C−H Alkylations and Alkynylations Using Ruthenium, Nickel and Manganese Complexes

Dissertation

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Contents

List of Abbreviations

Ac	acetyl
acac	acetyl acetonate
Ad	adamantyl
Alk	alkyl
AMLA	ambiphilic metal-ligand activation
aq.	aqueous
Ar	aryl
atm	atmospheric pressure
ATR	attenuated total reflectance
BDMAE	bis(2-dimethylaminoethyl)ether
BHT	2,6-di-*tert*-butyl-4-methylphenol
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-binaphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br s	broad singlet
Bu	butyl
calc.	calculated
cat.	catalytic
CDC	cross dehydrogenative coupling
CMD	concerted-metalation-deprotonation
cod	1,5-cyclooctadiene
conv.	conversion
Cp*	cyclopentadienyl
Cy	cyclohexyl
δ	chemical shift

d	doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
dcype	1,2-bis(dicyclohexylphosphino)ethane
dcypt	3,4-bis(dicyclohexylphosphino)thiophene
dppf	1,1'-bis(diphenylphosphino)-ferrocene
dppp	1,1'-bis(diphenylphosphino) propane
dd	doublet of doublet
de	diastereomeric excess
DFT	density functional theory
DG	directing group
Diglyme	1-methoxyl-2-(2-methoxylethoxy)ethane
DMA	*N,N*-dimethylacetamide
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPMS	diphenylmethylsilyl
dt	doublet of triplet
D*t*-BBPY	4,4'-di-*tert*-butyl-2,2'-dipyridyl
D*t*-BEDA	N^1,N^2-di-*tert*-butylethane-1,2-diamine
Ed.	edition
EDG	electron-donating group
EI	electron ionization
equiv	equivalent
ESI	electronspray ionization
Et	ethyl
EWG	electron-withdrawing group
FG	functional group
FTICR	Fourier transform ion cyclotron resonance

g	gram
GC	gas chromatography
GPC	gel permeation chromatography
h	hour
Hal	halogen
Het	hetero(aryl)
Hept	heptyl
Hex	hexyl
HPLC	high performance liquid chromatography
HR-MS	high resolution mass spectrometry
Hz	Hertz
i	*iso*
IPr	1,3-bis(2,6-diisopropylphenyl)
IR	infrared spectroscopy
J	coupling constant
KIE	kinetic isotope effect
KHMDS	Potassium bis(trimethylsilyl)amide
L	ligand
LiHMDS	Lithium bis(trimethylsilyl)amide
m	*meta*
m	multiplet
M	metal
$[M]^+$	molecular ion peak
Me	methyl
Mes	mesityl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter

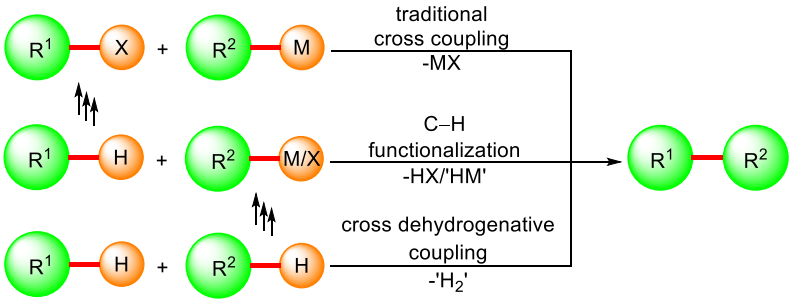
mmol	millimol
M. p.	melting point
MPAA	mono-*N*-protected amino acid
MS	mass spectrometry
MTHP	4-methyltetrahydro-2*H*-pyran
m/z	mass-to-charge ratio
NBS	*N*-bromosuccinimide
NHC	N-heterocyclic carbene
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance
o	*ortho*
OPV	oil pump vacuum
p	*para*
p-cymene	4-*iso*-propyltoluene
pent	pentyl
PG	protecting group
Ph	phenyl
Phth	phthaloyl
PIP	(pyridin-2-yl)isopropyl
Piv	2,2-dimethylpropanoyl
pKa	logarithmic acid dissociation constant
ppm	parts per million
Pr	propyl
py	pyridyl
pym	pyrimidyl
q	quartet
Q	8-aminoquinoline
DG	directing group
ref.	reference

RT	room temperature
s	singlet
sat.	saturated
SBM	σ-bond metathesis
S_EAr	electrophilic aromatic substitution
SPS	solvent purification system
t	*tert*
t	triplet
T	temperature
TBDMS	*tert*-butyldimethylsilyl
TBS	tri-*n*-butylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine-*N*-oxide
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2,-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TM	transition metal
TMEDA	*N,N,N',N'*-tetramethylethylendiamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TPS	triphenylsilyl
TS	transition state
Val	valine
X	(pseudo)halide
X-phos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

1 Introduction

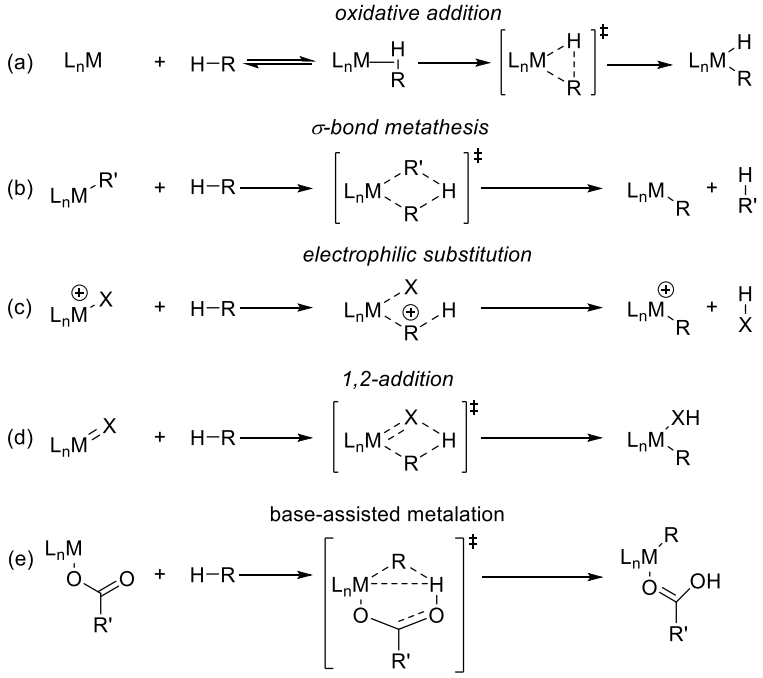
1.1 Transition Metal-Catalyzed C−H Activation

In the past decades, transition metal-catalyzed cross-coupling reactions have been considered as one of the most useful and reliable tools for carbon−carbon (C−C) or carbon−heteroatom (C−Het) bond formation,[1] including Kumada-Corriu,[2] Negishi,[3] Suzuki-Miyaura,[4] Migita-Kosugi-Stille,[5] Hiyama,[6] Mizoroki-Heck[7] and Sonogashira-Hagihara[8] cross-couplings. These reactions have been employed in the synthesis of pharmaceuticals, natural products, agrochemicals, polymers and feedstock commodity chemicals.[9] Despite the enormous progress achieved by cross-coupling reactions,[10] they still show some opportunities for improvement, especially the necessity for pre-functionalized substrates is a major limitation. These pre-functionalization steps are accompanied with the generation of stoichiometric amounts of undesired byproducts and metal containing wastes. As a more atom- and step-economical alternative,[11] direct C−H functionalization has recently emerged as a powerful tool allowing the transformation of otherwise unreactive C−H bonds, which bears the potential for the construction of C−C or C−Het bonds without pre-functionalization steps.[12] Furthermore, the direct formation of C−C bonds by activating two C−H bonds, including C(sp^3)−H bonds,[13] which was termed cross-dehydrogenative coupling (CDC), has also been extensively studied (Scheme 1.1.1).[14]



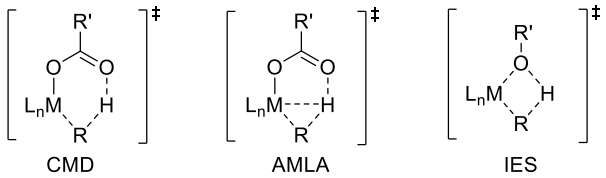
Scheme 1.1.1 Strategies for C−C and C−Het formation.

The key step, the C–H metalation can be accomplished depending on the nature of the transition metal species L_nM. Five generally accepted pathways of these mechanisms have been summarized by Ackermann[12n] as well as Eisenstein and co-workers,[15] which is shown in Scheme 1.1.2. The mechanistic modes include (a) oxidative addition with electron-rich and low-valent late transition metals, (b) σ-bond metathesis with early transition metals and lanthanides, (c) electrophilic substitution with electron-deficient late transition metals, (d) 1,2-addition onto unsaturated M−X bonds, and (e) the base-assisted deprotonation, called either concerted metalation-deprotonation (CMD) or ambiphilic metal ligand activation (AMLA) (Scheme 1.1.2).



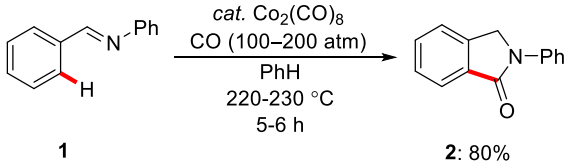
Scheme 1.1.2 Plausible mechanisms for C−H activations.

The concerted metalation-deprotonation (CMD)[16] or ambiphilic metal ligand activation (AMLA)[17] is based on a six-membered transition state. Metals with alkoxy ligands favors an internal electrophilic substitution (IES), which is based on a four-membered transition state.[18] Recently, a related base-assisted internal electrophilic substitution (BIES) has been proposed for electron-rich arenes with acetate or carboxylate ligands (Scheme 1.1.3).[19]



Scheme 1.1.3 Proposed transition states for the base-assisted metalation.

In 1955, an early example of directed C–H functionalization reactions was reported by Murahashi. The treament of imine **1** with catalytic amounts of cobalt at high temperature and pressure of CO led to the formation of 2-phenylisoindolin-1-one (**2**) (Scheme 1.1.4).[20]



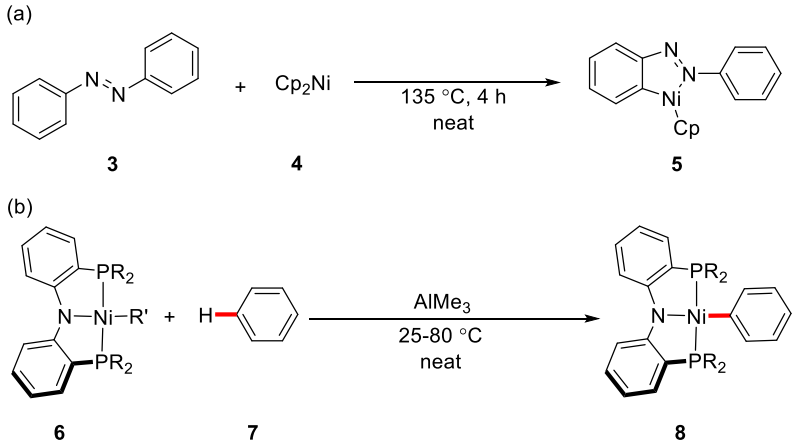
Scheme 1.1.4 Cobalt-catalyzed C–H carbonylation.

Thereafter, a variety of transition metal-catalyzed C–H functionalizations have been explored, using 4d and 5d transition metals, for instance by palladium, platinum, rhodium, ruthenium and iridium, as well as the inexpensive, naturally abundant 3d base metals, such as iron, cobalt, nickel and copper.[12, 21]

1.2 Nickel-Catalyzed C−H Activation

During the past decade, catalytic reactions based on inexpensive naturally abundant base metals have become a significant research area, driven by declining natural resources of precious metals and their enormous price increases. Therefore, C–H functionalization using nickel catalysts has recently received considerable attention from synthetic chemists because nickel catalysts are more cost effective than noble transition metal catalysts, in particular palladium.[22] The cost of nickel (10 €/kg) in its elemental form is roughly 0.04% of the price of palladium (24017 €/kg).[23] Moreover, unlike palladium, nickel has specified key properties, such as facile oxidative addition and a number of readily available oxidation states, which allows to develop innovative reactions.[24]

Important contributions to nickel-catalyzed C–H activation were made as early as the 1960s. Indeed, an adduct of a C–H bond of azobenzene (**3**) onto a nickel complex **4** was reported by Dubeck and Kleiman in 1963 (Scheme 1.2.1a).[25] Thereafter, Liang and coworkers disclosed the pincer nickel complex **6** could react with benzene (**7**) to achieve complex **8** under mild conditions *via* the oxidative addition of the C–H bond of benzene without any directing group (Scheme 1.2.1b).[26]



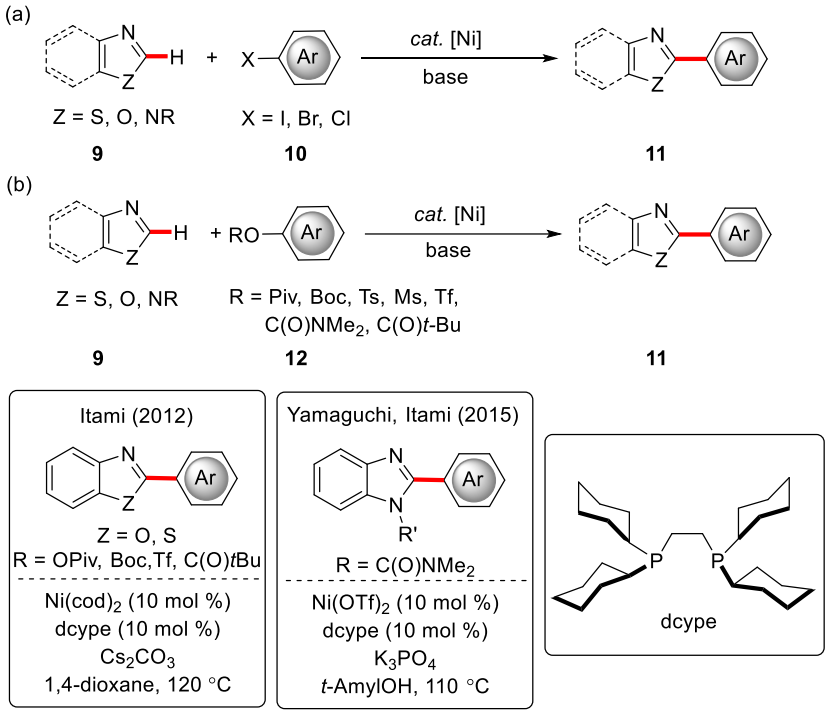
Scheme 1.2.1 Stoichiometric C–H activation using nickel complexes.

Early examples of catalytic C–H activation focused on electronically-biased azole substrates as investigated by the groups of Miura, Itami, Hu and Ackermann.[27] These C–H functionalization reactions include arylations, alkenylations, alkylations as well as alkynylations. The latter two reactions will be described in the following sections separately.

(a) Nickel-Catalyzed C–H Activation without Directing Group

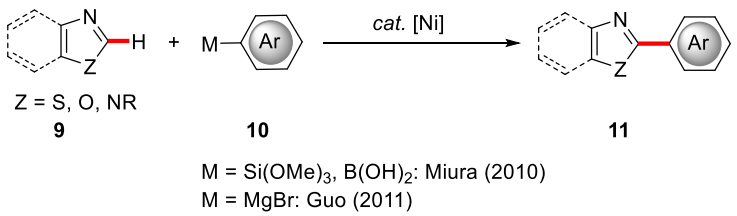
In 2009, examples of nickel-catalyzed C–H arylation of 1,3-azoles **9** with aryl halides **10** to synthesize 2-ary-1,3-azoles **11** were reported.[27d, 27e] In both reactions, it was essential to use the strong base LiO*t*-Bu. The Itami group developed the nickel-catalyzed C–H/C–O coupling of 1,3-azoles **9** and phenol derivatives **12**,[28] while cobalt-catalyzed direct arylation and benzylation through C–H/C–O bond cleavage were reported by Ackermann.[29] Interestingly, 1,2-bis(dicyclohexylphosphino)ethane (dcype) as the ligand was key success for this transformation, while other ligands did not deliver the desired products. The $Ni(cod)_2$/dcype catalytic system was also active for the coupling of other phenol derivatives such as aryl

carbonates, sulfamates, triflates, tosylates, and mesylates. However, the $Ni(cod)_2$/dcype catalyst was limited by a narrow substrate scope, as imidazoles were unreactive under these reaction conditions. More recently, Itami and Yamaguchi reported a method for the C–H arylation of imidazoles with aryl carbamates using nickel(II) instead of nickel(0), which is a less expensive complex [$Ni(OTf)_2$/dcype] as compared to [$Ni(cod)_2$/dcype] (Scheme 1.2.2).[30]



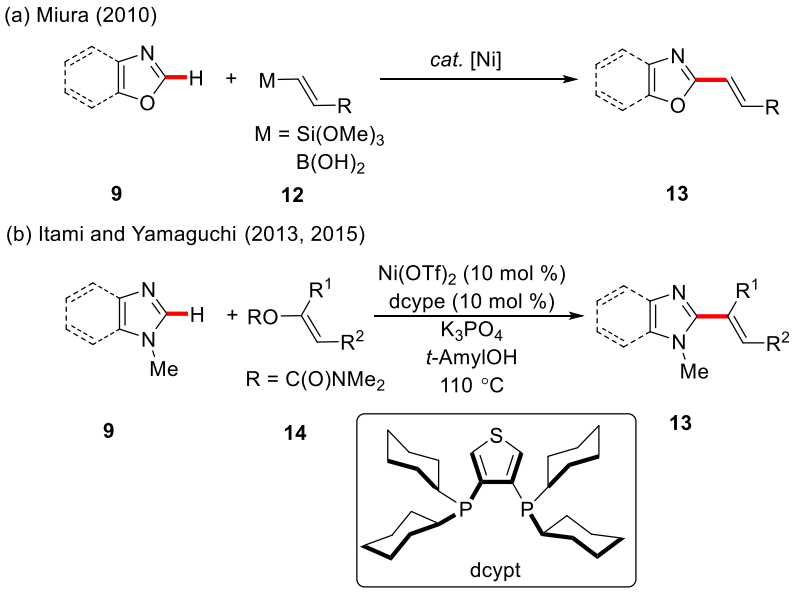
Scheme 1.2.2 C–H arylation of azoles **9** with aryl electrophiles **10** and **12**.

Nickel-catalyzed oxidative C–H arylations using organometallic species as the aryl source have also been reported in recent years (Scheme 1.2.3). In 2010, Miura and coworkers developed an oxidative direct arylation of 1,3-azoles with arylsilanes[31] or arylboronic acids[32] in the presence of copper salts or air as the oxidants. These reports could be regarded as a significant finding because oxidative C–H arylation with arylsilanes were rare.[33] One year later, nickel-catalyzed oxidative direct arylations using aryl Grignard reagents were reported by Guo and coworkers.[34]



Scheme 1.2.3 C–H arylation of azoles with organosilicon, boron, and Grignard reagents.

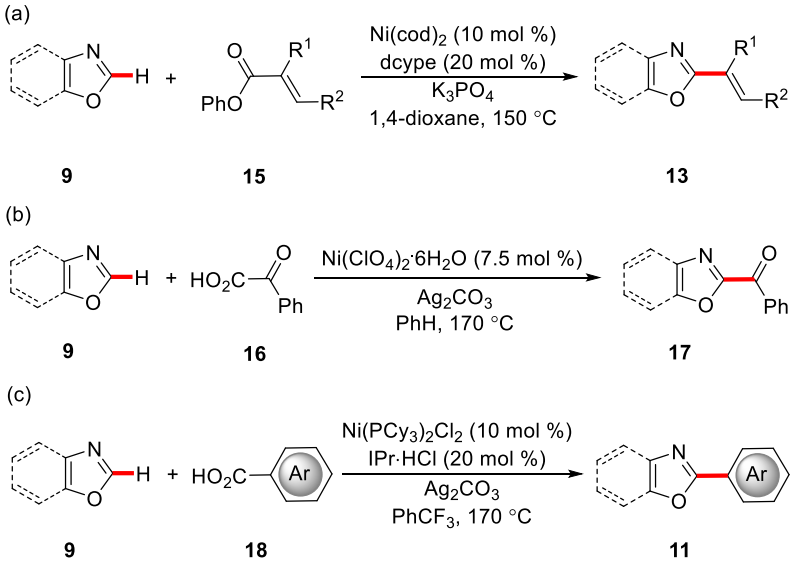
Miura's oxidative arylation strategy (see Scheme 1.2.3) could also be applied for the C–H alkenylation of oxazole with alkenylsilanes and alkenylboronic acids, as shown in Scheme 1.2.4a.[31] The oxidative alkenylation was observed in moderate yield at high temperature. Likewise, Itami's conditions for the C–H arylation (see Scheme 1.2.2) were suitable for the C–H/C–O alkenylation with enol derivatives as coupling partners using nickel/dcype or nickel/dcypt catalytic system in good yields (Scheme 1.2.4b).[30, 35]



Scheme 1.2.4 C–H alkenylation of azoles with organosilicon, boron and carbamate reagents.

In 2012, Itami discovered the nickel-catalyzed decarbonylative C–H biaryl coupling of azoles and aryl esters (Scheme 1.2.5a).[36] Under a catalytic system similar to the aforementioned nickel-catalyzed C–H/C–O coupling (see Scheme 1.2.2), the decarbonylative C–H arylation of oxazole **9** with heteroaromatic esters **15** proceeded efficiently to afford the corresponding coupling products **13**. Additionally, these reaction conditions could be applied to the decarbonylative C–H alkenylation of benzoxazole and α,ß-unsaturated phenyl esters.[35]

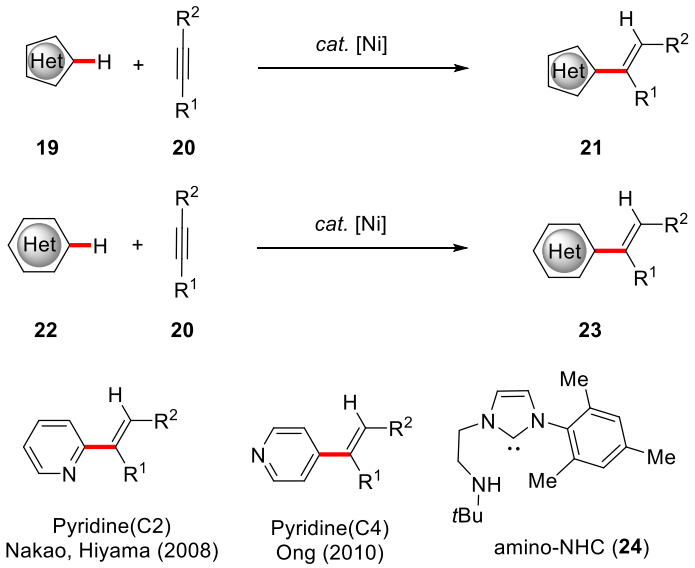
Thereafter, Ge and coworkers reported a nickel-catalyzed decarboxylative coupling using α-oxoglyoxylic acids **16** as coupling partners (Scheme 1.2.5b).[37] In the meantime, Zhang and coworkers performed a nickel-catalyzed decarboxylative coupling of benzoxazoles and carboxylic acid derivatives **18** employing nickel(II) catalyst in conjunction with N-heterocyclic carbene (NHC) IPr·HCl as the ligand (Scheme 1.2.5c).[38] Although the nickel-catalyzed decarboxylation needed harsh conditions, including stoichiometric silver salts used and high reaction temperature), it was still the first example of this type of reaction using a nickel catalyst.



Scheme 1.2.5 Nickel-catalyzed decarbonylative and decarboxylative C–H activation of azoles.

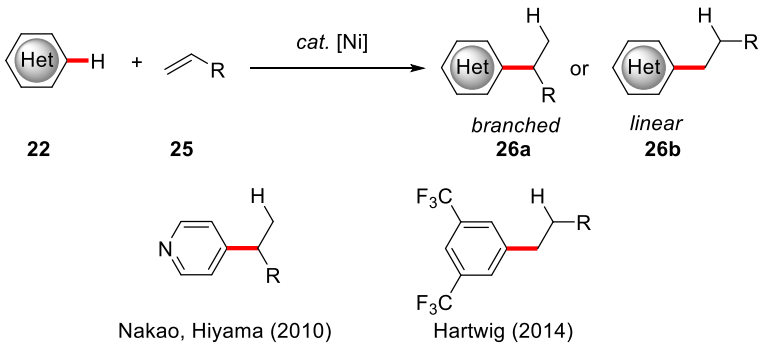
As early as 2006, Nakao, Hiyama, and coworkers developed a nickel-catalyzed hydroarylation of alkynes with heteroarenes.[39] In recent years, the catalytic hydroarylation system was improved by Nakao and Hiyama using nickel(0) and phosphine ligands. This nickel-catalyzed hydroarylation was applicable not only for five-membered heteroarenes **19** such as benzoxazole, thiazole,[39] oxadiazole,[40] pyrazole[41] and imidazole,[42] but also electron-deficient arenes **22**, such as azine-*N*-oxide,[43] pyridine[44] and pentafluorobenzene.[45] Notably, the nickel-catalyzed hydroarylation occured in high regioselectively at the C2 position on pyridines with the addition of Lewis acids such as $ZnMe_2$ or $ZnPh_2$ instead of using *N*-oxides. In contrast, a nickel-catalyzed hydroarylation of alkynes and pyridines at the C4 position was reported by Ong and

coworkers. They showed that the complexation of amino-NHC (**24**) and $AlMe_3$ activated a C–H bond on pyridine at the C4 position.[46]



Scheme 1.2.6 Hydroarylation of alkynes **20** with heteroarenes.

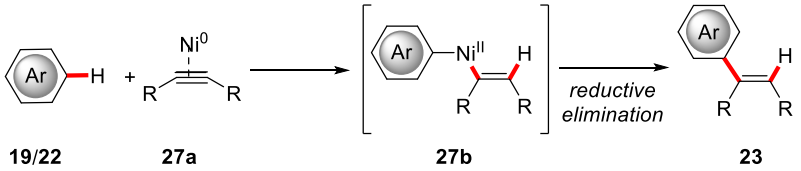
The hydroarylations were not only applicable for alkynes **20**, but also for alkenes **25** (Scheme 1.2.7). The groups of Nakao, Hiyama,[47] Hartwig[48] and Ong[49] mainly contributed to these achievements. Similar to the hydroarylation of alkynes **20**, the hydroarylation of alkenes only worked well for the electron-deficient aromatics such as pyridine (occurred at C4 postion)[50] and 1,3-bis(trifluoromethyl)benzene.[51]



Scheme 1.2.7 Hydroarylation of alkenes **25** with heteroarenes.

As to mechanism, nickel-catalyzed hydroarylation C–H functionalization typically starts with the coordination of the alkyne to the nickel(0) species. Then, an aromatic C–H bond reacts with the nickel complex *via* oxidative addition, followed by hydronickelation forming an Ar–

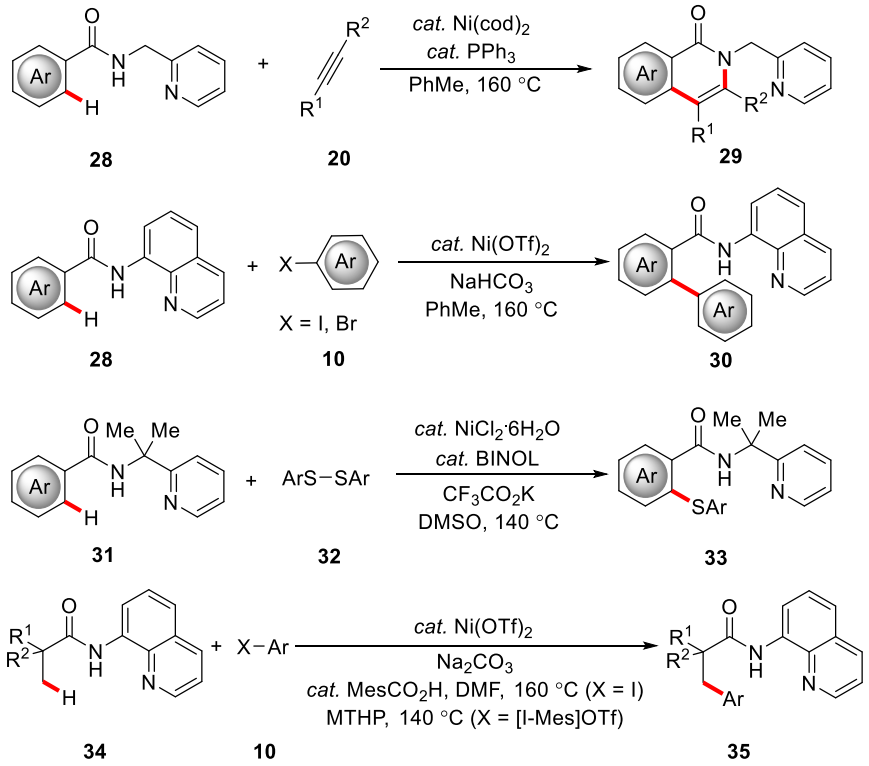
nickel(II)–alkenyl intermediate **27b**, which then undergoes reductive elimination to furnish hydroarylation products **23** (Scheme 1.2.8).[39]



Scheme 1.2.8 Hydroarylation-type C–H functionalization.

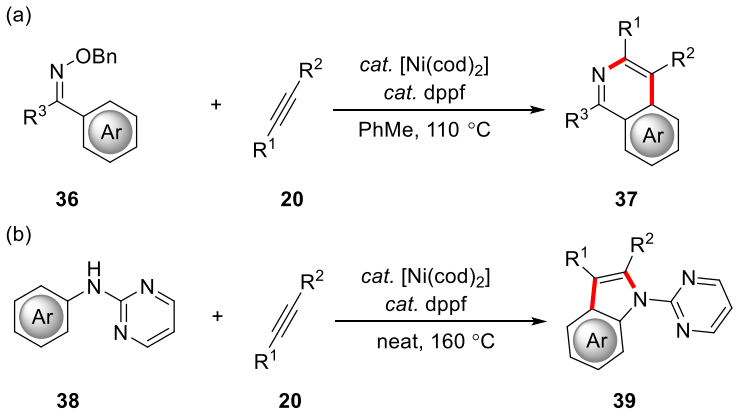
(b) Nickel-Catalyzed C–H Activation under Chelation-Assistance

Despite these important contributions, all the aforementioned C–H transformations were applicable only for the activation of relatively acidic C–H bonds on heteroaromatic and specific arenes. In the case of simple arenes, such as benzoic acid derivatives and anilines, the utilization of a chelation assistance for site-selective nickel-catalyzed C–H functionalization was achieved, after the conception of bidentate auxiliaries by the group of Daugulis for palladium-catalyzed C–H activations.[12d] Based on these findings, Chatani and coworkers attempted a nickel-catalyzed annulation of inert C–H bonds of benzamides containing a 2-pyridylaminomethane moiety as a bidentate directing group.[52] More recently, nickel-catalyzed C–H arylation,[53] carbonylation,[54] sulfonylation,[55] thiolation,[55a, 56] amidation,[57] amination,[58] halogenation,[59] alkenylation,[60] allylation,[61] alkylation[62] and alkynyltation[63] of benzamides were reported using bidentate auxiliaries such as 8-aminoquinoline (Q) and (pyridin-2-yl)isopropyl (PIP) amine (Scheme 1.2.9).



Scheme 1.2.9 Selected examples of nickel-catalyzed C–H activation under bidentate assistance.

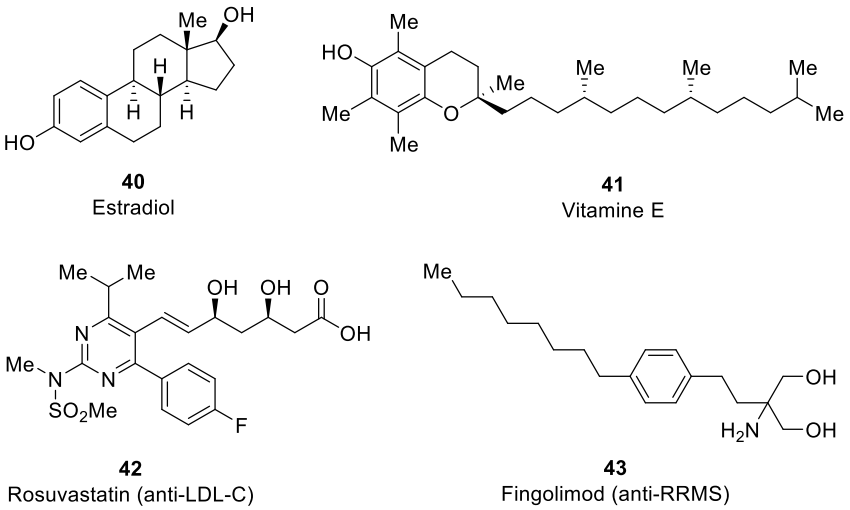
The bidentate directing group strategy has remained most widely used within directed nickel-catalyzed C–H functionalization. However, scarce examples involving monodentate approaches have been reported. One example is the nickel-catalyzed oxidative annulation of oximes **36** developed by Matsubara (Scheme 1.2.10a).[64] Another is the nickel-catalyzed alkyne annulation of electron-rich anilines **38** to form substituted indoles with removable directing groups performed by Ackermann (Scheme 1.2.10b).[65] It is noteworthy that the C–H/N–H bond activation strategy efficiently occurred in the absence of any metal oxidants and with excellent selectivities.



Scheme 1.2.10 Nickel-catalyzed C–H functionalization with monodentate auxiliaries.

1.2.1 Nickel-Catalyzed C–H Alkylation

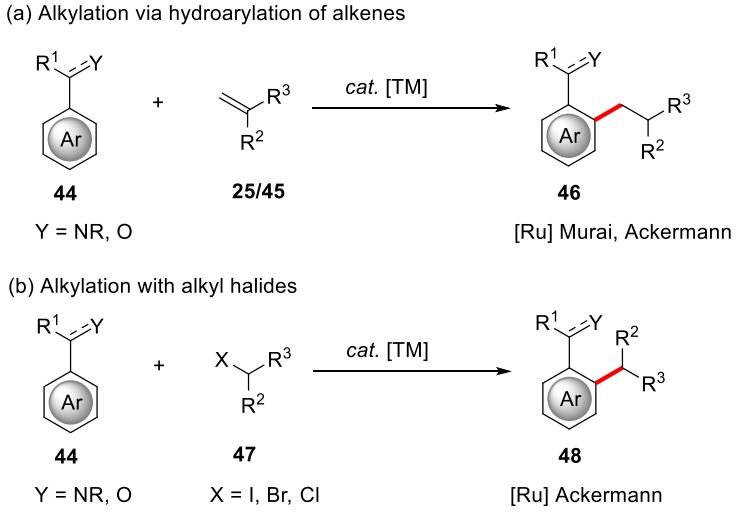
Compounds bearing alkyl groups have attracted significant attention in organic chemistry.[66] This is due to their abundance in natural products, and their effect on the pharmacokinetic of drug moleculars in medicinal chemistry.[67] Therefore, aliphatic substrates with various substituents and functional groups can be commonly found in a wide range of top-selling drugs (Scheme 1.2.1.1).[68]



Scheme 1.2.1.1 Selection of bioactive compounds containing aliphatic groups.

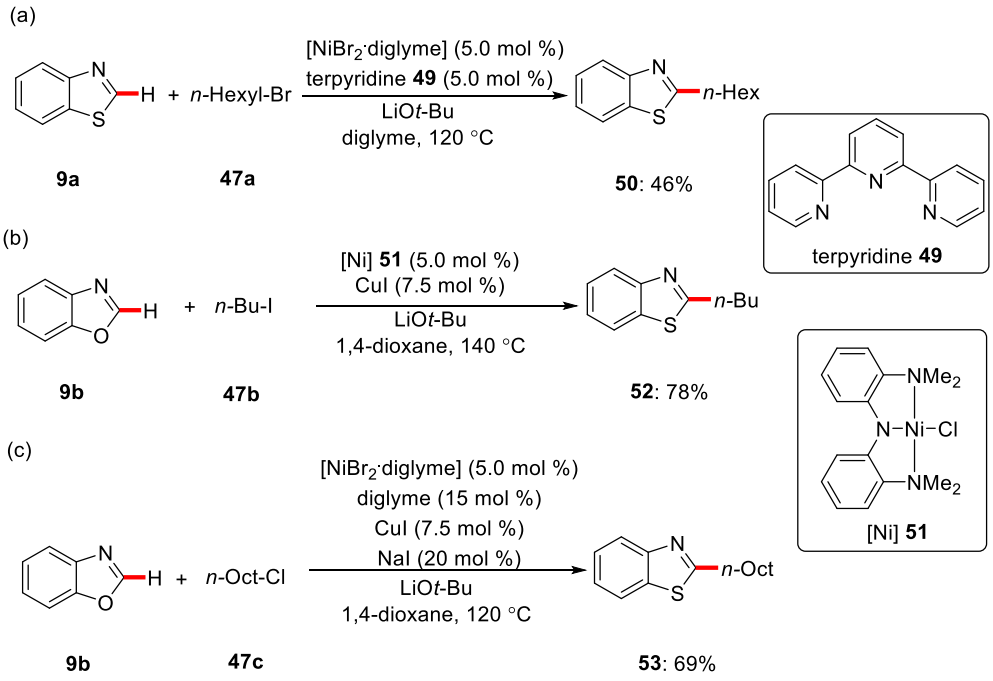
Regarding transition metal-catalyzed direct C–H alkylations two approaches have been commonly followed: hydroarylation of alkenes, which has been discussed above (Scheme 1.2.7 & Scheme 1.2.1.2a),[69] and the use of electrophilic alkyl halides directly for C–H activation,

which was first developed by Ackermann in 2009 using ruthenium catatalysis (Scheme 1.2.1.2b).[70]



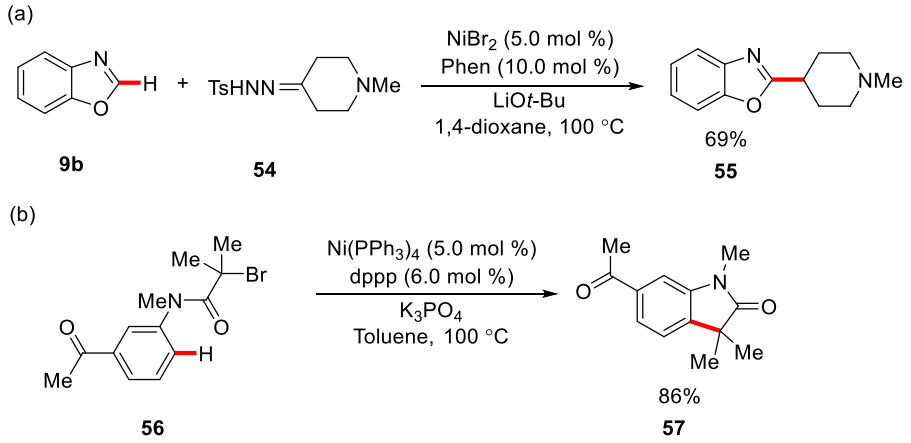
Scheme 1.2.1.2 Strategies for transition metal-catalyzed C–H alkylation.

Recently, nickel-catalyzed C–H alkylations of 1,3-azoles with alkyl halides were reported independently by the groups of Miura,[71] Hu[27c] and Ackermann (Scheme 1.2.1.3).[72] Direct C–H activation using alkyl halides is relatively rare compared to hydroarylation of olefins due to the facile β-hydrogen elimination of alkylmetal reagents.[70i]



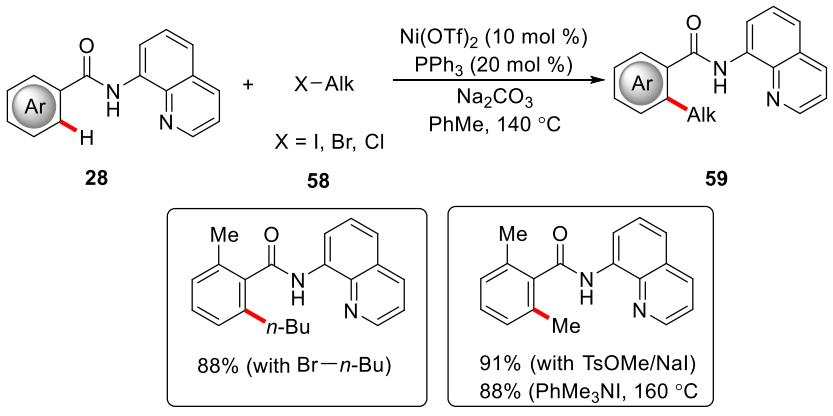
Scheme 1.2.1.3 Nickel-catalyzed C–H alkylations of 1,3-azoles with alkyl halides **47**.

To suppress ß-hydrogen elimination, the Miura group developed a C–H alkylation of benzoxazole with alkyl hydrazones **54** as the alkylating reagent instead of alkyl halides (Scheme 1.2.1.4a).[73] Furthermore, an intramolecular C–H alkylation of arenes *via* a radical pathway was reported by Lei in 2013 (Scheme 1.2.1.4b).[74]



Scheme 1.2.1.4 Nickel-catalyzed aromatic C–H alkylation.

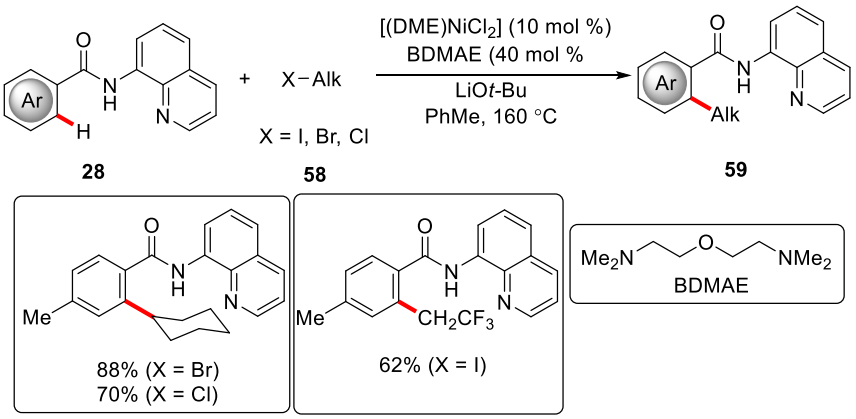
Intermolecular C–H alkylation of benzamides through nickel catalysis was achieved using a bidentate directing group by Chatani and coworkers (Scheme 1.2.1.5).[62b] Although, only primary alkyl bromides reacted in the presence of $Ni(OTf)_2/PPh_3$, the reaction conditions could be applied to methylation when using MeOTs and NaI or $PhMe_3NI$ as the methylating reagent.[62c]



Scheme 1.2.1.5 C–H Alkylation with primary alkyl halides **58**.

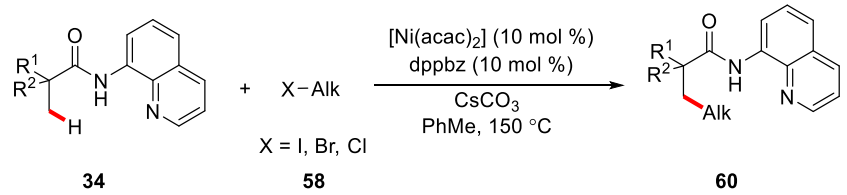
In 2014, Ackermann group realized the nickel-catalyzed C–H alkylation of unreactive arenes with challenging secondary alkyl halides (Scheme 1.2.1.6).[62a] Bis(2-dimethylaminoethyl)ether

(BDMAE) was found to be an effective ligand for secondary alkylation as well as for C–H trifluoroethylations.



Scheme 1.2.1.6 C–H Alkylation with secondary alkyl halides.

The Ge group reported the direct alkylation of unactivated C(sp^3)–H bonds of aliphatic amides *via* nickel catalysis under the assistance of the 8-aminoquinoline directing group (Scheme 1.2.1.7).[62d] The reaction favored the C–H bonds of methyl groups over the methylene C–H bonds and tolerated various functional groups. However, the reaction was specific with regard to the structure of substrates, thus limiting its application to only aliphatic amides bearing a quaternary α-carbon and containing at least one β-methyl group. In this catalytic system, the authors proposed a mechanism through a nickel(II)/nickel(III) manifold from the oxidation of the nickel(II) species generated after the concerted metalation-deprotonation (CMD) by an alkyl radical.

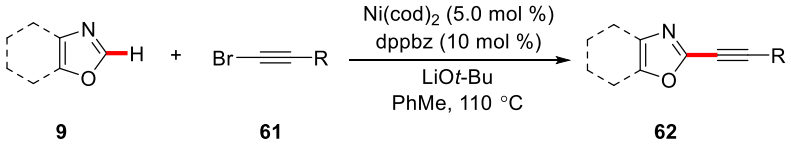


Scheme 1.2.1.7 Nickel-catalyzed C(sp^3)–H alkylation of aliphatic amides **34**.

Indeed, in nickel-catalyzed alkylation chemistry several readily available oxidation states involved in catalytic cycles need to be recognized as 2-electron changes, these being nickel(0)/nickel(II) but also nickel(I)/nickel(III) as well as nickel(II)/nickel(IV), with the latter typically formed under excess oxidant reaction conditions.[75]

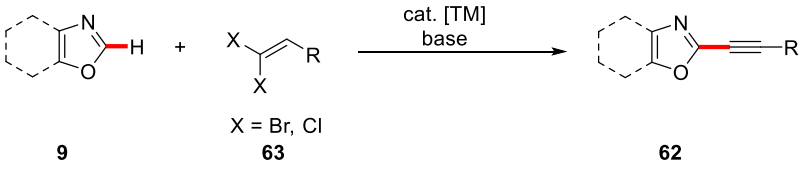
1.2.2 Nickel-Catalyzed C–H Alkynylation

Alkynes are versatile building blocks in organic synthesis. Consequently, C–H alkynylations have been identified as increasingly powerful alternatives to the conventional Sonogashira–Hagihara cross-coupling reaction.[76] An early example of nickel-catalyzed C–H alkynylation of oxazoles **9** was reported by Miura and coworkers in 2009 (Scheme 1.2.2.1),[77] where bromoalkynes **61** were used as the electrophiles to afford the corresponding alkynyl products **62**.



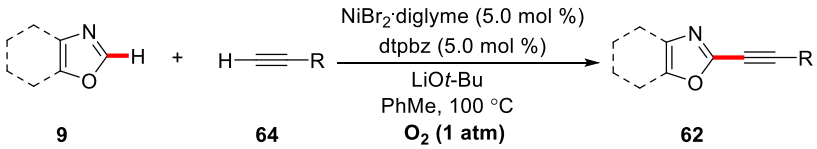
Scheme 1.2.2.1 Nickel-catalyzed alkynylation of oxazoles.

Instead of bromoalkynes, the more stable and easier accessible *gem*-dibromoalkenes **63** were also used for the alkynylation of 1,3-azoles, as mainly described by the groups of Ackermann,[78] Piguel[79] and Das (Scheme 1.2.2.2).[80]



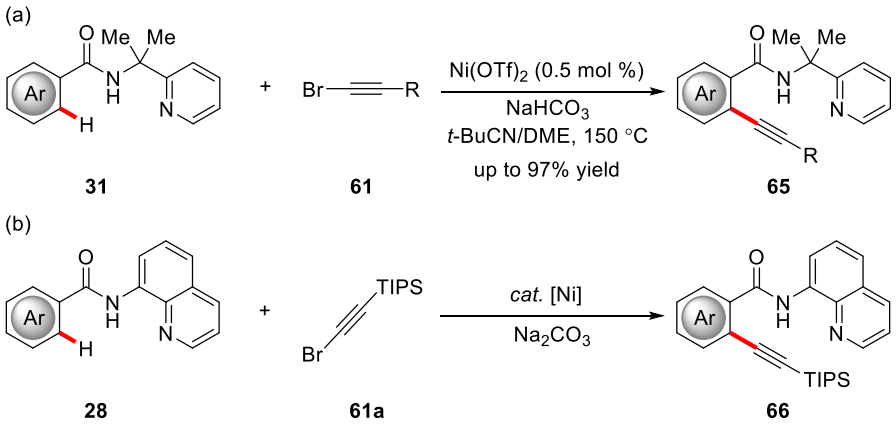
Scheme 1.2.2.2 C–H Alkynylations with *gem*-dibromoalkenes.

Such a promising methodology has not yet been used for nickel. However, nickel-catalyzed oxidative C–H functionalization involving terminal alkynes **64** directly without pre-functionalization, was achieved by Miura group,[81] for the dehydrogenative C–H alkynylation of oxazoles **9** under aerobic conditions (Scheme 1.2.2.3).



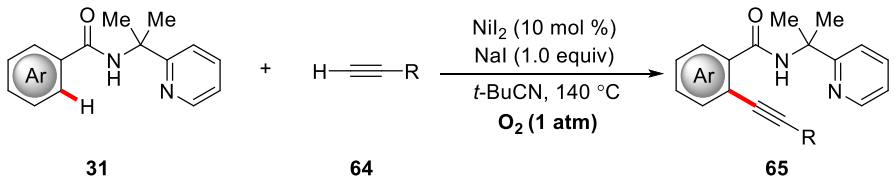
Scheme 1.2.2.3 Nickel-catalyzed oxidative alkynylation of oxazoles.

As discussed above, directing groups are often not necessary for transition metal-catalyzed direct functionalizations in the more acidic C2 position of 1,3-azoles and related compounds, which is not the case for carbocyclic arenes. In 2015, the groups of Shi,[63a] Li,[82] and Balaraman[83] independently disclosed the C–H alkynylation of six-membered arenes with alkynyl bromides using chelation-assisted groups to give the corresponding *ortho*-substituted products in good yields (Scheme 1.2.2.4).



Scheme 1.2.2.4 Nickel-catalyzed direct C–H alkynylation under bidentate assistance.

Thereafter, Shi and coworkers developed an oxidative C–H alkynylation of arylamides containing PIP moiety in the presence of NiI_2 and NaI under an oxygen atmosphere. (Scheme 1.2.2.5).[63b]



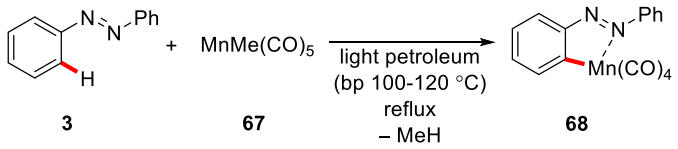
Scheme 1.2.2.5 Oxidative C–H alkynylation of benzamides.

1.3 Manganese-Catalyzed C–H Functionalization

The recent few years have witnessed the emergence of 3d transition metals for C–H bond transformation by the complexes derived from inexpensive iron, cobalt or nickel catalysts.[12h, 21a, 21c-k]

Manganese, which is the twelfth most abundant element and the third most abundant transition metal after iron and titanium in the earth's crust, is found as an essential trace element for life on the earth.[84] Furthermore, the low toxicity[85] and low cost of manganese[86] present a useful alternative for catalytic C–H activation to the typically used 4d or 5d transition metal catalysts derived from platinum, palladium, rhodium, or ruthenium.[21b]

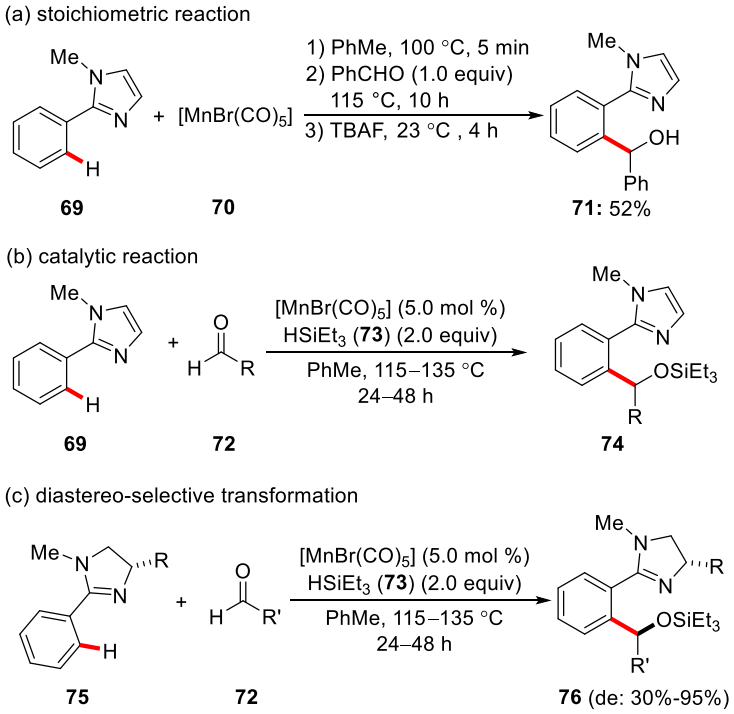
In 1970, an early report of stoichiometric direct C–H manganesation of arene was reported by Stone, Bruce and co-workers, where manganacycle **68** was isolated from the reaction of azobenzene (**3**) with $MnMe(CO)_5$ (Scheme 1.3.1).[87] Following similar cyclomanganation protocols, a variety of manganacycle complexes could later on be obtained.[88]



Scheme 1.3.1 Stoichiometric manganese-mediated C–H activation.

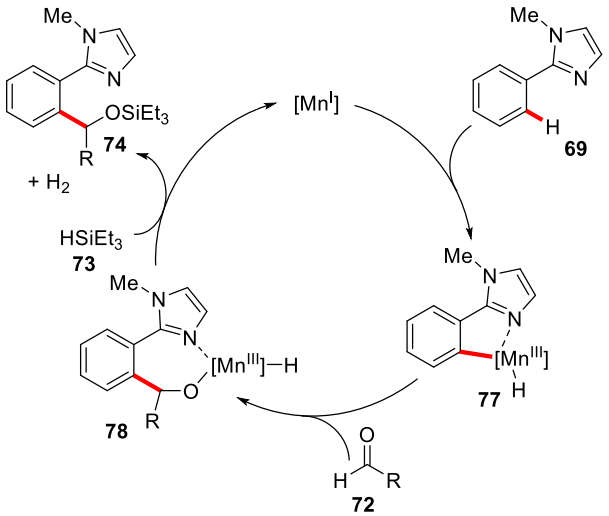
1.3.1 Addition to C–Het Multiple Bonds

Based on pioneering stoichiometric transformations, manganese(I)-catalyzed C–H bond activation has been investigated, with major contributions performed by the groups of Kuninobu/Takai, Wang and Ackermann.[89] Especially, early progress in manganese(I)-catalyzed C–H activation was achieved by the group of Kuninobu/Takai in 2007.[90] Thus, they revealed the manganese(I)-catalyzed aromatic C–H bond addition onto the polar C=O bond of aldehydes **72** with imidazole as a directing group, initiated by probing the stoichiometric C–H manganesation (Scheme 1.3.2a). Notably, the use of Et_3SiH (**73**) as additive was found to be crucial, as only trace amounts of the C=O bond insertion product was observed in the absence of additive **73** (Scheme 1.3.2b). Furthermore, manganese(I)-catalyzed diastereo-selective C–H transformation could be achieved by assistance of chiral imidazolines as the directing groups (Scheme 1.3.2c).



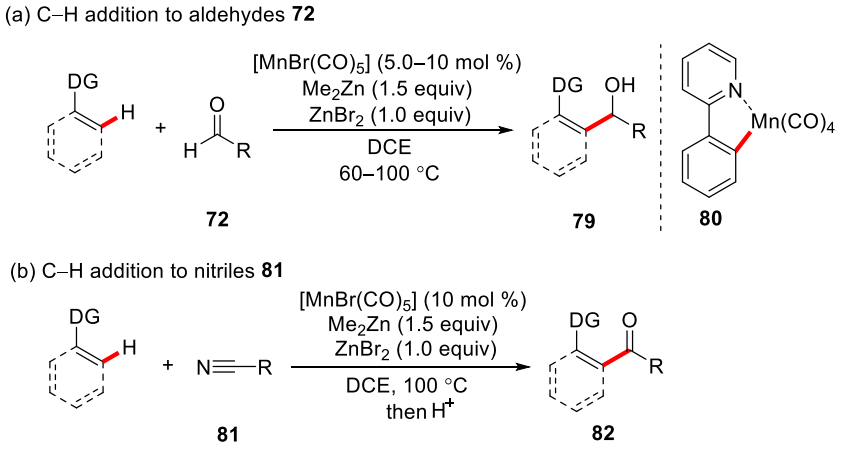
Scheme 1.3.2 Manganese(I)-catalyzed C–H addition to aldehydes **72**.

A plausible catalytic cycle for the C–H activation was proposed by Kuninobu/Takai, which is initiated by oxidative addition of the aromatic C–H bond to the manganese center, thereby delivering the manganese(III) intermediate **77**. Subsequent insertion of a C=O bond into the manganese-carbon bond forms the seven-membered manganacycle **78**. Finally, the treatment of Et_3SiH (**73**) furnishes the desired product **74** *via* the release of H_2 (Scheme 1.3.3).



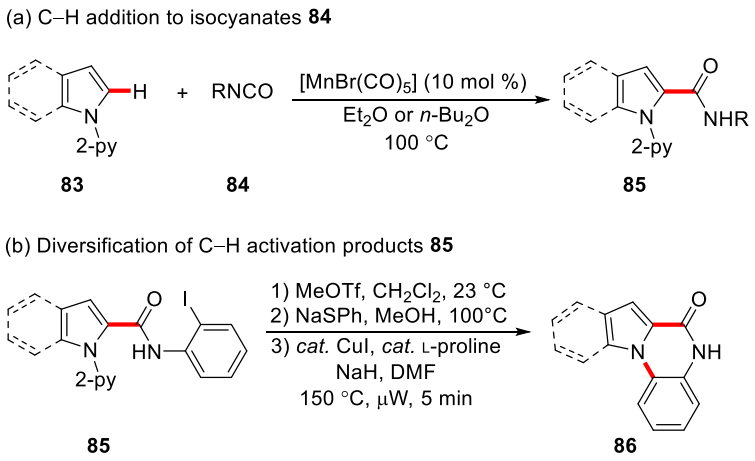
Scheme 1.3.3 Proposed catalytic cycle for manganese(I)-catalyzed C–H addition to aldehydes **72**.

In 2015, Wang and coworkers developed a manganese(I)-catalyzed nucleophilic addition of C(sp^2)–H to aldehydes **72** or nitriles **81** to access the alcohols **79** or ketones **82** with good yields and excellent positional and stereoselectivity (Scheme 1.3.4).[91] Compared to the work of Kuninobu/Takai, the achievement of Wang circumvented the use of external silanes to guarantee catalytic turnover by the aid of $ZnMe_2$ and $ZnBr_2$. Importantly, $ZnMe_2$ was found to be indispensable for the C–H activation step to form manganacycle complex **80**, whereas Lewis-acid $ZnBr_2$ was essential to the aldehyde-activation step.



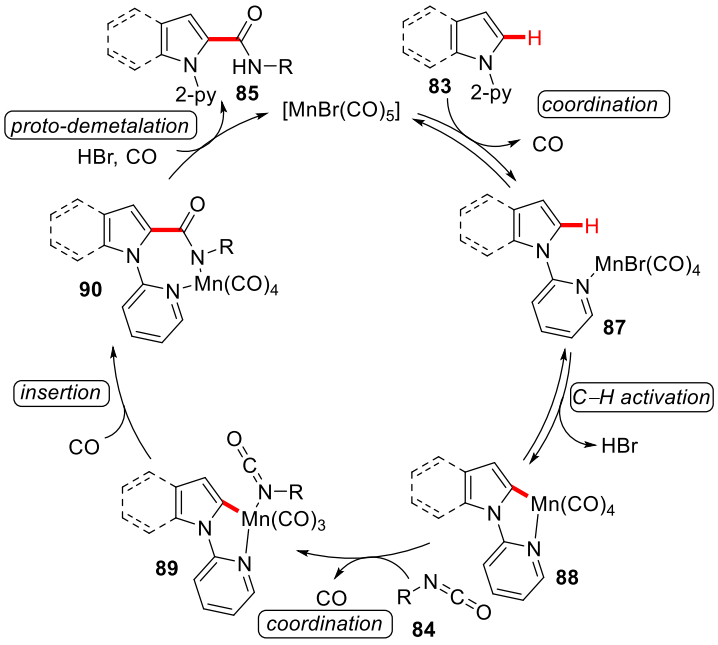
Scheme 1.3.4 Manganese(I)-catalyzed C–H addition to aldehydes **72** and nitriles **81**.

The first example of manganese(I)-catalyzed C–H amidation by using isocyanates **84** was accomplished by Ackermann and co-workers (Scheme 1.3.5),[92] constituting a competent alternative to processes involving relatively expensive rhodium,[93] rhenium,[94] ruthenium[95] or Cp*-containing cobalt(III) catalysts.[96] The C–H aminocarbonylation of heteroarenes **83** were well tolerated with both aryl and alkyl isocyanates **84**, leading to the formation of aminocarbonylated products **85**, which could be easily converted into substituted quinoxalinones **86** by facile late-stage diversification through a removable directing group strategy.



Scheme 1.3.5 Manganese(I)-catalyzed C–H aminocarbonylation of heteroarenes.

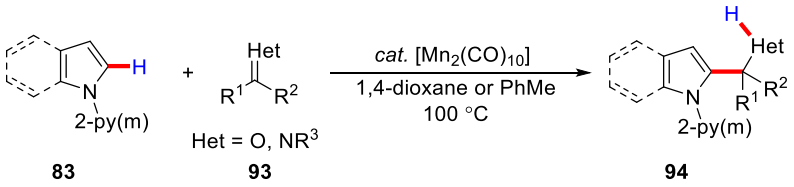
A catalytic cycle for the manganese(I)-catalyzed C–H aminocarbonylation was proposed to be initiated by the precoordination of the substrate's pyridine moiety. The subsequent C–H metalation formed the cyclometalated complex **88**, followed by coordination and rate determining insertion of isocyanate **84**. Finally, the desired product **85** is released by proto-demetalation (Scheme 1.3.6).



Scheme 1.3.6 Proposed catalytic cycle for manganese(I)-catalyzed C–H aminocarbonylation.

Thereafter, a significant advance was achieved by Ackermann and coworkers, for the unprecedented additive-free manganese(I)-catalyzed hydroarylation of C=Het multiple bonds (Het=heteroatom) (Scheme 1.3.7).[97] Thus, indoles **83** underwent C2-selective C–H

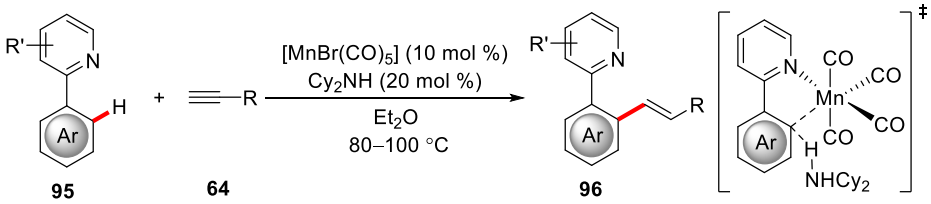
functionalizations with aldehydes, ketones and imines, overcoming the innate substrate selectivity.



Scheme 1.3.7 Additive-free manganese(I)-catalyzed C=Het hydroarylation.

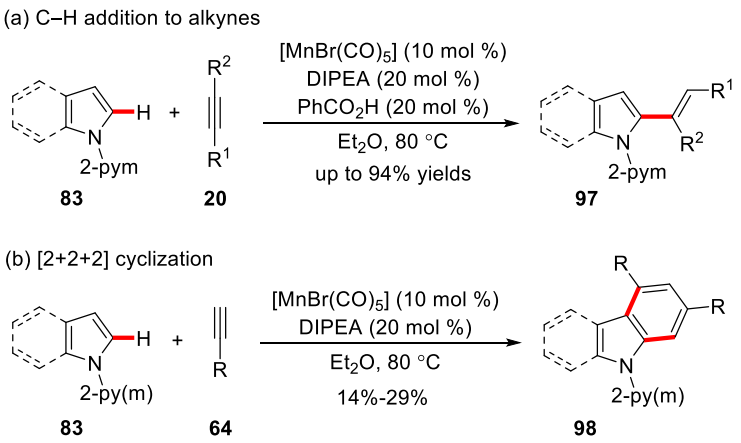
1.3.2 Addition to C–C Multiple Bond

Manganese(I)-catalyzed C–H activation was not limited to additions onto polar C=Het bonds. Indeed, Wang reported a manganese(I)-catalyzed C–H alkenylation *via* hydroarylation of alkynes **64** in the presence of $HNCy_2$ as the additive. However, the C–H alkenylation was thus far largely restricted to terminal alkynes (Scheme 1.3.8). The reaction was suggested to be initiated by base-assisted deprotonative C–H activation resulting in the five-membered manganacycle **80**.[98]



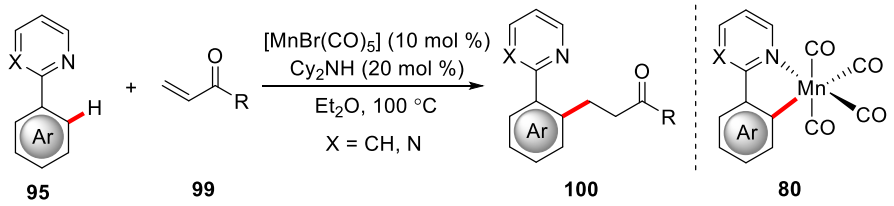
Scheme 1.3.8 Manganese(I)-catalyzed C–H alkenylation with terminal alkynes **64**

A similar work on manganese(I)-catalyzed C–H alkenylation with highly extended substrate scope was later performed by Li and coworkers (Scheme 1.3.9).[99] Compared to the previous work from Wang, the C–H olefination was not limited to terminal alkynes **64** but also the internal alkynes **20**, furnishing various indolyl-alkenes products, by using a catalytic amount of acid as additive. Interestingly, carbazoles **98** were formed in low yields *via* a [2+2+2] cycloaddition pathway in the absence of the acid (Scheme 1.3.9b). The additive $PhCO_2H$ was considered as the key to control the chemo-selectivity *via* a proton-transfer process



Scheme 1.3.9 Manganese(I)-catalyzed C–H alkenylation and cyclization of indoles **83**

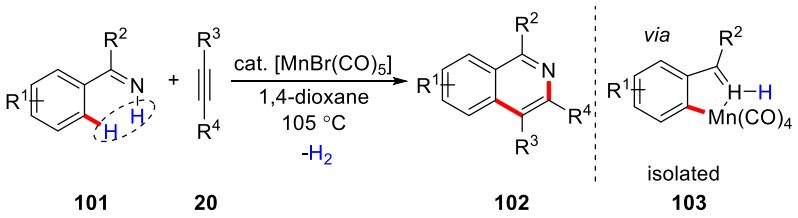
The C–H addition strategy was also applicable to alkenes, as demonstrated by Wang and coworkers, with a manganese(I)-catalyzed C–H addition to α,β-unsaturated carbonyls **99** in the presence of catalytic $MnBr(CO)_5$ and $HNCy_2$ as base (Scheme 1.3.10).[100]



Scheme 1.3.10 Manganese(I)-catalyzed C–H addition to *α,β*-unsaturated carbonyls **99**.

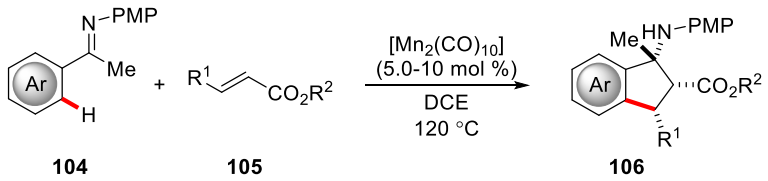
(c) Annulation

The synthesis of isoquinoline derivatives **102** was accomplished by Wang and coworkers *via* dehydrogenative [4+2] annulation of N−H free imines **101** with alkynes **20** in the presence of $MnBr(CO)_5$ (Scheme 1.3.11).[101] Compared to other well-known isoquinoline synthesis process,[102] this highly atom-economical and user-friendly strategy only produced H_2 as the byproduct without any oxidants, ligands, or additives. Importantly, the five-membered manganacycle **103** could be isolated.



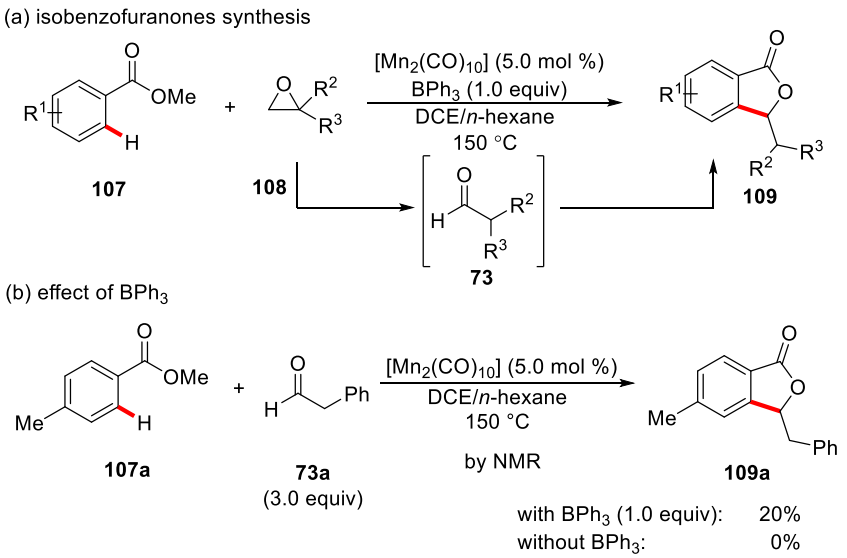
Scheme 1.3.11 Manganese(I)-catalyzed C−H annulation of N−H imines **101** with alkynes **20**.

In 2015, Ackermann and co-workers illustrated the first manganese(I)-catalyzed step-economical C−H annulation of imines **104** with acrylates **105** in DCE or toluene as the solvents. The valuable carbocyclic β-amino acids **106** were provided by the annulation with either terminal alkenes or more challenging internal alkenes **105** in high efficacy, good functional group tolerance and high *cis*-diastereoselectivity (Scheme 1.3.12).[103]



Scheme 1.3.12 Manganese(I)-catalyzed C–H annulation of iminines **104** with acrylates **105**.

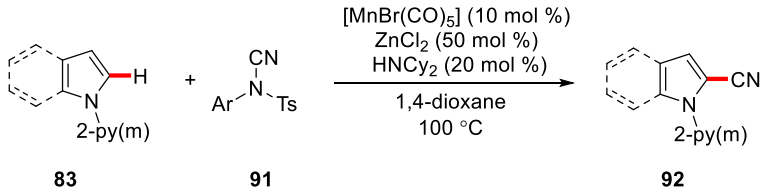
Recently, Kuninobu and co-workers developed the preparation of isobenzofuranones **109** from aromatic esters **107** and oxiranes **108** *via* manganese-catalyzed C−H bond activation with the assistance of Lewis-acid BPh_3 at high temperature (Scheme 1.3.13a).[104] Indeed, key to success was constituted by using BPh_3 as the additive, which was found to be indispensable for promoting the C−H functionalization by cooperation with the manganese catalyst (Scheme 1.3.13b).[104]



Scheme 1.3.13 Manganese(I)-catalyzed isobenzofuranones synthesis and the effect of BPh_3.

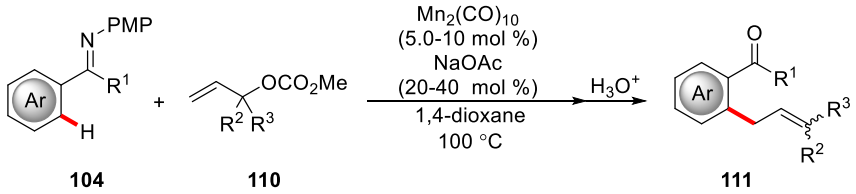
1.3.4 Substitutive C−H Functionalization and others

The manganese-catalyzed C–H cyanation on indoles, pyrroles and tryptophans by means of synergistic manganese and $ZnCl_2$ as co-catalyst was presented by Ackermann and coworkers (Scheme 1.3.14).[105] The role of the Lewis-acid $ZnCl_2$ was the first time illustrated by experimental mechanistic studies and DFT calculations, which disclosed the synergistic effect of the catalysis through stabilizing coordinative interactions of the zinc(II) additive on the cyclomanganated transition state.



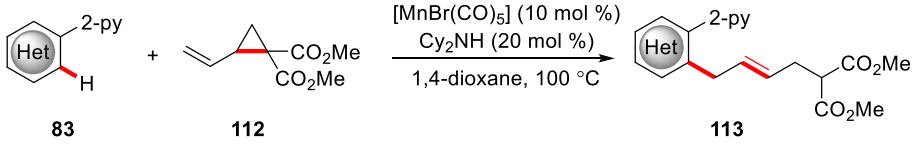
Scheme 1.3.14 Manganese(I)-catalyzed C–H cyanation on indoles.

In 2016, Ackermann and co-workers established an unprecedented manganese(I)-catalyzed substitutive C−H allylation with allyl carbonates **110** (Scheme 1.3.15). This example constitutes the first manganese(I)-catalyzed C−H activation of imines and heterocycles to give the linear allylation products **111** through general C−H metalation, migratory insertion, ß-oxygen elimination and decarboxylation process.[106]



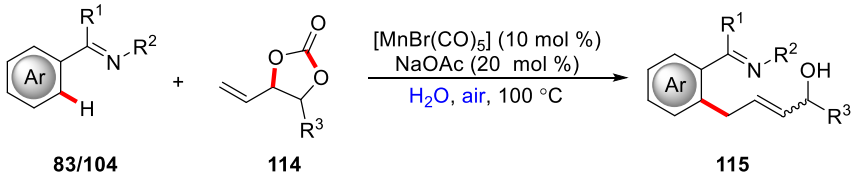
Scheme 1.3.15 Manganese(I)-catalyzed substitutive C−H allylation imines.

Based on the previous work, Ackermann and co-workers consistently realized manganese(I)-catalyzed dispersion-enabled C−H/C−C activation of indole with vinylcyclopropane substrates **112** (Scheme 1.3.16).[107] The silver-free C−H/C−C transformations led to the obtention of allylated heterocycle **113** in high yields and with excellent (*E*)-diastero-selectivities that was complementary to the one observed with the Cp*Co(III)/Ag catalytic system.[108] Moreover, the robustness of the manganese(I) catalyst set the stage for the first application of C−H/C−C functionalization strategy to the late-stage diversification of amino acids under racemization-free reaction conditions.



Scheme 1.3.16 Manganese(I)-catalyzed C−H/C−C activation

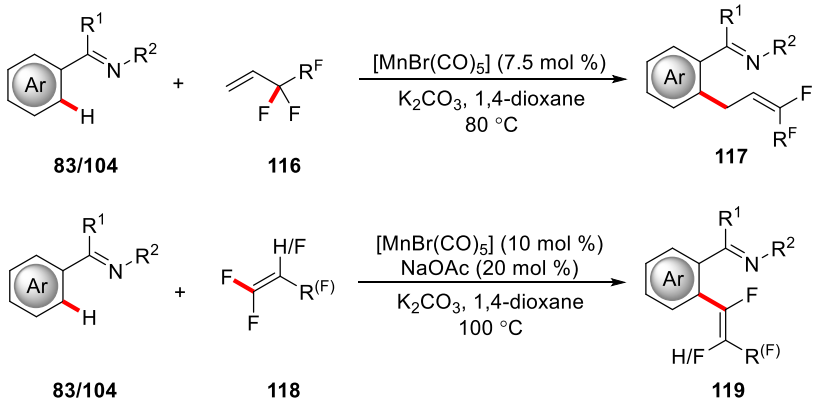
Inspired by the robustness of manganese catalysis in C−H activation, an air- and water-tolerant manganese(I)-catalyzed decarboxylative C−H/C−O activation of indoles, ketimines and tryptophan derivatives with dioxolanone **114** was accomplished by the group of Ackermann,[109] as well as other related work were reported by other groups (Scheme 1.3.17).[110]



Scheme 1.3.17 Air- and H_2O-tolerant manganese(I)-catalyzed C−H/C−O activation

Very recently, Ackermann and co-workers reported the first examples of manganese-catalyzed C−H/C−F functionalizations, which set the stage for a variety of step-economical (per)fluoro-

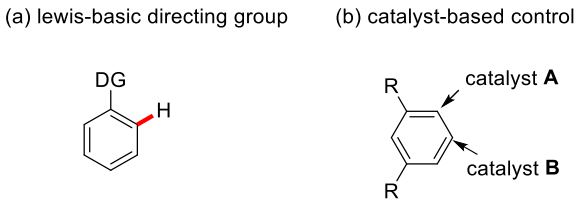
allylations and alkenylations (Scheme 1.3.18).[111] These manganese-catalyzed C−H activation involved a base-assisted C−H metalation, and insertion of unsaturated multiple bonds into the Mn−C bond *via* an overall isohypsic mode of action.



Scheme 1.3.18 Manganese(I)-catalyzed C−H/C−F activation

1.4 Ruthenium-Catalyzed *meta*-Selective C−H Functionalization

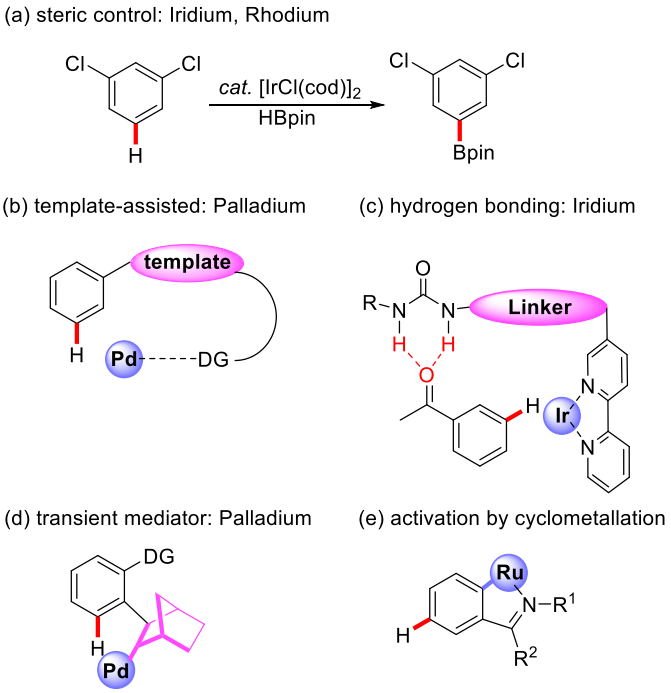
Achieving site-selectivity is of great importance in C–H functionalization chemistry. The arenes of interest bear many C–H bonds with comparable dissociation energies and therefore controlling chemo- and regioselectivity can be a significant challenge. Several strategies have been developed to achieve site-selectivity between various chemically similar C–H bonds. These include the assistance of a Lewis-basic directing group facilitate the activation in the *ortho*-position (Scheme 1.4.1a); and catalyst-based control (Scheme 1.4.1b).[112]



Scheme 1.4.1 Site-selectivity in C−H functionalization.

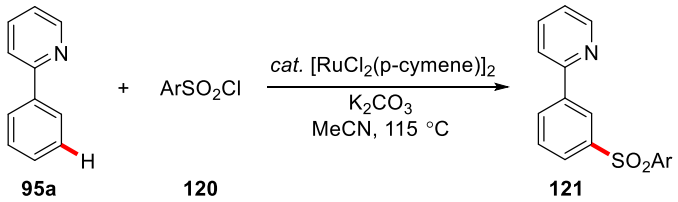
Despite significant recent advances, the chelation-assisted C−H activations provided mainly access to a plethora of *ortho*-functionalized products.[12b-n, 113] In stark contrast, general approaches for *meta*-selective C−H transformations continue to be scare.[112, 114] Notable exceptions for remote C−H functionalizations are exploiting the inherent steric features of substrate−catalyst interactions (Scheme 1.4.2a).[115] As an alternative, among others, Yu and co-

workers installed rationally designed auxiliaries, which bring the metal in close proximity to the *meta* position (Scheme 1.4.2b).[116] However, the synthesis and installation of these auxiliaries requires additional steps. Recently, Kanai and coworkers developed an approach based on a linker installed on the ligand which coordinates to the substrate *via* covalent or secondary hydrogen interactions and thus resulting the metal chelation to the *meta*-C–H bond (Scheme 1.4.2c).[117] Another catalytic strategy is based on the Catellani reaction, where a transient mediator, for example, norbornene, set the stage for *meta*-selective C−H activation, as reported by Yu and Dong (Scheme 1.4.2d).[118] In contrast, ruthenium catalysis was recently shown to facilitate *meta*-selective C−H activations by means of chelation-assisted cyclometalation (Scheme1.4.2e).[114d]



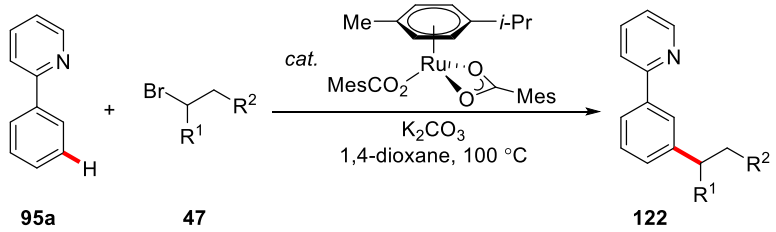
Scheme 1.4.2 Strategies for *meta*-selective C−H functionalization.

Frost and co-workers discovered that ruthenium catalysis led to *meta*-functionalization in direct C−H sulfonation of 2-phenylpyridine derivatives (**95a**) (Scheme 1.4.3).[119] To account for the regioselectivity of ruthenium, the authors hypothesized that the chelating group facilitates the formation of a stable cyclometalated ruthenium complex containing a Ru-C_{aryl} σ-bond that induces a strong *para*-directing effect.



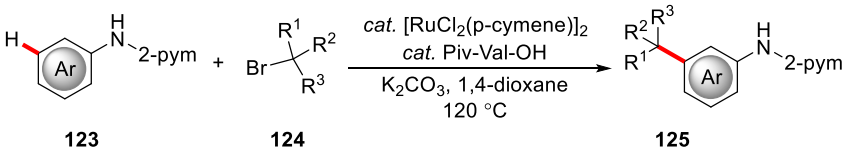
Scheme 1.4.3 *meta*-Sulfonation of phenylpyridine.

In 2008, the group of Ackermann first introduced carboxylates as ligands for robust and effective ruthenium(II)-catalyzed C−H bond arylations,[120] followed by oxidative alkenylations,[19d, 121] alkyne annulations[102c, 122] as well as primary alkylations,[70a, 70b, 123] which occurred exclusively at the *ortho*-position. In 2011, the same group devised the first direct C−H bond alkylations of arenes with unactivated alkyl halides **47** under mild reaction conditions (Scheme 1.4.4), while detailed mechanistic studies provided strong evidence for an initial *ortho*-C−H cyclometalation with subsequent remote *meta*-functionalization.[124]



Scheme 1.4.4 *meta*-Selective direct alkylation of phenylpyridine.

Very recently, Ackermann has developed a system for *meta*-selective *tert*-alkylation on electron-rich aniline derivatives with versatile removable directing groups (Scheme 1.4.5).[125] Interestingly, mono protected amino acids (MPAAs) were shown to be the best ligands for this ruthenium(II)-catalyzed remote C−H functionalizations. The robust nature of the versatile ruthenium(II)-MPAA system was mirrored by challenging remote C−H activations with tertiary alkyl halides **124** on anilines **123** as well as pyridyl-, pyrimidyl- and pyrazolyl-substituted arenes.[125] The authors also provided experimental evidence for an initial reversible C−H ruthenation, followed by a SET-type C−Hal activation through homolytic bond cleavage.

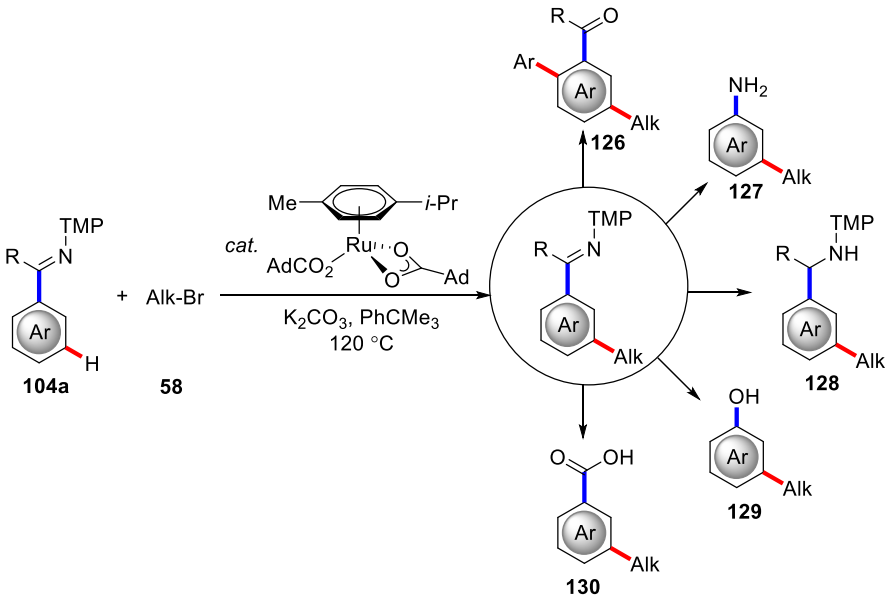


123 **124** **125**

Scheme 1.4.5 *meta*-Selective C−H *tert*-alkylation of anilines **123**.

At the same time Frost and coworkers presented the *meta*-C–H *tert*-alkylation of phenylpyridines with a somewhat narrow substrate scope.[126] Furthermore, recent progress has been made in *meta*-selective bromination[127] and nitration[128] of phenylpyridines as well as *meta*-alkylation[129] and sulfonation[130] of azoarenes.

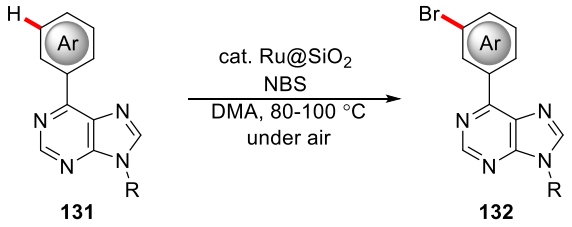
However, these strategies for ruthenium-catalyzed *meta*-C–H functionalization continue to be restricted to strongly coordinating heteroaromatic pyridyl, pyrazolyl, imidazolyl or pyrimidy directing groups, which are difficult to modify or remove. To address these limitation, Ackermann and coworkers developed a powerful ruthenium(II)-catalysis manifold that facilitated efficient secondary and tertiary C–H alkylations of easily accessible ketimines **104a** with exceptional levels of *meta*-selectivity. The transformative feature of this approach was emphasized by the preparation of a variety of *meta*-substituted arenes, including ketones, amines, indoles, acids and phenols through late-stage diversification (Scheme 1.4.6).[131]



104a **58**

Scheme 1.4.6 Versatility of the ruthenium(II)-catalyzed *meta*-alkylation.

Remarkably, in 2017, Ackermann and coworkers reported the first remote *meta*-C–H bromination on purine bases by a heterogeneous ruthenium catalyst, which could be easily recovered and reused (Scheme 1.4.7).[132]

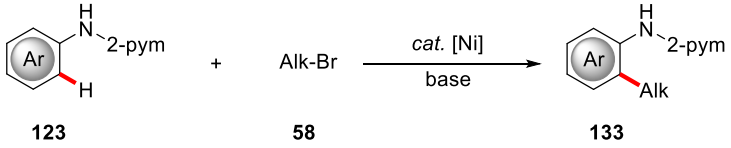


Scheme 1.4.7 Heterogeneous ruthenium catalyst for *meta*-C–H bromination on purines.

2 Objectives

Remarkable advances in transition metal-catalyzed C–H bond functionalization have been achieved by the group of Prof. Dr. Ackermann, especially in the chemo-, site- and enantioselective direct construction of C–C and C–Het bonds, with applications to material sciences, drug discovery and peptide assembly.[1c, 12i, 12n, 89, 124, 133] In this context, major efforts were made to develop novel C–H activation reactions by user-friendly nickel, manganese and ruthenium catalysis.

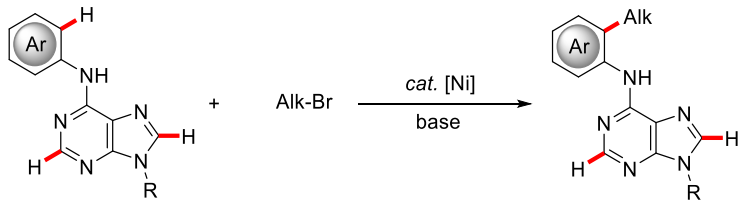
At the outset of this thesis, Ackermann and coworkers had developed a novel nickel-catalyzed C–H alkylation of benzamides with bidentate auxiliaries,[62a] as well as an efficient indole synthesis from 2-pyrimidyl anilines by nickel catalysis *via* alkyne annulation.[65] In consideration of the importance of 2-pyrimidyl anilines as structural motifs of bioactive compounds relevant to crop protection and medicinal chemistry,[134] the direct C–H functionalization of anilines **123** bearing a monodentate directing group with alkyl halides **58** was to be investigated (Scheme 2.1).



123 **58** **133**

Scheme 2.1 Nickel-catalyzed C–H alkylation of anilines **123**.

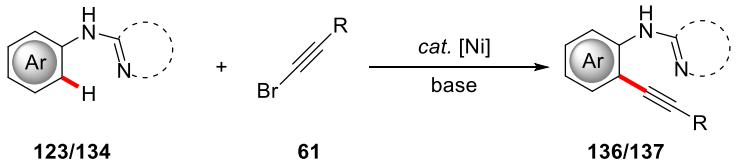
Likewise, purines represent an important and attractive structural motif in drug discovery,[135] and viable possibilities[136] of nucleobase modification are highly desired in synthetic chemistry. Therefore, the development of a protocol for versatile nickel-catalyzed C–H activation of 6-anilinopurines **134** with alkyl halides **58** was devised (Scheme 2.2).



134 **58** **135**

Scheme 2.2 Nickel-catalyzed C–H activation of purine bases **134** with alkyl halides **58**.

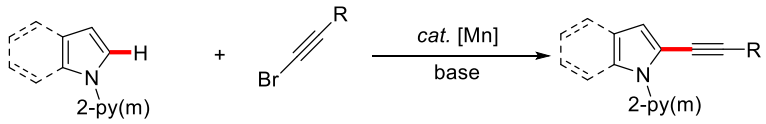
Compared to the palladium-catalyzed Sonogashira-Hagihara reaction, direct C–H alkynylations have been identified as more environment friendly alternatives.[76] In recent years, despite remarkable advances in nickel-catalyzed C–H alkynylations,[77, 137] most nickel-catalyzed C–H alkynylations were limited to the acidic C–H bonds of azoles or electron-deficient benzamide derivatives bearing *N*,*N*-bidentate auxiliaries. Thus, the development of novel strategies for nickel-catalyzed C–H alkynylations of electron-rich aniline derivatives **123** or **134** with alkynyl bromides **61** was to be achieved (Scheme 2.3).



123/134 **61** **136/137**

Scheme 2.3 Nickel-catalyzed C–H alkynylation of anilines **123**/**134**.

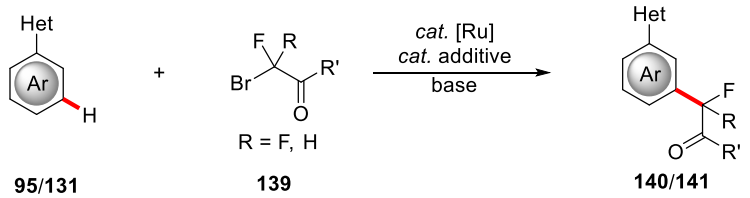
Based on research in transition-metal catalyzed C–H alkynylation, less toxic manganese has recently gained interest in C–H activation, yet limited to the insertion reactions of multiple C–Het or C–C bonds.[89] Therefore, it was of great interest to establish a novel approach for manganese-catalyzed substitutive C–H alkynylation with organic halides **61** (Scheme 2.4).



83 **61** **138**

Scheme 2.4 Manganese-catalyzed C–H alkynylation of indoles **83**.

The introduction of fluorine into bioactive compounds uniquely affects their properties, including solubility, bioavailability, and metabolic behavior.[138] For instance, fluorine atoms can be found in 30% of all agrochemicals and 20% of all marketed drugs.[138-139] As a result, suitable methodologies for the synthesis of fluorinated molecules are still strongly needed.[140] Based on the recent advances by the group of Ackermann on ruthenium(II)-catalyzed C–H activation by phosphorus ligand-acceleration,[12e, 120d, 122c, 141] and *meta*-C–H alkylations by a single-electron transfer (SET) pathway,[124-125] we set out to develop a strategy for the installation of fluorine through ruthenium-catalyzed remote C–H (di)fluoromethylation by phosphine/carboxylate cooperation (Scheme 2.5).



95/131 **139** **140/141**

Scheme 2.5 Ruthenium(II)-catalyzed *meta*-C–H mono- and difluoromethyaltions.

3 Results and Discussion

3.1 Nickel-Catalyzed C–H Alkylation of Anilines

2-Pyrimidyl anilines are privileged structural motifs of numerous bioactive compounds found in crop protection and medicinal chemistry, such as the anticancer drug Gleevec (Figure 3.1.1).[134, 142] In view of these biological importance, it is important to develop new methods for the direct preparation of *ortho*-functionalized aniline derivatives.

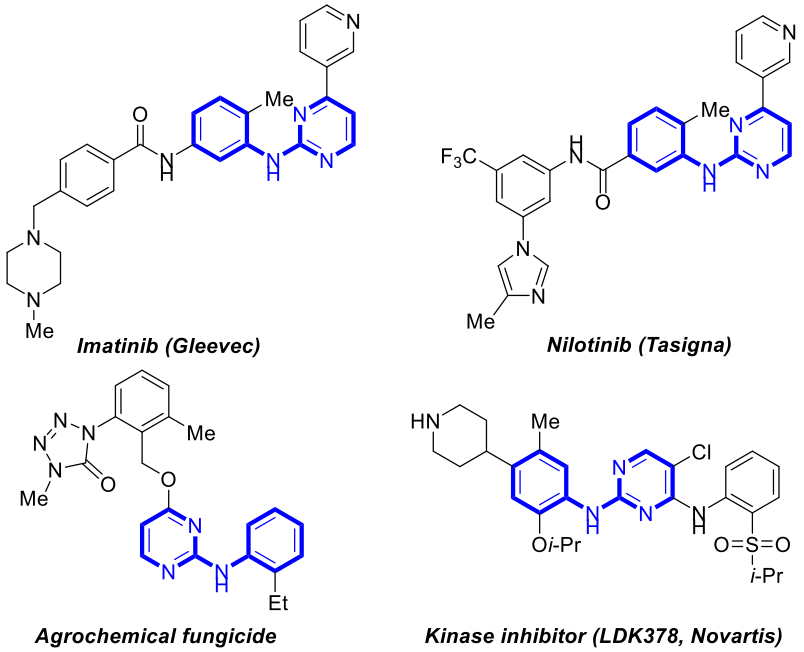


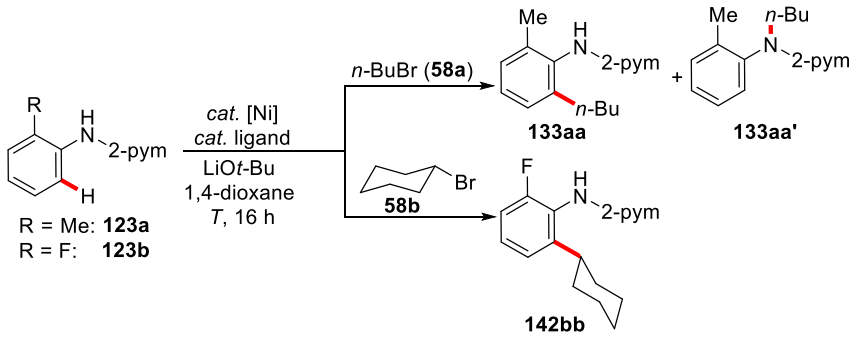
Figure 3.1.1 2-Pyrimidyl anilines in drugs and bioactive compounds.

3.1.1 Optimization of Nickel-Catalyzed C–H Alkylation with Anilines

We initiated our studies for the envisioned C–H alkylation of aniline **123a**, which contains a monodentate *N*-pyrimidyl directing goup, with alkyl bromide **58a** (Table 3.1.1). Catalytic systems previously reported for the nickel-catalyzed direct C–H alkylations of benzamides with primary alkyl halides, using bidentate directing groups, provided unsatisfactory results along with *N*-alkylation byproducts (entries 1–3). Likewise, the use of various N-heterocyclic carbene preligands resulted in just moderate yields (entries 4–6). In sharp contrast, extensive and

detailed optimization studies revealed that vicinal secondary diamines to be particularly suitable ligands for the transformation (entries 7-9). While tertiary amines, such as TMEDA gave undesired results, the secondary diamine D*t*-BEDA (**143**) showed high conversion to the desired product **133aa**. The optimal results were achieved in 1,4-dioxane as the solvent of choice at slightly reduced temperatures without forming side-product **133aa'** (entries 10–11). The control experiments verified the essential role of the nickel catalyst, while the C–H functionalization proceeded in a similar manner in the absence of an additional ligand (entries 12–13). It is noteworthy that the optimized nickel catalysis derived from vicinal diamine **143** was not limited to C–H activation with primary alkyl halides. Indeed, the versatile nickel catalyst set the stage for a general C–H alkylation strategy, also enabling C–H transformation with secondary alkyl halide **58b** under otherwise identical reaction conditions (Table 3.1.1, right column).

Table 3.1.1 Optimization of nickel-catalyzed C–H alkylation with anilines **123**[a]



Entry	[Ni]	Ligand	Yield [%] **133aa**	**133aa'**	**142bb**
1	[(DME)$NiCl_2$]	-	18[b]	0	---
2	$Ni(OTf)_2$	PPh_3	19[b]	8	5[c,d]
3	[(DME)$NiCl_2$]	PPh_3	26[b]	17	---
4	[(DME)$NiCl_2$]	**L1**	40[b]	4	66[c,d]
5	[(DME)$NiCl_2$]	**L2**	54	8	---
6	[(DME)$NiCl_2$]	**L3**	22[b]	4	---
7	[(DME)$NiCl_2$]	**L4**	43	0	---
8	[(DME)$NiCl_2$]	**L5**	31[b]	7	---

9	[(DME)$NiCl_2$]	**L6**	84	0	18[c,d]
10	[(DME)$NiCl_2$]	TMEDA	33[b]	0	19[c]
11	**[(DME)$NiCl_2$]**	**D*t*-BEDA (143)**	**87**	**0**	**99**[c]
12	-	D*t*-BEDA (**143**)	0	12	0
13	[(DME)$NiCl_2$]	-	45	0	24[c,d]

[a] Reaction conditions: **123a** or **123b** (0.50 mmol), **58a** or **58b** (1.0 mmol), [Ni] (5.0 mol %), ligand (10 mol %), LiO*t*-Bu (2.0 equiv), 1,4-dioxane (1.5 mL), 120 °C, 16 h; yields of isolated products are given. [b] [Ni] (10 mol %), ligand (20 mol %), PhMe (1.5 mL), 160 °C. [c] [Ni] (2.5 mol %), ligand (5.0 mol %), 1,4-dioxane (1.5 mL), 100 °C. [d] ^{19}F NMR analysis with C_6F_6 as internal standard, performed by Dr. Sebastian Lackner.

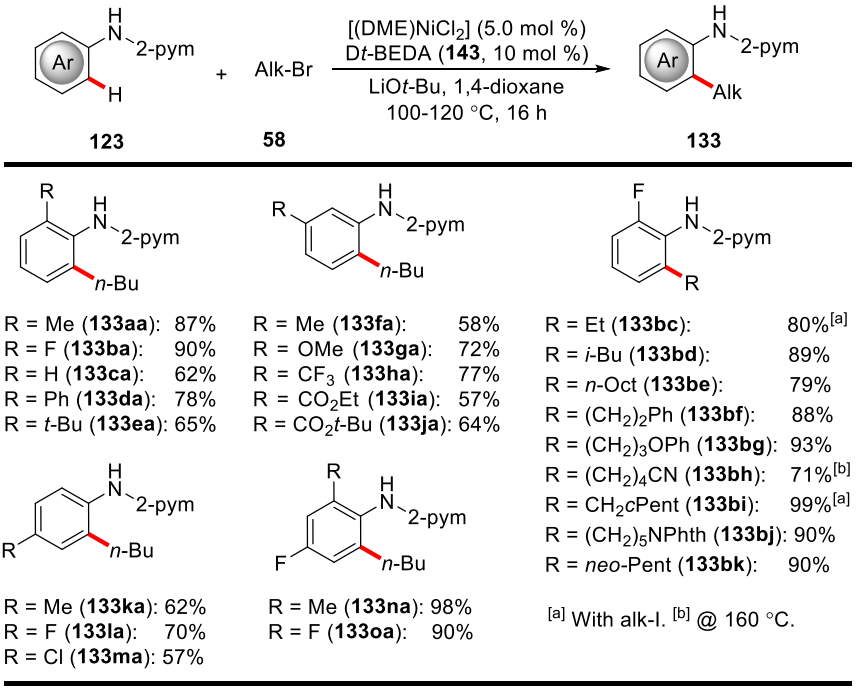
R = Cy (**L1**)
R = 2,6-*i*-$Pr_2C_6H_3$ (**L2**)
R = Mes (**L3**)

R = Cy (**L4**)
R = 2,6-*i*-$Pr_2C_6H_3$ (**L5**)
R = 1-Ad (**L6**)
R = *t*-Bu (D*t*-BEDA, **143**)

Figure 3.1.2 Ligands employed for C–H alkylation.

3.1.2 Scope of Nickel-Catalyzed C–H Activation with Primary Alkyl Halides

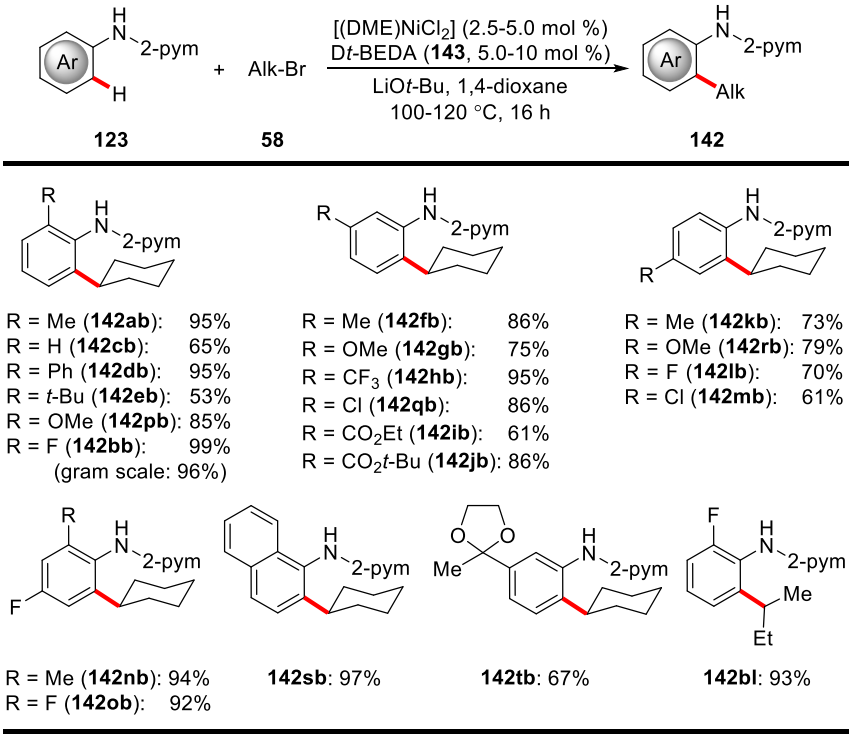
With the optimized catalytic system in hand, we probed the C–H alkylation with a wide variety of aniline derivatives **123** with primary alkyl halides **58** (Scheme 3.1.1). The nickel-catalyzed C–H activation strategy enabled highly chemo-selective transformations of *ortho*- and *para*-substituted arenes **123a**–**123e** and **123k**–**123o**, giving moderate to high yields of mono-alkylated products **133**. Moreover, we were particularly delighted to observe that *meta*-substituted substrates **123f**–**123j** containing useful ester functional groups, reacted exclusively at the sterically less hindered C–H bond. Furthermore, a variety of functionalized alkyl halides **58c**–**58j**, for instance, ether or nitrile, were well tolerated as well as various alkyl chain lengths. Remarkably, a sterically hindered neopentyl group could be directly introduced by the nickel-catalyzed C–H functionalization method to furnish product **133bk** in good selectivity and excellent yield.



Scheme 3.1.1 Scope of nickel-catalyzed C–H alkylation with primary alkyl halides **58**.

3.1.3 Scope of Nickel-Catalyzed C–H Activation with Secondary Alkyl Halides

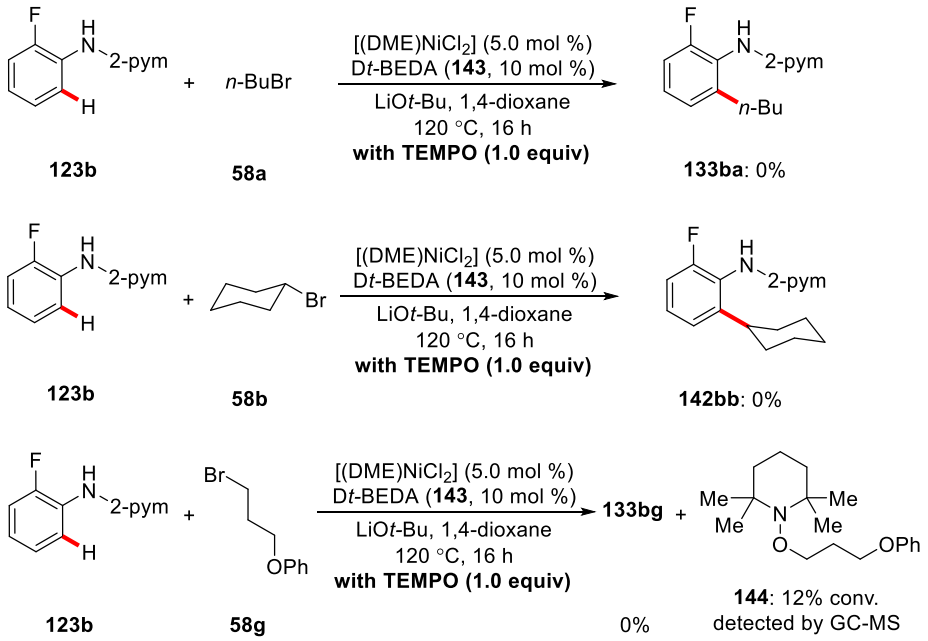
Thereafter, we probed the efficacy of the optimized nickel(II) catalysis derived from ligand **143** in challenging transformations with secondary alkyl halides (Scheme 3.1.2). The robustness of our approach was reflected by successful C–H activation with a broad range of different substituted anilines **123** with secondary alkyl bromide **58b**. Furthermore, the reactions could be performed on gram scale, which furnished the desired product in high efficiency as 96% isolated yield. The reactions with secondary alkyl halides proved to be in a site-selective fashion with *ortho*-, *meta*-, and *para*-substituted anilines, displaying halo, ether, ester and acetal substituents. Moreover, the user-friendly nickel catalysis system could not only be used for reactions with cyclic alkyl halide **58b**, but also acyclic electrophile **58l**. Obviously, the versatile nickel-catalyzed C–H functionalization with secondary alkyl halides could be performed with lower catalyst loading even at a lower temperature than that described in previous report.[62a, 62b]



Scheme 3.1.2 Scope of nickel-catalyzed C–H alkylation with secondary alkyl halides **58**.

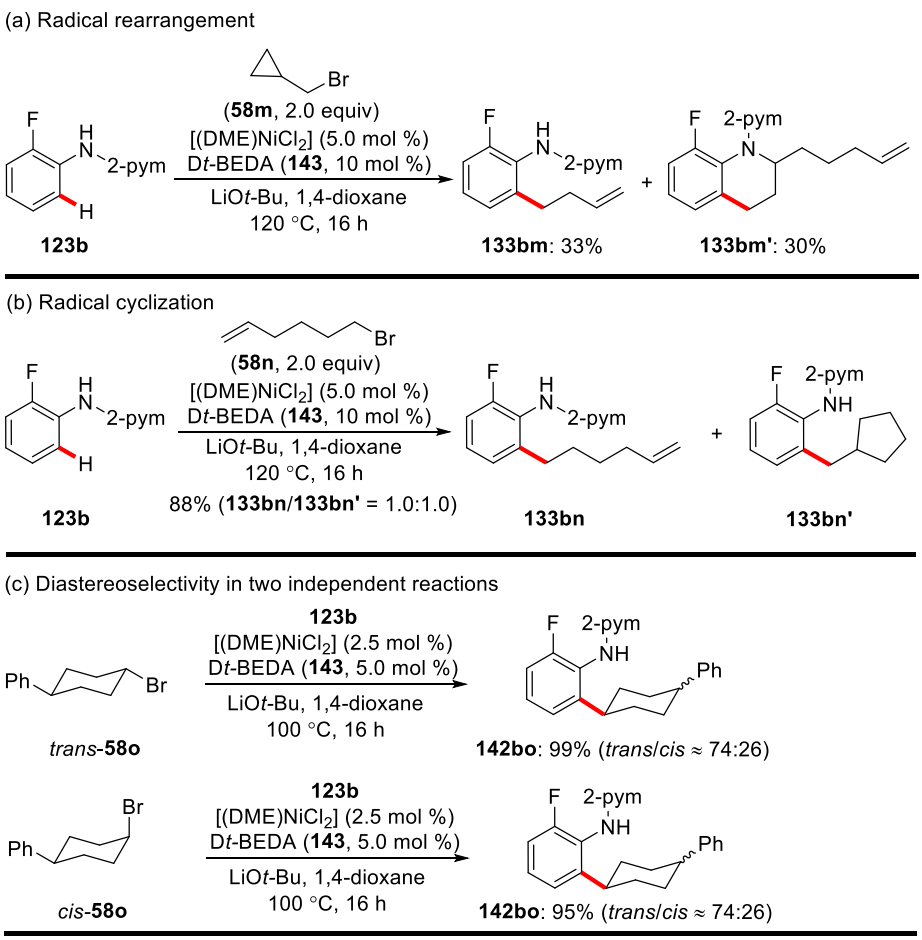
3.1.4 Mechanistic Studies

Considering the uniquely versatile of the nickel-catalyzed C–H alkylation process by monodentate chelation, mechanistic experiments were performed. To this end, the nickel-catalyzed C–H alkylations were performed in the presence of stoichiometric amounts of TEMPO. Primary alkyl halide **58a** or secondary alkyl halide **58b** led to catalyst inhibition by the radical scavenger without radical adduct formation. Howerver, by the use of alkyl halide **58g** in the presence of the radical scavenger TEMPO, the adduct **144** was observed. The detection of **144** might be contributed to the radical stabilized by the phenoxyl group of (3-bromopropoxy)benzene (**58g**) (Scheme 3.1.3).[143]



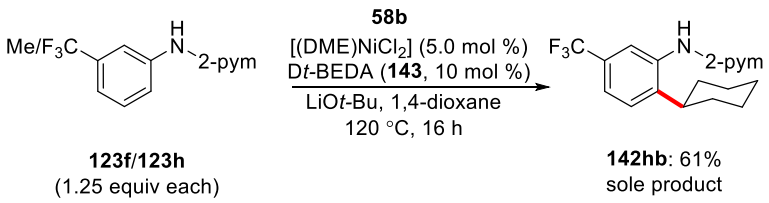
Scheme 3.1.3 C–H Alkylation in the presence of radical scavenger.

In good agreement with these observations, experiments with the radical clock cyclopropylmethyl bromide (**58m**) exclusively afforded alkylation products, resulting from a cyclopropylmethyl/homoallyl rearrangement with the notable formation of the 2-substituted tetrahydroquinoline **133bm'**. Likewise, 6-bromohexene (**58n**) delivered the mixtures of alkylated products **133bn** with retention of double bond, and **133bn'** of partial cyclization of substrate **58n**. Moreover, the well-defined *cis*- and *trans*-isomers of **58o** were utilized as electrophiles in two independent C–H alkylations, furnishing the same diastereomeric product mixture **142bo**. This epimerization can be rationalized in terms of a homolytic C–X cleavage process (Scheme 3.1.4).



Scheme 3.1.4 Key mechanistic findings for the C–X cleavage process.

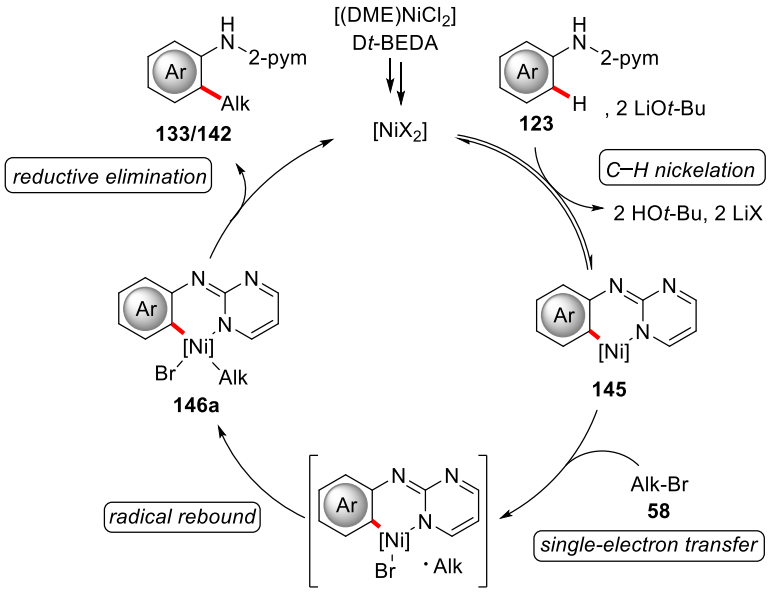
Additionally, an intermolecular competition experiment between electron-rich and electron-deficient anilines were conducted (Scheme 3.1.5). The results clearly showed substituents with electron-withdrawing groups to react preferentially, being indicative of the C–H bond acidity might be crucial for this type reaction.



Scheme 3.1.5 Intermolecular competition experiment.

3.1.5 Proposed Catalytic Cycle

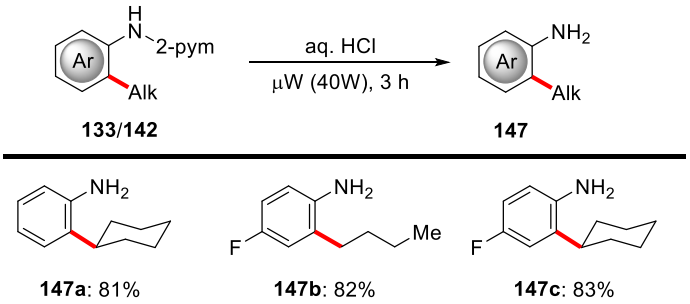
Based on our preliminary mechanistic findings, we propose a plausible catalytic cycle to be initiated by deprotonation of substrate **123**, followed by reversible C–H nickelation, delivering the six-membered[144] metallacycle **145** (Scheme 3.1.6). Thereafter, the nickel species is suggested to trigger the formation of the alkyl radical, which is followed by radical rebound to generate intermediate **146**. Finally, reductive elimination delivers the desired product and regenerates the active catalyst species. Whereas the formation of nickel(IV) species by the action of organic electrophiles,[75c, 75d, 145] radical addition[74] or Ni^{I}/Ni^{III} mechanisms[62b, 75b] cannot be ruled out at this stage.



Scheme 3.1.6 Proposed catalytic cycle.

3.1.6 Removal of the Directing Group

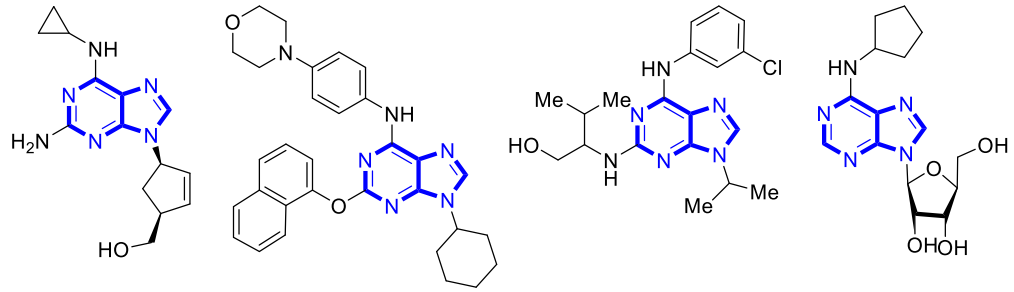
Finally, we illustrated the synthetic utility of our approach by the facile removal of the pyrimidyl group in a traceless fashion, yielding the corresponding anilines **147** in good yields (Scheme 3.1.7).



Scheme 3.1.7 Facile removal of the pyrimidyl group.

3.2 Nickel-Catalyzed C–H Alkylation of Purine Bases

Purines represent a privileged structural motif found in various biologically active compounds with *inter alia* anti-retroviral, anti-cancer and anti-malaria activities (Figure 3.2.1).[135] Thus, within our own program on nickel-catalyzed C–H alkylation, it is useful to further develop novel strategies for the preparation of non-natural purine analogs by atom-economical chemical syntheses.



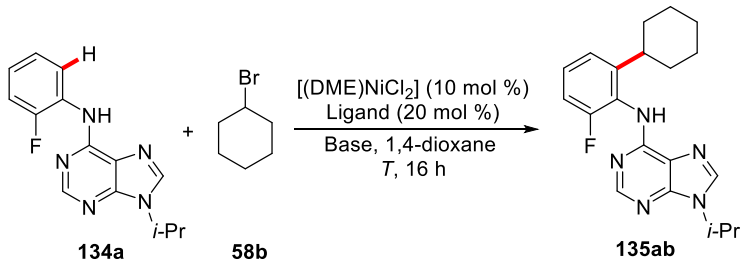
Abacavir (ABC) *(antiretroviral for HIV/AIDS)* ***Purmorphamine*** *(agonist for smoothened)* ***Purvalanol A*** *(inhibitor of Cdk1)* ***N-substituted adenosine*** *(adenosine receptor)*

Figure 3.2.1 Representative pharmaceutically bioactive purine bases.

3.2.1 Optimization of Nickel-Catalyzed C–H Alkylation with Purine Bases

At the outset of our studies, we explored a representative set of ligands for the envisioned nickel-catalyzed C–H alkylation of 6-anilinopurine **134a** with secondary alkyl bromide **58b** in 1,4-dioxane as the solvent (Table 3.2.1). While typical phosphine, N-heterocyclic carbene, or bipyridine ligands yielded desired product **135ab** with unsatisfactory results (entries 1−4). Interestingly, the vicinal diamine D*t*-BEDA (**143**) was identified as being the optimal ligand to afford the desired product **135ab** in 98% yield (entry 5). The conversion of substrate **134a** was not achieved with Na_2CO_3 or K_2CO_3 as the base (entries 6 and 7). Notably, the C−H transformation proceeded in a similar manner in the absence of an additional ligand, albeit with moderate efficiency (entry 8). However, the reaction temperature could be reduced to 100 °C (entry 9). Additionally, a control experiment verified the essential role of the nickel catalyst (entry 10).

Table 3.2.1. Optimization of C−H alkylation with purine **134a**.[a]

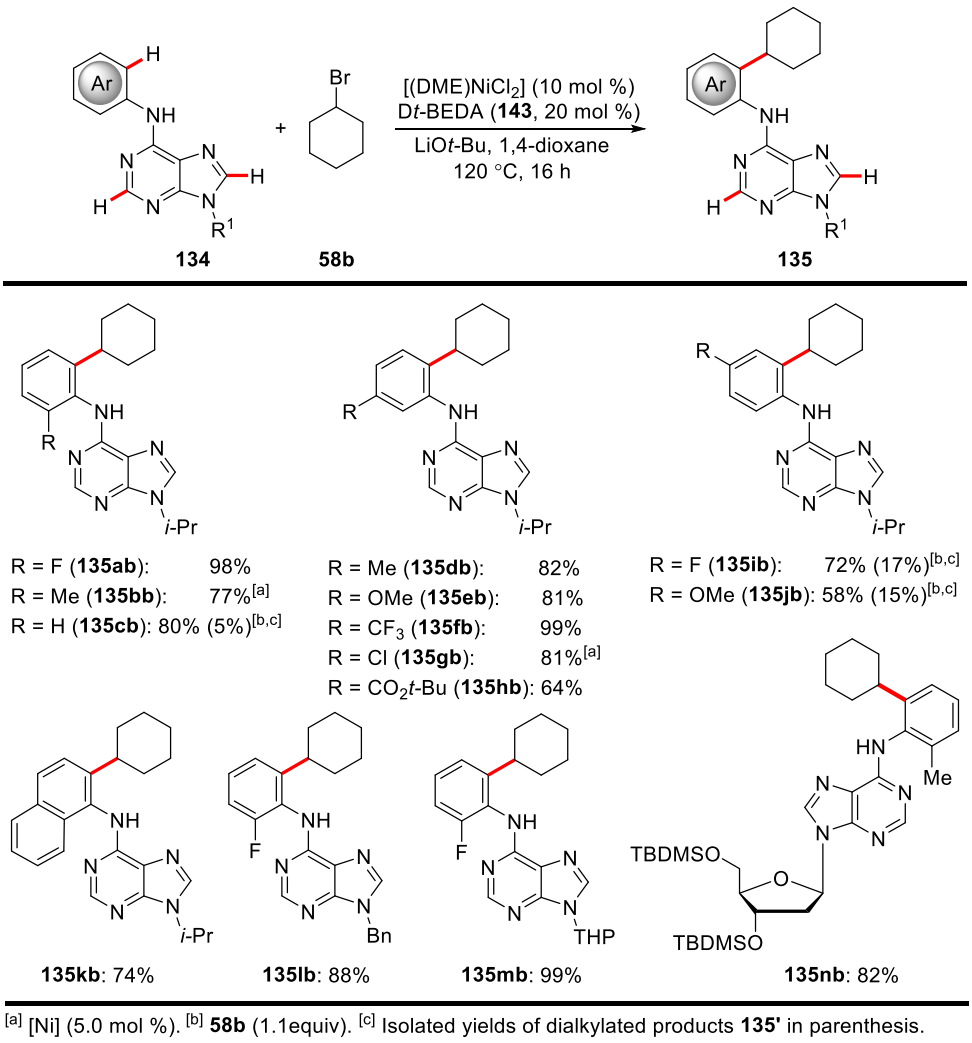


Entry	Ligand	Base	*T* [°C]	**3aa** [%]
1	PPh_3	LiO*t*-Bu	120	47
2	IPr·HCl	LiO*t*-Bu	120	70
3	IMes·HCl	LiO*t*-Bu	120	trace
4	D*t*-BBPY	LiO*t*-Bu	120	0
5	D*t*-BEDA (**143**)	LiO*t*-Bu	120	98
6	D*t*-BEDA (**143**)	Na_2CO_3	120	0
7	D*t*-BEDA (**143**)	K_2CO_3	120	0
8	-	LiO*t*-Bu	120	68
9	D*t*-BEDA (**143**)	LiO*t*-Bu	100	85
10	D*t*-BEDA (**143**)	LiO*t*-Bu	120	0[b]

[a] Reaction conditions: **134a** (0.30 mmol), **58b** (2.0 equiv), [(DME)$NiCl_2$] (10 mol %), ligand (20 mol %), base (2.0 equiv), 1,4-dioxane (1.5 mL), under N_2, 16 h. [b] Without [Ni]. D*t*-BBPY = 4,4'-di-*tert*-butyl-2,2'-dipyridyl.

3.2.2 Scope of Nickel-Catalyzed C–H Alkylation with Purine Bases

With the optimized condition in hand, we probed its versatility in the C–H alkylation of various substituted purine derivatives **134** (Scheme 3.2.1). The nickel-catalyzed C–H activation proved widely applicable and enabled highly chemo-selective transformations of *ortho*- and *para*-substituted arenes **134**. *meta*-Substituted anilines **134d-134h** furnished the desired products **135** with excellent regio selectivity control, which was governed by steric interactions. Moreover, the robustness of the user-friendly nickel catalyst was highlighted by fully tolerating both electron-rich groups as well as synthetically valuable electron-deficient functional groups, such as fluoro, chloro and ester substituents. Substrates displaying different *N*-substituents afforded the C–H alkylated products **135kb**–**135mb** in good yields. Furthermore, the strategy of the nickel-catalyzed C–H alkylation also enable the efficient transformation of purine nucleoside **134n**.



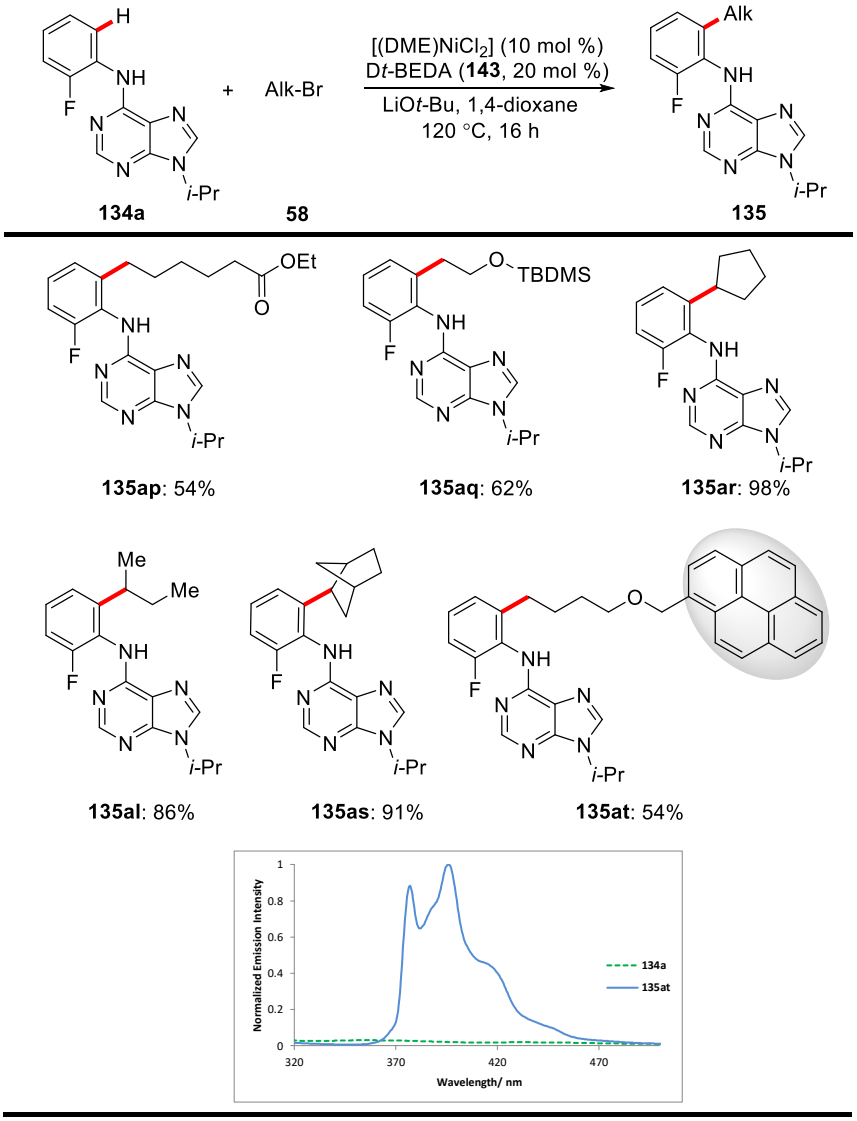
[a] [Ni] (5.0 mol %). [b] **58b** (1.1equiv). [c] Isolated yields of dialkylated products **135'** in parenthesis.

Scheme 3.2.1 C–H Alkylation of purine nucleoside **134**.

3.2.3 Scope of Nickel-Catalyzed C–H Alkylation with Alkyl Halides

Subsequently, we probed the scope of various unactivated primary and secondary alkyl halides **58** in the nickel-catalyzed C–H functionalization manifold (Scheme 3.2.2). The robustness of our method was highlighted by successful C–H alkylations with viable functionalized primary alkyl halides **58**, displaying ester or ether groups, among others. Furthermore, the inexpensive nickel catalyst could not only be applied for couplings with cyclic alkyl halide **58r** in excellent yield, but also the acyclic electrophile **58l**, which afforded the desired product **135al** in a chemoselective manner. Moreover, the C–H alkylation with a norbornyl bromide **58s** furnished the *exo* product **135as** with retention of configuration. Interestingly, the prominent synthetic utility of the nucleobase C–H transformation was demonstrated by introducing a pyrene

fluorescent label in a user-friendly fashion, highlighting the potential for the fluorescent labeling of nucleobases.[146]

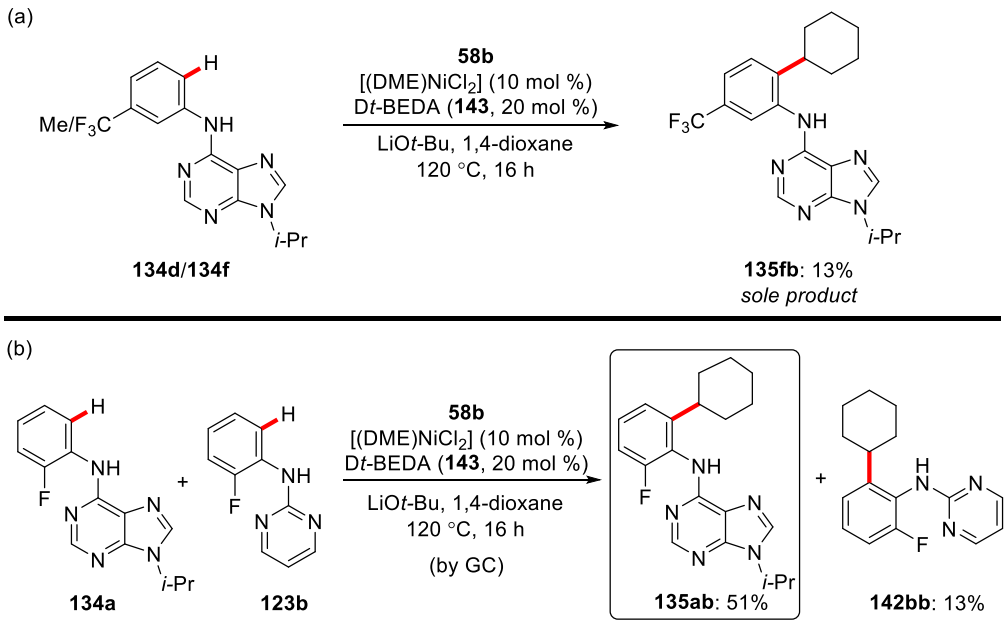


Scheme 3.2.2 C–H Alkylation of purine base **134a** with alkyl halides **58** and fluorescence spectra of **134a** and **135at**.

3.2.4 Mechanistic Studies

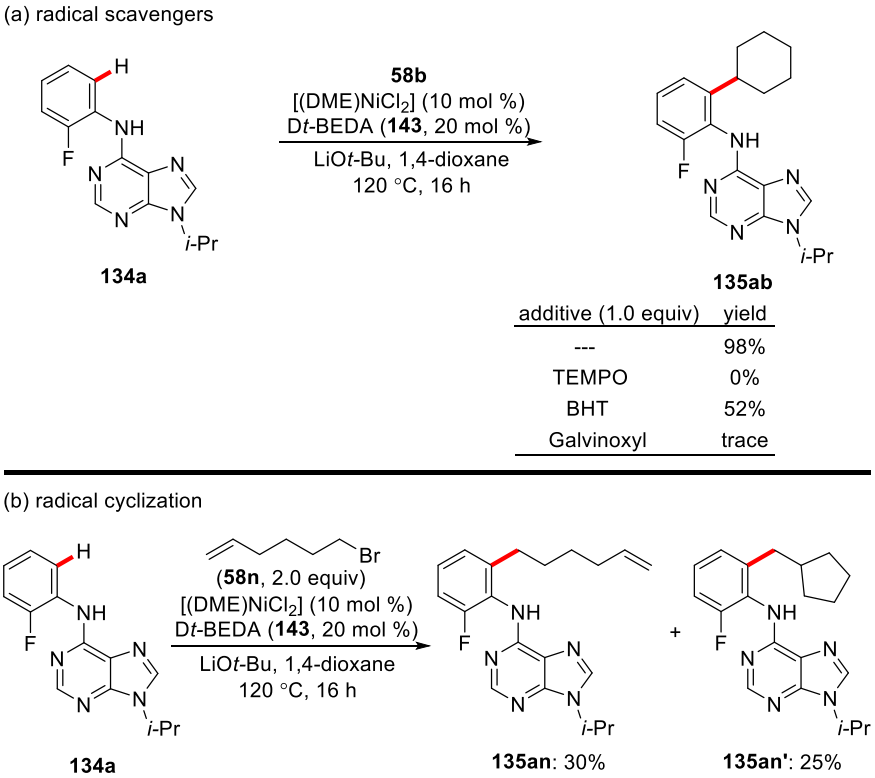
In consideration of the unique efficiency of the nickel catalysis regime, we became intrigued by rationalizing its mode of action. To this end, intermolecular competition experiments between differently *meta*-substituted arenes **134** emphasized that electron-deficient groups significant favors this reaction (Scheme 3.2.3a). Moreover, an intermolecular competition

experiment between the purinyl and the pyrimidyl groups revealed the former to be more powerful in the nickel-catalyzed C–H activation process (Scheme 3.2.3b).



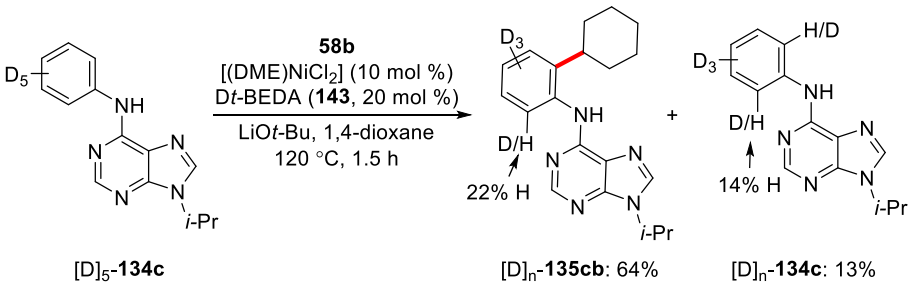
Scheme 3.2.3 Intermolecular competition experiments.

Thereafter, the nickel-catalyzed C–H functionalization was performed in the presence of a series of radical scavengers. As a result, the reaction was completely suppressed by the addition of typical radical scavengers (Scheme 3.2.4a), which can be rationalized in terms of SET-type processes being of key relevance. With good concurrence with this finding, the involvement of radical intermediates was confirmed through the partial cyclization of 6-bromohexene (**58n**) (Scheme 3.2.4b).



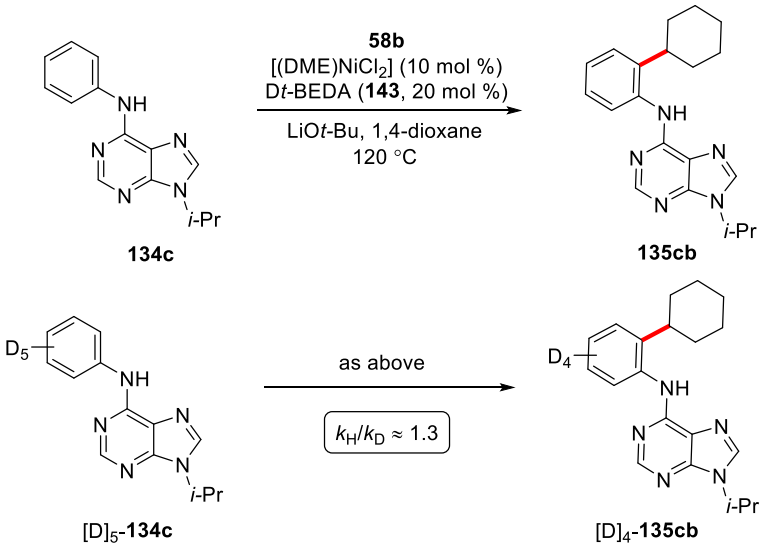
Scheme 3.2.4 Key mechanistic findings supporting SET-based mechanism.

Moreover, we performed the nickel-catalyzed C–H alkylation of the labeled $[D]_5$-**134c**, which revealed a reversible H/D exchange reaction, as observed by the reisolation of $[D]_5$-**134c** and the labeled alkylated product (Scheme 3.2.5).



Scheme 3.2.5 H/D Exchange experiment.

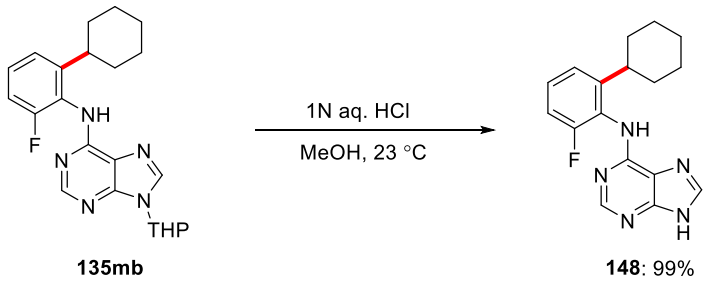
In addition, the intermolecular kinetic isotope effect (KIE) was found to be minor ($k_H/k_D \approx 1.3$) in independent experiments, being indicative of a facile C–H metalation manner (Scheme 3.2.6).



Scheme 3.2.6 Independent KIE studies.

3.2.5 Removal of the Protecting Group

Finally, the versatile synthetic utility of our strategy was demonstrated by the removal of the protecting group, yielding the corresponding alkylated product **148** of *NH*-free 6-anilinopurine in excellent yields (Scheme 3.2.7).



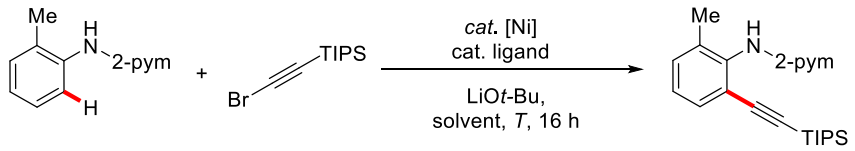
Scheme 3.2.7 Traceless removal of the THP group

3.3 Nickel-Catalyzed C–H Alkynylation of Anilines: Expedient Access to Functionalized Indoles and Purine Nucleobases

3.3.1 Optimization of Nickel-Catalyzed C–H Alkynylation with Anilines

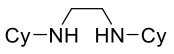
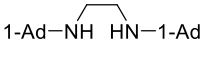
We initiated our studies by probing a variety of nickel catalysts for the envisioned C–H alkynylation of the 2-pyrimidyl substituted aniline **123a** with alkyne halide **61a** (Table 3.3.1). Thus, the user-friendly complex (DME)$NiCl_2$ proved to be highly effective while the $Ni(cod)_2$ gave unsatisfied results (entries 1–5). Among a set of represent ligands, such as mono-/di-phosphines, N-heterocyclic carbene, binaphthol and diamines, D*t*-BEDA (**143**) was identified once more as being optimal and powerful (entries 6–16), thereby leading to a significantly reduced catalyst loading (entry 5). Different solvents were tested, and ethereal solvents were found to be ideal (entries 17–23). Unfortunately, other bases, such as Na_2CO_3, K_2CO_3, LiHMDS and KHMDS failed to afford desired product, while KO*t*-Bu gave only trace amounts of the desired product **136aa** (entries 24–28). Control experiments showed that the C–H activation performed in a similar manner in the absence of an additional ligand with moderate efficiency, while the C–H functionalization failed to occur in the absence of a nickel complex (entries 29 and 30).

Table 3.3.1 Optimization of nickel-catalyzed C−H alkynylation with aniline **123a**.[a]



123a **61a** **136aa**

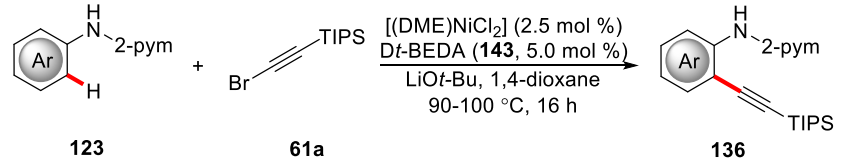
Entry	[Ni]	Ligand	Solvent	*T* [°C]	**136aa** [%]
1	(DME)$NiBr_2$	D*t*-BEDA (**143**)	1,4-dioxane	100	53
2	$Ni(acac)_2$	D*t*-BEDA (**143**)	1,4-dioxane	100	53
3	$Ni(OTf)_2$	D*t*-BEDA (**143**)	1,4-dioxane	100	51
4	$Ni(cod)_2$	PPh_3	1,4-dioxane	100	46
5	**(DME)$NiCl_2$**	**D*t*-BEDA (143)**	**1,4-dioxane**	**100**	**61 (68)[b]**
6	(DME)$NiCl_2$	D*t*-BEDA (**143**)	1,4-dioxane	85	56

7	(DME)$NiCl_2$	D*t*-BEDA (**143**)	1,4-dioxane	120	53
8	(DME)$NiCl_2$	BDMAE	1,4-dioxane	100	43
9	(DME)$NiCl_2$	Mes·HCl	1,4-dioxane	100	46
10	(DME)$NiCl_2$		1,4-dioxane	100	36
11	(DME)$NiCl_2$		1,4-dioxane	100	44
12	(DME)$NiCl_2$	PPh_3	1,4-dioxane	100	60
13	(DME)$NiCl_2$	dppe	1,4-dioxane	100	35
14	(DME)$NiCl_2$	BINOL	1,4-dioxane	100	45
15	(DME)$NiCl_2$	PCy_3	1,4-dioxane	100	46
16	(DME)$NiCl_2$	X-phos	1,4-dioxane	100	46
17	(DME)$NiCl_2$	D*t*-BEDA (**143**)	toluene	100	23
18	(DME)$NiCl_2$	D*t*-BEDA (**143**)	DCE	100	3
19	(DME)$NiCl_2$	D*t*-BEDA (**143**)	MeCN	100	0
20	(DME)$NiCl_2$	D*t*-BEDA (**143**)	DME	100	56
21	(DME)$NiCl_2$	D*t*-BEDA (**143**)	THF	100	57
22	(DME)$NiCl_2$	D*t*-BEDA (**143**)	DMF	100	0
23	(DME)$NiCl_2$	D*t*-BEDA (**143**)	NMP	100	0
24[c]	(DME)$NiCl_2$	D*t*-BEDA (**143**)	1,4-dioxane	100	0
25[d]	(DME)$NiCl_2$	D*t*-BEDA (**143**)	1,4-dioxane	100	0
26[e]	(DME)$NiCl_2$	D*t*-BEDA (**143**)	1,4-dioxane	100	0
27[f]	(DME)$NiCl_2$	D*t*-BEDA (**143**)	1,4-dioxane	100	0
28[g]	(DME)$NiCl_2$	D*t*-BEDA (**143**)	1,4-dioxane	100	trace
29	(DME)$NiCl_2$	-	1,4-dioxane	100	53
30	-	D*t*-BEDA (**143**)	1,4-dioxane	100	0

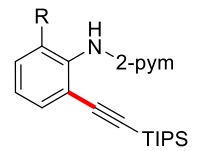
[a] Reaction conditions: **123a** (0.50 mmol), **61a** (2.0 equiv), [Ni] (10 mol %), ligand (20 mol %), LiO*t*-Bu (2.0 equiv), 1,4-dioxane (1.5 mL), 16h. [b] **123a** (0.50 mmol), **61a** (3.0 equiv), [Ni] (2.5 mol %), ligand (5.0 mol %), LiO*t*-Bu (2.0 equiv), 1,4-dioxane (1.5 mL), 100 °C, 16h. [c] Na_2CO_3. [d] K_2CO_3. [e] LiHMDS. [f] KHMDS. [g] KO*t*-Bu.

3.3.2 Scope of Nickel-Catalyzed C−H Alkynylation with Anilines

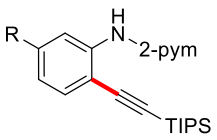
With the optimized catalytic condition in hand, we explored the scope of the nickel-catalyzed C–H alkynylation with diversely decorated anilines **123** (Scheme 3.3.1). Hence, under the optimized catalytic system, the conversion of unsubstituted as well as *ortho*- and *para*-substituted anilines (**123a–123c**, **123l**) was enabled in high efficacy and chemo-selectivity. Moreover, C–H functionalizations with *meta*-substituted arenes **123** occurred at the less sterical C–H bond with high levels of positional control. The robustness of the user-friendly nickel catalyst was specifically reflected by fully tolerating valuable functional groups, including chloro, bromo, ketone, ester, or amino substituents (**123j**, **123q**, **123u**–**123w**). Furthermore, the heterocyclic substrate **123x** afforded the desired product **136xa** with high levels of regio-control in moderate yield. Notably, the corresponding *N*-pyridin-2-yl-substituted aniline, as well as the pyrimidin-2-yl-substituted phenol, failed to afford the C–H alkynylation, revealing the unique nature of the deprotonable pyrimidyl aniline motif.



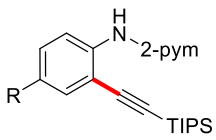
123 **61a** **136**



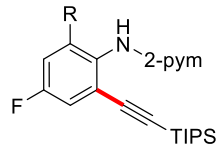
R = Me (**136aa**): 68%
R = F (**136ba**): 65%
R = Ph (**136da**): 51%



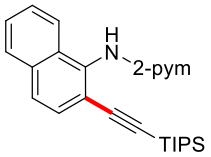
R = Me (**136fa**): 60%
R = OMe (**136ga**): 59%
R = CF_3 (**136ha**): 65%
R = Cl (**136qa**): 62%
R = Br (**136ua**): 57%
R = C(O)Ph (**136va**): 45%
R = CO_2t-Bu (**136ja**): 56%
R = NMe_2 (**136wa**): 56%



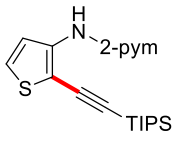
R = F (**136la**): 52% (11%)[a]
R = H (**136ca**): 42% (19%)[a]



R = Me (**136na**): 71%
R = F (**136oa**): 75%



136sa: 84%



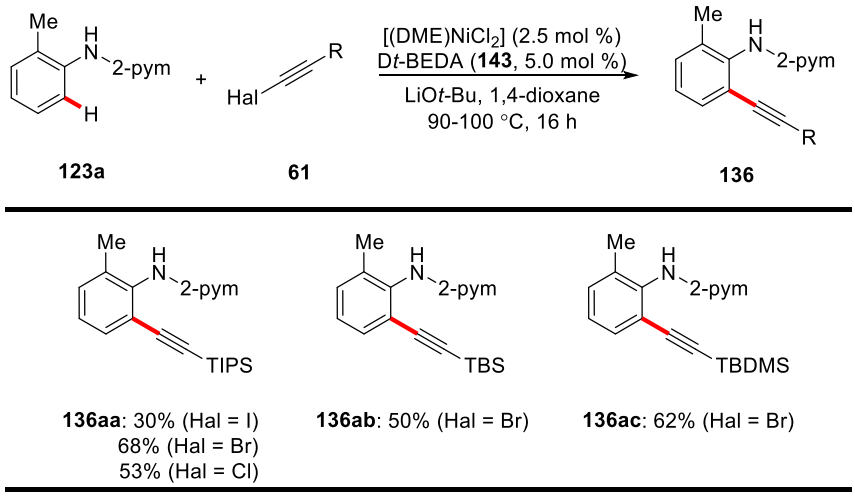
136xa: 45% (10%)[a]

[a] Isolated yields of the dialkynylated products **136'** in parenthesis.

Scheme 3.3.1 Scope of C−H Alkynylation of Anilines **123**.

3.3.3 Scope of Nickel-Catalyzed C−H Alkynylation with Alkynes

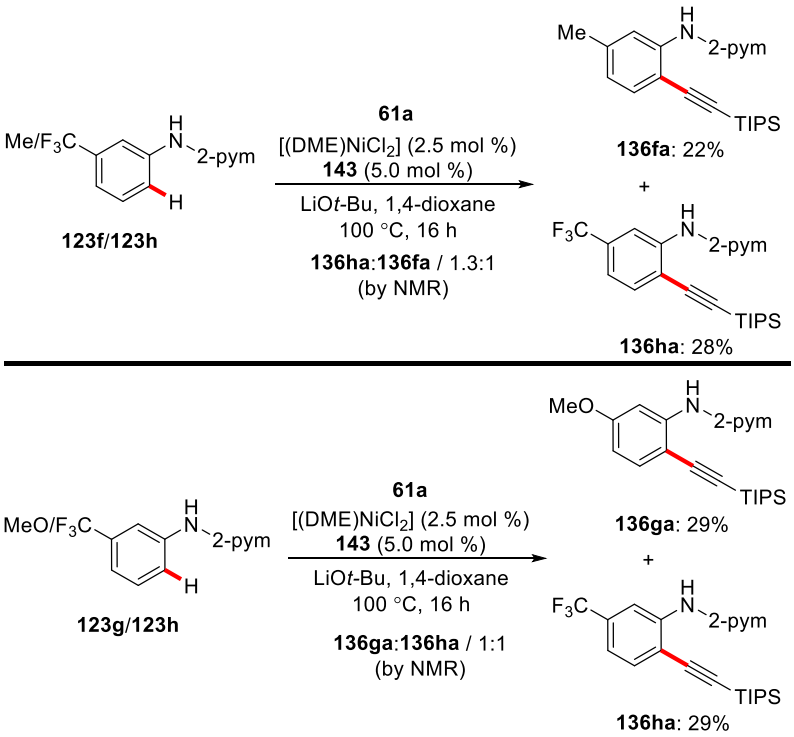
Moreover, the robustness of nickel catalysis derived from ligand **143** was demonstrated by the C–H transformation with different alkynyl halides **61**, such as alkynyl chloride, as well as different silyl groups, with best results being achieved with alkynyl bromides **61a–61c** (Scheme 3.3.2). However, the 1-octyne was not a viable substrate for the nickel-catalyzed C–H alkynylation under otherwise identical reaction conditions.



Scheme 3.3.2 Scope of C−H alkynylation with alkynes **61**.

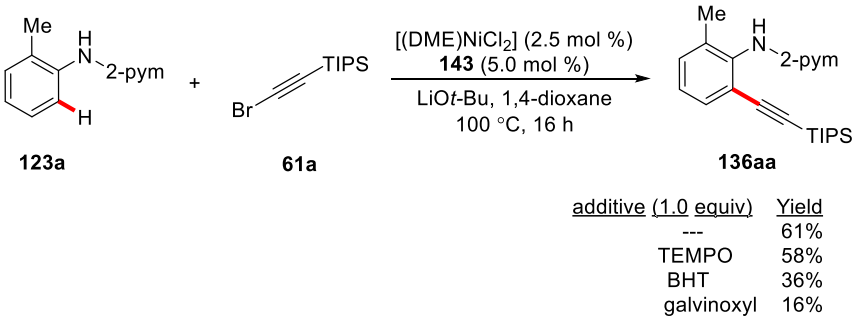
3.3.4 Mechanistic Studies

In consideration of the efficient performance of the optimized nickel(II) precatalyst, we became inquisitive to delineating its mode of action. To this end, intermolecular competition experiments between electron-rich and electron-deficient anilines **123** did not show a significant difference in relative reaction efficacy (Scheme 3.3.3).



Scheme 3.3.3 Intermolecular competition between different anilines.

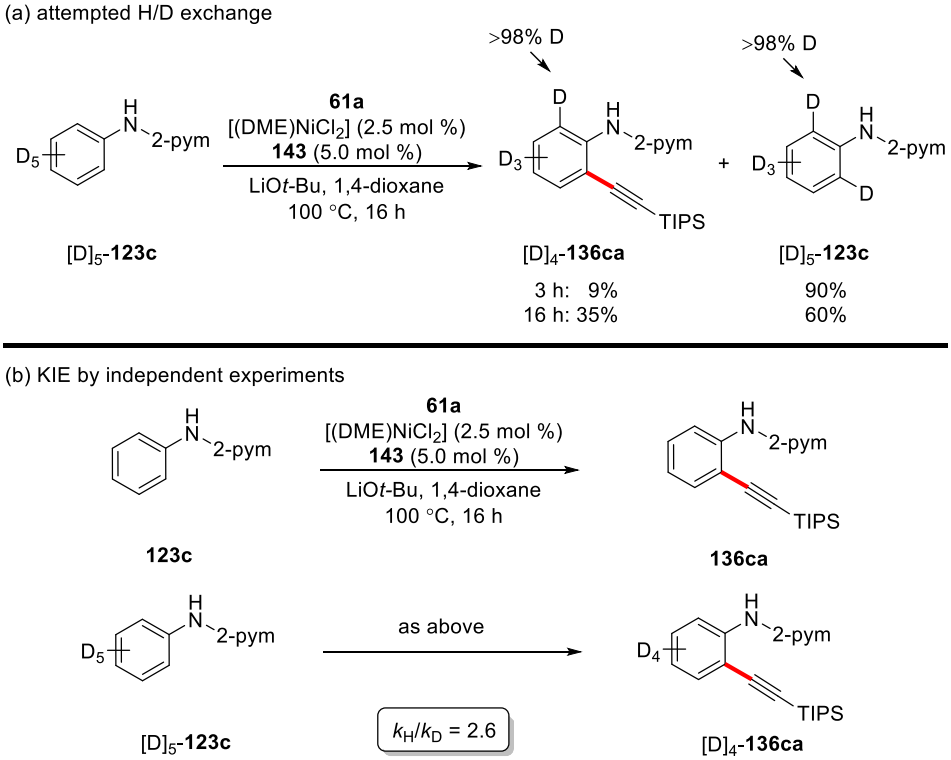
The C–H transformation was found to be almost unaltered in the presence of stoichiometric amounts of TEMPO, rendering a SET-type mechanism unlikely to be operative here, while the addition of typical radical scavengers led to diminished yields somehow of product **136aa** (Scheme 3.3.4).



Scheme 3.3.4 C−H Alkynylation in the presence of radical scavengers.

Furthermore, in contrast to aforementioned nickel-catalyzed C–H alkylation of anilines **123** (Chapters 3.1 & 3.2), the C–H alkynylation of isotopically labeled substrate [D_5]-**123c** was not accompanied by a H/D exchange reaction in different reaction times (Scheme 3.3.5a). This observation is in consistence with a kinetic isotope effect (KIE) of $k_H/k_D \approx 2.6$ (Scheme 3.3.5b)

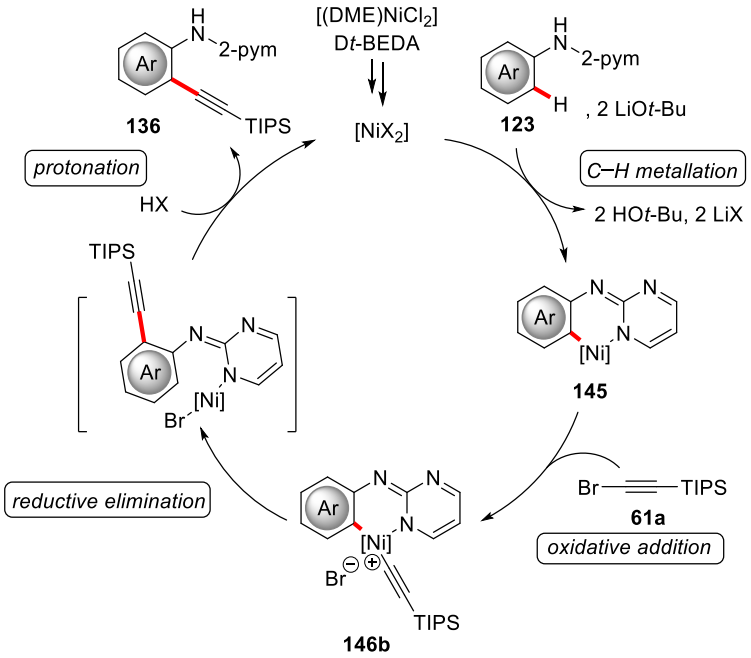
in independent experiments between substrates **123c** and [D_5]-**123c**, which is indicative of a kinetically relevant C–H metalation step.



Scheme 3.3.5 H/D Exchange and KIE experiments

3.3.5 Proposed Catalytic Cycle

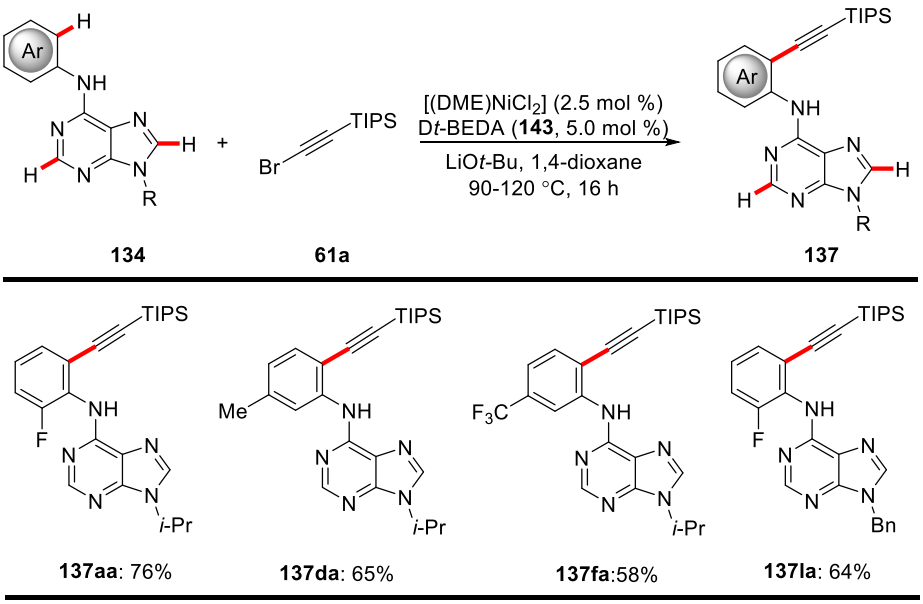
Based on our mechanistic studies and previous reports,[137b, 137c] we propose a plausible catalytic cycle as shown in Scheme 3.3.6. Initially coordination of substrate **123** to nickel(II) was followed by a ligand exchange and C–H cyclometalation to form complex **145**. The oxidative addition of alkynyl bromide **61a** afforded the intermediate **146b**, which underwent reductive elimination and protonation to furnish the alkynylated product **136** with regeneration of the nickel(II) catalyst.



Scheme 3.3.6 Proposed catalytic cycle

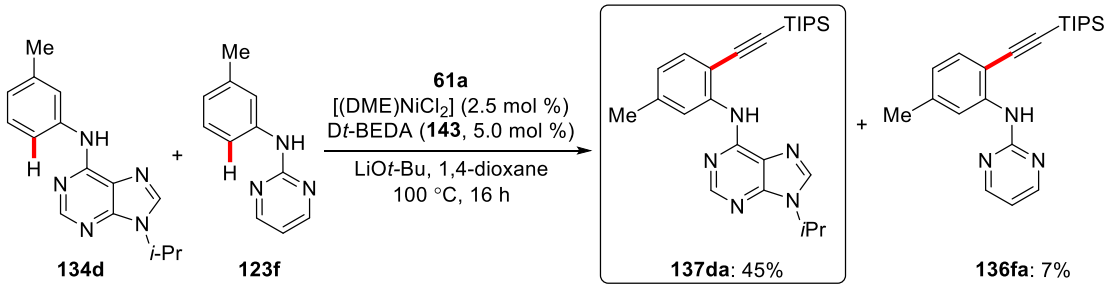
3.3.6 Nickel-Catalyzed C–H Alkynylation of Purine Bases

Likewise, the versatile nickel-catalyzed C–H functionalization approach developed by us was also highlighted by performing the first C–H alkynylation with purine nucleobases **134** (Scheme 3.3.7). Thus, the C–H activation of the adenines **134** occurred exclusively by the N1-chelation assistance on the aniline moiety, while the significantly more acidic imidazole and pyrimidine C–H bonds remained unactivated. Thereby, the sole products **137** were achieved by the alkynylation of purines **134**, which should prove instrumental for future applications to DNA and RNA chemistry.



Scheme 3.3.7. Nickel-catalyzed C–H alkynylation of purine bases **134**

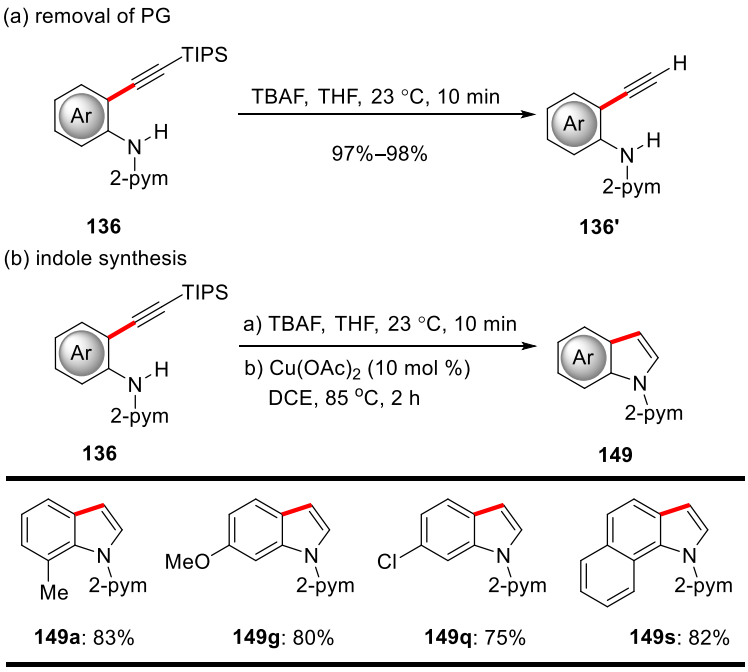
Interestingly, the purinyl moiety proved again to be a more powerful directing group in the nickel-catalyzed C–H activation process through an intermolecular competition experiment between the pyrimidyl and the purinyl substituted anilines (Scheme 3.3.8).



Scheme 3.3.8 Directing group ability.

3.3.7 Diversification of C–H Alkynylation Products

Finally, we illustrated the synthetic utility of our approach by the facile removal of the protecting group in traceless fashion. Additionally, the unprecedented nickel-catalyzed C–H alkynylation of *NH*-free anilines **123** sets the stage for the expedient synthesis of diversely decorated indoles **149** in good yields *via* a copper-catalyzed intramolecular hydroamination[147] approach (Scheme 3.3.9).



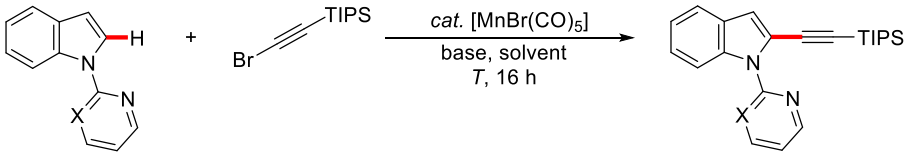
Scheme 3.3.9 (a) Diversification and (b) preparation of indoles **149**.

3.4 Manganese(I)-Catalyzed C–H Alkynylation: Expedient Peptide Synthesis and Modification of Peptides

3.4.1 Optimization of Manganese(I)-Catalyzed C–H Alkynylation

At the outset of our studies, we probed the effect of representative bases and solvents on the envisioned manganese(I)-catalyzed C–H alkynylation of indoles **83** with silyl bromoalkyne **61a** (Table 3.4.1). Among a variety of organic and inorganic bases, dicyclohexyl amine afforded satisfactory results at 120 °C with 1,4-dioxane as the solvent while inorganic bases such as NaOAc and Na_2CO_3 resulted in unsatisfactory yields (entries 1–7). DCE was identified as the optimal solvent for the C–H alkynylation with reduced catalyst loadings and reaction temperatures as low as 60 °C (entries 10–13). Further control experiments verified the essential role of the manganese catalyst and the amine base likewise (entries 14 and 15).

Table 3.4.1 Optimization of manganese(I)-catalyzed C–H alkynylation.



X = CH (**83a**)
X = N (**83b**)

61a

X = CH (**138aa**)
X = N (**138ba**)

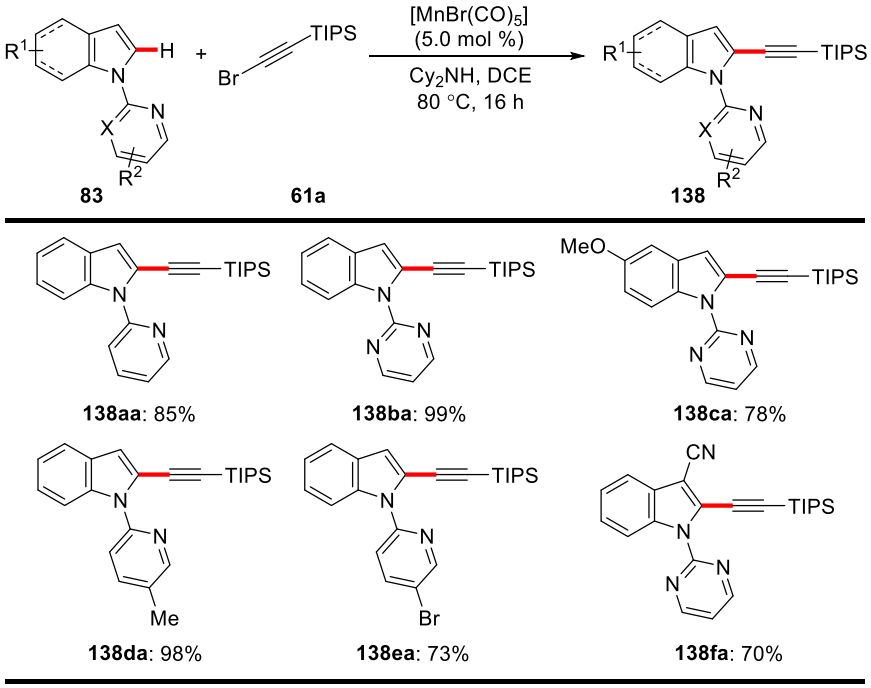
Entry	X	Mn (mol %)	Base	Solvent	*T* [°C]	Yield [%][b]
1	CH	10.0	Cy_2NH	1,4-dioxane	120	93
2	CH	5.0	Cy_2NH	1,4-dioxane	100	78
3	CH	5.0	Cy_2NH	DCE	80	85
4	N	10.0	Cy_2NH	1,4-dioxane	120	94
5	N	5.0	Cy_2NH	1,4-dioxane	120	71
6	N	5.0	NaOAc	1,4-dioxane	120	41[c]
7	N	5.0	Na_2CO_3	1,4-dioxane	120	33[c]
8	N	5.0	Cy_2NH	TFE	120	15[c]
9	N	5.0	Cy_2NH	DCE	120	96
10	N	2.5	Cy_2NH	DCE	120	71

11	N	5.0	Cy_2NH	DCE	100	92
12	**N**	**5.0**	**Cy_2NH**	**DCE**	**80**	**95 (99)[d]**
13	N	5.0	Cy_2NH	DCE	60	71
14	N	-	Cy_2NH	DCE	80	0
15	N	5.0	-	DCE	80	< 5

[a] Reaction conditions: **83a** or **83b** (0.50 mmol), **61a** (0.75 mmol), $MnBr(CO)_5$ (Y mol %), base (1.0 mmol), solvent (1.0 mL), *T* °C, 16 h. [b] Yield of isolated product. [c] Determined by GC conversion using *n*-dodecane as internal standard. [d] **61a** (0.60 mmol).

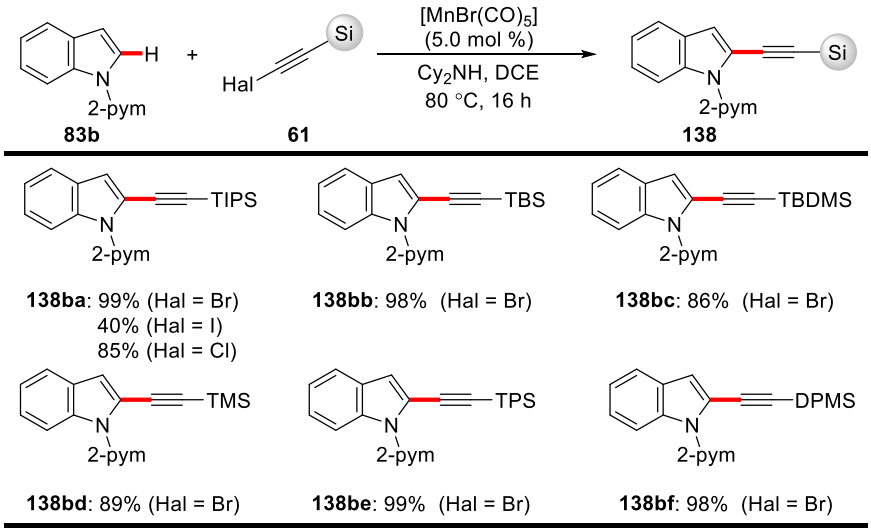
3.4.2 Scope of Manganese(I)-Catalyzed C–H Alkynylation

With the optimized catalytic system in hand, we explored the viability of indole substrates in the managanese(I)-catalyzed C–H alkynylation with TIPS-alkyne **61a** (Scheme 3.4.1). Thus, the manganese catalysis performed with excellent levels of site-selectivity with various indoles, displaying different substituted directing groups. Additionally, valuable functionalities, including sensitive bromo and cyano groups, were fully tolerated in this transformation, which could serve as a handle for future late-stage modifications.



Scheme 3.4.1 Scope of manganese(I)-catalyzed C–H alkynylation with indoles **83**.

Likewise, different silyl-substituted alkynyl halides **61** were tested in the C–H functionalization of indoles **83b**, illustrating excellent levels of catalytic efficacy (Scheme 3.4.2). In this regard, it is particularly noteworthy that the corresponding alkynyl chloride **61a"** was identified as a suitable electrophilic substrate.

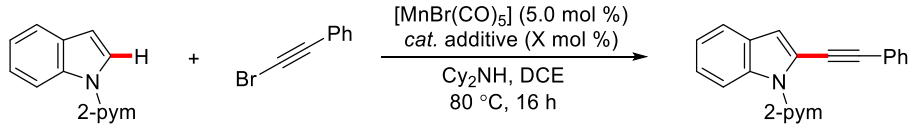


Scheme 3.4.2 Manganese-catalyzed C–H alkynylation with silyl haloalkynes.

3.4.3 Scope of Manganese(I)-Catalyzed C–H Alkynylation with Aryl and Alkyl Alkynes

Thus far, base metal-catalyzed C–H alkynylations, were particularly restricted to the use of activated alkynes featuring a silyl protecting group. Thereby, in consideration of the step- and atom-economical nature of the C–H activation strategy, we were delighted to observe that the manganese(I) catalysis enabled C–H alkynylations with aryl alkyne **61g** (Table 3.4.2). Here, the key to success was the addition of triphenylborane as the pivotal cocatalytic additive, while other Lewis-acidic additives, including zinc(II) salts (entries 4 and 5), yielded only traces of the product (entries 2–6). It is notable that the BPh_3 loading could be reduced to 0.05 mol % at a low manganese loading of 2.5 mol % (entry 7).

Table 3.4.2 Optimization of manganese-catalyzed C–H alkynylation with aryl alkyne **61g**.[a]

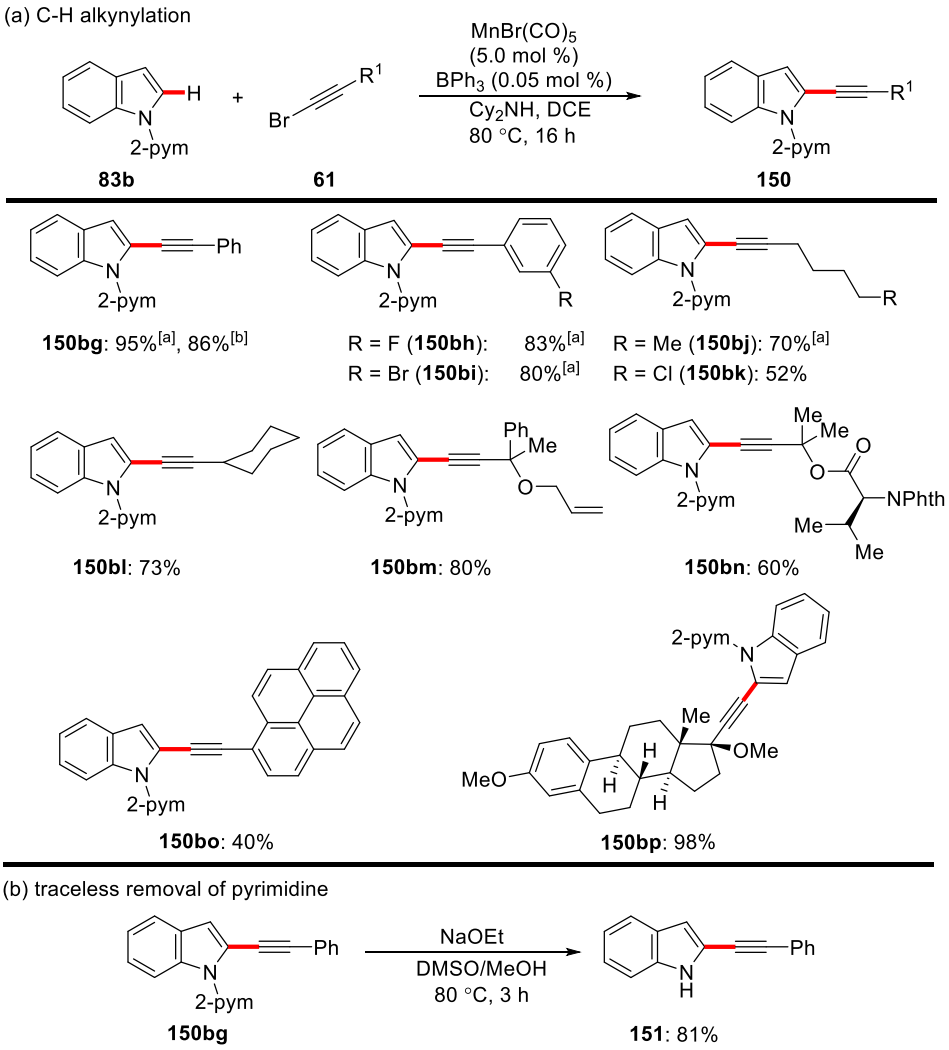


83b **61g** **150bg**

Entry	mol % additive	additive	Yield [%][b]
1	-	-	0
2	5.0	BPh_3	61
3	5.0	BPh_3	0[c]
4	5.0	$ZnBr_2$	trace
5	5.0	$ZnCl_2$	trace
6	0.05	BPh_3	92 (95) [d]
7	0.05	BPh_3	86[e]

[a] Reaction conditions: **83b** (0.5 mmol), **61g** (0.6 mmol), $MnBr(CO)_5$ (5.0 mol %), Cy_2NH (1.0 mmol), DCE (1.0 mL), 80 °C, 16 h. [b] Yields of isolated product. [c] Without [Mn]. [d] 1 h. [e] [Mn] (2.5 mol %).

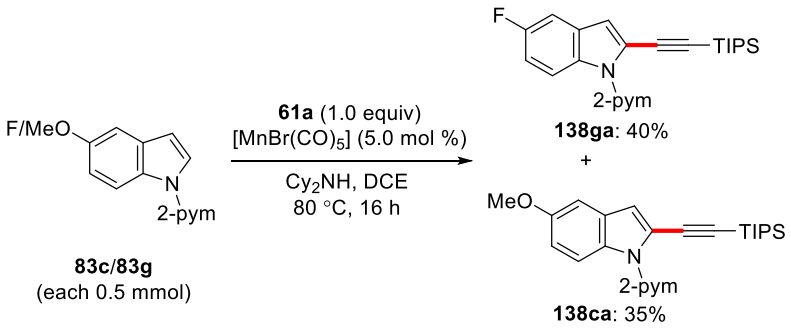
With the optimized catalytic system in hand, the remarkable versatility of the manganese(I)-catalyzed C–H alkynylation not only enabled the step-economic conversion of various aryl alkynes, but also alkyl alkynes, such as primary, secondary and tertiary alkyl alkynes, displaying synthetically meaningful functional groups (Scheme 3.4.3a). The practical utility of our strategy was further illustrated by smoothly introducing the desired C–H transformation with substrates bearing an enantiomerically pure amino acid (**150bn**), a fluorescent tag (**150bo**), or a complex steroid motif (**150bp**). Notably, the pyrimidyl group could be cleaved in a traceless fashion, yielding the corresponding alkynylated indole **151** (Scheme 3.4.3b).



Scheme 3.4.3 (a) Manganese-catalyzed C–H alkynylation with aryl and alkyl alkynes **61g**–**61p**. [a] 1 h. [b] [Mn] (2.5 mol %). (b) Removal of pyrimidine.

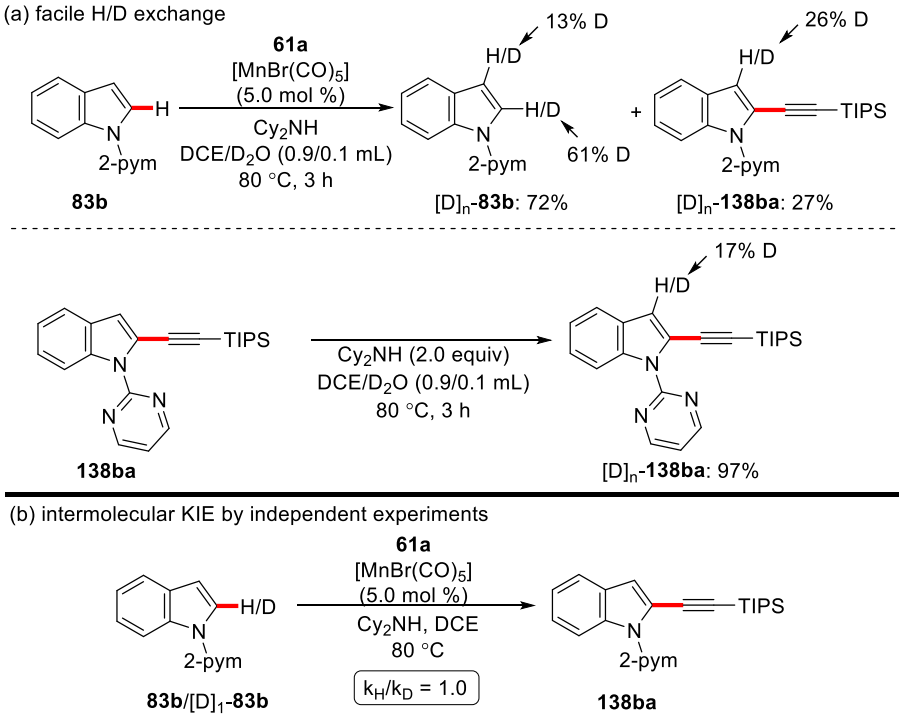
3.4.4 Mechanistic Studies

In consideration of the outstanding versatility of the C–H alkynylation we became attracted to clarifying its mode of action. To this end, intermolecular competition experiments between electron-rich and electron-deficient substituted indoles **83** revealed a slight preference for the more electron-deficient substrate, which contrasts with previous observations (Scheme 3.4.4).[92, 105-106]



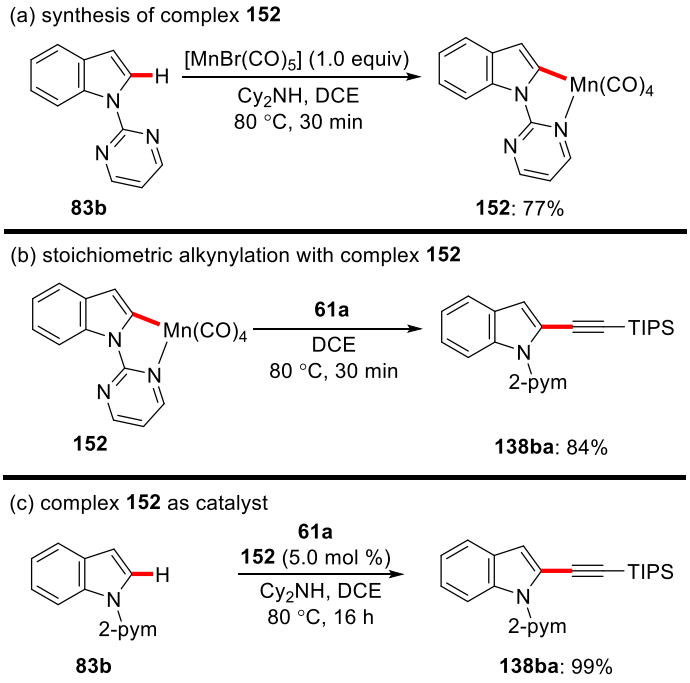
Scheme 3.4.4 Intermolecular competition experiment.

Moreover, C–H alkynylation experiments performed in the presence of D_2O as cosolvent unraveled a facile C–H metalation, as showed by the reisolation of the isotopically labeled substrate $[D]_n$-**83b** with significant H/D exchange at the C2 position as well as the labeled product $[D]_n$-**83ba**. The H/D scrambling at C3 was also observed due to an electrophilic substitution which is even operative in the absence of the metal catalyst (Scheme 3.4.5a).[76] In good agreement with this finding, a negligible KIE of $k_H/k_D \approx 1.0$ was determined by independent experiments (Scheme 3.4.5b).



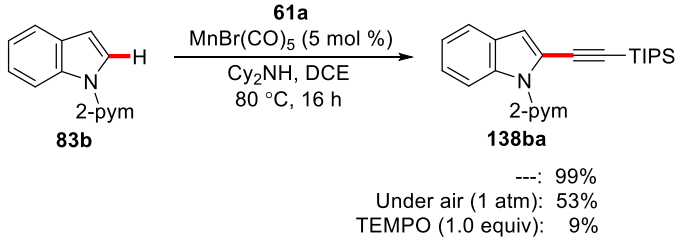
Scheme 3.4.5 (a) H/D Exchange and (b) KIE experiments.

Furthermore, the well-defined organometallic complex **152** could be prepared by the reaction of substrate **83b** with stoichiometric amounts of $MnBr(CO)_5$ (Scheme 3.4.6a). Thus, the manganese complex **152** delivered the C–H alkynylated product **138ba** both in a stoichiometric as well as a catalytic setting, suggesting the organometallic complex **152** to be a key on-cycle intermediate of the C–H activation regime (Scheme 3.4.6b–c).



Scheme 3.4.6 C–H Alkynylations with cyclometalated complex **152**.

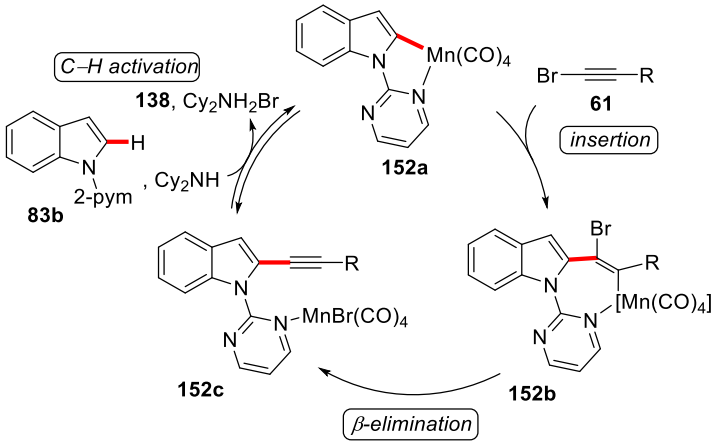
In addition, conducting the manganese-catalyzed C–H alkynylation under an atmosphere of air or in the presence of the radical scavenger TEMPO led to a significantly diminished catalytic efficacy, indicating a distinct mode of action. (Scheme 3.4.7)



Scheme 3.4.7 C–H Alkynylation under air or in the presence of radical scavenger.

3.4.5 Proposed Catalytic Cycle

Based on our experimental mechanistic studies we propose a plausible catalytic cycle to be initiated by a reversible and fast organometallic C–H bond activation (Scheme 3.4.8). Thereafter, a migratory insertion delivers the seven-membered metallacycle [Mn]-I, which undergoes ß-elimination, forming the desired product. Alternatively, a mechanism through oxidative addition and reductive elimination cannot be ruled out based on current limited mechanistic studies.

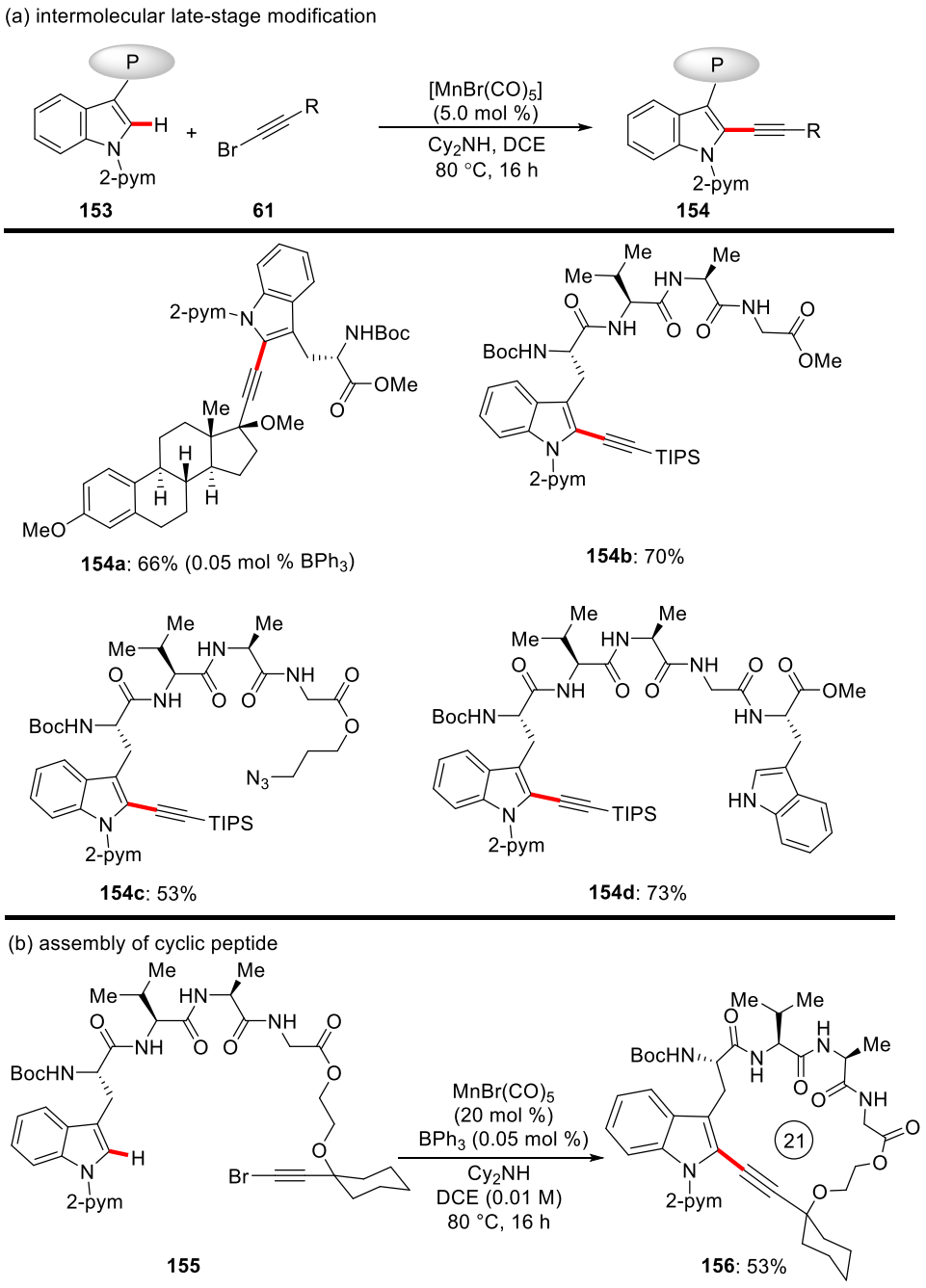


Scheme 3.4.8 Plausible proposed catalytic cycle.

3.4.6 Peptide Modification and Assembly by Manganese-Catalyzed C–H Alkynylation

The notably versatile transformation of the manganese-catalyzed C–H alkynylation finally set the stage for the efficient late-stage diversification of acyclic peptides **153** with high chemo and positional selectivity. Henceforth, the manganese-catalyzed C–H functionalization provided step-economical access to novel peptides for biochemistry, medicinal chemistry and drug discovery (Scheme 3.4.9a). In this context, viable alkynes especially alkyl alkynes featuring steroid moiety can be elegantly introduced by the robust manganese catalysis regime. It is particularly noteworthy that the azido-substituted peptide (**154c**) and a tryptophan-containing pentapeptide **154d** were fully tolerated in this protocol, which should prove invaluable for potential applications to bioorthogonal tag-and-modify approaches[148] or click chemistry[149] for peptide modification in living systems.

Finally, we were particularly delighted to develop the first intramolecular macrocyclization[150] by manganese(I)-catalyzed C–H activation. Hence, the manganese-catalyzed C–H alkynylation of substrate **155** under high-dilution conditions delivered the 21-membered cyclic peptide **156**, which enriched the database of novel peptidomimetic drugs with, for instance, antibacterial activities (Scheme 3.4.9b). Here, the addition of catalytic BPh_3 proved again essential to realize the challenging assembly of macrocycle **156**.



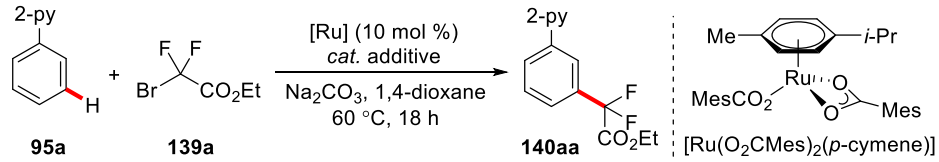
Scheme 3.4.9 Peptide modification and assembly by manganese-catalyzed C–H alkynylation.

3.5 Ruthenium(II)-Catalyzed *meta*-C–H Mono- and Difluoromethylations by Phosphine/Carboxylate Cooperation

3.5.1 Optimization of Ruthenium-Catalyzed C–H Difluoromethylation

We initiated our optimization studies by probing the effect of various additives on the envisioned ruthenium(II)-catalyzed C–H difluoromethylation on arene **95a** with bromodifluoroester **139a** (Table 3.5.1). Based on our recent findings on SET-type processes,[125] different nickel cocatalysts were tested and the desired C–H functionalization was proved to be highly effective by using $Ni(PPh_3)_2Cl_2$ as an addictive (entries 1–4). However, control experiments uncovered the crucial importance of phosphine ligands, furnishing the product **140aa** with excellent levels of *meta*-selectivity (entries 5–7). Thus, whereas a variety of electron-rich phosphines, phosphites, N-heterocyclic carbene precursors, *N*-protected amino acid provided unsatisfactory results (entries 8–18), triaryl phosphines showed outstanding catalytic efficacy for the *meta*-C–H activation (entries 7, 19, and 20). Here, the best catalytic performance was realized by employing the electron-deficient $P(4\text{-}C_6H_4CF_3)_3$ as the ligand with Na_2CO_3 as the base of choice, along with 1,4-dioxane as the optimal solvent (entry 19). The key importance of the synergistic phosphine/carboxylate assistance within the remote C–H functionalization regime was highlighted by the simple ruthenium complexes $RuCl_3{\cdot}(H_2O)_n$ and $[RuCl_2(p\text{-cymene})]_2$ failing in the challenging *meta*-C–H functionalization under otherwise identical reaction conditions (entries 21 and 22). Hence, the best results were obtained with the ruthenium(II)-biscarboxylate complex $[Ru(O_2CMes)_2(p\text{-cymene})]$ (entry 19).

Table 3.5.1 Optimization of ruthenium-catalyzed C−H difluoromethylation.[a]



95a **139a** **140aa** [Ru(O$_2$CMes)$_2$(*p*-cymene)]

Entry	[Ru]	Additive	Yield[%]
1	$[Ru(O_2CMes)_2(p\text{-cymene})]$	-	< 5
2	**$[Ru(O_2CMes)_2(p\text{-cymene})]$**	**$Ni(PPh_3)_2Cl_2$**	**72**

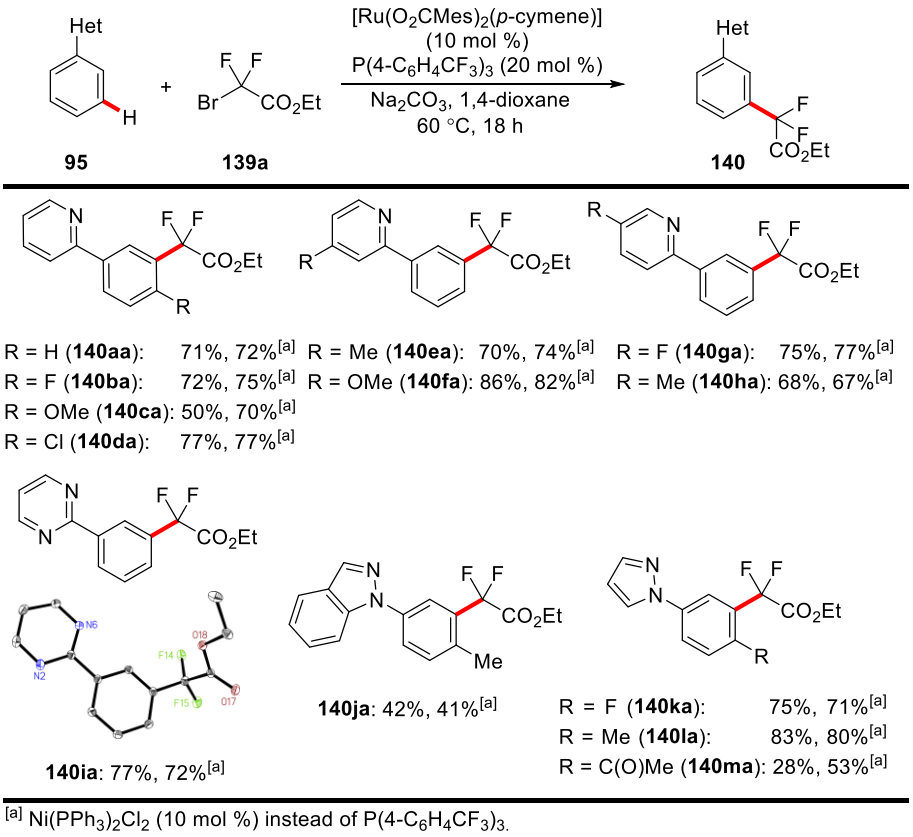
3	$[RuCl_2(p\text{-cymene})]_2$	$Ni(PPh_3)_2Cl_2$	---
4	-	$Ni(PPh_3)_2Cl_2$	---
5	$[Ru(O_2CMes)_2(p\text{-cymene})]$	$NiCl_2$	< 5
6	$[Ru(O_2CMes)_2(p\text{-cymene})]$	$NiCl_2 + PPh_3$	71
7	$[Ru(O_2CMes)_2(p\text{-cymene})]$	PPh_3	62
8	$[Ru(O_2CMes)_2(p\text{-cymene})]$	PCy_3	12[b]
9	$[Ru(O_2CMes)_2(p\text{-cymene})]$	IPr·HCl	---
10	$[Ru(O_2CMes)_2(p\text{-cymene})]$	Xantphos	---
11	$[Ru(O_2CMes)_2(p\text{-cymene})]$	$P(1\text{-Ad})_2n\text{-Bu}$	< 5
12	$[Ru(O_2CMes)_2(p\text{-cymene})]$	$P(n\text{-Bu})_3$	7
13	$[Ru(O_2CMes)_2(p\text{-cymene})]$	$P(OEt)_3$	---
14	$[Ru(O_2CMes)_2(p\text{-cymene})]$	X-Phos	---
15	$[Ru(O_2CMes)_2(p\text{-cymene})]$	$P(p\text{-Tol})_3$	< 5
16	$[Ru(O_2CMes)_2(p\text{-cymene})]$	$Ph_2P(O)H$	---
17	$[Ru(O_2CMes)_2(p\text{-cymene})]$	Piv-Val-OH	< 5
18	$[Ru(O_2CMes)_2(p\text{-cymene})]$	Ac-Val-OH	< 5
19	**$[Ru(O_2CMes)_2(p\text{-cymene})]$**	**$P(4\text{-}C_6H_4CF_3)_3$**	**71**
20	$[Ru(OAc)_2(p\text{-cymene})]$	$P(4\text{-}C_6H_4CF_3)_3$	63
21	$[RuCl_2(p\text{-cymene})]_2$	$P(4\text{-}C_6H_4CF_3)_3$	---
22	$[RuCl_3\cdot(H_2O)_n]$	$P(4\text{-}C_6H_4CF_3)_3$	---

[a] Reaction conditions: **95a** (0.5 mmol), **139a** (3.0 equiv), [Ru] (10 mol %), additive ([Ni]: 10 mol % or [P]: 20 mol %), Na_2CO_3 (2.0 equiv), 1,4-dioxane (2.0 mL), 60 °C, 18 h, isolated yield. [b] Conversion was determined by ^{19}F NMR using C_6F_6 as the internal standard.

3.5.2 Scope of Ruthenium(II)-Catalyzed C−H Difluoromethylation with Arenes

With the optimized catalytic systems in hand, we explored versatility in the *meta*-C–H difluoromethylation of heteroarenes **95** (Scheme 3.5.2). We were delighted to observe that a variety of pyridyl-substituted substrates **95a**–**95h** provided the *meta*-C–H difluoromethylation products **140** with high chemo-selectivity and good yields. Thereby, a variety of electron-donating and electron-withdrawing functional groups, such as methoxy, fluoro, chloro and ester

substituents, were fully tolerated. The remote functionalization strategy was not limited to pyridyl-guided reactivity. Indeed, pyrimidine, indazole and pyrazole containing substrates delivered the desired products **140ia**–**140ma** with high levels of *meta*-selectivity as well. Notably, in some cases, $Ni(PPh_3)_2Cl_2$ as the additive led to improved yields of products **140**, which could either be due to a low concentration of free phosphine or a heterobimetallic regime.



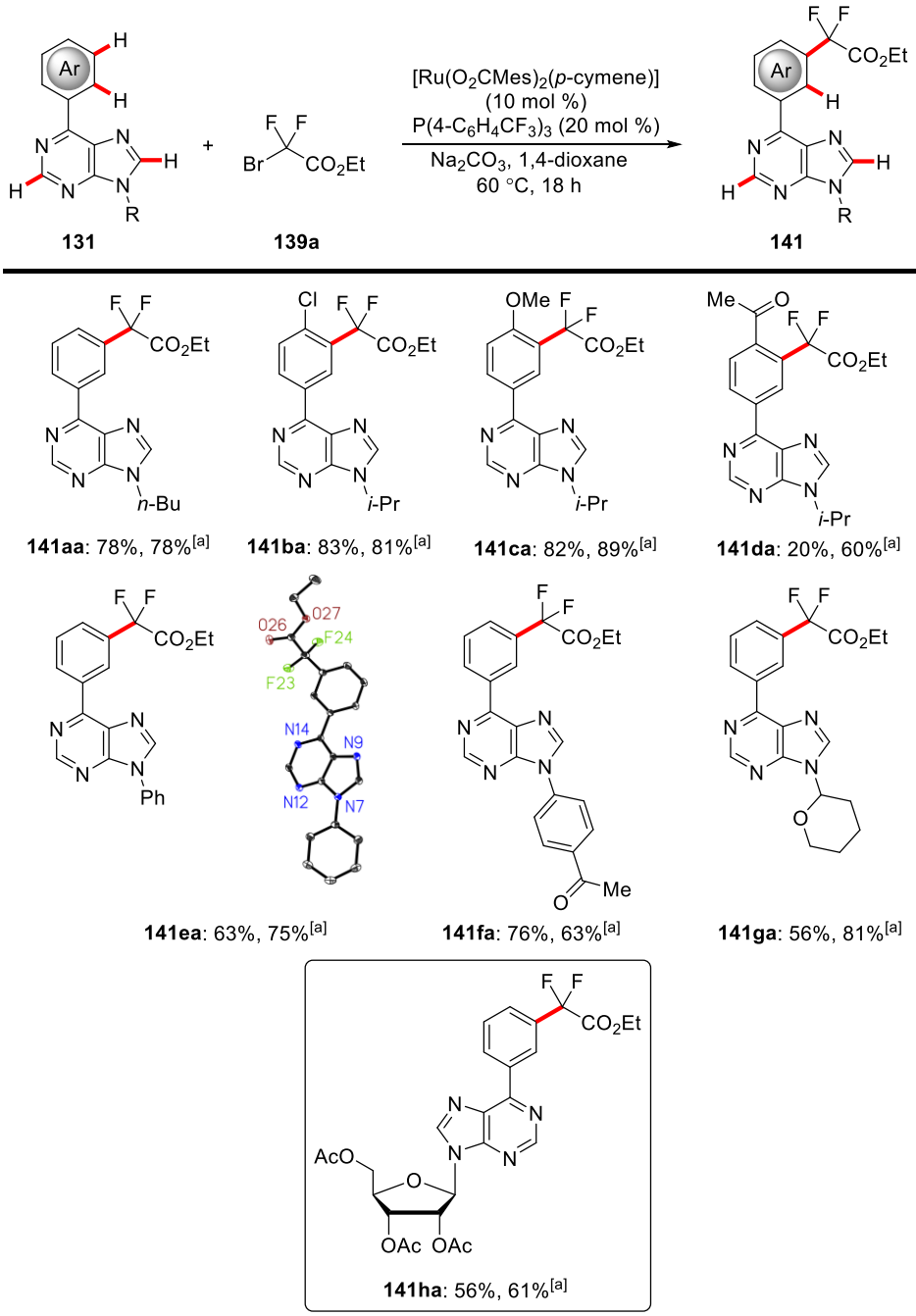
[a] $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$.

Scheme 3.5.1 Scope of ruthenium(II)-catalyzed C−H difluoromethylation with arenes **95**.

3.5.3 Scope of Ruthenium-Catalyzed C−H Difluoromethylation with Purine Bases

Likewise, the versatile ruthenium(II)-catalyzed direct remote C–H functionalization strategy sets the stage for the modification of purine nucleobases, which is significant for the preparation of bioactive compounds as well as the labelling of biologically relevant molecules. Thus, we were delighted to observe that various aryl purines **131** displaying synthetically useful groups, such as chloro, ketone, and ester as well as a nucleoside base, were site-selectively *meta*-difluoromethylated by the action of the versatile ruthenium(II)-regime (Scheme 3.5.2). It is

noteworthy that the C–H functionalization did not take place at the kinetically C–H acidic C8 position of the purine motif.

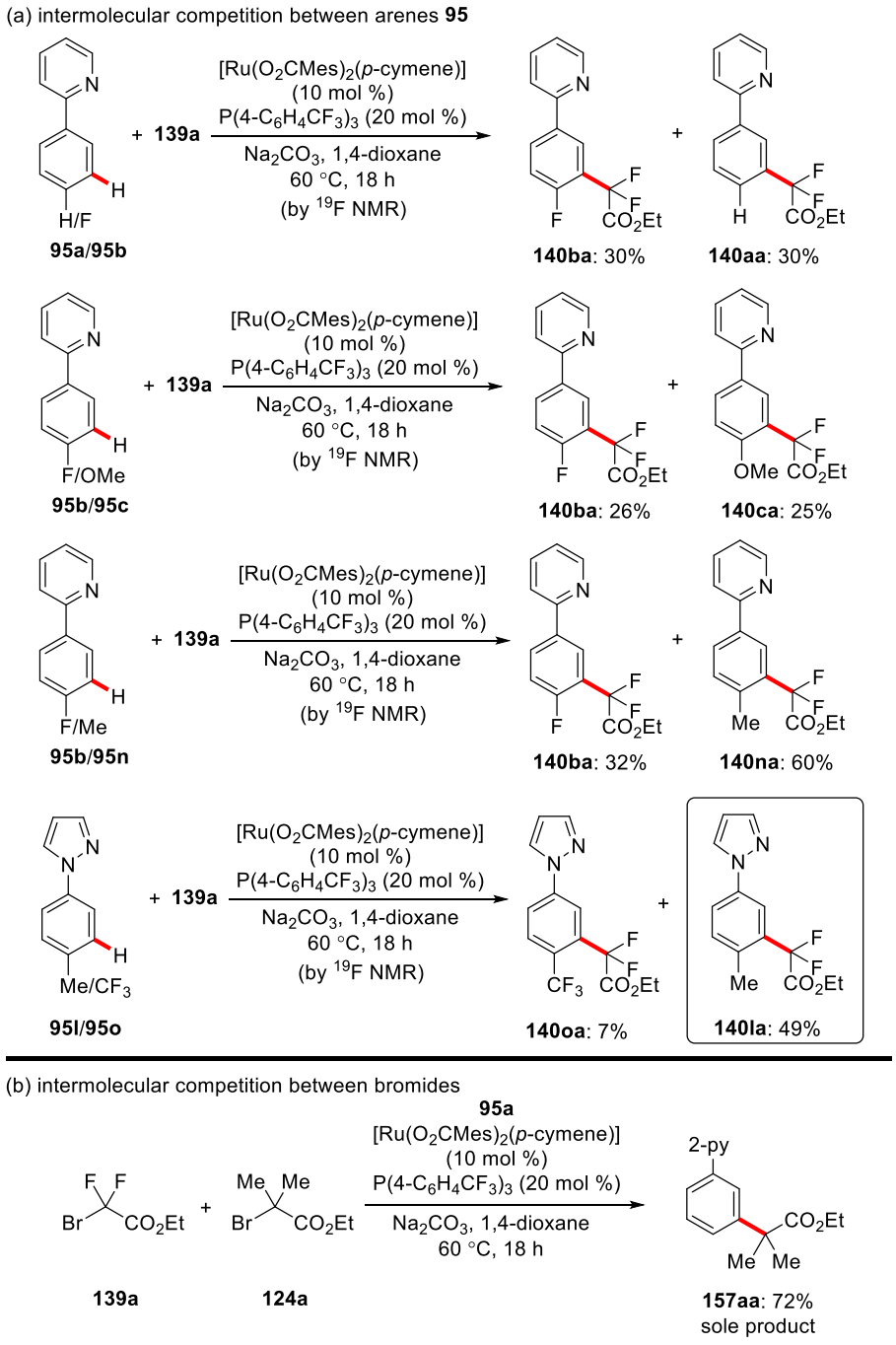


[a] $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$.

Scheme 3.5.2 Scope of ruthenium-catalyzed C−H difluoromethylation with purine bases **131**.

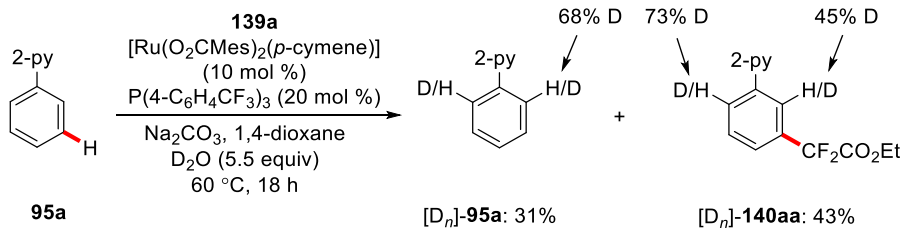
3.5.4 Mechanistic Studies

In consideration of the distinct selectivity of the ruthenium(II) catalyst, we became attracted to elucidating its mode of action (Scheme 3.5.3). To this end, intermolecular competition experiments between *para*-methoxy- and fluoro-substituted arenes **95** did not show a significantly electronic effect in this *meta*-C–H transformation. However, more extensive studies revealed that electron-rich substrates were inherently more reactive (Scheme 3.5.3a), which contrasts previous findings on *meta*-C–H alkylations.[125] Moreover, the challenging nature of the remote difluoromethylation reaction was reflected by intermolecular competition experiments between difluoromethyl- and dimethyl-substituted substrates **139a** and **124a**, exclusively affording the *tert*-alkylated product **157aa** as the sole product (Scheme 3.5.3b).



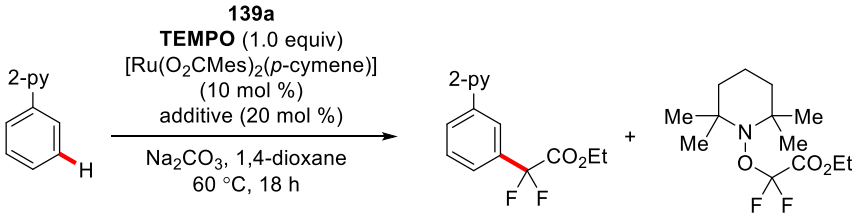
Scheme 3.5.3 Intermolecular competition experiments.

Furthermore, ruthenium(II)-catalyzed *meta*-C–H functionalizations was conducted in the presence of deuterated cosolvent D_2O (Scheme 3.5.4). The results showed a significant H/D scrambling in the *ortho*-position, revealing the reversible nature of the C–H metalation elementary step, while at the same time highlighting the robustness of the water-tolerant C–H activation.



Scheme 3.5.4 H/D Exchange experiment.

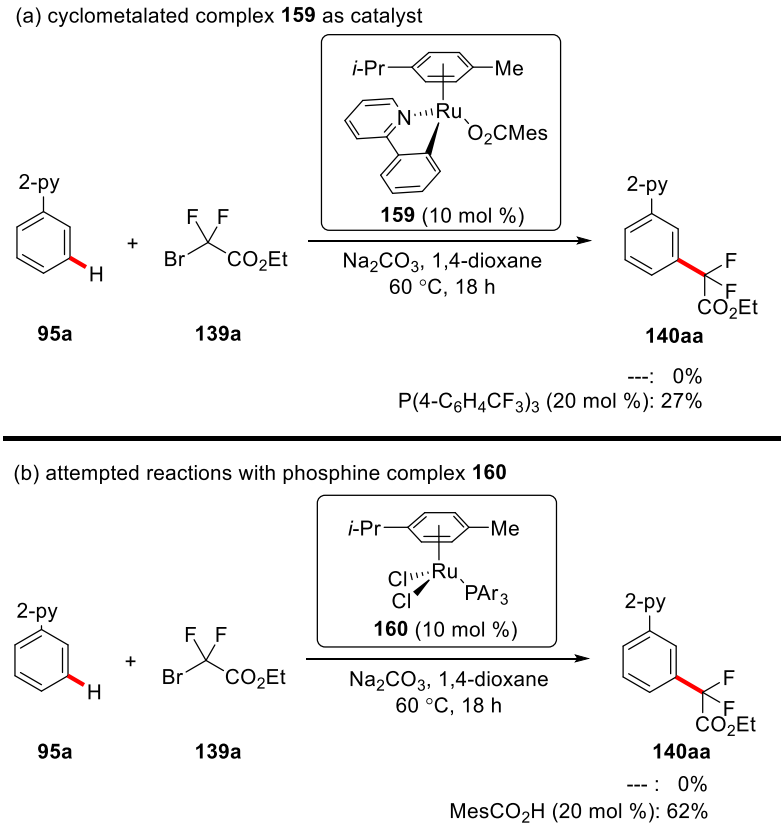
In addition, reactions performed in the presence of the typical radical scavenger TEMPO led to complete inhibition of the catalytic activity in both $P(4\text{-}C_6H_4CF_3)_3$ and $Ni(PPh_3)_2Cl_2$ ruthenium regime, with TEMPO adduct **150** being isolated in low yields (Scheme 3.5.5). This observation can be rationalized by a radical-involving C–X cleavage.



additive	**140aa**	**158**
$P(4\text{-}C_6H_4CF_3)_3$:	0%	15%
$Ni(PPh_3)_2Cl_2$:	0%	12%

Scheme 3.5.5 *meta*-C–H Difluoromethylation in the presence of TEMPO.

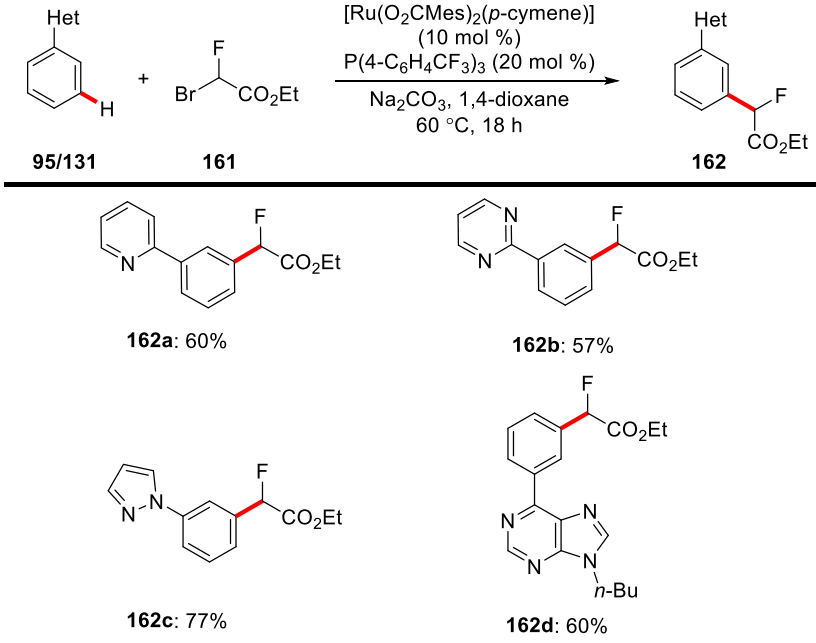
As to the nature of the catalytically active species, the remote C–H functionalization was conducted with the structurally well-defined cyclometalated complex **159** as catalyst (Scheme 3.5.6a). The complex **159** was identified as being competent albeit in low yield in the C–H transformations with phosphine ligand. The key importance of the synergistic phosphine/carboxylate assistance in the *meta*-C–H activation regime was highlighted by the attempted *meta*-C–H difluoromethylations with the carboxylate-free ruthenium(II)phosphine complex **160**,[151] which failed to yield the desired product (Scheme 3.5.6b). However, the catalytic efficacy could be restored by the simple addition of cocatalytic amounts of the proton shuttle $MesCO_2H$. However, the investigation for more detailed mechanistic study is currently underway.



Scheme 3.5.6 *meta*-C–H Difluoromethylation with complexes **159** and **160**.

3.5.5 Ruthenium(II)-Catalyzed *meta*-C–H mono-Fluoromethylation

Finally, the synthetic utility of our strategy was demonstrated by enabling the positionally selective *meta*-C–H monofluorometylation under otherwise identical reaction conditions (Scheme 3.5.7). Indeed, the unprecedented remote C–H mono-fluoromethylation was achieved with wide range of substrates, including pyridyl, pyrimidyl, pyrazolyl and even purinyl substituted arenes, furnishing the desired products **162a**–**162d** in high efficacy.

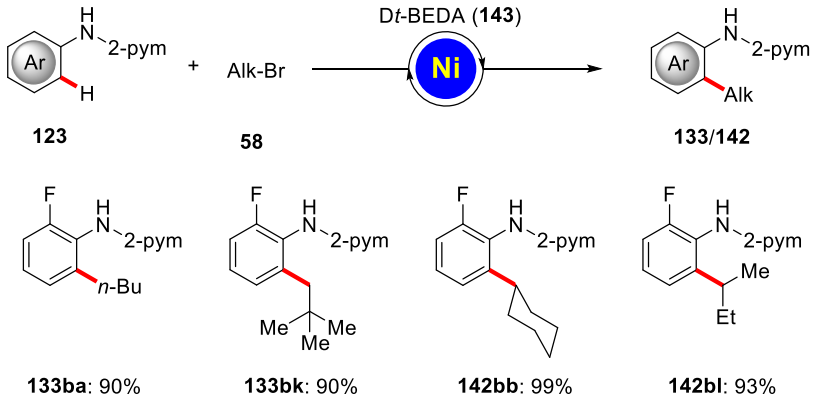


Scheme 3.5.7 *meta*-C–H Monofluoromethylation

4 Summary and Outlook

Transition metal-catalyzed C–H functionalizations have recently emerged as a reliable tool for the efficient chemo- and site-selective construction of C–C and C–Het bonds, which is of major importance for the preparation of pharmaceuticals, agrochemicals and functional materials. Within this thesis, efforts have been devoted to developing new step-economic synthetic methods employing versatile nickel-, manganese(I)-, or ruthenium(II)-catalyzed C–H activation.

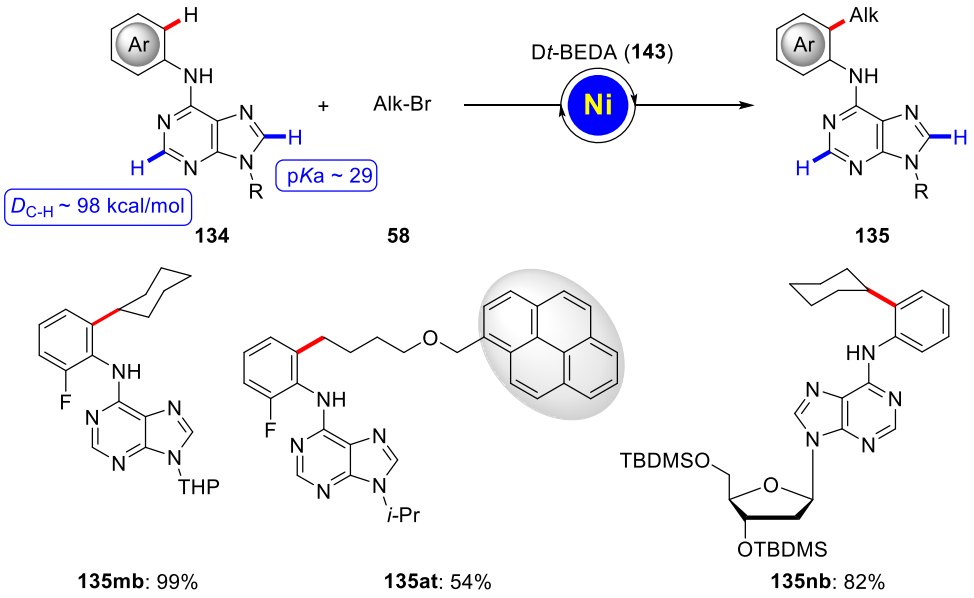
First, the C–H alkylation of aniline derivatives with alkyl halides was achieved with a versatile nickel catalyst through monodentate chelation assistance (Scheme 4.1). The nickel catalyst derived from the vicinal diamine ligand D*t*-BEDA set the stage for a unified strategy for C–H alkylations of 2-pyrimidyl anilines with primary and secondary alkyl halides. The corresponding products are key structural motifs of numerous bioactive compounds including anticancer drugs. A facile C–H activation step and SET-type C–X bond cleavage in this nickel catalyst regime were also revealed by detailed mechanistic studies.



Scheme 4.1 Nickel-catalyzed C–H alkylation of anilines **123**.

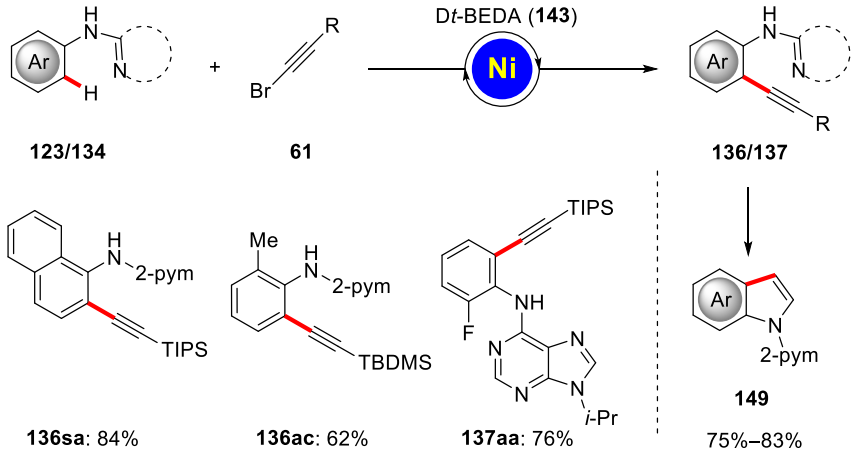
Second, based on the achievement of the nickel-catalyzed C–H alkylation of anilines, we were motivated to enable the C–H functionalization of more useful and challenging purine moieties. Therefore, C–H primary and secondary alkylations of purine nucleosides were achieved by means of user-friendly nickel catalysis with excellent positional selectivity, ample substrate scope and high functional group tolerance, providing access to key structural motifs of

numerous bioactive compounds and marketed drugs (Scheme 4.2). The novel synthetic strategy of the nickel catalysis regime also enabled the direct fluorescent labeling of nucleobases, highlighting the potential of our methodology for late stage diversification.



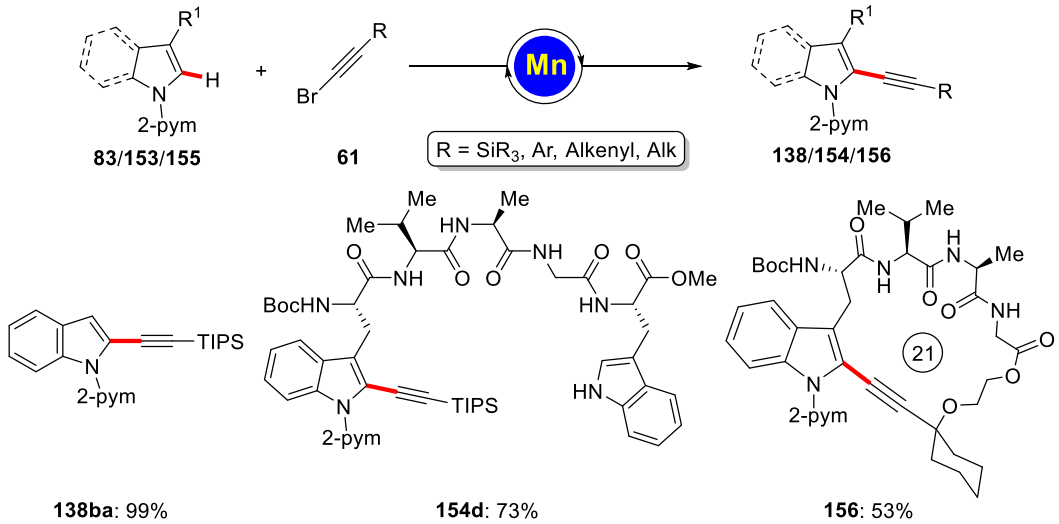
Scheme 4.2 Nickel-catalyzed C–H activation of purine bases **134** with alkyl halides **58**.

Third, the first nickel-catalyzed C–H alkynylation of electron-rich arenes was developed (Scheme 4.3). Thus, anilines were directly functionalized with high positional selectivity, ample scope and high functional group tolerance. Moreover, a kinetically relevant C–H metalation was disclosed by mechanistic studies. Thereby, the C–H alkynylation strategy set the stage for a novel step-economical synthesis of highly substituted indole, and modifications of purine nucleobases.



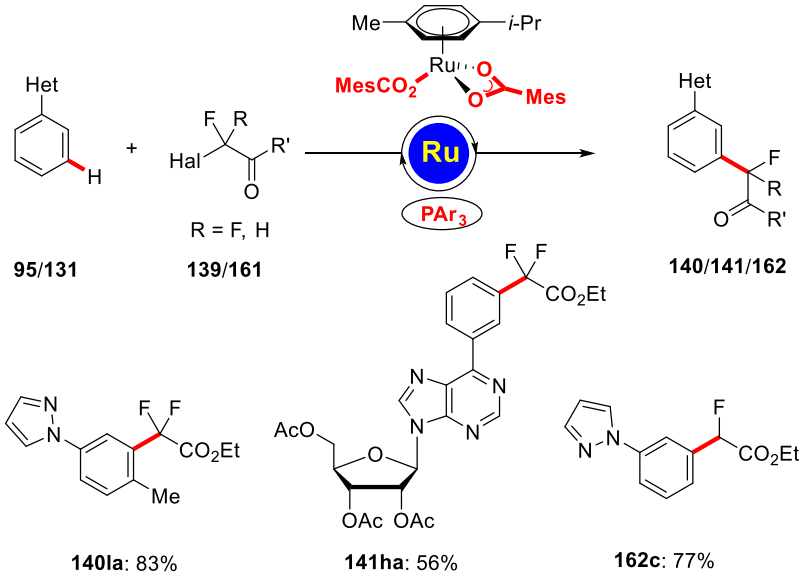
Scheme 4.3 Nickel-catalyzed C–H alkynylation of anilines.

Fourth, in continuation of our nickel-catalyzed C–H alkynylation, we devised a versatile C–H alkynylation by less toxic manganese(I) catalysis with silyl, aryl, alkenyl, and alkyl haloalkynes (Scheme 4.4). The transformative nature of the manganese(I) catalysis manifold facilitated the C–H coupling of alkynes featuring fluorescent labels, steroids, and amino acids. The versatility of the powerful C–H alkynylation approach set the stage for peptide ligation as well as the efficient modification and assembly of cyclic and acyclic peptides.



Scheme 4.4 Manganese-catalyzed C–H alkynylation

Fifth, we have developed a ruthenium(II)-catalyzed remote C–H mono- and difluoromethylation through cooperation of phosphine and carboxylate ligands (Scheme 4.5). Thereby, a versatile ruthenium(II) carboxylate catalyst modified with arylphosphines enabled expedient and *meta*-selective C–H functionalization of diversely decorated pyridyl, pyrimidyl, pyrazolyl, and purinyl arenes. Mechanistic studies were indicative of a radical-involved C–X cleavage process by facile organometallic *ortho*-C–H activation.



Scheme 4.5 Ruthenium(II)-catalyzed *meta* C–H mono- and difluoromethylations

5 Experimental Section

5.1 General Remarks

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

Solvents

All solvents for reactions involving moisture-sensitive reagents were dried, distilled and stored under inert atmosphere (N_2) according to the following standard procedures.

1,2-Dichloroethane was dried over CaH_2 for 8 h, degassed and distilled under reduced pressure.

Dimethylacetamide was dried over CaH_2 for 8 h, degassed and distilled under reduced pressure.

1,2-Dimethoxyether was used as supplied by Merck or stirred over sodium chips for 5 h at 120 °C and then distilled at ambient pressure.

Dichloromethane was purified using a solvent purification system (*SPS-800*) from M. BRAUN.

Diethyl ether was purified using a solvent purification system (*SPS-800*) from M. BRAUN.

Tetrahydrofuran was purified using a solvent purification system (*SPS-800*) from M. BRAUN.

1,4-Dioxane was distilled from sodium benzophenone ketyl.

Di-(*n*-butyl)-ether was distilled from sodium benzophenone ketyl.

Methanol was stirred over magnesium turnings at 65 °C for 3 h prior to distillation from $Mg(OMe)_2$.

***N*-Methyl-2-pyrrolidone** was stirred over CaH_2 at 200 °C for 4 h and distilled under reduced pressure.

Toluene was pre-dried over KH followed by distillation from sodium benzophenone ketyl.

***N*-Methyl-2-pyrrolidone** was dried over CaH_2 for 4 h at 150 °C and subsequently distilled under reduced pressure.

2,2,2-Trifluoroethanol was stirred over $CaSO_4$ and distilled under reduced pressure.

Water was degased by repeated *Freeze-Pump-Thaw* degasing procedure.

Vacuum

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

Melting Points (M. p.)

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

Chromatography and HPLC-Chromatography

Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60F-plates (MACHEREY-NAGEL) with 254 nm fluorescent indicator from MERCK. Plates were visualized under UV-light or developed by treatment with a $KMnO_4$ solution followed by carefully applying a heat gun. Chromatographic purification of products was accomplished by column chromatography on MERCK silica gel, grade 60 (0.040–0.063 mm and 0.063–0.200 mm). Analytical High-Performance-Liquid-Chromatography (HPLC) for determination of enantiomeric excess was conducted on an AGILENT *1260 Infinity* system with *Chiralpak IC-3* and *IF-3* as columns.

Gas Chromatograpgy (GC)

The conversion of the reactions was monitored applying coupled gas chromatography/mass spectrometry using G1760C GCD plus with mass detector *HP 5971*, *5890 Series II* with mass detector *HP 5972* from HEWLETT-PACKARD and 7890A *GC-System* with mass detector *5975C (Triplex-Axis-Detector)* from AGILENT TECHNOLOGIES equipped with *HP-5MS* columns (30 m × 0.25 mm × 0.25 m) were used.

Gel permeation chromatography (GPC)

GPC purifications were performed on a JAI system (JAI-*LC-9260 II NEXT*) equipped with two sequential columns (*JAIGEL-2HR*, gradient rate: 5.000; *JAIGEL-2.5HR*, gradient rate: 20.000; internal diameter: 20 mm; length: 600 mm; Flush rate = 10.0 mL/min and chloroform (HPLC-quality with 0.6% ethanol as stabilizer) was used as the eluent.

Fluorescence-Spectroscopy

The fluorescence-emission spectra were recorded on a JASCO *FP-6200* spectroscope with an *ETC 27 LCT* heater. Spectra were recorded as 1.0 mg/L-solutions of sample in EtOAc. Analyses of the recorded spectra was carried out using *Origin Pro 8.5G*.

Nuclear Magnetic Resonance Spectroscopy (NMR)

Nuclear magnetic resonance (NMR) spectroscopy was performed at 300, 400 or 600 MHz (^{1}H NMR), 75 or 125 MHz (^{13}C NMR, APT) and 283 MHz (^{19}F NMR) on BRUKER *AM 250*, VARIAN *Unity-300* and *Inova 500* instruments. Chemical shifts are reported as δ-values in ppm relative to the residual proton peak of the deuterated solvent or its carbon atom, respectively, or the standard tetramethylsilane (TMS) resonance. For characterization of the observed resonance multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet), or analogue representations. The coupling constants *J* are reported in Hertz (Hz).

Infrared Spectroscopy (IR)

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

Mass Spectrometry (MS)

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

Reagents

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

N-(pyrimidine-2-yl)anilines **1a**–**1w**,[152] **1x**,[153] $[D]_5$-**1c**,[65] purine bases **134a**–**134m**,[154] **134n**,[155] alkynes **61a**–**61g**,[156] **61h**–**61p**,[156-157] indoles **83**,[158] **153**,[105, 156, 159] **155**, [105, 156, 159] **95**,[160] **131**,[161] cyclometalated complex **159**,[162] {$RuCl_2$(*p*-cymene)[P(4-$C_6H_4CF_3$)$_3$]} (**160**).[163]

5.2 General Procedures

General Procedure A: Nickel-Catalyzed C–H Alkylation of Anilines

Anilines **123** (0.50 mmol), [(DME)$NiCl_2$] (5.5 mg, 5.0 mol %) and LiO*t*-Bu (80 mg, 1.0 mmol) were placed in a 25 mL Schlenk tube. The tube was degassed and purged with N_2 three times. D*t*-BEDA (**143**) (11.0 μL, 10 mol %), alkyl bromides **58** (1.0 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 120 °C for 16 h. At ambient temperature, CH_2Cl_2 (2 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure, purified by column chromatography on silica gel to afford the desired products **133** or **142**.

General Procedure B: Nickel-Catalyzed C–H Alkylation of Anilines

Anilines **123** (1.0 mmol), [(DME)$NiCl_2$] (5.5 mg, 2.5 mol %) and LiO*t*-Bu (160 mg, 2.0 mmol) were placed in a 25 mL Schlenk tube. The tube was degassed and purged with N_2 three times. D*t*-BEDA (**143**) (11.0 μL, 5.0 mol %), alkyl bromides **58** (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 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure, purified by column chromatography on silica gel to afford the desired products **142**.

General Procedure C: Nickel-Catalyzed C–H Alkylation of Purine Bases

6-Anilinopurines **134** (0.30 mmol), [(DME)$NiCl_2$] (6.6 mg, 10 mol %) and LiO*t*-Bu (48 mg, 0.60 mmol) were placed in a 25 mL Schlenk tube. The tube was degassed and purged with N_2 three times. D*t*-BEDA (**143**) (13 μL, 20 mol %), alkyl bromides **58** (0.60 mmol) and 1,4-dioxane (1.5 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, and the reaction mixture was transferred into a round

flask with CH_2Cl_2 and concentrated under reduced pressure, purified by column chromatography on silica gel to afford the desired products **135**.

General Procedure D: Nickel-Catalyzed C–H Alkylation of Purine Bases

6-Anilinopurines **134** (0.30 mmol), [(DME)$NiCl_2$] (3.3 mg, 5.0 mol %) and LiO*t*-Bu (48 mg, 0.60 mmol) were placed in a 25 mL Schlenk tube. The tube was degassed and purged with N_2 three times. D*t*-BEDA (**143**) (6.5 μL, 10 mol %), alkyl bromides **58** (0.60 mmol) and 1,4-dioxane (1.5 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, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure, purified by column chromatography on silica gel to afford the desired products **135**.

General Procedure E: Nickel-Catalyzed C–H Alkynylation of Anilines

Anilines **123** (0.50 mmol) or purine bases **134** (0.50 mmol), [(DME)$NiCl_2$] (2.8 mg, 2.5 mol %) and LiO*t*-Bu (80.0 mg, 1.00 mmol) were placed in a 25 mL Schlenk tube. The tube was degassed and purged with N_2 three times. D*t*-BEDA (**143**) (5.5 μL, 5.0 mol %), alkyne **61** (1.50 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 90–100 °C for 16 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure, purified by column chromatography on silica gel to afford the desired products **136** or **137**.

General Procedure F: Manganese-Catalyzed C–H Alkynylation

To a solution of substrates **83** (0.50 mmol) or **153** (0.50 mmol), $MnBr(CO)_5$ (6.9 mg, 5.0 mol %) and Cy_2NH (181 mg, 1.0 mmol) in DCE (1.0 mL), silyl bromoalkynes **61** (0.6 mmol) was added. The mixture was stirred at 80 °C for 16 h. After completion of the reaction, CH_2Cl_2 (3.0 mL) was added at ambient temperature and the volatiles were removed in *vacuo*. Purification by chromatography on silica gel afforded the desired products **138** or **154**.

General Procedure G: Manganese-Catalyzed C–H Alkynylation

To a solution of substrates **83** (0.50 mmol) or **153** (0.50 mmol), $MnBr(CO)_5$ (6.9 mg, 5.0 mol %), Cy_2NH (181 mg, 1.0 mmol) and BPh_3 (25 μL, 0.05 mol %, 0.01 M stock solution in DCE) in DCE (1 mL), aryl or alkyl bromoalkynes **61** (0.6 mmol) was added. The mixture was stirred at 80 °C for 16 h. After completion of the reaction, CH_2Cl_2 (3 mL) was added at ambient temperature and the volatiles were removed in vacuo. Purification by chromatography on silica gel afforded the desired products **150** or **154**.

General Procedure H: Ruthenium(II)-Catalyzed *meta*-C–H mono- and di-Fluoromethylation

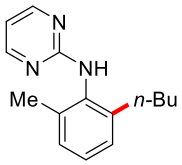
To a solution of substrates **95** (0.50 mmol), [$Ru(O_2CMes)_2$(*p*-cymene)] (28.1 mg, 10 mol %), $P(4\text{-}C_6H_4CF_3)_3$ (46.7 mg, 20 mol %) and Na_2CO_3 (106 mg, 1.0 mmol) in 1,4-dioxane (2.0 mL), bromodifluoroester **139a** (304 mg, 1.5 mmol) or bromofluoroester **161** (278 mg, 1.5 mmol) was added. The mixture was stirred at 60 °C for 18 h. After completion of the reaction, CH_2Cl_2 (3.0 mL) was added at ambient temperature and the volatiles were removed in *vacuo*. Purification by chromatography on silica gel afforded the desired products **140** or **162**.

General Procedure I: Ruthenium(II)-Catalyzed *meta*-C–H mono- and di-Fluoromethylation

To a solution of purine substrates **131** (0.25 mmol), [$Ru(O_2CMes)_2$(*p*-cymene)] (14.0 mg, 10 mol %), $P(4\text{-}C_6H_4CF_3)_3$ (23.4 mg, 20 mol %) and Na_2CO_3 (53.0 mg, 0.50 mmol) in 1,4-dioxane (2.0 mL), bromodifluoroester **139a** (152 mg, 0.75 mmol) or bromofluoroester **161** (139 mg, 0.75 mmol) was added. The mixture was stirred at 60 °C for 18 h. After completion of the reaction, CH_2Cl_2 (3.0 mL) was added at ambient temperature and the volatiles were removed in *vacuo*. Purification by chromatography on silica gel afforded the desired products **141** or **162**.

5.3 Experiments

5.3.1 Characterization Data: Nickel-Catalyzed C–H Alkylation of Anilines



***N*-(2-*n*-Butyl-6-methylphenyl)pyrimidin-2-amine (133aa)**: The general procedure **A** was followed using substrate **123a** (93 mg, 0.50 mmol) and bromide **58a** (107 µL, 1.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **133aa** (105 mg, 87%) as a yellow solid.

M. p. = 59–61 °C.

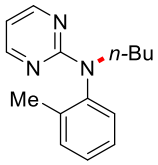
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.28 (d, J = 4.8 Hz, 2H), 7.21–7.04 (m, 4H), 6.56 (t, J = 4.8, 1H), 2.59 (t, J = 7.7 Hz, 2H), 2.22 (s, 3H), 1.58–1.43 (m, 2H), 1.36–1.20 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.8 (C_q), 158.3 (CH), 140.7 (C_q), 136.8 (C_q), 134.9 (C_q), 128.3 (CH), 127.3 (CH), 127.2 (CH), 111.1 (CH), 32.6 (CH_2), 31.7 (CH_2), 22.5 (CH_2), 18.6 (CH_3), 13.9 (CH_3).

IR (neat): 3223, 2951, 2924, 2860, 1576, 1519, 1445, 1406, 800 cm^{-1}.

MS (EI) *m/z* (relative intensity) 241 (24) [M^+], 212 (36), 184 (100).

HR-MS (EI) *m/z* calcd for $C_{15}H_{19}N_3$ [M^+] 241.1579, found 241.1581.



***N*-*n*-Butyl-*N*-(*o*-tolyl)pyrimidin-2-amine (133aa')**: Side product **133aa'** as a yellow solid.

M. p. = 51–52 °C.

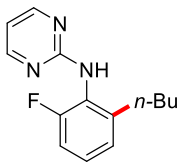
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.28 (d, J = 4.8 Hz, 2H), 7.33–7.28 (m, 1H), 7.28–7.19 (m, 2H), 7.18–7.13 (m, 1H), 6.47 (t, J = 4.8 Hz, 1H), 4.13–3.87 (m, 1H), 3.74–3.56 (m, 1H), 2.11 (s, 3H), 1.74–1.55 (m, 2H), 1.41–1.24 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.5 (C_q), 157.7 (CH), 142.8 (C_q), 136.4 (C_q), 131.0 (CH), 128.6 (CH), 127.0 (CH), 126.9 (CH), 109.9 (CH), 50.2 (CH_2), 30.0 (CH_2), 20.3 (CH_2), 18.1 (CH_3), 14.1 (CH_3).

IR (neat): 2964, 2928, 1572, 1547, 1472, 1369, 798, 765, 622 cm^{-1}.

MS (EI) *m/z* (relative intensity) 241 (15) [M^+], 226 (100), 198 (70), 170 (35).

HR-MS (EI) *m/z* calcd for $C_{15}H_{19}N_3$ [M^+] 241.1579, found 241.1587.



***N*-(2-*n*-Butyl-6-fluorophenyl)pyrimidin-2-amine (133ba)**: The general procedure **A** was followed using substrate **123b** (95 mg, 0.50 mmol) and bromide **58a** (107 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **133ba** (110 mg, 90%) as a yellow solid.

M. p. = 53–54 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.29 (d, J = 4.9 Hz, 2H), 7.91 (s, 1H), 7.18 (ddd, J = 8.0, 8.0, 5.4 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H), 6.99 (ddd, J = 9.6, 8.2, 1.4 Hz, 1H), 6.60 (t, J = 4.8 Hz, 1H), 2.61 (t, J = 7.8 Hz, 2H), 1.69–1.46 (m, 2H), 1.33–1.25 (m, 2H), 0.83 (t, J = 7.4 Hz, 3H).

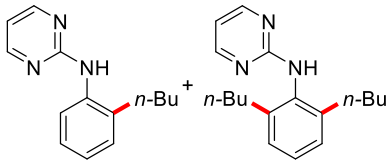
^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.5 (C_q), 158.6 (C_q, $^{1}J_{C\text{-}F}$ = 248.0 Hz), 158.0 (CH), 142.6 (C_q), 127.4 (CH, $^{3}J_{C\text{-}F}$ = 8.7 Hz), 124.7 (CH, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 124.4 (C_q, $^{2}J_{C\text{-}F}$ = 12.6 Hz), 113.3 (CH, $^{2}J_{C\text{-}F}$ = 20.8 Hz), 111.9 (CH), 32.4 (CH_2), 31.2 (CH_2, $J_{C\text{-}F}$ = 2.4 Hz), 22.5 (CH_2), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -119.6 (dd, J = 9.6, 5.5 Hz).

IR (neat): 3220, 2959, 2929, 1576, 1521, 1443, 1357, 1225, 968, 783, 638, 495 cm^{-1}.

MS (EI) *m/z* (relative intensity) 245 (45) [M^+], 226 (20), 216 (100), 188 (76).

HR-MS (EI) *m/z* calcd for $C_{14}H_{16}FN_3$ [M^+] 245.1328, found 245.1327.



The general procedure **A** was followed using substrate **123c** (86 mg, 0.50 mmol) and bromide **58a** (59 µL, 0.55 mmol). After 8 h, isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **133ca** (71 mg, 62%) as a colorless liquid and **133ca'** (20 mg, 14%) as a white solid.

***N*-(2-*n*-Butylphenyl)pyrimidin-2-amine (133ca)**:

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.36 (d, J = 4.8 Hz, 2H), 7.85 (dd, J = 8.0, 1.0 Hz, 1H), 7.23–7.18 (m, 2H), 7.07 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 6.92 (br s, 1H), 6.65 (t, J = 4.8 Hz, 1H), 2.63 (t, J = 7.9 Hz, 2H), 1.62–1.55 (m, 2H), 1.41–1.32 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.8 (C_q), 157.9 (CH), 136.4 (C_q), 134.1 (C_q), 129.5 (CH), 126.4 (CH), 124.3 (CH), 123.2 (CH), 112.1 (CH), 32.0 (CH_2), 31.4 (CH_2), 22.6 (CH_2), 14.0 (CH_3).

IR (neat): 3231, 2955, 2928, 1578, 1518, 1439, 1400, 797, 748, 639 cm^{-1}.

MS (EI) *m/z* (relative intensity) 227 (52) [M^+], 198 (85), 170 (100).

HR-MS (EI) *m/z* calcd for $C_{14}H_{17}N_3$ [M^+] 227.1422, found 227.1432.

***N*-(2,6-Di-*n*-butylphenyl)pyrimidin-2-amine (133ca')**:

M. p. = 73–74 °C.

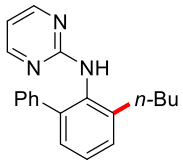
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.28 (d, J = 4.8 Hz, 2H), 7.19 (dd, J = 8.4, 6.7 Hz, 1H), 7.13 (dd, J = 8.4, 1.1 Hz, 2H), 6.68 (br s, 1H), 6.56 (t, J = 4.8 Hz, 1H), 2.50 (t, J = 7.9 Hz, 4H), 1.54–1.46 (m, 4H), 1.31–1.23 (m, 4H), 0.82 (t, J = 7.4 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.1 (C_q), 158.3 (CH), 141.2 (C_q), 134.4 (C_q), 127.4 (CH), 127.3 (CH), 111.2 (CH), 32.5 (CH_2), 31.7 (CH_2), 22.6 (CH_2), 13.9 (CH_3).

IR (neat): 3231, 2956, 2927, 2859, 1573, 1517, 1444, 1404, 799, 638 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 284 [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{18}H_{25}N_3$ [M+H^+] 284.2127, found 284.2129.



***N*-(3-*n*-Butylbiphenyl-2-yl)pyrimidin-2-amine (133da)**: The general procedure **A** was followed using substrate **123d** (124 mg, 0.50 mmol) and bromide **58a** (107 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **133da** (119 mg, 78%) as a white solid.

M. p. = 104–105 °C.

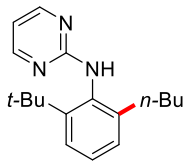
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.19 (d, J = 4.8 Hz, 2H), 7.37–7.15 (m, 8H), 6.80 (s, 1H), 6.48 (t, J = 4.8 Hz, 1H), 2.63 (t, J = 7.9 Hz, 2H), 1.67–1.53 (m, 2H), 1.36–1.27 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.8 (C_q), 158.0 (CH), 141.3 (C_q), 140.3 (C_q), 140.1 (C_q), 133.6 (C_q), 129.0 (CH), 128.8 (CH), 128.3 (CH), 127.9 (CH), 127.1 (CH), 126.9 (CH), 111.2 (CH), 32.3 (CH_2), 31.7 (CH_2), 22.6 (CH_2), 13.9 (CH_3).

IR (neat): 3216, 2952, 2927, 2869, 1576, 1525, 1445, 1408, 756, 670 cm^{-1}.

MS (EI) *m/z* (relative intensity) 303 (40) [M^+], 274 (41), 261 (27), 246 (100), 182 (10).

HR-MS (EI) *m/z* calcd for $C_{20}H_{21}N_3$ [M^+] 303.1735, found 303.1735.



***N*-(2-*tert*-Butyl-6-*n*-butylphenyl)pyrimidin-2-amine (133ea)**: The general procedure **A** was followed using substrate **123e** (114 mg, 0.50 mmol) and bromide **58a** (107 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **133ea** (92 mg, 65%) as a yellow solid.

M. p. = 128–129 °C.

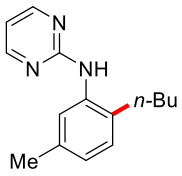
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, J = 4.8 Hz, 2H), 7.34 (dd, J = 7.6, 2.0 Hz, 1H), 7.24–7.16 (m, 2H), 6.77 (s, 1H), 6.54 (t, J = 4.8 Hz, 1H), 2.50–2.38 (m, 2H), 1.60–1.47 (m, 2H), 1.35 (s, 9H), 1.28–1.19 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.2 (C_q), 158.5 (CH), 158.2 (CH), 147.9 (C_q), 143.2 (C_q), 134.7 (C_q), 127.9 (CH), 127.6 (CH), 124.8 (CH), 111.0 (CH), 35.4 (C_q), 32.3 (CH_2), 31.6 (CH_2), 31.1 (CH_3), 22.7 (CH_2), 13.9 (CH_3).

IR (neat): 3212, 2951, 2863, 1594, 1527, 1448, 1410, 1265, 779, 648 cm^{-1}.

MS (EI) *m/z* (relative intensity) 283 (3) [M^+], 226 (100), 183 (12).

HR-MS (EI) *m/z* calcd for $C_{18}H_{25}N_3$ [M^+] 283.2048, found 283.2048.



***N*-(2-*n*-Butyl-5-methylphenyl)pyrimidin-2-amine (133fa)**: The general procedure **A** was followed using substrate **123f** (93 mg, 0.50 mmol) and bromide **58a** (107 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **133fa** (70 mg, 58%) as a colorless liquid.

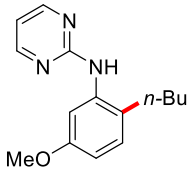
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.35 (d, J = 4.8 Hz, 2H), 7.64 (s, 1H), 7.09 (d, J = 7.7 Hz, 1H), 6.92 (br s, 1H), 6.90 (dd, J = 7.7, 1.2 Hz, 1H), 6.64 (t, J = 4.8 Hz, 1H), 2.58 (t, J = 7.9 Hz, 2H), 2.33 (s, 3H), 1.60–1.51 (m, 2H), 1.39–1.30 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.0 (C_q), 158.1 (CH), 136.3 (C_q), 136.1 (C_q), 131.6 (C_q), 129.5 (CH), 125.4 (CH), 124.1 (CH), 112.0 (CH), 32.2 (CH_2), 30.9 (CH_2), 22.5 (CH_2), 21.2 (CH_3), 13.9 (CH_3).

IR (neat): 3233, 2954, 2927, 2859, 1577, 1525, 1443, 1400, 797 cm^{-1}.

MS (EI) *m/z* (relative intensity) 241 (51) [M^+], 212 (73), 184 (100).

HR-MS (EI) *m/z* calcd for $C_{15}H_{19}N_3$ [M^+] 241.1579, found 241.1572.



***N*-(2-*n*-Butyl-5-methoxyphenyl)pyrimidin-2-amine (133ga)**: The general procedure **A** was followed using substrate **123g** (101 mg, 0.50 mmol) and bromide **58a** (107 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **133ga** (93 mg, 72%) as a colorless liquid.

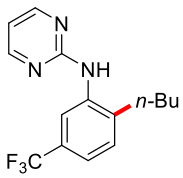
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.37 (d, J = 4.8 Hz, 2H), 7.67 (d, J = 2.7 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.99 (s, 1H), 6.67 (t, J = 4.8 Hz, 1H), 6.61 (dd, J = 8.4, 2.7 Hz, 1H), 3.79 (s, 3H), 2.57 (t, J = 7.9 Hz, 2H), 1.62–1.49 (m, 2H), 1.42–1.29 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.6 (C_q), 158.2 (C_q), 158.0 (CH), 137.5 (C_q), 130.0 (CH), 125.4 (C_q), 112.3 (CH), 109.2 (CH), 108.3 (CH), 55.2 (CH_3), 32.1 (CH_2), 30.6 (CH_2), 22.5 (CH_2), 13.9 (CH_3).

IR (neat): 3232, 2955, 2929, 2870, 1578, 1523, 1442, 1257, 1164, 796 cm^{-1}.

MS (EI) *m/z* (relative intensity) 257 (53) [M^+], 228 (42), 214 (100), 200 (70), 170 (40).

HR-MS (EI) *m/z* calcd for $C_{15}H_{19}N_3O$ [M^+] 257.1528, found 257.1530.



***N*-[2-*n*-Butyl-5-(trifluoromethyl)phenyl]pyrimidin-2-amine (133ha)**: The general procedure **A** was followed using substrate **123h** (120 mg, 0.50 mmol) and bromide **58a** (107 µL, 1.00 mmol) at 100 °C. Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **133ha** (114 mg, 77%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.39 (d, J = 4.8 Hz, 2H), 8.36 (s, 1H), 7.36 (br s, 1H), 7.29–7.28 (m, 2H), 6.71 (t, J = 4.8 Hz, 1H), 2.67 (t, J = 7.9 Hz, 2H), 1.66–1.56 (m, 2H), 1.43–1.31 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H).

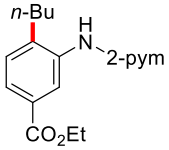
^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.4 (C_q), 158.1 (CH), 137.3 (C_q), 136.9 (C_q, d, $^4J_{C\text{-}F}$ = 1.0 Hz), 129.8 (CH), 128.8 (C_q, q, $^2J_{C\text{-}F}$ = 32.3 Hz), 124.2 (C_q, q, $^1J_{C\text{-}F}$ = 272.0 Hz), 120.2 (CH, q, $^3J_{C\text{-}F}$ = 3.8 Hz), 119.1 (CH, q, $^3J_{C\text{-}F}$ = 3.9 Hz), 112.8 (CH), 31.4 (CH_2), 31.2 (CH_2), 22.5 (CH_2), 13.8 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -62.3 (s).

IR (neat): 3445, 3273, 2959, 2873, 1578, 1427, 1327, 1161, 1116, 1074, 797 cm^{-1}.

MS (EI) *m/z* (relative intensity) 295 (45) [M^+], 266 (100), 238 (95), 183 (10).

HR-MS (EI) *m/z* calcd for $C_{15}H_{16}F_3N_3$ [M^+] 295.1296, found 295.1291.



Ethyl 4-*n*-butyl-3-(pyrimidin-2-ylamino)benzoate (133ia): The general procedure **A** was followed using substrate **123i** (122 mg, 0.50 mmol) and bromide **58a** (107 µL, 1.00 mmol) at 100 °C. Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **133ia** (86 mg, 57%) as a colorless liquid.

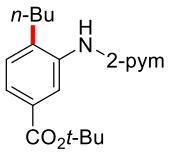
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.50 (d, *J* = 1.8 Hz, 1H), 8.35 (d, *J* = 4.8 Hz, 2H), 7.74 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.25 (br s, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 6.66 (t, *J* = 4.8 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.65 (t, *J* = 7.9 Hz, 2H), 1.65–1.50 (m, 2H), 1.36–1.29 (m, 5H), 0.86 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.4 (C_q), 160.8 (C_q), 158.1 (CH), 139.8 (C_q), 136.8 (C_q), 129.5 (CH), 128.9 (C_q), 125.4 (CH), 124.7 (CH), 112.4 (CH), 60.7 (CH_2), 31.6 (CH_2), 31.3 (CH_2), 22.4 (CH_2), 14.3 (CH_3), 13.8 (CH_3).

IR (neat): 3222, 2957, 2931, 2871, 1713, 1577, 1444, 1288, 1221, 1099, 798 cm^{-1}.

MS (EI) *m/z* (relative intensity) 299 (40) [M^+], 270 (92), 242 (100), 182 (20).

HR-MS (EI) *m/z* calcd for $C_{17}H_{21}N_3O_2$ [M^+] 299.1634, found 299.1646.



***tert*-Butyl 4-*n*-butyl-3-(pyrimidin-2-ylamino)benzoate (133ja)**: The general procedure **A** was followed using substrate **123j** (136 mg, 0.50 mmol) and bromide **58a** (107 µL, 1.00 mmol).

Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **133ja** (105 mg, 64%) as a white solid.

M. p. = 108–109 °C.

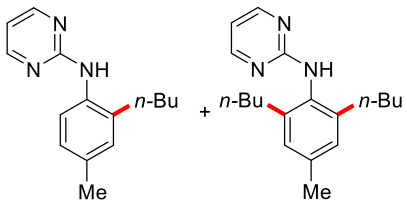
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.48 (d, J = 1.8 Hz, 1H), 8.37 (d, J = 4.8 Hz, 2H), 7.70 (dd, J = 7.9, 1.8 Hz, 1H), 7.27–7.22 (m, 2H), 6.67 (t, J = 4.8 Hz, 1H), 2.66 (t, J = 7,9 Hz, 2H), 1.62–1.54 (m, 11H), 1.41–1.26 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.5 (C_q), 160.8 (C_q), 158.1 (CH), 139.4 (C_q), 136.6 (C_q), 130.5 (C_q), 129.4 (CH), 125.4 (CH), 124.5 (CH), 112.3 (CH), 80.6 (C_q), 31.6 (CH_2), 31.3 (CH_2), 28.1 (CH_3), 22.4 (CH_2), 13.8 (CH_3).

IR (neat): 3225, 2968, 2930, 2862, 1704, 1583, 1447, 1305, 1126, 800 cm^{-1}.

MS (EI) *m/z* (relative intensity) 327 (23) [M^+], 271 (45), 242 (98), 214 (100), 182 (16).

HR-MS (EI) *m/z* calcd for $C_{19}H_{25}N_3O_2$ [M^+] 327.1947, found 327.1948.



133ka **133ka'**

The general procedure **A** was followed using substrate **123k** (93 mg, 0.50 mmol) and bromide **58a** (59 µL, 0.55 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **133ka** (75 mg, 62%) and **133ka'** (18 mg, 12%) as yellow solids.

***N*-(2-*n*-Butyl-4-methylphenyl)pyrimidin-2-amine (133ka)**:

M. p. = 57–58 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.32 (d, J = 4.8 Hz, 2H), 7.61–7.53 (m, 1H), 7.05–7.01 (m, 2H), 6.97 (br s, 1H), 6.61 (t, J = 4.8 Hz, 1H), 2.58 (t, J = 7.9 Hz, 2H), 2.30 (s, 3H), 1.61–1.51 (m, 2H), 1.40–1.28 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.4 (C_q), 158.1 (CH), 135.6 (C_q), 134.5 (C_q), 133.8 (C_q), 130.3 (CH), 127.1 (CH), 124.5 (CH), 111.7 (CH), 32.2 (CH_2), 31.3 (CH_2), 22.6 (CH_2), 21.0 (CH_3), 13.9 (CH_3).

IR (neat): 3232, 2955, 2927, 2859, 1581, 1516, 1444, 1402, 798, 636 cm^{-1}.

MS (EI) *m/z* (relative intensity) 241 (56) [M^+], 212 (82), 184 (100).

HR-MS (EI) *m/z* calcd for $C_{15}H_{19}N_3$ [M^+] 241.1579, found 241.1576.

***N*-(2,6-Di-*n*-butyl-4-methylphenyl)pyrimidin-2-amine (133ka')**:

M. p. = 99–100 °C.

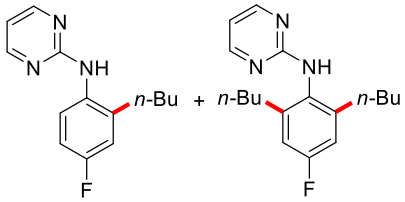
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.27 (d, J = 4.8 Hz, 2H), 6.93 (s, 2H), 6.58 (br s, 1H), 6.54 (t, J = 4.8 Hz, 1H), 2.50 (t, J = 7.9 Hz, 4H), 1.55–1.42 (m, 4H), 1.38–1.17 (m, 4H), 0.82 (t, J = 7.3 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.3 (C_q), 158.3 (CH), 145.0 (C_q), 136.9 (C_q), 131.7 (C_q), 128.2 (CH), 111.0 (CH), 32.6 (CH_2), 31.7 (CH_2), 22.7 (CH_2), 21.2 (CH_3), 13.9 (CH_3).

IR (neat): 3223, 2955, 2925, 2857, 1577, 1447, 1407, 1260, 800, 639 cm^{-1}.

MS (EI) *m/z* (relative intensity) 297 (35) [M^+], 240 (100), 210 (25), 197 (15).

HR-MS (ESI) *m/z* calcd for $C_{19}H_{27}N_3$ [M+H^+] 298.2283, found 298.2278.



133la **133la'**

The general procedure **A** was followed using substrate **123l** (95 mg, 0.50 mmol) and bromide **58a** (59 µL, 0.55 mmol). After 4 h, isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **133la** (86 mg, 70%) and **133la'** (20mg, 13%) as white solids.

***N*-(2-*n*-Butyl-4-fluorophenyl)pyrimidin-2-amine (133la)**:

M. p. = 63–64 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.32 (d, J = 4.8 Hz, 2H), 7.67–7.58 (m, 1H), 7.04 (br s, 1H), 6.96–6.85 (m, 2H), 6.63 (t, J = 4.8 Hz, 1H), 2.59 (t, J = 7.9 Hz, 2H), 1.65–1.49 (m, 2H), 1.40–1.27 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.1 (C_q), 160.0 (C_q, $^1J_{C\text{-}F}$ = 244.0 Hz), 158.0 (CH), 138.3 (C_q, $^3J_{C\text{-}F}$ = 7.5 Hz), 132.3 (C_q, $^4J_{C\text{-}F}$ = 2.7 Hz), 126.3 (CH, $^3J_{C\text{-}F}$ = 8.3 Hz), 115.9 (CH, $^2J_{C\text{-}F}$ = 22.6 Hz), 113.0 (CH, $^2J_{C\text{-}F}$ = 22.6 Hz), 112.0 (CH), 31.8 (CH_2), 31.3 (CH_2, $^4J_{C\text{-}F}$ = 1.1 Hz), 22.5 (CH_2), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -117.7 (ddd, J = 8.7, 8.7, 5.4 Hz).

IR (neat): 3234, 2957, 2930, 2870, 1582, 1518, 1446, 1192, 990, 864 cm^{-1}.

MS (EI) *m/z* (relative intensity) 245 (51) [M^+], 216 (100), 203 (40), 188 (81).

HR-MS (EI) *m/z* calcd for $C_{14}H_{16}FN_3$ [M^+] 245.1328, found 245.1331.

***N*-(2,6-Di-*n*-butyl-4-fluorophenyl)pyrimidin-2-amine (133la')**:

M. p. = 75–76 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.24 (d, J = 4.8 Hz, 2H), 7.30 (br s, 1H), 6.83 (d, J = 9.3 Hz, 2H), 6.55 (t, J = 4.8 Hz, 1H), 2.55 (t, J = 7.9 Hz, 4H), 1.55–1.45 (m, 4H), 1.32–1.20 (m, 4H), 0.81 (t, J = 7.3 Hz, 6H).

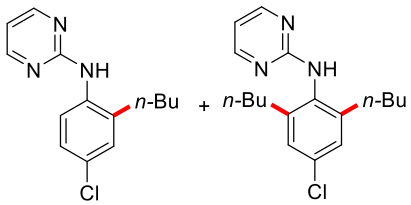
^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.1 (C_q), 161.4 (C_q, $^1J_{C\text{-}F}$ = 245.4 Hz), 158.2 (CH), 143.6 (C_q, $^3J_{C\text{-}F}$ = 8.3 Hz), 130.3 (C_q, $^4J_{C\text{-}F}$ = 2.9 Hz), 113.6 (CH, $^2J_{C\text{-}F}$ = 22.0 Hz), 111.1 (CH), 32.2 (CH_2), 31.7 (CH_2, $^4J_{C\text{-}F}$ = 1.2 Hz), 22.5 (CH_2), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -115.4 (t, J = 9.2 Hz).

IR (neat): 3214, 2957, 2927, 2860, 1581, 1520, 1446, 1409, 990, 800 cm^{-1}.

MS (EI) *m/z* (relative intensity) 301 (40) [M^+], 244 (100), 201 (25).

HR-MS (EI) *m/z* calcd for $C_{18}H_{24}FN_3$ [M^+] 301.1954, found 301.1951.



133ma **133ma'**

The general procedure **A** was followed using substrate **123m** (103 mg, 0.50 mmol) and bromide **58a** (59 µL, 0.55 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **133ma** (75 mg, 57%) and **133ma'** (24 mg, 15%) as yellow solids.

***N*-(2-*n*-Butyl-4-chlorophenyl)pyrimidin-2-amine (133ma)**:

M. p. = 57–58 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.35 (d, J = 4.8 Hz, 2H), 7.82 (d, J = 9.3 Hz, 1H), 7.19–7.16 (m, 2H), 7.00 (br s, 1H), 6.67 (t, J = 4.8 Hz, 1H), 2.59 (t, J = 7.9 Hz, 2H), 1.56–1.54 (m, 2H), 1.39–1.32 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.7 (C_q), 158.1 (CH), 136.1 (C_q), 135.2 (C_q), 129.4 (CH), 129.3 (C_q), 126.4 (CH), 124.5 (CH), 112.4 (CH), 31.6 (CH_2), 31.1 (CH_2), 22.5 (CH_2), 13.8 (CH_3).

IR (neat): 3054, 1649, 1547, 1462, 1437, 1294, 1181, 1121, 757, 690, 546, 505 cm^{-1}.

MS (EI) *m/z* (relative intensity) 261 (45) [M^+] (^{35}Cl), 263 (15) [M^+] (^{37}Cl), 232 (100) (^{35}Cl), 234 (33) (^{37}Cl), 204 (81), 183 (22).

HR-MS (EI) *m/z* calcd for $C_{14}H_{16}ClN_3$ [M^+] 261.1033, found 261.1041.

***N*-(2,6-Di-*n*-butyl-4-chlorophenyl)pyrimidin-2-amine (133ma')**:

M. p. = 97–98 °C.

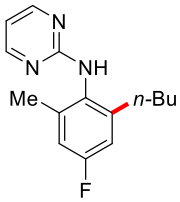
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.28 (d, J = 4.8 Hz, 2H), 7.11 (s, 2H), 6.59 (t, J = 4.8 Hz, 1H), 6.57 (br s, 1H), 2.51 (t, J = 7.9 Hz, 4H), 1.52–1.44 (m, 4H), 1.31–1.21 (m, 4H), 0.82 (t, J = 7.3 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.0 (C_q), 158.4 (CH), 143.2 (C_q), 133.1 (C_q), 132.9 (C_q), 127.3 (CH), 111.6 (CH), 32.2 (CH_2), 31.6 (CH_2), 22.5 (CH_2), 13.8 (CH_3).

IR (neat): 3222, 2955, 2927, 2857, 1580, 1519, 1445, 1408, 799, 638 cm^{-1}.

MS (EI) *m/z* (relative intensity) 317 (40) [M^+], 288 (65), 260 (100), 217 (20).

HR-MS (EI) *m/z* calcd for $C_{18}H_{24}ClN_3$ [M^+] 317.1659, found 317.1665.



***N*-(2-*n*-Butyl-4-fluoro-6-methylphenyl)pyrimidin-2-amine (133na)**: The general procedure **A** was followed using substrate **123n** (102 mg, 0.50 mmol) and bromide **58a** (107 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **133na** (127 mg, 98%) as a white solid.

M. p. = 75–76 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.27 (d, J = 4.8 Hz, 2H), 7.03 (br s, 1H), 6.82 (vd, J = 9.3 Hz, 2H), 6.57 (t, J = 4.8 Hz, 1H), 2.56 (t, J = 7.9 Hz, 2H), 2.20 (s, 3H), 1.55–1.42 (m, 2H), 1.35–1.19 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H).

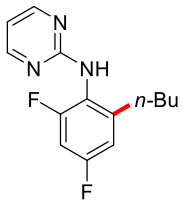
^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.9 (C_q), 161.2 (C_q, $J_{C\text{-}F}$ = 245.4 Hz), 158.4 (CH), 143.2 (C_q, $^3J_{C\text{-}F}$ = 8.1 Hz), 139.2 (C_q, $^3J_{C\text{-}F}$ = 8.7 Hz), 130.9 (C_q, $^4J_{C\text{-}F}$ = 2.8 Hz), 114.8 (CH, $^2J_{C\text{-}F}$ = 22.0 Hz), 113.7 (CH, $^2J_{C\text{-}F}$ = 21.8 Hz), 111.3 (CH), 32.2 (CH_2), 31.7 (CH_2, $^4J_{C\text{-}F}$ = 1.3 Hz), 22.4 (CH_2), 18.7 (CH_3, $^4J_{C\text{-}F}$ = 1.5 Hz), 13.8 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -115.8 (dd, J = 9.2. 9.2 Hz).

IR (neat): 3219, 2954, 2926, 2870, 1578, 1519, 1446, 1261, 1128, 995, 801, 535 cm^{-1}.

MS (EI) *m/z* (relative intensity) 259 (50) [M^+], 230 (80), 202 (100).

HR-MS (EI) *m/z* calcd for $C_{15}H_{18}FN_3$ [M^+] 259.1485, found 259.1481.



***N*-(2-*n*-Butyl-4,6-difluorophenyl)pyrimidin-2-amine (133oa)**: The general procedure **A** was followed using substrate **123o** (104 mg, 0.50 mmol) and bromide **58a** (107 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→5/1) yielded **133oa** (119 mg, 90%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.28 (d, J = 4.8 Hz, 2H), 7.59 (s, 1H), 6.83–6.69 (m, 2H), 6.61 (t, J = 4.8 Hz, 1H), 2.61 (t, J = 7.9 Hz, 2H), 1.57–1.47 (m, 2H), 1.33–1.21 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H).

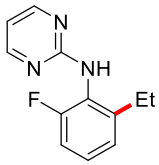
^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.6 (C_q), 160.8 (C_q, dd, $J_{C\text{-}F}$ = 247.2, 12.9 Hz), 158.9 (C_q, dd, $J_{C\text{-}F}$ = 249.4, 13.0 Hz), 158.0 (CH), 144.4 (C_q, dd, $J_{C\text{-}F}$ = 9.0, 1.2 Hz), 120.8 (C_q, dd, $J_{C\text{-}F}$ = 12.9, 3.9 Hz), 111.9 (CH), 111.4 (CH, dd, $J_{C\text{-}F}$ = 21.7, 3.4 Hz), 101.9 (CH, dd, $J_{C\text{-}F}$ = 26.1, 25.1 Hz), 32.0 (CH_2), 31.2 (CH_2, dd, $J_{C\text{-}F}$ = 2.0, 2.0 Hz), 22.4 (CH_2), 13.8 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -112.2 (dd, J = 15.7, 8.8 Hz), -115.2 (ddd, J = 9.4, 6.8, 1.5 Hz).

IR (neat): 3223, 2958, 2871, 1583, 1444, 1118, 993, 799, 535 cm^{-1}.

MS (EI) *m/z* (relative intensity) 263 (40) [M^+], 234 (100), 206 (60), 181 (5).

HR-MS (EI) *m/z* calcd for $C_{14}H_{15}F_2N_3$ [M^+] 263.1234, found 263.1230.



***N*-(2-Ethyl-6-fluorophenyl)pyrimidin-2-amine (133bc)**: The general procedure **A** was followed using substrate **123b** (95 mg, 0.50 mmol) and iodoethane **58c** (80 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **133bc** (87 mg, 80%) as a white solid.

M. p. = 108–109 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, J = 4.8 Hz, 2H), 7.56 (br s, 1H), 7.20 (ddd, J = 8.0, 8.0, 5.5 Hz, 1H), 7.10–7.06 (m, 1H), 7.00 (ddd, J = 9.6, 6.3, 1.4 Hz, 1H), 6.61 (t, J = 4.8 Hz, 1H), 2.68 (q, J = 7.6 Hz, 2H), 1.17 (t, J = 7.6 Hz, 3H).

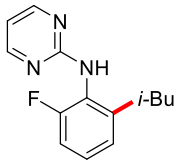
^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.7 (C_q), 158.6 (C_q, $^1J_{C\text{-}F}$ = 248.0 Hz), 158.2 (CH), 143.9 (C_q), 127.6 (CH, $^3J_{C\text{-}F}$ = 8.6 Hz), 124.4 (C_q, $^2J_{C\text{-}F}$ = 12.7 Hz), 124.0 (CH, $^4J_{C\text{-}F}$ = 3.3 Hz), 113.4 (CH, $^2J_{C\text{-}F}$ = 20.8 Hz), 111.9 (CH), 24.5 (CH_2, $^4J_{C\text{-}F}$ = 2.5 Hz), 14.3 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -119.9 (dd, J = 9.6, 5.5 Hz).

IR (neat): 3223, 2971, 2933, 1579, 1524, 1446, 1410, 918, 640 cm^{-1}.

MS (EI) *m/z* (relative intensity) 217 (40) [M^+], 202 (10), 188 (62).

HR-MS (EI) *m/z* calcd for $C_{12}H_{12}FN_3$ [M^+] 217.1015, found 217.1021.



***N*-(2-Fluoro-6-*iso*-butylphenyl)pyrimidin-2-amine (133bd)**: The general procedure **A** was followed using substrate **123b** (95 mg, 0.50 mmol) and bromide **58d** (109 µL, 1.00 mmol).

Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **133bd** (109 mg, 89%) as a white solid.

M. p. = 76–77 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.29 (d, J = 4.8 Hz, 2H), 7.21–7.14 (m, 2H), 7.05–6.92 (m, 2H), 6.61 (t, J = 4.8 Hz, 1H), 2.52 (d, J = 7.2 Hz, 2H), 1.94–1.76 (m, 1H), 0.85 (d, J = 6.6 Hz, 6H).

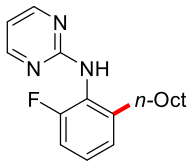
^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.5 (C_q), 158.6 (C_q, $^{1}J_{C\text{-}F}$ = 248.0 Hz), 158.0 (CH), 141.4 (C_q), 127.2 (CH, $^{3}J_{C\text{-}F}$ = 8.6 Hz), 125.7 (CH, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 124.8 (C_q, $^{2}J_{C\text{-}F}$ = 12.5 Hz), 113.5 (CH, $^{2}J_{C\text{-}F}$ = 20.8 Hz), 111.9 (CH), 40.8 (CH_2, $J_{C\text{-}F}$ = 2.3 Hz), 29.5 (CH_2), 22.5 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -119.0 (dd, J = 9.4, 5.4 Hz).

IR (neat): 3224, 2959, 2869, 1581, 1529, 1448, 1413, 1265, 799 cm^{-1}.

MS (EI) *m/z* (relative intensity) 245 (40) [M^+], 230 (55), 202 (45), 182 (15), 170 (7).

HR-MS (EI) *m/z* calcd for $C_{14}H_{16}FN_3$ [M^+] 245.1328, found 245.1326.



***N*-(2-Fluoro-6-*n*-octylphenyl)pyrimidin-2-amine (133be)**: The general procedure **A** was followed using substrate **123b** (95 mg, 0.50 mmol) and bromide **58e** (173 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **133be** (119 mg, 79%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.29 (d, J = 4.8 Hz, 2H), 7.53 (s, 1H), 7.24–7.14 (m, 1H), 7.08–6.93 (m, 2H), 6.61 (t, J = 4.8 Hz, 1H), 2.68–2.59 (m, 2H), 1.60–1.50 (m, 2H), 1.26–1.18 (m, 10H), 0.83 (t, J = 6.8 Hz, 3H).

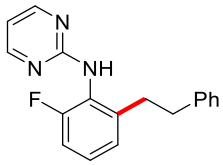
^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.6 (C_q), 158.6 (C_q, $^{1}J_{C\text{-}F}$ = 248.0 Hz), 158.0 (CH), 142.6 (C_q), 127.3 (CH, $^{3}J_{C\text{-}F}$ = 8.6 Hz), 124.7 (CH, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 124.5 (C_q, $^{2}J_{C\text{-}F}$ = 12.6 Hz), 113.3 (CH, $^{2}J_{C\text{-}F}$ = 20.8 Hz), 111.8 (CH), 31.8 (CH_2), 31.6 (CH_2, $^{4}J_{C\text{-}F}$ = 2.3 Hz), 30.2 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -119.5 (dd, J = 9.7, 5.5 Hz).

IR (neat): 3224, 2924, 2854, 1581, 1523, 1445, 1409, 1269, 782 cm^{-1}.

MS (EI) *m/z* (relative intensity) 301 (50) [M^+], 216 (100), 188 (83), 142 (12).

HR-MS (EI) *m/z* calcd for $C_{18}H_{24}FN_3$ [M^+] 301.1954, found 301.1943.



***N*-(2-Fluoro-6-phenethylphenyl)pyrimidin-2-amine (133bf)**: The general procedure **A** was followed using substrate **123b** (95 mg, 0.50 mmol) and bromide **58f** (137 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **133bf** (105 mg, 88%) as a white solid.

M. p. = 107–108 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (d, J = 4.8 Hz, 2H), 7.32 (br s, 1H), 7.26–7.14 (m, 4H), 7.10–7.06 (m, 3H), 7.04 (ddd, J = 9.6, 6.3, 1.5 Hz, 1H), 6.62 (t, J = 4.8 Hz, 1H), 3.02–2.95 (m, 2H), 2.93–2.86 (m, 2H).

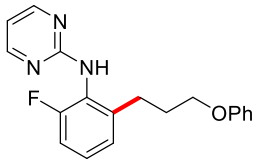
^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.7 (C_q), 158.8 (C_q, $^1J_{C\text{-}F}$ = 248.0 Hz), 158.2 (CH), 141.6 (C_q), 141.3 (C_q), 128.4 (CH), 128.3 (CH), 127.6 (CH, $^3J_{C\text{-}F}$ = 8.6 Hz), 126.0 (CH), 124.9 (CH, $^4J_{C\text{-}F}$ = 3.3 Hz), 124.8 (C_q, $^2J_{C\text{-}F}$ = 12.8 Hz), 113.8 (CH, $^2J_{C\text{-}F}$ = 20.8 Hz), 112.0 (CH), 36.5 (CH_2), 33.6 (CH_2, $^4J_{C\text{-}F}$ = 2.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -119.4 (dd, J = 9.6, 5.5 Hz).

IR (neat): 3220, 3026, 2928, 2861, 1579, 1524, 1442, 1412, 781, 719, 642 cm^{-1}.

MS (EI) *m/z* (relative intensity) 293 (40) [M^+], 202 (100), 188 (25), 170 (15).

HR-MS (EI) *m/z* calcd for $C_{18}H_{16}FN_3$ [M^+] 293.1328, found 293.1321.



***N*-[2-Fluoro-6-(3-phenoxypropyl)phenyl]pyrimidin-2-amine (133bg)**: The general procedure **A** was followed using substrate **123b** (95 mg, 0.50 mmol) and bromide **58g** (158 µL,

1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1→5/1) yielded **133bg** (150 mg, 93%) as a yellow solid.

M. p. = 92–93 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.29 (d, J = 4.8 Hz, 2H), 7.58 (br s, 1H), 7.27–7.16 (m, 3H), 7.12–7.09 (m, 1H), 7.02 (ddd, J = 9.6, 8.1, 1.6 Hz, 1H), 6.93–6.87 (m, 1H), 6.85–6.83 (m, 1H), 6.82–6.80 (m, 1H), 6.60 (t, J = 4.8 Hz, 1H), 3.89 (t, J = 6.2 Hz, 2H), 2.92–2.85 (m, 2H), 2.12–2.02 (m, 2H).

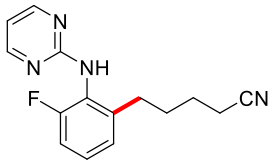
^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.4 (C_q), 158.6 (C_q, $^1J_{C\text{-}F}$ = 248.0 Hz), 158.6 (C_q), 158.0 (CH), 141.2 (C_q), 129.2 (CH), 127.4 (CH, $^3J_{C\text{-}F}$ = 8.6 Hz), 124.8 (C_q, $^2J_{C\text{-}F}$ = 12.8 Hz), 124.8 (CH, $^4J_{C\text{-}F}$ = 3.3 Hz), 120.4 (CH), 114.4 (CH), 113.7 (CH, $^2J_{C\text{-}F}$ = 20.8 Hz), 112.0 (CH), 66.5 (CH_2), 29.6 (CH_2), 27.8 (CH_2, $^4J_{C\text{-}F}$ = 2.3 Hz).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -119.0 (dd, J = 9.6, 5.5 Hz).

IR (neat): 3226, 3163, 2931, 2875, 1587, 1527, 1445, 1241, 1033, 690 cm^{-1}.

MS (EI) *m/z* (relative intensity) 323 (55) [M^+], 216 (100), 188 (75), 170 (15).

HR-MS (EI) *m/z* calcd for $C_{19}H_{18}FN_3O$ [M^+] 323.1434, found 323.1435.



5-[3-Fluoro-2-(pyrimidin-2-ylamino)phenyl]pentanenitrile (133bh): The general procedure **A** was followed using substrate **123b** (95 mg, 0.50 mmol) and bromide **58h** (117 µL, 1.00 mmol) at 160 °C. Isolation by column chromatography (*n*-hexane/EtOAc: 5/1→2/1) yielded **133bh** (96 mg, 71%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, J = 4.8 Hz, 2H), 7.26 (br s, 1H), 7.72–7.17 (m, 1H), 7.07–6.96 (m, 2H), 6.65 (t, J = 4.8 Hz, 1H), 2.68 (t, J = 7.5 Hz, 2H), 2.24 (t, J = 7.0 Hz, 2H), 1.78–1.67 (m, 2H), 1.65–1.55 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.7 (C_q), 158.8 (C_q, $^1J_{C\text{-}F}$ = 248.0 Hz), 158.2 (CH), 141.4 (C_q), 127.8 (CH, $^3J_{C\text{-}F}$ = 8.6 Hz), 124.7 (C_q, $^2J_{C\text{-}F}$ = 13.1 Hz), 124.7 (CH, $^4J_{C\text{-}F}$ = 3.3 Hz), 119.4

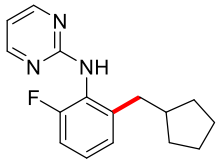
(C_q), 113.9 (CH, $^2J_{C\text{-}F}$ = 20.9 Hz), 112.3 (CH), 30.5 (CH_2, $^4J_{C\text{-}F}$ = 2.4 Hz), 28.9 (CH_2), 24.9 (CH_2), 16.9 (CH_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -119.55 (dd, J = 9.5, 5.5 Hz).

IR (neat): 3223, 2933, 2867, 2250, 1580, 1509, 1443, 1405, 1270, 785, 637 cm^{-1}.

MS (EI) *m/z* (relative intensity) 270 (30) [M^+], 216 (100), 188 (65), 170 (5).

HR-MS (EI) *m/z* calcd for $C_{15}H_{15}FN_4$ [M^+] 270.1281, found 270.1280.



***N*-[2-(Cyclopentylmethyl)-6-fluorophenyl]pyrimidin-2-amine (133bi)**: The general procedure **A** was followed using substrate **123b** (95 mg, 0.50 mmol) and (iodomethyl)cyclopentane **58i** (131 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **133bi** (134 mg, 99%) as a white solid.

M. p. = 89–90 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, J = 4.8 Hz, 2H), 7.19–7.14 (m, 2H), 7.05 (ddd, J = 7.8, 1.5, 0.8 Hz, 1H), 6.98 (ddd, J = 9.7, 7.8, 1.5 Hz, 1H), 6.62 (t, J = 4.8 Hz, 1H), 2.65 (d, J = 7.4 Hz, 2H), 2.13–1.96 (m, 1H), 1.70–1.51 (m, 4H), 1.51–1.37 (m, 2H), 1.19–1.03 (m, 2H).

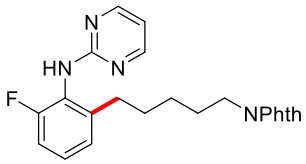
^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.6 (C_q), 160.0 (C_q, $^1J_{C\text{-}F}$ = 248.0 Hz), 158.1 (CH), 142.1 (C_q), 127.3 (CH, $^3J_{C\text{-}F}$ = 8.6 Hz), 125.3 (CH, $^4J_{C\text{-}F}$ = 3.3 Hz), 124.6 (C_q, $^2J_{C\text{-}F}$ = 12.5 Hz), 113.4 (CH, $^2J_{C\text{-}F}$ = 20.8 Hz), 111.9 (CH), 40.8 (CH), 37.3 (CH_2, $^4J_{C\text{-}F}$ = 2.2 Hz), 32.5 (CH_2), 24.7 (CH_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -119.2 (dd, J = 9.6, 5.4 Hz).

IR (neat): 3208, 2944, 2863, 1583, 1527, 1445, 1409, 1270, 786, 648 cm^{-1}.

MS (EI) *m/z* (relative intensity) 271 (40) [M^+], 203 (65), 188 (100), 170 (5).

HR-MS (EI) *m/z* calcd for $C_{16}H_{18}FN_3$ [M^+] 271.1485, found 271.1484.



2-{5-[3-Fluoro-2-(pyrimidin-2-ylamino)phenyl]pentyl}isoindoline-1,3-dione (133bj): The general procedure **A** was followed using substrate **123b** (95 mg, 0.50 mmol) and bromide **58j** (296 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1→2/1) yielded **133bj** (182 mg, 90%) as a white solid.

M. p. = 147–148 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.30 (d, J = 4.8 Hz, 2H), 7.81 (dd, J = 5.4, 3.1 Hz, 2H), 7.68 (dd, J = 5.5, 3.1 Hz, 2H), 7.15 (ddd, J = 7.9, 7.9, 5.4 Hz, 1H), 7.02 (d, J = 7.7, 1H), 6.95 (ddd, J = 9.6, 8.1, 1.5 Hz, 1H), 6.71–6.53 (m, 2H), 3.62 (t, J = 7.2 Hz, 2H), 2.62 (t, J = 7.9 Hz, 2H), 1.77–1.49 (m, 4H), 1.38–1.23 (m, 2H).

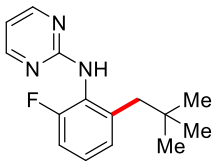
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.4 (C_q), 161.6 (C_q), 158.8 (C_q, $^{1}J_{C\text{-}F}$ = 248 Hz), 158.2 (CH), 142.4 (C_q), 133.8 (CH), 132.1 (C_q), 127.6 (CH, $^{3}J_{C\text{-}F}$ = 8.6 Hz), 124.9 (CH, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 124.4 (C_q, $^{2}J_{C\text{-}F}$ = 12.7 Hz), 123.2 (CH), 113.5 (CH, $^{2}J_{C\text{-}F}$ = 20.8 Hz), 112.2 (CH), 37.7 (CH_2), 31.4 (CH_2, $^{4}J_{C\text{-}F}$ = 2.4 Hz), 29.6 (CH_2), 28.2 (CH_2), 26.4 (CH_2).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -119.5 (dd, J = 9.6, 5.5 Hz).

IR (neat): 3326, 2936, 2862, 1705, 1508, 1440, 1367, 1406, 796, 718, 519 cm^{-1}.

MS (EI) *m/z* (relative intensity) 404 (50) [M^+], 216 (100), 188 (65).

HR-MS (EI) *m/z* calcd for $C_{23}H_{21}FN_4O_2$ [M^+] 404.1649, found 404.1643.



***N*-(2-Fluoro-6-neopentylphenyl)pyrimidin-2-amine (133bk)**: The general procedure **A** was followed using substrate **123b** (95 mg, 0.50 mmol) and bromide **58k** (126 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **133bk** (117 mg, 90%) as a white solid.

M. p. = 58–60 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.29 (d, J = 4.8 Hz, 2H), 7.24 (br s, 1H), 7.16 (ddd, J = 8.0, 8.0, 5.5 Hz, 1H), 7.06–6.94 (m, 2H), 6.60 (t, J = 4.8 Hz, 1H), 2.59 (s, 2H), 0.89 (s, 9H).

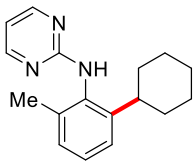
^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.4 (C_q), 158.8 (C_q, $^1J_{C\text{-}F}$ = 248.0 Hz), 158.1 (CH), 139.3 (C_q), 127.4 (CH, $^4J_{C\text{-}F}$ = 3.3 Hz), 126.6 (CH, $^3J_{C\text{-}F}$ = 8.6 Hz), 125.4 (C_q, $^2J_{C\text{-}F}$ = 12.4 Hz), 113.8 (CH, $^2J_{C\text{-}F}$ = 20.9 Hz), 111.9 (CH), 44.5 (CH_2, $^4J_{C\text{-}F}$ = 2.2 Hz), 32.9 (C_q), 29.5 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -117.8 (dd, J = 9.6, 5.6 Hz).

IR (neat): 3452, 3236, 2950, 2864, 1578, 1520, 1440, 1406, 1240, 797, 751 cm^{-1}.

MS (EI) *m/z* (relative intensity) 241 (35) [M^+], 184 (100), 170 (40).

HR-MS (EI) *m/z* calcd for $C_{15}H_{19}N_3$ [M^+] 241.1579, found 241.1576.



***N*-(2-Cyclohexyl-6-methylphenyl)pyrimidin-2-amine (142ab)**: The general procedure **B** was followed using substrate **123a** (185 mg, 1.0 mmol) and bromide **58b** (246 µL, 2.00 mmol) at 120 °C. Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **142ab** (254 mg, 95%) as a white solid.

M. p. = 113–114 °C.

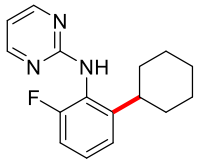
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.28 (d, J = 4.8 Hz, 2H), 7.23–7.17 (m, 2H), 7.12 (dd, J = 7.0, 2.6 Hz, 1H), 6.89 (br s, 1H), 6.56 (t, J = 4.8 Hz, 1H), 2.80 (tt, J = 11.9, 3.0 Hz, 1H), 2.21 (s, 3H), 1.80–1.64 (m, 5H), 1.45–1.15 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.1 (C_q), 158.3 (CH), 145.7 (C_q), 136.8 (C_q), 134.1 (C_q), 128.1 (CH), 127.5 (CH), 124.4 (CH), 111.2 (CH), 39.1 (CH), 33.9 (CH_2), 26.9 (CH_2), 26.2 (CH_2), 18.8 (CH_3).

IR (neat): 3220, 2922, 2852, 1578, 1519, 1446, 1407, 1262, 993, 781, 641 cm^{-1}.

MS (EI) *m/z* (relative intensity) 267 (15) [M^+], 184 (100), 170 (5).

HR-MS (EI) *m/z* calcd for $C_{17}H_{21}N_3$ [M^+] 267.1735, found 267.1741.



***N*-(2-Cyclohexyl-6-fluorophenyl)pyrimidin-2-amine (142bb)**: The general procedure **B** was followed using substrate **123b** (189 mg, 1.0 mmol) and bromide **58b** (246 µL, 2.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **142bb** (270 mg, 99%) 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).

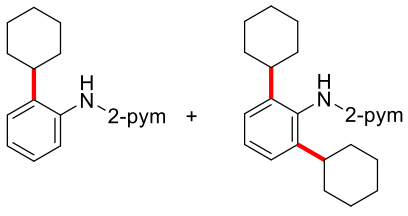
^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.9 (C_q), 158.6 (C_q, $^{1}J_{C\text{-}F}$ = 248.0 Hz), 158.2 (CH), 147.5 (C_q), 127.8 (CH, $^{3}J_{C\text{-}F}$ = 8.6 Hz), 123.6 (C_q, $^{2}J_{C\text{-}F}$ = 12.4 Hz), 122.0 (CH, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 113.2 (CH, $^{2}J_{C\text{-}F}$ = 20.8 Hz), 112.1 (CH),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

^{19}F NMR (283 MHz, $CDCl_3$) δ = -118.8 (dd, J = 9.8, 5.4 Hz).

IR (neat): 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.



142cb **142cb'**

The general procedure **A** was followed using substrate **123c** (86 mg, 0.50 mmol) and bromide **58b** (68 µL, 0.55 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **142cb** (83 mg, 65%) and **142cb'** (22 mg, 13%) as yellow solids.

***N*-(2-Cyclohexylphenyl)pyrimidin-2-amine (142cb)**:

M. p. = 93–94 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.33 (d, J = 4.8 Hz, 2H), 7.70 (dd, J = 7.9, 1.4 Hz, 1H), 7.34 (br s, 1H), 7.30 (dd, J = 7.7, 1.7 Hz, 1H), 7.22 (ddd, J = 7.9, 7.5, 1.7 Hz, 1H), 7.16 (ddd, J = 7.7, 7.5, 1.4 Hz, 1H), 6.62 (t, J = 4.8 Hz, 1H), 2.78 (tt, J = 11.8, 2.9 Hz, 1H), 1.87–1.67 (m, 5H), 1.49–1.18 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.2 (C_q), 157.9 (CH), 140.4 (C_q), 135.5 (C_q), 126.3 (CH), 126.0 (CH), 125.1 (CH), 124.6 (CH), 111.8 (CH), 38.5 (CH), 33.56 (CH_2), 26.9 (CH_2), 26.2 (CH_2).

IR (neat): 3224, 2922, 2848, 1571, 1516, 1442, 1402, 1253, 799, 752, 638 cm^{-1}.

MS (EI) *m/z* (relative intensity) 253 (25) [M^+], 170 (100), 93 (15).

HR-MS (EI) *m/z* calcd for $C_{16}H_{19}N_3$ [M^+] 253.1579, found 253.1584.

***N*-(2,6-Dicyclohexylphenyl)pyrimidin-2-amine (142cb')**:

M. p. = 204–205 °C.

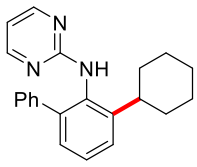
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.27 (d, J = 4.8 Hz, 2H), 7.30 (dd, J = 8.2, 7.2 Hz, 1H), 7.19 (dd, J = 8.2, 0.6 Hz, 2H), 6.88 (s, 1H), 6.55 (t, J = 4.8 Hz, 1H), 2.75 (tt, J = 11.6, 2.9 Hz, 2H), 1.78–1.66 (m, 10H), 1.42–1.15 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.8 (C_q), 158.2 (CH), 146.0 (C_q), 132.8 (C_q), 127.9 (CH), 124.3 (CH), 111.0 (CH), 39.4 (CH), 34.5 (CH_2), 33.3 (CH_2), 26.9 (CH_2), 26.2 (CH_2).

IR (neat): 3222, 2921, 2847, 1601, 1578, 1527, 1445, 1412, 777, 659 cm^{-1}.

MS (EI) *m/z* (relative intensity) 335 (10) [M^+], 252 (100).

HR-MS (EI) *m/z* calcd for $C_{22}H_{29}N_3$ [M^+] 335.2361, found 335.2356.



***N*-(3-Cyclohexylbiphenyl-2-yl)pyrimidin-2-amine (142db)**: The general procedure **A** was followed using substrate **123d** (124 mg, 0.50 mmol), bromide **58b** (123 µL, 1.00 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: 4/1) yielded **142db** (156 mg, 95%) as a white solid.

M. p. = 215–216 °C.

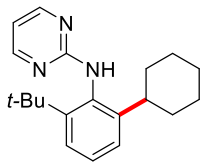
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.19 (d, J = 4.8 Hz, 2H), 7.41–7.31 (m, 2H), 7.27–7.17 (m, 6H), 6.49 (t, J = 4.8 Hz, 1H), 6.39 (s, 1H), 2.74 (tt, J = 11.9, 3.1 Hz, 1H), 1.89–1.63 (m, 6H), 1.44–1.38 (m, 2H), 1.28–1.16 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.1 (C_q), 158.0 (CH), 146.1 (C_q), 140.3 (C_q), 140.2 (C_q), 132.7 (C_q), 128.9 (CH), 128.2 (CH), 127.9 (CH), 127.5 (CH), 126.9 (CH), 126.4 (CH), 111.3 (CH), 39.2 (CH), 33.8 (CH_2), 26.9 (CH_2), 26.2 (CH_2).

IR (neat): 3205, 2923, 2849, 1593, 1520, 1441, 1410, 794, 756, 693, 644 cm^{-1}.

MS (EI) *m/z* (relative intensity) 329 (20) [M^+], 246 (100), 169 (10).

HR-MS (EI) *m/z* calcd for $C_{22}H_{23}N_3$ [M^+] 329.1892, found 329.1890.



***N*-(2-*tert*-Butyl-6-cyclohexylphenyl)pyrimidin-2-amine (142eb)**: The general procedure **A** was followed using substrate **123e** (114 mg, 0.50 mmol), bromide **58b** (123 µL, 1.00 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: 10/1→8/1) yielded **142eb** (82 mg, 53%) as a white solid.

M. p. = 175–176 °C.

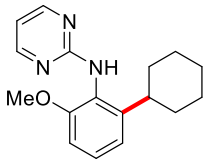
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.26 (d, J = 4.8 Hz, 2H), 7.35 (dd, J = 6.9, 2.7 Hz, 1H), 7.32 (s, 1H), 7.28–7.23 (m, 2H), 6.52 (t, J = 4.8 Hz, 1H), 2.61 (tt, J = 11.8, 3.2 Hz, 1H), 1.81–1.55 (m, 5H), 1.37 (s, 9H), 1.29–0.85 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.8 (C_q), 158.4 (CH), 158.0 (CH), 147.8 (C_q), 147.7 (C_q), 134.0 (C_q), 127.7 (CH), 125.5 (CH), 124.6 (CH), 110.8 (CH), 39.2 (CH), 35.5 (C_q), 35.4 (CH_2), 32.9 (CH_2), 31.1 (CH_3), 27.1 (CH_2), 26.9 (CH_2), 26.2 (CH_2).

IR (neat): 3211, 2918, 2847, 1580, 1522, 1448, 1410, 1264, 995, 802, 643 cm^{-1}.

MS (EI) *m/z* (relative intensity) 309 (1.4) [M^+], 252 (100), 226 (80), 170 (5).

HR-MS (ESI) *m/z* calcd for $C_{20}H_{28}N_3$ [M + H^+] 310.2283, found 310.2278.



***N*-(2-Cyclohexyl-6-methoxyphenyl)pyrimidin-2-amine (142pb)**: The general procedure **A** was followed using substrate **123p** (101 mg, 0.50 mmol), bromide **58b** (123 µL, 1.00 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: 10/1→8/1) yielded **142pb** (120 mg, 85%) as a white solid.

M. p. = 129–130 °C.

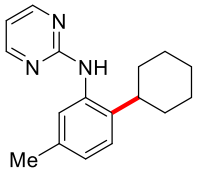
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.29 (d, J = 4.8 Hz, 2H), 7.23 (dd, J = 8.2, 7.9 Hz, 1H), 6.95 (dd, J = 7.9, 1.0 Hz, 1H), 6.78 (dd, J = 8.2, 1.1 Hz, 1H), 6.63 (br s, 1H), 6.58 (t, J = 4.8 Hz, 1H), 3.73 (s, 3H), 2.78 (tt, J = 11.8, 3.2 Hz, 1H), 1.88–1.61 (m, 5H), 1.48–1.16 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.6 (C_q), 158.0 (CH), 155.0 (C_q), 146.9 (C_q), 127.6 (CH), 124.6 (C_q), 118.8 (CH), 111.5 (CH), 108.6 (CH), 55.6 (CH_3), 39.0 (CH), 33.6 (CH_2), 26.8 (CH_2), 26.2 (CH_2).

IR (neat): 3207, 2920, 2849, 1576, 1519, 1446, 1404, 1264, 1065, 779, 640 cm^{-1}.

MS (EI) *m/z* (relative intensity) 283 (20) [M^+], 252 (100), 200 (30), 170 (8).

HR-MS (EI) *m/z* calcd for $C_{17}H_{21}N_3O$ [M^+] 283.1685, found 283.1691.



***N*-(2-Cyclohexyl-5-methylphenyl)pyrimidin-2-amine (142fb)**: The general procedure **A** was followed using substrate **123f** (93 mg, 0.50 mmol) and bromide **58b** (123 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **142fb** (115 mg, 86%) as a white solid.

M. p. = 89–90 °C.

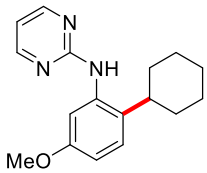
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.33 (d, J = 4.8 Hz, 2H), 7.49 (s, 1H), 7.37 (br s, 1H), 7.20 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 7.9 Hz, 1H), 6.61 (t, J = 4.8 Hz, 1H), 2.74 (tt, J = 11.9, 3.1 Hz, 1H), 2.34 (s, 3H), 1.87–1.67 (m, 5H), 1.48–1.17 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.5 (C_q), 158.0 (CH), 138.0 (C_q), 135.6 (C_q), 135.3 (C_q), 126.3 (CH), 126.3 (CH), 125.5 (CH), 111.6 (CH), 38.2 (CH), 33.6 (CH_2), 26.8 (CH_2), 26.1 (CH_2), 21.0 (CH_3).

IR (neat): 3209, 2923, 2847, 1595, 1526, 1447, 1416, 1278, 998, 800, 644, 564 cm^{-1}.

MS (EI) *m/z* (relative intensity) 267 (25) [M^+], 184 (100), 107 (20).

HR-MS (EI) *m/z* calcd for $C_{17}H_{21}N_3$ [M^+] 267.1735, found 267.1745.



***N*-(2-Cyclohexyl-5-methoxyphenyl)pyrimidin-2-amine (142gb)**: The general procedure **A** was followed using substrate **123g** (101 mg, 0.50 mmol) and bromide **58b** (123 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **142gb** (106 mg, 75%) as a white solid.

M. p. = 106–107 °C.

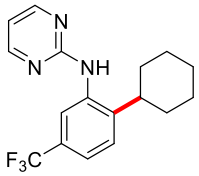
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.35 (d, J = 4.8 Hz, 2H), 7.45 (d, J = 2.7 Hz, 1H), 7.23 (br s, 1H), 7.17 (d, J = 8.6 Hz, 1H), 6.69 (dd, J = 8.6, 2.7 Hz, 1H), 6.64 (t, J = 4.8 Hz, 1H), 3.77 (s, 3H), 2.65 (tt, J = 11.9, 3.1 Hz, 1H), 1.85–1.66 (m, 5H), 1.45–1.17 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.0 (C_q), 158.0 (CH), 157.6 (C_q), 136.5 (C_q), 131.8 (C_q), 126.9 (CH), 112.0 (CH), 110.2 (CH), 109.4 (CH), 55.1 (CH_3), 37.9 (CH), 33.7 (CH_2), 26.9 (CH_2), 26.1 (CH_2).

IR (neat): 3222, 2923, 2849, 1754, 1499, 1419, 1308, 1172, 995, 791, 726 cm^{-1}.

MS (EI) *m/z* (relative intensity) 283 (30) [M^+], 200 (100), 170 (6).

HR-MS (EI) *m/z* calcd for $C_{17}H_{21}N_3O$ [M^+] 283,1685, found 283.1688.



***N*-[2-Cyclohexyl-5-(trifluoromethyl)phenyl]pyrimidin-2-amine (142hb)**: The general procedure **A** procedure was followed using substrate **123h** (120 mg, 0.50 mmol) and bromide **58b** (123 µL, 1.00 mmol) at 100 °C. Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→6/1) yielded **142hb** (153 mg, 95%) as a white solid.

M. p. = 79–81 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.37 (d, J = 4.8 Hz, 2H), 8.18 (s, 1H), 7.53 (br s, 1H), 7.42–7.30 (m, 2H), 6.69 (t, J = 4.8 Hz, 1H), 2.78 (tt, J = 11.6, 2.7 Hz, 1H), 1.91–1.68 (m, 5H), 1.49–1.19 (m, 5H).

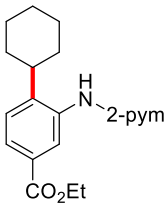
^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.8 (C_q), 158.1 (CH), 143.1 (C_q), 136.3 (C_q), 128.4 (C_q, $^2J_{C\text{-}F}$ = 32.4 Hz), 126.8 (CH), 124.2 (C_q, $^1J_{C\text{-}F}$ = 272.0 Hz), 121.1 (CH, $^3J_{C\text{-}F}$ = 3.7 Hz), 120.6 (CH, $^3J_{C\text{-}F}$ = 3.9 Hz), 112.7 (CH), 38.6 (CH), 33.2 (CH_2), 26.7 (CH_2), 26.0 (CH_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.3 (s).

IR (neat): 3215, 2926, 2851, 1585, 1529, 1450, 1414, 1328, 1121, 798, 645 cm^{-1}.

MS (EI) *m/z* (relative intensity) 321 (30) [M^+], 238 (100), 198 (5).

HR-MS (EI) *m/z* calcd for $C_{17}H_{18}F_3N_3$ [M^+] 321.1453, found 321.1445.



Ethyl 4-cyclohexyl-3-(pyrimidin-2-ylamino)benzoate (142ib): The general procedure **A** was followed using substrate **123i** (122 mg, 0.50 mmol) and bromide **58b** (123 µL, 1.00 mmol) at 100 °C. Isolation by column chromatography (*n*-hexane/EtOAc: 8/1→5/1) yielded **142ib** (99 mg, 61%) as a white solid.

M. p. = 120–121 °C.

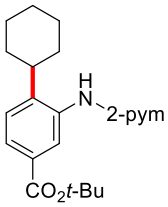
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.36 (d, J = 1.8 Hz, 1H), 8.33 (d, J = 4.8 Hz, 2H), 7.80 (dd, J = 8.2, 1.8 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.33 (br s, 1H), 6.64 (t, J = 4.8 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 2.78 (tt, J = 11.7, 2.9 Hz, 1H), 1.85–1.65 (m, 5H), 1.49–1.13 (m, 8H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.3 (C_q), 161.2 (C_q), 158.1 (CH), 145.7 (C_q), 135.8 (C_q), 128.5 (C_q), 126.5 (CH), 126.2 (CH), 125.9 (CH), 112.2 (CH), 60.7 (CH_2), 38.8 (CH), 33.2 (CH_2), 26.7 (CH_2), 26.0 (CH_2), 14.2 (CH_3).

IR (neat): 3222, 2979, 2851, 1713, 1615, 1524, 1446, 1220, 1107, 761 cm^{-1}.

MS (EI) *m/z* (relative intensity) 325 (25) [M^+], 242 (100), 214 (30).

HR-MS (EI) *m/z* calcd for $C_{19}H_{23}N_3O_2$ [M^+] 325.1790, found 325.1797.



***tert*-Butyl 4-cyclohexyl-3-(pyrimidin-2-ylamino)benzoate (142jb)**: The general procedure **A** was followed using substrate **123j** (136 mg, 0.50 mmol) and bromide **58b** (123 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→6/1) yielded **142jb** (152 mg, 86%) as a white solid.

M. p. = 122–123 °C.

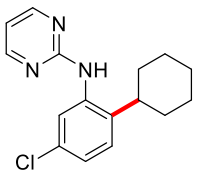
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.35 (d, J = 4.8 Hz, 2H), 8.34 (d, J = 1.8 Hz, 1H), 7.75 (dd, J = 8.2, 1.8 Hz, 1H), 7.31 (dd, J = 8.2 Hz, 1H), 7.03 (br s, 1H), 6.67 (t, J = 4.8 Hz, 1H), 2.75 (tt, J = 11.7, 2.9 Hz, 1H), 1.82–1.71 (m, 5H), 1.55 (s, 9H), 1.47–1.19 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.5 (C_q), 161.2 (C_q), 158.2 (CH), 145.1 (C_q), 135.7 (C_q), 130.1 (C_q), 126.4 (CH), 126.1 (CH), 125.5 (CH), 112.4 (CH), 80.7 (C_q), 38.8 (CH), 33.3 (CH_2), 28.2 (CH_3), 26.8 (CH_2), 26.1 (CH_2).

IR (neat): 2926, 2851, 1709, 1578, 1446, 1404, 1298, 1164, 1112, 798, 766 cm^{-1}.

MS (EI) *m/z* (relative intensity) 309 (2) [M^+], 252 (100), 226 (80), 170 (5).

HR-MS (EI) *m/z* calcd for $C_{21}H_{27}N_3O_2$ [M^+] 353.2103, found 353.2108.



***N*-(5-Chloro-2-cyclohexylphenyl)pyrimidin-2-amine (142qb)**: The general procedure **A** was followed using substrate **123q** (103 mg, 0.50 mmol) and bromide **58b** (123 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **142qb** (144 mg, 86%) as a colorless liquid.

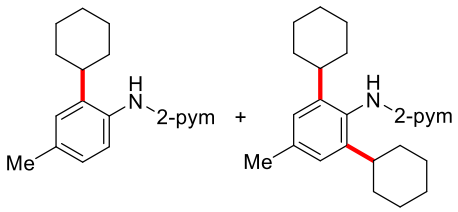
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.36 (d, J = 4.8 Hz, 2H), 7.93 (d, J = 2.2 Hz, 1H), 7.24 (br s, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 8.4, 2.2 Hz, 1H), 6.68 (t, J = 4.8 Hz, 1H), 2.68 (tt, J = 11.9, 3.1 Hz, 1H), 1.88–1.68 (m, 5H), 1.44–1.18 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.6 (C_q), 158.1 (CH), 137.4 (C_q), 136.8 (C_q), 131.4 (C_q), 127.4 (CH), 124.4 (CH), 123.2 (CH), 112.6 (CH), 38.2 (CH), 33.4 (CH_2), 26.8 (CH_2), 26.0 (CH_2).

IR (neat): 3231, 2927, 2851, 1579, 1516, 1446, 1412, 798 cm^{-1}.

MS (EI) *m/z* (relative intensity) 287 (25) [M^+], 204 (100), 161 (15).

HR-MS (EI) *m/z* calcd for $C_{16}H_{18}ClN_3$ [M^+] 287.1189, found 287.1192.



142kb **142kb'**

The general procedure **A** was followed using substrate **123k** (93 mg, 0.50 mmol) and bromide **58b** (68 µL, 0.55 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→6/1) yielded **142kb** (98 mg, 73%) and **142kb'** (19 mg, 11%) as white solids.

***N*-(2-Cyclohexyl-4-methylphenyl)pyrimidin-2-amine (142kb)**:

M. p. = 122–123 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.31 (d, J = 4.8 Hz, 2H), 7.46 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 1.7 Hz, 1H), 7.10 (br s, 1H), 7.02 (dd, J = 8.1, 1.7 Hz, 1H), 6.59 (t, J = 4.8 Hz, 1H), 2.74 (tt, J = 11.8, 3.0 Hz, 1H), 2.33 (s, 3H), 1.85–1.67 (m, 5H), 1.48–1.21 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.7 (C_q), 158.1 (CH), 141.3 (C_q), 135.2 (C_q), 132.9 (C_q), 127.2 (CH), 126.9 (CH), 125.5 (CH), 111.6 (CH), 38.5 (CH), 33.6 (CH_2), 26.9 (CH_2), 26.2 (CH_2), 21.2 (CH_3).

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

MS (EI) *m/z* (relative intensity) 267 (30) [M^+], 184 (100), 107 (20).

HR-MS (EI) *m/z* calcd for $C_{17}H_{21}N_3$ [M^+] 267.1735, found 267.1747.

***N*-(2,6-Dicyclohexyl-4-methylphenyl)pyrimidin-2-amine (142kb')**:

M. p. = 270–271 °C.

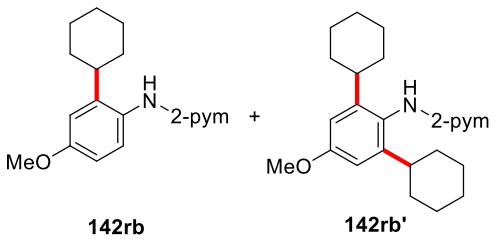
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.26 (d, J = 4.8 Hz, 2H), 6.98 (s, 2H), 6.55 (t, J = 4.8 Hz, 1H), 6.46 (s, 1H), 2.69 (tt, J = 11.6, 2.8 Hz, 2H), 2.33 (s, 3H), 1.74–1.63 (m, 10H), 1.44–1.02 (m, 10H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.9 (C_q), 158.3 (CH), 145.6 (C_q), 137.2 (C_q), 130.1 (C_q), 125.3 (CH), 111.0 (CH), 39.4 (CH), 34.6 (CH_2), 33.3 (CH_2), 27.0 (CH_2), 26.2 (CH_2), 21.7 (CH_3).

IR (neat): 3202, 2921, 2848, 1585, 1517, 1447, 1410, 1240, 787, 640 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 350 [$M+H^+$].

HR-MS (ESI) *m/z* calcd for $C_{23}H_{31}N_3$ [$M+H^+$] 350.2596, found 350.2594.



142rb **142rb'**

The general procedure **A** was followed using substrate **123r** (101 mg, 0.50 mmol) and bromide **58b** (68 µL, 0.55 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→6/1) yielded **142rb** (112 mg, 79%) and **142rb'** (24 mg, 13%) as white solids.

***N*-(2-Cyclohexyl-4-methoxyphenyl)pyrimidin-2-amine (142rb)**:

M. p. = 122–123 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, J = 4.8 Hz, 2H), 7.39 (d, J = 8.7 Hz, 1H), 6.94 (s, 1H), 6.84 (d, J = 3.0 Hz, 1H), 6.75 (dd, J = 8.7, 3.0 Hz, 1H), 6.57 (t, J = 4.8 Hz, 1H), 3.78 (s, 3H), 2.73 (tt, J = 11.8, 3.1 Hz, 1H), 1.83–1.64 (m, 5H), 1.43–1.16 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9 (C_q), 158.0 (CH), 157.6 (C_q), 144.1 (C_q), 128.4 (C_q), 127.5 (CH), 112.6 (CH), 111.4 (CH), 110.9 (CH), 55.3 (CH_3), 38.9 (CH), 33.6 (CH_2), 26.9 (CH_2), 26.2 (CH_2).

IR (neat): 3206, 2929, 2850, 1581, 1519, 1445, 1411, 1206, 1034, 799 cm^{-1}.

MS (EI) *m/z* (relative intensity) 283 (45) [M^+], 200 (100), 185 (5), 79 (8).

HR-MS (EI) *m/z* calcd for $C_{17}H_{21}N_3O$ [M^+] 283.1685, found 283.1684.

***N*-(2,6-Dicyclohexyl-4-methoxyphenyl)pyrimidin-2-amine (142rb')**:

M. p. = 267–268 °C.

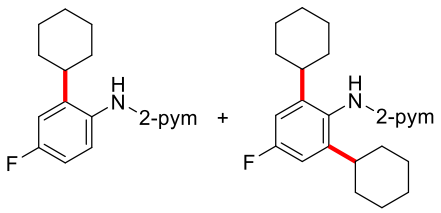
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.26 (d, J = 4.8 Hz, 2H), 6.71 (s, 2H), 6.55 (s, 1H), 6.54 (t, J = 4.8 Hz, 1H), 3.79 (s, 3H), 2.70 (tt, J = 11.5, 2.9 Hz, 2H), 1.78–1.56 (m, 10H), 1.40–1.01 (m, 10H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.9 (C_q), 158.7 (C_q), 158.1 (CH), 147.3 (C_q), 125.6 (C_q), 110.9 (CH), 109.8 (CH), 55.1 (CH_3), 39.7 (CH), 34.6 (CH_2), 33.3 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.2 (CH_2).

IR (neat): 3216, 2920, 2847, 1576, 1519, 1446, 1410, 1257, 803, 640 cm^{-1}.

MS (EI) *m/z* (relative intensity) 365 (15) [M^+], 282 (100).

HR-MS (EI) *m/z* calcd for $C_{23}H_{31}N_3O$ [M^+] 365.2467, found 365.2478.



142lb **142lb'**

The general procedure **A** was followed using substrate **123l** (95 mg, 0.50 mmol) and bromide **58b** (68 µL, 0.55 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→6/1) yielded **142lb** (95 mg, 70%) and **142lb'** (35 mg, 20%) as white solids.

***N*-(2-Cyclohexyl-4-fluorophenyl)pyrimidin-2-amine (142lb)**:

M. p. = 121–122 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, J = 4.8 Hz, 2H), 7.52 (dd, J = 8.8, 5.6 Hz, 1H), 7.22 (br s, 1H), 6.98 (dd, J = 10.2, 3.0 Hz, 1H), 6.89 (ddd, J = 8.7, 7.9, 3.0 Hz, 1H), 6.61 (t, J = 4.8 Hz, 1H), 2.74 (tt, J = 10.5, 1.5 Hz, 1H), 1.84–1.63 (m, 5H), 1.44–1.14 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.6 (C_q), 160.7 (C_q, $^1J_{C\text{-}F}$ = 244.0 Hz), 158.2 (CH), 144.2 (C_q, $^3J_{C\text{-}F}$ = 7.0 Hz), 131.4 (C_q, $^4J_{C\text{-}F}$ = 2.8 Hz), 127.3 (CH, $^3J_{C\text{-}F}$ = 8.3 Hz), 113.3 (CH, $^2J_{C\text{-}F}$ = 22.6 Hz), 112.9 (CH, $^2J_{C\text{-}F}$ = 22.3 Hz), 111.9 (CH), 38.7 (CH, $^4J_{C\text{-}F}$ = 1.1 Hz), 33.4 (CH_2), 26.7 (CH_2), 26.0 (CH_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -116.4 (ddd, J = 9.2, 7.3, 5.3 Hz).

IR (neat): 3232, 2924, 2850, 1575, 1518, 1445, 1403, 1259, 1191, 799, 638, 552, 457 cm^{-1}.

MS (EI) *m/z* (relative intensity) 271 (40) [M^+], 188 (100), 111 (10).

HR-MS (EI) *m/z* calcd for $C_{20}H_{21}N_3$ [M^+] 271.1485, found 271.1476.

***N*-(2,6-Dicyclohexyl-4-fluorophenyl)pyrimidin-2-amine (142lb')**:

M. p. = 222–223 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 (d, J = 4.8 Hz, 2H), 6.87 (d, J = 9.8 Hz, 2H), 6.86 (br s, 1H), 6.56 (t, J = 4.8 Hz, 1H), 2.73 (tt, J = 10.2, 1.5 Hz, 2H), 1.75–1.64 (m, 10H), 1.44–1.00 (m, 10H).

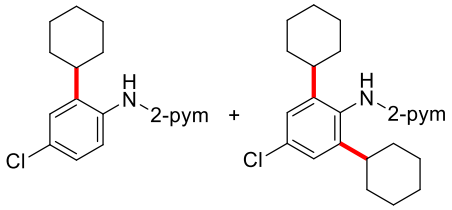
^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.8 (C_q), 162.3 (C_q $^1J_{C\text{-}F}$ = 244.4 Hz), 158.3 (CH), 148.6 (C_q, $^3J_{C\text{-}F}$= 7.6 Hz), 128.6 (C_q, $^4J_{C\text{-}F}$= 2.7 Hz), 111.3 (CH), 111.2 (CH, $^2J_{C\text{-}F}$= 22.5 Hz), 39.6 (CH, $^4J_{C\text{-}F}$ = 1.4 Hz), 34.4 (CH_2), 33.1 (CH_2), 26.8 (CH_2), 26.0 (CH_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -113.8 (t, J = 9.7 Hz).

IR (neat): 3222, 2922, 2848, 1583, 1525, 1445, 1412, 856, 802, 642 cm^{-1}.

MS (EI) *m/z* (relative intensity) 353 (10) [M^+], 270 (100).

HR-MS (EI) *m/z* calcd for $C_{22}H_{28}FN_3$ [M^+] 353.2267, found 353.2277.



142mb **142mb'**

The general procedure **A** was followed using substrate **123m** (103 mg, 0.50 mmol) and bromide **58b** (68 µL, 0.55 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→6/1) yielded **142mb** (88 mg, 61%) and **142mb'** (35 mg, 19 %) as white solids.

***N*-(4-Chloro-2-cyclohexylphenyl)pyrimidin-2-amine (142mb)**:

M. p. = 147–148 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.35 (d, J = 4.6 Hz, 2H), 7.68 (d, J = 8.6 Hz, 1H), 7.23 (d, J = 2.5 Hz, 1H), 7.16 (dd, J = 8.6, 2.5 Hz, 1H), 6.97 (br s, 1H), 6.67 (t, J = 4.6 Hz, 1H), 2.75–2.63 (m, 1H), 1.86–1.65 (m, 5H), 1.47–1.17 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.1 (C_q), 158.1 (CH), 142.0 (C_q), 134.2 (C_q), 130.3 (C_q), 126.7 (CH), 126.2 (CH), 125.7 (CH), 112.4 (CH), 38.6 (CH), 33.4 (CH_2), 26.8 (CH_2), 26.0 (CH_2).

IR (neat): 3205, 2927, 2849, 1579, 1523, 1443, 1264, 994, 800, 644, 456 cm^{-1}.

MS (EI) *m/z* (relative intensity) 287 (45) [M^+], 204 (100), 127 (15).

HR-MS (EI) *m/z* calcd for $C_{16}H_{18}ClN_3$ [M^+] 287.1189, found 287.1195.

***N*-(4-Chloro-2,6-dicyclohexylphenyl)pyrimidin-2-amine (142mb')**:

M. p. = 273–274 °C.

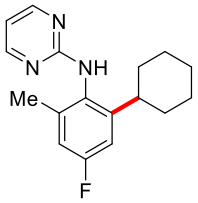
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.27 (d, J = 4.8 Hz, 2H), 7.13 (s, 2H), 6.58 (t, J = 4.8 Hz, 1H), 6.57 (br s, 1H), 2.69 (tt, J = 11.5, 2.8 Hz, 2H), 1.73–1.68 (m, 10H), 1.41–0.97 (m, 10H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.6 (C_q), 158.3 (CH), 148.0 (C_q), 133.7 (C_q), 131.4 (C_q), 124.8 (CH), 111.5 (CH), 39.5 (CH), 33.4 (CH_2), 33.1 (CH_2), 26.8 (CH_2), 26.1 (CH_2).

IR (neat): 3206, 2923, 2848, 1581, 1525, 1439, 1406, 1004, 800, 644 cm^{-1}.

MS (EI) *m/z* (relative intensity) 369 (10) [M^+], 286 (100).

HR-MS (EI) *m/z* calcd for $C_{22}H_{28}ClN_3$ [M^+] 369.1972, found 369.1966.



***N*-(2-Cyclohexyl-4-fluoro-6-methylphenyl)pyrimidin-2-amine (142nb)**: The general procedure **A** was followed using substrate **123n** (102 mg, 0.50 mmol), bromide **58b** (123 µL, 1.00 mmol), [(DME)$NiCl_2$] (2.8 mg, 2.5 mol %) and D*t*-BEDA (5.5 µL, 5.0 mol %). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→6/1) yielded **142nb** (134 mg, 94%) as a white solid.

M. p. = 137–138 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.25 (d, J = 4.8 Hz, 2H), 7.38 (br s, 1H), 6.87 (dd, J = 10.0, 2.9 Hz, 1H), 6.81 (dd, J = 8.8, 2.9 Hz, 1H), 6.55 (t, J = 4.8 Hz, 1H), 2.81 (tt, J = 11.0, 1.1 Hz, 1H), 2.20 (s, 3H), 1.82–1.59 (m, 5H), 1.39–1.12 (m, 5H).

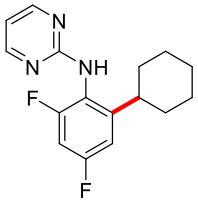
^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.1 (C_q), 161.6 (C_q, $^1J_{C\text{-}F}$ = 245.0 Hz), 158.3 (CH), 148.2 (C_q, $^3J_{C\text{-}F}$ = 7.8 Hz), 139.1 (C_q, $^3J_{C\text{-}F}$ = 8.6 Hz), 130.0 (C_q, $^4J_{C\text{-}F}$ = 2.8 Hz), 114.6 (CH, $^2J_{C\text{-}F}$ = 22.1 Hz), 111.4 (CH), 111.1 (CH, $^2J_{C\text{-}F}$ = 22.1 Hz), 39.2 (CH, $^4J_{C\text{-}F}$ = 1.3 Hz), 33.7 (CH_2), 26.7 (CH_2), 26.0 (CH_2), 18.8 (CH_3, $^4J_{C\text{-}F}$ = 1.6 Hz).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -115.0 (dd, J = 9.7, 9.1 Hz).

IR (neat): 3208, 2926, 2852, 1580, 1519, 1442, 1409, 1262, 952, 786 cm^{-1}.

MS (EI) *m/z* (relative intensity) 285 (20) [M^+], 202 (100), 125 (10).

HR-MS (EI) *m/z* calcd for $C_{17}H_{20}FN_3$ [M^+] 285.1641, found 285.1648.



***N*-(2-Cyclohexyl-4,6-difluorophenyl)pyrimidin-2-amine (142ob)**: The general procedure **A** was followed using substrate **123o** (104 mg, 0.50 mmol), bromide **58b** (123 µL, 1.00 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: 10/1→6/1) yielded **142ob** (133 mg, 92%) as a white solid.

M. p. = 111–112 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.29 (d, J = 4.8 Hz, 2H), 7.09 (br s, 1H), 6.83 (ddd, J = 9.9, 2.8, 1.7 Hz, 1H), 6.72 (ddd, J = 9.6, 8.3, 2.9 Hz, 1H), 6.63 (t, J = 4.8 Hz, 1H), 2.84 (tt, J = 10.1, 1.1 Hz, 1H), 1.84–1.61 (m, 5H), 1.38–1.13 (m, 5H).

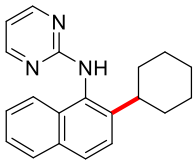
^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.0 (C_q), 161.4 (C_q, dd, $J_{C\text{-}F}$ = 247.0, 13.0 Hz), 158.4 (C_q, dd, $J_{C\text{-}F}$ = 250.0, 13.5 Hz), 158.2 (CH), 149.3 (C_q, $J_{C\text{-}F}$ = 8.4 Hz), 120.0 (C_q, dd, $J_{C\text{-}F}$ = 12.8, 3.9 Hz), 112.1 (CH), 109.0 (CH, dd, $J_{C\text{-}F}$ = 22.2, 3.4 Hz), 101.8 (CH, dd, $J_{C\text{-}F}$ = 26.3, 25.1 Hz), 39.0 (CH, dd, $J_{C\text{-}F}$ = 1.3, 1.3 Hz), 33.5 (CH_2), 26.6 (CH_2), 26.0 (CH_2).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -111.5 (dd, J = 16.6, 8.2 Hz), -114.5 (ddd, J = 9.6, 6.9, 1.6 Hz).

IR (neat): 3222, 2926, 2853, 1577, 1520, 1445, 1260, 1116, 994, 640 cm^{-1}.

MS (EI) *m/z* (relative intensity) 289 (25) [M^+], 206 (40), 166 (4).

HR-MS (EI) *m/z* calcd for $C_{16}H_{17}F_2N_3$ [M^+] 289.1391, found 289.1396.



***N*-(2-Cyclohexylnaphthalen-1-yl)pyrimidin-2-amine (142sb)**: The general procedure **A** was followed using substrate **123s** (111 mg, 0.50 mmol), bromide **58b** (123 µL, 1.00 mmol), [(DME)$NiCl_2$] (2.8 mg, 2.5 mol %) and D*t*-BEDA (5.5 µL, 5.0 mol %). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **142sb** (147 mg, 97%) as a white solid.

M. p. = 80–81 °C.

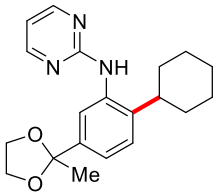
^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.25 (br s, 2H), 7.99–7.94 (m, 1H), 7.86–7.80 (m, 2H), 7.58 (s, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.45–7.39 (m, 2H), 6.56 (t, J = 4.8 Hz, 1H), 3.08 (tt, J = 12.0, 3.2 Hz, 1H), 1.89–1.68 (m, 5H), 1.57–1.50 (m, 2H), 1.37–1.27 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.8 (C_q), 158.2 (CH), 142.8 (C_q), 132.9 (C_q), 131.6 (C_q), 130.2 (C_q), 128.0 (CH), 127.8 (CH), 126.3 (CH), 125.2 (CH), 124.9 (CH), 123.4 (CH), 111.3 (CH), 39.6 (CH), 33.7 (CH_2), 26.9 (CH_2), 26.3 (CH_2).

IR (neat): 3206, 3059, 3005, 2922, 2849, 1584, 1507, 1446, 1375, 1261, 800, 747, 641 cm^{-1}.

MS (EI) *m/z* (relative intensity) 303 (5) [M^+], 220 (40), 180 (2), 143 (2).

HR-MS (EI) *m/z* calcd for $C_{20}H_{21}N_3$ [M^+] 303.1735, found 303.1739.



***N*-[2-Cyclohexyl-5-(2-methyl-1,3-dioxolan-2-yl)phenyl]pyrimidin-2-amine (142tb)**: The general procedure **A** was followed using substrate **123t** (129 mg, 0.50 mmol) and bromide **58b** (123 µL, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded **142tb** (152 mg, 67%) as a white solid.

M. p. = 129–130 °C.

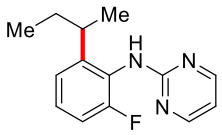
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.33 (d, J = 4.8 Hz, 2H), 7.80 (s, 1H), 7.28–7.19 (m, 2H), 7.06 (br s, 1H), 6.63 (t, J = 4.8 Hz, 1H), 4.03–3.96 (m, 2H), 3.84–3.77 (m, 2H), 2.71 (tt, J = 11.8, 2.9 Hz, 1H), 1.86–1.68 (m, 5H), 1.66 (s, 3H), 1.47–1.18 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.3 (C_q), 158.1 (CH), 141.0 (C_q), 139.9 (C_q), 135.4 (C_q), 126.3 (CH), 122.1 (CH), 121.5 (CH), 112.0 (CH), 108.7 (C_q), 64.4 (CH_2), 38.4 (CH), 33.5 (CH_2), 27.4 (CH_3), 26.9 (CH_2), 26.1 (CH_2).

IR (neat): 3241, 2928, 2851, 1580, 1528, 1448, 1396, 1196, 1032, 799, 628 cm^{-1}.

MS (EI) *m/z* (relative intensity) 339 (30) [M^+], 294 (60), 256 (100), 169 (10).

HR-MS (EI) *m/z* calcd for $C_{20}H_{25}N_3O_2$ [M^+] 339.1947, found 339.1938.



***N*-(2-*sec*-Butyl-6-fluorophenyl)pyrimidin-2-amine (142bl)**: The general procedure **B** was followed using substrate **123b** (189 mg, 1.0 mmol) and bromide **58l** (220 µL, 2.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1→8/1) yielded **142bl** (228 mg, 93%) as a white solid.

M. p. = 98–99 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.31 (d, J = 4.8 Hz, 2H), 7.29–7.18 (m, 1H), 7.07 (d, J = 7.9 Hz, 1H), 6.98 (ddd, J = 9.5, 8.2, 1.4 Hz, 1H), 6.70 (br s, 1H), 6.63 (t, J = 4.8 Hz, 1H), 2.97 (qt, J = 7.0, 7.0 Hz, 1H), 1.67–1.42 (m, 2H), 1.17 (d, J = 6.9 Hz, 3H), 0.77 (t, J = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.8 (C_q), 158.4 (C_q, $^1J_{C\text{-}F}$ = 248.2 Hz), 158.3 (CH), 147.7 (C_q), 128.0 (CH, $^3J_{C\text{-}F}$ = 8.6 Hz), 124.1 (C_q, $^2J_{C\text{-}F}$ = 12.5 Hz), 121.8 (CH, $^4J_{C\text{-}F}$ = 3.3 Hz), 113.2 (CH, $^2J_{C\text{-}F}$ = 20.8 Hz), 112.1 (CH), 35.3 (CH, $^4J_{C\text{-}F}$ = 2.1 Hz), 30.6 (CH_2), 21.1 (CH_3), 12.1 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -119.1 (dd, J = 9.6, 5.6 Hz).

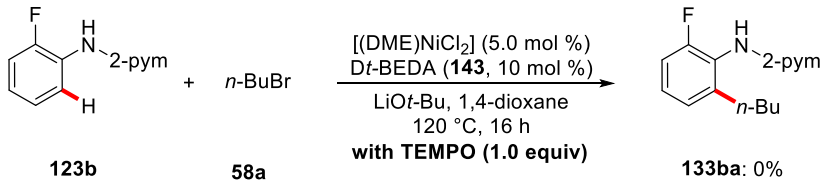
IR (neat): 3209, 2958, 2930, 2871, 1581, 1524, 1447, 1413, 1270, 786, 501 cm^{-1}.

MS (EI) *m/z* (relative intensity) 245 (40) [M^+], 188 (65), 138 (15).

HR-MS (EI) *m/z* calcd for $C_{14}H_{16}FN_3$ [M^+] 245.1328, found 245.1326.

Mechanistic Studies

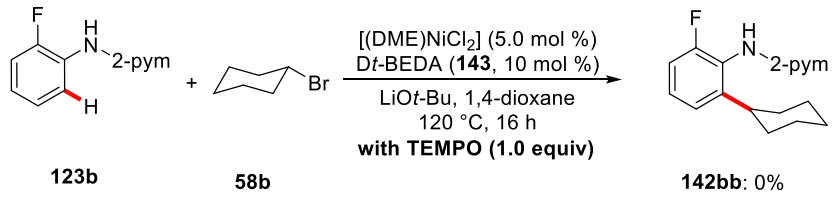
Reactions with TEMPO



123b **58a** **133ba**: 0%

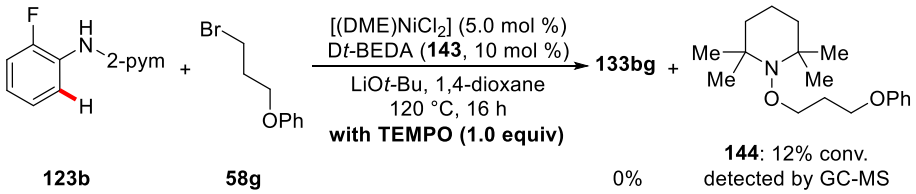
N-(2-Fluorophenyl)pyrimidin-2-amine (**123b**) (95 mg, 0.5 mmol), [(DME)$NiCl_2$] (5.5 mg, 5.0 mol %), TEMPO (78 mg, 0.5 mmol) and LiO*t*Bu (80 mg, 1.0 mmol) were placed in a 25 mL Schlenk tube. The tube was degassed and purged with N_2 three times. D*t*-BEDA (**143**) (11 µL, 10 mol %), 1-bromobutane (**58a**) (107 µL, 1.0 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 120 °C for 16 h. After cooling to ambient temperature,

CH_2Cl_2 (2 mL) was added. No conversion was observed by GC-MS and ^1H NMR analysis of the crude reaction mixture.



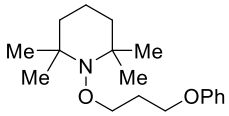
123b **58b** **142bb**: 0%

N-(2-Fluorophenyl)pyrimidin-2-amine (**123b**) (95 mg, 0.5 mmol), [(DME)$NiCl_2$] (5.5 mg, 5.0 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 degassed and purged with N_2 three times. D*t*-BEDA (**143**) (11.0 µL, 10 mol %), bromocyclohexane (**58b**) (123 µL, 1.0 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 120 °C for 16 h. After cooling to ambient temperature, CH_2Cl_2 (2 mL) was added. No conversion was observed by GC-MS and ^1H NMR analysis of the crude reaction mixture.



123b **58g** 0% **144**: 12% conv. detected by GC-MS

N-(2-Fluorophenyl)pyrimidin-2-amine (**123b**) (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 degassed and purged with N_2 three times. D*t*-BEDA (**143**) (22.0 µL, 20 mol %), (3-bromopropoxy)benzene (**58g**) (158 µL, 1.0 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 120 °C for 16 h. After cooling to ambient temperature, CH_2Cl_2 (2 mL) was added. TEMPO adduct **144** was observed as minor side-product by GC-MS analysis, while alkylated product **133bg** could not be observed. The TEMPO adduct **144** was independently prepared in a stoichiometric reaction as described below.



2,2,6,6-Tetramethyl-1-(3-phenoxypropoxy)piperidine (144): *N*-(2-Fluorophenyl)pyrimidin-2-amine (**123b**) (95 mg, 0.5 mmol), [(DME)$NiCl_2$] (110 mg, 0.5 mmol), TEMPO (78 mg, 0.5 mmol) and Li*O*t-Bu (80 mg, 1.0 mmol) were placed in a 25 mL Schlenk tube. The tube was degassed and purged with N_2 three times. D*t*-BEDA (**143**) (215 µL, 1.0 mmol), (3-bromopropoxy)benzene (**58g**) (158 µL, 1.0 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 120 °C for 16 h. After cooling to ambient temperature, CH_2Cl_2 (2 mL) was added, the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure. Isolation by column chromatography (*n*-pentane/Et_2O: 200/1) yielded **144** (19 mg, 13%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.29–7.23 (m, 2H), 6.94–6.87 (m, 3H), 4.07 (t, *J* = 6.6 Hz, 2H), 3.90 (t, *J* = 6.2 Hz, 2H), 2.00 (tt, *J* = 6.4, 6.4 Hz, 2H), 1.59–1.35 (m, 6H), 1.14 (s, 6H), 1.07 (s, 6H).

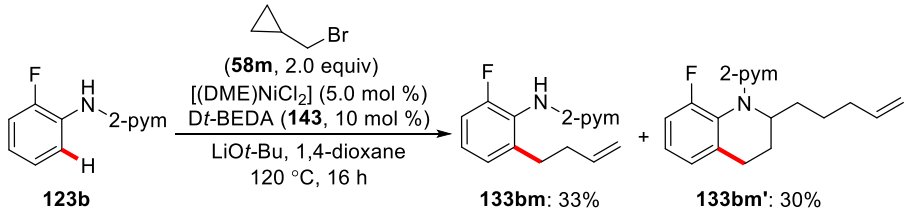
^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.9 (C_q), 129.3 (CH), 120.5 (CH), 114.5 (CH), 72.8 (CH_2), 65.0 (CH_2), 59.7 (C_q), 39.6 (CH_2), 33.0 (CH_3), 28.8 (CH_2), 20.1 (CH_3), 17.1 (CH_2).

IR (neat): 2974, 2930, 2871, 1600, 1497, 1470, 1243, 1062, 751, 690 cm^{-1}.

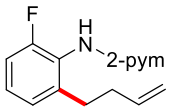
MS (EI) *m/z* (relative intensity) 291 (10) [M^+], 276 (100), 156 (30).

HR-MS (EI) *m/z* calcd for $C_{18}H_{29}NO_2$ [M^+] 291.2198, found 291.2188.

Reaction with (bromomethyl)cyclopropane (58m)



The general procedure **A** was followed using substrate **123b** (95 mg, 0.5 mmol) and (bromomethyl)cyclopropane **58m** (97 µL, 1.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 20/1→5/1) yielded **133bm** (40 mg, 33%) as a colorless liquid and **133bm'** (45 mg, 30%) as a colorless liquid.



***N*-[2-(But-3-enyl)-6-fluorophenyl]pyrimidin-2-amine (133bm)**:

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.30 (d, J = 4.8 Hz, 2H), 7.42 (s, 1H), 7.19 (ddd, J = 8.0, 8.0, 5.5 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H), 7.00 (ddd, J = 9.2, 8.0, 1.4 Hz, 1H), 6.62 (t, J = 4.8 Hz, 1H), 5.78 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 4.99–4.88 (m, 2H), 2.75 (t, J = 7.5 Hz, 2H), 2.35–2.29 (m, 2H).

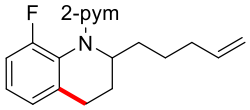
^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.6 (C_q), 158.7 (C_q, $^{1}J_{C\text{-}F}$ = 248.0 Hz), 158.2 (CH), 141.7 (C_q), 137.6 (CH), 127.6 (CH, $^{3}J_{C\text{-}F}$ = 8.3 Hz), 124.9 (CH, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 124.6 (C_q, $^{2}J_{C\text{-}F}$ = 12.6 Hz), 115.3 (CH_2), 113.7 (CH, $^{2}J_{C\text{-}F}$ = 20.8 Hz), 112.2 (CH), 34.2 (CH_2), 31.0 (CH_2, $^{4}J_{C\text{-}F}$ = 2.4 Hz).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -119.5 (ddd, J = 9.5, 5.5, 0.6 Hz).

IR (neat): 3223, 2929, 1579, 1520, 1443, 1406, 1268, 911, 783, 638 cm^{-1}.

MS (EI) *m/z* (relative intensity) 243 (52) [M^+], 202 (100), 188 (45), 148 (15).

HR-MS (EI) *m/z* calcd for $C_{14}H_{14}FN_3$ [M^+] 243.1172, found 243.1177.



8-Fluoro-2-(pent-4-enyl)-1-(pyrimidin-2-yl)-1,2,3,4-tetrahydroquinoline (133bm'):

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.36 (d, J = 4.7 Hz, 2H), 7.05 (ddd, J = 7.9, 5.1, 5.1 Hz, 1H), 6.98–6.91 (m, 2H), 6.62 (t, J = 4.7 Hz, 1H), 5.76 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.00 (tt, J = 6.8, 6.1 Hz, 1H), 4.95 (ddt, J = 17.1, 2.4, 1.6 Hz, 1H), 4.89 (ddt, J = 10.2, 2.3, 1.2 Hz, 1H), 2.75–2.69 (m, 1H), 2.69–2.62 (m, 1H), 2.27 (ddt, J = 20.2, 7.0, 6.2 Hz, 1H), 2.10–2.02 (m, 2H), 1.68–1.61 (m, 2H), 1.51–1.43 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.9 (C_q), 157.6 (CH), 157.2 (C_q, $^{1}J_{C\text{-}F}$ = 251.5 Hz), 138.8 (CH), 135.8 (C_q, $^{3}J_{C\text{-}F}$ = 2.4 Hz), 126.7 (C_q, $^{2}J_{C\text{-}F}$ = 11.5 Hz), 125.0 (CH, $^{3}J_{C\text{-}F}$ = 8.3 Hz), 123.1 (CH, $^{4}J_{C\text{-}F}$ = 3.1 Hz), 114.3 (CH_2), 113.4 (CH, $^{2}J_{C\text{-}F}$ = 20.3 Hz), 111.9 (CH), 53.5 (CH), 33.6 (CH_2), 32.8 (CH_2), 29.5 (CH_2), 25.0 (CH_2), 24.9 (CH_2 $^{4}J_{C\text{-}F}$ = 2.3 Hz).

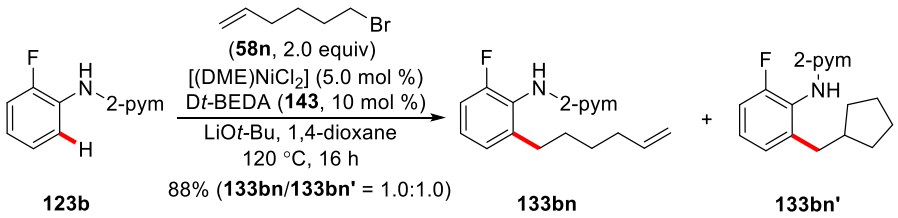
^{19}F NMR (283 MHz, $CDCl_3$) δ = -114.7 (dd, J = 10.6, 5.1 Hz).

IR (neat): 2930, 1578, 1550, 1484, 1417, 1261, 780 cm^{-1}.

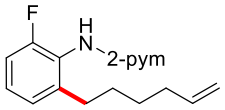
MS (EI) *m/z* (relative intensity) 297 (35) [M^+], 228 (100), 208 (30), 148 (15).

HR-MS (EI) *m/z* calcd for $C_{18}H_{20}FN_3$ [M^+] 297.1641, found 297.1632.

Reaction with 6-bromohex-1-ene (58n)



The general procedure **A** was followed using substrate **123b** (95 mg, 0.5 mmol) and 6-bromohex-1-ene (**58n**) (134 µL, 1.0 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded a mixture of **133bn** and **133bn'** as a colorless liquid (120 mg, 88%). ^{19}F NMR analysis disclosed the ratio of **133bn**/**133bn'** to be 1.0:1.0. Purification by GPC yielded isomer **133bn** (56 mg, 41%) as a colorless liquid and **133bn'** (59 mg, 42%) as a white solid. The spectral data of **133bn'** was identical to those reported above.



***N*-[2-Fluoro-6-(hex-5-enyl)phenyl]pyrimidin-2-amine (133bn)**:

^{1}H NMR (500 MHz, at -25°C, $CDCl_3$) δ = 8.30 (d, J = 4.6 Hz, 2H), 8.24 (s, 1H), 7.20 (ddd, J = 8.1, 7.8, 5.6 Hz, 1H), 7.07 (d, J = 7.8 Hz, 1H), 7.01 (dd, J = 9.6, 8.1 Hz, 1H), 6.64 (t, J = 4.6 Hz, 1H), 5.68 (ddt, J = 16.9, 10.1, 6.7 Hz, 1H), 4.89 (dd, J = 17.1, 1.7 Hz, 1H), 4.84 (dd, J = 10.1, 1.7 Hz, 1H), 2.64 (t, J = 7.8 Hz, 2H), 1.98–1.93 (m, 2H), 1.54 (dt, J = 15.7, 7.8 Hz, 2H), 1.38–1.29 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.7 (C_q), 158.8 (C_q, $^1J_{C\text{-}F}$ = 249.0 Hz), 158.1 (CH), 142.5 (C_q), 138.6 (CH), 127.5 (CH, $^3J_{C\text{-}F}$ = 8.6 Hz), 124.8 (CH, $^4J_{C\text{-}F}$ = 3.2 Hz), 124.5 (C_q, $^2J_{C\text{-}F}$ = 12.6 Hz), 114.4 (CH_2), 113.5 (CH, $^2J_{C\text{-}F}$ = 21.2 Hz), 112.1 (CH), 34.4 (CH_2), 31.4 (CH_2, $^4J_{C\text{-}F}$ = 2.1 Hz), 29.6 (CH_2), 28.5 (CH_2).

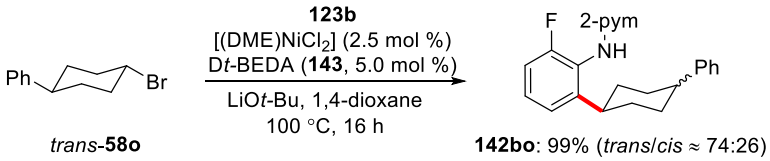
^{19}F NMR (283 MHz, $CDCl_3$) δ = -119.5 (dd, J = 9.5, 5.5 Hz).

IR (neat): 3226, 2932, 2861, 1580, 1444, 1270, 782, 638 cm^{-1}.

MS (EI) *m/z* (relative intensity) 271 (35) [M^+], 188 (100), 148 (15).

HR-MS (EI) *m/z* calcd for $C_{16}H_{18}FN_3$ [M^+] 271.1485, found 271.1481.

Reaction with *trans*-58o



trans-**58o** → **142bo**: 99% (*trans*/*cis* ≈ 74:26)

The general procedure **A** was followed using substrate **123b** (95 mg, 0.50 mmol), *trans*- **58o** (239 mg, 1.00 mmol), [(DME)$NiCl_2$] (2.8 mg, 2.5 mol %) and D*t*-BEDA (**143**) (5.5 µL, 5.0 mol %) at 100 °C. Isolation by column chromatography (*n*-hexane/EtOAc: 4/1) yielded a mixture of *trans*-**142bo** and *cis*-**142bo** (^{1}H NMR ratio 74:26, 173 mg, 99%) as a white solid.

IR (neat): 3215, 2931, 2852, 1579, 1529, 1445, 1413, 1274, 954, 699 cm^{-1}.

MS (EI) *m/z* (relative intensity) 347 (85) [M^+], 188 (100), 91 (25).

HR-MS (EI) *m/z* calcd for $C_{22}H_{22}FN_3$ [M^+] 347.1798, found 347.1794.

For major diastereomer *trans*-**58o**:

M. p. = 146–147 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.34 (d, J = 4.8 Hz, 2H), 7.27–7.26 (m, 3H), 7.22–7.15 (m, 5H), 7.04–6.99 (m, 1H), 6.65 (t, J = 4.8 Hz, 1H), 2.97 (tt, J = 11.9, 2.8 Hz, 1H), 2.59 (tt, J = 12.0, 2.8 Hz, 1H), 1.98 (d, J = 11.3 Hz, 4H), 1.64 (dt, J = 12.5, 7.1 Hz, 2H), 1.54 (dt, J = 12.5, 7.2 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.0 (C_q), 158.7 (C_q, $^1J_{C\text{-}F}$ = 249.8 Hz), 158.2 (CH), 147.2 (C_q), 147.1 (C_q), 128.3 (CH), 128.0 (CH, $^3J_{C\text{-}F}$ = 8.6 Hz), 126.7 (CH), 125.9 (CH), 124.0 (C_q, $^2J_{C\text{-}F}$ = 12.5 Hz), 121.9 (CH, $^4J_{C\text{-}F}$ = 3.2 Hz), 113.4 (CH, $^2J_{C\text{-}F}$ = 20.9 Hz), 112.1 (CH), 44.0 (CH), 38.3(CH, $^4J_{C\text{-}F}$ = 1.9 Hz), 34.3 (CH_2), 33.7(CH_2).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -118.7 (dd, J = 9.6, 5.5 Hz).

For minor diastereomer *cis*-**58o**:

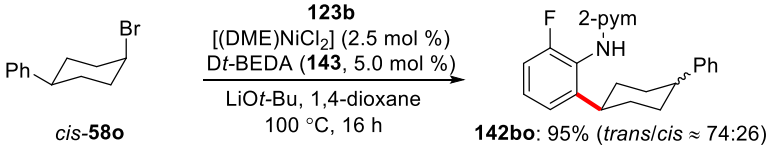
M. p. = 116–118 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.34 (d, J = 4.8 Hz, 2H), 7.36–7.29 (m, 4H), 7.20–7.15 (m, 2H), 7.05 (d, J = 7.9 Hz, 1H), 6.96 (ddd, J = 9.5, 8.2, 1.3 Hz, 1H), 6.67 (t, J = 4.8 Hz, 1H), 6.48 (s, 1H), 3.06–3.02(m, 1H), 3.02–2.99 (m, 1H), 2.23–2.16 (m, 2H), 1.84 (m, 2H), 1.74–1.68 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.0 (C_q), 159.0 (C_q, $^1J_{C\text{-}F}$ = 247.6 Hz), 157.7 (CH), 147.0 (C_q), 145.0 (C_q), 128.2 (CH), 127.8 (CH, $^3J_{C\text{-}F}$ = 8.7 Hz), 127.5 (CH), 125.5 (CH), 123.5 (C_q, $^2J_{C\text{-}F}$ = 12.5 Hz), 122.4 (CH, $^4J_{C\text{-}F}$ = 3.2 Hz), 113.41 (CH, $^2J_{C\text{-}F}$ = 21.0 Hz), 112.2 (CH), 37.6 (CH, $^4J_{C\text{-}F}$ = 1.9 Hz), 37.3 (CH), 30.2 (CH_2), 29.0 (CH_2).

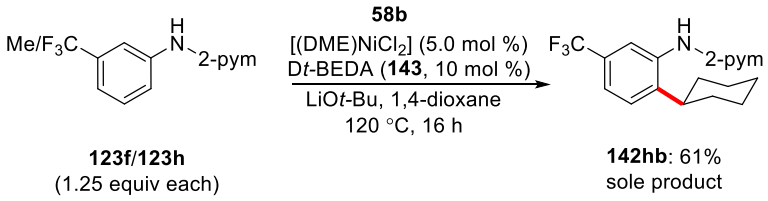
^{19}F NMR (283 MHz, $CDCl_3$) δ = -118.8 (dd, J = 9.6, 5.6 Hz).

Reaction with *cis*-58o



The general procedure **A** was followed using substrate **123b** (95 mg, 0.50 mmol), *cis*-**58o** (239 mg, 1.00 mmol), [(DME)$NiCl_2$] (2.8 mg, 2.5 mol %) and D*t*-BEDA (**143**) (5.5 µL, 5.0 mol %) at 100 °C. Isolation by column chromatography (*n*-hexane/EtOAc: 4/1) yielded a mixture of *trans*-**142bo** and *cis*-**142bo** (^{1}H NMR ratio 74:26, 165 mg, 99%) as a white solid.

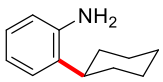
Intermolecular Competition Experiment between 123f and 123h



N-*m*-Tolylpyrimidin-2-amine (**123f**) (93 mg, 0.5 mmol), *N*-[3-(trifluoromethyl)phenyl]pyrimidin-2-amine (**123h**) (120 mg, 0.5 mmol), [(DME)$NiCl_2$] (5.5 mg, 5.0 mol %) and LiO*t*-Bu (80 mg, 1.0 mmol) were placed in a 25 mL Schlenk tube. The

tube was degassed and purged with N_2 for three times. D*t*-BEDA (**143**) (11 µL, 10 mol %), alkyl bromides **58b** (49 µL, 0.4 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 120 °C for 16 h. At ambient temperature, CH_2Cl_2 (2 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1→5/1) to afford **142hb** (58 mg, 61%) as the sole product.

Removal of the Directing Group



2-Cyclohexylaniline (147a): *ortho*-Alkylated compound **142cb** (55mg, 0.22 mmol) was dissolved in aqueous HCl (37%, 1.5 mL) in a microwave vial. The vial was heated up to 150 °C (40 W) for 3 h in the microwave oven. The reaction mixture was allowed to cool to ambient temperature and poured into EtOAc (10 mL), and then saturated aqueous $NaHCO_3$ solution was added until the pH was adjusted to 7. The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* affording **147a** (31 mg, 81%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.10 (dd, J = 7.7, 1.4 Hz, 1H), 7.00 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 6.67 (dd, J = 7.9, 1.2 Hz, 1H), 3.62 (s, 2H), 2.49 – 2.43 (m, 1H), 1.93–1.80 (m, 4H), 1.79–1.70 (m, 1H), 1.47–1.35 (m, 4H), 1.33–1.19 (m, 1H).

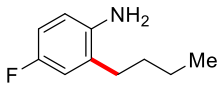
^{13}C NMR (125 MHz, $CDCl_3$) δ = 143.3 (C_q), 131.9 (C_q), 126.4 (CH), 126.0 (CH), 119.0 (CH), 115.8 (CH), 38.4 (CH), 32.8 (CH_2), 27.1 (CH_2), 26.3 (CH_2).

IR (neat): 3462, 3374, 2922, 2850, 1618, 1494, 1448, 1292, 1254, 744 cm^{-1}.

MS (EI) *m/z* (relative intensity) 175 (82) [M^+], 106 (100), 91 (20).

HR-MS (EI) *m/z* calcd for $C_{12}H_{17}N$ [M^+] 175.1361, found 175.1362.

Analytical data for compound **147a** was consistent with the literature.[164]



2-Butyl-4-fluoroaniline (147b): *ortho*-Alkylated compound **133la** (79 mg, 0.32 mmol) was dissolved in aqueous HCl (37%, 1.5 mL) in a microwave vial. The vial was heated up to 150 °C (40 W) for 3 h in the microwave oven. The reaction mixture was allowed to cool to ambient temperature and poured into to EtOAc (10 mL), and then saturated aqueous $NaHCO_3$ solution was added until the pH was adjusted to 7. The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* affording **147b** (44 mg, 82%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.76 (dd, J = 9.6, 3.0 Hz, 1H), 6.71 (ddd, J = 8.6, 8.4, 3.0 Hz, 1H), 6.58 (dd, J = 8.6, 5.0 Hz, 1H), 3.45 (br s, 2H), 2.44–2.41 (m, 2H), 1.62 –1.53 (m, 2H), 1.46–1.35 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H).

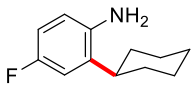
^{13}C NMR (125 MHz, $CDCl_3$) δ = 156.4 (C_q, $^1J_{C\text{-}F}$ = 235.7 Hz), 140.0 (C_q, $^4J_{C\text{-}F}$ = 2.2 Hz), 128.6 (C_q, $^3J_{C\text{-}F}$ = 6.4 Hz), 116.2 (CH, $^3J_{C\text{-}F}$ = 7.2 Hz), 115.6 (CH, $^2J_{C\text{-}F}$ = 22.6 Hz), 112.8 (CH, $^2J_{C\text{-}F}$ = 22.5 Hz), 30.9 (CH_2, $^4J_{C\text{-}F}$ = 1.2 Hz), 30.6 (CH_2), 22.6 (CH_2), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -126.6 (ddd, J = 9.6, 8.3, 5.0 Hz).

IR (neat): 3460, 3375, 2957, 2862, 1624, 1498, 1232, 1147, 864, 809 cm^{-1}.

MS (EI) *m/z* (relative intensity) 167 (28) [M^+], 124 (100), 77 (6).

HR-MS (EI) *m/z* calcd for $C_{10}H_{14}FN$ [M^+] 167.1110, found 167.1116.



2-Cyclohexyl-4-fluoroaniline (147c): *ortho*-Alkylated compound **142lb** (41 mg, 0.15 mmol) was dissolved in aqueous HCl (37%, 1 mL) in a microwave vial. The vial was heated up to 150 °C (40 W) for 3 h in the microwave oven. The reaction mixture was allowed to cool to ambient temperature and poured into to EtOAc (10 mL), and then saturated aqueous $NaHCO_3$ solution was added until the pH was adjusted to 7. The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* affording **147c** (24 mg, 83%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.81 (dd, J = 10.4, 2.9 Hz, 1H), 6.70 (ddd, J = 8.6, 8.2, 2.9 Hz, 1H), 6.59 (dd, J = 8.6, 5.1 Hz, 1H), 3.48 (s, 2H), 2.44 (t, J = 10.7 Hz, 1H), 1.90– 1.82 (m, 4H), 1.80–1.72 (m, 1H), 1.48–1.21 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.9 (C_q, $^1J_{C\text{-}F}$ = 235.8 Hz), 139.2 (C_q, $^4J_{C\text{-}F}$ = 2.1 Hz), 133.8 (C_q, $^3J_{C\text{-}F}$ = 6.2 Hz), 116.6 (CH, $^3J_{C\text{-}F}$ = 7.9 Hz), 112.7 (CH, $^2J_{C\text{-}F}$ = 22.6 Hz), 112.6 (CH, $^2J_{C\text{-}F}$ = 22.5 Hz), 38.6 (CH, $^4J_{C\text{-}F}$ = 1.5 Hz), 32.7 (CH_2), 27.0 (CH_2), 26.2 (CH_2).

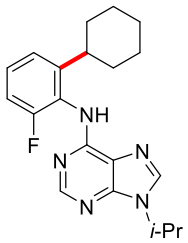
^{19}F NMR (376 MHz, $CDCl_3$) δ = -125.6 (dddd, J = 9.8, 8.4, 5.1, 1.0 Hz).

IR (neat): 3464, 3373, 2924, 2852, 1624, 1494, 1272, 1150, 949, 862, 807 cm^{-1}.

MS (EI) *m/z* (relative intensity) 193 (95) [M^+], 124 (100), 77 (6).

HR-MS (EI) *m/z* calcd for $C_{12}H_{16}FN$ [M^+] 1193.1267, found 193.1263.

5.3.2 Characterization Data: Nickel-Catalyzed C–H Alkylation of Purine Bases



***N*-(2-Cyclohexyl-6-fluorophenyl)-9-*iso*-propyl-9*H*-purin-6-amine (135ab)**: The general procedure **C** was followed using substrate **134a** (81 mg, 0.30 mmol) and bromide **58b** (74 µL, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135ab** (104 mg, 98%) as a white solid.

M. p. = 90 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.37 (s, 1H), 7.78 (s, 1H), 7.63 (s, 1H), 7.26 (ddd, J = 8.2, 7.9, 5.5 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 6.99 (ddd, J = 9.5, 8.2, 1.4 Hz, 1H), 4.83 (hept, J = 6.8 Hz, 1H), 2.82 (tt, J = 12.0, 3.2 Hz, 1H), 1.81–1.74 (m, 2H), 1.73–1.70 (m, 2H), 1.67–1.61 (m, 1H), 1.58 (d, J = 6.8 Hz, 6H), 1.41–1.34 (m, 2H), 1.24–1.16 (m, 3H).

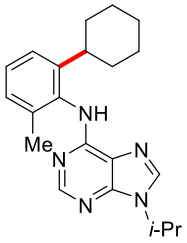
^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.6 (C_q, $^1J_{C\text{-}F}$ = 247.6 Hz), 154.1 (C_q), 152.8 (CH), 149.4 (C_q), 147.9 (C_q), 137.9 (CH), 128.3 (CH, $^3J_{C\text{-}F}$ = 8.5 Hz), 122.8 (C_q, $^2J_{C\text{-}F}$ = 12.7 Hz), 122.0 (CH, $^4J_{C\text{-}F}$ = 3.3 Hz), 120.2 (C_q), 113.2 (CH, $^2J_{C\text{-}F}$ = 20.8 Hz), 47.1 (CH), 39.0 (CH, $^4J_{C\text{-}F}$ = 2.2 Hz), 33.8 (CH_2), 26.8 (CH_2), 26.1 (CH_2), 22.7 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -118.7 (dd, J = 9.6, 5.5 Hz).

IR (neat): 3181, 2925, 2850, 1607, 1468, 1223, 648 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 354 (100) $[M+H^+]$.

HR-MS (ESI) *m/z* calcd for $C_{20}H_{25}FN_5$ $[M+H^+]$ 354.2089, found 354.2089.



***N*-(2-Cyclohexyl-6-methylphenyl)-9-*iso*-propyl-9*H*-purin-6-amine (135bb)**: The general procedure **D** was followed using substrate **134b** (80 mg, 0.30 mmol) and bromide **58b** (74 µL, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135bb** (81 mg, 77%) as a white solid.

M. p. = 156–157 °C.

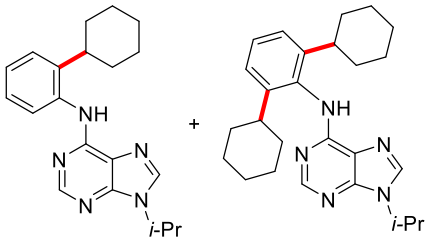
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.38 (s, 1H), 8.36 (s, 1H), 7.51 (s, 1H), 7.36–7.20 (m, 2H), 7.16 (dd, J = 6.5, 2.2 Hz, 1H), 4.82 (hept, J = 6.8 Hz, 1H), 2.83 (tt, J = 12.1, 3.2 Hz, 1H), 2.20 (s, 3H), 1.89–1.60 (m, 5H), 1.57 (d, J = 6.8 Hz, 6H), 1.48–1.31 (m, 2H), 1.21–1.17 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.4 (C_q), 153.3 (CH), 149.1 (C_q), 146.2 (C_q), 137.5 (CH), 136.9 (C_q), 133.4 (C_q), 128.1 (CH), 127.9 (CH), 124.5 (CH), 119.8 (C_q), 47.0 (CH), 39.2 (CH), 34.0 (CH_2), 26.9 (CH_2), 26.2 (CH_2), 22.7 (CH_3), 18.9 (CH_3).

IR (neat): 3228, 2925, 2850, 1606, 1468, 1217, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 350 (100) $[M+H^+]$.

HR-MS (ESI) *m/z* calcd for $C_{21}H_{28}N_5$ $[M+H^+]$ 350.2339, found 350.2339.



135cb **135cb'**

The general procedure **C** was followed using substrate **134c** (76 mg, 0.30 mmol) and bromide **58b** (41 µL, 0.33 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135cb** (80 mg, 80%) as a colorless oil and **135cb'** (7 mg, 5%) as a white solid.

***N*-(2-Cyclohexylphenyl)-9-*iso*-propyl-9*H*-purin-6-amine (135cb)**:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.41 (s, 1H), 7.81 (s, 1H), 7.77–7.69 (m, 2H), 7.32 (dd, *J* = 7.3, 2.1 Hz, 1H), 7.27–7.17 (m, 2H), 4.84 (hept, *J* = 6.8 Hz, 1H), 2.80 (tt, *J* = 11.7, 3.2 Hz, 1H), 1.88–1.74 (m, 4H), 1.73–1.63 (m, 1H), 1.60 (d, *J* = 6.8 Hz, 6H), 1.50–1.15 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 153.5 (C_q), 152.8 (CH), 149.2 (C_q), 141.5 (C_q), 137.9 (CH), 134.7 (C_q), 126.6 (CH), 126.2 (CH), 126.1 (CH), 125.7 (CH), 120.5 (C_q), 47.0 (CH), 38.7 (CH), 33.6 (CH_2), 26.8 (CH_2), 26.1 (CH_2), 22.7 (CH_3).

IR (neat): 3235, 2925, 2851, 1606, 1467, 1220, 648 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 336 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{20}H_{26}N_5$ [M+H$^+$] 336.2183, found 336.2183.

***N*-(2,6-Dicyclohexylphenyl)-9-*iso*-propyl-9*H*-purin-6-amine (135cb')**:

M. p. = 220 °C.

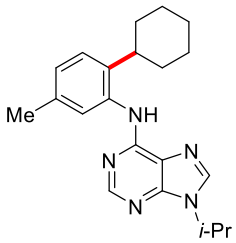
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (s, 1H), 7.73 (s, 1H), 7.41 (br s, 1H), 7.32 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 2H), 4.85 (hept, *J* = 6.8 Hz, 1H), 2.71 (tt, *J* = 11.9, 3.2 Hz, 2H), 1.85–1.58 (m, 16H), 1.40–1.31 (m, 4H), 1.24–1.16 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.9 (C_q), 153.2 (CH), 149.1 (C_q), 146.1 (C_q), 137.6 (CH), 131.9 (C_q), 128.3 (CH), 124.4 (CH), 119.7 (C_q), 47.0 (CH), 39.5 (CH), 34.6 (CH_2), 33.4 (CH_2), 26.9 (CH_2), 26.1 (CH_2), 22.8 (CH_3).

IR (neat): 3180, 2921, 2849, 1612, 1470, 1226, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 418 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{26}H_{36}N_5$ [M+H$^+$] 418.2965, found 418.2962.



***N*-(2-Cyclohexyl-5-methylphenyl)-9-*iso*-propyl-9*H*-purin-6-amine (135db)**: The general procedure **C** was followed using substrate **134d** (80 mg, 0.30 mmol) and bromide **58b** (74 µL, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135db** (86 mg, 82%) as a white solid.

M. p. = 126 °C.

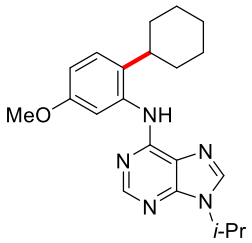
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.42 (s, 1H), 7.78 (s, 1H), 7.68 (br s, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.02 (dd, J = 8.0, 1.8 Hz, 1H), 4.83 (hept, J = 6.8 Hz, 1H), 2.74 (tt, J = 11.8, 3.2 Hz, 1H), 2.32 (s, 3H), 1.86–1.64 (m, 5H), 1.59 (d, J = 6.8 Hz, 6H), 1.47–1.15 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.6 (C_q), 152.9 (CH), 149.2 (C_q), 138.8 (C_q), 137.8 (CH), 135.8 (C_q), 134.5 (C_q), 127.1 (CH), 126.5 (CH), 126.4 (CH), 120.5 (C_q), 47.0 (CH), 38.4 (CH), 33.7 (CH_2), 26.9 (CH_2), 26.1 (CH_2), 22.7 (CH_3), 21.0 (CH_3).

IR (neat): 3211, 2924, 2851, 1604, 1468, 1223, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 350 (100) [$M+H^+$].

HR-MS (ESI) *m/z* calcd for $C_{21}H_{28}N_5$ [$M+H^+$] 350.2339, found 350.2339.



***N*-(2-Cyclohexyl-5-methoxyphenyl)-9-*iso*-propyl-9*H*-purin-6-amine (135eb)**: The general procedure **C** was followed using substrate **134e** (85 mg, 0.30 mmol) and bromide **58b** (74 µL, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135eb** (89 mg, 81%) as a white solid.

M. p. = 130 °C.

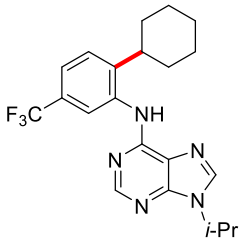
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.44 (s, 1H), 7.83 (s, 1H), 7.61 (br s, 1H), 7.50 (d, J = 2.7 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 6.75 (dd, J = 8.6, 2.7 Hz, 1H), 4.84 (hept, J = 6.8 Hz, 1H), 3.78 (s, 3H), 2.70 (tt, J = 11.1, 3.0 Hz, 1H), 1.95–1.64 (m, 5H), 1.60 (d, J = 6.8 Hz, 6H), 1.51–1.12 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.7 (C_q), 153.2 (C_q), 152.7 (CH), 149.3 (C_q), 138.0 (CH), 135.6 (C_q), 132.8 (C_q), 127.1 (CH), 120.7 (C_q), 111.4 (CH), 110.3 (CH), 55.2 (CH_3), 47.1 (CH), 38.2 (CH), 33.8 (CH_2), 26.9 (CH_2), 26.2 (CH_2), 22.7 (CH_3).

IR (neat): 3241, 2925, 2850, 1602, 1467, 1224, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 366 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{21}H_{27}N_5O$ [M+H$^+$] 366.2288, found 366.2288.



***N*-[2-Cyclohexyl-5-(trifluoromethyl)phenyl]-9-*iso*-propyl-9*H*-purin-6-amine (135fb)**: The general procedure **C** was followed using substrate **134f** (96 mg, 0.30 mmol) and bromide **58b** (74 µL, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135fb** (120 mg, 99%) as a white solid.

M. p. = 68 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.43 (s, 1H), 8.14 (s, 1H), 8.09 (br s, 1H), 7.76 (s, 1H), 7.42–7.41 (m, 2H), 4.83 (hept, J = 6.8 Hz, 1H), 2.93–2.68 (m, 1H), 1.92–1.67 (m, 5H), 1.57 (d, J = 6.8 Hz, 6H), 1.50–1.15 (m, 5H).

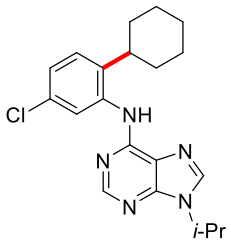
^{13}C NMR (125 MHz, $CDCl_3$) δ = 152.9 (C_q), 152.5 (CH), 149.4 (C_q), 144.3 (C_q), 138.2 (CH), 135.5 (C_q), 128.4 (q, $^{2}J_{C\text{-}F}$ = 32.6 Hz, C_q), 127.0 (CH), 124.0 (q, $^{1}J_{C\text{-}F}$ = 271.7 Hz, C_q), 122.0 (q, $^{3}J_{C\text{-}F}$ = 4.1 Hz, CH), 121.9 (q, $^{3}J_{C\text{-}F}$ = 4.1 Hz, CH), 120.7 (C_q), 47.2 (CH), 38.9 (CH), 33.4 (CH_2), 26.8 (CH_2), 26.1 (CH_2), 22.7 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -62.3 (s).

IR (neat): 2928, 2853, 1607, 1328, 1118, 1010, 648 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 404 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{21}H_{25}F_3N_5$ [M+H$^+$] 404.2057, found 404.2066.



***N*-(5-Chloro-2-cyclohexylphenyl)-9-*iso*-propyl-9*H*-purin-6-amine (135gb)**: The general procedure **D** was followed using substrate **134g** (86 mg, 0.30 mmol) and bromide **58b** (74 µL, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135gb** (90 mg, 81%) as a colorless oil.

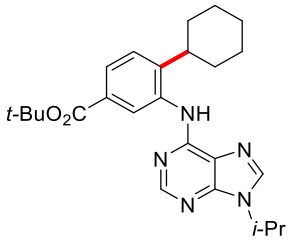
^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.46 (s, 1H), 7.95 (d, J = 2.2 Hz, 1H), 7.82 (s, 1H), 7.75 (br s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.13 (dd, J = 8.4, 2.2 Hz, 1H), 4.84 (hept, J = 6.8 Hz, 1H), 2.74 (tt, J = 11.7, 3.2 Hz, 1H), 1.83–1.77 (m, 4H), 1.73–1.67 (m, 1H), 1.57 (d, J = 6.8 Hz, 6H), 1.43–1.28 (m, 4H), 1.26–1.18 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 152.8 (C_q), 152.5 (CH), 149.4 (C_q), 138.7 (C_q), 138.2 (CH), 136.0 (C_q), 131.4 (C_q), 127.5 (CH), 125.4 (CH), 124.5 (CH), 120.6 (C_q), 47.2 (CH), 38.8 (CH), 33.5 (CH_2), 26.8 (CH_2), 26.1 (CH_2), 22.7 (CH_3).

IR (neat): 2925, 2851, 1612, 1464, 1220, 1009, 646 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 370 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{20}H_{25}ClN_5$ [M+H$^+$] 370.1793, found 370.1806.



***tert*-Butyl 4-cyclohexyl-3-[(9-*iso*-propyl-9*H*-purin-6-yl)amino]benzoate (135hb)**: The general procedure **C** was followed using substrate **134h** (106 mg, 0.30 mmol) and bromide **58b** (74 µL, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135hb** (84 mg, 64%) as a white solid.

M. p. = 88 °C.

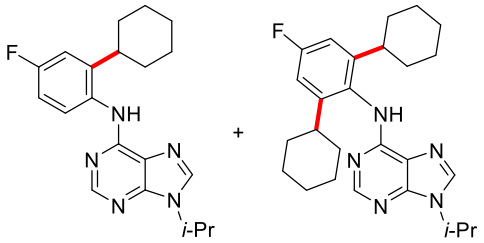
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.41 (s, 1H), 8.29 (d, J = 1.8 Hz, 1H), 8.05 (br s, 1H), 7.82 (dd, J = 8.2, 1.8 Hz, 1H), 7.74 (s, 1H), 7.36 (d, J = 8.2 Hz, 1H), 4.81 (hept, J = 6.8 Hz, 1H), 2.91–2.73 (m, 1H), 1.86–1.62 (m, 5H), 1.56 (d, J = 6.8 Hz, 6H), 1.53 (s, 9H), 1.36–1.13 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.2 (C_q), 153.4 (C_q), 152.6 (CH), 149.3 (C_q), 146.7 (C_q), 138.0 (CH), 134.8 (C_q), 130.2 (C_q), 127.0 (CH), 127.0 (CH), 126.5 (C_q), 120.4 (CH), 80.7 (C_q), 47.1 (CH), 39.0 (CH), 33.4 (CH_2), 28.2 (CH_3), 26.7 (CH_2), 26.1 (CH_2), 22.7 (CH_3).

IR (neat): 2977, 2927, 2852, 1710, 1604, 1298, 648 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 436 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{25}H_{33}N_5O_2Na$ [M+Na$^+$] 458.2526, found 458.2533.



135ib **135ib'**

The general procedure **C** was followed using substrate **134i** (81 mg, 0.30 mmol) and bromide **58b** (41 µL, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135ib** (76 mg, 72%) and **135ib'** (23 mg, 17%) as white solids.

***N*-(2-Cyclohexyl-4-fluorophenyl)-9-*iso*-propyl-9*H*-purin-6-amine (135ib)**:

M. p. = 137 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.38 (s, 1H), 7.83 (br s, 1H), 7.74 (s, 1H), 7.54 (dd, J = 8.8, 5.6 Hz, 1H), 7.01 (dd, J = 10.2, 3.0 Hz, 1H), 6.91 (ddd, J = 8.8, 7.8, 3.0 Hz, 1H), 4.82 (hept, J = 6.8 Hz, 1H), 2.86–2.71 (m, 1H), 1.87–1.62 (m, 5H), 1.58 (d, J = 6.8 Hz, 6H), 1.47–1.10 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.0 (C_q, $^1J_{C\text{-}F}$ = 244.1 Hz), 153.7 (C_q), 152.7 (CH), 149.2 (C_q), 145.1 (C_q, $^3J_{C\text{-}F}$ = 7.2 Hz), 137.9 (CH), 130.6 (C_q), 128.1 (CH, $^3J_{C\text{-}F}$ = 8.4 Hz), 120.3 (C_q), 113.4 (CH, $^2J_{C\text{-}F}$ = 22.7 Hz), 113.0 (CH, $^2J_{C\text{-}F}$ = 22.6 Hz), 47.1 (CH), 39.0 (CH), 33.5 (CH_2), 26.7 (CH_2), 26.1 (CH_2), 22.7 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -115.5 (dd, J = 7.9, 2.2 Hz).

IR (neat): 3235, 2927, 2852, 1606, 1468, 1221, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 354 (100) $[M+H^+]$.

HR-MS (ESI) *m/z* calcd for $C_{20}H_{24}FN_5$ $[M+H^+]$ 354.2089, found 354.2104.

***N*-(2,6-Dicyclohexyl-4-fluorophenyl)-9-*iso*-propyl-9*H*-purin-6-amine (135ib')**:

M. p. = 250 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.31 (s, 1H), 7.72 (s, 1H), 7.38 (br s, 1H), 6.89 (d, J = 9.8 Hz, 2H), 4.85 (hept, J = 6.8 Hz, 1H), 2.73–2.65 (m, 2H), 1.87–1.50 (m, 16H), 1.39–0.91 (m, 10H).

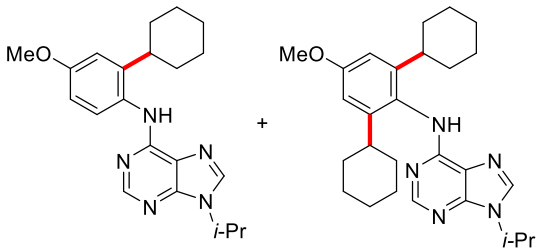
^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.6 (C_q, $^1J_{C\text{-}F}$ = 244.8 Hz), 154.9 (C_q), 153.2 (CH), 149.1 (C_q), 148.8 (C_q, $^3J_{C\text{-}F}$ = 7.5 Hz), 137.8 (CH), 127.6 (C_q), 119.8 (C_q), 111.4 (CH, $^2J_{C\text{-}F}$ = 22.6 Hz), 47.0 (CH), 39.6 (CH, $^4J_{C\text{-}F}$ = 1.6 Hz), 34.5 (CH_2), 33.2 (CH_2), 26.7 (CH_2), 26.0 (CH_2), 22.7 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -113.6 (t, J = 9.7 Hz).

IR (neat): 3178, 2926, 2850, 1609, 1470, 1224, 650 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 436 (100) $[M+H^+]$.

HR-MS (ESI) *m/z* calcd for $C_{26}H_{34}FN_5Na$ $[M+Na^+]$ 458.2690, found 458.2695.



135jb **135jb'**

The general procedure **C** was followed using substrate **134j** (85 mg, 0.30 mmol) and bromide **58b** (41 µL, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135jb** (64 mg, 58%) and **135jb'** (20 mg, 15%) as white solids.

***N*-(2-Cyclohexyl-4-methoxyphenyl)-9-*iso*-propyl-9*H*-purin-6-amine (135jb)**:

M. p. = 150 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.36 (s, 1H), 7.76 (s, 1H), 7.73 (s, 1H), 7.41 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 2.9 Hz, 1H), 6.76 (dd, J = 8.7, 2.9 Hz, 1H), 4.81 (hept, J = 6.8 Hz, 1H), 3.79 (s, 3H), 2.80–2.70 (m, 1H), 1.83–1.61 (m, 5H), 1.57 (d, J = 6.8 Hz, 6H), 1.45–1.11 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.2 (C_q), 154.3 (C_q), 153.0 (CH), 149.1 (C_q), 144.9 (C_q), 137.7 (CH), 128.2 (CH), 127.6 (C_q), 120.2 (C_q), 112.7 (CH), 111.0 (CH), 55.3 (CH_3), 47.0 (CH), 38.9 (CH), 33.6 (CH_2), 26.8 (CH_2), 26.1 (CH_2), 22.7 (CH_3).

IR (neat): 3242, 2926, 2851, 1612, 1469, 1223, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 366 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{21}H_{27}N_5O$ [M+H$^+$] 366.2288, found 366.2299.

***N*-(2,6-Dicyclohexyl-4-methoxyphenyl)-9-*iso*-propyl-9*H*-purin-6-amine (135jb')**:

M. p. = 210 °C.

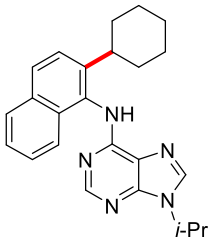
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.31 (s, 1H), 7.77 (s, 1H), 7.21 (s, 1H), 6.73 (s, 2H), 4.85 (hept, J = 6.8 Hz, 1H), 3.81 (s, 3H), 2.78–2.59 (m, 2H), 1.76–1.56 (m, 16H), 1.36–1.04 (m, 10H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1 (C_q), 155.2 (C_q), 153.3 (CH), 149.0 (C_q), 147.5 (C_q), 137.6 (CH), 124.6 (C_q), 119.8 (C_q), 109.9 (CH), 55.1 (CH_3), 47.0 (CH), 39.6 (CH), 34.6 (CH_2), 33.3 (CH_2), 26.8 (CH_2), 26.1 (CH_2), 22.8 (CH_3).

IR (neat): 3225, 2925, 2850, 1611, 1468, 1227, 650 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 448 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{27}H_{37}N_5O$ [M+H$^+$] 448.3071, found 448.3084.



***N*-(2-Cyclohexylnaphthalen-1-yl)-9-*iso*-propyl-9*H*-purin-6-amine (135kb)**: The general procedure **C** was followed using substrate **134k** (91 mg, 0.30 mmol) and bromide **58b** (74 µL, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135kb** (85 mg, 74%) as a white solid.

M. p. = 120 °C.

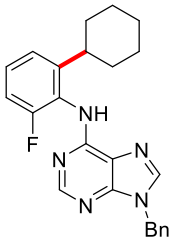
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.56 (br s, 1H), 8.29 (s, 1H), 7.94–7.78 (m, 3H), 7.56 (d, J = 8.7 Hz, 1H), 7.51 (s, 1H), 7.40 (ddd, J = 8.0, 6.8, 1.3 Hz, 1H), 7.32 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 4.74 (hept, J = 6.8 Hz, 1H), 3.04 (tt, J = 12.4, 2.8 Hz, 1H), 1.85–1.52 (m, 7H), 1.47 (d, J = 6.8 Hz, 6H), 1.31–1.07 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 155.0 (C_q), 153.2 (CH), 149.1 (C_q), 143.3 (C_q), 137.6 (CH), 132.8 (C_q), 131.4 (C_q), 129.3 (C_q), 128.0 (CH), 127.9 (CH), 126.2 (CH), 125.2 (CH), 124.8 (CH), 123.3 (CH), 119.8 (C_q), 46.9 (CH), 39.6 (CH), 33.5 (CH_2), 26.8 (CH_2), 26.2 (CH_2), 22.6 (CH_3).

IR (neat): 3179, 2926, 2851, 1711, 1605, 1220, 648 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 386 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{24}H_{28}N_5$ [M+H$^+$] 386.2339, found 386.2348.



9-Benzyl-*N*-(2-cyclohexyl-6-fluorophenyl)-9*H*-purin-6-amine (135lb): The general procedure **C** was followed using substrate **134l** (96 mg, 0.30 mmol) and bromide **58b** (74 µL, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135lb** (106 mg, 88%) as a white solid.

M. p. = 95 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.41 (s, 1H), 7.72 (br s, 1H), 7.65 (s, 1H), 7.42–7.21 (m, 6H), 7.12 (d, J = 7.9 Hz, 1H), 6.98 (ddd, J = 9.5, 8.1, 1.4 Hz, 1H), 5.34 (s, 2H), 2.81 (tt, J = 12.0, 3.2 Hz, 1H), 1.84–1.52 (m, 5H), 1.50–0.96 (m, 5H).

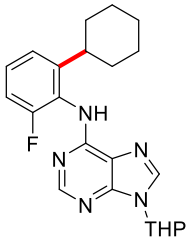
^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.7 (C_q, $^1J_{C\text{-}F}$ = 248.0 Hz), 154.3 (C_q), 153.4 (CH), 150.0 (C_q), 148.0 (C_q), 140.3 (CH), 135.4 (C_q), 129.0 (CH), 128.4 (CH, $^3J_{C\text{-}F}$ = 8.9 Hz), 128.3 (CH), 127.9 (CH), 122.8 (C_q, $^2J_{C\text{-}F}$ = 12.7 Hz), 122.1 (CH, $^4J_{C\text{-}F}$ = 3.3 Hz), 119.8 (C_q), 113.2 (CH, $^2J_{C\text{-}F}$ = 20.7 Hz), 47.2 (CH_2), 38.9 (CH, $^4J_{C\text{-}F}$ = 2.3 Hz), 33.7 (CH_2), 26.7 (CH_2), 26.0 (CH_2).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -118.7 (dd, J = 9.6, 5.6 Hz).

IR (neat): 3180, 2925, 2851, 1605, 1469, 1295, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 402 (100) $[M+H^+]$.

HR-MS (ESI) *m/z* calcd for $C_{24}H_{25}FN_5$ $[M+H^+]$ 402.2089, found 402.2103.



***N*-(2-Cyclohexyl-6-fluorophenyl)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine (135mb)**: The general procedure **C** was followed using substrate **134m** (94 mg, 0.30 mmol) and bromide **58b** (74 µL, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135mb** (117 mg, 99%) as a white solid.

M. p. = 97 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.36 (s, 1H), 7.93 (s, 1H), 7.77 (br s, 1H), 7.26 (ddd, J = 8.1, 7.9, 6.0 Hz, 1H), 7.12 (dd, J = 7.9, 1.4 Hz, 1H), 6.98 (ddd, J = 9.5, 8.1, 1.4 Hz, 1H), 5.69 (dd, J = 9.8, 2.8 Hz, 1H), 4.13 (ddd, J = 12.9, 2.9, 2.9 Hz, 1H), 3.74 (ddd, J = 11.5, 2.9, 2.9 Hz, 1H), 2.80 (tt, J = 12.0, 3.2 Hz, 1H), 2.20–1.94 (m, 3H), 1.84–1.54 (m, 8H), 1.50–1.30 (m, 2H), 1.26–1.13 (m, 3H).

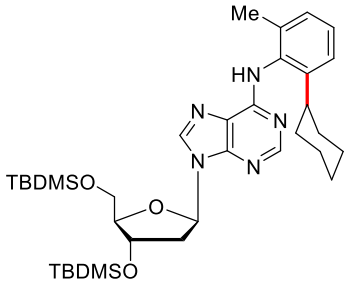
^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.6 (C_q, $^{1}J_{C\text{-}F}$ = 247.8 Hz), 154.1 (C_q), 153.1 (CH), 149.1 (C_q), 147.9 (C_q), 138.2 (CH), 128.3 (CH, $^{3}J_{C\text{-}F}$ = 8.5 Hz), 122.7 (C_q, $^{2}J_{C\text{-}F}$ = 12.7 Hz), 122.0 (CH, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 119.8 (C_q), 113.1 (CH, $^{2}J_{C\text{-}F}$ = 20.7 Hz), 81.8 (CH), 68.7 (CH_2), 39.0 (CH, $^{4}J_{C\text{-}F}$ = 2.1 Hz), 33.7 (CH_2), 31.8 (CH_2), 26.7, (CH_2), 26.1 (CH_2), 24.9 (CH_2), 22.8 (CH_2).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -118.8 (dd, J = 9.5, 5.6 Hz).

IR (neat): 3183, 2926, 2852, 1711, 1449, 1221, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 396 (100) $[M+H^+]$.

HR-MS (ESI) *m/z* calcd for $C_{22}H_{27}FN_5O$ $[M+H^+]$ 396.2194, found 396.2205.



9-{(2*R*,4*S*,5*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl} tetrahydrofuran-2-yl}-*N*-(2-cyclohexyl-6-methylphenyl)-9*H*-purin-6 amine (135nb): The general procedure **C** was followed using substrate **134n** (171 mg, 0.30 mmol) and bromide **58b** (74 µL, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135nb** (160 mg, 82%) as a colorless oil.

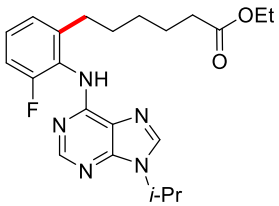
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (s, 1H), 8.06 (br s, 1H), 7.23–7.18 (m, 2H), 7.13 (dd, *J* = 7.0, 2.0 Hz, 1H), 6.45 (dd, *J* = 6.5, 6.5 Hz, 1H), 4.62 (m, 1H), 4.01 (m, 1H), 3.85 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.76 (dd, *J* = 11.2, 3.4 Hz, 1H), 2.89–2.62 (m, 2H), 2.42 (ddd, *J* = 13.1, 6.1, 3.6 Hz, 1H), 2.19 (s, 3H), 1.82–1.56 (m, 5H), 1.40–1.33 (m, 2H), 1.25–1.19 (m, 3H), 0.90 (s, 19H), 0.10 (s, 6H), 0.07 (d, *J* = 2.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.2 (CH), 153.5 (C_q), 149.1 (C_q), 145.9 (CH), 138.7 (C_q), 136.8 (C_q), 133.1 (C_q), 128.2 (CH), 128.0 (CH), 124.5 (CH), 120.0 (C_q), 87.9 (CH), 84.3 (CH), 72.1 (CH), 62.9 (CH_2), 41.0 (CH_2), 39.2 (CH), 33.9 (CH_2), 26.8 (CH_2), 26.1 (CH_2), 25.9 (CH_3), 25.8 (CH_3), 18.8 (CH_3), 18.4 (C_q), 18.0 (C_q), -4.7 (CH_3), -4.8 (CH_3), -5.4 (CH_3), -5.5 (CH_3).

IR (neat): 2954, 2925, 2856, 1712, 1612, 1360, 1219, 835 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 652 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{35}H_{58}N_5O_3Si_2$ [M+H$^+$] 652.4073, found 652.4068.



Ethyl-6-{3-fluoro-2-[(9-*iso*-propyl-9*H*-purin-6-yl)amino]phenyl}hexanoate (135ap): The general procedure **C** was followed using substrate **134a** (81 mg, 0.30 mmol) and bromide **58p**

(134 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135ap** (67 mg, 54%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.34 (s, 1H), 8.15 (s, 1H), 7.69 (s, 1H), 7.21 (ddd, *J* = 8.0, 7.7, 4.8 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 6.99 (ddd, *J* = 9.6, 8.0, 1.5 Hz, 1H), 4.79 (hept, *J* = 6.6 Hz, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 2.62 (t, *J* = 7.7 Hz, 2H), 2.12 (t, *J* = 7.5 Hz, 2H), 1.54 (d, *J* = 6.6 Hz, 6H), 1.50–1.42 (m, 4H), 1.26–1.21 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 3H).

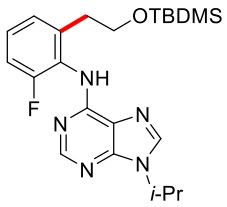
^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.5 (C_q), 158.8 (C_q, $^1J_{C\text{-}F}$ = 248.0 Hz), 154.0 (C_q), 152.8 (CH), 149.4 (C_q), 142.9 (C_q), 138.0 (CH), 128.1 (CH, $^3J_{C\text{-}F}$ = 8.6 Hz), 124.7 (CH, $^4J_{C\text{-}F}$ = 3.3 Hz), 123.8 (C_q, $^2J_{C\text{-}F}$ = 13.1 Hz), 120.2 (C_q), 113.5 (CH, $^2J_{C\text{-}F}$ = 20.7 Hz), 60.0 (CH_2), 47.0 (CH), 34.0 (CH_2), 31.2 (CH_2, $^4J_{C\text{-}F}$ = 2.4 Hz), 29.6 (CH_2), 28.7 (CH_2), 24.6 (CH_2), 22.5 (CH_3), 14.1 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -119.4 (dd, *J* = 9.5, 5.6 Hz).

IR (neat): 3179, 2933, 2861, 1606, 1467, 1223, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 414 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{22}H_{29}FN_5O_2$ [M+H$^+$] 414.2300, found 414.2303.



***N*-{2-[2-(*tert*-Butyldimethylsilyl)oxyethyl]-6-fluorophenyl}-9-*iso*-propyl-9*H*-purin-6-amine (135aq)**: The general procedure **C** was followed using substrate **134a** (81 mg, 0.30 mmol) and bromide **58q** (143 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135aq** (80 mg, 62%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.38 (s, 1H), 8.17 (br s, 1H), 7.81 (s, 1H), 7.19 (ddd, *J* = 8.2, 8.0, 5.3 Hz, 1H), 7.07–7.01 (m, 2H), 4.82 (hept, *J* = 6.8 Hz, 1H), 3.83 (t, *J* = 6.1 Hz, 2H), 2.89 (t, *J* = 6.1 Hz, 2H), 1.57 (d, *J* = 6.8 Hz, 6H), 0.79 (s, 9H), -0.05 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.4 (C_q, $^1J_{C\text{-}F}$ = 249.1 Hz), 153.3 (C_q), 152.6 (CH), 149.5 (C_q), 138.7 (C_q), 138.0 (CH), 127.4 (CH, $^3J_{C\text{-}F}$ = 8.5 Hz), 125.4 (CH, $^4J_{C\text{-}F}$ = 3.2 Hz), 125.0 (C_q,

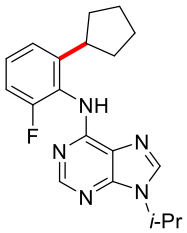
$^{2}J_{C\text{-}F}$ = 12.8 Hz), 120.6 (C_q), 114.2 (CH, $^{2}J_{C\text{-}F}$ = 20.7 Hz), 64.8 (CH_2), 46.9 (CH), 34.9 (CH_2, $^{4}J_{C\text{-}F}$ = 2.3 Hz), 25.9 (CH_3), 22.6 (CH_3), 18.4 (C_q), -5.6 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -117.4 (dd, J = 9.6, 5.3 Hz).

IR (neat): 3172, 2926, 2854, 1611, 1470, 1228, 833, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 430 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{22}H_{33}FN_5OSi$ [M+H$^+$] 430.2433, found 430.2437.



***N*-(2-Cyclopentyl-6-fluorophenyl)-9-*iso*-propyl-9*H*-purin-6-amine (135ar)**: The general procedure **C** was followed using substrate **134a** (81 mg, 0.30 mmol) and bromide **58r** (89 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135ar** (100 mg, 98%) as a white solid.

M. p. = 145 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.38 (s, 1H), 7.79 (s, 1H), 7.55 (br s, 1H), 7.26 (ddd, J = 8.1, 8.0, 5.6 Hz, 1H), 7.16 (dd, J = 8.0, 1.5 Hz, 1H), 7.00 (ddd, J = 9.5, 8.1, 1.5 Hz, 1H), 4.83 (hept, J = 6.8 Hz, 1H), 3.25 (p, J = 8.4 Hz, 1H), 2.04–1.87 (m, 2H), 1.86–1.68 (m, 2H), 1.59 (d, J = 6.8 Hz, 6H), 1.57–1.47 (m, 4H).

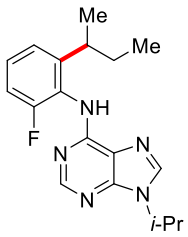
^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.7 (C_q, $^{1}J_{C\text{-}F}$ = 247.7 Hz), 154.0 (C_q), 152.8 (CH), 149.4 (C_q), 147.0 (C_q), 138.0 (CH), 128.3 (CH, $^{3}J_{C\text{-}F}$ = 8.7 Hz), 123.4 (C_q, $^{2}J_{C\text{-}F}$ = 12.9 Hz), 121.9 (CH, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 120.3 (C_q), 113.2 (CH, $^{2}J_{C\text{-}F}$ = 20.7 Hz), 47.1 (CH), 40.4 (CH, $^{4}J_{C\text{-}F}$ = 2.2 Hz), 34.2 (CH_2), 25.7 (CH_2), 22.8 (CH_3).

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

IR (neat): 3189, 2945, 1605, 1470, 1222, 1006, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 340 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{19}H_{23}FN_5$ [M+H$^+$] 340.1932, found 340.1932.



***N*-[2-(*sec*-Butyl)-6-fluorophenyl]-9-*iso*-propyl-9*H*-purin-6-amine (135al)**: The general procedure **C** was followed using substrate **134a** (81 mg, 0.30 mmol) and bromide **58l** (82 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135al** (84 mg, 86%) as a white solid.

M. p. = 180 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.36 (s, 1H), 7.79 (br s, 1H), 7.75 (s, 1H), 7.28 (ddd, J = 8.1, 8.0, 5.5 Hz, 1H), 7.09 (dd, J = 8.0, 1.4 Hz, 1H), 7.00 (ddd, J = 9.5, 8.1, 1.4 Hz, 1H), 4.81 (hept, J = 6.8 Hz, 1H), 2.96 (m, 1H), 1.65–1.40 (m, 8H), 1.13 (d, J = 6.9 Hz, 3H), 0.69 (t, J = 7.4 Hz, 3H).

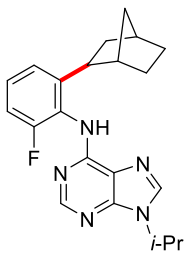
^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.7 (d, J = 247.4 Hz), 154.2 (C_q), 152.7 (CH), 149.3 (C_q), 148.2 (C_q), 137.8 (CH), 128.4 (CH, $^{3}J_{C\text{-}F}$ = 8.5 Hz), 123.4 (C_q, $^{2}J_{C\text{-}F}$ = 12.8 Hz), 121.7 (CH, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 120.2 (C_q), 113.2 (CH, $^{2}J_{C\text{-}F}$ = 20.7 Hz), 47.0 (CH), 35.4 (CH, $^{4}J_{C\text{-}F}$ = 2.0 Hz), 30.5 (CH_2), 22.7 (CH_3), 21.1 (CH_3), 12.1 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -119.1 (dd, J = 9.5, 5.6 Hz).

IR (neat): 3180, 2962, 2931, 1610, 1470, 1224, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 328 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{18}H_{23}FN_5$ [M+H$^+$] 328.1932, found 328.1934.



***N*-{2-[(2*S*)-Bicyclo[2.2.1]heptan-2-yl]-6-fluorophenyl}-9-*iso*-propyl-9*H*-purin-6-amine (135as)**: The general procedure **C** was followed using substrate **134a** (81 mg, 0.30 mmol) and

bromide **58s** (105 mg, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135as** (100 mg, 91%) as a white solid.

M. p. = 92 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.39 (s, 1H), 7.76 (s, 1H), 7.73 (s, 1H), 7.26 (ddd, J = 8.1, 8.0, 5.5 Hz, 1H), 7.16 (dd, J = 8.0, 1.4 Hz, 1H), 7.01 (ddd, J = 9.5, 8.1, 1.5 Hz, 1H), 4.83 (hept, J = 6.8 Hz, 1H), 2.92 (dd, J = 8.9, 5.7 Hz, 1H), 2.41 (d, J = 2.6 Hz, 1H), 2.25 (d, J = 4.3 Hz, 1H), 1.70 (ddd, J = 12.0, 9.1, 2.3 Hz, 1H), 1.59 (d, J = 6.8 Hz, 6H), 1.53–1.43 (m, 4H), 1.26–1.09 (m, 3H).

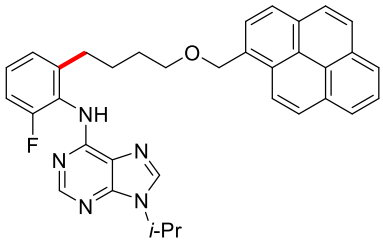
^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1 (C_q, $^1J_{C\text{-}F}$ = 248.9 Hz), 153.9 (C_q), 152.8 (CH), 149.6 (C_q), 147.5 (C_q), 138.1 (CH), 128.0 (CH, $^3J_{C\text{-}F}$ = 8.5 Hz), 123.5 (C_q, $^2J_{C\text{-}F}$ = 12.6 Hz), 121.2 (CH, $^4J_{C\text{-}F}$ = 3.1 Hz), 120.3 (C_q), 113.3 (CH, $^2J_{C\text{-}F}$ = 20.6 Hz), 47.1 (CH), 42.6 (CH, $^4J_{C\text{-}F}$ = 2.1 Hz), 41.3 (CH), 39.3 (CH_2), 36.9 (CH), 36.4 (CH_2), 30.2 (CH_2), 28.7 (CH_2), 22.7 (CH_3).

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

IR (neat): 3226, 2950, 2870, 1711, 1468, 1220, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 366 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{21}H_{25}FN_5$ [M+H$^+$] 366.2089, found 366.2090.



***N*-{2-Fluoro-6-[4-(pyren-1-ylmethoxy)butyl]phenyl}-9-*iso*-propyl-9*H*-purin-6-amine (135at)**: The general procedure **C** was followed using substrate **134a** (81 mg, 0.30 mmol) and bromide **58t** (74 µL, 0.60 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **135at** (90 mg, 54%) as a white solid.

M. p. = 110 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.41 (s, 1H), 8.27 (d, J = 9.2 Hz, 1H), 8.16–8.13 (m, 2H), 8.09–8.04 (m, 3H), 8.00 (d, J = 0.7 Hz, 2H), 7.97 (dd, J = 7.5, 7.5 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.70 (br s, 1H), 7.15 (ddd, J = 8.1, 8.0, 5.5 Hz, 1H), 7.04–6.95 (m, 2H), 5.07 (s, 2H), 4.74

(hept, J = 6.7 Hz, 1H), 3.47 (t, J = 6.1 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 1.71–1.53 (m, 4H), 1.49 (d, J = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.8 (C_q, $^1J_{C\text{-}F}$ = 247.9 Hz), 153.9 (C_q), 152.7 (CH), 149.5 (C_q), 142.8 (C_q), 138.0 (CH), 131.6 (C_q), 131.1 (C_q), 131.0 (C_q), 130.7 (C_q), 129.1 (C_q), 128.1 (CH, $^3J_{C\text{-}F}$ = 8.5 Hz), 127.5 (CH), 127.3 (CH), 127.2 (CH), 126.7 (CH), 125.8 (CH), 125.1 (CH), 125.0 (CH), 124.8 (CH, $^4J_{C\text{-}F}$ = 3.2 Hz), 124.8 (C_q), 124.6 (C_q), 124.4 (CH), 123.7 (C_q, $^2J_{C\text{-}F}$ = 13.1 Hz), 123.4 (CH), 120.2 (C_q), 113.5 (CH, $^2J_{C\text{-}F}$ = 20.7 Hz), 71.3 (CH_2), 70.0 (CH_2), 47.0 (CH), 31.1 (CH_2, $^4J_{C\text{-}F}$ = 2.3 Hz), 29.4 (CH_2), 26.6 (CH_2), 22.5 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -119.3 (dd, J = 9.3, 5.5 Hz).

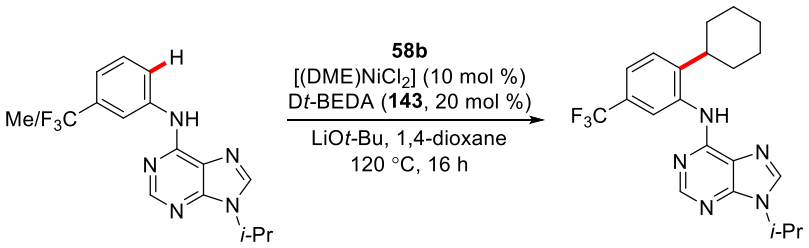
IR (neat): 3039, 2929, 2858, 1606, 1467, 845, 648 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 558 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{35}H_{32}FN_5O$ [M+H$^+$] 558.2664, found 558.2668.

Mechanistic Studies

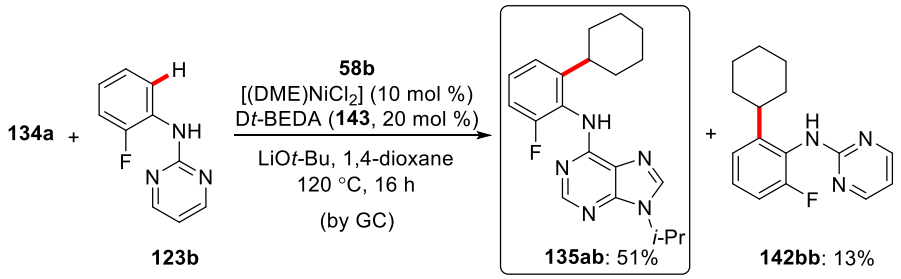
Intermolecular Competition Experiment between 134d and 134f



9-*iso*-Propyl-*N*-(*m*-tolyl)-9*H*-purin-6-amine **(134d)** (80 mg, 0.30 mmol), 9-*iso*-propyl-*N*-[3-(trifluoromethyl)phenyl]-9*H*-purin-6-amine (**134f**) (96 mg, 0.30 mmol), [(DME)$NiCl_2$] (6.6 mg, 10 mol %) and LiO*t*-Bu (48 mg, 0.60 mmol) were placed in a Schlenk tube. The tube was degassed and purged with N_2 for three times. D*t*-BEDA (**143**) (13 µL, 20 mol %), alkyl bromide **58b** (49 mg, 0.30 mmol) and 1,4-dioxane (1.5 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, and the reaction

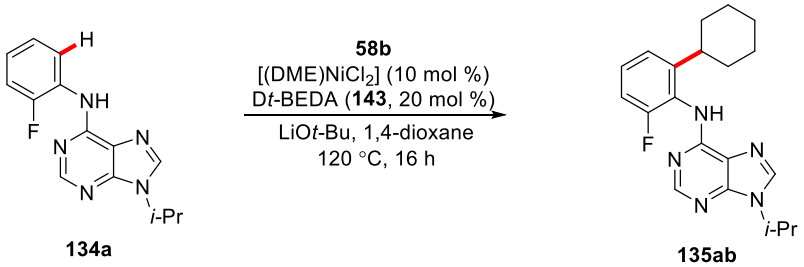
mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1→1/1) to afford **135fb** (16 mg, 13%) as the sole product, and the starting materials **134d** (77 mg, 96%) and **134f** (76 mg, 79%) were reisolated.

Intermolecular Competition Experiment between Different Directing Groups



N-(2-Fluorophenyl)-9-*iso*-propyl-9*H*-purin-6-amine **(134a)** (81 mg, 0.30 mmol), *N*-(2-fluorophenyl)pyrimidin-2-amine (**123b**) (57 mg, 0.30 mmol), [(DME)$NiCl_2$] (6.6 mg, 10 mol %) and LiO*t*-Bu (48 mg, 0.60 mmol) were placed in a Schlenk tube. The tube was degassed and purged with N_2 for three times. D*t*-BEDA (**143**) (13 μL, 20 mol %), alkyl bromide **58b** (49 mg, 0.30 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 120 °C for 16 h. After cooling to ambient temperature, the GC conversions were determined by using *n*-dodecane (51 mg, 0.30 mmol) as internal standard.

Reactions in the Presence of Radical Scavengers



additive (1.0 equiv)	yield
---	98%
TEMPO	0%
BHT	52%
Galvinoxyl	trace

(a)

N-(2-Fluorophenyl)-9-*iso*-propyl-9*H*-purin-6-amine **(134a)** (81 mg, 0.30 mmol), [(DME)$NiCl_2$] (6.6 mg, 10 mol %), TEMPO (47 mg, 0.30 mmol) and LiO*t*-Bu (48 mg, 0.6 mmol) were placed in a 25 mL Schlenk tube. The tube was degassed and purged with N_2 three times. D*t*-BEDA (**143**) (13 µL, 20 mol %), bromocyclohexane (**58b**) (74 µL, 0.6 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 120 °C for 16 h. After cooling to ambient temperature, CH_2Cl_2 (2 mL) was added. No conversion was observed by GCMS and ^{1}H NMR analysis of the crude reaction mixture. Starting material **1a** (80 mg, 98%) and TEMPO (45 mg, 96%) were reisolated by column chromatography on silica gel (*n*-hexane/EtOAc: 200/1→1/1).

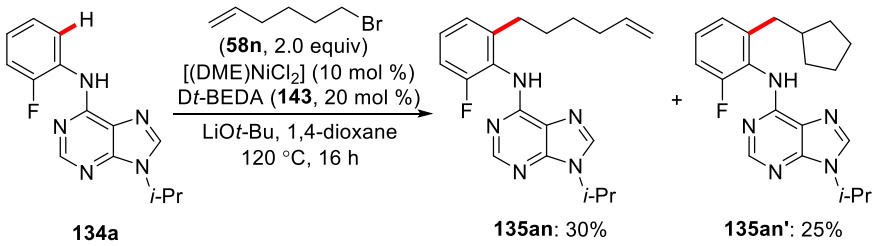
(b)

N-(2-Fluorophenyl)-9-*iso*-propyl-9*H*-purin-6-amine **(134a)** (81 mg, 0.30 mmol), [(DME)$NiCl_2$] (6.6 mg, 10 mol %), BHT (66 mg, 0.30 mmol) and LiO*t*-Bu (48 mg, 0.6 mmol) were placed in a Schlenk tube. The tube was degassed and purged with N_2 three times. D*t*-BEDA (**143**) (13 µL, 20 mol %), bromocyclohexane (**58b**) (74 µL, 0.6 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 120 °C for 16 h. At ambient temperature, CH_2Cl_2 (2 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1→1/1) to afford **135ab** (55 mg, 52%).

(c)

N-(2-Fluorophenyl)-9-*iso*-propyl-9*H*-purin-6-amine **(134a)** (81 mg, 0.30 mmol), [(DME)$NiCl_2$] (6.6 mg, 10 mol %), Galvinoxyl (127 mg, 0.30 mmol) and LiO*t*-Bu (48 mg, 0.6 mmol) were placed in a Schlenk tube. The tube was degassed and purged with N_2 three times. D*t*-BEDA (**143**) (13 µL, 20 mol %), bromocyclohexane (**58b**) (74 µL, 0.6 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 120 °C for 16 h. After cooling to ambient temperature, CH_2Cl_2 (2.0 mL) was added. Trace conversion was observed by GCMS analysis of the crude reaction mixture.

Reaction with 6-Bromohexene (58n)



N-(2-Fluorophenyl)-9-*iso*-propyl-9*H*-purin-6-amine **(134a)** (81 mg, 0.30 mmol), [(DME)$NiCl_2$] (6.6 mg, 10 mol %) and LiO*t*-Bu (48 mg, 0.6 mmol) were placed in a 25 mL Schlenk tube. The tube was degassed and purged with N_2 three times. D*t*-BEDA (**143**) (13 µL, 20 mol %), 6-bromohexene (**58n**) (98 mg, 0.6 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 120 °C for 16 h. At ambient temperature, CH_2Cl_2 (2 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure. Isolation by GPC ($CHCl_3$) yielded **135an** (32 mg, 30%) and **135an'** (26 mg, 25%) as colorless oils.

***N*-[2-Fluoro-6-(hex-5-en-1-yl)phenyl]-9-*iso*-propyl-9*H*-purin-6-amine (135an)**:

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.33 (s, 1H), 7.78 (s, 1H), 7.71 (br s, 1H), 7.18 (ddd, J = 8.1, 7.2, 5.5 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.97 (ddd, J = 9.6, 8.1, 1.5 Hz, 1H), 5.59 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 4.83 (dd, J = 17.1, 1.7 Hz, 1H), 4.78 (dd, J = 10.1, 1.7 Hz, 1H), 4.75 (hept, J = 6.9 Hz, 1H), 2.60 (t, J = 7.8 Hz, 2H), 1.88 (q, J = 7.1 Hz, 2H), 1.54 (d, J = 6.8 Hz, 6H), 1.52–1.42 (m, 2H), 1.26 (p, J = 7.5 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.7 (C_q, $^1J_{C\text{-}F}$ = 247.6 Hz), 153.9 (C_q), 152.7 (CH), 149.4 (C_q), 142.9 (C_q), 138.4 (CH), 138.1(CH), 128.1 (CH, $^3J_{C\text{-}F}$ = 8.5 Hz), 124.8 (CH, $^4J_{C\text{-}F}$ = 3.2 Hz), 123.6 (C_q, $^2J_{C\text{-}F}$ = 12.9 Hz), 120.3 (C_q), 114.3 (CH_2), 113.5 (CH, $^2J_{C\text{-}F}$ = 20.6 Hz), 47.2 (CH), 33.5 (CH_2), 31.5 (CH_2), 29.6 (CH_2), 28.6 (CH_2), 22.7 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -119.4 (dd, J = 9.5, 5.5 Hz).

IR (neat): 3198, 2977, 2930, 1612, 1470, 1227, 668 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 354 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{20}H_{25}FN_5$ [M+H$^+$] 354.2089, found 354.2089.

***N*-[2-(Cyclopentylmethyl)-6-fluorophenyl]-9-*iso*-propyl-9*H*-purin-6-amine (135an')**:

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.34 (s, 1H), 7.75 (s, 1H), 7.58 (s, 1H), 7.17 (ddd, J = 8.1, 7.1, 5.3 Hz, 1H), 7.04 (d, J = 7.1 Hz, 1H), 6.97 (ddd, J = 9.6, 8.1, 1.5 Hz, 1H), 4.79 (hept, J = 6.9 Hz, 1H), 2.61 (d, J = 7.4 Hz, 2H), 2.12–1.87 (m, 1H), 1.68–1.40 (m, 10H), 1.39–1.32 (m, 2H), 1.11–0.93 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.7 (C_q, $^1J_{C\text{-}F}$ = 247.7 Hz), 153.8 (C_q), 152.7 (CH), 149.5 (C_q), 142.5 (C_q), 138.1(CH), 127.9 (CH, $^3J_{C\text{-}F}$ = 8.4 Hz), 125.3 (CH, $^4J_{C\text{-}F}$ = 3.0 Hz), 123.68 (C_q, $^2J_{C\text{-}F}$ = 13.0 Hz), 120.3 (C_q), 113.4 (CH, $^2J_{C\text{-}F}$ = 20.6 Hz), 47.2 (CH), 40.8 (CH), 37.5 (CH_2), 32.6 (CH_2), 24.8 (CH_2), 22.8 (CH_3).

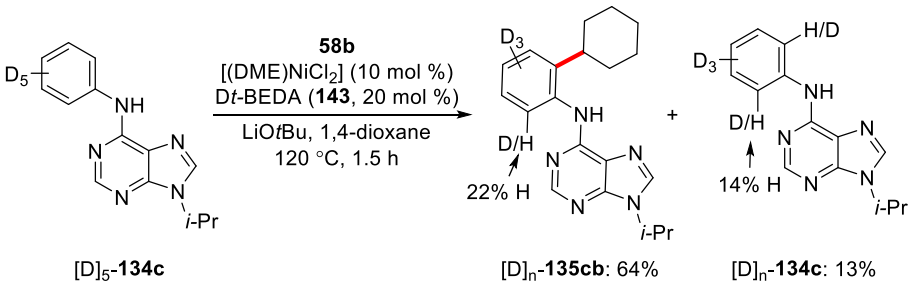
^{19}F NMR (283 MHz, $CDCl_3$) δ = -119.2 (dd, J = 9.5, 5.5 Hz).

IR (neat): 3181, 2948, 2867, 1608, 1468, 1225, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 354 (100) [M+H$^+$].

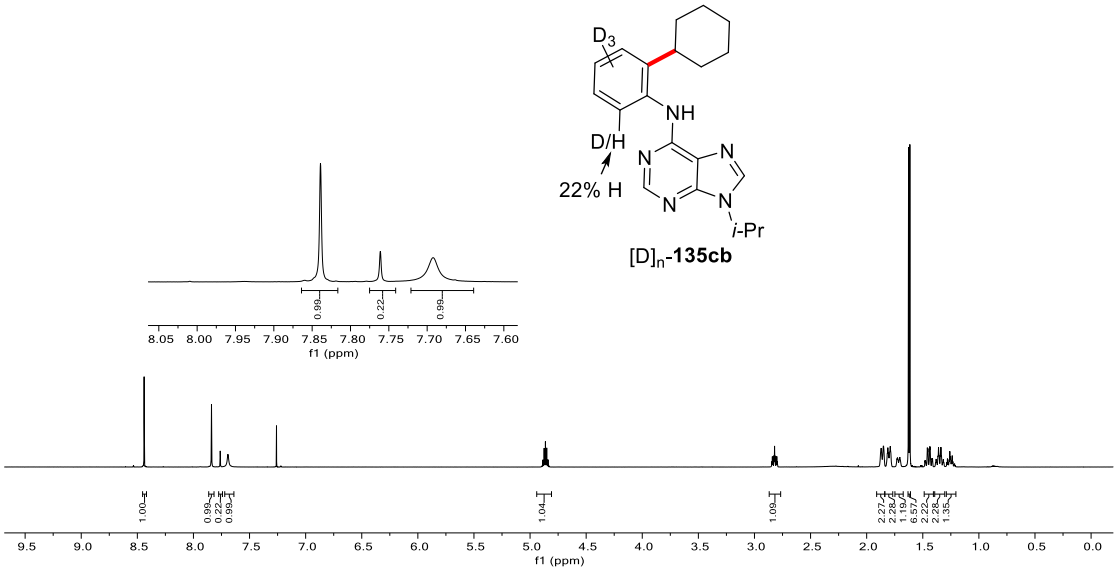
HR-MS (ESI) *m/z* calcd for $C_{20}H_{25}FN_5$ [M+H$^+$] 354.2089, found 354.2090.

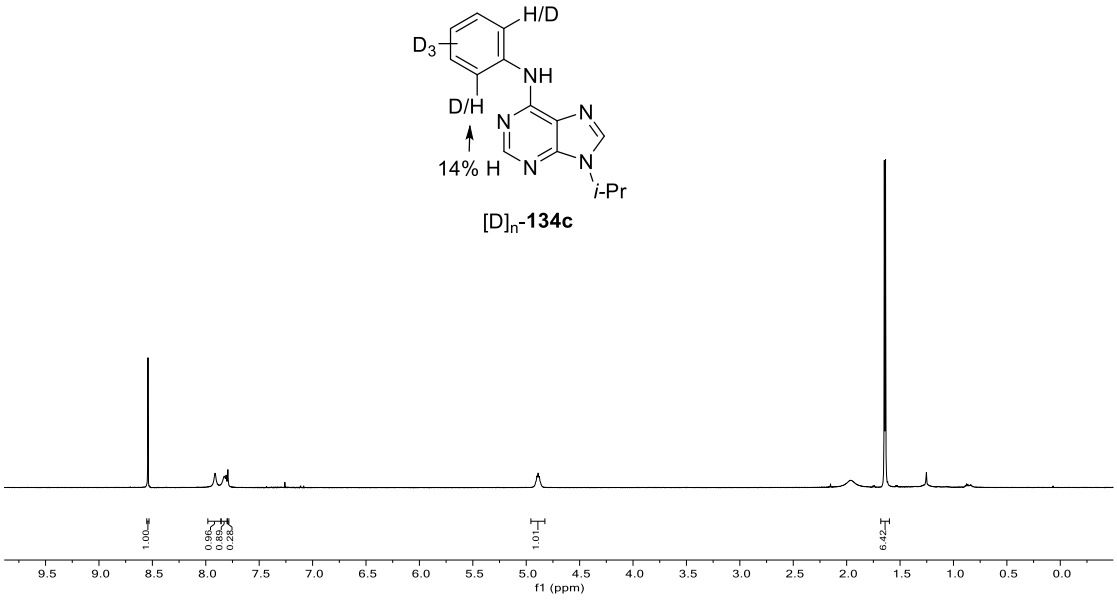
H/D Exchange Experiments with [D]$_5$-134c as the Substrate:



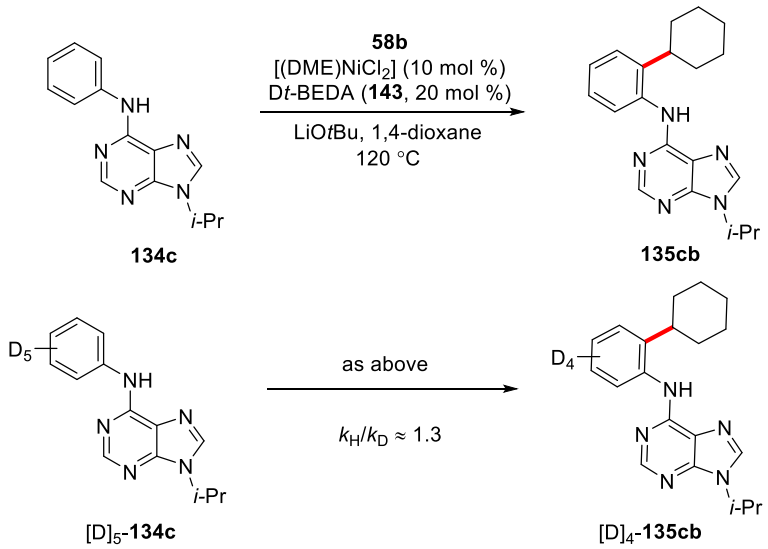
[D]$_5$-**134c** [D]$_n$-**135cb**: 64% [D]$_n$-**134c**: 13%

Substrate [D]$_5$-**134c** (77 mg, 0.3 mmol), [(DME)$NiCl_2$] (6.6 mg, 10 mol %) and LiO*t*-Bu (48 mg, 0.60 mmol) were placed in a Schlenk tube. The tube was degassed and purged with N_2 three times. D*t*-BEDA (**143**) (13 µL, 20 mol %), bromocyclohexane (**58b**) (41 µL, 0.33 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 120 °C for 1.5 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1→1/1) to afford [D]$_4$-**135cb** (65 mg, 64%) and [D]$_5$-**134c** (10 mg, 13%).


D3
NH
D/H
22% H
N
N
N
N
i-Pr
[D]n-135cb
f1 (ppm)

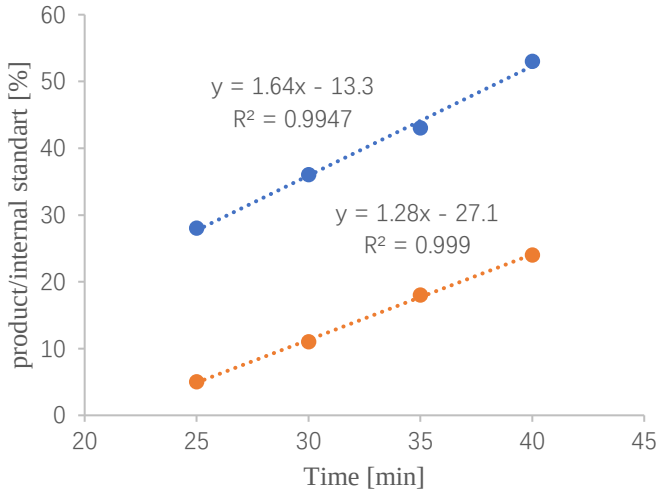

H/D
D3
NH
D/H
14% H
N
N
N
N
i-Pr
[D]n-134c
f1 (ppm)

KIE Experiments with 134c and [D]$_5$-134c as the Substrates

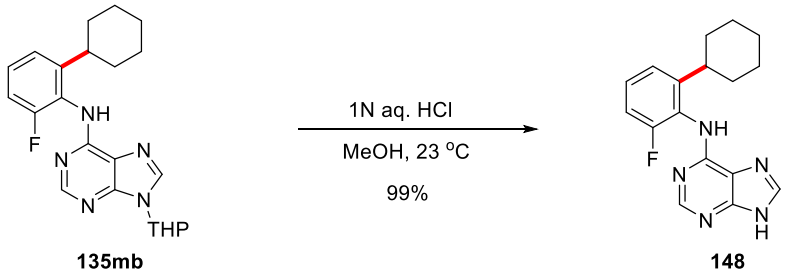


Independent reactions of **134c** or [D]$_5$-**134c** with **58b** were performed to determine the corresponding KIE value. Following general procedure **C**, **134c** (76 mg, 0.3 mmol) or [D]$_5$-**134c** (77 mg, 0.3 mmol) were reacted with **58b** (41µL, 0.33 mmol). After cooling to ambient temperature, the GC conversions were determined using *n*-dodecane (51 mg, 0.30 mmol) as internal standard:

T [min]	25	30	35	40
5ca/%	28	36	43	53
[D]$_n$-**5ca**/%	5	11	18	24



Removal of the THP Group



135mb **148**

***N*-(2-Cyclohexyl-6-fluorophenyl)-9*H*-purin-6-amine (148)**: To a solution of **135mb** (79mg, 0.20 mmol) in MeOH (1.0 mL), aqueous HCl (1N, 1.0 mL) was added and stirred for 3 h at 23 °C. The reaction mixture was poured into EtOAc (10 mL), and then saturated aqueous Na_2CO_3 solution was added until the pH was adjusted to 8. The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to afford **148** (62 mg, 99%) as a white solid.

M. p. = 270 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ = 9.14 (br s, 1H), 8.16 (s, 1H), 8.10 (s, 1H), 7.28 (ddd, J = 8.0, 7.8, 5.6 Hz, 1H), 7.15 (dd, J = 7.8, 1.4 Hz, 1H), 7.05 (ddd, J = 9.7, 8.1, 1.4 Hz, 1H), 3.34 (br s, 1H), 2.84 (tt, J = 12.1, 3.1 Hz, 1H), 1.79–1.56 (m, 5H), 1.43–1.24 (m, 2H), 1.23–1.10 (tt, J = 11.6, 5.9 Hz, 3H).

^{13}C NMR (125 MHz, DMSO-d_6) δ = 158.6 (C_q, $^1J_{C\text{-}F}$ = 245.5 Hz), 153.6 (C_q), 151.9 (CH), 151.5 (C_q), 147.9 (C_q), 140.1 (CH), 127.6 (CH, $^3J_{C\text{-}F}$ = 8.8 Hz), 124.2 (C_q, $^2J_{C\text{-}F}$ = 13.0 Hz), 121.7 (CH, $^4J_{C\text{-}F}$ = 3.1 Hz), 118.2 (C_q), 112.7 (CH, $^2J_{C\text{-}F}$ = 21.0 Hz), 38.1 (CH, $^4J_{C\text{-}F}$ = 2.1 Hz), 32.9 (CH_2), 26.4 (CH_2), 25.5 (CH_2).

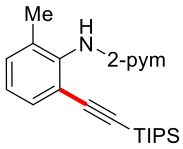
^{19}F NMR (471 MHz, DMSO-d_6) δ = -118.9 (dd, J = 9.8, 5.6 Hz).

IR (neat): 3197, 2929, 2850, 1611, 1591, 1246, 649 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 312 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{17}H_{19}FN_5$ [M+H$^+$] 312.1619, found 312.1630.

5.3.3 Characterization Data: Nickel-Catalyzed C–H Alkynylation of Anilines



***N*-{2-Methyl-6-[(triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136aa)**: The general procedure **E** was followed using substrate **123a** (93 mg, 0.50 mmol) and (bromoethynyl)triisopropylsilane (**61a)** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **136aa** (124 mg, 68%) as a yellow solid.

M. p. = 96–97 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.31 (d, J = 4.8 Hz, 2H), 7.39 (dd, J = 7.6, 1.2 Hz, 1H), 7.23 (dd, J = 7.6, 1.2 Hz, 1H), 7.11 (dd, J = 7.6, 7.6 Hz, 1H), 7.00 (s, 1H), 6.60 (t, J = 4.8 Hz, 1H), 2.26 (s, 3H), 1.02–0.99 (m, 21H).

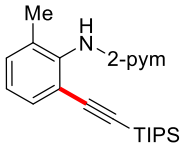
^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.4 (C_q), 158.1 (CH), 138.5 (C_q), 136.2 (C_q), 131.0 (CH), 130.6 (CH), 126.1 (CH), 121.5 (C_q), 111.9 (CH), 104.0 (C_q), 95.8 (C_q), 18.7 (CH_3), 18.5 (CH_3), 11.2 (CH).

IR (neat): 3233, 2940, 2862, 2142, 1574, 1528, 1457, 1404, 1246, 882 cm^{-1}.

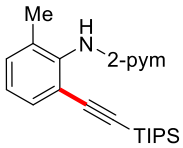
MS (EI) *m/z* (relative intensity) 365 (20) [M^+], 322 (100).

HR-MS (EI) *m/z* calcd for $C_{22}H_{31}N_3Si$ [M^+] 365.2287, found 365.2293.

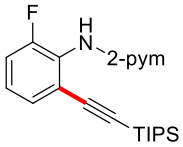
Analytical data for compound **136aa** was consistent with the literature.[165]



***N*-{2-Methyl-6-[(triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136aa)**: The general procedure **E** was followed using substrate **123a** (93 mg, 0.50 mmol) and (iodoethynyl)triisopropylsilane (**61a'**) (462 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **136aa** (55 mg, 30%) as a yellow solid.



***N*-{2-Methyl-6-[(triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136aa)**: The general procedure **E** was followed using substrate **123a** (93 mg, 0.50 mmol) and (chloroethynyl)triisopropylsilane (**61a"**) (325 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **136aa** (97 mg, 53%) as a yellow solid.



***N*-{2-Fluoro-6-[(triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136ba)**: The general procedure **E** was followed using substrate **123b** (95 mg, 0.5 mmol) and alkyne **61a** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **136ba** (120 mg, 65%) as a yellow solid.

M. p. = 98–99 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.36 (d, J = 4.8 Hz, 2H), 7.69 (s, 1H), 7.33–7.28 (m, 1H), 7.16–7.05 (m, 2H), 6.66 (t, J = 4.8 Hz, 1H).

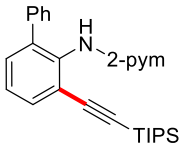
^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.7 (C_q), 157.4 (C_q, $^{1}J_{C\text{-}F}$ = 249.3 Hz), 157.9 (CH), 128.5 (CH, $^{4}J_{C\text{-}F}$= 3.3 Hz), 128.4 (C_q, $^{2}J_{C\text{-}F}$ = 13.1 Hz), 126.1 (CH, $^{3}J_{C\text{-}F}$= 8.7 Hz), 122.2 (C_q, $^{3}J_{C\text{-}F}$= 3.0 Hz), 116.6 (CH, J = 20.7 Hz), 112.6 (CH), 102.4 (C_q, $^{4}J_{C\text{-}F}$ = 4.1 Hz), 97.7 (C_q), 18.5 (CH_3), 11.1 (CH).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -117.3 (dd, J = 8.8, 6.5 Hz).

IR (neat): 3229, 2941, 2862, 2157, 1583, 1446, 1413, 996, 795, 665 cm^{-1}.

MS (EI) *m/z* (relative intensity) 369 (10) [M^+], 326 (100).

HR-MS (EI) *m/z* calcd for $C_{21}H_{28}FN_3Si$ [M^+] 369.2037, found 369.2047.



N-{3-[(Triisopropylsilyl)ethynyl]-[1,1'-biphenyl]-2-yl}pyrimidin-2-amine (136da): The general procedure **E** was followed using substrate **123d** (124 mg, 0.50 mmol) and alkyne **61a** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **136da** (109 mg, 51%) as a yellow solid.

M. p. = 122–123 °C.

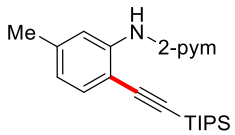
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.17 (d, J = 4.8 Hz, 2H), 7.56 (dd, J = 7.6, 1.7 Hz, 1H), 7.42 – 7.30 (m, 3H), 7.30 – 7.08 (m, 4H), 6.89 (s, 1H), 6.49 (t, J = 4.8 Hz, 1H), 1.03 – 0.97 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.8 (C_q), 157.7 (CH), 139.5 (C_q), 138.9 (C_q), 137.1 (C_q), 132.7 (CH), 130.9 (CH), 128.6 (CH), 128.1 (CH), 127.1 (CH), 126.0 (CH), 122.0 (C_q), 111.8 (CH), 104.1 (C_q), 96.2 (C_q), 18.5 (CH), 11.1 (CH_3).

IR (neat): 3057, 2942, 2863, 2157, 1570, 1512, 1430, 1406, 880, 757 cm^{-1}.

MS (EI) *m/z* (relative intensity) 427 (30) [M^+], 384 (100).

HR-MS (EI) *m/z* calcd for $C_{27}H_{33}N_3Si$ [M^+] 427.2444, found 427.2454.



***N*-{5-Methyl-2-[(triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136fa)**: The general procedure **E** was followed using substrate **123f** (93 mg, 0.50 mmol) and alkyne **61a** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **123fa** (110 mg, 60%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.42 (d, J = 4.8 Hz, 2H), 8.37 (s, 1H), 7.99 (br s, 1H), 7.34 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.71 (t, J = 4.8 Hz, 1H), 2.38 (s, 3H), 1.17–1.13 (m, 21H).

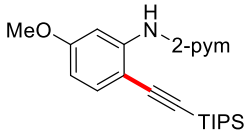
^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9 (C_q), 157.8 (CH), 141.0 (C_q), 139.9 (C_q), 131.9 (CH), 122.2 (CH), 118.3 (CH), 112.9 (CH), 109.1 (C_q), 103.0 (C_q), 97.3 (C_q), 22.1 (CH_3), 18.7 (CH_3), 11.3 (CH).

IR (neat): 3377, 2941, 2864, 2143, 1576, 1526, 1442, 1248, 989, 795 cm^{-1}.

MS (EI) *m/z* (relative intensity) 365 (20) [M^+], 322 (100).

HR-MS (EI) *m/z* calcd for $C_{22}H_{31}N_3Si$ [M^+] 365.2287, found 365.2280.

The analytical data for compound **136fa** was consistent with the literature.[165]



***N*-{5-Methoxy-2-[(triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136ga):** The general procedure **E** was followed using substrate **123g** (101 mg, 0.50 mmol) and alkyne **61a** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **136ga** (113 mg, 59%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.43 (d, J = 4.8 Hz, 2H), 8.32 (d, J = 2.5 Hz, 1H), 8.08 (s, 1H), 7.37 (d, J = 8.5 Hz, 1H), 6.72 (t, J = 4.8 Hz, 1H), 6.48 (dd, J = 8.5, 2.5 Hz, 1H), 3.84 (s, 3H), 1.27–0.93 (m, 21H).

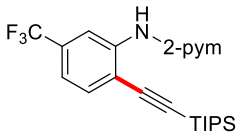
^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.6 (C_q), 159.8 (C_q), 157.8 (CH), 142.6 (C_q), 133.0 (CH), 113.0 (CH), 106.9 (CH), 104.3 (C_q), 103.6 (CH), 102.9 (C_q), 96.5 (C_q), 55.4 (CH_3), 18.7 (CH_3), 11.3 (CH).

IR (neat): 3376, 2941, 2863, 2141, 1576, 1523, 1250, 989, 794, 675 cm^{-1}.

MS (EI) *m/z* (relative intensity) 381 (30) [M^+], 338 (100).

HR-MS (EI) *m/z* calcd for $C_{22}H_{31}N_3OSi$ [M^+] 381.2236, found 381.2231.

The analytical data for compound **136ga** was consistent with the literature.[165]



N-{5-(Trifluoromethyl)-2-[(triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136ha): The general procedure **E** was followed using substrate **123h** (120 mg, 0.50 mmol) and alkyne **61a** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 15/1) yielded **136ha** (136 mg, 65%) as a yellow solid.

M. p. = 60–61 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.00 (s, 1H), 8.47 (d, J = 4.8 Hz, 2H), 8.15 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.15 (ddd, J = 8.8, 1.7, 0.7 Hz, 1H), 6.79 (t, J = 4.8 Hz, 1H), 1.43 – 0.83 (m, 21H).

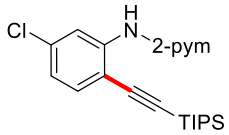
^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.6 (C_q), 157.9 (CH), 141.6 (C_q), 132.2 (CH), 131.1 (q, ^{2}J = 32.9 Hz, C_q), 124.0 (q, ^{1}J = 272.8 Hz, C_q), 117.3 (q, ^{3}J = 4.0 Hz, CH), 114.6 (C_q), 114.3 (C_q, ^{3}J = 4.0 Hz, CH), 113.7 (CH), 101.4 (C_q), 101.0 (C_q), 18.7 (CH), 11.2 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -62.8 (s).

IR (neat): 3372, 2943, 2965, 2148, 1580, 1533, 1446, 1327, 1124, 774 cm^{-1}.

MS (EI) *m/z* (relative intensity) 419 (15) [M^+], 376 (100).

HR-MS (EI) *m/z* calcd for $C_{22}H_{28}F_3N_3Si$ [M^+] 419.2005, found 419.1999.



N-{5-Chloro-2-[(triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136qa): The general procedure **E** was followed using substrate **123q** (103 mg, 0.50 mmol) and alkyne **61a** (392 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **136qa** (120 mg, 62%) as a colorless liquid.

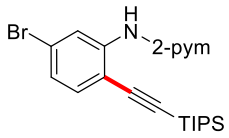
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.73 (d, J = 2.1 Hz, 1H), 8.45 (d, J = 4.8 Hz, 2H), 8.07 (s, 1H), 7.35 (d, J = 8.2 Hz, 1H), 6.89 (dd, J = 8.2, 2.1 Hz, 1H), 6.77 (t, J = 4.8 Hz, 1H), 1.24–1.09 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.5 (C_q), 157.9 (CH), 142.1 (C_q), 135.3 (C_q), 132.7 (CH), 121.1 (CH), 117.5 (CH), 113.5 (CH), 109.9 (C_q), 101.8 (C_q), 99.3 (C_q), 18.7 (CH_3), 11.3 (CH).

IR (neat): 3375, 2942, 2864, 2146, 1574, 1515, 1443, 1243, 795, 689 cm^{-1}.

MS (EI) *m/z* (relative intensity) 385 (20) [M^+], 342 (100).

HR-MS (EI) *m/z* calcd for $C_{21}H_{28}ClN_3Si$ [M^+] 385.1741, found 385.1743.



***N*-{5-Bromo-2-[(triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136ua)**: The general procedure **E** was followed using substrate **123u** (125 mg, 0.50 mmol) and alkyne **61a** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **136ua** (122 mg, 57%) as a yellow solid.

M. p. = 40–41 °C.

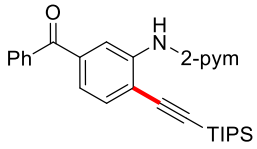
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.89 (d, J = 2.0 Hz, 1H), 8.45 (d, J = 4.8 Hz, 2H), 8.05 (s, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.05 (dd, J = 8.2, 2.0 Hz, 1H), 6.76 (t, J = 4.8 Hz, 1H), 1.38–0.93 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.4 (C_q), 157.8 (CH), 142.1 (C_q), 132.8 (CH), 123.9 (CH), 123.6 (C_q), 120.3 (CH), 113.5 (CH), 110.3 (C_q), 101.8 (C_q), 99.6 (C_q), 18.7 (CH_3), 11.2 (CH).

IR (neat): 3365, 2940, 2863, 2146, 1576, 1555, 1444, 1243, 882, 668 cm^{-1}.

MS (EI) *m/z* (relative intensity) 429 (20) [M^+], 386 (100).

HR-MS (EI) *m/z* calcd for $C_{21}H_{28}BrN_3Si$ [M^+] 429.1236, found 429.1234.



Phenyl{3-(pyrimidin-2-ylamino)-4-[(triisopropylsilyl)ethynyl}phenylmethanone (136va): The general procedure **E** was followed using substrate **123v** (138 mg, 0.50 mmol) and alkyne **61a** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **136va** (103 mg, 45%) as a colorless liquid.

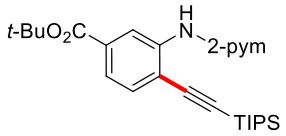
^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.09 (d, J = 1.6 Hz, 1H), 8.39 (d, J = 4.8 Hz, 2H), 8.09 (s, 1H), 7.94 – 7.80 (m, 2H), 7.65 – 7.52 (m, 2H), 7.50 – 7.42 (m, 2H), 7.35 (dd, J = 8.0, 1.6 Hz, 1H), 6.72 (t, J = 4.8 Hz, 1H), 1.22 – 1.12 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 196.0 (C_q), 159.6 (C_q), 157.8 (CH), 141.1 (C_q), 137.8 (C_q), 137.4 (C_q), 132.4 (CH), 131.7 (CH), 130.2 (CH), 128.1 (CH), 122.4 (CH), 119.5 (CH), 115.3 (C_q), 113.4 (CH), 102.0 (C_q), 101.4 (C_q), 18.7 (CH), 11.2 (CH_3).

IR (neat): 3379, 2942, 2890, 2145, 1659, 1574, 1443, 1236, 881, 649 cm^{-1}.

MS (EI) *m/z* (relative intensity) 455 (20) [M^+], 412 (100).

HR-MS (EI) *m/z* calcd for $C_{28}H_{33}N_3OSi$ [M^+] 455.2393, found 455.2384.



***tert*-Butyl 3-(pyrimidin-2-ylamino)-4-[(triisopropylsilyl)ethynyl]benzoate (136ja)**: The general procedure **E** was followed using substrate **123j** (136 mg, 0.50 mmol) and alkyne **61a** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **136ja** (127 mg, 56%) as a colorless liquid.

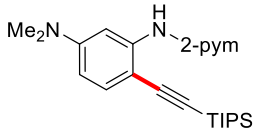
^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.21 (d, J = 1.6 Hz, 1H), 8.45 (d, J = 4.8 Hz, 2H), 8.02 (s, 1H), 7.53 (dd, J = 8.0, 1.6 Hz, 1H), 7.45 (dd, J = 8.0, 0.5 Hz, 1H), 6.75 (s, 1H), 1.59 (s, 9H), 1.20–1.12 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.4 (C_q), 159.7 (C_q), 157.9 (CH), 141.1 (C_q), 132.5 (C_q), 131.7 (CH), 121.9 (CH), 118.6 (CH), 115.4 (C_q), 113.3 (CH), 102.2 (C_q), 101.0 (C_q), 81.1 (C_q), 28.1 (CH_3), 18.7 (CH), 11.2 (CH_3).

IR (neat): 3380, 2942, 2865, 2146, 1713, 1575, 1523, 1444, 1292, 766 cm^{-1}.

MS (EI) *m/z* (relative intensity) 451 (15) [M^+], 352 (100).

HR-MS (ESI) *m/z* calcd for $C_{26}H_{38}N_3O_2Si$ [$M+H^+$] 452.2728, found 452.2732.



***N*^{1},*N*^{1}-Dimethyl-*N*^{3}-(pyrimidin-2-yl)-4-[(triisopropylsilyl)ethynyl]benzene-1,3-diamine (136wa)**: The general procedure **E** was followed using substrate **123w** (107 mg, 0.50 mmol)

and alkyne **61a** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **136wa** (110 mg, 56%) as a colorless liquid.

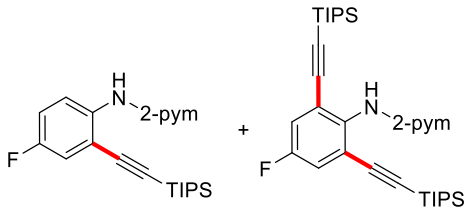
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.41 (d, J = 4.8 Hz, 2H), 8.08 (d, J = 2.5 Hz, 1H), 8.04 (br s, 1H), 7.32 (d, J = 8.6 Hz, 1H), 6.69 (t, J = 4.8 Hz, 1H), 6.29 (dd, J = 8.6, 2.5 Hz, 1H), 3.00 (s, 6H), 1.17–1.16 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.1 (C_q), 157.7 (CH), 151.2 (C_q), 142.1 (C_q), 132.7 (CH), 112.6 (CH), 105.5 (CH), 104.1 (C_q), 101.5 (CH), 99.7 (C_q), 95.1 (C_q), 40.3 (CH_3), 18.8 (CH_3), 11.4 (CH_3).

IR (neat): 3377, 2941, 2863, 2134, 1615, 1573, 1527, 1399, 1284, 793 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 395 [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{23}H_{35}N_4Si$ [M+H$^+$] 395.2626, found 395.2624.



136la **136la'**

The general procedure **E** was followed using substrate **123l** (95 mg, 0.50 mmol) and alkyne **61a** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 50/1) yielded **136la** (96 mg, 52%) as a colorless liquid and **136la'**(30 mg, 11%) as a white solid.

***N*-{4-Fluoro-2-[(triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136la)**:

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.47 (dd, J = 9.2, 5.2 Hz, 1H), 8.41 (d, J = 4.8 Hz, 2H), 7.86 (br s, 1H), 7.13 (dd, J = 8.1, 3.0 Hz, 1H), 7.04 (ddd, J = 9.2, 8.1, 3.0 Hz, 1H), 6.72 (t, J = 4.8 Hz, 1H), 1.23–1.07 (m, 21H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.3 (C_q), 159.7 (C_q, $^1J_{C\text{-}F}$ = 235 Hz), 157.7 (CH), 137.5 (C_q), 119.6 (CH, $^3J_{C\text{-}F}$ = 7.7 Hz), 118.1 (CH, $^2J_{C\text{-}F}$ = 24.0 Hz), 116.3 (CH, $^2J_{C\text{-}F}$ = 22.1 Hz), 113.2 (C_q, $^3J_{C\text{-}F}$ = 9.2 Hz), 112.9 (CH), 101.6 (C_q), 99.4 (C_q), 18.8 (CH_3), 11.4 (CH).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -121.9 (ddd, J = 8.4, 8.4, 5.4 Hz).

IR (neat): 3382, 2943, 2865, 2144, 1569, 1523, 1449, 1417, 882, 663 cm^{-1}.

MS (EI) *m/z* (relative intensity) 369 (25) [M$^+$], 326 (100).

HR-MS (EI) *m/z* calcd for $C_{21}H_{28}FN_3Si$ [M^+] 369.2037, found 369.2032.

***N*-{4-Fluoro-2,6-bis[(triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136la')**:

M. p. = 99–100 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (d, J = 4.8 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 6.88 (br s, 1H), 6.62 (t, J = 4.8 Hz, 1H), 0.97–0.98 (m, 42H).

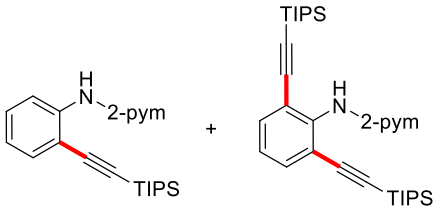
^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.9 (C_q), 159.2 (C_q, $^1J_{C\text{-}F}$ = 246.2 Hz), 157.8 (CH), 137.9 (C_q, $^4J_{C\text{-}F}$ = 3.0 Hz), 123.2 (C_q, $^3J_{C\text{-}F}$ = 10.5 Hz), 119.9 (CH, $^2J_{C\text{-}F}$ = 23.8 Hz), 112.5 (CH), 102.2 (C_q, $^4J_{C\text{-}F}$ = 2.9 Hz), 98.1 (C_q), 18.5 (CH_3), 11.1 (CH).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -116.6 (t, J = 8.5 Hz).

IR (neat): 3201, 2943, 2864, 2156, 1577, 1514, 1439, 1404, 1004, 882 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 550 [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{32}H_{49}FN_3Si_2$ [M+H^+] 550.3444, found 550.3440.



136ca **136ca'**

The general procedure **E** was followed using substrate **123c** (86 mg, 0.5 mmol) and alkyne **61a** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **136ca** (74 mg, 42%) as a colorless liquid and **136ca'** (50mg, 19%) as a white solid.

***N*-{2-[(Triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136ca)**:

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.56 (dd, J = 8.4, 1.0 Hz, 1H), 8.43 (d, J = 4.8 Hz, 2H), 8.06 (br s, 1H), 7.46 (dd, J = 7.7, 1.6 Hz, 1H), 7.34 (ddd, J = 8.4, 7.6, 1.6 Hz, 1H), 6.93 (ddd, J = 7.7, 7.6, 1.0 Hz, 1H), 6.72 (t, J = 4.8 Hz, 1H), 1.30 – 1.02 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9 (C_q), 157.8 (CH), 141.1 (C_q), 132.1 (CH), 129.4 (CH), 121.1 (CH), 117.7 (CH), 113.0 (CH), 111.8 (C_q), 102.7 (C_q), 98.1 (C_q), 18.7 (CH_3), 11.3 (CH).

IR (neat): 3379, 2942, 2864, 2145, 1715, 1576, 1518, 1437, 989, 752 cm^{-1}.

MS (EI) *m/z* (relative intensity) 351 (20) [M^+], 308 (100).

HR-MS (EI) *m/z* calcd for $C_{21}H_{29}N_3Si$ [M^+] 351.2131, found 351.2129.

***N*-{2,6-Bis[(triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136ca')**:

M. p. = 87–88 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (d, J = 4.8 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.10 (t, J = 7.8 Hz, 1H), 7.04 (br s, 1H), 6.63 (t, J = 4.8 Hz, 1H), 0.98–0.97 (m, 42H).

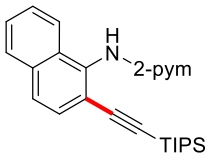
^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.7 (C_q), 157.8 (CH), 141.4 (C_q), 133.3 (CH), 125.2 (CH), 121.1 (C_q), 112.6, 103.3 (C_q), 96.9 (C_q), 18.6 (CH_3), 11.2 (CH).

IR (neat): 3379, 2941, 2864, 2147, 1576, 1518, 1438, 1407, 981, 882 cm^{-1}.

MS (EI) *m/z* (relative intensity) 531 (25) [M^+], 488 (100).

HR-MS (EI) *m/z* calcd for $C_{32}H_{49}N_3Si_2$ [M^+] 531.3465, found 531.3463.

The analytical data for compound **136ca'** was consistent with the literature.[165]



***N*-{2-[(Triisopropylsilyl)ethynyl]naphthalen-1-yl}pyrimidin-2-amine (136sa)**: The general procedure **E** was followed using substrate **123s** (111 mg, 0.50 mmol) and alkyne **61a** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **136sa** (169 mg, 84%) as a yellow solid.

M. p. = 189–190 °C.

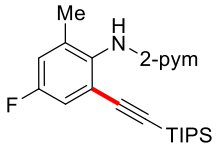
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.28 (d, J = 4.8 Hz, 2H), 8.01(dd, J = 6.8, 2.5 Hz, 1H), 7.82 (dd, J = 7.2, 2.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.55 (br s, 1H), 7.46 (ddd, J = 7.2, 6.8, 2.5 Hz, 1H), 7.43 (ddd, J = 7.2, 6.8, 2.5 Hz, 1H), 6.60 (t, J = 4.8 Hz, 1H), 1.02 (s, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.1 (C_q), 158.1 (CH), 137.2 (C_q), 134.0 (C_q), 130.7 (C_q), 129.0 (CH), 128.1 (CH), 126.8 (CH), 126.7 (CH), 126.6 (CH), 124.0 (CH), 118.7 (C_q), 112.1 (CH), 104.4 (C_q), 97.3 (C_q), 18.6 (CH), 11.2 (CH_3).

IR (neat): 3212, 2940, 2862, 2151, 1582, 1460, 1380, 994, 791, 658 cm^{-1}.

MS (EI) *m/z* (relative intensity) 401 (30) [M^+], 358 (100).

HR-MS (EI) *m/z* calcd for $C_{25}H_{31}N_3Si$ [M^+] 401.2287, found 401.2295.



***N*-{4-Fluoro-2-methyl-6-[(triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136na)**: The general procedure **E** was followed using substrate **123n** (102 mg, 0.5 mmol) and alkyne **61a** (392 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **136na** (136 mg, 71%) as a yellow solid.

M. p. = 95–96 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.29 (d, J = 4.8 Hz, 2H), 7.06 (dd, J = 8.5, 2.8 Hz, 1H), 6.96–6.94 (m, 2H), 6.60 (t, J = 4.8 Hz, 1H), 2.24 (s, 3H), 1.12–0.89 (m, 21H).

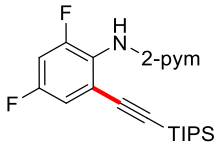
^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.1 (d, $^1J_{C\text{-}F}$ = 245.6 Hz, C_q), 161.5 (C_q), 158.1 (CH), 139.0 (d, $^3J_{C\text{-}F}$ = 8.9 Hz, C_q), 134.8 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, C_q), 123.4 (d, $^3J_{C\text{-}F}$ = 10.6 Hz, C_q), 117.9 (d, $^2J_{C\text{-}F}$ = 22.1 Hz, CH), 116.9 (d, $^2J_{C\text{-}F}$ = 23.6 Hz, CH), 112.0 (CH), 102.8 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, C_q), 96.9 (C_q), 18.9 (d, $^4J_{C\text{-}F}$ = 1.4 Hz, CH_3), 18.5 (CH_3), 11.1 (CH).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -116.4 (t, J = 8.8 Hz).

IR (neat): 3372, 2944, 2865, 2151, 1580, 1533, 1446, 1327, 1123, 795 cm^{-1}.

MS (EI) *m/z* (relative intensity) 383 (15) [M^+], 340 (100).

HR-MS (EI) *m/z* calcd for $C_{22}H_{30}FN_3Si$ [M^+] 383.2193, found 383.2196.



***N*-{2,4-Difluoro-6-[(triisopropylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136oa)**: The general procedure **E** was followed using substrate **123o** (104 mg, 0.50 mmol) and alkyne **61a** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **136oa** (145 mg, 75%) as a yellow solid.

M. p. = 102–103 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.32 (d, J = 4.8 Hz, 2H), 7.78 (br s, 1H), 7.04 (ddd, J = 8.2, 2.9, 1.3 Hz, 1H), 6.89 (ddd, J = 9.8, 8.4, 2.9 Hz, 1H), 6.64 (d, J = 4.8 Hz, 1H), 0.98–0.97 (m, 21H).

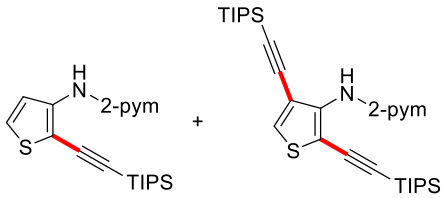
^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.8 (C_q) 159.8 (C_q, d, $J_{C\text{-}F}$ = 233.5, 13.0 Hz), 158.0 (CH), 157.9 (C_q, d, $J_{C\text{-}F}$ = 252.2, 13.5 Hz), 125.0 (C_q, dd, $J_{C\text{-}F}$ = 13.3, 4.4 Hz), 123.5 (C_q, dd, $J_{C\text{-}F}$ = 11.5, 4.3 Hz), 115.0 (CH, dd, $J_{C\text{-}F}$ = 23.2, 4.0 Hz), 112.5 (CH), 105.3 (CH, dd, $J_{C\text{-}F}$ = 26.4, 24.8 Hz), 101.4 (C_q, dd, $J_{C\text{-}F}$ = 3.4, 3.3 Hz), 99.1 (C_q), 18.4 (CH), 11.0 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -(113.1–113.3) (m).

IR (neat): 3224, 2961, 2942, 2863, 1584, 1532, 1446, 1128, 992, 883 cm^{-1}.

MS (EI) *m/z* (relative intensity) 387 (10) [M^+], 344 (100).

HR-MS (EI) *m/z* calcd for $C_{21}H_{27}F_2N_3Si$ [M^+] 387.1942, found 387.1946.



136xa **136xa'**

The general procedure **E** was followed using substrate **123x** (89 mg, 0.50 mmol) and alkyne **61a** (392 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 50/1) yielded **136xa** (80 mg, 45%) as a colorless liquid and **136xa'** (28 mg, 10%) as a white solid.

***N*-{2-[(Triisopropylsilyl)ethynyl]thiophen-3-yl}pyrimidin-2-amine (136xa)**:

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.40 (d, J = 4.8 Hz, 2H), 7.97 (d, J = 5.5 Hz, 1H), 7.54 (br s, 1H), 7.14 (d, J = 5.5 Hz, 1H), 6.70 (t, J = 4.8 Hz, 1H), 1.25–0.97 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.1 (C_q), 158.1 (CH), 143.0 (C_q), 125.3 (CH), 121.3 (CH), 112.9 (CH), 103.9 (C_q), 101.0 (C_q), 97.3 (C_q), 18.7 (CH_3), 11.3 (CH).

IR (neat): 3412, 3230, 2941, 2864, 2142, 1586, 1509, 1444, 1414, 882 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 358 (100) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{19}H_{28}N_3SSi$ [M+H^+] 358.1768, found 358.1768.

***N*-{2,4-Bis[(triisopropylsilyl)ethynyl]thiophen-3-yl}pyrimidin-2-amine (136xa')**:

M. p. = 100–101 °C.

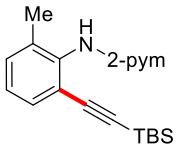
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.35 (d, J = 4.8 Hz, 2H), 7.32 (s, 1H), 6.90 (br s, 1H), 6.64 (t, J = 4.8 Hz, 1H), 0.99–0.97 (m, 42H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.4 (C_q), 158.0 (CH), 141.5 (C_q), 128.6 (CH), 120.7 (C_q), 114.3 (C_q), 112.6 (CH), 101.2 (CH), 99.2 (CH), 97.1 (CH), 94.5 (CH), 18.5 (CH_3), 18.5 (CH_3), 11.1 (CH), 11.1 (CH).

IR (neat): 3398, 2942, 2864, 2864, 2131, 1573, 1576, 1549, 1422, 669 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 538 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{30}H_{48}N_3SSi_2$ [M+H$^+$] 538.3102, found 538.3095.



***N*-{2-Methyl-6-[(tri-*n*-butylsilyl)ethynyl]phenyl}pyrimidin-2-amine (136ab)**: The general procedure **E** was followed using substrate **123a** (93 mg, 0.50 mmol) and alkyne **61b** (455 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **136ab** (101 mg, 50%) as a brown solid.

M. p. = 85–86 °C.

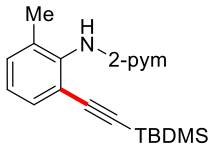
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.32 (d, J = 4.8 Hz, 2H), 7.36 (dd, J = 7.6, 1.6 Hz, 1H), 7.22 (dd, J = 7.6, 1.6 Hz, 1H), 7.10 (dd, J = 7.6, 7.6 Hz, 1H), 6.89 (s, 1H), 6.62 (t, J = 4.8 Hz, 1H), 2.25 (s, 3H), 1.40–1.21 (m, 12H), 0.87–0.82 (m, 9H), 0.62–0.47 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.4 (C_q), 158.1 (CH), 138.6 (C_q), 136.0 (C_q), 131.1 (CH), 130.4 (CH), 123.0 (CH), 121.0 (CH), 112.0 (C_q), 103.1 (C_q), 98.0 (C_q), 26.4 (CH_2), 26.0 (CH_2), 18.9 (CH_3), 13.7 (CH_3), 12.9 (CH_2).

IR (neat): 3223, 2955, 2921, 2869, 2153, 1577, 1521, 1463, 1409, 785 cm^{-1}.

MS (EI) *m/z* (relative intensity) 407 (60) [M$^+$], 350 (100).

HR-MS (ESI) *m/z* calcd for $C_{25}H_{37}N_3Si$ [M$^+$] 407.2757, found 407.2740.



***N*-{2-[(*tert*-Butyldimethylsilyl)ethynyl]-6-methylphenyl}pyrimidin-2-amine (136ac)**: The general procedure **E** was followed using substrate **123a** (93 mg, 0.50 mmol) and alkyne **61c** (455 mg, 1.50 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **136ac** (100 mg, 62%) as a brown solid.

M. p. = 149–150°C.

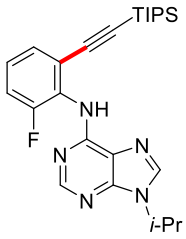
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.33 (d, J = 4.8 Hz, 2H), 7.37 (ddd, J = 7.6, 1.6 Hz, 1H), 7.24 (dd, J = 7.6, 1.6, Hz 1H), 7.19 (br s, 1H), 7.10 (dd, J = 7.6, 7.6 Hz, 1H), 6.61 (t, J = 4.8 Hz, 1H), 2.26 (s, 3H), 0.85 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.3 (C_q), 157.9 (CH), 138.6 (C_q), 136.0 (C_q), 131.0 (CH), 130.3 (CH), 125.9 (CH), 121.1 (C_q), 111.9 (CH), 102.8 (C_q), 97.8 (C_q), 26.1 (CH_3), 18.8 (CH_3), 16.5 (C_q), -4.6 (CH_3).

IR (neat): 3221, 2952, 2927, 2856, 2149, 1577, 1444, 1407, 1248, 836 cm^{-1}.

MS (EI) *m/z* (relative intensity) 323 (10) [M^+], 266 (100).

HR-MS (ESI) *m/z* calcd for $C_{19}H_{25}N_3Si$ [M+H^+] 323.1818, found 323.1823.



***N*-{2-Fluoro-6-[(triisopropylsilyl)ethynyl]phenyl}-9-isopropyl-9*H*-purin-6-amine (137aa)**: The general procedure **E** was followed using purine base **134a** (136 mg, 0.50 mmol) and alkyne **61a** (261 mg, 1.00 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1 + 10% CH_2Cl_2) yielded **137aa** (171 mg, 76%) as a white solid.

M. p. = 107–108 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.42 (s, 1H), 7.92 (s, 1H), 7.83 (br s, 1H), 7.36–7.31 (m, 1H), 7.22–7.09 (m, 2H), 4.82 (hept, J = 6.8 Hz, 1H), 1.58 (d, J = 6.8 Hz, 6H), 0.88–0.87 (m, 21H).

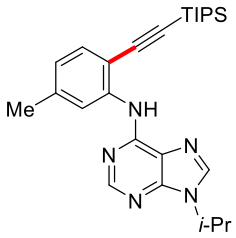
^{13}C NMR (76 MHz, $CDCl_3$) δ = 157.8 (C_q, $^1J_{C\text{-}F}$ = 249.0 Hz), 153.0 (C_q), 152.5 (CH), 149.7 (C_q), 138.2 (CH), 128.6 (CH, $^4J_{C\text{-}F}$ = 3.4 Hz), 127.4 (C_q, $^3J_{C\text{-}F}$ = 13.8 Hz), 127.0 (CH, $^3J_{C\text{-}F}$ = 8.7 Hz), 123.3 (C_q, $^4J_{C\text{-}F}$ = 2.6 Hz), 120.9 (C_q), 116.6 (CH, ^2J = 20.7 Hz), 102.2 (C_q, ^4J = 4.0 Hz), 97.9 (C_q), 47.0 (CH), 22.6 (CH_3), 18.4 (CH_3), 11.0 (CH).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -117.8 (dd, J = 9.3, 5.6 Hz).

IR (neat): 3168, 2940, 2863, 2156, 1611, 1463, 1304, 1230, 985, 700 cm^{-1}.

MS (EI) *m/z* (relative intensity) 451 (15) [M$^+$], 408 (100).

HR-MS (ESI) *m/z* calcd for $C_{25}H_{34}FN_5Si$ [M$^+$] 451.2568, found 451.2574.



9-Isopropyl-*N*-{5-methyl-2-[(triisopropylsilyl)ethynyl]phenyl}-9*H*-purin-6-amine(137da): The general procedure **E** was followed using purine base **5d** (134 mg, 0.50 mmol) and alkyne **61a** (392 mg, 1.50 mmol) at 100 °C. Isolation by column chromatography (*n*-hexane/EtOAc: 4/1) yielded **137da** (145 mg, 65%) as a red solid.

M. p. = 89–90 °C.

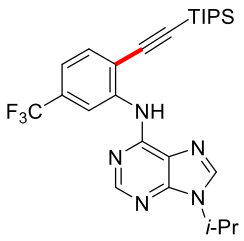
^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.64 (s, 1H), 8.56 (s, 1H), 8.49 (s, 1H), 7.83 (s, 1H), 7.37 (d, J = 7.8 Hz, 1H), 6.81 (dd, J = 7.8, 1.6 Hz, 1H), 4.85 (hept, J = 6.8 Hz, 1H), 2.41 (s, 3H), 1.61 (d, J = 6.8 Hz, 6H), 1.20 – 1.12 (m, 21H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 152.0 (CH), 151.9 (C_q), 149.2 (C_q), 140.1 (C_q), 139.8 (C_q), 137.9 (CH), 132.1 (CH), 123.0 (CH), 121.4 (C_q), 119.6 (CH), 110.0 (C_q), 102.4 (C_q), 97.8 (C_q), 47.1 (CH), 22.8 (CH_3), 22.2 (CH_3), 18.9 (CH), 11.4 (CH_3).

IR (neat): 3356, 2940, 2863, 2144, 1621, 1428, 1305, 1219, 1018, 881 cm^{-1}.

MS (EI) *m/z* (relative intensity) 447 (20) [M$^+$], 404 (100).

HR-MS (ESI) *m/z* calcd for $C_{26}H_{37}N_5Si$ [M$^+$] 447.2818, found 447.2821.



9-Isopropyl-*N*-(5-(trifluoromethyl)-2-((triisopropylsilyl)ethynyl)phenyl)-9*H*-purin-6-amine (137fa): The general procedure **E** was followed using purine base **134f** (160 mg, 0.50 mmol) and alkyne **61a** (261 mg, 1.00 mmol) at 90 °C. Isolation by column chromatography (*n*-hexane/EtOAc: 6/1) yielded **137fa** (145 mg, 58%) as a white solid.

M. p. = 147–148 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.32 (d, J = 1.7 Hz, 1H), 8.64 (br s, 1H), 8.60 (s, 1H), 7.87 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.21 (dd, J = 8.0, 1.7 Hz, 1H), 4.86 (hept, J = 6.8 Hz, 1H), 1.62 (d, J = 6.8 Hz, 6H), 1.30–1.20 (m, 3H), 1.21–1.15 (m, 18H).

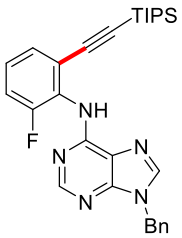
^{13}C NMR (125 MHz, $CDCl_3$) δ = 151.9 (CH), 151.5 (C_q), 149.5 (C_q), 140.8 (C_q), 138.4 (CH), 132.4 (CH), 130.9 (C_q, q, $^2J_{C\text{-}F}$= 32.4 Hz), 124.9 (C_q, q, $^1J_{C\text{-}F}$= 272.2 Hz), 118.0 (CH, d, $^3J_{C\text{-}F}$= 4.0 Hz), 115.7 (CH, d, $^3J_{C\text{-}F}$ = 4.5 Hz), 115.4 (C_q), 101.7 (C_q), 100.8 (C_q), 47.2 (CH), 22.8 (CH), 18.8 (CH_3), 11.4 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -62.8 (s).

IR (neat): 3345, 2942, 2867, 2151, 1621, 1432, 1328, 1111, 823, 660 cm^{-1}.

MS (EI) *m/z* (relative intensity) 501 (20) [M^+], 458 (100).

HR-MS (ESI) *m/z* calcd for $C_{26}H_{34}F_3N_5Si$ [M^+] 501.2536, found 501.2537.



9-Benzyl-*N*-{2-fluoro-6-[(triisopropylsilyl)ethynyl]phenyl}-9*H*-purin-6-amine (137la): The general procedure **E** was followed using purine base **134l** (160 mg, 0.50 mmol) and alkyne **61a** (261 mg, 1.00 mmol) at 120 °C. Isolation by column chromatography (*n*-hexane/EtOAc: 2/1 + 10% CH_2Cl_2) yielded **137la** (160 mg, 64%) as a white solid.

M. p. = 156–157 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.46 (s, 1H), 7.84 (br s, 1H), 7.74 (s, 1H), 7.37–7.23 (m, 6H), 7.21–7.10 (m, 2H), 5.36 (s, 2H), 0.88–0.87 (m, 21H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 157.7 (C_q, $^1J_{C\text{-}F}$ = 249.1 Hz), 152.9 (CH), 152.9 (C_q), 150.2 (C_q), 140.4 (CH), 135.5 (C_q), 128.9 (CH), 128.5 (CH, $^4J_{C\text{-}F}$ = 3.3 Hz), 128.3 (CH), 127.6 (CH), 127.2 (C_q, $^2J_{C\text{-}F}$ = 13.8 Hz), 126.9 (CH, $^3J_{C\text{-}F}$ = 8.7 Hz), 123.1 (C_q, $^4J_{C\text{-}F}$ = 2.5 Hz), 120.3 (C_q), 116.6 (CH, $^2J_{C\text{-}F}$ = 20.6 Hz), 102.1 (C_q, $^4J_{C\text{-}F}$ = 4.1 Hz), 98.0 (C_q), 47.2 (CH_2), 18.5 (CH_3), 11.1 (CH).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -(102.1–135.8) (m).

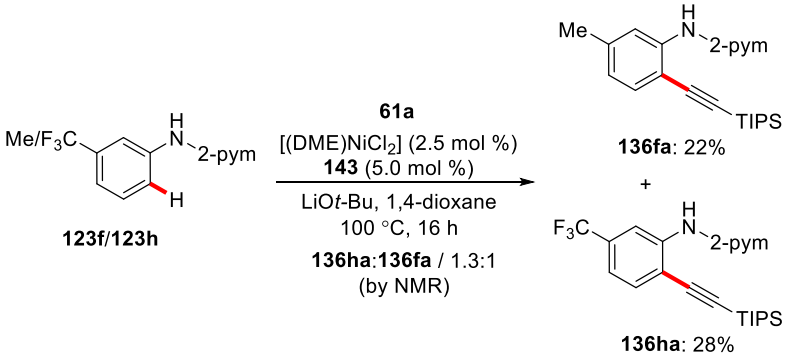
IR (neat): 3174, 2940, 2891, 2157, 1605, 1465, 1301, 1275, 992, 647 cm^{-1}.

MS (EI) *m/z* (relative intensity) 499 (10) [M^+], 456 (80), 91 (100).

HR-MS (ESI) *m/z* calcd for $C_{29}H_{34}FN_5Si$ [M^+] 499.2568, found 499.2574.

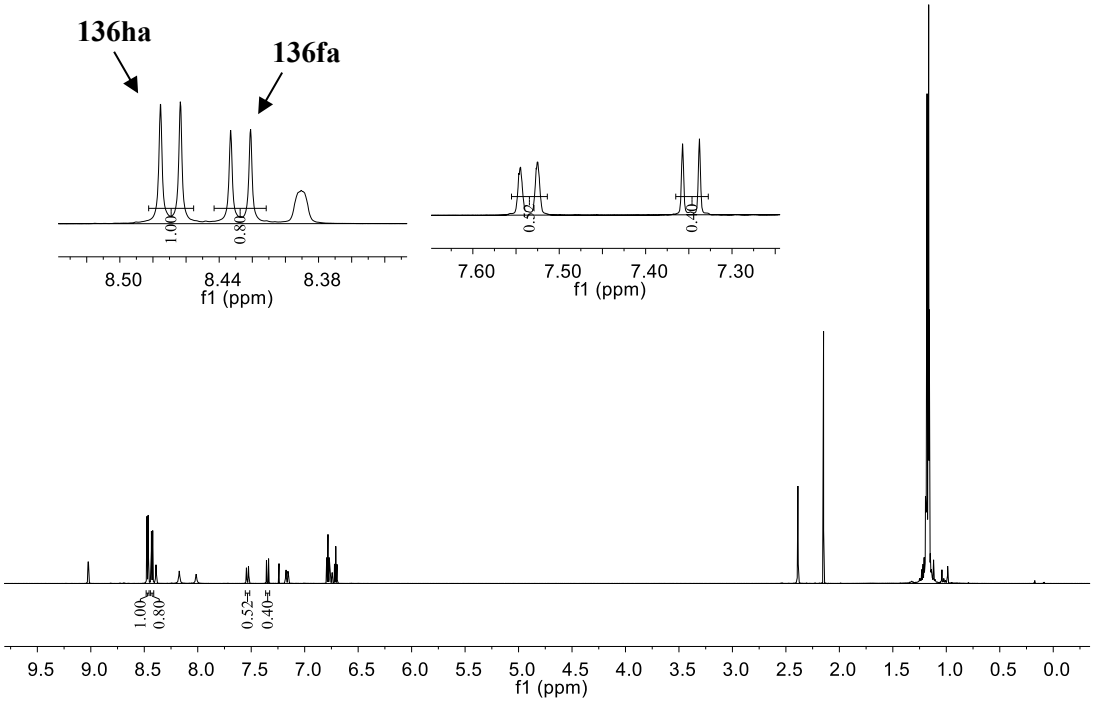
Mechanistic Studies

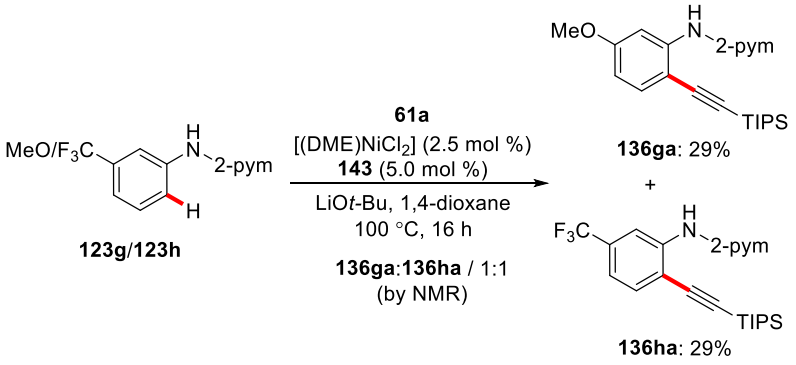
Intermolecular Competition Experiments



N-(*m*-Tolyl)pyrimidin-2-amine (**123f**) (93 mg, 0.5 mmol), *N*-[3-(trifluoromethyl)phenyl]pyrimidin-2-amine (**123h**) (120 mg, 0.5 mmol), [(DME)$NiCl_2$] (2.8 mg, 2.5 mol %) and LiO*t*-Bu(80 mg, 1.0 mmol) were placed in a 25 mL Schlenk tube. The tube was degassed and purged with N_2 for three times. D*t*-BEDA (**143**) (5.5 µL, 5.0 mol %), alkyne **61a** (130 mg, 0.5 mmol) and 1,4-dioxane (1.5 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, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced

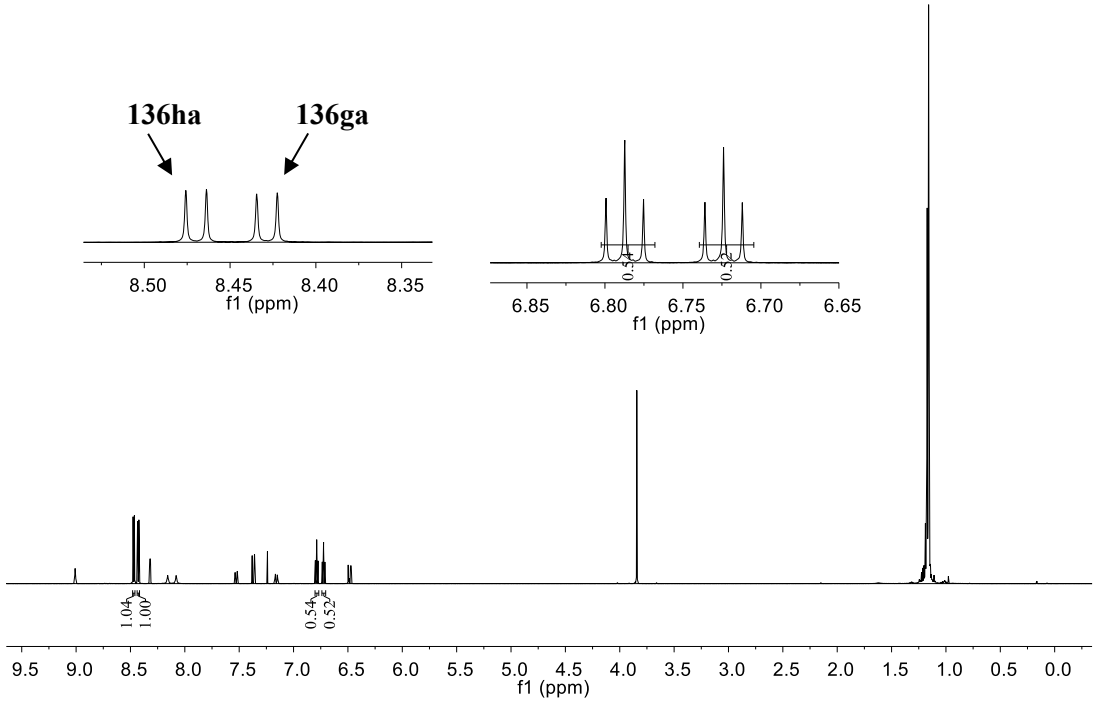
pressure. Isolation by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) afforded a mixture of **136fa** and **136ha** with the ratio being determined by ^{1}H-NMR spectroscopy.

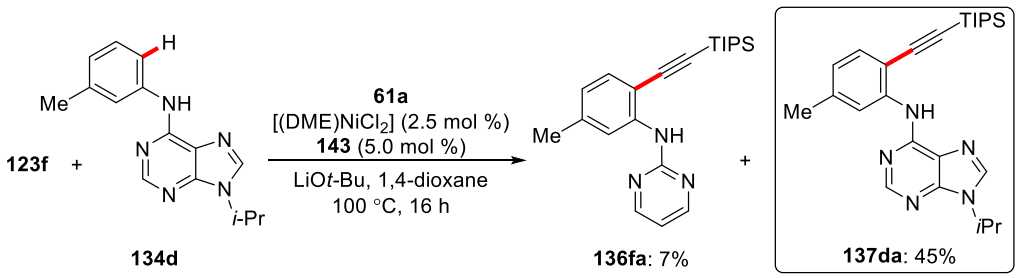




N-(3-Methoxyphenyl)pyrimidin-2-amine (**123g**) (101 mg, 0.50 mmol), *N*-[3-(trifluoromethyl)phenyl]pyrimidin-2-amine (**123h**) (120 mg, 0.50 mmol), [(DME)$NiCl_2$] (2.8 mg, 2.5 mol %) and LiO*t*-Bu (80 mg, 1.00 mmol) were placed in a 25 mL Schlenk tube. The tube was degassed and purged with N_2 for three times. D*t*-BEDA (**143**) (5.5 µL, 5.0 mol %), alkyne **61a** (130 mg, 0.5 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 100 °C for 16 h. At ambient temperature, CH_2Cl_2 (2 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced

pressure. Isolation by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) afforded a mixture of **136ga** and **136ha** with the ratio being determined by ^{1}H-NMR spectroscopy.

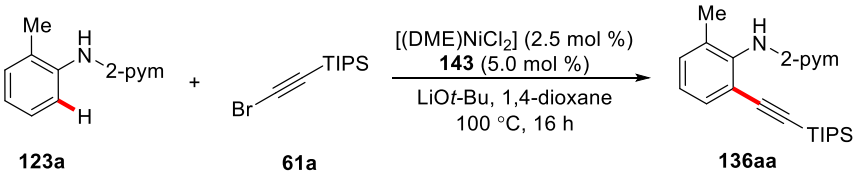




N-(*m*-Tolyl)pyrimidin-2-amine (**123f**) (93 mg, 0.5 mmol), 9-isopropyl-*N*-{5-methyl-2-[(triisopropylsilyl)ethynyl]phenyl}-9*H*-purin-6-amine (**134d**) (134 mg, 0.5 mmol), [(DME)$NiCl_2$] (2.8 mg, 2.5 mol %) and LiO*t*-Bu (80 mg, 1.0 mmol) were placed in a 25 mL Schlenk tube. The tube was degassed and purged with N_2 for three times. D*t*-BEDA (**143**) (5.5 μL, 5.0 mol %), alkyne **61a** (130 mg, 0.5 mmol) and 1,4-dioxane (1.5 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, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated

under reduced pressure. Isolation by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1 → 4/1) afforded **136fa** (10mg, 7%) and **137da** (101 mg, 45%).

Radical scavengers

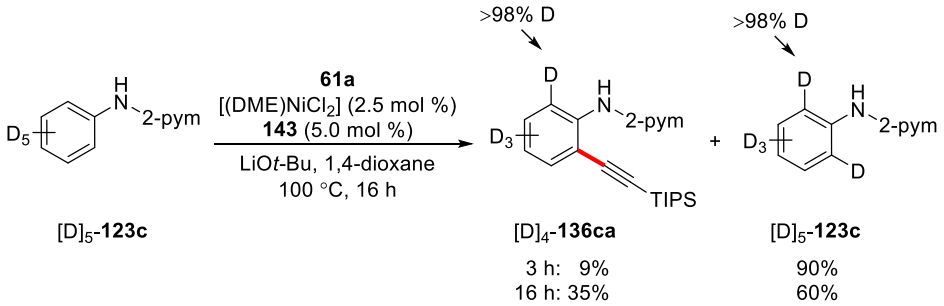


additive (1.0 equiv)	Yield
---	61%
TEMPO	58%
BHT	36%
galvinoxyl	16%

N-(*o*-Tolyl)pyrimidin-2-amine **123a** (93 mg, 0.50 mmol), [(DME)$NiCl_2$] (2.8 mg, 2.5 mol %), additive (1.0 equiv, 0.50 mmol) and LiO*t*-Bu (80 mg, 1.0 mmol) were placed in a 25 mL Schlenk tube. The tube was degassed and purged with N_2 three times. D*t*-BEDA (**143**) (5.5 μL, 5.0 mol %), alkyne **61a** (261 mg, 1.00 mmol) and 1,4-dioxane (1.5 mL) were then added, and the mixture was stirred at 100 °C for 16 h. After cooling to ambient temperature, CH_2Cl_2 (2.0 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure, purified by column chromatography on silica gel to afford the desired product **136aa**.

H/D Exchange Experiments

Following the general procedure **E**, $[D]_5$-**123c** (88 mg, 0.5 mmol) was reacted with **61a** (157 mg, 0.6mmol). After 3.5 h or 16 h, the reaction was cooled to ambient temperature, CH_2Cl_2 (2.0 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure, purified by column chromatography on silica gel to afford the desired product $[D]_4$-**136ca** and reisolated $[D]_5$-**123c.**



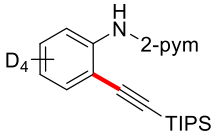
[D]$_5$-**123c**

[D]$_4$-**136ca**

3 h: 9%
16 h: 35%

[D]$_5$-**123c**

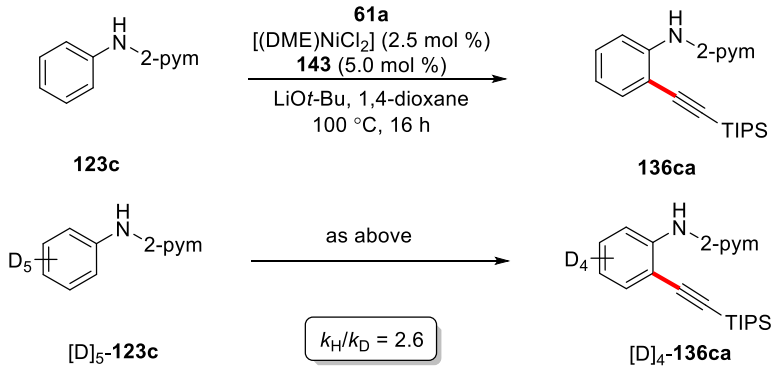
90%
60%



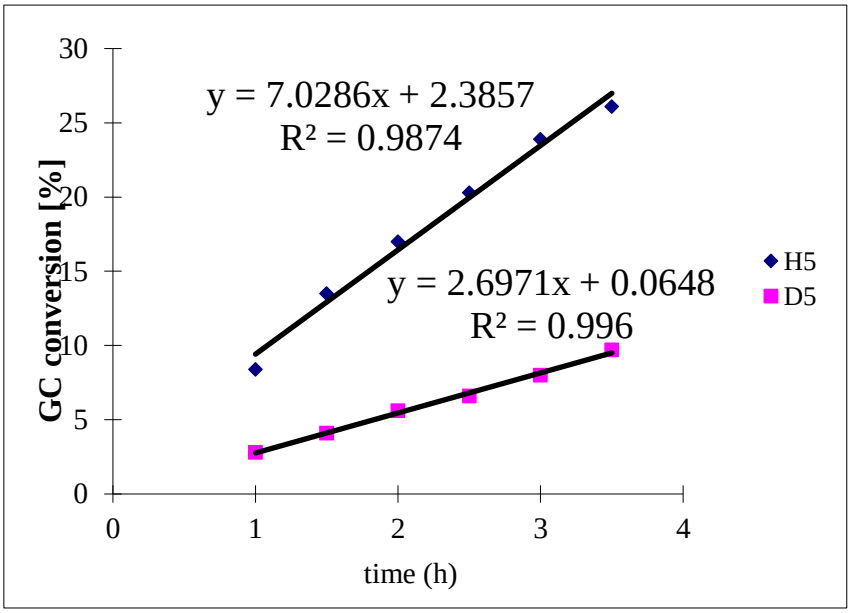
[D]$_4$-**136ca**

KIE Study Experiments

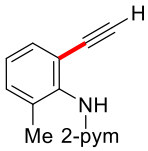
Independent parallel reactions with **123c** or [D]$_5$-**123c** were run for different reaction times. Following general procedure **E**, **123c** (86 mg, 0.5 mmol) or [D]$_5$-**123c** (88 mg, 0.5 mmol) with internal standard *n*-dodecane (85 mg, 0.5 mmol) were reacted with **61a** (157 mg, 0.6 mmol). After the reaction times indicated below, the conversion to the products **136ca** or [D]$_4$-**136ca** was monitored by GC analysis.



Time [h]	1.0	1.5	2.0	2.5	3.0	3.5
136ca [%]	8.4	13.5	17.0	20.3	23.9	26.1
D_4-136ca [%]	2.8	4.1	5.6	6.6	8.0	9.7



Diversification to access indoles



***N*-(2-Ethynyl-6-methylphenyl)pyrimidin-2-amine (136aa')**: To a solution of **136aa** (73 mg, 0.2 mmol) in dry THF (1.0 mL) and H_2O (0.05 mL) was added TBAF in THF (1M, 3.0 ml) at

23 °C and stirred for 10 minutes. H_2O (5 mL) was added and the mixture was extracted with EtOAc (3 × 7.0 mL). The organic layer was combined, washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 4/1) to afford the desired product **136aa'** (41 mg, 98%) as a yellow solid.

M. p. = 105–106 °C.

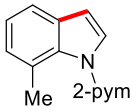
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.35 (d, J = 4.8 Hz, 2H), 7.39 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.13 (dd, J = 7.6, 7.6 Hz, 1H), 6.99 (s, 1H), 6.65 (t, J = 4.8 Hz, 1H), 3.19 (s, 1H), 2.25 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.2 (C_q), 158.2 (CH), 138.8 (C_q), 136.3 (C_q), 131.7 (CH), 130.6 (CH), 126.1 (CH), 119.6 (C_q), 112.2 (CH), 82.2 (CH), 80.8 (C_q), 18.9 (CH_3).

IR (neat): 3283, 3212, 2957, 2924, 1573, 1510, 1443, 1406, 1259, 634 cm^{-1}.

MS (EI) *m/z* (relative intensity) 209 (90) [M^+], 194 (100).

HR-MS (ESI) *m/z* calcd for $C_{13}H_{11}N_3$ [M^+] 209.0953, found 209.0961.



7-Methyl-1-(pyrimidin-2-yl)-1*H*-indole (149a): *N*-(2-Ethynyl-6-methylphenyl)pyrimidin-2-amine (**136aa'**) (21 mg, 0.1mmol) and $Cu(OAc)_2$ (2.0 mg, 0.01 mmol) were placed in a 10 mL Schlenk tube.The tube was degassed and purged with N_2 three times, then DCE (2.0 mL) was added, and the mixture was stirred at 85 °C for 2 h. At ambient temperature, CH_2Cl_2 (2 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure, purified by column chromatography on silica gel (*n*-hexane/EtOAc: 4/1) to afford the desired product **149a** (17 mg, 85%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.73 (d, J = 4.8 Hz, 2H), 7.78 (d, J = 3.6 Hz, 1H), 7.48 (dd, J = 7.7, 1.5 Hz, 1H), 7.15 (dd, J = 7.7, 7.4 Hz, 1H), 7.12 (t, J = 4.8 Hz, 1H), 6.69 (dd, J = 7.4, 1.5 Hz, 1H), 2.40 (s, 3H).

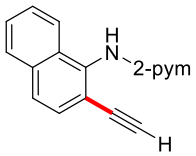
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2 (CH), 158.1 (C_q), 134.7 (C_q), 131.8 (C_q), 129.8 (CH), 126.6 (CH), 124.2 (C_q), 122.2 (CH), 118.7 (CH), 117.3 (CH), 107.0 (CH), 22.2 (CH_3).

IR (neat): 3042, 2965, 2926, 1697, 1561, 1412, 1348, 1227, 1078, 720 cm^{-1}.

MS (EI) *m/z* (relative intensity) 209 (85) [M^+], 208 (100), 130 (20).

HR-MS (ESI) *m/z* calcd for $C_{13}H_{11}N_3$ [M^+] 209.0953, found 209.0958.

The analytical data are in accordance with those previously published in the literature.[166]



***N*-(2-Ethynylnaphthalen-1-yl)pyrimidin-2-amine (136sa')**

To a solution of **136sa** (80 mg, 0.2mmol) in THF (1.0 mL) and H_2O (0.05 mL) was added TBAF in THF (1M, 3.0 ml) at 23 °C and stirred for 10 minutes. H_2O (5.0 mL) was added and the mixture was extracted with EtOAc (3 × 7.0 mL). The organic layer was combined, washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 4/1) to afford the desired product **136sa'** (48 mg, 97%) as a yellow solid.

M. p. = 181–182 °C.

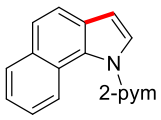
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.32 (d, J = 4.8 Hz, 2H), 7.99–7.92 (m, 1H), 7.87–7.80 (m, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.53–7.41 (m, 3H), 6.66 (t, J = 4.8 Hz, 1H), 3.30 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.2 (C_q), 158.2 (CH), 138.0 (C_q), 134.3 (C_q), 130.5 (C_q), 128.6 (CH), 128.2 (CH), 127.0 (CH), 126.8 (CH), 126.6 (CH), 124.4 (CH), 116.8 (C_q), 112.4 (CH), 83.3 (C_q), 81.2 (C_q).

IR (neat): 3236, 1596, 1512, 1445, 1415, 1379, 818, 787, 557 cm^{-1}.

MS (EI) *m/z* (relative intensity) 245 (100) [M^+], 218 (70).

HR-MS (ESI) *m/z* calcd for $C_{16}H_{11}N_3$ [M^+] 245.0953, found 245.0946.



1-(Pyrimidin-2-yl)-1*H*-benzo[*g*]indole (149s): *N*-(2-Ethynylnaphthalen-1-yl)pyrimidin-2-amine (**136sa'**) (25 mg, 0.10 mmol) and $Cu(OAc)_2$ (2.0 mg, 0.01 mmol) were placed in a 10 mL Schlenk tube. The tube was degassed and purged with N_2 three times, then DCE (2.0 mL) was added, and the mixture was stirred at 85 °C for 2 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure, purified by column chromatography on silica gel (*n*-hexane/EtOAc: 4/1) to afford the desired product **149s** (21 mg, 84%) as a colorless liquid.

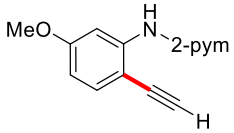
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.81 (d, J = 4.8 Hz, 2H), 7.94 (dd, J = 8.4, 1.4 Hz, 1H), 7.91 (dd, J = 8.0, 1.4 Hz, 1H), 7.84 (d, J = 3.4 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.39 (ddd, J = 8.0, 6.9, 1.3 Hz, 1H), 7.33 (ddd, J = 8.4, 6.9, 1.6 Hz, 1H), 7.24 (d, J = 4.8 Hz, 1H), 6.81 (d, J = 3.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.1 (C_q), 158.7 (CH), 132.1 (C_q), 129.8 (C_q), 129.5 (CH), 129.0 (CH), 128.8 (C_q), 124.3 (CH), 124.0 (CH), 123.9 (CH), 123.7 (CH), 123.1 (C_q), 120.4 (CH), 118.3 (CH), 107.6 (CH).

IR (neat): 3039, 1708, 1592, 1507, 1339, 1198, 805, 727cm^{-1}.

MS (EI) *m/z* (relative intensity) 245 (100) [M^+], 139 (15).

HR-MS (ESI) *m/z* calcd for $C_{16}H_{11}N_3$ [M^+] 245.0953, found 245.0957.



***N*-(2-Ethynyl-5-methoxyphenyl)pyrimidin-2-amine (136ga')**: To a solution of **136ga** (76 mg, 0.2 mmol) in dry THF (1.0 mL) and H_2O (0.05 mL) was added TBAF in THF (1M, 3.0 ml) at 23 °C and stirred for 10 minutes. H_2O (5.0 mL) was added and the mixture was extracted with EtOAc (3 × 7 mL). The organic layer was combined, washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 4/1) to afford the desired product **136ga'** (44 mg, 98%) as a light yellow solid.

M. p. = 113–114 °C.

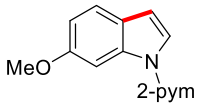
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.45 (d, J = 4.8 Hz, 2H), 8.32 (d, J = 2.5 Hz, 1H), 7.96 (brs, 1H), 7.37 (d, J = 8.5 Hz, 1H), 6.76 (t, J = 4.8 Hz, 1H), 6.50 (dd, J = 8.6, 2.5 Hz, 1H), 3.84 (s, 3H), 3.45 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.8 (C_q), 159.6 (C_q), 157.8 (CH), 142.6 (C_q), 133.2 (CH), 113.2 (CH), 107.2 (CH), 103.8 (CH), 102.6 (C_q), 83.0 (CH), 79.9 (C_q), 55.4 (CH).

IR (neat): 3390, 3164, 1577, 1446, 1401, 1254, 858, 787, 599 cm^{-1}.

MS (EI) *m/z* (relative intensity) 225 (100) [M^+], 210 (50).

HR-MS (ESI) *m/z* calcd for $C_{13}H_{11}N_3O$ [M^+] 225.0902, found 225.0900.



6-Methoxy-1-(pyrimidin-2-yl)-1*H*-indole (149g): *N*-(2-Ethynyl-5-methoxyphenyl)pyrimidin-2-amine (**136ga'**) (23 mg, 0.10 mmol) and $Cu(OAc)_2$ (2.0 mg, 0.01 mmol) were placed in a 10 mL Schlenk tube. The tube was degassed and purged with N_2 three times, then DCE (2.0 mL) was added, and the mixture was stirred at 85 °C for 2 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure, purified by column chromatography on silica gel (*n*-hexane/EtOAc: 4/1) to afford the desired product **149g** (19 mg, 82%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.67 (d, J = 4.8 Hz, 2H), 8.43 (d, J = 2.4 Hz, 1H), 8.15 (d, J = 3.7 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.01 (t, J = 4.8 Hz, 1H), 6.88 (d, J = 8.6 Hz, 1H), 6.61 (d, J = 3.7 Hz, 1H), 3.92 (s, 3H).

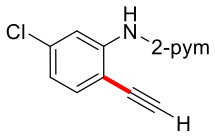
^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.0 (CH), 157.8 (C_q), 157.3 (C_q), 136.2 (C_q), 125.3 (C_q), 124.7 (CH), 121.0 (CH), 115.9 (CH), 111.0 (CH), 106.7 (CH), 101.0 (CH), 55.8 (CH_3).

IR (neat): 3126, 2937, 2832, 1575, 1438, 1269, 1074, 921, 795 cm^{-1}.

MS (EI) *m/z* (relative intensity) 225 (100) [M^+], 182 (60).

HR-MS (ESI) *m/z* calcd for $C_{13}H_{11}N_3O$ [M^+] 225.0902, found 225.0896.

The analytical data are in accordance with those previously published in the literature.[167]



***N*-(5-Chloro-2-ethynylphenyl)pyrimidin-2-amine (136qa')**: To a solution of **136qa** (77 mg, 0.20 mmol) in dry THF (1.0 mL) and H_2O (0.05 mL) was added 1.0 mol/L TBAF in THF (3.0 mL) at 23 °C and stirred for 10 minutes. H_2O (5 mL) was added and the mixture was extracted with EtOAc (3 × 7.0 mL). The organic layer was combined, washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporatedand the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 4/1) to afford the desired product **136qa'** (45 mg, 98%) as a yellow solid.

M. p. = 159–160 °C.

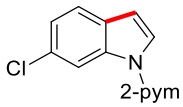
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.74 (d, J = 2.1 Hz, 1H), 8.47 (d, J = 4.8 Hz, 2H), 7.95 (br s, 1H), 7.36 (d, J = 8.3 Hz, 1H), 6.91 (dd, J = 8.3, 2.1 Hz, 1H), 6.80 (t, J = 4.8 Hz, 1H), 3.55 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.3 (C_q), 157.9 (CH), 142.2 (C_q), 135.9 (C_q), 133.0 (CH), 121.3 (CH), 117.8 (CH), 113.7 (CH), 108.4 (C_q), 85.1 (CH), 78.9 (C_q).

IR (neat): 3372, 3193, 1524, 1397, 1242, 941, 777, 584 cm^{-1}.

MS (EI) *m/z* (relative intensity) 229 (75) [M^+], 228 (100).

HR-MS (ESI) *m/z* calcd for $C_{12}H_8ClN_3$ [M^+] 229.0407, found 229.0406.



6-Chloro-1-(pyrimidin-2-yl)-1*H*-indole (149q): *N*-(5-Chloro-2-ethynylphenyl)pyrimidin-2-amine (**136qa'**) (23 mg, 0.10 mmol) and $Cu(OAc)_2$ (2.0 mg, 0.01 mmol) were placed in a 10 mL Schlenk tube. The tube was degassed and purged with N_2 three times, then DCE (2.0 mL) was added, and the mixture was stirred at 85 °C for 16 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure, purified by column chromatography on silica gel (*n*-hexane/EtOAc: 4/1) to afford the desired product **149q** (18 mg, 78%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.86 (d, *J* = 2.0 Hz, 1H), 8.69 (d, *J* = 4.8 Hz, 2H), 8.24 (d, *J* = 3.7 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.20 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.06 (t, *J* = 4.8 Hz, 1H), 6.65 (d, *J* = 3.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.2 (CH), 157.4 (C_q), 135.6 (C_q), 129.7 (C_q), 129.4 (C_q), 126.4 (CH), 122.6 (CH), 121.4 (CH), 116.5 (CH), 116.4 (CH), 106.6 (CH).

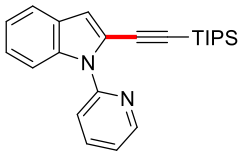
IR (neat): 3145, 3116, 1574, 1521, 1437, 1201, 1146, 795 cm^{-1}.

MS (EI) *m/z* (relative intensity) 229 (100) [M^+], 176 (15).

HR-MS (ESI) *m/z* calcd for $C_{12}H_8ClN_3$ [M^+] 229.0407, found 229.0403.

The analytical data are in accordance with those previously published in the literature.[168]

5.3.4 Characterization Data: Manganese-Catalyzed C–H Alkynylation: Expedient Peptide Synthesis and Modification of Peptides



1-(Pyridin-2-yl)-2-[(triisopropylsilyl)ethynyl]-1*H*-indole (138aa): The general procedure **F** was followed using substrate **83a** (97 mg, 0.5 mmol) and **61a** (157 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **138aa** (159 mg, 85%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.64 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.80 (ddd, *J* = 8.1, 7.4, 1.9 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.68 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.60 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.29–7.24 (m, 2H), 7.18 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.01 (s, 1H), 1.28–0.84 (m, 21H).

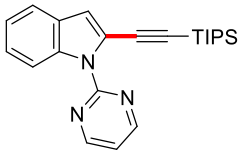
^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.1 (C_q), 148.8 (CH), 137.7 (CH), 136.6 (C_q), 127.7 (C_q), 124.3 (CH), 121.6 (CH), 121.5 (CH), 120.8 (CH), 120.7 (C_q), 120.6 (CH), 112.4 (CH), 112.1 (CH), 98.4 (C_q), 98.2 (C_q), 18.5 (CH_3), 11.2 (CH).

IR (neat): 2944, 2864, 2149, 1559, 1466, 1448, 1327, 708 cm^{-1}.

MS (EI) *m/z* (relative intensity) 374 (25) [M^+], 331 (100), 289 (33).

HR-MS (EI) *m/z* calcd for $C_{24}H_{30}N_2Si$ [M^+] 374.2178, found 374.2174.

The analytical data are in accordance with those previously published in the literature.[158]



1-(Pyrimidin-2-yl)-2-[(triisopropylsilyl)ethynyl]-1*H*-indole (138ba): The general procedure **F** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61a** (157 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 9/1) yielded **138ba** (186 mg, 99%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.75 (d, J = 4.8 Hz, 2H), 8.30 (dd, J = 8.5, 0.9 Hz, 1H), 7.58 (dd, J = 8.0, 1.0 Hz, 1H), 7.34 (ddd, J = 8.5, 7.1, 1.3 Hz, 1H), 7.23 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H), 7.12 (t, J = 4.8 Hz, 1H), 7.10 (s, 1H), 1.15–1.14 (m, 21H).

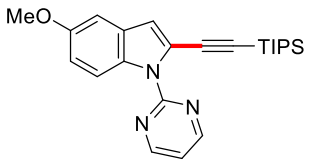
^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.9 (CH), 157.2 (C_q), 136.1 (C_q), 128.4 (C_q), 124.7 (CH), 122.3 (CH), 120.8 (C_q), 120.6 (CH), 117.5 (CH), 115.6 (CH), 114.0 (CH), 98.7 (C_q), 97.7 (C_q), 18.6 (CH_3), 11.3 (CH).

IR (neat): 2957, 2151, 1561, 1421, 1248, 839, 746 cm^{-1}.

MS (EI) *m/z* (relative intensity) 375 (30) [M^+], 332 (100).

HR-MS (ESI) *m/z* calcd for $C_{23}H_{30}N_3Si$ [$M+H^+$] 375.2131, found 375.2125.

The analytical data are in accordance with those previously published in the literature.[158]



5-Methoxy-1-(pyrimidin-2-yl)-2-[(triisopropylsilyl)ethynyl]-1*H*-indole (138ca): The general procedure **F** was followed using substrate **83c** (113 mg, 0.5 mmol) and **61a** (157 mg, 0.6 mmol). Isolation by column chromatography (*n*-pentane/EtOAc: 9/1) yielded **138ca** (158 mg, 78%) as a white solid.

M. p. = 115–116 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.73 (d, J = 4.8 Hz, 2H), 8.22 (dd, J = 9.0, 0.7 Hz, 1H), 7.11 (t, J = 4.8 Hz, 1H), 6.99–6.97 (m, 2H), 6.94 (dd, J = 9.0, 2.6 Hz, 1H), 3.83 (s, 3H), 1.12–1.13 (m, 21H).

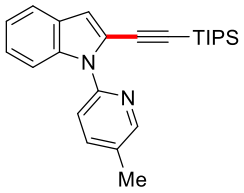
^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.9 (CH), 157.3 (C_q), 155.6 (C_q), 131.1 (C_q), 129.2 (C_q), 121.2 (C_q), 117.3 (CH), 115.6 (CH), 115.3 (CH), 114.4 (CH), 102.1 (CH), 98.9 (C_q), 97.8 (C_q), 55.6 (CH_3), 18.6 (CH_3), 11.4 (CH).

IR (neat): 2941, 2864, 2144, 1561, 1417, 1207, 660 cm^{-1}.

MS (EI) *m/z* (relative intensity) 405 (35) [M^+], 362 (100).

HR-MS (EI) *m/z* calcd for $C_{24}H_{31}N_3OSi$ [M^+] 405.2236, found 405.2225

The analytical data are in accordance with those previously published in the literature.[158]



1-(5-Methylpyridin-2-yl)-2-[(triisopropylsilyl)ethynyl]-1*H*-indole (138da): The general procedure **F** was followed using substrate **83d** (104 mg, 0.5 mmol) and **61a** (157 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 15/1) yielded **138da** (190 mg, 98%) as a colorless liquid.

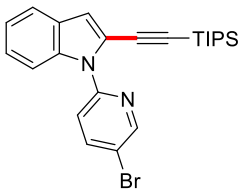
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.46 (d, J = 2.5 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.63–7.57 (m, 2H), 7.54 (d, J = 8.2 Hz, 1H), 7.26 (ddd, J = 8.4, 7.1, 1.3 Hz, 1H), 7.16 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 6.99 (s, 1H), 2.40 (s, 3H), 1.06–1.05 (m, 21H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 148.9 (CH), 148.8 (C_q), 138.1 (CH), 136.8 (C_q), 131.4 (C_q), 127.5 (C_q), 124.1 (CH), 121.2 (CH), 120.8 (C_q), 120.7 (CH), 120.1 (CH), 111.8 (CH), 111.8 (CH), 98.4 (C_q), 98.0 (C_q), 18.6 (CH_3), 18.0 (CH_3), 11.4 (CH).

IR (neat): 2941, 2863, 2147, 1597, 1446, 720 cm^{-1}.

MS (EI) *m/z* (relative intensity) 388 (30) [M^+], 345 (100), 303 (33).

HR-MS (EI) *m/z* calcd for $C_{25}H_{32}N_2Si$ [M^+] 388.2335, found 388.2327.



1-(5-Bromopyridin-2-yl)-2-[(triisopropylsilyl)ethynyl]-1*H*-indole (138ea): The general procedure **F** was followed using substrate **83e** (136 mg, 0.5 mmol) and **61a** (157 mg, 0.6 mmol). Isolation by column chromatography (*n*-pentane/EtOAc: 15/1) yielded **138ea** (165 mg, 73%) as a colorless liquid.

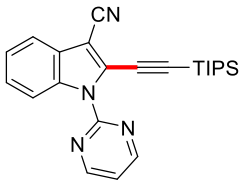
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.68 (dd, J = 2.5, 0.7 Hz, 1H), 7.89 (dd, J = 8.6, 2.5 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.66–7.56 (m, 2H), 7.28 (ddd, J = 8.4, 7.1, 1.3 Hz, 1H), 7.19 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H), 7.02 (s, 1H), 1.08–1.07 (m, 21H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 149.6 (CH), 149.5 (C_q), 140.1 (CH), 136.3 (C_q), 127.7 (C_q), 124.5 (CH), 121.8 (CH), 121.4 (CH), 120.8 (CH), 120.4 (C_q), 117.7 (C_q), 113.1 (CH), 112.1 (CH), 99.1 (C_q), 97.9 (C_q), 18.6 (CH_3), 11.3 (CH).

IR (neat): 2941, 2863, 2146, 1572, 1446, 1381, 714 cm^{-1}.

MS (EI) *m/z* (relative intensity) 452 (23) [M$^+$] (^{79}Br), 454 (25) [M$^+$] (^{81}Br), 411 (100) (^{81}Br), 409 (95) (^{79}Br).

HR-MS (EI) *m/z* calcd for $C_{24}H_{29}BrN_2Si$ [M$^+$] 452.1283 (^{79}Br), found 452.1277 (^{79}Br).



1-(Pyrimidin-2-yl)-2-[(triisopropylsilyl)ethynyl]-1*H*-indole-3-carbonitrile (138fa): The general procedure **F** was followed using substrate **83f** (73 mg, 0.5 mmol) and **61a** (157 mg, 0.6 mmol) at 100 °C. Isolation by column chromatography (*n*-pentane/EtOAc: 9/1) yielded **138fa** (140 mg, 70%) as a white solid.

M. p. = 78–80 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.83 (d, J = 4.8 Hz, 2H), 8.86 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.44–7.33 (m, 2H), 7.31 (t, J = 4.8 Hz, 1H), 1.14–1.13 (m, 21H).

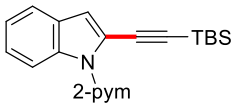
^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.3 (CH), 156.3 (C_q), 134.8 (C_q), 127.8 (C_q), 127.0 (C_q), 126.3 (CH), 124.1 (CH), 119.4 (CH), 119.0 (CH), 114.7 (CH), 114.3 (C_q), 106.7 (C_q), 98.6 (C_q), 94.8 (C_q), 18.7 (CH_3), 11.3 (CH).

IR (neat): 2940, 2862, 2226, 2156, 1566, 1414, 657 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 439 (6) [M+K^+], 423 (23) [M+Na^+], 401(100) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{24}H_{29}N_4Si$ [M+H^+] 401.2161, found 401.2156.

The analytical data are in accordance with those previously published in the literature.[169]



1-(Pyrimidin-2-yl)-2-[(tri-*n*-butylsilyl)ethynyl]-1*H*-indole (138bb): The general procedure **F** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61b** (182 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **138bb** (204 mg, 98%) as a colorless liquid.

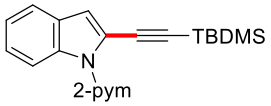
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.80 (d, *J* = 4.8 Hz, 2H), 8.26 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.58 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.33 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.27–7.21 (m, 1H), 7.19 (t, *J* = 4.8 Hz, 1H), 7.06 (s, 1H), 1.41–1.35 (m, 12H), 0.91 (t, *J* = 7.1 Hz, 9H), 0.75–0.60 (m, 6H).

^{13}C NMR (76 MHz, $CDCl_3$) δ = 158.0 (CH), 157.3 (C_q), 136.1 (C_q), 128.5 (C_q), 124.8 (CH), 122.3 (CH), 120.8 (CH), 120.8 (C_q), 117.6 (CH), 115.5 (CH), 113.9 (CH), 99.6 (C_q), 97.9 (C_q), 26.5 (CH_2), 26.1 (CH_2), 13.8 (CH_3), 13.0 (CH_2).

IR (neat): 2955, 2869, 2153, 1577, 1447,1409, 784 cm^{-1}.

MS (EI) *m/z* (relative intensity) 417 (80) [M^+], 222 (100).

HR-MS (EI) *m/z* calcd for $C_{26}H_{35}N_3Si$ [M^+] 417.2600, found 417.2599.



2-[(*tert*-Butyldimethylsilyl)ethynyl]-1-(pyrimidin-2-yl)-1*H*-indole (138bc): The general procedure **F** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61c** (132 mg, 0.6 mmol).

Isolation by column chromatography (*n*-hexane/EtOAc: 20/1) yielded **138bc** (143 mg, 86%) as a white solid.

M. p. = 66–67 °C.

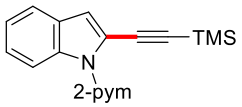
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.77 (d, *J* = 4.8 Hz, 2H), 8.28 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.57 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.32 (ddd, *J* = 8.5, 7.1, 1.3 Hz, 1H), 7.21 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 7.15 (t, *J* = 4.8 Hz, 1H), 7.06 (s, 1H), 0.98 (s, 9H), 0.19 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.0 (CH), 157.2 (C_q), 136.1 (C_q), 128.4 (C_q), 124.8 (CH), 122.4 (CH), 120.8 (CH), 120.7 (C_q), 117.6 (CH), 115.6 (CH), 114.1 (CH), 99.5 (C_q), 97.6 (C_q), 26.1 (CH_3), 16.8 (C_q), -4.72 (CH_3).

IR (neat): 2950, 2929, 2856, 2148, 1573, 1416, 1250, 835 cm^{-1}.

MS (EI) *m/z* (relative intensity) 333 (25) [M^+], 276 (100).

HR-MS (EI) *m/z* calcd for $C_{20}H_{23}N_3Si$ [M^+] 333.1661, found 333.1660.



1-(Pyrimidin-2-yl)-2-[(trimethylsilyl)ethynyl]-1*H*-indole (138bd): The general procedure **F** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61d** (106 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **138bd** (130 mg, 89%) as brown solid.

M. p. = 75–76 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.77 (d, *J* = 4.8 Hz, 2H), 8.28 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.58 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.33 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.21 (ddd, *J* = 7.7, 7.1, 1.3 Hz, 1H), 7.14 (t, *J* = 4.8 Hz, 1H), 7.06 (s, 1H), 0.25 (s, 9H).

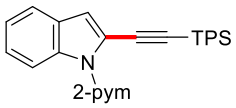
^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.9 (CH), 157.1 (C_q), 136.1 (C_q), 128.3 (C_q), 124.9 (CH), 122.3 (CH), 120.8 (CH), 120.5 (C_q), 117.6 (CH), 115.3 (CH), 114.0 (CH), 101.0 (C_q), 97.1 (C_q), -0.28 (CH_3).

IR (neat): 3091, 2962, 2149, 1563, 1448, 1420, 831 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 314(100) [$M+Na^+$], 292 (80) [$M+H^+$].

HR-MS (ESI) *m/z* calcd for $C_{17}H_{18}N_3Si$ [$M+H^+$] 292.1265, found 292.1265.

The analytical data are in accordance with those previously published in the literature.[158]



1-(Pyrimidin-2-yl)-2-[(triphenylsilyl)ethynyl]-1*H*-indole (138be): The general procedure **F** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61e** (218 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **138be** (237 mg, 99%) as a light yellow solid.

M. p. = 114–115 °C.

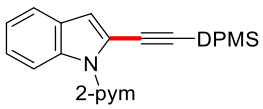
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.64 (d, J = 4.8 Hz, 2H), 8.42 (dd, J = 8.5, 0.9 Hz, 1H), 7.86–7.79 (m, 6H), 7.65 (dd, J = 7.8, 1.0 Hz, 1H), 7.54–7.37 (m, 12H), 7.32–7.28 (m, 1H), 7.27 (s, 1H), 7.07 (t, J = 4.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.9 (CH), 157.1 (C_q), 136.3 (C_q), 135.6 (CH), 133.5 (C_q), 129.9 (CH), 128.3 (C_q), 127.9 (CH), 125.2 (CH), 122.5 (CH), 120.9 (CH), 120.2 (C_q), 117.5 (CH), 116.5 (CH), 114.4 (CH), 101.7 (C_q), 95.9 (C_q).

IR (neat): 2943, 2865, 2148, 1563, 1447, 1112, 697 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 478 (20) [$M+H^+$].

HR-MS (ESI) *m/z* calcd for $C_{32}H_{24}N_3Si$ [$M+H^+$] 478.1734, found 478.1725.



2-[(Methyldiphenylsilyl)ethynyl]-1-(pyrimidin-2-yl)-1*H*-indole (138bf): The general procedure **F** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61f** (181 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **138bf** (203 mg, 98%) as a yellow solid.

M. p. = 99–100 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.67 (d, J = 4.8 Hz, 2H), 8.40 (dd, J = 8.5, 0.9 Hz, 1H), 7.83–7.75 (m, 4H), 7.65 (dd, J = 7.9, 1.0 Hz, 1H), 7.49–7.37 (m, 7H), 7.29 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H), 7.23 (s, 1H), 7.08 (t, J = 4.8 Hz, 1H), 0.85 (s, 3H).

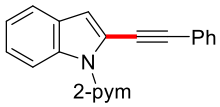
^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.9 (CH), 157.1 (C_q), 136.2 (C_q), 135.2 (C_q), 134.6 (CH), 129.6 (CH), 128.3 (C_q), 127.8 (CH), 125.1 (CH), 122.5 (CH), 120.9 (CH), 120.2 (C_q), 117.5 (CH), 116.2 (CH), 114.3 (CH), 100.4 (C_q), 97.2 (C_q), -2.2 (CH_3).

IR (neat): 3000, 2148, 1561, 1422, 1112, 806, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity) 415 (73) [M^+], 338 (15).

HR-MS (EI) *m/z* calcd for $C_{27}H_{21}N_3Si$ [M^+] 415.1505, found 415.1492.

The analytical data are in accordance with those previously published in the literature.[158]



2-(Phenylethynyl)-1-(pyrimidin-2-yl)-1*H*-indole (150bg): The general procedure **G** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61g** (108 mg, 0.6 mmol) for 1 h. Isolation by column chromatography (*n*-pentane/EtOAc: 5/1) yielded **150bg** (141 mg, 95%) as a colorless oil.

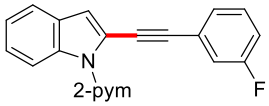
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.85 (d, *J* = 4.9 Hz, 2H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.52–7.48 (m, 2H), 7.35–7.31 (m, 4H), 7.25–7.21 (m, 1H), 7.21 (t, *J* = 4.9 Hz, 1H), 7.08 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.1 (CH), 157.4 (C_q), 136.4 (C_q), 131.3 (CH), 128.8 (C_q), 128.4 (CH), 128.3 (CH), 124.8 (CH), 123.3 (C_q), 122.4 (CH), 120.9 (C_q), 120.8 (CH), 117.7 (CH), 114.6 (CH), 114.1 (CH), 95.0 (C_q), 82.5 (C_q).

IR (neat): 3048, 2963, 2851, 1560, 1418, 1081, 741, 686, 521 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 296 (5) [M^+], 214 (11), 196 (100), 173 (20), 149 (15).

HR-MS (ESI) *m/z* calcd for $C_{20}H_{14}N_3$ [$M+H^+$] 296.1182, found 296.1188.



2-[(3-Fluorophenyl)ethynyl]-1-(pyrimidin-2-yl)-1*H*-indole (150bh): The general procedure **G** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61h** (120 mg, 0.6 mmol) for 1 h.

Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **150bh** (130 mg, 83%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.83 (d, J = 4.8 Hz, 2H), 8.35 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.31–7.22 (m, 3H), 7.21–7.15 (m, 2H), 7.11 (s, 1H), 7.05–7.00 (m, 1H).

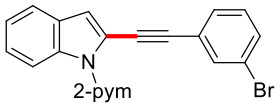
^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.3 (C_q, $^1J_{C\text{-}F}$ = 246.6 Hz), 158.0 (CH), 157.3 (C_q), 136.4 (C_q), 129.9 (CH, $^3J_{C\text{-}F}$ = 8.7 Hz), 128.6 (C_q), 127.1 (CH, $^4J_{C\text{-}F}$ = 3.0 Hz), 125.1 (C_q, $^3J_{C\text{-}F}$ = 9.6 Hz), 125.0 (CH), 122.5 (CH), 120.8 (CH), 120.3 (C_q), 118.0 (CH), 117.9 (CH, $^2J_{C\text{-}F}$ = 22.8 Hz), 115.6 (CH, $^2J_{C\text{-}F}$ = 21.2 Hz), 115.1 (CH), 114.2 (CH), 93.6 (C_q, $^4J_{C\text{-}F}$ = 3.4 Hz), 83.5 (C_q).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -112.8 (ddd, J = 9.6, 9.6, 3.9 Hz).

IR (neat): 3065, 2208, 1711, 1561, 1419, 1333, 727 cm^{-1}.

MS (EI) *m/z* (relative intensity) 313 (83) [M^+], 156 (15).

HR-MS (EI) *m/z* calcd for $C_{20}H_{13}FN_3$ [$M+H^+$] 313.1015, found 313.1012.



2-[(3-Bromophenyl)ethynyl]-1-(pyrimidin-2-yl)-1*H*-indole (150bi): The general procedure **G** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61i** (156 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **150bi** (150 mg, 80%) as a colorless liquid.

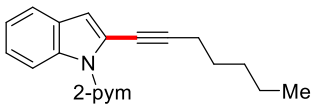
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.81 (d, J = 4.8 Hz, 2H), 8.36 (d, J = 8.4 Hz, 1H), 7.65 (dd, J = 1.8, 1.8 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.43 (dd, J = 7.6, 1.2 Hz, 2H), 7.36 (ddd, J = 8.4, 7.0, 1.3 Hz, 1H), 7.29–7.22 (m, 1H), 7.21–7.13 (m, 2H), 7.11 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.0 (CH), 157.2 (C_q), 136.4 (C_q), 133.8 (CH), 131.3 (CH), 129.7 (CH), 129.7 (CH), 128.6 (C_q), 125.3 (C_q), 125.0 (CH), 122.5 (CH), 122.0 (C_q), 120.8 (CH), 120.2 (C_q), 117.7 (CH), 115.2 (CH), 114.2 (CH), 93.3 (C_q), 84.0 (C_q).

IR (neat): 3054, 2929, 1987, 1906, 1885, 1450, 810 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 374 (35) [$M+H^+$] (^{79}Br), 376 (33) [$M+H^+$] (^{81}Br).

HR-MS (ESI) *m/z* calcd for $C_{20}H_{13}BrN_3$ [$M+H^+$] 374.0287 (^{79}Br), found 374.0278 (^{79}Br).



2-(Hept-1-yn-1-yl)-1-(pyrimidin-2-yl)-1*H*-indole (150bj): The general procedure **G** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61j** (105 mg, 0.6 mmol) for 1 h. Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **150bj** (101 mg, 70%) as a colorless oil.

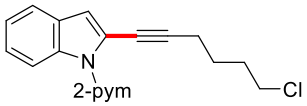
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.79 (d, J = 4.8 Hz, 2H), 8.20 (dd, J = 8.3, 1.0 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.28 (ddd, J = 8.4, 7.1, 1.4 Hz, 1H), 7.22–7.19 (m, 1H), 7.16 (t, J = 4.8 Hz, 1H), 6.91 (s, 1H), 2.45 (t, J = 7.0 Hz, 2H), 1.70–1.53 (m, 2H), 1.47–1.22 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.0 (CH), 157.3 (C_q), 136.0 (C_q), 128.6 (C_q), 124.2 (CH), 122.2 (CH), 121.5 (C_q), 120.4 (CH), 117.6 (CH), 113.6 (CH), 113.5 (CH), 96.5 (C_q), 73.2 (C_q), 31.0 (CH_2), 28.1 (CH_2), 22.2 (CH_2), 19.8 (CH_2), 14.0 (CH_3).

IR (neat): 3048, 2954, 2928, 2857, 1561, 1420, 801, 745 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 312 (46) [M+Na^+], 290 (55) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{19}H_{20}N_3$ [M+H^+] 290.1652, found 290.1651.



2-(6-Chlorohex-1-yn-1-yl)-1-(pyrimidin-2-yl)-1*H*-indole (150bk): The general procedure **G** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61k** (117 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **150bk** (81 mg, 52%) as a colorless oil.

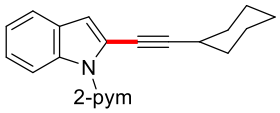
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.80 (d, J = 4.8 Hz, 2H), 8.22 (dd, J = 8.4, 0.9 Hz, 1H), 7.55 (dd, J = 7.7, 1.0 Hz, 1H), 7.29 (ddd, J = 8.5, 7.1, 1.4 Hz, 1H), 7.21 (dd, J = 7.8, 1.1 Hz, 1H), 7.16 (t, J = 4.8 Hz, 1H), 6.92 (s, 1H), 3.56 (t, J = 6.6 Hz, 2H), 2.51 (t, J = 6.8 Hz, 2H), 1.95 (tt, J = 8.7, 6.4 Hz, 2H), 1.80–1.65 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.1 (CH), 157.2 (C_q), 136.0 (C_q), 128.5 (C_q), 124.3 (CH), 122.2 (CH), 121.1 (C_q), 120.5 (CH), 117.6 (CH), 113.8 (CH), 113.7 (CH), 95.3 (C_q), 73.9 (C_q), 44.5 (CH_2), 31.5 (CH_2), 25.5 (CH_2), 19.2 (CH_2).

IR (neat): 3001, 2929, 1709, 1563, 1422, 1220, 748 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 332 (18) [M+Na^+], 310 (60) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{18}H_{17}ClN_3$ [M+H^+] 310.1106, found 310.1104.



2-(Cyclohexylethynyl)-1-(pyrimidin-2-yl)-1*H*-indole (150bl): The general procedure **G** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61l** (56 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **150bl** (110 mg, 73%) as a colorless oil.

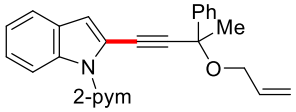
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.78 (d, *J* = 4.8 Hz, 2H), 8.20 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.28 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H), 7.20 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.15 (d, *J* = 4.8 Hz, 1H), 6.90 (d, *J* = 0.7 Hz, 1H), 2.67 (tt, *J* = 8.4, 3.7 Hz, 1H), 1.88–1.80 (m, 2H), 1.77–1.68 (m, 2H), 1.62–1.46 (m, 3H), 1.43–1.24 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.9 (CH), 157.3 (C_q), 136.0 (C_q), 128.6 (C_q), 124.1 (CH), 122.1 (CH), 121.5 (C_q), 120.4 (CH), 117.6 (CH), 113.6 (CH), 113.2 (CH), 100.2 (C_q), 73.3 (C_q), 32.2 (CH_2), 29.9 (CH), 25.9 (CH_2), 24.6 (CH_2).

IR (neat): 3046, 2926, 2851, 1561, 1418, 1217, 799, 738 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 324 (12) [M+Na^+], 302 (64) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{20}H_{20}N_3$ [M+H^+] 302.1652, found 302.1652.



2-[3-(Allyloxy)-3-phenylbut-1-yn-1-yl]-1-(pyrimidin-2-yl)-1*H*-indole (150bm): The general procedure **G** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61m** (159 mg, 0.6 mmol).

Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **150bm** (152 mg, 80%) as a colorless oil.

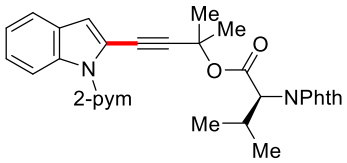
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.76 (d, *J* = 4.8 Hz, 2H), 8.37 (ddd, *J* = 8.5, 0.8, 0.8 Hz, 1H), 7.79–7.73 (m, 2H), 7.61 (ddd, *J* = 7.9, 1.3, 0.8 Hz, 1H), 7.41–7.35 (m, 3H), 7.35–7.28 (m, 1H), 7.28–7.21 (m, 1H), 7.14 (t, *J* = 4.8 Hz, 1H), 7.12 (s, 1H), 5.97 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.29 (ddt, *J* = 17.2, 1.7, 1.3 Hz, 1H), 5.15 (ddt, *J* = 10.4, 1.9, 1.3 Hz, 1H), 4.25 (ddt, *J* = 12.2, 5.5, 1.5 Hz, 1H), 3.76 (ddt, *J* = 12.2, 5.7, 1.5 Hz, 1H), 1.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.0 (CH), 157.3 (C_q), 143.1 (C_q), 136.3 (C_q), 135.0 (CH), 128.6 (C_q), 128.2 (CH), 127.7 (CH), 126.1 (CH), 124.8 (CH), 122.5 (CH), 120.7 (CH), 120.1 (C_q), 117.6 (CH), 116.4 (CH), 115.1 (CH), 114.3 (C_q), 95.2 (C_q), 80.5 (C_q), 76.7 (CH_2), 66.4 (CH_2), 32.6 (CH_3).

IR (neat): 3057, 2984, 2929, 2858, 1561, 1420, 1071, 698 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 380 (18) [$M+H^+$].

HR-MS (ESI) *m/z* calcd for $C_{25}H_{22}N_3O$ [$M+H^+$] 380.1757, found 380.1745.



2-Methyl-4-[1-(pyrimidin-2-yl)-1*H*-indol-2-yl]but-3-yn-2-yl-(*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-methylbutanoate (150bn): The general procedure **G** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61n** (235 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded **150bn** (304 mg, 60%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.78 (d, *J* = 4.8 Hz, 2H), 8.27 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.87–7.80 (m, 2H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.54 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H), 7.29 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.18 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.14 (t, *J* = 4.8 Hz, 1H), 6.97 (d, *J* = 0.8 Hz, 1H), 4.54 (d, *J* = 8.2 Hz, 1H), 2.76 (m, 1H), 1.74 (s, 3H), 1.67 (s, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H).

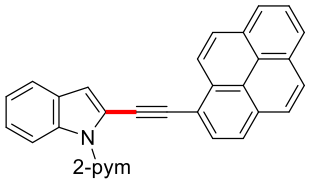
^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.7 (C_q), 166.7 (C_q), 158.0 (CH), 157.2 (C_q), 136.2 (C_q), 134.1 (CH), 131.7 (C_q), 128.5 (C_q), 124.7 (CH), 123.4 (CH), 122.3 (CH), 120.8 (CH), 120.1

(C_q), 117.6 (CH), 115.1 (CH), 114.1 (CH), 95.0 (C_q), 77.6 (C_q), 74.2 (C_q), 58.4 (CH), 28.9 (CH_3), 28.5 (CH_3), 28.3 (CH), 20.9 (CH_3), 19.6 (CH_3).

IR (neat): 2966, 2935, 1713, 1562, 1422, 1116, 716 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 529 (65) [M+Na^+], 507 (10) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{34}H_{36}N_3O_2$ [M+H^+] 507.2027, found 507.2016.



2-(Pyren-1-ylethynyl)-1-(pyrimidin-2-yl)-1*H*-indole (150bo): The general procedure **G** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61o** (183 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 6/1) yielded **150bo** (84 mg, 40%) as a yellow solid.

M. p. = 165–166 °C.

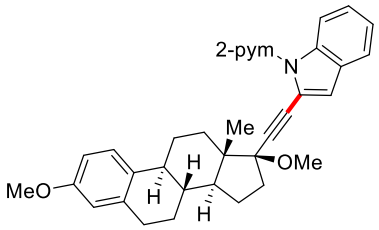
^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.94 (d, *J* = 4.8 Hz, 2H), 8.78 (d, *J* = 9.0 Hz, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 8.21 (d, *J* = 7.6 Hz, 1H), 8.19–8.18 (m, 2H), 8.15 (d, *J* = 9.1 Hz, 1H), 8.12–8.08 (m, 2H), 8.04–8.00 (m, 2H), 7.66 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.38 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.29–7.27 (m, 1H), 7.28 (t, *J* = 4.8 Hz, 1H), 7.27–7.26 (m, 1H), 7.24 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.3 (CH), 157.6 (C_q), 136.5 (C_q), 132.1 (C_q), 131.3 (C_q), 131.2 (C_q), 131.0 (C_q), 129.3 (CH), 129.0 (C_q), 128.2 (CH), 128.1 (CH), 127.2 (CH), 126.2 (CH), 125.8 (CH), 125.6 (CH), 125.5 (CH), 124.9 (CH), 124.6 (CH), 124.5 (C_q), 124.3 (C_q), 122.6 (CH), 121.0 (C_q), 120.8 (CH), 117.9 (C_q), 117.7 (CH), 115.2 (CH), 114.4 (CH), 94.6 (C_q), 88.2 (C_q).

IR (neat): 3030, 1575, 1557, 1452, 1432, 1350, 837, 729 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 442 (5) [M+Na^+], 420 (15) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{30}H_{18}N_3$ [M+H^+] 420.1495, found 420.1485.



2-{[(8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dimethoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl]ethynyl}-1-(pyrimidin-2-yl)-1*H*- indole (150bp): The general procedure **G** was followed using substrate **83b** (98 mg, 0.5 mmol) and **61p** (242 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **150bp** (254 mg, 98%) as a light yellow solid.

M. p. = 140–141 °C.

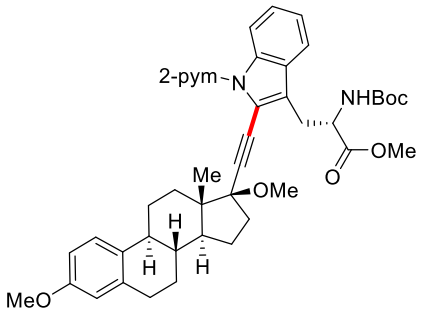
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.78 (d, J = 4.8 Hz, 2H), 8.28 (dd, J = 8.4, 0.9 Hz, 1H), 7.56 (dd, J = 7.8, 1.0 Hz, 1H), 7.31 (ddd, J = 8.5, 7.2, 1.3 Hz, 1H), 7.25–7.20 (m, 2H), 7.17 (t, J = 4.8 Hz, 1H), 7.03 (s, 1H), 6.70 (dd, J = 8.6, 2.8 Hz, 1H), 6.62 (d, J = 2.7 Hz, 1H), 3.76 (s, 3H), 3.48 (s, 3H), 2.93–2.76 (m, 2H), 2.43–2.25 (m, 2H), 2.20–1.99 (m, 3H), 1.93–1.75 (m, 4H), 1.53–1.31 (m, 4H), 0.91 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.0 (CH), 157.3 (C_q), 137.8 (C_q), 136.1 (C_q), 132.5 (C_q), 128.6 (C_q), 126.2 (CH), 124.6 (CH), 122.4 (C_q),122.3 (CH), 120.6 (C_q), 120.5 (CH), 117.5 (CH), 114.6 (CH), 114.0 (CH), 113.7 (CH), 111.4 (CH), 96.3 (C_q), 86.6 (C_q), 80.8 (C_q), 55.2 (CH_3), 53.6 (CH_3), 49.8 (CH), 48.2 (C_q), 43.6 (CH), 39.3 (CH), 36.6 (CH_2), 34.4 (CH_2), 29.9 (CH_2), 27.4 (CH_2), 26.7 (CH_2), 23.0 (CH_2), 12.9 (CH_3).

IR (neat): 2930, 2867, 1562, 1449, 1422, 1091, 805, 746 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 540 (48) [M+Na^+], 518 (10) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{34}H_{36}N_3O_2$ [M+H^+] 518.2802, found 518.2796.



Methyl-(*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-{2-{[(8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dimethoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl]ethynyl}-1-(pyrimidin-2-yl)-1*H*-indol-3-yl}propanoate (154a): The general procedure **G** was followed using substrate **153a** (198 mg, 0.5 mmol) and **61p** (242 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 4/1) yielded **154a** (235 mg, 66%) as a light yellow solid.

M. p. = 163–164 °C.

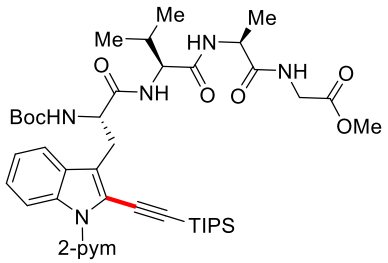
^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.77 (d, J = 4.8 Hz, 2H), 8.31 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.32 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 7.16 (t, J = 4.8 Hz, 1H), 6.69 (dd, J = 8.6, 2.8 Hz, 1H), 6.61 (d, J = 2.8 Hz, 1H), 5.19 (d, J = 7.7 Hz, 1H), 4.61 (q, J = 7.2 Hz, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 3.51 (s, 3H), 3.38 (d, J = 7.0 Hz, 2H), 2.94–2.75 (m, 2H), 2.49–2.37 (m, 1H), 2.33–2.30 (m, 1H), 2.19–2.16 (m, 1H), 2.11–2.06 (m, 2H), 1.95–1.81 (m, 4H), 1.55–1.43 (m, 4H), 1.34 (s, 9H), 0.92 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 172.7 (C_q), 158.0 (CH), 157.4 (C_q), 157.3 (C_q), 155.2 (C_q), 137.9 (C_q), 136.0 (C_q), 132.5 (C_q), 128.4 (C_q), 126.3 (CH), 125.1 (CH), 122.4 (CH), 121.8 (C_q), 119.6 (C_q), 119.0 (CH), 117.5 (CH), 114.2 (CH), 113.7 (CH), 111.4 (CH), 99.8 (C_q), 86.8 (C_q), 79.8 (C_q), 79.8 (C_q), 55.2 (CH_3), 54.0 (CH), 53.6 (CH_3), 52.3 (CH_3), 49.9 (CH), 48.1 (C_q), 43.5 (CH), 39.2 (CH), 36.8 (CH_2), 34.5 (CH_2), 29.8 (CH_2), 28.3 (CH_2), 28.2 (CH_3), 27.3 (CH_2), 26.6 (CH_2), 22.9 (CH_2), 12.8 (CH_3).

IR (neat): 2976, 2930, 2868, 1714, 1498, 1423, 1156, 745 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 741 (32) [M+Na$^+$].

HR-MS (ESI) *m/z* calcd for $C_{43}H_{50}N_4O_6Na$ [M+Na$^+$] 741.3623, found 741.3622.



Methyl-{(*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-{1-(pyrimidin-2-yl)-2-[(triisopropylsilyl)ethynyl]-1*H*-indol-3-yl}propanoyl}-*L*-valyl-L-alanylglycinate (154b): The general procedure **F** was followed using substrate **153b** (156 mg, 0.25 mmol) and **61a** (78 mg, 0.3 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 1/2) yielded **154b** (141 mg, 70%) as a white solid.

M. p. = 207–208 °C.

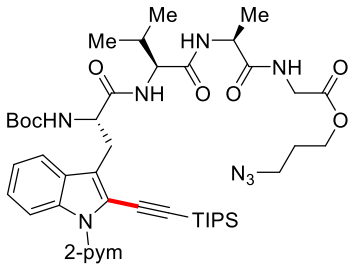
^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.77 (d, J = 4.8 Hz, 2H), 8.30 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 5.9 Hz, 1H), 7.31 (ddd, J = 8.5, 7.1, 1.3 Hz, 1H), 7.23–7.19 (m, 2H), 6.14 (d, J = 5.5 Hz, 1H), 5.82 (d, J = 2.2 Hz, 1H), 4.51 (m, 1H), 4.34 (td, J = 5.8, 2.2 Hz, 1H), 4.19 (dd, J = 17.6, 6.4 Hz, 1H), 3.92 (dd, J = 17.7, 5.2 Hz, 1H), 3.89 (dd, J = 5.6, 3.5 Hz, 1H), 3.72 (s, 3H), 3.54–3.41 (m, 2H), 2.07–2.03 (m, 1H), 1.41 (d, J = 7.4 Hz, 3H), 1.36 (s, 9H), 1.19–1.08 (m, 21H), 0.64 (d, J = 7.0 Hz, 3H), 0.29 (d, J = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 173.1 (C_q), 172.8 (C_q), 170.4 (C_q), 169.9 (C_q), 158.0 (CH), 157.0 (C_q), 156.6 (C_q), 135.8 (C_q), 127.9 (C_q), 125.8 (CH), 122.9 (CH), 122.5 (C_q), 119.8 (C_q), 119.3 (CH), 117.7 (CH), 114.5 (CH), 102.4 (C_q), 98.1 (C_q), 81.6 (C_q), 59.6 (CH), 57.8 (CH), 52.0 (CH_3), 49.1 (CH), 41.3 (CH_2), 28.5 (CH_3), 28.2 (CH), 26.5 (CH_2), 18.8 (CH_3), 18.5 (CH_3), 17.3 (CH_3), 16.7 (CH_3), 11.5 (CH).

IR (neat): 3285, 2940, 2865, 1721, 1634, 1451, 1339, 1161, 678 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 826 (80) [M+Na^+].

HR-MS (ESI) *m/z* calcd for $C_{42}H_{61}N_7O_7SiNa$ [M+Na^+] 826.4294, found 826.4289.



Azidopropyl-{(*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-{1-(pyrimidin-2-yl)-2-[(triisopropylsilyl)ethynyl]-1*H*-indol-3-yl}propanoyl}-*L*-valyl-*L*-alanylglycinate (154c): The general procedure **F** was followed using substrate **153c** (346 mg, 0.5 mmol) and **61a** (157 mg, 0.6 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 1/1 → 1/2) yielded **154c** (230 mg, 53%) as a white solid.

M. p. = 190–191 °C.

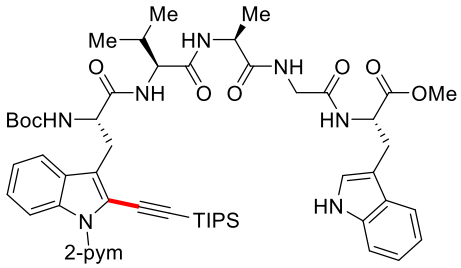
^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.78 (d, J = 4.8 Hz, 2H), 8.31 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.44–7.42 (m, 2H), 7.32 (ddd, J = 8.4, 7.1, 1.2 Hz, 1H), 7.25–7.20 (m, 1H), 7.20 (d, J = 4.8 Hz, 1H), 6.12 (d, J = 5.4 Hz, 1H), 5.84 (d, J = 1.9 Hz, 1H), 4.52–4.47 (m, 1H), 4.33 (td, J = 5.0, 2.1 Hz, 1H), 4.26–4.18 (m, 2H), 4.13 (dd, J = 17.6, 6.1 Hz, 1H), 3.98 (dd, J = 17.6, 5.6 Hz, 1H), 3.86 (dd, J = 5.4, 3.4 Hz, 1H), 3.52–3.43 (m, 2H), 3.44–3.37 (m, 2H), 2.08–2.03 (m, 1H), 1.91 (tt, J = 6.5, 6.5 Hz, 2H), 1.42 (d, J = 7.4 Hz, 3H), 1.36 (s, 9H), 1.18–1.11 (m, 21H), 0.63 (d, J = 7.0 Hz, 3H), 0.27 (d, J = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 173.2 (C_q), 172.9 (C_q), 170.3 (C_q), 169.4 (C_q), 158.0 (CH), 157.0 (C_q), 156.7 (C_q), 135.8 (C_q), 127.9 (C_q), 125.9 (CH), 122.9 (CH), 122.4 (C_q), 119.8 (C_q), 119.2 (CH), 117.7 (CH), 114.6 (CH), 102.4 (C_q), 98.1 (C_q), 81.7 (C_q), 61.8 (CH_2), 59.7 (CH), 57.9 (CH), 49.2 (CH), 48.1 (CH_2), 41.5 (CH_2), 28.5 (CH_3), 28.3 (CH_2), 28.2 (CH), 26.5 (CH_2), 18.8 (CH_3), 18.5 (CH_3), 17.3 (CH_3), 16.7 (CH_3), 11.5 (CH).

IR (neat): 3283, 2941, 2864, 2141, 1634, 1451, 1164, 675 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 895 (20). [M+Na$^+$]

HR-MS (ESI) *m/z* calcd for $C_{44}H_{64}N_{10}O_7SiNa$ [M+Na$^+$] 895.4621, found 895.4627.



Methyl-{(S)-2-[(*tert*-butoxycarbonyl)amino]-3-{1-(pyrimidin-2-yl)-2-[(triisopropylsilyl)ethynyl]-1*H*-indol-3-yl}propanoyl}-*L*-valyl-*L*-alanylglycyl-*L*-tryptophanate (154d): The general procedure **F** was followed using substrate **153d** (203 mg, 0.25 mmol) and **61a** (78 mg, 0.30 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 1/2 → 0/1) yielded **154d** (181 mg, 73%) as a white solid.

M. p. = 219–220 °C.

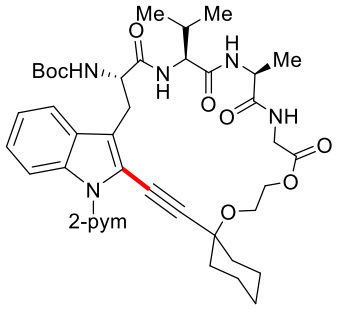
^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.78 (d, J = 4.8 Hz, 2H), 8.57 (br s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 7.60 (t, J = 6.2 Hz, 1H), 7.53–7.50 (m, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.30 (ddd, J = 8.3, 7.0, 1.2 Hz, 2H), 7.20 (t, J = 4.8 Hz, 1H), 7.19–7.15 (m, 2H), 7.14 (d, J = 2.5 Hz, 1H), 7.11 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.05 (ddd, J = 7.9, 6.9, 1.0 Hz, 1H), 6.14 (d, J = 5.1 Hz, 1H), 5.86 (d, J = 2.1 Hz, 1H), 4.88 (dt, J = 8.1, 5.7 Hz, 1H), 4.53–4.48 (m, 1H), 4.35 (ddd, J = 6.4, 4.6, 2.0 Hz, 1H), 4.12 (dd, J = 16.5, 6.5 Hz, 1H), 3.91 (dd, J = 16.4, 5.7 Hz, 1H), 3.80 (dd, J = 5.1, 3.6 Hz, 1H), 3.54 (s, 3H), 3.50–3.41 (m, 2H), 3.38–3.25 (m, 2H), 2.03–1.98 (m, 1H), 1.38 (d, J = 7.3 Hz, 3H), 1.30 (s, 9H), 1.21–1.10 (m, 21H), 0.65 (d, J = 7.0 Hz, 3H), 0.30 (d, J = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 173.6 (C_q), 173.2 (C_q), 171.6 (C_q), 170.8 (C_q), 169.0 (C_q), 158.0 (CH), 157.0 (C_q), 156.9 (C_q), 135.9 (C_q), 135.8 (C_q), 127.9 (C_q), 127.4 (C_q), 125.9 (CH), 123.8 (CH), 123.0 (CH), 122.3 (C_q), 121.5 (CH), 119.7 (C_q), 119.1 (CH), 119.0 (CH), 118.4 (CH), 117.7 (CH), 114.6 (CH), 111.0 (CH), 109.7 (C_q), 102.4 (C_q), 98.1 (C_q), 81.7 (C_q), 59.9 (CH), 58.0 (CH), 52.5 (CH), 52.1 (CH_3), 49.3 (CH), 43.9 (CH_2), 28.5 (CH_3), 28.1 (CH), 27.5 (CH_2), 26.4 (CH_2), 18.8 (CH_3), 18.4 (CH_3), 17.4 (CH_3), 16.8 (CH_3), 11.5 (CH).

IR (neat): 3274, 2953, 2863, 2161, 1626, 1423, 1214, 794 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 1012 (90) [M+Na^+].

HR-MS (ESI) *m/z* calcd for $C_{53}H_{71}N_9O_8SiNa$ [M+Na^+] 1012.5087, found 1012.5079.



Cyclic peptide 10: The general procedure **G** was followed using substrate **155** (84 mg, 0.10 mmol) and $MnBr(CO)_5$ (5.5 mg, 20 mol %) in DCE (10 mL). Isolation by column chromatography ($EtOAc/CH_2Cl_2$: 4/1) yielded **156** (40 mg, 53%) as a light yellow solid.

M. p. = 160 °C (decomp.).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.79 (d, J = 4.8 Hz, 2H), 8.29 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.39 (ddd, J = 8.4, 7.1, 1.3 Hz, 1H), 7.33 (ddd, J = 7.8, 7.1, 1.1 Hz, 1H), 7.23 (t, J = 4.8 Hz, 1H), 7.22–7.18 (m, 1H), 7.07 (d, J = 5.7 Hz, 1H), 6.68 (d, J = 6.1 Hz, 1H), 5.05 (d, J = 2.6 Hz, 1H), 4.44–4.40 (m, 2H), 4.39–4.32 (m, 2H), 4.31–4.24 (m, 1H), 4.14–4.09 (m, 1H), 4.02 (dt, J = 9.9, 6.5 Hz, 1H), 3.94 (dt, J = 9.9, 6.1 Hz, 1H), 3.73 (dd, J = 17.8, 3.3 Hz, 1H), 3.54 (dd, J = 14.5, 5.1 Hz, 1H), 3.10 (dd, J = 14.5, 10.6 Hz, 1H), 2.45 (ddt, J = 10.1, 7.1, 2.6 Hz, 1H), 2.05–1.95 (m, 2H), 1.68–1.61 (m, 4H), 1.55–1.44 (m, 4H), 1.41 (d, J = 7.4 Hz, 3H), 1.34 (s, 9H), 1.01 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H).

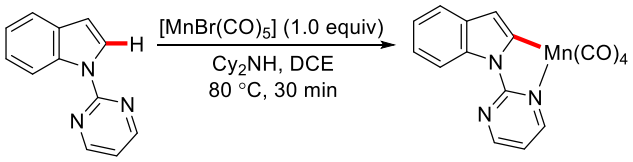
^{13}C NMR (125 MHz, $CDCl_3$) δ = 172.7 (C_q), 171.9 (C_q), 170.2 (C_q), 169.1 (C_q), 158.0 (CH), 156.8 (C_q), 156.4 (C_q), 135.7 (C_q), 128.6 (C_q), 125.4 (CH), 122.9 (CH), 119.8 (C_q), 119.5 (C_q), 118.0 (CH), 117.6 (CH), 114.6 (CH), 101.3 (C_q), 81.5 (C_q), 74.8 (C_q), 64.0 (C_q), 61.3 (CH_2), 59.7 (CH), 56.9 (CH), 49.5 (CH), 41.8 (CH_2), 37.1 (CH_2), 37.0 (CH_2), 28.8 (CH), 28.1 (CH_3), 27.2 (CH_2), 25.4 (CH_2), 22.6 (CH_2), 19.6 (CH_3), 17.1 (CH_3).

MS (ESI) *m/z* (relative intensity): 780 (90) [M+Na^+].

HR-MS (ESI) *m/z* calcd for $C_{40}H_{51}N_7O_8Na$ [M+Na^+] 780.3691, found 780.3689.

Mechanistic Studies

C–H Alkynylations with Cyclometalated Complex 152



Following a modification of a reported procedure,[106] 1-(pyrimidin-2-yl)-1*H*-indole (**83b**) (195 mg, 1.0 mmol), $MnBr(CO)_5$ (274 mg, 1.0 mmol), Cy_2NH (362 mg, 2.0 mmol) and DCE (2.0 mL) were placed in a 25 mL Schlenk tube under N_2 and then stirred at 80 °C for 30 min. At ambient temperature, the mixture was diluted with EtOAc (20 ml) and filtered through a short pad of celite. The solvent was removed by rotary evaporation and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) afforded **152** (279 mg, 77%) as a yellow solid.

M. p. = 150–151 °C.

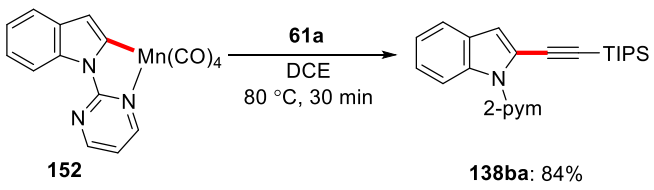
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.69 (dd, J = 4.8, 2.4 Hz, 1H), 8.57 (dd, J = 5.6, 2.4 Hz, 1H), 8.50 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.20 (dd, J = 7.5, 7.3 Hz, 1H), 7.12 (dd, J = 7.5, 7.2, 1H), 6.85 (t, J = 5.2 Hz, 1H), 6.79 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 218.4 (C_q), 213.1 (C_q), 210.7 (Cq), 162.2 (CH), 161.3 (C_q), 160.9 (C_q), 160.1 (CH), 138.5 (C_q), 136.0 (C_q), 122.9 (CH), 120.7 (CH), 119.3 (CH), 117.5 (CH), 114.1 (CH), 113.6 (CH).

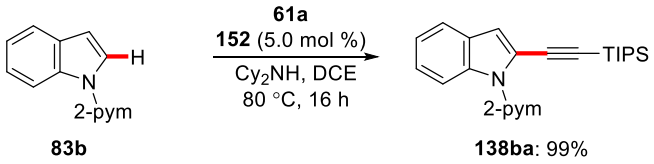
IR (neat): 2078, 1974, 1937, 1920, 1575, 1491, 1380, 787, 639 cm^{-1}.

MS (EI) *m/z* (relative intensity): 360 (5) [M^+], 249 (35), 195 (100).

HR-MS (EI) *m/z* calcd for $C_{16}H_8MnN_3O_4$ [M^+] 360.9895, found 360.9880.

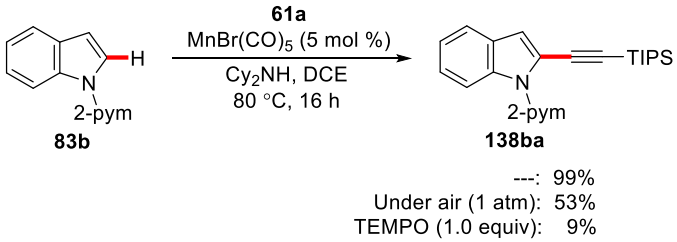


Complex **152** (72 mg, 0.2 mmol), bromoalkyne **61a** (62 mg, 0.24 mmol), and DCE (0.5 mL) were placed in a 25 mL Schlenk tube under N_2 and were then stirred at 80 °C for 30 min. At ambient temperature, CH_2Cl_2 (2 mL) was added, and the reaction mixture was transferred into a round bottom flask with CH_2Cl_2 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) afforded **138ba** (64 mg, 84%).



1-(Pyrimidin-2-yl)-1*H*-indole (**83b**) (98 mg, 0.5 mmol), bromoalkyne **61a** (157 mg, 0.6 mmol), **152** (9 mg, 5.0 mol %), Cy_2NH (181 mg, 1.0 mmol) and DCE (1.0 mL) were placed in a 25 mL Schlenk tube under N_2 and then stirred at 80 °C for 16 h. At ambient temperature, the mixture was diluted with EtOAc (20 ml) and filtered through a short pad of celite. The solvent was removed by rotary evaporation and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) afforded **138ba** (197 mg, 99% based on 0.525 mmol).

Reactions under air or in the presence of radical scavenger

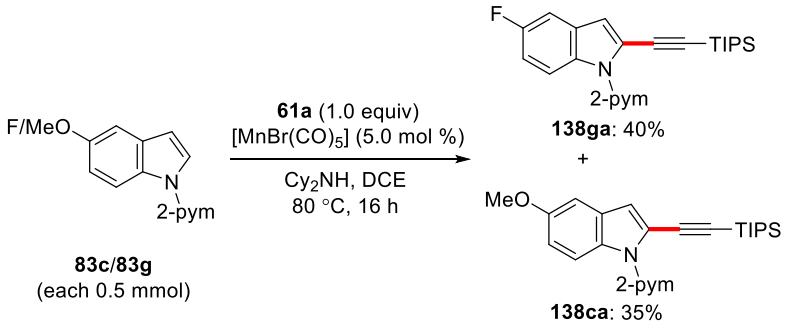


(a) 1-(Pyrimidin-2-yl)-1*H*-indole (**83b**) (98 mg, 0.5 mmol), $MnBr(CO)_5$ (6.9 mg, 5.0 mol %), bromoalkyne (**61a**) (157 mg, 0.6 mmol), Cy_2NH (181 mg, 1.0 mmol) and DCE (1.0 mL) were placed in a 25 mL Schlenk tube under air and were then stirred at 80 °C for 16 h. At ambient

temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **138ba** (99 mg, 53%).

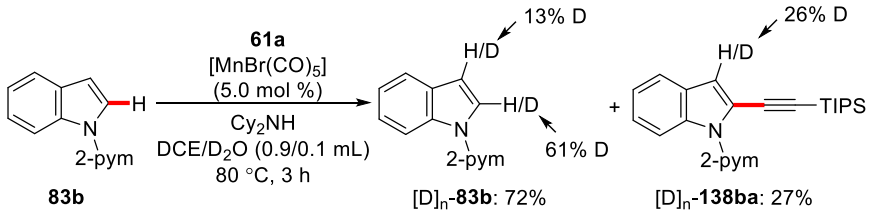
(b) 1-(Pyrimidin-2-yl)-1*H*-indole (**83b**) (98 mg, 0.5 mmol), $MnBr(CO)_5$ (6.9 mg, 5.0 mol %), bromoalkyne (**61a**) (157 mg, 0.6 mmol), Cy_2NH (181 mg, 1.0 mmol), TEMPO (78 mg, 0.5 mmol) and DCE (1.0 mL) were placed in a 25 mL Schlenk tube under N_2 and were then stirred at 80 °C for 16 h. At ambient temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **138ba** (17 mg, 9%).

Intermolecular Competition Experiment

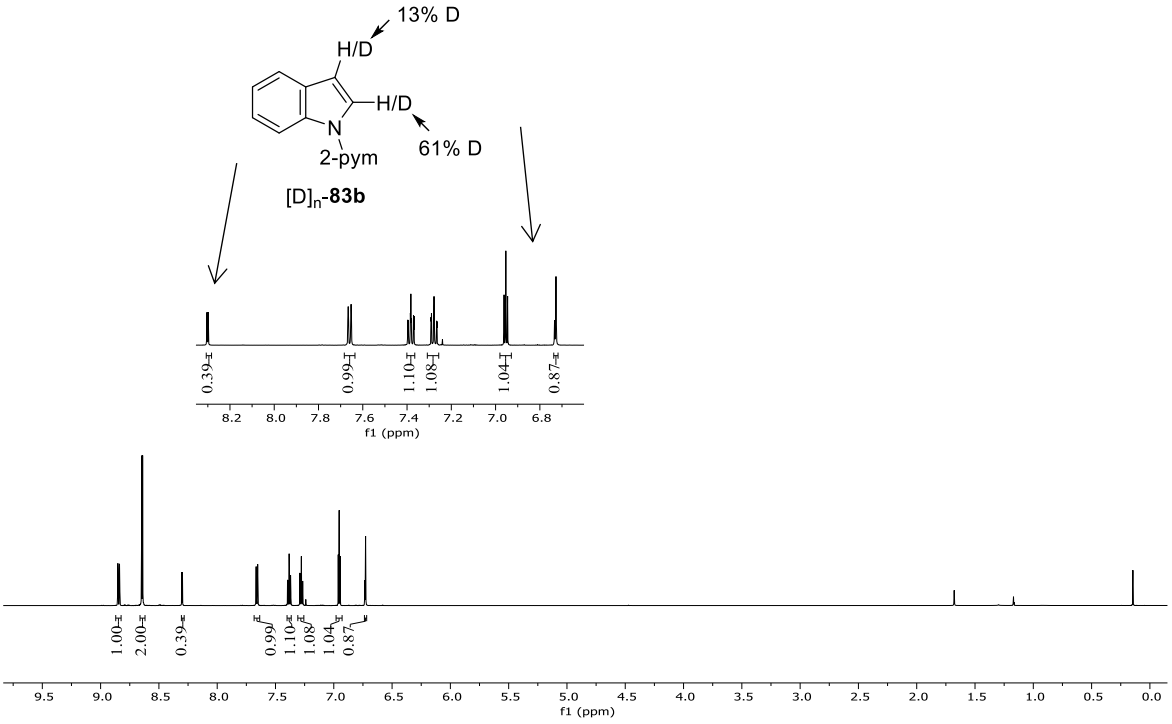


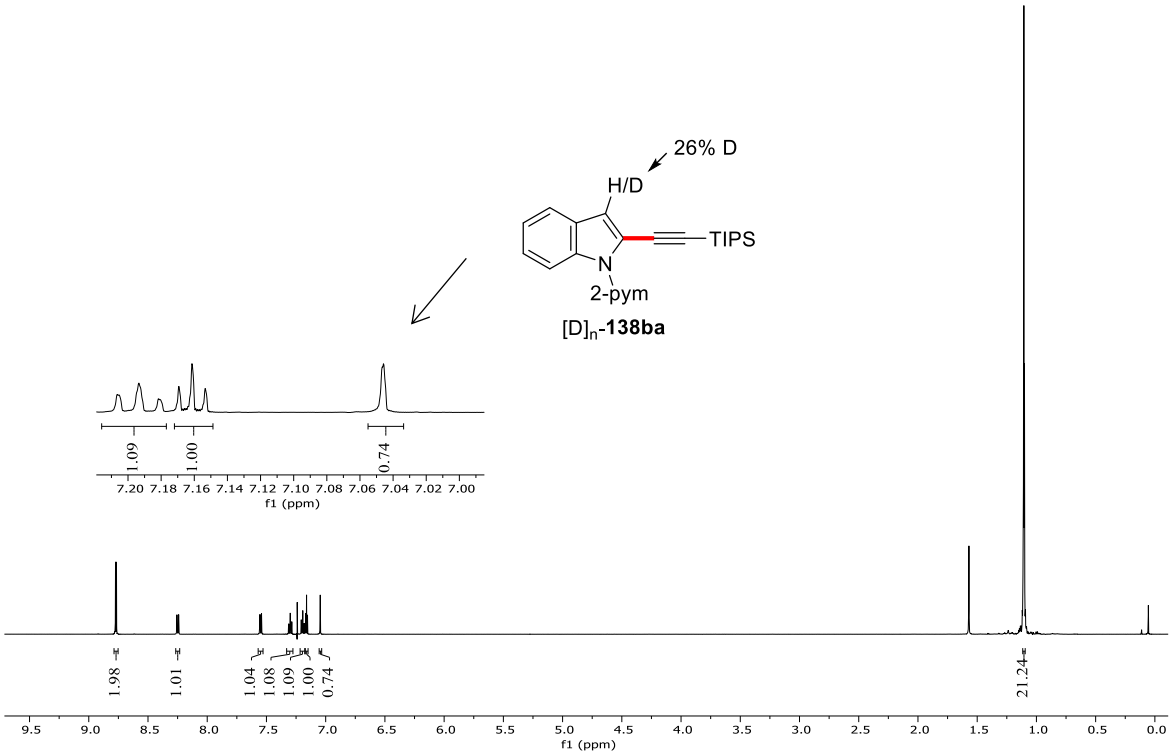
5-Methoxy-1-(pyrimidin-2-yl)-1*H*-indole (**83c**) (113 mg, 0.5 mmol), 5-fluoro-1-(pyrimidin-2-yl)-1*H*-indole (**83g**) (107 mg, 0.5 mmol), bromoalkyne **61a** (157 mg, 0.6 mmol), $MnBr(CO)_5$ (6.9 mg, 5.0 mol %), Cy_2NH (181.3 mg, 1.0 mmol), and DCE (1.0 mL) were placed in a 25 mL Schlenk tube under N_2 and were then stirred at 80 °C for 16 h. At ambient temperature, CH_2Cl_2 (2.0 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 40/1→20/1) afforded **138ca** (72 mg, 35%) and **138ga** (78 mg, 40%).

H/D Exchange experiments

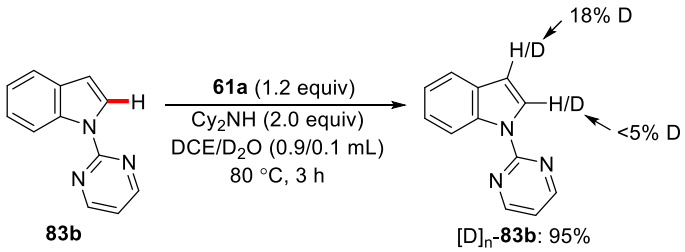


1-(Pyrimidin-2-yl)-1*H*-indole (**83b**) (98 mg, 0.5 mmol), $MnBr(CO)_5$ (6.9 mg, 5.0 mol %), bromoalkyne **61a** (157 mg, 0.6 mmol), Cy_2NH (181 mg, 1.0 mmol), DCE (0.9 mL) and D_2O (0.1 mL) were placed in a 25 mL Schlenk tube under N_2 and were then stirred at 80 °C for 3 h. At ambient temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded $[D]_n$-**83b** (71 mg, 72%) and $[D]_n$-**138ba** (50 mg, 27%). The D incorporation was determined by ^{1}H-NMR spectroscopy.

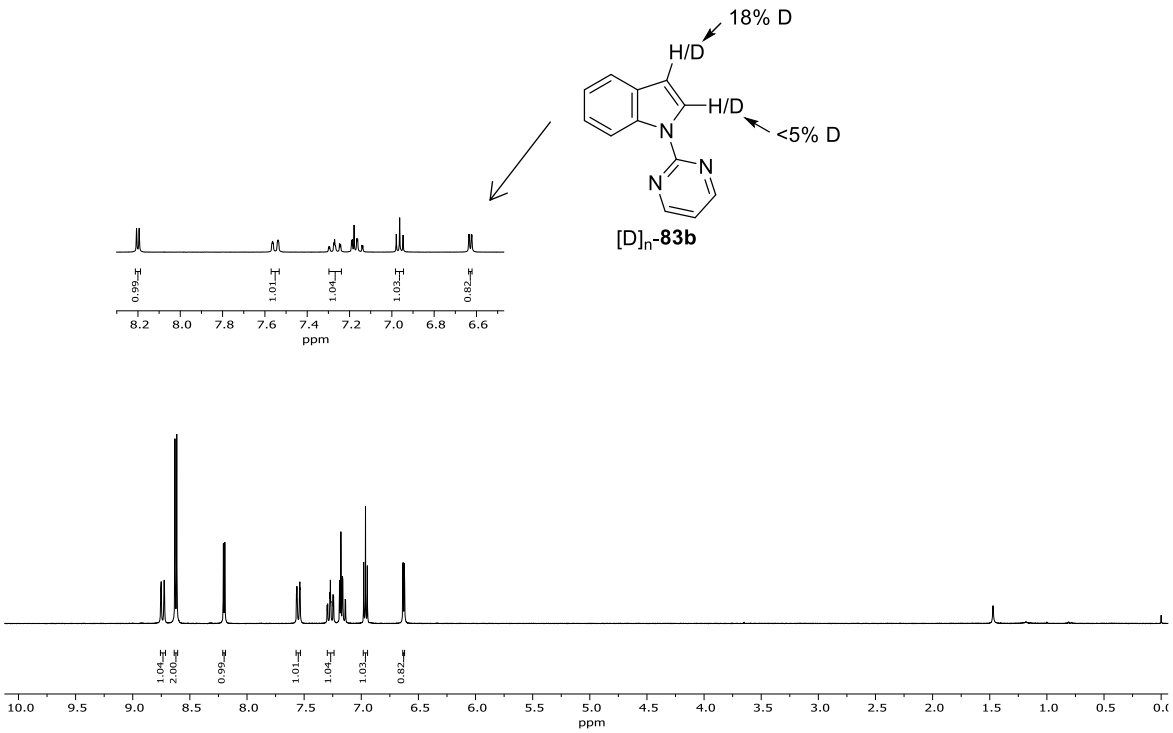


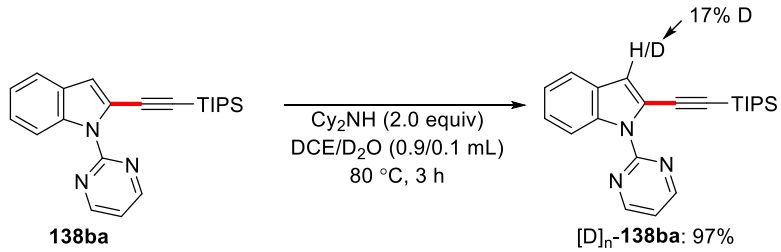


H/D Exchange experiments in the absence of $MnBr(CO)_5$

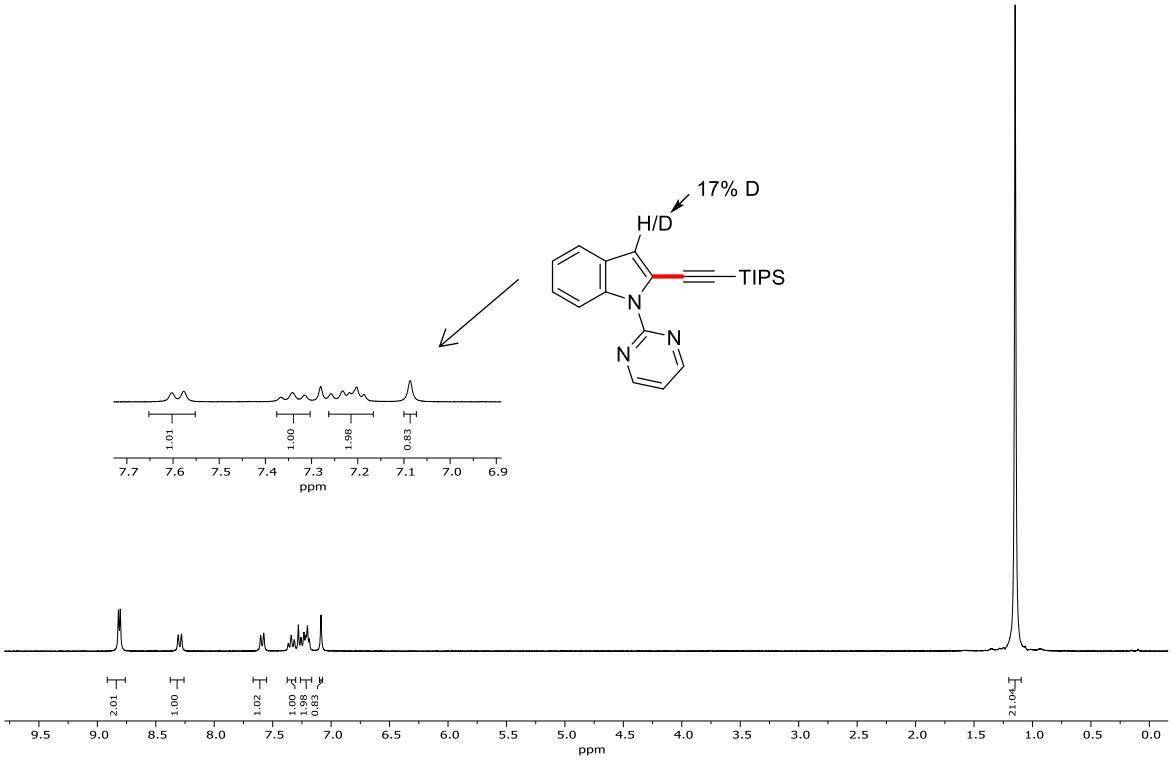


1-(Pyrimidin-2-yl)-1*H*-indole (**83b**) (49 mg, 0.25 mmol), bromoalkyne **61a** (77 mg, 0.3 mmol), Cy_2NH (93 mg, 0.5 mmol), DCE (0.9 mL) and D_2O (0.1 mL) were placed in a 25 mL Schlenk tube under N_2 and were then stirred at 80 °C for 3 h. At ambient temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded $[D]_n$-**83b** (47 mg, 95%). The D incorporation was determined by ^{1}H-NMR spectroscopy.

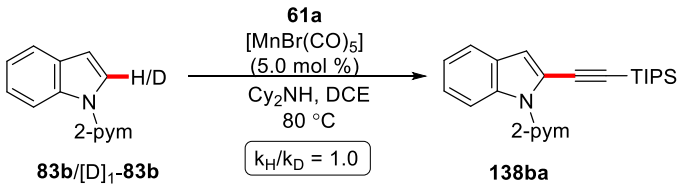




1-(Pyrimidin-2-yl)-2-[(triisopropylsilyl)ethynyl]-1*H*-indole (**138ba**) (95 mg, 0.25 mmol), Cy_2NH (190 mg, 0.5 mmol), DCE (0.9 mL) and D_2O (0.1 mL) were placed in a 25 mL Schlenk tube under N_2 and were then stirred at 80 °C for 3 h. At ambient temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded $[D]_n$-**138ba** (91 mg, 97%). The D incorporation was determined by ^{1}H-NMR spectroscopy.



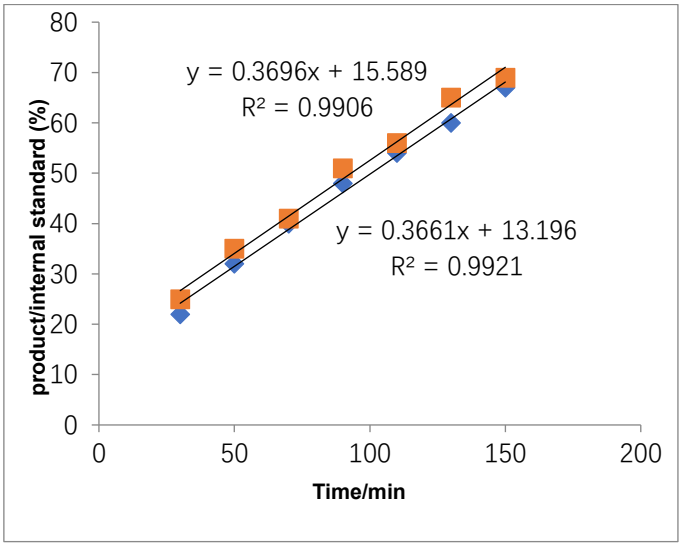
KIE experiments



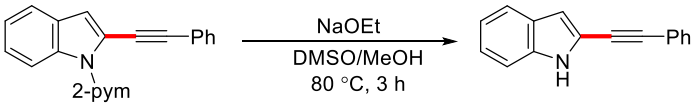
83b/[D]$_1$-**83b** **138ba**

Seven independent reactions of **83b** or [D]$_1$-**83b** with **61a** were performed to determine the corresponding KIE value. **83b** (98 mg, 0.50 mmol) or [D]$_1$-**83b** (98 mg, 0.50 mmol), **61a** (157 mg, 0.6 mmol), $MnBr(CO)_5$ (6.9 mg, 5.0 mol %), and DCE (1.0 mL) were placed in 25 mL Schlenk tubes. The mixtures were stirred at 80 °C. After cooling to ambient temperature, the GC conversions were determined by using *n*-dodecane as internal standard:

T [min]	30	50	70	90	110	130	150
138ba/%	22	32	40	48	54	60	67
[D]$_1$-**138ba**/%	25	35	41	51	56	65	69



Removal of the Directing Group



150bg **151**: 81%

2-(Phenylethynyl)-1*H*-indole (151): To a solution of **150bg** (59 mg, 0.2 mmol) in dry DMSO (1.5 mL) and dry MeOH (0.5 mL), NaOEt (41mg, 0.6 mmol, 3.0 equiv) was added and stirred for 3 h at 80 °C. Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **151** (35 mg, 81%) as a yellow solid.

M. p. = 160–161 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (br s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.58–7.51 (m, 2H), 7.38–7.35 (m, 3H), 7.32 (dd, J = 8.2, 1.0 Hz, 1H), 7.28–7.20 (m, 1H), 7.14 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 6.84 (dd, J = 2.3, 1.1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.1 (C_q), 131.4 (CH), 128.6 (CH), 128.4 (CH), 127.8 (C_q), 123.5 (CH), 122.6 (C_q), 120.8 (CH), 120.5 (CH), 118.8 (C_q), 110.7 (CH), 108.8 (CH), 92.5 (C_q), 81.8 (C_q).

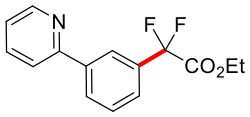
IR (neat): 3368, 1594, 1351, 1305, 795, 745, 689, 657 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 218 [M+H$^+$] (30).

HR-MS (ESI) *m/z* calcd for $C_{16}H_{12}N$ [M+H$^+$] 218.0964, found 218.0963.

The analytical data are in accordance with those previously published in the literature.[170]

5.3.5 Characterization Data: Ruthenium(II)-Catalyzed *meta*-C–H Mono- and Difluoromethylations by Phosphine/Carboxylate Cooperation



Ethyl 2,2-difluoro-2-[3-(pyridin-2-yl)phenyl]acetate (140aa): The general procedure **H** was followed using substrate **95a** (78 mg, 0.50 mmol) and **139a** (304 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 9/1) yielded **140aa** (99 mg, 71%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **140aa** (100 mg, 72%).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.71 (ddd, J = 4.8, 1.6, 1.1 Hz, 1H), 8.24 (ddt, J = 1.9, 1.3, 0.7 Hz, 1H), 8.16 (dddt, J = 7.6, 1.9, 1.4, 0.7 Hz, 1H), 7.83–7.73 (m, 2H), 7.66 (ddd, J = 7.8, 1.9, 1.3 Hz, 1H), 7.57 (dd, J = 7.8, 7.6 Hz, 1H), 7.30–7.25 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H).

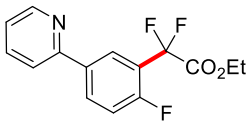
^{13}C NMR (125 MHz, $CDCl_3$) δ = 164.0 (t, $^2J_{C\text{-}F}$ = 35.2 Hz, C_q), 156.0 (C_q), 149.7 (CH), 139.8 (C_q), 136.8 (CH), 133.3 (t, $^2J_{C\text{-}F}$ = 25.5 Hz, C_q), 129.4 (t, $^4J_{C\text{-}F}$ = 1.7 Hz, CH), 129.1 (CH), 125.8 (t, $^3J_{C\text{-}F}$ = 6.0 Hz, CH), 123.9 (t, $^3J_{C\text{-}F}$ = 6.3 Hz, CH), 122.6 (CH), 120.6 (CH), 113.3 (t, $^1J_{C\text{-}F}$ = 252.0 Hz, C_q), 63.2 (CH_2), 14.0 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -103.7 (s).

IR (neat): 2986, 1761, 1585, 1463, 1290, 1100, 777 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 278 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{15}H_{14}F_2NO_2$ [M+H$^+$] 278.0987, found 278.0994.



Ethyl 2,2-difluoro-2-[2-fluoro-5-(pyridin-2-yl)phenyl]acetate (140ba): The general procedure **H** was followed using substrate **95b** (87 mg, 0.50 mmol) and **139a** (304 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **140ba** (106 mg,

72%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **140ba** (110 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.60 (ddd, J = 4.8, 1.8, 1.0 Hz, 1H), 8.21 (dd, J = 7.0, 2.2 Hz, 1H), 8.06 (dddt, J = 8.8, 4.9, 2.2, 0.8 Hz, 1H), 7.81–7.49 (m, 2H), 7.21–7.16 (m, 1H), 7.15–7.11 (m, 1H), 4.28 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H).

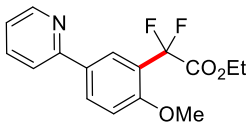
^{13}C NMR (125 MHz, $CDCl_3$) δ =162.9 (t, $^2J_{C\text{-}F}$ = 33.9 Hz, C_q), 160.1 (dt, $^{1,3}J_{C\text{-}F}$ = 254.5, 4.6 Hz, C_q), 155.0 (C_q), 149.6 (CH), 136.9 (CH), 135.7 (d, $^4J_{C\text{-}F}$ = 3.5 Hz, C_q), 131.3 (d, $^3J_{C\text{-}F}$ = 8.7 Hz, CH), 125.6 (td, $^{3,3}J_{C\text{-}F}$ = 7.1, 2.6 Hz, CH), 122.5 (CH), 121.1 (td, $^{2,2}J_{C\text{-}F}$ = 25.7, 12.9 Hz, C_q), 120.2 (CH), 116.6 (d, $^2J_{C\text{-}F}$ = 21.1 Hz, CH), 111.5 (t, $^1J_{C\text{-}F}$ = 251.1 Hz, C_q), 63.4 (CH_2), 13.8 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -102.0 (d, J = 7.5 Hz), -114.8 (s).

IR (neat): 2987, 1763, 1589, 1465, 1218, 1088, 779 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 318 (20) [M+Na^+], 296 (100) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{15}H_{13}F_3NO_2$ [M+H^+] 296.0893, found 296.0902.



Ethyl 2,2-difluoro-2-[2-methoxy-5-(pyridin-2-yl)phenyl]acetate (140ca): The general procedure **H** was followed using substrate **95c** (93 mg, 0.50 mmol) and **139a** (304 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **140ca** (77 mg, 50%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **140ca** (108 mg, 70%).

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.69 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H), 7.85 (ddd, J = 7.8, 1.7, 0.8 Hz, 1H), 7.75 (dd, J = 7.9, 1.0 Hz, 1H), 7.72–7.65 (m, 2H), 7.29 (dd, J = 7.7, 7.7 Hz, 1H), 7.24–7.22 (m, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.37 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H).

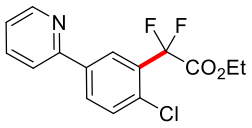
^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.6 (t, $^2J_{C\text{-}F}$ = 33.7 Hz, C_q), 155.5 (t, $^3J_{C\text{-}F}$ = 5.2 Hz, C_q), 154.9 (C_q), 149.8 (CH), 136.2 (CH), 134.3 (t, $^4J_{C\text{-}F}$ = 1.8 Hz, CH), 133.5 (C_q), 127.7 (t, $^2J_{C\text{-}F}$ = 24.5 Hz, C_q), 126.6 (t, $^3J_{C\text{-}F}$ = 7.2 Hz, CH), 124.2 (CH), 124.1 (CH), 122.3 (CH), 112.2 (t, $^1J_{C\text{-}F}$ = 248.0 Hz, C_q), 62.7 (CH_2), 61.9 (CH_3), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -100.8 (s).

IR (neat): 2986, 1772, 1586, 1457, 1304, 1091, 765 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 330 (10) [M+Na^+], 308 (100) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{16}H_{16}F_2NO_3$ [M+H^+] 308.1093, found 308.1094.



Ethyl 2-[2-chloro-5-(pyridin-2-yl)phenyl]-2,2-difluoroacetate (140da): The general procedure **H** was followed using substrate **95d** (95 mg, 0.50 mmol) and **139a** (304 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 5/1) yielded **140da** (120 mg, 77%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **140da** (120 mg, 77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.69 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 8.36 (d, *J* = 2.3 Hz, 1H), 8.08 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.83–7.70 (m, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.27 (ddd, *J* = 7.3, 4.8, 1.5 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).

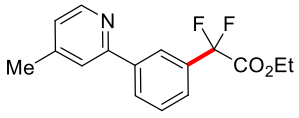
^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.9 (t, $^2J_{C\text{-}F}$ = 33.9 Hz, C_q), 155.0 (C_q), 149.8 (CH), 138.2 (C_q), 136.9 (CH), 132.4 (t, $^3J_{C\text{-}F}$ = 4.3 Hz, C_q), 131.5 (t, $^2J_{C\text{-}F}$ = 24.2 Hz, C_q), 130.9 (CH), 130.1 (CH), 125.7 (t, $^3J_{C\text{-}F}$ = 8.6 Hz, CH), 122.8 (CH), 120.4 (CH), 112.1 (t, $^1J_{C\text{-}F}$ = 250.8 Hz, C_q), 63.4 (CH_2), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -102.3 (s).

IR (neat): 2986, 1772, 1588, 1460, 1304, 1080, 778 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 334 (5) [M+Na^+], 312 (100) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{15}H_{13}ClF_2NO_2$ [M+H^+] 312.0597, found 312.0602.



Ethyl 2,2-difluoro-2-[3-(4-methylpyridin-2-yl)phenyl]acetate (140ea): The general procedure **H** was followed using substrate **95e** (85 mg, 0.50 mmol) and **139a** (304 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **140ea** (102 mg,

70%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **140ea** (108 mg, 74%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.56 (d, J = 5.0 Hz, 1H), 8.20 (d, J = 1.8 Hz, 1H), 8.15 (d, J = 7.8 Hz, 1H), 7.64 (dd, J = 7.9, 1.8 Hz, 1H), 7.57 (d, J = 1.8 Hz, 1H), 7.55 (dd, J = 7.9, 7.8 Hz, 1H), 7.09 (dd, J = 5.0, 1.8 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H).

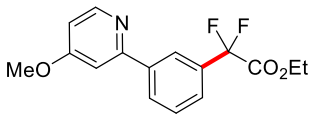
^{13}C NMR (125 MHz, $CDCl_3$) δ = 164.0 (t, $^2J_{C\text{-}F}$ = 35.2 Hz, C_q), 155.9 (C_q), 149.4 (CH), 147.9 (C_q), 134.0 (C_q), 133.2 (t, $^2J_{C\text{-}F}$ = 25.5 Hz, C_q), 129.4 (t, $^4J_{C\text{-}F}$ = 1.8 Hz, CH), 129.0 (CH), 125.7 (t, $^3J_{C\text{-}F}$ = 6.1 Hz, CH), 123.8 (t, $^3J_{C\text{-}F}$ = 6.2 Hz, CH), 123.6 (CH), 121.5 (CH), 113.3 (t, $^1J_{C\text{-}F}$ = 251.9 Hz, C_q), 63.2 (CH_2), 21.2 (CH_3), 13.9 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -103.7 (s).

IR (neat): 2986, 1761, 1603, 1244, 1099, 1025, 803 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 314 (5) [M+Na^+], 292 (100) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{16}H_{15}F_2NO_2Na$ [M+Na^+] 314.0963, found 314.0959.



Ethyl 2,2-difluoro-2-[3-(4-methylpyridin-2-yl)phenyl]acetate (140fa): The general procedure **H** was followed using substrate **95f** (93 mg, 0.50 mmol) and **139a** (304 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **140fa** (132 mg, 86%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **140fa** (126 mg, 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.50 (d, J = 5.7 Hz, 1H), 8.17 (ddt, J = 1.9, 1.3, 0.7 Hz, 1H), 8.10 (ddd, J = 7.7, 1.9, 1.3 Hz, 1H), 7.63 (dddt, J = 7.8, 1.9, 1.3, 0.6 Hz, 1H), 7.53 (dd, J = 7.8, 7.7 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 6.79 (dd, J = 5.7, 2.4 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.4 (C_q), 164.0 (t, $^2J_{C\text{-}F}$ = 35.1 Hz, C_q), 157.7 (C_q), 150.9 (CH), 139.9 (C_q), 133.2 (t, $^2J_{C\text{-}F}$ = 25.4 Hz, C_q), 129.5 (t, $^4J_{C\text{-}F}$ = 1.6 Hz, CH), 129.0 (CH), 125.9

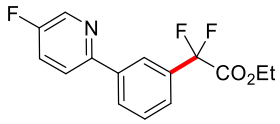
(t, $^{3}J_{C\text{-}F}$ = 6.1 Hz, CH), 123.9 (t, $^{3}J_{C\text{-}F}$ = 6.3 Hz, CH), 113.3 (t, $^{2}J_{C\text{-}F}$ = 251.9 Hz, C_q), 108.5 (CH), 107.1 (CH), 63.2 (CH_2), 55.3 (CH_3), 14.0 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -103.7.

IR (neat): 2985, 1761, 1592, 1474, 1300, 1098, 805 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 308 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{16}H_{16}F_2NO_3$ [M+H$^+$] 308.1093, found 308.1097.



Ethyl 2,2-difluoro-2-[3-(5-fluoropyridin-2-yl)phenyl]acetate (140ga): The general procedure **H** was followed using substrate **95g** (87 mg, 0.50 mmol) and **139a** (304 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **140ga** (111 mg, 75%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **140ga** (114 mg, 77%).

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.52 (d, *J* = 2.9 Hz, 1H), 8.17 (s, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.72 (dd, *J* = 8.8, 4.2 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.53 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.46 (ddd, *J* = 8.9, 8.0, 2.9 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

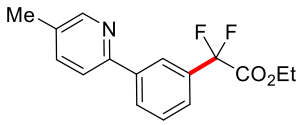
^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.9 (t, $^{2}J_{C\text{-}F}$ = 35.1 Hz, C_q), 158.9 (d, $^{1}J_{C\text{-}F}$ = 256.8 Hz, C_q), 152.2 (d, $^{4}J_{C\text{-}F}$ = 4.0 Hz, C_q), 138.8 (C_q), 137.8 (d, $^{2}J_{C\text{-}F}$ = 23.6 Hz, CH), 133.4 (t, $^{2}J_{C\text{-}F}$ = 25.5 Hz, C_q), 129.1 (CH), 129.0 (CH), 125.7 (t, $^{3}J_{C\text{-}F}$ = 6.0 Hz, CH), 123.7 (t, $^{3}J_{C\text{-}F}$ = 6.3 Hz, CH), 123.5 (d, $^{2}J_{C\text{-}F}$ = 18.6 Hz, CH), 121.3 (d, $^{3}J_{C\text{-}F}$ = 4.4 Hz, CH), 113.2 (t, $^{1}J_{C\text{-}F}$ = 252.0 Hz, C_q), 63.2 (CH_2), 13.9 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -103.7 (s, 2F), -128.6 (dd, *J* = 8.0, 4.3 Hz, 1F).

IR (neat): 2986, 1761, 1470, 1286, 1226, 1084, 837 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 318 (30) [M+Na$^+$], 296 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{15}H_{13}F_3NO_2$ [M+H$^+$] 296.0893, found 296.0893.



Ethyl 2,2-difluoro-2-[3-(5-methylpyridin-2-yl)phenyl]acetate (140ha): The general procedure **H** was followed using substrate **95h** (85 mg, 0.50 mmol) and **139a** (304 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **140ha** (99 mg, 68%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **140ha** (97 mg, 67%).

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.50 (s, 1H), 8.18 (s, 1H), 8.10 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.55 (d, J = 8.0, 1H), 7.52 (dd, J = 8.0, 7.8 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.35 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H).

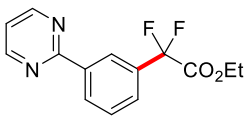
^{13}C NMR (125 MHz, $CDCl_3$) δ = 164.0 (t, $^2J_{C\text{-}F}$ = 35.2 Hz, C_q), 153.3 (C_q), 150.1 (CH), 139.9 (C_q), 137.3 (CH), 133.2 (t, $^2J_{C\text{-}F}$ = 25.5 Hz, C_q), 132.2 (C_q), 129.1 (t, $^4J_{C\text{-}F}$ = 1.8 Hz, CH), 128.9 (CH), 125.4 (t, $^3J_{C\text{-}F}$ = 6.0 Hz, CH), 123.6 (t, $^3J_{C\text{-}F}$ = 6.2 Hz, CH), 120.0 (CH), 113.3 (t, $^1J_{C\text{-}F}$ = 251.8 Hz, C_q), 63.1 (CH_2), 18.2 (CH_3), 13.9 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -103.7 (s).

IR (neat): 2986, 1761, 1471, 1289, 1216, 1099, 802 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 314 (5) [M+Na$^+$], 292 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{16}H_{16}F_3NO_2$ [M+H$^+$] 292.1144, found 292.1151.



Ethyl 2,2-difluoro-2-[3-(pyrimidin-2-yl)phenyl]acetate (140ia): The general procedure **H** was followed using substrate **95i** (78 mg, 0.50 mmol) and **139a** (304 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **140ia** (107 mg, 77%) as a white solid. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded**140ia** (100 mg, 72%).

M. p. = 74–75 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.80 (d, J = 4.8 Hz, 2H), 8.72 (s, 1H), 8.56 (dd, J = 7.9, 1.8 Hz, 1H), 7.71 (dd, J = 7.8, 1.8 Hz, 1H), 7.56 (dd, J = 7.9, 7.8 Hz, 1H), 7.20 (t, J = 4.8 Hz, 1H), 4.29 (q, J = 7.1, 2H), 1.28 (t, J = 7.1 Hz, 3H).

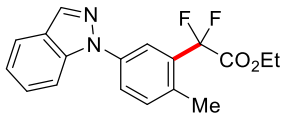
^{13}C NMR (125 MHz, $CDCl_3$) δ = 164.0 (t, $^2J_{C\text{-}F}$ = 35.1 Hz, C_q), 163.4 (C_q), 157.2 (CH), 138.1 (C_q), 133.3 (t, $^2J_{C\text{-}F}$ = 25.6 Hz, C_q), 130.5 (t, $^4J_{C\text{-}F}$ = 1.9 Hz, CH), 128.9 (CH), 127.5 (t, $^3J_{C\text{-}F}$ = 6.0 Hz, CH), 125.3 (t, $^3J_{C\text{-}F}$ = 6.3 Hz, CH), 119.5 (CH), 113.3 (t, $^1J_{C\text{-}F}$ = 251.9 Hz, C_q), 63.2 (CH_2), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -103.6 (s).

IR (neat): 2996, 1766, 1557, 1410, 1132, 1021, 806 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 301 (50) [M+Na$^+$], 279 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{14}H_{13}F_2N_2O_2$ [M+H$^+$] 279.0940, found 279.0946.



Ethyl 2-[5-(1*H*-indazol-1-yl)-2-methylphenyl]-2,2-difluoroacetate (140ja): The general procedure **H** was followed using substrate **95j** (104 mg, 0.50 mmol) and **139a** (304 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **140ja** (69 mg, 42%) as a white solid. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **140ja** (68 mg, 41%).

M. p. = 77–78 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.20 (s, 1H), 7.98 (d, J = 2.3 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.74 (dd, J = 8.2, 2.4 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.46–7.42 (m, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.23 (m, 1H), 4.33 (q, J = 7.1 Hz, 2H), 2.48 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H).

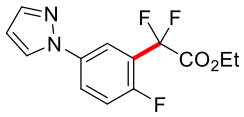
^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.6 (t, $^2J_{C\text{-}F}$ = 34.8 Hz, C_q), 138.6 (C_q), 138.2 (C_q), 135.6 (CH), 134.5 (t, $^3J_{C\text{-}F}$ = 3.1 Hz, C_q), 132.9 (CH), 132.2 (t, $^2J_{C\text{-}F}$ = 23.7 Hz, C_q), 127.3 (CH), 125.3 (C_q), 124.5 (t, $^4J_{C\text{-}F}$ = 1.4 Hz, CH), 121.6 (CH), 121.3 (CH), 120.2 (t, $^3J_{C\text{-}F}$ = 9.3 Hz, CH), 113.6 (t, $^1J_{C\text{-}F}$ = 252.1 Hz, C_q), 110.1 (CH), 63.3 (CH_2), 19.3 (t, $^4J_{C\text{-}F}$ = 2.7 Hz, CH_3), 13.9 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -101.6 (d, J = 2.3 Hz).

IR (neat): 2999, 1754, 1508, 1283, 1239, 1093, 738 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 353 (50) [M+Na$^+$], 331 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{18}H_{17}F_2N_2O_2$ [M+H$^+$] 331.1253, found 331.1255.



Ethyl 2,2-difluoro-2-[2-fluoro-5-(1*H*-pyrazol-1-yl)phenyl]acetate (140ka): The general procedure **H** was followed using substrate **95k** (81 mg, 0.50 mmol) and **139a** (304 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **140ka** (107 mg, 75%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **140ka** (101 mg, 71%).

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.96 (dd, J = 6.1, 2.8 Hz, 1H), 7.91 (d, J = 2.5, 1H), 7.84 (ddd, J = 8.7, 4.2, 2.8 Hz, 1H), 7.73 (d, J = 1.8 Hz, 1H), 7.23 (dd, J = 9.8, 8.9 Hz, 1H), 6.49 (dd, J = 2.5, 1.8 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H).

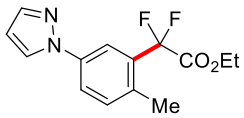
^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.6 (t, $^2J_{C\text{-}F}$ = 33.6 Hz, C_q), 157.6 (dt, $^{1,3}J_{C\text{-}F}$ = 251.8, 4.6 Hz, C_q), 141.5 (CH), 136.6 (d, $^4J_{C\text{-}F}$ = 3.0 Hz, C_q), 126.8 (CH), 123.4 (d, $^3J_{C\text{-}F}$ = 8.5 Hz, CH), 121.9 (td, $^{2,2}J_{C\text{-}F}$ = 25.9, 14.1 Hz, C_q), 117.8 (td, $^3J_{C\text{-}F}$ = 7.4, 2.5 Hz, CH), 117.3 (d, $^2J_{C\text{-}F}$ = 22.4 Hz, CH), 111.1 (t, $^1J_{C\text{-}F}$ = 252.0 Hz, C_q), 108.2 (CH), 63.5 (CH_2), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -102.3 (d, J = 7.6 Hz, 2F), -117.6 (t, J = 7.6 Hz, 1F).

IR (neat): 2987, 1764, 1504, 1224, 1088, 1016, 748 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 307 (60) [M+Na$^+$], 285 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{13}H_{12}F_3N_2O_2$ [M+H$^+$] 285.0845, found 285.0848.



Ethyl 2,2-difluoro-2-[2-methyl-5-(1*H*-pyrazol-1-yl)phenyl]acetate (140la): The general procedure **H** was followed using substrate **95l** (79 mg, 0.50 mmol) and **139a** (304 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **140la** (116 mg, 83%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **140la** (112 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.94–7.87 (m, 2H), 7.75–7.65 (m, 2H), 7.30 (d, J = 8.3 Hz, 1H), 6.46 (dd, J = 2.5, 1.8 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H).

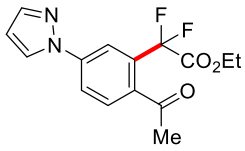
^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.5 (t, $^2J_{C\text{-}F}$ = 34.8 Hz, C_q), 141.1 (CH), 138.2 (C_q), 134.2 (t, $^3J_{C\text{-}F}$ = 3.2 Hz, C_q), 132.8 (CH), 132.2 (t, $^2J_{C\text{-}F}$ = 23.6 Hz, C_q), 126.6 (CH), 121.1 (t, $^4J_{C\text{-}F}$ = 1.6 Hz, CH), 116.8 (t, $^3J_{C\text{-}F}$ = 9.5 Hz, CH), 113.5 (t, $^1J_{C\text{-}F}$ = 252.0 Hz, C_q), 107.7 (CH), 63.2 (CH_2), 19.1 (t, $^4J_{C\text{-}F}$ = 2.7 Hz, CH_3), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -101.8 (s).

IR (neat): 2985, 1761, 1521, 1282, 1226, 1085, 747 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 303 (20) [M+Na^+], 281 (100) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{14}H_{15}F_2N_2O_2$ [M+H^+] 281.1096, found 281.1100.



Ethyl 2-(2-acetyl-5-(1*H*-pyrazol-1-yl)phenyl)-2,2-difluoroacetate (140ma): The general procedure **H** was followed using substrate **95m** (93 mg, 0.50 mmol) and **139a** (304 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 4/1) yielded **140ma** (43 mg, 28%) as a brown solid. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **140ma** (83 mg, 53%).

M. p. = 106–107 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.18 (d, J = 1.9 Hz, 1H), 8.04 (d, J = 2.7 Hz, 1H), 7.99–7.93 (m, 2H), 7.77 (d, J = 1.7 Hz, 1H), 6.52 (dd, J = 2.6, 1.7 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 2.60 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H).

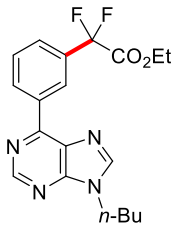
^{13}C NMR (125 MHz, $CDCl_3$) δ = 197.9 (C_q), 162.7 (t, $^2J_{C\text{-}F}$ = 32.9 Hz, C_q), 142.6 (C_q), 142.4 (CH), 134.6 (t, $^2J_{C\text{-}F}$ = 23.7 Hz, C_q), 133.0 (t, $^3J_{C\text{-}F}$ = 2.8 Hz, C_q), 131.9 (CH), 126.9 (CH), 119.8 (CH), 117.3 (t, $^3J_{C\text{-}F}$ = 11.4 Hz, CH), 112.9 (t, $^1J_{C\text{-}F}$ = 250.5 Hz, C_q), 109.0 (CH), 62.8 (CH_2), 28.0 (CH_3), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -99.8.

IR (neat): 3130, 2923, 1762, 1387, 1268, 1120, 1006, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 331 (85) [M+Na^+], 309 (100) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{15}H_{15}F_2N_2O_3$ [M+H^+] 309.1045, found 309.1048.



Ethyl 2-[3-(9-*n*-butyl-9*H*-purin-6-yl)phenyl]-2,2-difluoroacetate (141aa): The general procedure **I** was followed using substrate **131a** (63 mg, 0.25 mmol) and **139a** (152 mg, 0.75 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 3/1) yielded **141aa** (73 mg, 78%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **141aa** (73 mg, 78%).

^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.06 (t, J = 1.9 Hz, 1H), 9.00 (s, 1H), 8.97 (dd, J = 7.9, 1.9 Hz, 1H), 8.10 (s, 1H), 7.73 (ddt, J = 7.8, 1.9, 1.2 Hz, 1H), 7.62 (dd, J = 7.9, 7.8 Hz, 1H), 4.38–4.24 (m, 4H), 1.98–1.87 (m, 2H), 1.43–1.32 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H).

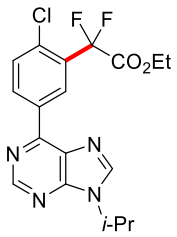
^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.9 (t, $^2J_{C\text{-}F}$ = 35.1 Hz, C_q), 153.0 (C_q), 152.6 (C_q), 152.1 (CH), 144.5 (CH), 136.3 (C_q), 133.3 (t, $^2J_{C\text{-}F}$ = 25.6 Hz, C_q), 132.3 (CH), 131.1 (C_q), 128.8 (CH), 127.6 (t, $^3J_{C\text{-}F}$ = 5.9 Hz, CH), 126.7 (t, $^3J_{C\text{-}F}$ = 6.3 Hz, CH), 113.3 (t, $^1J_{C\text{-}F}$ = 252.0 Hz, C_q), 63.2 (CH_2), 43.8 (CH_2), 32.0 (CH_2), 20.0 (CH_2), 13.9 (CH_3), 13.5 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -103.5 (s).

IR (neat): 2962, 1761, 1572, 1323, 1084, 800, 645 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 397 (40) [M+Na^+], 375 (100) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{19}H_{21}F_2N_4O_2$ [M+H^+] 375.1627, found 375.1629.



Ethyl 2-[2-chloro-5-(9-isopropyl-9*H*-purin-6-yl)phenyl]-2,2-difluoroacetate (141ba): The general procedure **I** was followed using substrate **131b** (68 mg, 0.25 mmol) and **139a** (152 mg, 0.75 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **141ba** (82 mg, 83%) as a brown solid. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **141ba** (80 mg, 81%) as a brown solid.

M. p. = 78–79 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.26 (d, J = 2.1 Hz, 1H), 9.01 (s, 1H), 8.99 (dd, J = 8.4, 2.1 Hz, 1H), 8.21 (s, 1H), 7.61 (d, J = 8.5 Hz, 1H), 4.98 (hept, J = 6.8 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.67 (d, J = 6.8 Hz, 6H), 1.30 (t, J = 7.1 Hz, 3H).

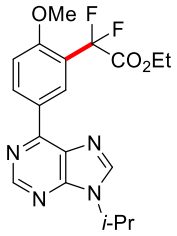
^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.0 (t, $^2J_{C\text{-}F}$ = 33.8 Hz, C_q), 152.4 (C_q), 152.0 (C_q), 151.9 (CH), 142.5 (CH), 134.8 (C_q), 134.4 (t, $^3J_{C\text{-}F}$ = 5.0 Hz, C_q), 133.2 (CH), 131.6 (t, $^2J_{C\text{-}F}$ = 25.2 Hz, C_q), 131.4 (C_q), 130.8 (CH), 128.6 (t, $^3J_{C\text{-}F}$ = 8.7 Hz, CH), 112.1 (t, $^1J_{C\text{-}F}$ = 251.2 Hz, C_q), 63.3 (CH_2), 47.4 (CH), 22.5 (CH_3), 13.8 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -102.2 (s).

IR (neat): 3113, 2983, 1757, 1682, 1228, 1078, 837, 635 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 417 (10) [M+Na^+], 395 (100) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{18}H_{18}ClF_2N_4O_2$ [M+H^+] 395.1081, found 395.1081.



Ethyl 2,2-difluoro-2-[5-(9-isopropyl-9*H*-purin-6-yl)-2-methoxyphenyl]acetate (141ca): The general procedure **I** was followed using substrate **131c** (67 mg, 0.25 mmol) and **139a** (152 mg, 0.75 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **141ca**

(80 mg, 82%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **141ca** (87 mg, 89%).

^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.15 (d, J = 2.1 Hz, 1H), 9.01 (dd, J = 8.7, 2.1 Hz, 1H), 8.93 (s, 1H), 8.14 (s, 1H), 7.07 (d, J = 8.7 Hz, 1H), 4.93 (hept, J = 6.8 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 1.62 (d, J = 6.8 Hz, 6H), 1.25 (t, J = 7.1 Hz, 3H).

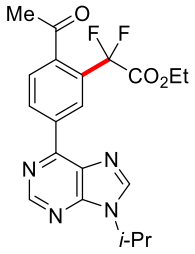
^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.7 (t, $^2J_{C\text{-}F}$ = 33.9 Hz, C_q), 158.5 (t, $^3J_{C\text{-}F}$ = 4.6 Hz, C_q), 152.9 (C_q), 151.8 (C_q), 151.7 (CH), 141.7 (CH), 134.1 (CH), 130.8 (C_q), 128.4 (C_q), 128.0 (t, $^3J_{C\text{-}F}$ = 7.6 Hz, CH), 122.1 (t, $^2J_{C\text{-}F}$ = 24.1 Hz, C_q), 112.0 (t, $^1J_{C\text{-}F}$ = 248.5 Hz, C_q), 111.1 (CH), 62.6 (CH_2), 55.9 (CH_3), 47.2 (CH), 22.5 (CH_3), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -102.8 (s).

IR (neat): 2981, 1758, 1575, 1507, 1274, 1022, 645 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 413 (25) [M+Na^+], 319 (100) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{19}H_{21}F_2N_4O_3$ [M+H^+] 391.1576, found 391.1576.



Ethyl 2-[2-acetyl-5-(9-isopropyl-9*H*-purin-6-yl)phenyl]-2,2-difluoroacetate (141da): The general procedure **I** was followed using substrate **131d** (70 mg, 0.25 mmol) and **139a** (152 mg, 0.75 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **141da** (20 mg, 20%) as a brown solid. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **141da** (60 mg, 60%).

M. p. = 125–126 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.33 (d, J = 1.6 Hz, 1H), 9.12 (dd, J = 8.1, 1.6 Hz, 1H), 9.04 (s, 1H), 8.22 (s, 1H), 7.97 (d, J = 8.1 Hz, 1H), 4.98 (hept, J = 6.8 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 2.64 (s, 3H), 1.67 (d, J = 6.8 Hz, 6H), 1.31 (t, J = 7.1 Hz, 3H).

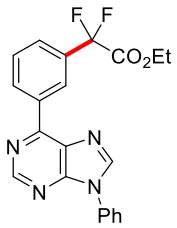
^{13}C NMR (125 MHz, $CDCl_3$) δ = 199.5 (C_q), 163.0 (t, $^2J_{C\text{-}F}$ = 33.5 Hz, C_q), 152.5 (C_q), 151.9 (CH), 151.7 (C_q), 142.8 (CH), 139.2 (C_q), 137.5 (t, $^3J_{C\text{-}F}$ = 3.8 Hz, C_q), 132.6 (t, $^2J_{C\text{-}F}$ = 23.8 Hz, C_q), 131.9 (CH), 131.8 (C_q), 129.8 (CH), 128.3 (t, $^3J_{C\text{-}F}$ = 10.4 Hz, CH), 113.3 (t, $^1J_{C\text{-}F}$ = 250.0 Hz, C_q), 62.7 (CH_2), 47.6 (CH), 28.5 (CH_3), 22.6 (CH_3), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -99.3 (s).

IR (neat): 2985, 1773, 1582, 1224, 1109, 1022, 764 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 425 (40) [M+Na$^+$], 403 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{20}H_{21}F_2N_4O_3$ [M+H$^+$] 403.1576, found 403.1576.



Ethyl 2,2-difluoro-2-[3-(9-phenyl-9*H*-purin-6-yl)phenyl]acetate (141ea): The general procedure **I** was followed using substrate **131e** (68 mg, 0.25 mmol) and **139a** (152 mg, 0.75 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 4/1) yielded **141ea** (62 mg, 63%) as a white solid. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **141ea** (74 mg, 75%).

M. p. = 81–82 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.12 (d, *J* = 1.8 Hz, 1H), 9.07 (s, 1H), 9.02 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.39 (s, 1H), 7.77 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 7.75–7.71 (m, 2H), 7.66 (dd, *J* = 7.9, 7.8 Hz, 1H), 7.62–7.56 (m, 2H), 7.51–7.45 (m, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

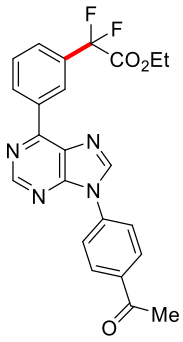
^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.0 (t, $^2J_{C\text{-}F}$ = 35.1 Hz, C_q), 153.8 (C_q), 153.0 (CH), 152.4 (C_q), 143.6 (CH), 136.1 (C_q), 134.2 (C_q), 133.4 (t, $^2J_{C\text{-}F}$ = 25.7 Hz, C_q), 132.4 (t, $^4J_{C\text{-}F}$ = 1.7 Hz, CH), 131.6 (C_q), 123.0 (CH), 129.0 (CH), 128.6 (CH), 127.9 (t, $^3J_{C\text{-}F}$ = 6.0 Hz, CH), 126.8 (t, $^3J_{C\text{-}F}$ = 6.4 Hz, CH), 123.7 (CH), 113.3 (t, $^1J_{C\text{-}F}$ = 252.4 Hz, C_q), 63.2 (CH_2), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -103.5 (s).

IR (neat): 3103, 2988, 1767, 1566, 1443, 1287, 1076, 679 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 417 (10) [M+Na$^+$], 395 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{21}H_{17}F_2N_4O_2$ [M+H$^+$] 395.1314, found 395.1314.



Ethyl 2-{3-[9-(4-acetylphenyl)-9*H*-purin-6-yl]phenyl}-2,2-difluoroacetate (141fa): The general procedure **I** was followed using substrate **131f** (79 mg, 0.25 mmol) and **139a** (152 mg, 0.75 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **141fa** (83 mg, 76%) as a light yellow solid. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of P(4-$C_6H_4CF_3)_3$ yielded **141fa** (69 mg, 63%).

M. p. = 134–135 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.11 (d, J = 1.8 Hz, 1H), 9.10 (s, 1H), 9.01 (d, J = 8.2 Hz, 1H), 8.47 (s, 1H), 8.19 (d, J = 8.6 Hz, 2H), 7.95 (d, J = 8.6 Hz, 2H), 7.79 (dd, J = 7.6, 1.4 Hz, 1H), 7.67 (dd, J = 8.2, 7.6 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 2.66 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H).

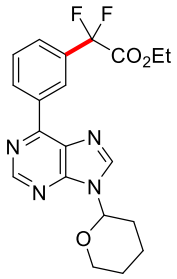
^{13}C NMR (125 MHz, $CDCl_3$) δ = 196.3 (C_q), 163.9 (t, $^2J_{C\text{-}F}$ = 35.3 Hz, C_q), 154.1 (C_q), 153.1 (CH), 152.2 (C_q), 142.7 (CH), 138.0 (C_q), 136.5 (C_q), 135.8 (C_q), 133.4 (t, $^2J_{C\text{-}F}$ = 25.7 Hz, C_q), 132.4 (CH), 131.7 (C_q), 130.1 (CH), 129.0 (CH), 128.0 (t, $^3J_{C\text{-}F}$ = 5.9 Hz, CH), 126.9 (t, $^3J_{C\text{-}F}$ = 6.3 Hz, CH), 123.0 (CH), 113.2 (t, $^1J_{C\text{-}F}$ = 251.5 Hz, C_q), 63.3 (CH_2), 26.7 (CH_3), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -103.6 (s).

IR (neat): 3078, 2982, 1757, 1682, 1572, 1227, 1099, 836 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 475 (55) [M+K$^+$], 437 (40) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{23}H_{19}F_2N_4O_3$ [M+H$^+$] 437.1420, found 437.1415.



Ethyl 2,2-difluoro-2-{3-[9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-yl]phenyl}acetate (141ga): The general procedure **I** was followed using substrate **131g** (70 mg, 0.25 mmol) and **139a** (152 mg, 0.75 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **141ga** (56 mg, 56%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **141ga** (82 mg, 81%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.07 (d, J = 1.9 Hz, 1H), 9.03 (s, 1H), 9.00 (dd, J = 7.8, 1.9 Hz, 1H), 8.35 (s, 1H), 7.77 (ddd, J = 7.8, 1.9, 1.3 Hz, 1H), 7.65 (dd, J = 7.8, 7.8 Hz, 1H), 5.86 (dd, J = 10.0, 2.8 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.25–4.09 (m, 1H), 3.82 (td, J = 11.5, 3.0 Hz, 1H), 2.27–1.99 (m, 3H), 1.91–1.70 (m, 3H), 1.32 (t, J = 7.1 Hz, 3H).

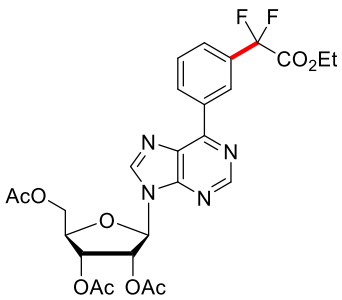
^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.9 (t, $^2J_{C\text{-}F}$ = 35.1 Hz, C_q), 153.1 (C_q), 152.2 (CH), 151.8 (C_q), 142.4 (CH), 136.1 (C_q), 133.3 (t, $^2J_{C\text{-}F}$ = 25.6 Hz, C_q), 132.4 (CH), 131.1 (C_q), 128.9 (CH), 127.7 (t, $^3J_{C\text{-}F}$ = 5.9 Hz, CH), 126.7 (t, $^3J_{C\text{-}F}$ = 6.3 Hz, CH), 113.2 (t, $^1J_{C\text{-}F}$ = 252.0 Hz, C_q), 82.0 (CH), 68.9 (CH_2), 63.2 (CH_2), 31.9 (CH_2), 24.9 (CH_2), 22.8 (CH_2), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -103.5 (d, J = 2.0 Hz).

IR (neat): 2945, 1761, 1572, 1217, 1081, 728, 575 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 425 (50) [M+Na$^+$], 403 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{20}H_{21}F_2N_4O_3$ [M+H$^+$] 403.1576, found 403.1574.



(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-{6-[3-(2-ethoxy-1,1-difluoro-2-oxoethyl)phenyl]-9*H*-purin-9-yl}tetrahydrofuran-3,4-diyl diacetate (141ha): The general procedure **I** was followed using substrate **131h** (114 mg, 0.25 mmol) and **139a** (152 mg, 0.75 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **141ha** (81 mg, 56%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **141ha** (88 mg, 61%).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.06 (d, J = 1.8 Hz, 1H), 9.02 (s, 1H), 8.96 (dd, J = 7.9, 1.9 Hz, 1H), 8.29 (s, 1H), 7.76 (ddd, J = 7.8, 1.9, 1.2 Hz, 1H), 7.64 (dd, J = 7.9, 7.8 Hz, 1H), 6.29 (d, J = 5.3 Hz, 1H), 6.00 (dd, J = 5.4 Hz, 1H), 5.69 (dd, J = 5.6, 4.4 Hz, 1H), 4.51–4.35 (m, 3H), 4.31 (q, J = 7.1 Hz, 2H), 2.15 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H).

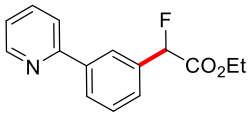
^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.1 (C_q), 169.4 (C_q), 169.2 (C_q), 163.9 (t, $^2J_{C\text{-}F}$ = 35.1 Hz, C_q), 153.6 (C_q), 152.4 (CH), 152.1 (C_q), 142.8 (CH), 135.9 (C_q), 133.3 (t, $^2J_{C\text{-}F}$ = 25.7 Hz, C_q), 132.3 (CH), 131.6 (C_q), 128.9 (CH), 127.8 (t, $^3J_{C\text{-}F}$ = 5.9 Hz, CH), 126.7 (t, $^3J_{C\text{-}F}$ = 6.3 Hz, CH), 113.2 (t, $^1J_{C\text{-}F}$ = 252.0 Hz, C_q), 86.4 (CH), 80.4 (CH), 73.0 (CH), 70.6 (CH), 63.2 (CH_2), 63.0 (CH_2), 20.8 (CH_3), 20.5 (CH_3), 20.4 (CH_3), 13.9 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -103.6 (s).

IR (neat): 2987, 1745, 1209, 1095, 910, 800, 729 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 599 (50) [M+Na^+], 577 (100) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{26}H_{27}F_2N_4O_9$ [M+H^+] 577.1741, found 577.1734.



Ethyl 2-fluoro-2-[3-(pyridin-2-yl)phenyl]acetate (162a): The general procedure **H** was followed using substrate **95a** (78 mg, 0.50 mmol) and **161** (278 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **162a** (78 mg, 60%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.68 (ddd, J = 4.8, 1.8, 1.0 Hz, 1H), 8.08 (s, 1H), 8.04–7.98 (m, 1H), 7.77–7.67 (m, 2H), 7.50–7.49 (m, 2H), 7.27–7.19 (m, 1H), 5.84 (d, J = 47.7 Hz, 1H), 4.29–4.17 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H).

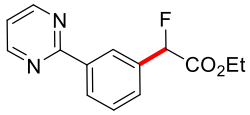
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.3 (d, $^2J_{C\text{-}F}$ = 27.5 Hz, C_q), 156.4 (C_q), 149.6 (CH), 139.9 (C_q), 136.7 (CH), 134.8 (d, $^2J_{C\text{-}F}$ = 20.5 Hz, C_q), 129.1 (CH), 128.0 (d, $^4J_{C\text{-}F}$ = 2.1 Hz, CH), 126.9 (d, $^3J_{C\text{-}F}$ = 5.9 Hz, CH), 125.2 (d, $^3J_{C\text{-}F}$ = 6.3 Hz, CH), 122.4 (CH), 120.5 (CH), 89.3 (d, $^1J_{C\text{-}F}$ = 185.5 Hz, CH), 61.9 (CH_2), 14.1 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -180.3 (d, J = 47.5 Hz).

IR (neat): 2983, 1754, 1585, 1462, 1205, 1055, 769 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 282 (10) [M+Na$^+$], 260 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{15}H_{14}FNO_2$ [M+H$^+$] 260.1081, found 260.1086.



Ethyl 2-fluoro-2-[3-(pyrimidin-2-yl)phenyl]acetate (162b): The general procedure **H** was followed using substrate **95i** (78 mg, 0.50 mmol) and **161** (278 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **162b** (74 mg, 57%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.80 (d, J = 4.8 Hz, 2H), 8.56 (d, J = 1.6 Hz, 1H), 8.47 (dd, J = 7.8, 1.5 Hz, 1H), 7.58 (dd, J = 7.7, 1.5 Hz, 1H), 7.52 (dd, J = 7.8, 7.7 Hz, 1H), 7.20 (t, J = 4.8 Hz, 1H), 5.86 (d, J = 47.6 Hz, 1H), 4.44–4.01 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H).

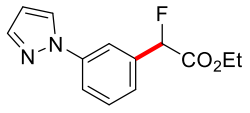
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.4 (d, $^2J_{C\text{-}F}$ = 27.5 Hz, C_q), 163.9 (C_q), 157.3 (CH), 138.1 (C_q), 134.8 (d, $^2J_{C\text{-}F}$ = 20.5 Hz, C_q), 129.2 (d, $^4J_{C\text{-}F}$ = 2.1 Hz, CH), 129.1 (CH), 128.7 (d, $^3J_{C\text{-}F}$ = 5.8 Hz, CH), 126.7 (d, $^3J_{C\text{-}F}$ = 6.5 Hz, CH), 119.4 (CH), 89.3 (d, $^1J_{C\text{-}F}$ = 185.8 Hz, CH), 61.9 (CH_2), 14.0 (CH_3).

^{19}F NMR (471 MHz, $CDCl_3$) δ = -180.1 (d, J = 47.8 Hz).

IR (neat): 2983, 1754, 1567, 1410, 1204, 1054, 775 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 283 (100) [M+Na$^+$], 261 (90) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{14}H_{14}FN_2O_2$ [M+H$^+$] 261.1034, found 261.1042.



Ethyl 2-[3-(1*H*-pyrazol-1-yl)phenyl]-2-fluoroacetate (162c): The general procedure **H** was followed using 1-phenyl-1*H*-pyrazole (**95p)** (72 mg, 0.50 mmol) and **161** (278 mg, 1.5 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 8/1) yielded **162c** (96 mg, 77%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.93 (dd, J = 2.5, 0.6 Hz, 1H), 7.80 (s, 1H), 7.73 (dd, J = 8.2, 1.1 Hz, 1H), 7.70 (d, J = 1.8 Hz, 1H), 7.46 (dd, J = 8.2, 7.6 Hz, 1H), 7.36 (dd, J = 7.6, 1.2 Hz, 1H), 6.45 (dd, J = 2.5, 1.8 Hz, 1H), 5.81 (d, J = 47.6 Hz, 1H), 4.36–4.09 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H).

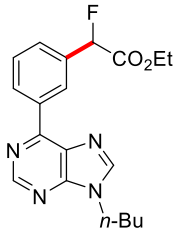
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.1 (d, $^{2}J_{C\text{-}F}$ = 27.2 Hz, C_q), 141.3 (CH), 140.4 (C_q), 135.7 (d, $^{2}J_{C\text{-}F}$ = 20.7 Hz, C_q), 129.9 (CH), 126.7 (CH), 124.2 (d, $^{3}J_{C\text{-}F}$ = 6.3 Hz, CH), 120.0 (d, $^{4}J_{C\text{-}F}$ = 1.9 Hz, CH), 117.0 (d, $^{3}J_{C\text{-}F}$ = 6.9 Hz, CH), 107.9 (CH), 88.8 (d, $^{1}J_{C\text{-}F}$ = 186.7 Hz, CH), 62.0 (CH_2), 14.0 (CH_3).

^{19}F NMR (471 MHz, $CDCl_3$) δ = -181.8 (d, J = 47.2 Hz).

IR (neat): 2984, 1754, 1596, 1392, 1204, 1042, 749 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 271 (100) [M+Na^+], 249 (90) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{13}H_{14}FN_2O_2$ [M+H^+] 249.1034, found 249.1037.



Ethyl 2-[3-(9-*n*-butyl-9*H*-purin-6-yl)phenyl]-2-fluoroacetate (162d): The general procedure **I** was followed using substrate **131a** (63 mg, 0.25 mmol) and **161** (139 mg, 0.75 mmol). Isolation by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **162d** (54 mg, 60%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.01 (s, 1H), 8.90 (d, J = 1.6 Hz, 1H), 8.88 (d, J = 7.3 Hz, 1H), 8.11 (s, 1H), 7.67–7.55 (m, 2H), 5.91 (d, J = 47.6 Hz, 1H), 4.50–4.01 (m, 4H), 1.97–1.82 (m, 2H), 1.43–1.33 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.4 (d, $^{2}J_{C\text{-}F}$ = 27.4 Hz, C_q), 153.6 (C_q), 152.6 (C_q), 152.2 (CH), 144.5 (CH), 136.2 (C_q), 134.8 (d, $^{2}J_{C\text{-}F}$ = 20.7 Hz, C_q), 131.1 (C_q), 131.0 (d, $^{4}J_{C\text{-}F}$ = 2.0

Hz, CH), 129.1 (CH), 128.7 (d, $^{3}J_{C\text{-}F}$ = 5.8 Hz, CH), 128.2 (d, $^{3}J_{C\text{-}F}$ = 6.3 Hz, CH), 89.3 (d, $^{1}J_{C\text{-}F}$ = 186.0 Hz, C_q), 61.9 (CH_2), 43.7 (CH_2), 31.9 (CH_2), 19.9 (CH_2), 14.0 (CH_3), 13.5 (CH_3).

^{19}F NMR (471 MHz, $CDCl_3$) δ = -180.3 (d, J = 48.0 Hz).

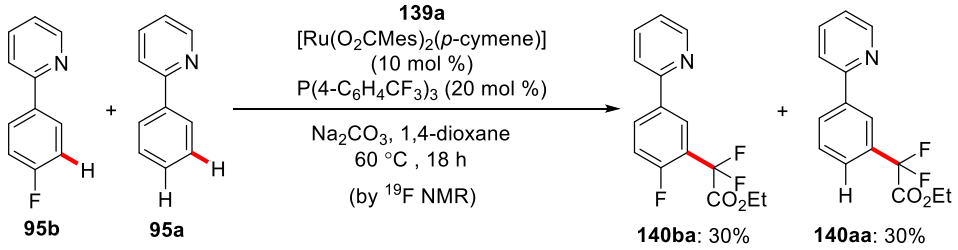
IR (neat): 2961, 2935, 1754, 1572, 1204, 1057, 700 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 379 (30) [M+Na$^+$], 357 (100) [M+H$^+$].

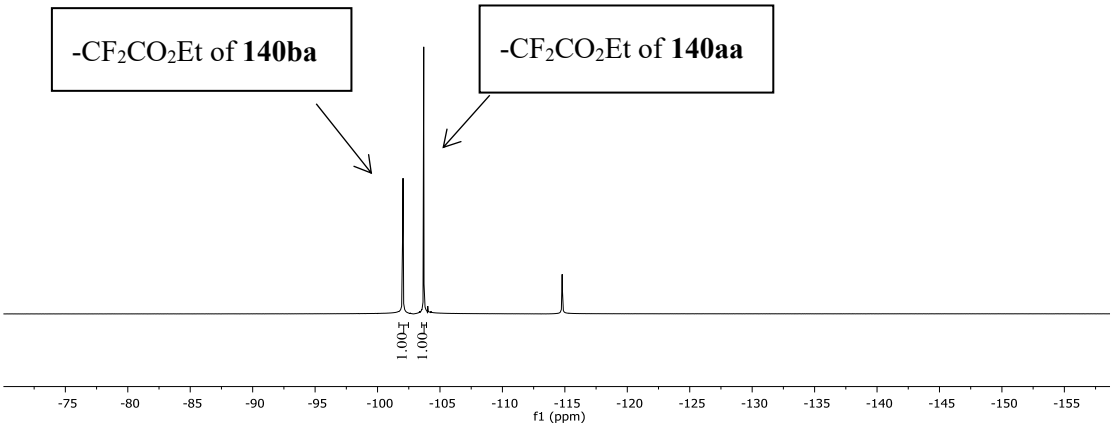
HR-MS (ESI) *m/z* calcd for $C_{19}H_{22}FN_4O_2$ [M+H$^+$] 357.1721, found 357.1726.

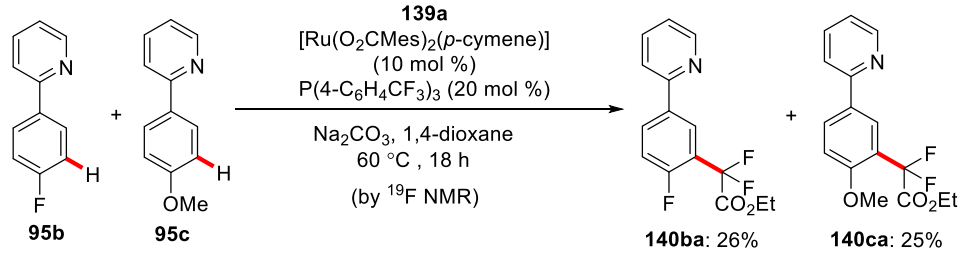
Mechanistic Studies

(a) Intermolecular competition between arenes 95

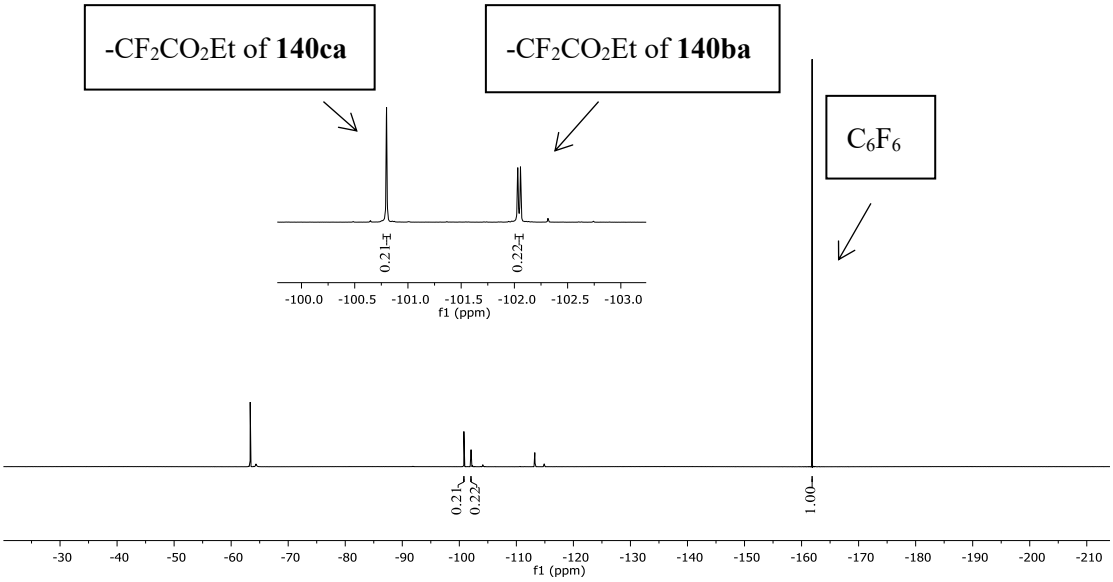


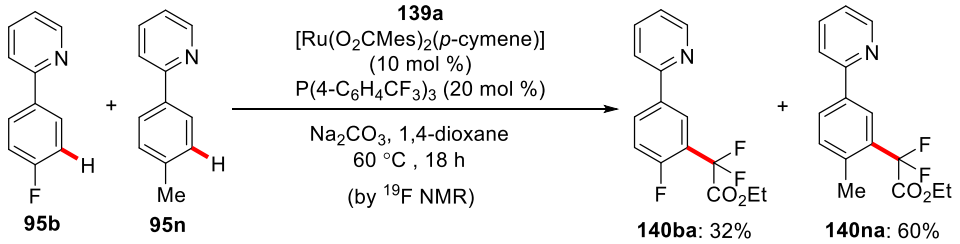
2-(4-Fluorophenyl)pyridine (**95b**) (87 mg, 0.5 mmol), 2-phenylpyridine (**95a**) (78 mg, 0.5 mmol), **139a** (102 mg, 0.5 mmol), [Ru(O_2CMes)$_2$(*p*-cymene)] (28.1 mg, 10 mol %), P(4-$C_6H_4CF_3$)$_3$ (46.7 mg, 20 mol %), Na_2CO_3 (106 mg, 1.0 mmol) and 1,4-dioxane (2.0 mL) were placed in a 25 mL Schlenk tube under N_2. The mixture was stirred at 60 °C for 18 h. At ambient temperature, CH_2Cl_2 (3 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure. Isolation of the residue by column chromatography (n-hexane/EtOAc: 10/1) afforded the mixture **140aa** and **140ba** (86 mg). Careful ^{19}F NMR analysis disclosed the ratio of **140aa** /**140ba** to be 1.0/1.0. Their spectral data were identical to those reported above.





2-(4-Fluorophenyl)pyridine (**95b**) (87 mg, 0.5 mmol), 2-(4-methoxyphenyl)pyridine (**95c**) (93 mg, 0.5 mmol), **139a** (102 mg, 0.5 mmol), [$Ru(O_2CMes)_2$(*p*-cymene)] (28.1 mg, 10 mol %), $P(4\text{-}C_6H_4CF_3)_3$ (46.7 mg, 20 mol %), Na_2CO_3 (106 mg, 1.0 mmol) and 1,4-dioxane (2.0 mL) were placed in a 25 mL Schlenk tube under N_2. The mixture was stirred at 60 °C for 18 h. At ambient temperature, EtOAc (20 mL) was added, and the mixture was filtered through a short pad of silica gel and concentrated *in vacuo*. Yields of products were determined by crude ^{19}F NMR spectroscopy using C_6F_6 (37.2 mg, 0.20 mmol) as internal standard. Their spectral data were identical to those reported above.





2-(4-Fluorophenyl)pyridine (**95b**) (87 mg, 0.50 mmol), 2-(*p*-tolyl)pyridine (**95n**) (85 mg, 0.50 mmol), **139a** (102 mg, 0.50 mmol), [$Ru(O_2CMes)_2$(*p*-cymene)] (28.1 mg, 10 mol %), P(4-$C_6H_4CF_3)_3$ (46.7 mg, 20 mol %), Na_2CO_3 (106 mg, 1.0 mmol) and 1,4-dioxane (2.0 mL) were placed in a 25 mL Schlenk tube under N_2. The mixture was stirred at 60 °C for 18 h. At ambient temperature, EtOAc (20 mL) was added, and the mixture was filtered through a short pad of silica gel and concentrated *in vacuo*. Conversions of products were determined by crude ^{19}F NMR spectroscopy using C_6F_6 (37.2 mg, 0.20 mmol) as internal standard.

Ethyl 2,2-difluoro-2-[2-methyl-5-(pyridin-2-yl)phenyl]acetate (140na):

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.67 (ddd, J = 4.8, 1.3, 1.2 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 8.00 (dd, J = 7.9, 1.9 Hz, 1H), 7.77–7.67 (m, 2H), 7.31 (d, J = 7.9 Hz, 1H), 7.21 (ddd, J = 6.2, 4.8, 2.3 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 2.44 (t, J = 2.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H).

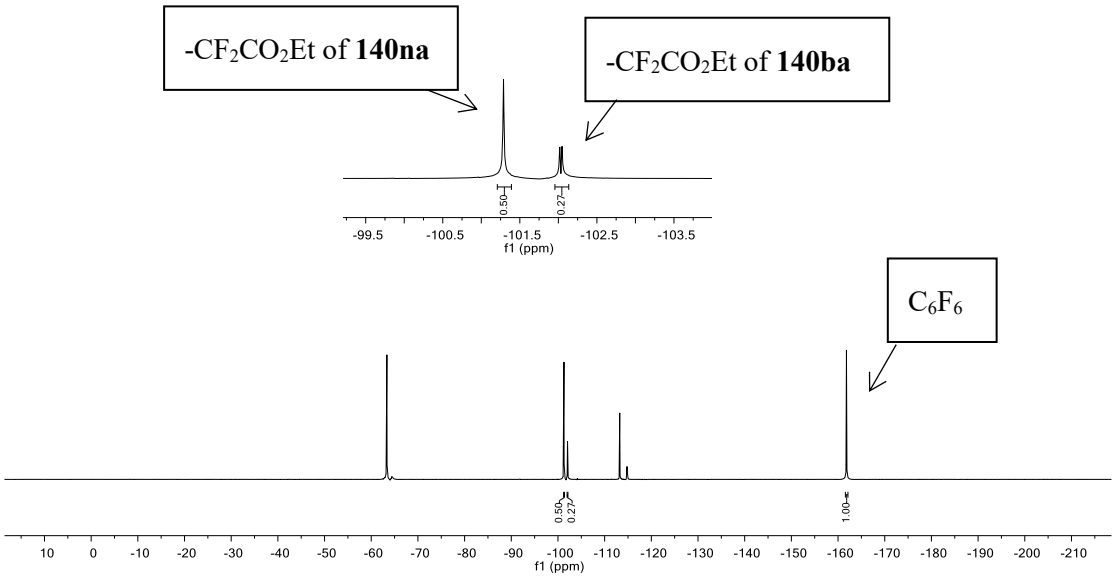
^{13}C NMR (125 MHz, $CDCl_3$) δ = 164.0 (t, $^{2}J_{C\text{-}F}$ = 35.1 Hz, C_q), 156.1 (C_q), 149.6 (CH), 137.2 (C_q), 137.1 (t, $^{3}J_{C\text{-}F}$ = 3.1 Hz, C_q), 136.8 (CH), 132.4 (CH), 131.5 (t, $^{2}J_{C\text{-}F}$ = 23.3 Hz, C_q), 129.0 (t, $^{4}J_{C\text{-}F}$ = 1.5 Hz, CH), 124.6 (t, $^{3}J_{C\text{-}F}$ = 9.0 Hz, CH), 122.3 (CH), 120.3 (CH), 114.1 (t, $^{1}J_{C\text{-}F}$ = 251.9 Hz, C_q), 63.1 (CH_2), 19.4 (t, $^{3}J_{C\text{-}F}$ = 2.6 Hz, CH_2), 13.8 (CH_3).

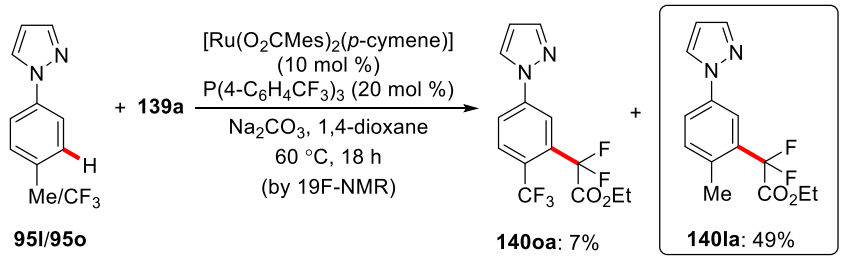
^{19}F NMR (471 MHz, $CDCl_3$) δ = -101.3 (s).

IR (neat): 2985, 1761, 1465, 1294, 1227, 1015, 779 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 314 (10) [M+Na$^+$], 292 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{16}H_{16}F_2NO_2$ [M+H$^+$] 292.1144, found 292.1147.





1-[4-(Trifluoromethyl)phenyl]-1*H*-pyrazole (**95o**) (106 mg, 0.50 mmol), 1-(*p*-tolyl)-1*H*-pyrazole (**95l**) (79 mg, 0.50 mmol), **139a** (102 mg, 0.50 mmol), $[Ru(O_2CMes)_2(p\text{-cymene})]$ (28.1 mg, 10 mol %), $P(4\text{-}C_6H_4CF_3)_3$ (46.7 mg, 20 mol %), Na_2CO_3 (106 mg, 1.0 mmol) and 1,4-dioxane (2.0 mL) were placed in a 25 mL Schlenk tube under N_2. The mixture was stirred at 60 °C for 18 h. At ambient temperature, EtOAc (20 mL) was added, and the mixture was filtered through a short pad of silica gel and concentrated *in vacuo*. Conversions of products were determined by crude ^{19}F NMR spectroscopy using C_6F_6 (37.2 mg, 0.20 mmol) as internal standard.

Ethyl 2-[5-(1*H*-pyrazol-1-yl)-2-(trifluoromethyl)phenyl]-2,2-difluoroacetate (140oa):

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.19 (d, J = 2.3 Hz, 1H), 8.05 (dd, J = 2.6, 0.6 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.87 (dd, J = 8.6, 2.3 Hz, 1H), 7.79 (dd, J = 1.8, 0.6 Hz, 1H), 6.55 (dd, J = 2.6, 1.8 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H).

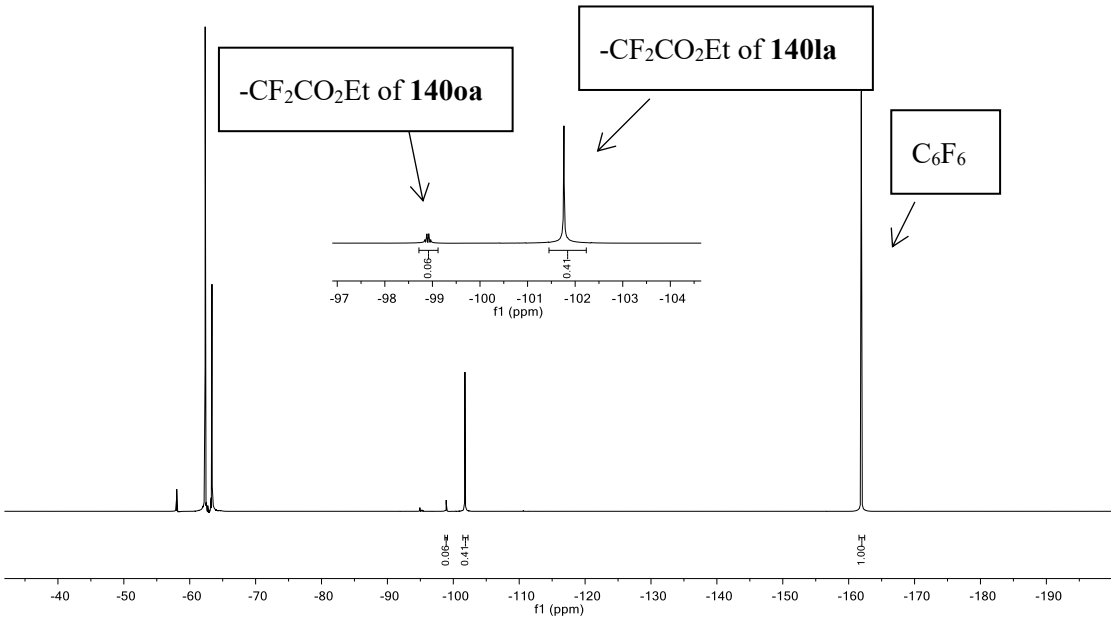
^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.8 (t, $^2J_{C\text{-}F}$ = 34.0 Hz, C_q), 142.5 (CH), 140.1 (C_q), 132.8 (t, $^2J_{C\text{-}F}$ = 25.8 Hz, C_q), 129.3 (q, $^3J_{C\text{-}F}$ = 5.7 Hz, CH), 126.9 (CH), 125.0 (qt, $^{2,3}J_{C\text{-}F}$ = 33.0, 2.7 Hz, C_q), 123.2 (q, $^1J_{C\text{-}F}$ = 271.3 Hz, C_q), 120.2 (CH), 118.0 (t, $^3J_{C\text{-}F}$ = 10.8 Hz, CH), 112.4 (t, $^1J_{C\text{-}F}$ = 253.8 Hz, C_q), 109.1 (CH), 63.6 (CH_2), 13.7 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -58.0 (t, J = 11.1 Hz, 3F), -98.9 (q, J = 11.1 Hz, 2F).

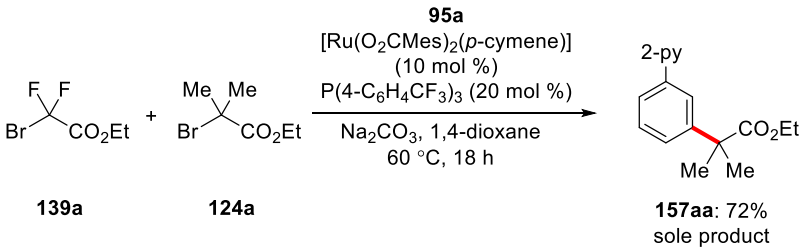
IR (neat): 2988, 1775, 1619, 1310, 1132, 1035, 751 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 357 [M+Na^+] (40), 335 [M+H^+] (100).

HR-MS (ESI) *m/z* calcd for $C_{14}H_{12}F_5N_2O_2$ [M+H^+] 335.0813, found 335.0820.



(b) Intermolecular competition between bromides



Ethyl 2-bromo-2,2-difluoroacetate (**139a**) (102 mg, 0.50 mmol), ethyl 2-bromo-2-methylpropanoate (**124a**) (98 mg, 0.50 mmol), 2-phenylpyridine (**95a)** (78 mg, 0.50 mmol), $[Ru(O_2CMes)_2(p\text{-cymene})]$ (28.1 mg, 10 mol %), $P(4\text{-}C_6H_4CF_3)_3$ (46.7 mg, 20 mol %), Na_2CO_3 (106 mg, 1.0 mmol) and 1,4-dioxane (2.0 mL) were placed in a 25 mL Schlenk tube under N_2 and were then stirred at 60 °C for 18 h. At ambient temperature, CH_2Cl_2 (3.0 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 8/1) yielded **157aa** (97 mg, 72%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.69 (ddd, J = 4.8, 1.7, 1.1 Hz, 1H), 8.00 (dd, J = 1.8, 1.7 Hz, 1H), 7.84 (ddd, J = 7.1, 1.8, 1.8 Hz, 1H), 7.80–7.64 (m, 2H), 7.49–7.33 (m, 2H), 7.22 (ddd, J = 6.7, 4.8, 1.7 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 1.64 (s, 6H), 1.18 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.7 (C_q), 157.5 (C_q), 149.6 (CH), 145.4 (C_q), 139.5 (C_q), 136.7 (CH), 128.7 (CH), 126.5 (CH), 125.3 (CH), 124.2 (CH), 122.1 (CH), 120.7 (CH), 60.8 (C_q), 46.6 (CH_2), 26.6 (CH_3), 14.1 (CH_3).

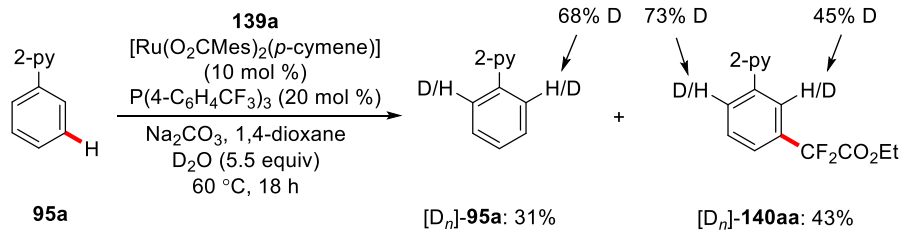
IR (neat): 2977, 1723, 1584, 1462, 1251, 1142, 769 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 270 (100) [M+H$^+$].

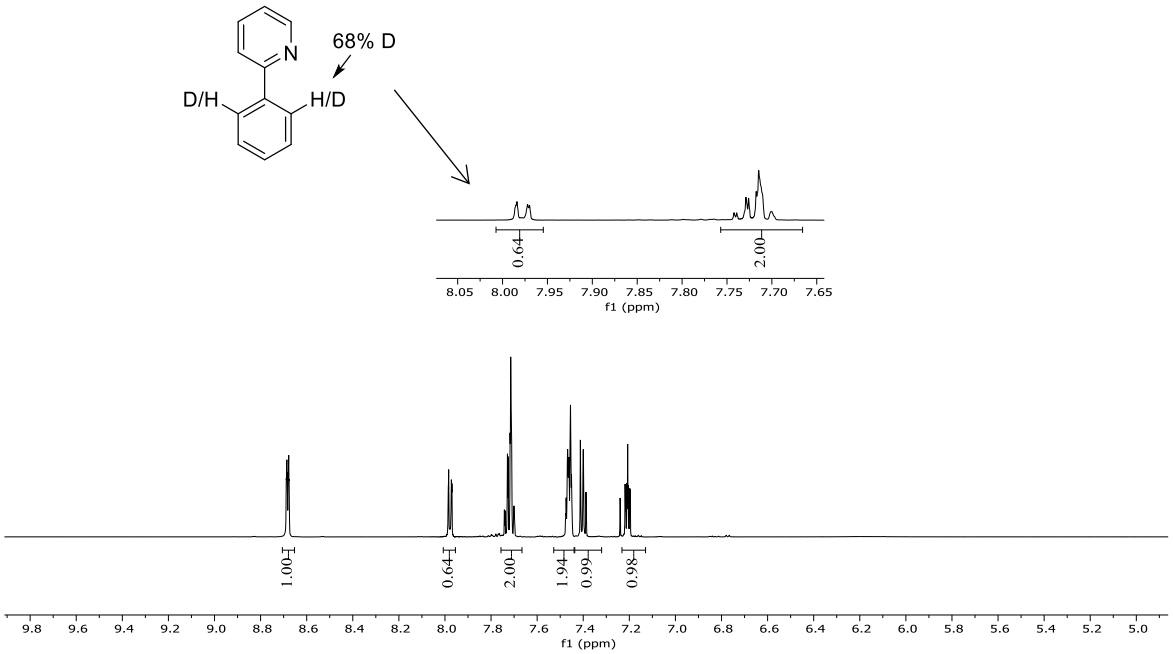
HR-MS (ESI) *m/z* calcd for $C_{17}H_{19}NO_2$ [M+H$^+$] 270.1489, found 270.1493.

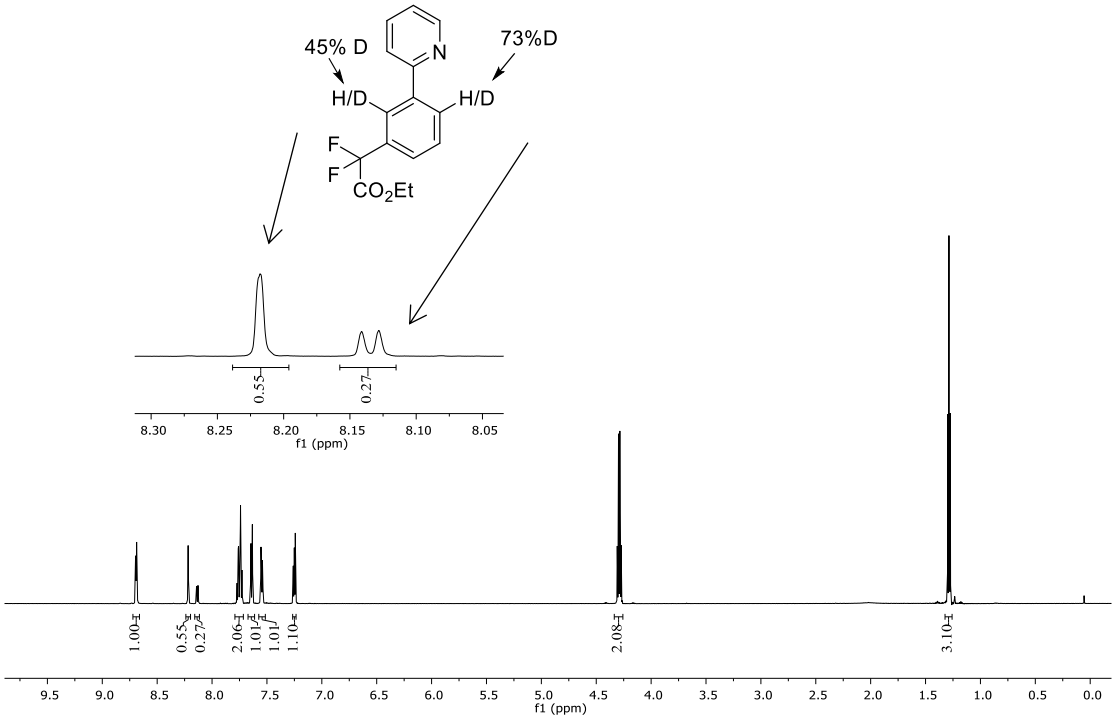
The analytical data are in accordance with those previously reported in the literature.[126]

(c) H/D Exchange experiment

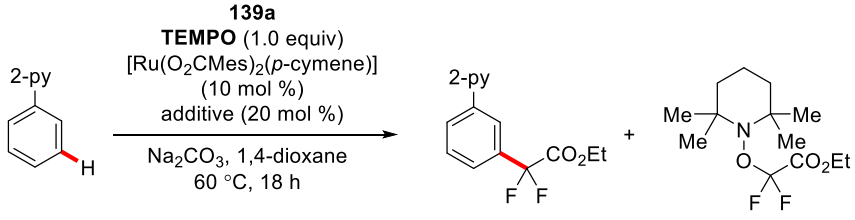


2-Phenylpyridine (**95a**) (78 mg, 0.50 mmol), **139a** (304 mg, 1.5 mmol), [Ru(O_2CMes)$_2$(p-cymene)] (28.1 mg, 10 mol %), P(4-$CF_3C_6H_4$)$_3$ (46.7 mg, 20 mol %), Na_2CO_3 (106 mg, 1.0 mmol), D_2O (50 µL, 2.75 mmol) and 1,4-dioxane (2.0 mL) were placed in a 25 mL Schlenk tube under N_2 and were then stirred at 60 °C for 1 h. At ambient temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded [D]$_n$-**95a** (24 mg, 31%) and [D]$_n$-**140aa** (59 mg, 43%). The D incorporation was determined by ^{1}H-NMR spectroscopy.


68% D
D/H
H/D
N
0.64
2.00
8.05 8.00 7.95 7.90 7.85 7.80 7.75 7.70 7.65
f1 (ppm)
1.00
0.64
2.00
1.94
0.99
0.98
9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0
f1 (ppm)


45% D
73%D
H/D
H/D
N
F
F
CO2Et
0.55
0.27
8.30 8.25 8.20 8.15 8.10 8.05
f1 (ppm)
1.00
0.55
0.27
2.06
1.01
1.01
1.10
2.08
3.10
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)

(d) *meta*-C–H Difluoromethylation in the presence of TEMPO



additive	140aa	158
$P(4\text{-}C_6H_4CF_3)_3$:	0%	15%
$Ni(PPh_3)_2Cl_2$:	0%	12%

2-Phenylpyridine (**95a**) (78 mg, 0.50 mmol), **139a** (304 mg, 1.5 mmol), TEMPO (78 mg, 0.50 mmol), $[Ru(O_2CMes)_2(p\text{-cymene})]$ (28.1 mg, 10 mol %), $P(4\text{-}C_6H_4CF_3)_3$ (46.7 mg, 20 mol %), Na_2CO_3 (106 mg, 1.0 mmol) and 1,4-dioxane (2.0 mL) were placed in a 25 mL Schlenk tube under N_2 and were then stirred at 60 °C for 18 h. After completion of the reaction, CH_2Cl_2 (3.0 mL) was added at ambient temperature and the volatiles were removed *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 50/1) yielded **95a** (74 mg, 95%) as a colorless oil and **158** (21 mg, 15%) as a colorless oil. A reaction using $Ni(PPh_3)_2Cl_2$ (10 mol %) instead of $P(4\text{-}C_6H_4CF_3)_3$ yielded **158** (17 mg, 12%).

^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.35 (q, J = 7.1 Hz, 2H), 1.63–1.51 (m, 6H), 1.37 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 2.6 Hz, 6H), 1.17 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.6 (t, $^2J_{C\text{-}F}$ = 42.6 Hz, C_q), 115.4 (t, $^1J_{C\text{-}F}$ = 271.1 Hz, C_q), 63.0 (CH_2), 61.4 (C_q), 40.3 (CH_2), 33.5 (t, $^5J_{C\text{-}F}$ = 4.3 Hz, CH_3), 20.8 (CH_3), 17.0 (CH_2), 14.0 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = -73.5.

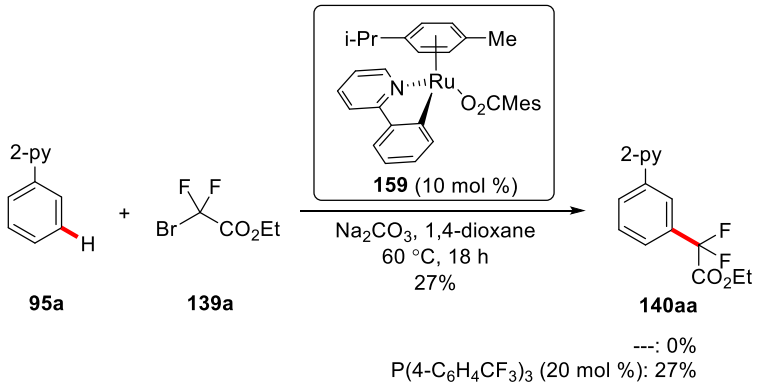
IR (neat): 2980, 2938, 1772, 1467, 1323, 1120, 688 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 280 [M+H$^+$] (100).

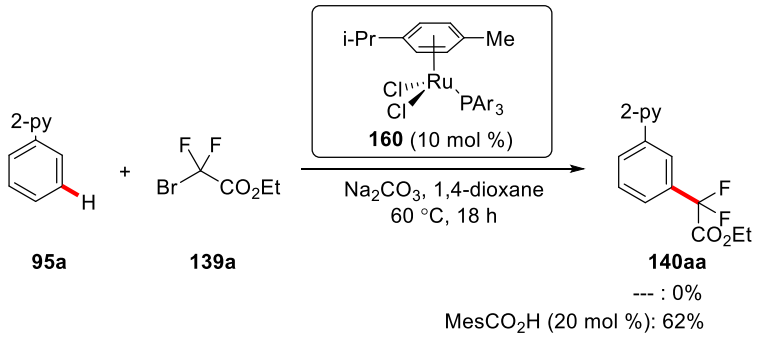
HR-MS (ESI) *m/z* calcd for $C_{13}H_{24}F_2NO_3$ [M+H$^+$] 280.1719, found 280.1721.

The analytical data are in accordance with those previously published in the literature.[171]

(e) *meta*-C–H Difluoromethylation with complexes 159 and 160



2-Phenylpyridine (**95a)** (31 mg, 0.20 mmol), ethyl 2-bromo-2,2-difluoroacetate (**139a**) (122 mg, 0.60 mmol), complex **159** (11.0 mg, 10 mol %), P(4-$C_6H_4CF_3$)$_3$ (19.0 mg, 20 mol %), Na_2CO_3 (43 mg, 0.40 mmol) and 1,4-dioxane (1.0 mL) were placed in a 25 mL Schlenk tube under N_2 and were then stirred at 60 °C for 18 h. At ambient temperature, CH_2Cl_2 (3.0 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 9/1) yielded **140aa** (15 mg, 27%) as a colorless oil and **95a** (21 mg, 70%) as a colorless oil.



2-Phenylpyridine (**95a)** (78 mg, 0.50 mmol), ethyl 2-bromo-2,2-difluoroacetate (**139a**) (304 mg, 1.5 mmol), complex **160** (39.0 mg, 10 mol %), $MesCO_2H$ (16.4 mg, 20 mol %), Na_2CO_3 (106 mg, 1.0 mmol) and 1,4-dioxane (2.0 mL) were placed in a 25 mL Schlenk tube under N_2 and were then stirred at 60 °C for 18 h. At ambient temperature, CH_2Cl_2 (3 mL) was added, and the reaction mixture was transferred into a round flask with CH_2Cl_2 and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 9/1) yielded **140aa** (86 mg, 62%) as a colorless oil.

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Poster

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