyrimidin-2(1*H*)-imine (157a)



The general procedure **E2** was followed using **69a** (57 mg, 0.3 mmol) and Langlois' reagent (94 mg, 0.6 mmol). After purification by column chromatography (*n*-hexane/EtOAc 85:18), **157a** (4 mg, 4%) was obtained as a yellow solid.

M.p.: 130–132 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (dd, J = 3.6, 2.5 Hz, 1H), 7.70 (t, J = 60.2 Hz, 1H), 7.56 (dd, J = 7.2, 2.5 Hz, 1H), 7.12 – 6.92 (m, 4H), 6.01 (dd, J = 7.2, 3.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.7 (CH), 154.7 (C_q, d, $^{1}J_{C–F}$ = 244.4 Hz), 147.4 (C_q), 138.1 (CH, t, $^{4}J_{C–F}$ = 2.6 Hz), 135.3 (C_q, d, $^{2}J_{C–F}$ = 11.5 Hz), 124.6 (CH, d, $^{4}J_{C–F}$ = 2.4 Hz), 124.1 (CH, d, $^{3}J_{C–F}$ = 3.8 Hz), 124.0 (CH, d, $^{3}J_{C–F}$ = 7.4 Hz), 115.8 (CH, d, $^{4}J_{C–F}$ = 20.5 Hz), 108.6 (CH, t, $^{1}J_{C–F}$ = 255.6 Hz), 102.4 (CH).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -104.02 (d, J = 60.2 Hz), -124.96 – -125.11 (m).

IR (neat): $\tilde{\nu}$ = 3503, 3094, 1678, 1568, 1499, 1411, 1310, 1075, 746, 693 cm^{-1}.

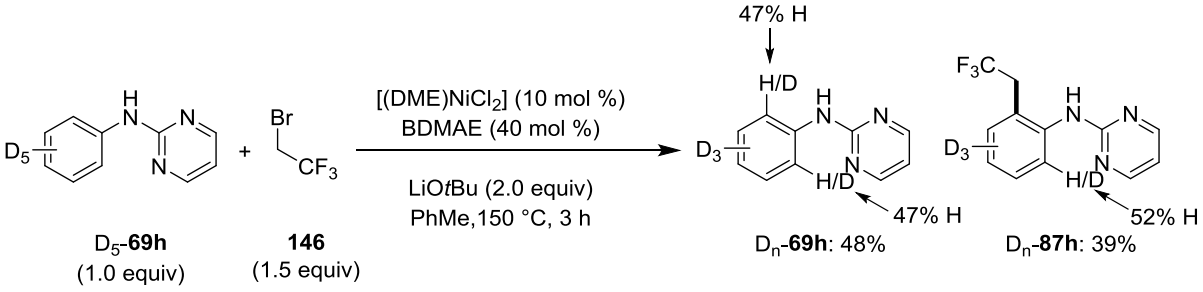
MS (EI): *m/z* (relative intensity) 217 (3), 188 (40), 170 (100), 136 (5), 109 (4), 85 (11).

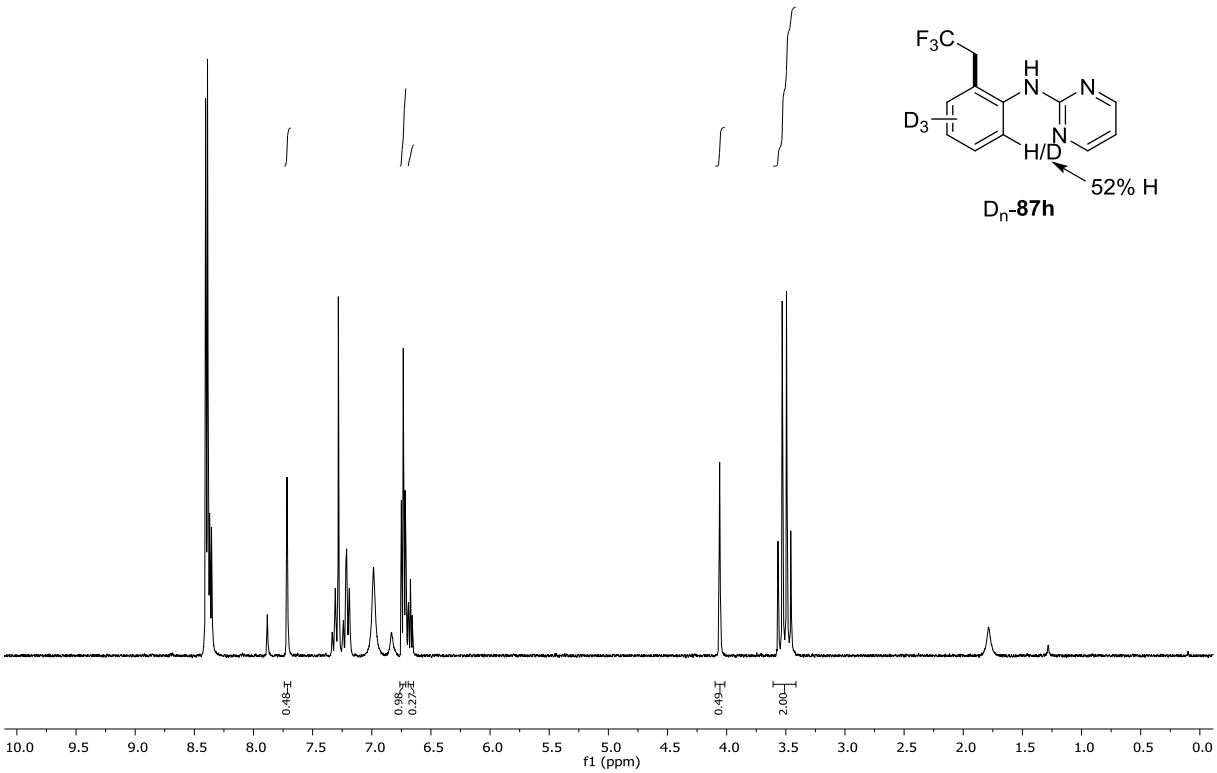
HR-MS (EI): m/z calcd for $C_{10}H_9FN_3$ [M+2H-$SO_2CHF_2^+$] 190.0781, found 190.0776.

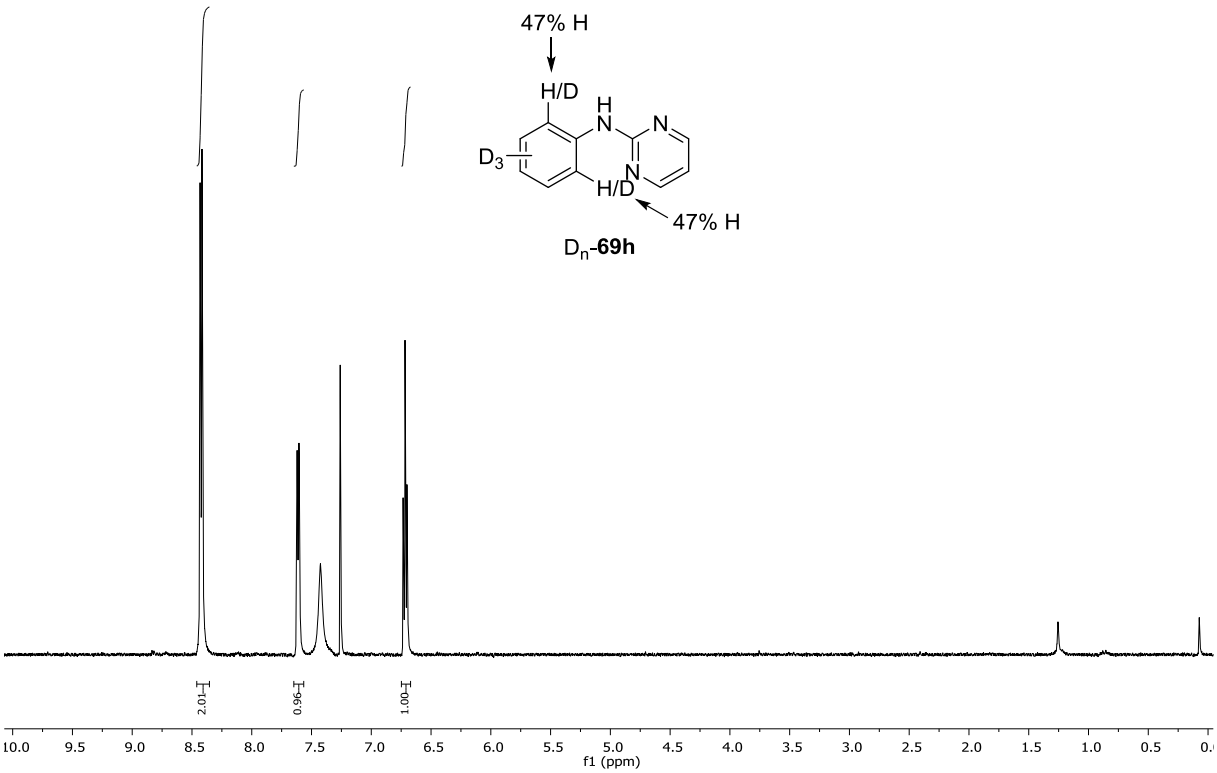
Mechanistic studies

H/D exchange experiments with $[D]_5$-69h as the substrate:

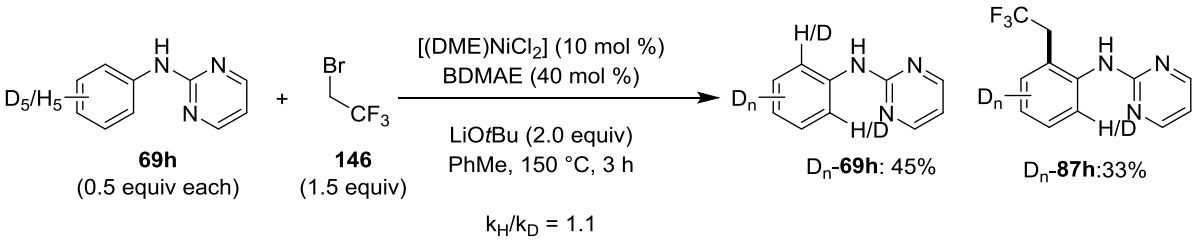
Following the general procedure **E2** $[D]_5$-**69h** (176 mg, 1.0 mmol) was reacted with **146** (245 mg, 1.5 mmol). After 3 h, the reaction was cooled to 0 °C, filtered through a silica pad and concentrated *in vacuo*. Purification by GPC yielded **69h** (85 mg, 48%) and **87h** (99 mg, 39%). **87h** was isolated as a mixture with a benzylated side-product from reaction with PhMe and yields were calculated from ^{1}H NMR ratio.




F3C
H
N
N
D3
N
H/D
52% H
Dn-87h
0.48
0.98
0.27
0.49
2.00
10.0 9.5 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 0.0
f1 (ppm)

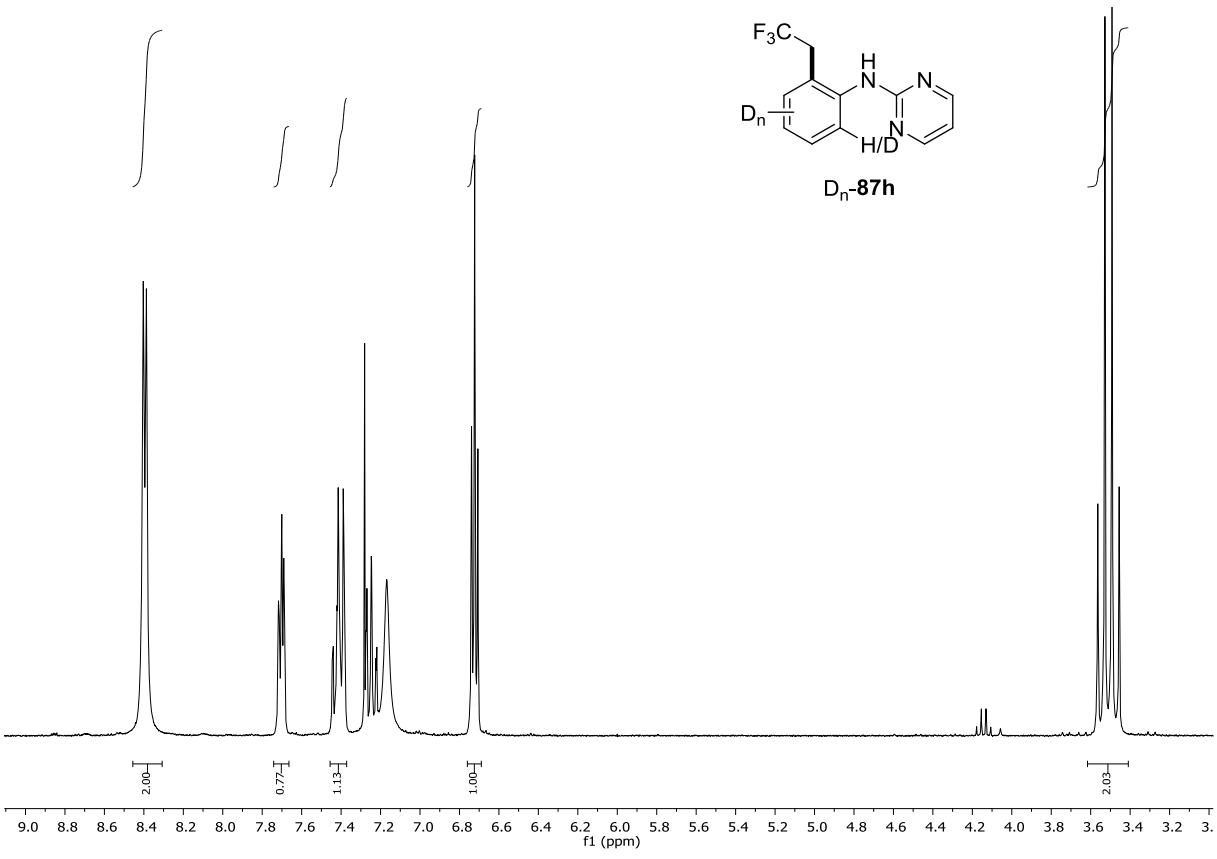

47% H
H/D
H
N
N
D3
N
H/D
47% H
Dn-69h
2.01
0.96
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

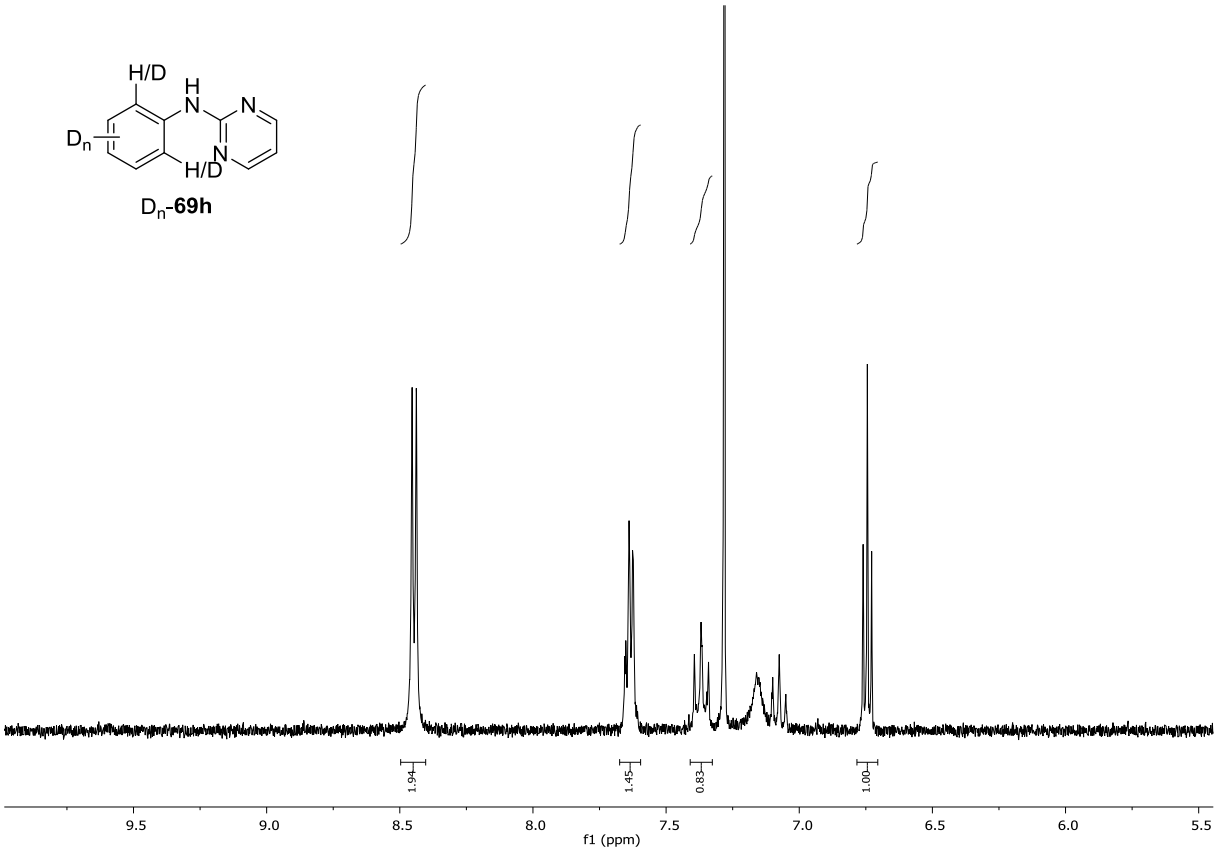
Intermolecular KIE Experiment between 69h and [D_5]-69h



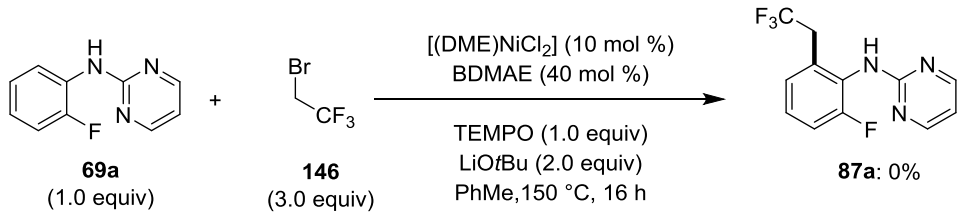
k_H/k_D = 1.1

69h (86 mg, 0.5 mmol), [D_5]-**69h** (88 mg, 0.5 mmol), [(DME)$NiCl_2$] (22 mg, 10 mol %) and LiO*t*Bu (160 mg, 2.0 mmol) were placed in a 25 mL sealed tube. The tube was evacuated and purged with Ar three times. BDMAE (76 µL, 40 mol %), trifluoroethylbromide **146** (245 mg, 1.5 mmol) and PhMe (2.0 mL) were added, and the mixture was stirred at 150 °C for 3 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added and concentrated under reduced pressure. Purification of the crude reaction mixture by flash column chromatography and GPC yielded **69h** (78 mg, 45%) and **87h** (84 mg, 33%) as white solids.



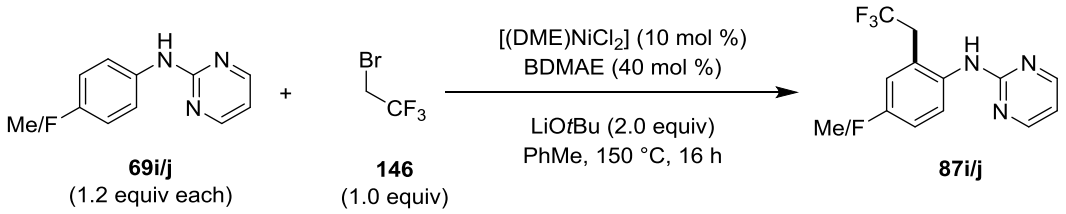


Reaction with TEMPO



N-(2-Fluorophenyl)pyrimidin-2-amine (**69a**) (95 mg, 0.5 mmol), [(DME)$NiCl_2$] (11 mg, 10 mol %), TEMPO (78 mg, 0.5 mmol) and LiO*t*Bu (80 mg, 1.0 mmol) were placed in a 25 mL Schlenk tube. The tube was evacuated and purged with Ar three times. BDMAE (38 µL, 40 mol %), trifluoroethyl bromide (**146**) (245 mg, 1.5 mmol) and PhMe (1.5 mL) were then added, and the mixture was stirred at 150 °C for 16 h. After cooling to ambient temperature, CH_2Cl_2 (2.0 mL) was added. No conversion was observed through ^{19}F NMR analysis of the crude reaction mixture.

Intermolecular Competition Experiment between 69k and 69l



69i/j (1.2 equiv each) **146** (1.0 equiv) **87i/j**

69k (223 mg, 1.2 mmol), **69l** (227 mg, 1.2 mmol), [(DME)$NiCl_2$] (22 mg, 10 mol %) and Li*O*t*Bu (160 mg, 2.0 mmol) were placed in a 25 mL sealed tube. The tube was evacuated and purged with Ar three times. BDMAE (76 µL, 40 mol %), trifluoroethylbromide (**146**) (163 mg, 1.0 mmol) and PhMe (2.0 mL) were then added, and the mixture was stirred at 150 °C for 16 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, and the reaction mixture was concentrated under reduced pressure. Analysis of the crude reaction mixture by ^{19}F NMR with 29 µL C_6F_6 as internal standard gave 3% of **87l** and 1% of **87k**.

6 List of Abbreviations

[M^+]	Molecular ion peak
Ac	acyl
Ad	adamantyl
Alk	alkyl
Ar	aryl
aq.	aqueous
BDC	1,4-benzenedicarboxylate
BDMAE	bis(2-dimethylaminoethyl)ether
BINOL	1,1'-binaphthol
Bn	benzyl
*n*Bu	*n*-butyl
br s	broad singlet
*t*Bu	*tert*-butyl
calc.	calculated
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
CPME	cyclopentyl methyl ether
δ	chemical shift
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DFT	density functional theory
DIPP	2,6-di-*iso*-propyl-phenyl
DME	dimethoxyethane
dppbz	1,2-bis(diphenylphosphino)benzene
dppf	1,1'-bis(diphenylphosphino)ferrocene
D*t*BEDA	*N*',*N*''-di-*tert*-Butylethane-1,2-diamine
ee	enantiomeric excess
EI	electron ionization
ESI	electronspray ionization
Et	ethyl
et al	*et alia*
equiv	equivalents
g	gramm
h	hours
hept	heptet
HR	high resolution
Hz	Hertz
IES	internal electrophilic substitution
IR	infrared (spectroscopy)
J	coupling constant
L	ligand
LDL-C	low-density lipoprotein - cholesterol

M	metal
m	multiplet
Me	methyl
2-Me-THF	2-Methyltetrahydrofuran
mg	milligramm
mL	milliliter
mmol	millimol
MEM	methoxy ethoxyl
M.p.	melting point
Mes	mesityl
MS	mass spectrometry
MTHP	tetrahydro-3-methyl-*2H*-pyran
m/z	mass-to-charge ratio
n. d.	not determined
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Ph	phenyl
PhthN	phthalimidyl
Pr	propyl
2-py	2-pyridyl
2-pym	2-pyrimidyl
Q	8-quinolyl
R	rest
RRMS	relapsing-remitting multiple sclerosis
s	singlet
SEM	[2-(trimethylsilyl)ethoxy]methyl acetal
SET	single electron transfer
t	triplet
T	temperature
THF	tetrahydrofuran
TM	transition metal
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethane-1,2-diamine
TMP	2,2,6,6-tetramethylpiperidine
Tf	triflate
Ts	tosyl
q	quartet
UV	ultraviolet
X	(pseudo)halide

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My parents, for their immense support during not just my educational path but all stages of my life, without which none of all this would have been possible.

8 Curriculum Vitae

Personal Details:

Date of birth: 04.02.1986

Place of birth: Schwandorf

Nationality: German

Education:

01/2012 – present	PhD studies under the supervision of Prof. Dr. Lutz Ackermann, Institute of Organic and Biomolecular Chemistry, Georg-August-University, Göttingen: "Nickel-Catalyzed Secondary Alkylations and Fluoroalkylations *via* C–H Activation."
12/2010 – 06/2011	Master thesis in organic chemistry in the group of Jr.-Prof. Dr. Stefan Kirsch, University of Technology Munich: "Development of transitionmetal-catalysed cyclisation-migration and cyclisation-additions domino reactions of keto-, ester- and amide-alkynyl derivatives"
11/2009 – 02/2010	Research internship in organic chemistry in the group of Prof. Dr. Mark Lautens, Lash Miller Chemical Laboratories, University of Toronto: "Rhodium(I)-catalysed domino transformation of o-alkynyl phenols to 2,3-disubstituted benzofurans"
03/2009 – 06/2011	Graduate studies (M. Sc.) in chemistry at the Department of Chemistry and Biochemistry, Faculty of Chemistry and Pharmacy, LudwigMaximilians-University Munich, Grade: 1.43 (Very Good)
06/2008 – 10/2008	Bachelor thesis in organic chemistry in the group of Prof. Dr. Thomas Carell: "Synthesis of the natural tRNA-modifications Wybutosine and Lysidine"
10/2005 – 11/2008	Undergraduate studies (B. Sc.) in chemistry and biochemistry at the Department of Chemistry and Biochemistry, Faculty of Chemistry and Pharmacy, Ludwig-Maximilians-University Munich, Grade: 2.18 (Good)
09/1996 – 07/2005	Grammar School: Regental Gymnasium, Nittenau, A Levels: 2.5
09/1992 – 07/1996	Primary School: Volksschule Wald, Wald

Teaching Experience:

10/2012 – 09/2014 Teaching Assistant for “Catalysis Practical Course” and seminar for the lectures “Introduction to Catalysis Chemistry” and “Modern Advances in Catalysis”

04/2008 – 02/2009 Tutor for undergraduate students at Ludwig-Maximilians-University, Munich

Publications:

[4] Ruan, Z.; Lackner, S.; Ackermann, L. "*A General Strategy for Nickel-Catalyzed C–H Alkylation of Anilines" Angew. Chem. Int. Ed.* **2016**, *55*, 3153–3157.

[3] Song, W.; Lackner, S.; Ackermann, L. *"Nickel-Catalyzed C–H Alkylations: Direct Secondary Alkylations and Trifluoroethylations of Arenes" Angew. Chem. Int. Ed.* **2014**, *53*, 2477–2480.

[2] Boyer, A.; Isono, N.; Lackner, S.; Lautens, M. “Domino rhodium(I)-catalysed reactions for the efficient synthesis of substituted benzofurans and indoles” *Tetrahedron* **2010**, *66*, 6468–6482.

[1] Tegel, M.; Hummel, F.; Lackner, S.; Schellenberg, I.; Poettgen, R.; Johrendt, D. „The layered Iron arsenides oxides Sr_2CrO_3FeAs and Ba_2ScO_3FeAs“ *Z. Anorg. Allg. Chem.* **2009**, *635*, 2242–2248.

Conferences, Oral Presentations:

12/2014 10th J-NOST Conference, IIT Madras, Chennai, India

Conferences, Poster Presentations:

07/2015 7th Göttinger Chemieforum, Göttingen

10/2014 NiKaS 2014, Göttingen

09/2014 Orchem 2014, Weimar

Extracurricular Activities and Memberships:

02/2013 – present Student Member of the GDCh

08/2011 – present	Member of the Tierschutzverein München e.V. (Society for the prevention of cruelty to animals Munich)
06/2006 – 03/2011	Member of the Students' Council of Chemistry at the Ludwig-Maximilians-University, Munich

Languages:

German (Native)

English (Fluent)

Japanese (Basic)