Cobalt-catalyzed directed ortho-C-H alkylation of arenes via radical processes

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**NANYANG
TECHNOLOGICAL
UNIVERSITY**

SINGAPORE

**COBALT-CATALYZED DIRECTED *ORTHO*-C–H
ALKYLATION OF ARENES VIA RADICAL PROCESSES**

SUN QIAO

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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SUN QIAO

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

A thesis submitted to the Nanyang Technological
University in partial fulfilment of the requirement for the
degree of Doctor of Philosophy

2019

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The contributions of the co-authors are as follows:

- Prof Yoshikai gave me the project direction, helped me analyze the problems encountered in the project and edited the manuscript draft and supporting information for me.
- I performed all the laboratory work, analyzed the experimental and spectroscopic data, and prepared the supporting information for this paper.

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- I performed all the laboratory work, analyzed the experimental and spectroscopic data, and prepared the supporting information for this paper.

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Summary

Alkylated arenes are important structural moieties that are prevalent in many natural products, pharmaceuticals and functional materials. Therefore, significant efforts from the synthetic community have been devoted to the synthesis of these structural motifs. In this context, transition metal-catalyzed, directing group-assisted arene C–H alkylation represents an attractive means for the introduction of alkyl groups to arenes because of the atom- and step-economical nature of the process as well as the predictable regioselectivity. In particular, C–H alkylation using alkyl halides as the alkylating agents has been extensively developed over the last decade, using precious transition metal catalysts as well as earth-abundant first-row transition metal catalysts. The latter catalysts have received significant attention not only for their cost-effectiveness but also for their distinct mode of activation of alkyl halides, that is, single electron transfer to generate alkyl radicals.

Given the above background, this thesis research has focused on the development of cobalt-catalyzed directed *ortho*-C–H alkylation reactions of arenes with novel alkylating agents, capitalizing on the radical nature of the cobalt catalysis. Chapter 1 describes a brief review of the transition metal-catalyzed alkylation of arenes, with a particular focus on aryl-alkyl cross-coupling and directed arene C–H alkylation reactions using first-row transition metals including cobalt. The single electron transfer from an arylmetal species to an alkyl halide, which is commonly involved in these reactions, has provided inspiration for this thesis work. Specifically, reaction systems comprised of cobalt–N-heterocyclic carbene (NHC) catalysts and Grignard reagents, which

have proved successful in a series of cross-coupling and C–H functionalization reactions, allowed the design of the whole project. Chapter 2 describes a C(sp²)–H/C(sp³)–H coupling reaction between aryl imines and 2-bromobenzyl-protected secondary amines promoted by the combination of a cobalt–NHC catalyst and a Grignard reagent. Featuring a merger of directed C–H activation and 1,5-hydrogen atom transfer, the reaction allows for *ortho*- α -aminoalkylation of the aryl imine at a mild temperature. Chapter 3 describes a tandem radical cyclization/C–C coupling between tethered bromo-alkenes and aryl N–H imines initiated by imine-directed C–H activation. Fine-tuning of the NHC ligand allowed the reaction to proceed smoothly, allowing for the introduction of a pyrrolidinylmethyl group to the *ortho* position of the imine. Chapter 4 describes *ortho*-methylation of arenes using methyl tosylate as a readily available and convenient methylation agent. Using CD₃OTs instead of MeOTs, the reaction also allows facile incorporation of a CD₃ group into arenes. Lastly, Chapter 5 is a concluding chapter that summarizes the whole thesis research.

List of Abbreviations

δ	chemical shift (ppm)
$^{\circ}\text{C}$	degree centigrade
Ac	acetyl
Alk	alkyl
Ar	aryl (substituted aromatic ring)
aq	aqueous
acac	acetylacetonate
AQ	8-aminoquinoline
br	broad
brs	broad singlet
9-BBN	9-borabicyclo(3.3.1)nonane
Boc	<i>tert</i> -butyloxycarbonyl
<i>n</i> -Bu	<i>n</i> -butyl
<i>sec</i> -Bu	<i>sec</i> -butyl
<i>t</i> -Bu	<i>tert</i> -butyl
cod	1,5-cyclooctadiene
COSY	Correlation Spectroscopy
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
Cy	cyclohexyl
<i>m</i> CBA	3-chlorobenzoate
d	doublet
dd	doublet of doublet
ddd	doublet of doublet of doublet

dt	doublet of triplet
DCB	2,3-dichlorobutane
DCE	1,2-dichloroethane
DCIB	1,2-dichloroisobutane
DtBEDA	<i>N,N'</i> -di- <i>tert</i> -butylethane-1,2-diamine
DME	1,2-dimethoxyethane
DABCO	1,4-diazabicyclo[2.2.2]octane
DCP	dicumyl peroxide
dppbz	1,2-bis(diphenylphosphino)benzene
dppe	1,2-bis(diphenylphosphino)ethane
dppen	<i>cis</i> -1,2-bis(diphenylphosphino)ethylene
dppp	1,3-bis(diphenylphosphino)propane
dpph	1,3-bis(diphenylphosphino)hexane
DEPT	Distortionless Enhancement by Polarization Transfer
DMPU	<i>N,N'</i> -dimethylpropyleneurea
equiv	equivalent
Et	ethyl
g	gram
h	hour
H	hydrogen
HAT	hydrogen atom transfer
HMTA	hexamethylenetetramine
HRMS	High Resolution Mass Spectrometry
HPLC	High Performance Liquid Chromatography
HMQC	Heteronuclear Multiple Quantum Coherence

Hz	hertz
IPr•HCl	1,3-bis(2,6-diisopropylphenyl)imidazonium chloride
IMes•HCl	1,3-bis(2,4,6-trimethylphenyl)imidazonium chloride
<i>J</i>	coupling constants
m	multiplet
m/z	mass per charge ratio
M	concentration (mol/L)
M ⁺	parent ion peak (mass spectrum)
Me	methyl
mg	milligram
min	minute
mL	milliliter
mmol	millimole
m.p.	melting point
mol %	mole percent
NHC	N-heterocyclic carbene
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Ph	phenyl
PA	picolinoylamide
PCET	proton-coupled electron transfer
PMP	<i>p</i> -methoxyphenyl
ppm	parts per million
<i>i</i> -Pr	<i>iso</i> -propyl

Py	pyridine
q	quartet
rt	room temperature
s	singlet
SET	single electron transfer
SIPr•HCl	1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride
t	triplet
td	triplet of doublet
TBS	<i>tert</i> -butyldimethylsilyl
TEA	triethylamine
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMCD	(<i>R,R</i>)-tetramethylcyclohexan-1,2-diamine
Tf	triflyl
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	<i>p</i> -toluenesulfonyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl

Chapter 1. Introduction

1.1 Transition Metal-Catalyzed Alkylation of Arenes

Alkylated arenes are important structural moieties widely prevalent in many natural products, pharmaceuticals and functional materials. Therefore, significant efforts from the synthetic community have been devoted to the synthesis of these structural motifs. Traditionally, there are several ways to form the aryl-alkyl bond, which includes Friedel-Crafts alkylation,¹ radical alkylation of arenes² and stoichiometric deprotonation of arenes and subsequent alkylation reactions.³ However, these methods all bear some limitations. For instance, the Friedel-Crafts alkylation is often associated with low regioselectivity, poor linear/branched selectivity and narrow substrate scope. The radical alkylation often suffers from poor regioselectivity and low yields. The deprotonation/alkylation process generally requires cryogenic reaction conditions and nontrivial protection and deprotection steps.

In the last few decades, transition metal-catalyzed cross-couplings between organometallic reagents and organic electrophiles have become one of the most efficient methods for C–C bond formation in organic synthesis. Although less straightforward than C(sp²)–C(sp²) or C(sp²)–C(sp) forming reactions, C(sp²)–C(sp³) cross-couplings have evolved as a powerful strategy for the synthesis of alkylated arenes. The aryl-alkyl cross-coupling reactions can be divided into two types, ie., reactions between aryl halides and alkylmetals and reactions between arylmetals and alkyl halides. On the basis of the organometallic reagents used, these cross-coupling reactions can be categorized as Kumada, Suzuki, Negishi, Stille and Hiyama cross-coupling.⁴ Various transition metal catalysts including palladium, nickel, iron, cobalt

have been used in the cross-coupling reactions.

1.1.1 Aryl Halide-Alkylmetal Cross-Coupling

Since the early development of the cross-coupling chemistry, transition metal-catalyzed cross-couplings between aryl (pseudo)halides and alkylmetals have been extensively studied.⁴ Palladium is the most predominant transition metal in this field and a diversity of cross-coupling reactions have been achieved with various types of alkylmetal reagents.⁵ Not only primary but also secondary alkyl nucleophiles have been successfully cross-coupled with aryl (pseudo)halides under Pd catalysis.⁶ However, due to economical and toxicity issues of palladium catalysts, there is a growing need for cheap and less-toxic catalysts. As economical alternatives to the palladium catalysts, nickel catalysts have been increasingly used in cross-coupling reactions of alkylmetal reagents. Besides primary and secondary alkyl nucleophiles, reactive nickel catalysts even allow cross-coupling reactions of tertiary alkylmetal reagents.⁷ However, the scope of the Ni-catalyzed cross-coupling is limited to more reactive alkylzinc and alkyl Grignard reagents. Similar to the palladium catalysts, toxicity issues also cause problems for the nickel catalysts. Later, iron- and cobalt-catalyzed cross-coupling reactions of aryl halides with alkylmetal reagents have evolved as attractive and environmentally more benign alternatives to related palladium- and nickel-catalyzed processes.⁸ However, only alkyl Grignard reagents are successfully employed in these reactions. Moreover, there is only one report of cobalt-catalyzed alkylation of aryl halides.⁹

1.1.2 Arylmetal-Alkyl Halide Cross-Coupling

In order to expand the scope of $C(sp^2)$ – $C(sp^3)$ cross-coupling reactions, the reverse cross-coupling between arylmetal reagents and alkyl (pseudo)halides has been studied. Compared with the first type of cross-coupling reactions, the reactions between arylmetals and alkyl halides (especially the nonactivated ones with β -H atoms) are less-straightforward due to the relative slower rate of oxidative addition of alkyl halides to transition metals and the tendency of resulting alkylmetals to undergo β -H elimination. However, these problems can be circumvented by careful choice of reaction conditions such as transition metals, ligands and organometallic reagents. Consequently, the cross-coupling between arylmetals and alkyl halides has emerged as an alternative approach to construct the alkylated arenes. The reactions can be achieved with a series of transition metals such as palladium, nickel, iron and cobalt.

Palladium catalysts have been used in a diversity of cross-coupling reactions between various arylmetal reagents and alkyl halides.⁴ However, only primary alkyl halides are suitable substrates for the Pd-catalyzed reactions. Since palladium catalysts are generally very expensive, they are gradually replaced by other earth-abundant, first-row transition metal catalysts such as nickel, iron and cobalt catalysts.

1.1.2.1 Nickel-Catalyzed Cross-Coupling

Ni-catalyzed cross-coupling has become a powerful alternative to the Pd-catalyzed process because of the lower costs of nickel catalysts. Not only primary but also secondary and tertiary alkyl halides have been used in Ni-catalyzed cross-coupling reactions with arylmetal reagents ($M = Zn, Mg, B, Si, Sn$).¹⁰

In 1998, Knochel and coworkers reported $Ni(acac)_2$ -catalyzed Negishi reactions of primary alkyl iodides with arylzinc reagents in the presence 4-(trifluoromethyl)styrene as the reductive elimination promoter (Scheme 1.1a).¹¹

Later, Gagné and coworkers reported Ni(cod)₂-catalyzed stereoselective synthesis of C-aryl glycosides through cross-coupling reactions between glycosyl halides and arylzinc reagents (Scheme 1.1b).¹² By using the stereoselective arylation as a key step, the first total synthesis of Salmochelin SX was achieved.

Scheme 1.1. Ni-catalyzed Negishi cross-coupling of alkyl halides

As for Ni-catalyzed Kumada reactions, in 2002, Kambe and coworkers reported two examples of Ni-catalyzed cross-couplings between primary alkyl halides and PhMgBr using 1,3-butadiene as the additive (Scheme 1.2a).¹³ Later, Oshima and coworkers developed the first Ni/phosphine-catalyzed cross-coupling of primary alkyl halides with aryl Grignard reagents using Cp*CH₂PPh₂ as the ligand (Scheme 1.2b).¹⁴ In 2009, Hu and coworkers reported highly functional group tolerant Kumada reactions of primary and secondary alkyl bromides and iodides with (hetero)aryl Grignards using a nickel pincer complex as the catalyst (Scheme 1.2c).¹⁵

Later, Hor and coworkers demonstrated that a dinuclear Ni(II) complex bearing a furan tethered amine-pyrazolyl tripodal ligand could catalyze reactions of primary alkyl bromides and iodides with aryl Grignard reagents in the presence of TMEDA (Scheme 1.2d).¹⁶

Scheme 1.2. Ni-catalyzed Kumada cross-coupling of alkyl halides

As for Ni-catalyzed Suzuki reactions, in 2004, Fu and coworkers developed the first cross-coupling of secondary alkyl bromides and iodides with (hetero)aryl boronic acids under the catalysis of Ni(cod)₂/bathophen (Scheme 1.3a).¹⁷ Later, they

expanded the scope of Ni-catalyzed Suzuki reactions to secondary alkyl chlorides by the use of a $\text{NiCl}_2\cdot\text{glyme}/\text{prolinol}$ catalytic system (Scheme 1.3b).¹⁸ Using $\text{NiBr}_2\cdot\text{diglyme}/4,4'$ -di-*tert*-butyl-2,2'-bipyridine as the catalyst, they further reported the first Ni-catalyzed Suzuki reactions of tertiary alkyl halides with aryl-(9-BBN) reagents (Scheme 1.3c).¹⁹ Later, Shuto and coworkers described the tertiary alkylation of (hetero)aryl boronic acids with iodocyclopropanes for the synthesis of quaternary arylcyclopropanes (Scheme 1.3d).²⁰ The reaction was promoted by a $\text{NiCl}_2(\text{PCy}_3)_2/\text{bathophen}$ catalytic system using *tert*-butanol as the solvent.

Scheme 1.3. Ni-catalyzed Suzuki cross-coupling of alkyl halides

As for Ni-catalyzed Hiyama reactions, in 2004, Fu and coworkers reported the

first Ni-catalyzed cross-coupling of secondary alkyl bromides and iodides with aryl trifluorosilanes in the presence of a $\text{NiBr}_2 \cdot \text{diglyme}$ /bathophen catalytic system and CsF promoter (Scheme 1.4a).²¹ Later, a more efficient $\text{NiCl}_2 \cdot \text{diglyme}$ /norephedrine catalytic system was developed by the same group for analogous Hiyama cross-couplings (Scheme 1.4b).²²

Scheme 1.4. Ni-catalyzed Hiyama cross-coupling of alkyl halides

In 2005, Fu and coworkers reported the first Stille cross-coupling of secondary alkyl bromides and iodides with aryltrichlorotin reagents in the presence of a NiCl_2 /bipyridine catalytic system (Scheme 1.5).²³ Commercially available aryltributylstannanes, on the other hand, were reactive for the cross-coupling only after conversion into the aryltrichlorotin reagents.

Scheme 1.5. Ni-catalyzed Stille cross-coupling of alkyl halides

1.1.2.2 Iron-Catalyzed Cross-Coupling

Fe-catalyzed cross-coupling has emerged as an attractive alternative to Ni- and Pd-catalyzed processes due to the natural abundance, environmental benignity, low-cost and low-toxicity of iron catalysts. Nowadays, various alkyl halides including less reactive alkyl chlorides and fluorides have been cross-coupled with a series of arylmetal reagents ($M = \text{Mg}, \text{Zn}, \text{B}, \text{Mn}$) under iron catalysis.^{8a}

As for Fe-catalyzed Kumada reactions, in 2004, Hayashi and coworkers reported $\text{Fe}(\text{acac})_3$ -catalyzed, ligand-free cross-couplings of primary and secondary alkyl bromides with aryl Grignard reagents (Scheme 1.6a).²⁴ Independently in the same year, Nakamura and coworkers reported analogous transformations using FeCl_3 as the catalyst and a stoichiometric amount of TMEDA as the additive (Scheme 1.6b).²⁵ Although Fe-catalyzed Kumada reactions of nonactivated alkyl halides have been extensively reported since then, most of these reactions involved the use of alkyl bromides and iodides whereas less reactive alkyl chlorides and fluorides were rarely used.^{8a} In 2012, Nakamura and coworkers reported highly efficient cross-couplings of chloroalkanes with aryl Grignard reagents by virtue of a FeCl_3/IPr catalytic system (Scheme 1.6c).²⁶ Besides primary and secondary chloroalkanes, tertiary as well as polychlorinated alkanes were also suitable partners for the reaction. In the same year, Deng and coworkers reported the first Fe-catalyzed cross-coupling of primary alkyl fluorides with aryl Grignard reagents using an NHC-bearing dinuclear iron complex as the catalyst (Scheme 1.6d).²⁷ Fe-catalyzed diastereoselective Kumada reactions have also been reported. In 2014, Cossy and workers disclosed a highly diastereoselective cross-coupling between a 2,3-disubstituted iodo-azetidine and PhMgBr using FeCl_2 as the catalyst and (*R,R*)-tetramethylcyclohexan-1,2-diamine

(TMCD) as the ligand (Scheme 1.6e).²⁸

Scheme 1.6. Fe-catalyzed Kumada cross-coupling of alkyl halides

a) Hayashi (2004)

b) Nakamura (2004)

c) Nakamura (2012)

d) Deng (2012)

e) Cossy (2014)

As for Fe-catalyzed Negishi reactions, in 2005, Nakamura and coworkers reported cross-coupling reactions of primary and secondary alkyl halides with diarylzinc or mixed diorganozinc reagents in the presence of a $\text{FeCl}_3/\text{TMEDA}$ catalytic system and an in-situ generated magnesium salt (Scheme 1.7a).²⁹ Later, they developed the first

Fe-catalyzed cross-coupling of alkyl tosylates with arylzinc reagent using a similar catalytic system (Scheme 1.7b).³⁰ More recently, the same group reported the synthesis of aryl C-glycosides via diastereoselective cross-couplings between glycosyl halides and di(hetero)arylzinc reagents in the presence of a well-defined $\text{FeCl}_2(\text{TMS-SCiOPP})$ complex (Scheme 1.7c).³¹

Scheme 1.7. Fe-catalyzed Negishi cross-coupling of alkyl halides

a) Nakamura (2005)

b) Nakamura (2009)

c) Nakamura (2017)

Fe-catalyzed aluminium-variants of Negishi cross-coupling have also been reported. In 2010, Nakamura and coworkers developed the first Fe-catalyzed Negishi cross-coupling between alkyl halides and triarylaluminium reagents prepared from 1 equiv of AlCl_3 and 3 equiv of PhMgCl (Scheme 1.8a).³² Later, the same group

reported highly diastereoselective cross-couplings of non-protected halohydrins with tetraarylaluminates using a well-defined $\text{FeCl}_2(\text{TMS-SciOPP})$ complex as the catalyst (Scheme 1.8b).³³ In 2013, Bedford and coworkers reported Negishi cross-couplings between alkyl bromides and tetraarylaluminates in the presence of a simplified iron(II) bis(dppe) complex (Scheme 1.8c).³⁴

Scheme 1.8. Fe-catalyzed aluminium-variants of Negishi cross-coupling of alkyl halides

a) Nakamura (2010)

b) Nakamura (2012)

c) Bedford (2013)

As for Fe-catalyzed Suzuki reactions, in 2010, Nakamura and coworkers reported Fe-catalyzed cross-couplings of primary and secondary alkyl halides with lithium arylborates in the presence of a sterically demanding $\text{FeCl}_2(\text{TMS-SciOPP})$ complex and MgBr_2 cocatalyst (Scheme 1.9a).³⁵ The lithium arylborates were prepared from arylboronic acid pinacol esters and alkyllithium reagents. Several years later, Bedford

and coworkers demonstrated that the coupling system could be simplified by using either $\text{Fe}(\text{acac})_3$, $\text{FeCl}_2(\text{dppe})$ or $\text{FeCl}_2(\text{dppp})$ as the catalyst (Scheme 1.9b).³⁶ In 2018, Byers and coworkers reported Mg-free Fe-catalyzed cross-couplings between alkyl halides and nonactivated arylboronic esters in the presence of a lithium amide base and an iron-complex containing an anionic cyanobis(oxazoline) ligand.³⁷ Using the cross-coupling as the first step, the shortest total synthesis of the pharmaceutical Cinacalcet was achieved (Scheme 1.9c).

Scheme 1.9. Fe-catalyzed Suzuki cross-coupling of alkyl halides

Besides the above-mentioned arylmetal reagents, arylmanganese reagents are also viable partners for the Fe-catalyzed cross-coupling. In 2018, Knochel and coworkers reported FeCl_2 -catalyzed (hetero)arylations of primary and secondary alkyl halides

with di(hetero)arylmanganese reagents in the absence of any additional ligands.³⁸ The reaction of a diastereomerically pure TBS-protected cyclic iodohydrin afforded the product in an excellent diastereoselectivity (d.r. = 99/1) (Scheme 1.10).

Scheme 1.10. Fe-catalyzed cross-coupling between alkyl halides and arylmanganese reagents

1.1.2.3 Cobalt-Catalyzed Cross-Coupling

As an extension to the Pd- and Ni-catalyzed reactions, the Co-catalyzed cross-coupling has been achieved with aryl Grignard, arylzinc and arylmanganese reagents.^{8b} Cross-coupling reactions of not only diastereomerically pure but also enantiopure substrates have been reported.

As for Co-catalyzed Kumada reactions, in 2006, Oshima and coworkers reported cross-coupling reactions of primary alkyl bromides with aryl Grignard reagents in the presence of a CoCl₂/dppp catalytic system (Scheme 1.11a).³⁹ Later, by using TMCD as the ligand, they achieved cross-coupling reactions of secondary alkyl bromides and iodides (Scheme 1.11b).⁴⁰ Moreover, the same catalytic system allowed highly diastereoselective arylations of 5-membered cyclic halo acetals (Scheme 1.11c). With the aid of a CoCl₂(PPh₃)₂/TMEDA catalytic system, Wu and coworkers later achieved the synthesis of enantiopure 2-(arylmethyl)pyrrolidines through cross-coupling reactions between 2-(iodomethyl)pyrrolidines and aryl Grignard reagents

(Scheme 1.11d).⁴¹ In 2012, Cossy and coworkers reported α -diastereoselective cross-coupling reactions between *C*-bromo glycosides and aryl Grignard reagents using a combination of Co(acac)₃ and TMEDA (Scheme 1.11e).⁴² Later, they extended the protocol for the diastereoselective synthesis of *C*-aryl furanosides from *C*-halogeno furanosides (Scheme 1.11f).⁴³ In 2014, Linclau and coworkers reported a short total synthesis of (±)-Paroxetine through a diastereoselective and diastereoconvergent Co-catalyzed arylation of an *N*-Boc-4-bromopiperidine derivative in the presence of Co(acac)₃/TMEDA/HMTA catalytic system.⁴⁴

Scheme 1.11. Co-catalyzed Kumada cross-coupling of alkyl halides

a) Oshima (2006)

b) Oshima (2006)

c) Oshima (2006)

d) Wu (2011)

e) Cossy (2012)

f) Cossy (2013)

Co-catalyzed Negishi reactions of alkyl halides are relatively rare. In 2015, Knochel and workers developed the first Co-catalyzed Negishi cross-coupling of primary and secondary alkyl halides with di(hetero)arylzinc reagents in the presence of a $\text{CoCl}_2 \cdot 2\text{LiCl}/\text{TMEDA}$ catalytic system.⁴⁵ The reaction of TBS-protected cyclic iodohydrins afforded *trans*-2-arylcylohexanol derivatives with excellent diastereoselectivities (up to d.r. = 99/1) (Scheme 1.12).

Scheme 1.12. Co-catalyzed Negishi cross-coupling of alkyl halides

In 2016, Knochel and coworkers reported ligand-free cross-coupling reactions between diarylmanganese reagents and secondary alkyl iodides using $\text{CoCl}_2 \cdot 2\text{LiCl}$ as the catalyst.⁴⁶ The reaction was successfully employed in the preparation of a key intermediate for the synthesis of ($\pm$)-Preclamol (Scheme 1.13).

Scheme 1.13. Co-catalyzed cross-coupling between alkyl halides and diarylmanganese reagents

1.1.2.4 Mechanisms of Arylmatal-Alkyl Halide Coupling

As to the mechanism of Pd-catalyzed processes, a general catalytic cycle involves two-electron oxidative addition of alkyl halides to palladium followed by transmetalation of the resulting alkylpalladium halide with arylmetal reagents. Subsequent reductive elimination of the arylalkylpalladium species would afford an alkylated arene along with regeneration of the palladium catalyst. The first-row

transition metal-catalyzed arylmetal-alkyl halide coupling is mechanistically distinct from the conventional Pd cross-coupling in that the oxidative addition step can proceed via a radical pathway featuring a single-electron transfer (SET)/oxidative radical addition sequence.⁴⁷ Thus, SET between a low-valent transition metal species and an alkyl halide would afford an oxidized transition metal species and an alkyl radical anion. Loss of a halide anion from the alkyl radical anion would generate an alkyl radical species, which would rebound with the oxidized species to give the oxidative addition intermediate.

The SET mechanism of the first-row transition metal-catalyzed arylmetal-alkyl halide coupling has been supported by the following experimental evidences: (1) The reaction of an enantiomerically or diastereomerically pure alkyl halide leads to a racemic product or a mixture of diastereomeric products (Scheme 1.14).^{19, 25-26, 42, 48} (2) The reactions of two diastereomeric alkyl halides give the same thermodynamically favored cross-coupling product with the same diastereomeric ratio (Scheme 1.15).^{18, 25, 33, 40} (3) 6-Halo-1-hexene derivatives undergo radical cyclization/cross-coupling to afford the cyclized products (Scheme 1.16).^{14, 18, 23, 28-29, 31, 36-37, 40, 42, 48-49} (4) (Bromomethyl)cyclopropane undergoes ring-opening/cross-coupling to afford the homoallyl cross-coupling product (Scheme 1.17).^{14-15, 27, 35-37, 48b} (5) The addition of radical scavengers leads to decreased amounts of cross-coupling products.⁵⁰

Scheme 1.14. Cross-coupling of enantiomerically or diastereomerically pure alkyl halides

a) Fu (2013)

b) Furstner (2004)

c) Cossy (2012)

Scheme 1.15. Diastereoconvergent cross-coupling

Scheme 1.16. Tandem radical cyclization/cross-coupling of 6-halo-1-hexene derivatives

Scheme 1.17. Tandem ring-opening/cross-coupling of (bromomethyl)cyclopropane

1.1.2.5 Alkyl Radical-Enabled Aryl-Alkyl Coupling

Since cross-coupling reactions mediated by first-row transition metals often involve generation of an alkyl radical species from the alkyl halide, it is possible to

take advantage of the radical nature of these reactions to enable new transformations. In 2001, Oshima and coworkers reported the synthesis of various arymethyl-substituted heterocycles via cobalt-catalyzed arylative radical cyclization of tethered halo-alkenes with aryl Grignard reagents (Scheme 1.18).⁵¹ Since then, the scope of the tandem radical cyclization/cross-coupling reactions has been extended using nickel,⁵² iron^{29, 53} and copper⁵⁴ catalysts. A common mechanistic pathway for this type of reaction involves SET between an arylmetal species and a tethered halo-alkene, radical cyclization, rebound of the resulting radical with an arylmetal halide, and C–C reductive elimination (Scheme 1.19).

Scheme 1.18. Cobalt-catalyzed tandem radical cyclization/C(sp²)–C(sp³) cross-coupling

Scheme 1.19. Transition metal-catalyzed tandem radical cyclization/C(sp²)–C(sp³) cross-coupling

1,5-Hydrogen atom transfer (HAT) is another notable reactivity of radicals that can be integrated into transition metal-catalyzed cross-coupling. For example, in 2010, Nakamura and coworkers reported Fe-catalyzed α -arylation of aliphatic amines bearing an *o*-halobenzyl group with aryl Grignard reagents (Scheme 1.20).⁵⁵ The reaction was proposed to proceed via SET from an aryliron species to the aryl iodide, 1,5-HAT of the resulting aryl radical to generate a more stable α -amino radical, and Fe-mediated C–C coupling.

Scheme 1.20. Fe-catalyzed C(sp²)–C(sp³) cross-coupling involving a 1,5-HAT process

Despite its high reliability and robustness, the conventional cross-coupling reaction relies on the use of prefunctionalized starting materials, which makes it a time-consuming and waste-generating process. Therefore, it is highly desirable to develop more step- and atom-economic methods to access alkylated arenes. In this regard, transition metal-catalyzed C–H alkylation of arenes has emerged as a powerful and straightforward approach for the introduction of alkyl groups to arenes. This approach has proved particularly successful with the use of directing groups to ensure the site selectivity of the C–H alkylation. Alkyl (pseudo)halides, alkylmetal reagents, and alkenes⁵⁶ are the most frequently used alkylating reagents for this type

of reaction. In the following sections, arene C–H alkylation reactions with alkylmetal reagents and alkyl (pseudo)halides, which are more relevant to this thesis work, are discussed.

1.1.3 Directed Oxidative Arene C–H Alkylation

Since Yu's first report in 2006,⁵⁷ alkylmetal reagents have been used in a series of oxidative C(sp²)–H alkylation reactions mediated by both noble transition metals (Pd, Rh, Ir)⁵⁸⁻⁶⁰ and earth-abundant first-row transition metals (Co, Fe, Mn). Alkylmetal reagents including alkyltin, alkylboron, alkylaluminum, alkylzinc and alkyl Grignard reagents are feasible coupling partners in these transformations. Although alkylmetal reagents are known to undergo facile β -hydrogen elimination and transition metal-mediated homocoupling, these undesired side-reactions can be efficiently suppressed by careful choice of reaction parameters such as ligands and directing groups. In the following sections, only first-row transition metal-catalyzed directed oxidative arene C–H alkylation are discussed.

1.1.3.1 Cobalt-Catalyzed Oxidative Alkylation

In 2010, Shi and coworkers reported the first use of Grignard reagents in cobalt-catalyzed oxidative alkylation of benzo[*h*]quinoline (Scheme 1.21a).⁶¹ MeMgBr showed the best reactivity while other primary alkyl Grignard reagents gave much inferior results. In their mechanistic hypothesis, cyclometalation of benzo[*h*]quinoline with a low-valent alkylcobalt species generates a cobaltacycle, which is oxidized by 2,3-dichlorobutane (DCB) to produce a Co(III) species. Double transmetalations and reductive elimination of the Co(III) species would furnish the alkylated product and regenerate the catalytically active Co(I) species. Subsequently,

Nakamura and coworkers developed cobalt-catalyzed oxidative alkylation of benzamides and 2-phenylpyridine derivatives with primary alkyl Grignard reagents using DMPU as the ligand and air as the sole oxidant (Scheme 1.21b).⁶² In 2016, Xu and coworkers achieved cobalt-catalyzed oxidative methylation and ethylation of *N*-quinolylylbenzamides with AlMe₃ and AlEt₃ using DCB as the oxidant.⁶³ In contrast to Nakamura's method, this reaction exhibited excellent selectivity for monoalkylation.

Scheme 1.21. Cobalt-catalyzed directed oxidative alkylation of arenes

1.1.3.2 Iron-Catalyzed Oxidative Alkylation

As for iron catalysis, in 2015, Nakamura and coworkers reported the use of primary and secondary alkylzinc halides in Fe-catalyzed, 8-aminoquinoline (AQ)-directed oxidative alkylation of benzamides using dppen as a bidentate ligand and 1,2-dichloroisobutane (DCIB) as the oxidant (Scheme 1.22a).⁶⁴ Later, similar iron/diphosphine catalytic systems were developed by Ackermann and coworkers for the triazole-directed oxidative methylation of benzamides⁶⁵ and benzyl amines⁶⁶ using a combination of methyl Grignard reagent and zinc chloride. As reported by

Nakamura and coworkers, trimethylaluminum has also been employed in Fe-catalyzed oxidative methylation of arenes bearing picolinoylamide (PA), 8-quinolylamide⁶⁷ (Scheme 1.22b) and ketone⁶⁸ directing groups.

Scheme 1.22. Fe-catalyzed directed oxidative alkylation of arenes

1.1.3.3 Manganese-Catalyzed Oxidative Alkylation

As for manganese catalysis, in 2017, Nakamura and coworkers reported the first Mn-catalyzed, ligand-free oxidative methylation of arenes with MeMgBr using 1-bromo-2-chloroethane as the oxidant (Scheme 1.23a).⁶⁹ A methylmanganese(III) ate complex is believed to be the catalytically active species in this reaction, which undergoes deprotonative cyclometalation and reductive elimination to give an *ortho*-methylated Mn(I) intermediate. Reoxidation of the Mn(I) intermediate by dihalide would afford a Mn(III) intermediate, which undergoes transmetalation and ligand

exchange with the starting material to give the methylated product along with regeneration of the catalytically active Mn(III) ate complex. Independently in the same year, Ackermann and coworkers achieved Mn-catalyzed selective oxidative monomethylation of triazolylmethyl (TAM)-substituted benzamides with MeMgBr (Scheme 1.23b).⁷⁰ More recently, they reported an isolated example of Mn-catalyzed oxidative ethylation of *N*-(1-phenylethyl)picolinamide using *vis*-dichloroalkane as the oxidant.⁷¹

Scheme 1.23. Mn-catalyzed directed oxidative methylation of arenes

1.1.4 Directed Arene C–H Alkylation with Alkyl (Pseudo)halides

Despite the significant development of the transition metal-catalyzed oxidative alkylation reactions of arenes, the moisture/air-sensitivity and the nucleophilicity of the alkylmetal reagents used in many of these reactions limit the functional group tolerance and the overall practical applicability. To address this limitation, more stable and easily accessible alkyl (pseudo)halides can be considered as attractive alternative alkylating agents. However, compared to well-developed arene C–H

functionalization with aryl⁷² and alkenyl^{72a, 73} halides, arene C–H alkylation with unactivated alkyl halides is challenging, mainly due to the reluctance of alkyl halides toward oxidative addition and the tendency of the resulting alkylmetal complexes to undergo β -H elimination. Regardless of this difficulty, a series of highly efficient arene C–H alkylations using alkyl halides have been developed using noble transition metals such as palladium^{4, 74} and ruthenium⁷⁵ as well as first-row transition metals including cobalt, nickel, iron, and manganese. In the following sections, only first-row transition metal-catalyzed directed arene C–H alkylation reactions are discussed.

1.1.4.1 Cobalt-Catalyzed Arene C–H Alkylation

In 2011, Nakamura and coworkers reported a cobalt-catalyzed *ortho*-alkylation of secondary benzamides with primary alkyl chlorides using CyMgCl as the base and reductant (Scheme 1.24a).⁷⁶ In 2013, Ackermann and coworkers demonstrated the utility of a Co–IPr–CyMgCl catalytic system in *ortho*-alkylation of 2-arylpyridines and *N*-pyri(mi)dylindoles with alkyl chlorides (Scheme 1.24b).⁷⁷ Besides various primary chlorides, chlorocyclohexane also participated in the alkylation reaction to afford cyclohexylated products in reasonably good yields. Independently in the same year, we reported *ortho*-alkylation of aryl ketimines with a variety of primary and secondary alkyl chlorides and bromides using similar Co–N-heterocyclic carbene (NHC)–Grignard systems (Scheme 1.24c).⁷⁸ Simple NHC preligands *N,N'*-diisopropylimidazolium tetrafluoroborate and its benzo-fused analogue proved effective. The scope of the Co–NHC–Grignard systems was further extended by Ackermann and us in oxazoline-,⁷⁹ pyridine-⁸⁰ and pivalophenone N–H imine-directed⁸¹ C(sp²)–H alkylation reactions.

Scheme 1.24. Cobalt-catalyzed arene C–H alkylation with alkyl halides

a) Nakamura (2011)

b) Ackermann (2013)

c) Yoshikai (2013)

A generally proposed mechanism for the Co–NHC–Grignard-mediated arene C–H alkylation is shown in Scheme 1.25. The reaction is initiated by cyclometalation of the arene with a low-valent alkylcobalt species generated from the cobalt precatalyst and the Grignard reagent. The resulting cobaltacycle is often proposed to undergo SET to the alkyl halide to generate an oxidized cobaltacycle and an alkyl radical. Further radical rebound and reductive elimination would afford the *ortho*-alkylated arene and a cobalt halide species, the latter of which undergoes transmetalation with the Grignard reagent to regenerate the alkylcobalt species.

Scheme 1.25. Plausible catalytic cycle for the cobalt-catalyzed, directed arene C–H alkylation.

Proposed mechanism:

1.1.4.2 Nickel-Catalyzed Arene C–H Alkylation

Chatani and coworkers reported the first example of nickel-catalyzed arene *ortho* C–H alkylation using 8-aminoquinolynyl benzamides as the substrates and a variety of primary alkyl halides as the alkylating agents (Scheme 1.26a).⁸² A proposed catalytic cycle of this reaction involves reversible cyclometallation of the benzamide with a ligated Ni–X species followed by oxidative addition of the alkyl halide on the resulting nickelacycle to generate a Ni(IV) intermediate. Reductive elimination of the Ni(IV) species and protonation would furnish the alkylated product along with regeneration of the catalytically active NiX₂ species. Later, the same group achieved *ortho*-C–H methylation of the same type of substrates under similar conditions using methyl iodide generated in-situ from equal equivalents of MeOTf and NaI.^{82b} In 2014, Ackermann and coworkers reported the first Ni-catalyzed secondary alkylation and trifluoroethylation of 8-aminoquinolyl benzamides using secondary alkyl

bromides, chlorides and trifluoroethyl iodide as the alkyl sources (Scheme 1.26b).⁸³

Nickel-catalyzed, monodentate directing group-assisted arene C–H alkylation reactions have also been reported. In 2016, Ackermann and coworkers disclosed Ni-catalyzed *ortho*-alkylation of 2-pyrimidyl anilines with primary and secondary halides using *N,N'*-di-*tert*-butylethane-1,2-diamine (DtBEDA) as the ligand (Scheme 1.26c).⁸⁴ The reaction was believed to involve a rare six-membered nickelacycle intermediate, which undergoes SET with an alkyl halide to generate an oxidized nickelacycle and an alkyl radical. Radical recombination and subsequent reductive elimination would furnish the alkylated product. In the same year, Punji and coworkers disclosed the utility of a well-designed (quinolinyl)amino-nickel catalyst in Ni-catalyzed, monodentate-chelate-assisted C–H alkylation of *N*-pyridyl- as well as *N*-pyrimidylindoles with primary and secondary alkyl halides (Scheme 1.26d).⁸⁵ Similar to Ackermann's proposal, this reaction is also considered to involve SET type activation of the alkyl halide. More recently, Ackermann and coworkers disclosed a homobimetallic Ni(II)–Ni(II) complex as an efficient catalyst for the *ortho*-alkylation of 2-pyrimidyl anilines with primary and secondary bromides (Scheme 1.26e).⁸⁶ The bimetallic complex was considered to retain its integrity during the reaction, and a catalytic cycle was proposed to start with SET to the alkyl halide and subsequent radical rebound to generate a Ni(III)–halide/Ni(III)–alkyl species, followed by C–H activation by the Ni(III)–halide moiety.

Scheme 1.26. Ni-catalyzed arene C–H alkylation with alkyl halides

PhMgBr as the base and reductant, which was fast enough to complete in less than 10 minutes.⁸⁸ Cook and coworkers also disclosed Fe-catalyzed secondary alkylation of the same type of substrates with alkyl bromides and iodides.⁸⁹ A similar catalytic system was employed except that one equivalent of BHT was added to prevent overalkylation (Scheme 1.27b). Independently in 2014, Nakamura and coworkers demonstrated the utility of primary and secondary alkyl tosylates and halides in Fe-catalyzed, 8-AQ-directed alkylation of benzamides and acrylamides using NaI as an additive and *p*-anisylzinc bromide as a base (Scheme 1.27c).⁹⁰ Later, Ackermann and coworkers reported Fe-catalyzed, triazole-directed *ortho*-alkylation of benzamides with primary and secondary alkyl bromides using similar catalytic system as Cook's report (Scheme 1.27d).⁹¹ Based on radical trapping and radical clock experiments, these reactions were proposed to involve a SET-type mechanism.

Scheme 1.27. Fe-catalyzed arene C–H alkylation with alkyl (pseudo)halides

a) Cook (2014)

b) Cook (2014)

c) Nakamura (2014)

d) Ackermann (2016)

1.1.4.4 Manganese-Catalyzed Arene C–H Alkylation

In recent years, manganese catalysts have also been increasingly used in C–H activation due to their cost-effective and non-toxic nature.⁹² In 2017, Mn-catalyzed, triazole-assisted primary alkylation of benzamides was achieved by Ackermann and coworkers under phosphine-free conditions (Scheme 1.28a).⁷⁰ More recently, the same group reported Mn-catalyzed *ortho*-alkylation of pyridinylamide derivatives with primary and secondary alkyl halides using Grignard reagents as the base and reductant (Scheme 1.28b).⁷¹ Based on radical-clock experiments, the reaction was believed to involve a C–H manganation to generate a manganacycle intermediate. SET between the manganacycle and the alkyl halide affords an oxidized

manganacycle and an alkyl radical. Subsequent radical rebound and reductive elimination would furnish the alkylated product.

Scheme 1.28. Mn-catalyzed arene C–H alkylation with alkyl halides

a) Ackermann (2017)

b) Ackermann (2019)

1.2 Design and Summary of Thesis Research

As discussed in Section 1.1.4.1, over the last several years, we and others have developed a series of low-valent cobalt-catalyzed directed alkylation reactions of arenes with alkyl (pseudo)halides, which are typically promoted by a catalytic system consisting of a cobalt(II) salt, an NHC ligand, and a Grignard reagent. These reactions commonly involve an alkyl radical species generated from single electron reduction of the alkyl halide. Several lines of evidence supported the radical mechanism. For example, radical clock experiments using 6-bromohex-1-ene afforded a mixture of cyclized and uncyclized alkylation products (Scheme 1.29).⁸⁰ The reaction of an enantiomerically enriched secondary alkyl bromide afforded a racemic alkylation product. Furthermore, the reactions of diastereomeric alkyl chlorides stereoconvergently afforded alkylated arenes of the same diastereomer ratio.

Scheme 1.29. Radical clock experiments using 6-bromohex-1-ene

Inspired by Nakamura's Fe-catalyzed, 1,5-HAT-mediated $C(sp^2)$ – $C(sp^3)$ cross-coupling and Oshima's cobalt-catalyzed tandem radical cyclization/arylation of tethered halo-alkenes (see Section 1.1.2.5), we became interested in the integration of the cobalt-catalyzed directed C–H activation with such radical-specific reactivities. We first hypothesized that, with appropriate design of an electrophile, SET from the putative cobaltacycle intermediate to the electrophile would generate a reactive carbon radical capable of 1,5-HAT, thus allowing C–C bond formation at the remote $C(sp^3)$ –H bond of the electrophile. With this hypothesis in mind, in Chapter 2, we have developed a cobalt-catalyzed α -arylation of 2-bromobenzyl-protected secondary amines with aryl imines, where a $C(sp^2)$ – $C(sp^3)$ bond is selectively constructed between the *ortho*-position of the imine and the α position of the amine (Scheme 1.30).⁹³

Scheme 1.30. Cobalt-catalyzed $C(sp^2)$ –H/ $C(sp^3)$ –H coupling via directed C–H activation and 1,5-HAT

Besides our previous work (Scheme 1.29), 6-bromohex-1-ene has been used as the mechanistic probe to highlight the radical nature of the above-discussed first-row transition metal-catalyzed C–H alkylation reactions.^{70-71, 82b, 84-86, 91, 94} However, this mechanistic probe often gave a mixture of cyclized and uncyclized alkylation products in varying ratios, and the merger of the C–H activation and the radical cyclization has not been proactively pursued in the context of carbo- and heterocycle synthesis. We reasoned that selective tandem radical cyclization/C–H alkylation reactions could be achieved with halo-alkene substrates displaying Thorpe-Ingold effect. Based on this hypothesis, in Chapter 3, we have developed a cobalt-catalyzed tandem radical cyclization/C–C coupling between tethered bromo-alkenes and aryl N–H imines initiated by imine-directed C–H activation (Scheme 1.31).⁹⁵ A series of benzylated pyrrolidines and related cyclic products were obtained in moderate to good yields.

Scheme 1.31. Cobalt-catalyzed tandem radical cyclization/C–C coupling initiated by directed C–H activation

As described in Section 1.1.4.1, we previously reported cobalt–NHC–Grignard-mediated *ortho*-alkylation of aryl ketimines with primary and secondary alkyl chlorides and bromides. While analogous *ortho*-methylation would be potentially useful in the context of magic methyl effect in medicinal chemistry, the use of methyl chloride and bromide as the methylating agents appeared nontrivial due to their volatility. In Chapter 4, we have developed a cobalt-catalyzed directed *ortho*-methylation of arenes using methyl tosylate as a readily available and convenient methylating agent.⁹⁶ The reaction is achieved using a modified catalytic system consisting of $\text{Co}(\text{acac})_3$, N,N' -di(2-butyl)benzimidazolium bromide, and $t\text{-BuCH}_2\text{MgBr}$ (Scheme 1.32). Using CD_3OTs instead of MeOTs , the reaction also allows facile incorporation of a CD_3 group into arenes.

Scheme 1.32. Cobalt-catalyzed directed *ortho*-methylation of arenes with MeOTs

Overall, this thesis research has led to significant advancement in directed *ortho*-alkylation of arenes using earth-abundant cobalt catalysts. We have demonstrated that cobalt-catalyzed directed arene C–H activation can be integrated with either a 1,5-HAT or a radical cyclization process in a single catalytic cycle to achieve novel $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^3)$ bond-forming reactions. Furthermore, we have developed directed

arene C–H methylation and (trideuterio)methylation reactions employing the corresponding tosylates as convenient methylating agents.

1.3 References

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Chapter 2. Cobalt-Catalyzed C(sp²)-H/C(sp³)-H Coupling via Directed C-H Activation and 1,5-Hydrogen Atom Transfer

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ivAbstract

2.1 Introduction

As a revolutionary trend in organic synthesis, C-H bond activation has attracted significant attention from the synthetic community for the last few decades. Compared with the traditional cross-coupling reactions that rely on prefunctionalized starting materials, the direct C-H functionalization offers a more atom- and step-economical way to construct C-C and C-heteroatom bonds using readily available unfunctionalized starting materials. As such, C-H activation reactions could not only streamline existing synthetic pathways and lead-optimization process of bioactive molecules, but also help develop new synthetic strategies for otherwise challenging targets.¹ Since C-H bonds are omnipresent in various organic molecules, to achieve C-H bond functionalization in a practically useful manner, issues regarding selectivity must be addressed.

One of the most common and practical approaches to achieve site-selective C-H functionalization is the transition metal-mediated, directing group-assisted C-H activation (Scheme 2.1a).² This approach allows for regioselective cleavage of a C-H bond in the proximity of a chelating functional group. The resulting cyclometalated intermediate then undergoes conversion of the carbon-metal bond

into a new C–C or C–heteroatom bond. One of the earliest implementations of this concept was reported by Murai and coworkers in 1993, who developed a Ru-catalyzed, ketone-directed *ortho*-C(sp²)–H alkylation with terminal olefins (Scheme 2.1b).³ Since then, a large number of chelation-assisted C–H functionalization reactions have been developed with various transition metals across the periodic table.

Scheme 2.1. Transition metal-catalyzed, directing group-assisted C–H activation

Another powerful approach to site-selective C–H activation is intramolecular hydrogen atom transfer (HAT).⁴ Generation of a reactive carbon- or heteroatom-centered radical is followed by intramolecular HAT and trapping of the resulting radical, thus enabling remote and selective functionalization of an inert C(sp³)–H bonds (Scheme 2.2). Among various radical translocation modes, 1,5-HAT is the most common due to the involvement of a favored six-membered cyclic transition state, which ensures exclusive δ regioselectivity.⁵

Scheme 2.2. 1,5-HAT-mediated remote and selective C–H functionalization

The first example of 1,5-HAT-mediated selective C-H functionalization was reported by Hofmann in 1883 via sp^3 *N*-radical initiation (Scheme 2.3).⁶ Now known as the Hofmann-Löffler-Freytag (HLF) reaction, this remote C-H amination strategy enables the synthesis of pyrrolidines from *N*-halogenated amines via a 1,5-HAT from the δ C-H bond to the aminium radical cation produced by the homolysis of the cationic *N*-haloamine. In 2015, Muñiz and coworkers reported the first iodine-catalyzed HLF reaction using 2.5 mol % of I_2 and one equivalent of a hypervalent iodine oxidant (Scheme 2.4).⁷ *I(mCBA)* is the active catalyst in this reaction to promote in-situ formation of an N-I bond, which subsequently undergoes photoinduced homolysis to generate the *N*-radical.

Scheme 2.3. Hofmann-Löffler-Freytag (HLF) reaction

Scheme 2.4. Iodine-catalyzed remote C(sp^3)-H amination enabled by an *N*-radical-

mediated 1,5-HAT

In 2016, the Knowles⁸ and Rovis⁹ groups independently reported the first examples of photoredox-catalyzed HLF reaction that enables δ C–H alkylation of secondary *N*-alkyl amides via *N*-radical-initiated 1,5-HAT (Scheme 2.5). Unlike the classical HLF reaction where pre-installation or in-situ generation of an N–X bond is needed, the nitrogen-centered radical is generated either via a PCET-mediated homolysis of *N*-alkyl amide N–H bond or stepwise deprotonation/single-electron transfer (SET) oxidation. For the PCET activation, an excited Ir photocatalyst and a phosphate base work cooperatively to remove both a proton and an electron from the amide substrate to form an amidyl radical. After 1,5-HAT, the resulting carbon-centered radical undergoes a 1,4-Michael addition to produce the distal C–C bond.

Scheme 2.5. Photoredox-catalyzed remote C(sp³)–H alkylation via an *N*-radical-mediated 1,5-HAT

In 2012, Chiba and coworkers reported the first use of amidinyl radical in HAT reactions. By using O_2 or $\text{PhI}(\text{OAc})_2$ as the oxidant, they achieved the Cu-catalyzed, amidine-directed β -C–H oxygenation¹⁰ (Scheme 2.6) or amination¹¹ (Scheme 2.7) of *N*-alkylamidines for the synthesis of dihydrooxazoles or dihydroimidazoles, respectively. In both the reactions, Cu-mediated single-electron oxidation of amidine and subsequent deprotonation affords an amidinyl radical, which undergoes a 1,5-HAT to generate a carbon radical. When O_2 is used as the radical trap, a superoxo radical is formed, which then undergoes Cu-mediated fragmentation and cyclization to form an oxazoline via β oxygenation. When $\text{PhI}(\text{OAc})_2$ is used in place of O_2 , the carbon radical undergoes a single-electron oxidation and subsequent cyclization to afford an imidazoline via β amination.

Scheme 2.6. Cu-catalyzed O_2 -mediated β -C–H oxygenation via amidinyl radical-mediated 1,5-HAT

Scheme 2.7. Cu-catalyzed $\text{PhI}(\text{OAc})_2$ -mediated β -C–H amination via amidinyl radical-mediated 1,5-HAT

In 2017, Nevado and coworkers described the first example of photocatalyzed 1,5-HAT of an iminyl radical using an acyl oxime as the radical precursor (Scheme 2.8).¹² Selective formation of a tetralone derivative or a 3,4-dihydro-2*H*-pyrrole can be achieved via $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ or $\text{C}(\text{sp}^3)\text{--N}$ bond formation under either aqueous or basic anhydrous conditions. In these reactions, the iminyl radical is generated via photoexcited Ir^{III} -mediated reduction of the acyl oxime and concomitant cleavage of the N–O bond.

Scheme 2.8. Photoredox-catalyzed γ C–H functionalization via iminyl radical-mediated 1,5-HAT

In analogy to *N*-radicals, *O*-radicals can also mediate selective remote C(sp³)-H functionalization via a 1,5-HAT process. In 1960, the first example of alkoxy radical-initiated 1,5-HAT was reported by Derek Barton and the reaction was later recognized with a Noble prize in 1969.¹³ In this case, a nitrite synthesized from an alcohol and nitrosyl chloride undergoes photolytic homolysis to generate an alkoxy radical and a nitrosyl radical. Upon 1,5-HAT of the alkoxy radical, the resulting δ C-radical of the alcohol recombines with the nitrosyl radical to form a δ -nitroso alcohol, which tautomerizes to form the δ -aminated oxime product (Scheme 2.9). In 2016, Chen and coworkers reported the first alkoxy radical-enabled C(sp³)-H allylation and alkenylation of *N*-alkoxyphthalimides via photoredox catalysis (Scheme 2.10a).¹⁴ The alkoxy radical is generated via a single-electron reduction of the *N*-alkoxyphthalimide by Hantzsch ester-reduced Ir^{II} catalyst. Subsequent 1,5-HAT and carbon radical trapping afford the C-C coupling product. Later in the same

year, Meggers and co-workers demonstrated the first photocatalyzed asymmetric C(sp³)–H alkylation of *N*-alkoxyphthalimides via the merger of photocatalyzed 1,5-HAT and chiral Rh-based Lewis acid-mediated stereocontrolled alkene addition (Scheme 2.10b).¹⁵

Scheme 2.9. The Barton reaction: δ C–H amination via O-centered radicals

Scheme 2.10. Photoredox-catalyzed remote C(sp³)–H alkylation via alkoxy radical-enabled 1,5-HAT

a) Chen's work

b) Meggers' work

For the heteroatom-initiated 1,5-HAT reactions, the driving force for radical translocation is provided by the formation of a stronger $X-H$ bond ($X = N$ or O) from a weaker $C-H$ bond.^{4a} On the other hand, C -centered radical-mediated HAT would require more judicious substrate design to ensure sufficient energy gain through carbon-to-carbon radical translocation. This is most commonly achieved by initiating the reaction with a reactive $C(sp^2)$ radical to generate a more stable $C(sp^3)$ radical. In addition, introduction of an α -heteroatom to the desired radical translocation site can further increase the driving force for the intermolecular HAT between carbon centers.

In 2016, Gevorgyan and coworkers reported the synthesis of silyl enol ethers via

photoinduced Pd-catalyzed oxidation of *o*-iodophenyl silyl ether (Scheme 2.11).¹⁶ Upon SET from a photoexcited Pd(0) complex to the aryl iodide, a hybrid aryl Pd-radical species is formed, which undergoes subsequent 1,5-HAT and β -hydride elimination to afford the silyl enol ether product. The driving force of the 1,5-HAT is the generation of a stabilized α -oxy radical from the C(sp²)-radical intermediate.

Scheme 2.11. α -Ether C–H functionalization via aryl radical-enabled 1,5-HAT

Like alcohols, amines can also be converted into radical precursors that can mediate intramolecular HAT. In 2010, Nakamura and coworkers reported Fe-catalyzed α -arylation of aliphatic amines bearing an *o*-halobenzyl group with aryl Grignard reagents (Scheme 2.12).¹⁷ The reaction was proposed to proceed via SET from an aryliron species (Ar[Fe]) to the aryl iodide, 1,5-HAT of the resulting aryl radical to generate a more stable α -amino radical, and iron-mediated C–C coupling. In 2013, the Kalyani group reported Ni-mediated intramolecular arylation of C(sp³)–H bonds adjacent to *o*-halobenzamide nitrogen (Scheme 2.13).¹⁸ The initiating aryl radical is generated via SET from Ni(0) to the aryl halide, and the following 1,5-HAT, intramolecular radical addition, and oxidation afford the isoindolinone product.

Scheme 2.12. Fe-catalyzed α -arylation of amines via aryl radical-enabled 1,5-HAT **Scheme 2.13.** Ni-catalyzed intramolecular α -arylation of amines via aryl radical-enabled 1,5-HAT

The most challenging radical translocation is the one between two $\text{C}(\text{sp}^3)$ -radicals due to the small energy difference involved. An elegant solution to this challenge was reported in 2017 by Gevorgyan and co-workers, who achieved Pd-catalyzed, photoinduced β,γ -desaturation of secondary and tertiary alcohols bearing an isopropyl group by the installation of a (halomethyl)silane auxiliary (Scheme 2.14).¹⁹ Similar to the example shown in Scheme 2.11, a hybrid Pd-radical mechanism is proposed featuring 1,5-HAT as the key step. The driving force of the 1,5-HAT is the generation of a more stabilized tertiary radical from a primary radical species.

Scheme 2.14. Photoinduced Pd-catalyzed β,γ -desaturation of aliphatic alcohols via alkyl radical-enabled 1,5-HAT

As discussed in Chapter 1 and above, both the transition metal-mediated directed C–H activation and the radical-mediated 1,5-HAT have been extensively exploited for selective C–H functionalization reactions. Meanwhile, these two mechanistically distinct C–H activation modes have not been utilized simultaneously to forge a C–C bond from two C–H bonds.

Over the last few years, we and others have developed a series of low-valent cobalt-catalyzed chelation-assisted arene C–H functionalization reactions with diverse organic electrophiles such as alkyl and aryl (pseudo)halides,²⁰ which are typically promoted by a catalytic system consisting of a cobalt(II) salt, a N-heterocyclic carbene ligand, and a Grignard reagent (Scheme 2.15). These reactions would be commonly initiated by cyclometalation of the arene with a low-valent organocobalt species generated from the cobalt precatalyst and the Grignard reagent. The resulting cobaltacycle is often proposed to undergo SET to the electrophile to generate an oxidized cobaltacycle and an organic radical ($\text{R}^\cdot$). Further radical rebound and reductive elimination would afford the *ortho*-functionalized arene.

Scheme 2.15. Cobalt-catalyzed directed C–H/electrophile coupling

In light of the above mechanistic model involving organometallic C–H activation and radical processes, we became interested in a possible merger of the cobalt-mediated directed C–H activation and 1,5-HAT. We hypothesized that, with appropriate design of an electrophile, SET from the putative cobaltacycle intermediate to the electrophile would generate a reactive carbon radical capable of 1,5-HAT, thus allowing C–C bond formation at the remote C(sp³)–H bond of the electrophile. With this hypothesis in mind, we have developed a cobalt-catalyzed α -arylation of 2-bromobenzyl-protected secondary amines with aryl imines, where a C(sp²)–C(sp³) bond is selectively constructed between the *ortho*-position of the imine and the α position of the amine (Scheme 2.16).²¹

Scheme 2.16. Cobalt-catalyzed C(sp²)-H/C(sp³)-H coupling via directed C-H activation and 1,5-HAT

2.2 Results and Discussion

We initiated the present study by screening conditions for the reaction between acetophenone *N*-PMP imine **1a** and *N*-(2-bromobenzyl)pyrrolidine **2a** (Table 2.1). The Co-IMes-*t*BuCH₂MgBr system we previously used for the *ortho*-arylation reaction²² promoted the reaction to a small extent, affording the desired alkylation product **3aa** in 7% yield (entry 1). The use of IPr•HCl or SIPr•HCl in place of IMes•HCl slightly improved the yield of **3aa** to 13% and 17%, respectively (entries 2 and 3). With SIPr•HCl as the preligand, we explored the reaction of **1a** with the chloro- and iodo analogues of **2a**. While 1-(2-chlorobenzyl)pyrrolidine did not undergo the desired reaction at all (entry 4), the reaction of 1-(2-iodobenzyl)pyrrolidine afforded a slightly higher yield of **3aa** (entry 5). Next, we screened the reaction of **1a** and **2a** by replacing neopentylmagnesium bromide with other Grignard reagents. While secondary acyclic Grignard reagents such as *i*-PrMgBr and *sec*-BuMgBr further improved the yield of **3aa** to 23% and 30%, respectively (entries 6 and 7), the use of cycloalkyl Grignard reagents proved to be detrimental (entries 8 and 9). In contrast to this observation, *sec*-BuMgBr was entirely ineffective for the reaction using 1-(2-iodobenzyl)pyrrolidine in place of **2a**

(entry 10). Phosphine ligands such as PPh₃ and dppe failed to promote the reaction between **1a** and **2a** (entries 11 and 12). The yield of **3aa** was further improved to 37% using 2.2 equivalents of *sec*-BuMgBr (entry 13). After screening the solvent system (entries 14-16), we found that the yield of **3aa** could be improved to near 50% using a 1:1 mixture of THF and DME (entry 15). Furthermore, by using **2a** as the limiting reagent and 2 equiv of **1a** and lowering the reaction temperature to 0 °C, **3aa** could be obtained in 55% yield (entry 17). Despite extensive screening of other conditions, we could not further improve the yield of this reaction. It is noteworthy that none or only a trace amount of **3aa** was obtained when NiBr₂ or FeBr₂ was used instead of CoBr₂ under otherwise identical conditions (entries 18 and 19).

Table 2.1. Optimization of reaction conditions^a

entry	ligand	RMgX	solvent	yield ^b [%]
1	IMes•HCl	<i>t</i> -BuCH ₂ MgBr	THF	7
2	IPr•HCl	<i>t</i> -BuCH ₂ MgBr	THF	13
3	SIPr•HCl	<i>t</i> -BuCH ₂ MgBr	THF	17
4 ^c	SIPr•HCl	<i>t</i> -BuCH ₂ MgBr	THF	0
5 ^d	SIPr•HCl	<i>t</i> -BuCH ₂ MgBr	THF	20
6	SIPr•HCl	<i>i</i> -PrMgBr	THF	23
7	SIPr•HCl	<i>sec</i> -BuMgBr	THF	30
8	SIPr•HCl	<i>o</i> -C ₅ H ₉ MgBr	THF	5
9	SIPr•HCl	CyMgCl	THF	8
10 ^d	SIPr•HCl	<i>sec</i> -BuMgBr	THF	0
11	PPh ₃ ^e	<i>sec</i> -BuMgBr	THF	0
12	dppe	<i>sec</i> -BuMgBr	THF	0
13	SIPr•HCl	<i>sec</i> -BuMgBr ^f	THF	37
14	SIPr•HCl	<i>sec</i> -BuMgBr ^f	THF/Et ₂ O ^g	34
15	SIPr•HCl	<i>sec</i> -BuMgBr ^f	THF/DME ^g	47
16	SIPr•HCl	<i>sec</i> -BuMgBr ^f	THF/toluene ^g	42
17 ^h	SIPr•HCl	<i>sec</i> -BuMgBr	THF/DME ^g	55
18 ^{h,i}	SIPr•HCl	<i>sec</i> -BuMgBr	THF/DME ^g	0
19 ^{h,j}	SIPr•HCl	<i>sec</i> -BuMgBr	THF/DME ^g	6

^a The reaction was performed using 0.3 mmol of **1a** (*c* = 0.3 M) and 0.6 mmol of **2a**. ^b The yield was determined by ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard. ^c 1-(2-chlorobenzyl)pyrrolidine was used. ^d 1-(2-iodobenzyl)pyrrolidine was used. ^e 20% PPh₃ was used. ^f 2.2 equiv of *sec*-BuMgBr was used. ^g The ratio of the solvents was 1:1. ^h The reaction was performed using 0.2 mmol of **2a** (*c* = 0.2 M) and 0.4 mmol of **1a** at 0 °C. ⁱ NiBr₂ was used. ^j FeBr₂ was used.

During the optimization process of this reaction, we observed the persistent formation of by-products **4–8** (Table 2.2), which can be attributed to aryl-aryl coupling between **1a** and **2a** (**4**),^{22–23} *ortho-sec*-butylation of **1a** (**5**),²⁴ direct cross-coupling between *sec*-BuMgBr and **2a** (**6**),²⁵ hydrodebromination of **2a** (**7**), and

reduction of **1a** (**8**). The desired catalytic cycle (*vide infra*) can be interrupted by these undesired reactions at different stages, which highlights the difficulty in achieving selective C(sp²)–H/C(sp³)–H coupling.

Table 2.2. Formation of byproducts^a

entry	solvent	yield (%) ^b					
		3aa	4	5	6	7	8
1	THF	30	3	3	13	19	3
2 ^c	THF/Et ₂ O (1:1)	34	4	1	2	14	5
3 ^c	THF/DME (1:1)	47	5	1	16	20	2
4 ^d	THF/DME (1:1)	55	0	5	0	19	6

^a The reaction was performed using 0.3 mmol of **1a** (*c* = 0.3 M) and 0.6 mmol of **2a**. ^b The yield of **3aa** was determined by ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard. The yields of **4–8** were estimated by GC using *n*-tridecane as the internal standard. ^c 2.2 equiv of *sec*-BuMgBr was used. ^d The reaction was performed using 0.2 mmol of **2a** (*c* = 0.2 M) and 0.4 mmol of **1a** at 0 °C.

With the optimized conditions in hand (Table 2.1, entry 17), we explored the reaction of **2a** with various *N*-PMP ketimines (Table 2.3). Acetophenone imines bearing a series of *para*-substituents participated in the reaction to afford the corresponding products **3ba–3ga** in moderate yields. The presence of strong electron-

donating or -withdrawing *para*-substituents was harmful to the reaction (see **3fa** and **3ga**). While the alkylation of *meta*-trifluoromethyl and *meta*-chloro-substituted imines exclusively occurred at the less hindered *ortho* position (see **3ha** and **3ia**), the reaction of *meta*-fluoro-substituted imine resulted in regioselective alkylation in proximity to the fluorine atom, presumably as a result of the secondary directing effect. Acetophenone imine bearing an *ortho*-methyl group failed to participate in the reaction (see **3ka**). In addition to the acetophenone derivatives, imines derived from propiophenone and tetralone also participated in the present reaction to afford **3la** and **3ma** in low to moderate yields. The reaction of the parent acetophenone imine could be performed on a 5 mmol scale, affording **3aa** in a decreased yield of 37%.

Table 2.3. Scope of aryl imines^a

^a The reaction was performed on a 0.2 mmol scale under the conditions in Table 2.1, entry 17. ^b The yield of a 5 mmol-scale reaction is shown in parentheses. ^c GC yield. ^d The reaction time was 24 h.

Next, we used the *meta*-trifluoromethyl-substituted acetophenone imine **1h** as the reaction partner to explore the scope of *N*-(2-bromobenzyl)amine substrates (Table 2.4). Compared with the pyrrolidine derivative **2a**, the desired alkylation reactions of six-membered piperidine, morpholine and tetrahydroquinoline derivatives were much more sluggish, affording products **3hb-3hd** in low yields. On the other hand, the reaction of 7-membered azepane derivative smoothly afforded the desired product

3he in 64% yield. Besides cyclic amines, acyclic diethylamine and dibutylamine derivatives were also amenable substrates for the present reaction, affording the products **3hf** and **3hg** in moderate yields.

We also explored the reaction of **1h** with other amine substrates, the results of which are summarized in Table 2.5. *N*-(2-bromobenzyl)amine substrates bearing six-membered cyclic amines such as tetrahydroisoquinoline, 4-methylpiperazine and thiomorpholine were poorly reactive or totally unreactive (see **3hh-3hj**). The reaction of indoline-derived substrate afforded the desired **3hk** in a low yield. Furthermore, substrates derived from acyclic amines such as *N*-methylaniline, *N*-methylbenzylamine and dibenzylamine also proved to be poor substrates for the present reaction (see **3hl-3hn**).

Table 2.4. Scope of *N*-(2-bromobenzyl)amines (^BBn = 2-bromobenzyl)^a

^a The reaction was performed on a 0.2 mmol scale under the conditions in Table 2.1, entry 17.

Table 2.5. Reaction of other amines^a

^a The reaction was performed on a 0.2 mmol scale under the conditions in Table 2.1, entry 17 and the yield refers to the GC yield.

The utility of the present C(sp²)–H/C(sp³)–H coupling could be demonstrated by the two-step synthesis of a spirocyclic compound from the alkylation product **3aa** (Scheme 2.17). Thus, diazotization of the acetyl group of **3aa** gave the diazoethanone derivative **9**. Subsequent rhodium-catalyzed intramolecular C–H insertion afforded indanone **10** in 68% yield (22% overall yield).

Scheme 2.17. Product transformation to a spirocycle

On the basis of previous reports of cobalt-catalyzed C–H alkylation and arylation reactions,^{20a, 20d} we propose a catalytic cycle for the present cobalt-catalyzed C(sp²)–

H/C(sp³)-H coupling reaction as shown in Scheme 2.18. An organocobalt species **A**, generated from the cobalt precatalyst and the Grignard reagent, would undergo cyclometalation of the imine to give a cobaltacycle species **B**. SET from the cobalt center to the aryl bromide would generate a pair of oxidized cobaltacycle and aryl radical (**C**).²⁶ 1,5-HAT of the aryl radical would afford a more stable α -amino radical (**D**), which would undergo radical rebound and reductive elimination of the resulting aryl-alkyl cobalt intermediate to give the aryl-alkyl coupling product. Transmetalation of the resulting cobalt bromide species **E** with the Grignard reagent would regenerate the low-valent cobalt species **A**. As a support for the radical mechanism, the addition of a stoichiometric amount of a radical scavenger to the reaction significantly reduced the yield of **3aa** (28% and 22% yields with 1,1-diphenylethylene and TEMPO, respectively), while the formation of radical trapping products could not be confirmed. As suggested from Table 2.2, the desired catalytic cycle can be interrupted by several side reactions at different steps. Thus, before 1,5-HAT, the intermediate **C** can undergo direct aryl-aryl coupling to afford the biaryl product **4**. The oxidized arylcobalt species **C** or **D** may undergo transmetalation with the Grignard reagent, thus affording the *ortho-sec*-butylation product **5**. Moreover, competitive reaction of the low-valent cobalt species **A** with *N*-(2-bromobenzyl)amine would afford the direct cross-coupling product **6** and the hydrodebromination product **7**. The formation of the reduced imine **8** may be mediated by β -H elimination of the species **A** and subsequent addition of the resulting cobalt hydride on the imine. The resulting amidocobalt species would undergo transmetalation with the Grignard reagent to afford the reduction product **8** and regenerate the low-valent cobalt species **A** (Scheme 2.19).

Scheme 2.18. Proposed catalytic cycle for the cobalt-catalyzed C(sp²)-H/C(sp³)-H coupling

Scheme 2.19. Possible catalytic cycle for the generation of reduced imine product **8**

2.3 Conclusion

In summary, we have developed a cobalt-catalyzed C(sp²)-H/C(sp³)-H coupling

reaction between an aryl imine and a secondary amine bearing *N*-(2-bromobenzyl) group. Promoted by a cobalt–NHC catalyst and a secondary alkyl Grignard reagent, this reaction allows for *ortho*- α -aminoalkylation of the imine at a mild temperature. The reaction is considered to proceed via directed C–H activation, single electron transfer and 1,5-hydrogen atom transfer as key steps. The success of the present reaction may be attributed to the ability of low-valent cobalt species to engage in both inner-sphere C–H activation and single electron transfer, while other transition metals such as iron may also be endowed with similar attributes.^{17, 27}

2.4 Experimental Section

Materials. Unless otherwise noted, commercial reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. Anhydrous CoBr₂ (> 98%) and 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride (SIPr•HCl) were purchased from Alfa Aesar and used as received. THF and 1,2-dimethoxyethane (DME) were distilled over Na/benzophenone. Grignard reagents were prepared from the corresponding alkyl halides and magnesium turnings in anhydrous THF, and titrated before use.

Preparation of Starting Materials

Preparation of Aryl Imines

All imines (see below) were synthesized according to the literature procedures,²⁸ and purified by recrystallization or distillation. Spectral data for these compounds showed good agreement with the literature data.²⁹

Preparation of *N*-(2-Bromobenzyl)amines

Cyclic amines were alkylated with 2-bromobenzyl bromide using the method reported by Li (2-bromobenzyl bromide/KOH/EtOH).³⁰ Acyclic amines were alkylated with 2-bromobenzyl bromide using the method reported by Mugesh (2-bromobenzyl bromide/TEA/toluene).³¹ Spectral data for **2a**,³² **2c**,³³ **2d**,³⁴ **2f**,³⁵ **2h**,³⁶ **2k**,³⁷ **2l**,³⁸ **2m**,³³ and **2n**³⁶ showed good agreement with the literature data.

1-(2-Bromobenzyl)piperidine (2b): Obtained in 74% yield as a light yellow oil. R_f 0.44 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.53-7.49 (m, 2H), 7.29-7.25 (m, 1H), 7.09 (td, $J = 7.6, 1.6$ Hz, 1H), 3.55 (s, 2H), 2.47-2.44 (m, 4H), 1.62-1.56 (m, 4H), 1.48-1.42 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 138.2, 132.5, 130.6, 128.0, 127.1, 124.5, 62.5, 54.6, 26.0, 24.3; HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_{17}\text{NBr}$ $[\text{M} + \text{H}]^+$ 254.0544, found 254.0536.

1-(2-Bromobenzyl)azepane (2e): Obtained in 71% yield as a light yellow oil. R_f 0.35 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.56-7.51 (m, 2H), 7.30-7.26 (m, 1H), 7.08 (td, $J = 7.6, 1.6$ Hz, 1H), 3.71 (s, 2H), 2.70-2.67 (m, 4H), 1.64-1.62 (m, 8H); ^{13}C NMR (100 MHz, CDCl_3): δ 139.4, 132.5, 130.4, 127.9, 127.1, 124.2, 61.7, 55.8, 28.4, 27.1; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{19}\text{NBr}$ $[\text{M} + \text{H}]^+$ 268.0701, found 268.0703.

N-(2-Bromobenzyl)-N-butylbutan-1-amine (2g): obtained in 70% yield as a light yellow oil. R_f 0.67 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.59-7.50 (m, 2H), 7.30-7.26 (m, 1H), 7.08 (td, $J = 7.6, 1.4$ Hz, 1H), 3.63 (s, 2H), 2.46 (t, $J = 7.3$ Hz, 4H), 1.50-1.42 (m, 4H), 1.31 (sextet, $J = 7.4$ Hz, 4H), 0.89 (t, $J = 7.3$ Hz,

6H); ^{13}C NMR (100 MHz, CDCl_3): δ 139.8, 132.4, 130.5, 127.8, 127.1, 124.0, 58.3, 54.0, 29.4, 20.6, 14.1; HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{25}\text{NBr}$ $[\text{M} + \text{H}]^+$ 298.1170, found 298.1170.

1-(2-Bromobenzyl)-4-methylpiperazine (2i): obtained in 67% yield as a light yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 7.52 (d, $J = 8.0$ Hz, 1H), 7.46 (d, $J = 7.6$ Hz, 1H), 7.26 (t, $J = 7.5$ Hz, 1H), 7.09 (t, $J = 7.6$ Hz, 1H), 3.60 (s, 2H), 2.56-2.45 (m, 8H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 137.6, 132.7, 130.7, 128.3, 127.1, 124.6, 61.7, 55.2, 53.1, 46.1.

4-(2-Bromobenzyl)thiomorpholine (2j): obtained in 65% yield as a light yellow oil. ^1H NMR (500 MHz, CDCl_3): δ 7.54 (dd, $J = 8.0, 0.9$ Hz, 1H), 7.45 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.29-7.26 (m, 1H), 7.11 (td, $J = 7.6, 1.5$ Hz, 1H), 3.59 (s, 2H), 2.79-2.77 (m, 4H), 2.70-2.68 (m, 4H).

Cobalt-Catalyzed $\text{C}(\text{sp}^2)\text{-H}/\text{C}(\text{sp}^3)\text{-H}$ Coupling between Aryl Imines and *N*-(2-Bromobenzyl)amines

Typical Procedure: 1-(2-(1-Benzylpyrrolidin-2-yl)phenyl)ethan-1-one (3aa). In a 10 ml Schlenk tube were placed 1-(2-bromobenzyl)pyrrolidine (**2a**, 48.0 mg, 0.20 mmol), (*E*)-*N*-(4-methoxyphenyl)-1-phenylethan-1-imine (**1a**, 90.1 mg, 0.40 mmol), 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride (SIPr•HCl, 8.5 mg, 0.020 mmol), a freshly prepared THF solution of CoBr₂ (0.10 M, 0.20 mL, 0.020 mmol), and DME (0.50 mL). The resulting solution was cooled in an ice bath and a THF solution of *sec*-BuMgBr (1.34 M, 0.30 mL, 0.40 mmol) was added. After stirring in the ice bath for 12 h, the mixture was quenched by the addition of 3 N HCl (1.0 mL). The resulting mixture was stirred at room temperature for 1 h, and then neutralized with 3 N NaOH (2.0 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a light yellow oil (27.4 mg, 49%).

R_f 0.32 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.11 (d, J = 7.8 Hz, 1H), 7.59 (dd, J = 7.7, 0.7 Hz, 1H), 7.55-7.51 (m, 1H), 7.32-7.21 (m, 6H), 3.92 (t, J = 8.2 Hz, 1H), 3.81 (d, J = 13.1 Hz, 1H), 3.14-3.08 (m, 1H), 3.10 (d, J = 13.2 Hz, 1H), 2.61 (s, 3H), 2.51-2.42 (m, 1H), 2.24 (q, J = 8.9 Hz, 1H), 1.93-1.75 (m, 2H), 1.70-1.61 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 202.4, 144.2, 139.7, 139.0, 131.7, 128.5, 128.0 (two signals overlapped), 127.9, 126.6, 126.1, 65.3, 58.5, 53.3, 35.0, 30.2, 22.7; HRMS (ESI) Calcd for C₁₉H₂₂NO [M + H]⁺ 280.1701, found 280.1699.

1-(2-(1-Benzylpyrrolidin-2-yl)-4-methylphenyl)ethan-1-one (3ba): Brown oil (28.2 mg, 48%; eluent: hexane/EtOAc = 20/1). R_f 0.23 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.91 (s, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.31-7.28 (m, 4H), 7.24-7.19 (m, 1H), 7.09 (d, J = 7.6 Hz, 1H), 3.95 (t, J = 8.2 Hz, 1H), 3.77 (d, J = 13.0 Hz, 1H), 3.11-3.03 (m, 1H), 3.05 (d, J = 13.0 Hz, 1H), 2.58 (s, 3H), 2.49-2.40 (m, 1H), 2.42 (s, 3H), 2.22 (q, J = 8.9 Hz, 1H), 1.89-1.73 (m, 2H), 1.63-1.54 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 201.7, 144.7, 142.4, 139.9, 135.9, 128.8, 128.6, 128.5, 128.1, 126.8, 126.7, 65.3, 58.7, 53.4, 34.9, 30.0, 22.7, 21.7; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{24}\text{NO}$ $[\text{M} + \text{H}]^+$ 294.1858, found 294.1863.

1-(2-(1-Benzylpyrrolidin-2-yl)-4-fluorophenyl)ethan-1-one (3ca): White solid (30.4 mg, 51%; eluent: hexane/EtOAc = 30/1). R_f 0.35 (hexane/EtOAc = 10/1); m.p. 92.9-95.9 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 7.86 (dd, J = 11.0, 2.7 Hz, 1H), 7.66 (dd, J = 8.6, 5.7 Hz, 1H), 7.31-7.27 (m, 4H), 7.25-7.19 (m, 1H), 6.96 (td, J = 8.1, 2.7 Hz, 1H), 4.03 (td, J = 8.0, 1.4 Hz, 1H), 3.76 (d, J = 13.1 Hz, 1H), 3.14-3.07 (m, 1H), 3.13 (d, J = 13.1 Hz, 1H), 2.58 (s, 3H), 2.52-2.42 (m, 1H), 2.25 (q, J = 8.9 Hz, 1H), 1.89-1.75 (m, 2H), 1.60-1.51 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 200.3, 165.1 ($^1J_{\text{C-F}}$ = 250.5 Hz), 149.6 (d, $^3J_{\text{C-F}}$ = 7.6 Hz), 139.6, 134.3 (d, $^4J_{\text{C-F}}$ = 2.6 Hz), 131.2 (d, $^3J_{\text{C-F}}$ = 8.8 Hz), 128.6, 128.1, 126.8, 114.8 (d, $^2J_{\text{C-F}}$ = 22.8 Hz), 113.1 (d, $^2J_{\text{C-F}}$ = 22.1 Hz), 65.0, 58.8, 53.5, 35.0, 29.9, 22.9; ^{19}F NMR (376 MHz, CDCl_3): δ -106.7;

HRMS (ESI) Calcd for $C_{19}H_{21}NOF$ $[M + H]^+$ 298.1607, found 298.1616.

1-(2-(1-Benzylpyrrolidin-2-yl)-4-chlorophenyl)ethan-1-one (3da): Light yellow oil (24.8 mg, 39%; eluent: hexane/EtOAc = 40/1). R_f 0.33 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 2.1 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.31-7.19 (m, 6H), 3.93 (t, J = 8.1 Hz, 1H), 3.74 (d, J = 13.0 Hz, 1H), 3.14-3.07 (m, 1H), 3.13 (d, J = 13.0 Hz, 1H), 2.57 (s, 3H), 2.49-2.40 (m, 1H), 2.25 (q, J = 8.9 Hz, 1H), 1.89-1.72 (m, 2H), 1.62-1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9, 147.4, 139.4, 138.2, 136.6, 129.8, 128.6, 128.3, 128.1, 126.8, 126.3, 64.9, 58.8, 53.5, 35.0, 30.0, 22.9; HRMS (ESI) Calcd for $C_{19}H_{21}NOCl$ $[M + H]^+$ 314.1312, found 314.1316.

1-(3-(1-Benzylpyrrolidin-2-yl)-[1,1'-biphenyl]-4-yl)ethan-1-one (3ea): White solid (23.5 mg, 33%; eluent: hexane/EtOAc = 20/1). R_f 0.27 (hexane/EtOAc = 10/1); m.p. 98.5-101.5 $^{\circ}C$; 1H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, J = 1.7 Hz, 1H), 7.70-7.65 (m, 3H), 7.52 (dd, J = 8.0, 1.8 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 7.3 Hz, 1H), 7.32-7.27 (m, 4H), 7.20 (t, J = 6.9 Hz, 1H), 4.03 (t, J = 8.1 Hz, 1H), 3.85 (d, J = 13.2 Hz, 1H), 3.17-3.11 (m, 1H), 3.15 (d, J = 13.3 Hz, 1H), 2.63 (s, 3H), 2.54-2.45 (m, 1H), 2.27 (q, J = 8.9 Hz, 1H), 1.92-1.75 (m, 2H), 1.70-1.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 145.4, 144.4, 140.3, 139.8, 137.3, 129.1, 128.9, 128.5, 128.1, 127.9, 127.3, 126.7 (two signals overlapped), 124.7, 65.4, 58.7, 53.6, 35.1,

30.1, 22.8; HRMS (ESI) Calcd for $C_{25}H_{26}NO$ $[M + H]^+$ 356.2014, found 356.2014.

1-(2-(1-Benzylpyrrolidin-2-yl)-4-methoxyphenyl)ethan-1-one (3fa): Light yellow oil (18.4 mg, 30%; eluent: hexane/EtOAc = 8/1). R_f 0.17 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 2.7 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.32-7.27 (m, 4H), 7.23-7.19 (m, 1H), 6.79 (dd, J = 8.7, 2.7 Hz, 1H), 4.16 (t, J = 8.1 Hz, 1H), 3.88 (s, 3H), 3.80 (d, J = 13.2 Hz, 1H), 3.12-3.07 (m, 1H), 3.09 (d, J = 13.2 Hz, 1H), 2.57 (s, 3H), 2.54-2.47 (m, 1H), 2.24 (q, J = 8.9 Hz, 1H), 1.84-1.75 (m, 2H), 1.58-1.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.8, 162.8, 148.9, 140.1, 131.9, 130.5, 128.4, 128.1, 126.6, 112.3, 111.8, 65.4, 58.7, 55.4, 53.5, 34.7, 29.5, 22.9; HRMS (ESI) Calcd for $C_{20}H_{24}NO_2$ $[M + H]^+$ 310.1807, found 310.1805.

1-(2-(1-Benzylpyrrolidin-2-yl)-4-(trifluoromethyl)phenyl)ethan-1-one (3ga): Light yellow oil (14.5 mg, 21%; eluent: hexane/EtOAc = 30/1). R_f 0.33 (hexane/EtOAc = 10/1); 1H NMR (500 MHz, $CDCl_3$): δ 8.36 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.28-7.19 (m, 5H), 3.85 (t, J = 8.1 Hz, 1H), 3.69 (d, J = 12.9 Hz, 1H), 3.17-3.09 (m, 1H), 3.16 (d, J = 12.9 Hz, 1H), 2.60 (s, 3H), 2.46-2.39 (m, 1H), 2.29 (q, J = 8.9 Hz, 1H), 1.91-1.75 (m, 2H), 1.65-1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 145.5, 141.9, 139.1, 133.1 (q, $^2J_{C-F}$ = 31.7 Hz), 128.7, 128.2, 127.8, 126.9, 125.4, 123.8 (q, $^1J_{C-F}$ = 272.0 Hz), 123.1, 65.1, 58.8, 53.6,

35.3, 30.4, 22.9; ^{19}F NMR (376 MHz, CDCl_3): δ -63.0; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{21}\text{NOF}_3$ $[\text{M} + \text{H}]^+$ 348.1575, found 348.1578.

1-(2-(1-Benzylpyrrolidin-2-yl)-5-(trifluoromethyl)phenyl)ethan-1-one (3ha):

Light yellow oil (42.1 mg, 61%; eluent: hexane/EtOAc = 30/1). R_f 0.40 (hexane/EtOAc = 10/1); ^1H NMR (500 MHz, CDCl_3): δ 8.22 (d, J = 8.3 Hz, 1H), 7.77 (s, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.29-7.20 (m, 5H), 3.92 (t, J = 8.2 Hz, 1H), 3.71 (d, J = 13.1 Hz, 1H), 3.16-3.10 (m, 1H), 3.15 (d, J = 13.1 Hz, 1H), 2.62 (s, 3H), 2.49-2.41 (m, 1H), 2.27 (q, J = 8.9 Hz, 1H), 1.91-1.76 (m, 2H), 1.64-1.56 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 201.1, 148.8, 139.2 (two signals overlapped), 128.9, 128.6 (q, $^2J_{\text{C-F}}$ = 32.5 Hz), 128.5, 128.1 (two signals overlapped), 126.8, 124.6 (q, $^3J_{\text{C-F}}$ = 3.3 Hz), 123.8 (q, $^1J_{\text{C-F}}$ = 270.7 Hz), 65.1, 58.6, 53.5, 35.2, 30.2, 22.9; ^{19}F NMR (376 MHz, CDCl_3): δ -62.5; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{21}\text{NOF}_3$ $[\text{M} + \text{H}]^+$ 348.1575, found 348.1582.

1-(2-(1-Benzylpyrrolidin-2-yl)-5-chlorophenyl)ethan-1-one (3ia): Silica gel chromatography (eluent: hexane/Et₂O = 20/1) of the crude product afforded the compound **3ia** in a pure form (14.2 mg, 23%) as a light yellow oil and a mixture of **3ia** and *N*-(1-(3-chlorophenyl)ethyl)-4-methoxyaniline (reduced product of **1i**; 16.3 mg, 26%, ratio = 5:1 as determined by ^1H NMR) as a yellow oil. Characterization data of **3ia** are given below.

R_f 0.46 (hexane/EtOAc = 10/1); ^1H NMR (400MHz, CDCl_3): δ 8.01 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 2.2 Hz, 1H), 7.46 (dd, J = 8.5, 2.2 Hz, 1H), 7.30-7.19 (m, 5H), 3.82 (t, J = 8.1 Hz, 1H), 3.73 (d, J = 13.1 Hz, 1H), 3.10-3.06 (m, 1H), 3.09 (d, J = 13.0 Hz, 1H), 2.57 (s, 3H), 2.44-2.35 (m, 1H), 2.22 (q, J = 8.9 Hz, 1H), 1.89-1.72 (m, 2H), 1.62-1.53 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 201.1, 142.9, 140.3, 139.5, 131.9, 131.6, 129.8, 128.5, 128.1, 127.7, 126.8, 64.9, 58.5, 53.4, 35.1, 30.2, 22.8; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{21}\text{NOCl}$ $[\text{M} + \text{H}]^+$ 314.1312, found 314.1310.

1-(2-(1-Benzylpyrrolidin-2-yl)-3-fluorophenyl)ethan-1-one (3ja): Light yellow oil (31.6 mg, 53%; eluent: Hex/EtOAc = 10/1). R_f 0.17 (hexane/EtOAc = 10/1); ^1H NMR (500 MHz, CDCl_3): δ 7.29-7.18 (m, 6H), 7.07 (t, J = 9.3 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 3.97 (t, J = 8.5 Hz, 1H), 3.76 (d, J = 13.6 Hz, 1H), 3.23 (d, J = 13.6 Hz, 1H), 3.01-2.98 (m, 1H), 2.51 (s, 3H), 2.34 (q, J = 8.8 Hz, 1H), 2.28-2.21 (m, 1H), 2.04-1.86 (m, 2H), 1.75-1.68 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 202.8 (d, $^4J_{\text{C-F}}$ = 2.0 Hz), 161.1 (d, $^1J_{\text{C-F}}$ = 247.0 Hz), 143.6 (d, $^3J_{\text{C-F}}$ = 3.0 Hz), 137.8, 129.3, 128.6 (d, $^2J_{\text{C-F}}$ = 13.0 Hz), 128.1, 128.0, 126.8, 121.8 (d, $^3J_{\text{C-F}}$ = 3.0 Hz), 116.4 (d, $^2J_{\text{C-F}}$ = 23.0 Hz), 60.5, 58.0, 52.8, 32.6, 31.7, 23.1; ^{19}F NMR (376 MHz, CDCl_3): δ -114.4; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{21}\text{NOF}$ $[\text{M} + \text{H}]^+$ 298.1607, found 298.1612.

1-(2-(1-Benzylpyrrolidin-2-yl)phenyl)propan-1-one (3la): The reaction time was 24 h. Light yellow oil (12.4 mg, 21%; eluent: hexane/EtOAc = 30/1). R_f 0.35

(hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.04 (d, $J = 7.5$ Hz, 1H), 7.51-7.48 (m, 2H), 7.30-7.26 (m, 5H), 7.24-7.19 (m, 1H), 3.78 (d, $J = 13.1$ Hz, 1H), 3.72 (t, $J = 8.2$ Hz, 1H), 3.10-2.80 (m, 4H), 2.44-2.35 (m, 1H), 2.20 (q, $J = 8.9$ Hz, 1H), 1.91-1.72 (m, 2H), 1.69-1.60 (m, 1H), 1.21 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 206.1, 143.6, 139.7, 139.6, 131.2, 128.6, 128.1, 127.9, 126.9, 126.7, 126.2, 65.6, 58.4, 53.3, 35.7, 35.3, 22.7, 8.4; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{24}\text{NO}$ $[\text{M} + \text{H}]^+$ 294.1858, found 294.1860.

8-(1-Benzylpyrrolidin-2-yl)-3,4-dihydronaphthalen-1(2H)-one (3ma): Light yellow oil (27.1 mg, 44%; eluent: hexane/EtOAc = 10/1). R_f 0.20 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.12 (d, $J = 7.7$ Hz, 1H), 7.46 (t, $J = 7.7$ Hz, 1H), 7.33-7.29 (m, 4H), 7.21 (t, $J = 6.8$ Hz, 1H), 7.12 (d, $J = 7.3$ Hz, 1H), 4.41 (t, $J = 8.0$ Hz, 1H), 3.78 (d, $J = 13.1$ Hz, 1H), 3.11-3.05 (m, 1H), 3.07 (d, $J = 13.1$ Hz, 1H), 2.98-2.94 (m, 2H), 2.76-2.55 (m, 3H), 2.24 (q, $J = 8.8$ Hz, 1H), 2.16-2.05 (m, 2H), 1.84-1.76 (m, 2H), 1.53-1.44 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 200.2, 148.2, 145.3, 140.2, 132.9, 131.5, 128.5, 128.1, 127.0, 126.6, 125.9, 65.5, 59.0, 53.5, 41.2, 34.2, 31.1, 22.94, 22.90; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{24}\text{NO}$ $[\text{M} + \text{H}]^+$ 306.1858, found 306.1859.

1-(2-(1-Benzylpiperidin-2-yl)-5-(trifluoromethyl)phenyl)ethan-1-one (3hb): Light yellow oil (15.9 mg, 22%; eluent: hexane/EtOAc = 60/1). R_f 0.38 (hexane/EtOAc =

10/1); ^1H NMR (500 MHz, CDCl_3): δ 8.17 (d, $J = 8.7$ Hz, 1H), 7.73-7.71 (m, 2H), 7.29-7.19 (m, 5H), 3.66 (dd, $J = 10.4, 2.5$ Hz, 1H), 3.59 (d, $J = 13.5$ Hz, 1H), 2.97 (d, $J = 11.5$ Hz, 1H), 2.84 (d, $J = 13.6$ Hz, 1H), 2.63 (s, 3H), 1.99-1.92 (m, 2H), 1.79 (d, $J = 12.5$ Hz, 1H), 1.64-1.36 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3): δ 201.8, 148.9, 139.6, 139.2, 129.2, 128.7 (q, $^2J_{\text{C-F}} = 32.8$ Hz), 128.4, 128.1, 127.8 (q, $^3J_{\text{C-F}} = 3.3$ Hz), 126.8, 124.1 (q, $^3J_{\text{C-F}} = 4.0$ Hz), 123.7 (q, $^1J_{\text{C-F}} = 270.5$ Hz), 63.8, 60.1, 53.2, 36.5, 30.7, 25.8, 24.9; ^{19}F NMR (376 MHz, CDCl_3): δ -62.5; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{23}\text{NOF}_3$ $[\text{M} + \text{H}]^+$ 362.1732, found 362.1730.

1-(2-(4-Benzylmorpholin-3-yl)-5-(trifluoromethyl)phenyl)ethan-1-one (3hc):

Light yellow oil (12.4 mg, 17%; eluent: hexane/EtOAc = 10/1). R_f 0.22 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.21 (d, $J = 8.2$ Hz, 1H), 7.79-7.76 (m, 2H), 7.31-7.21 (m, 5H), 4.01-3.96 (m, 2H), 3.86 (d, $J = 11.2$ Hz, 1H), 3.71-3.62 (m, 2H), 3.35 (t, $J = 11.2$ Hz, 1H), 2.93 (d, $J = 13.3$ Hz, 1H), 2.79 (d, $J = 11.8$ Hz, 1H), 2.66 (s, 3H), 2.32 (td, $J = 11.8, 3.3$ Hz, 1H); ^{13}C NMR (100MHz, CDCl_3): δ 200.9, 143.1, 140.6, 137.9, 129.9, 129.6 (q, $^2J_{\text{C-F}} = 32.7$ Hz), 128.6, 128.3, 127.9 (q, $^3J_{\text{C-F}} = 3.3$ Hz), 127.1, 124.6 (q, $^3J_{\text{C-F}} = 3.7$ Hz), 123.6 (q, $^1J_{\text{C-F}} = 270.7$ Hz), 72.9, 67.4, 62.7, 59.6, 51.8, 30.3; ^{19}F NMR (376 MHz, CDCl_3): δ -62.7; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_2\text{F}_3$ $[\text{M} + \text{H}]^+$ 364.1524, found 364.1520.

1-(2-(1-Benzyl-1,2,3,4-tetrahydroquinolin-2-yl)-5-(trifluoromethyl)phenyl)ethan-

1-one (3hd): Light yellow solid (16.4 mg, 20%; eluent: hexane/EtOAc = 60/1). R_f 0.42 (hexane/EtOAc = 10/1); m.p. 126.7-129.5 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.94 (s, 1H), 7.65 (d, $J = 7.9$ Hz, 1H), 7.53 (d, $J = 8.1$ Hz, 1H), 7.30-7.27 (m, 2H), 7.24-7.20 (m, 1H), 7.17 (d, $J = 7.2$ Hz, 2H), 7.07-7.02 (m, 2H), 6.65 (t, $J = 7.2$ Hz, 1H), 6.57 (d, $J = 8.2$ Hz, 1H), 5.43-5.41 (m, 1H), 4.63 (d, $J = 17.2$ Hz, 1H), 4.08 (d, $J = 17.2$ Hz, 1H), 2.69-2.49 (m, 5H), 2.45-2.36 (m, 1H), 2.13-2.07 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 200.2, 148.9, 145.1, 137.9, 137.2, 129.4, 129.3 (q, $^2J_{\text{C-F}} = 32.8$ Hz), 128.9, 128.7, 128.0 (q, $^3J_{\text{C-F}} = 3.5$ Hz), 127.6, 126.9, 126.4 (two signals overlapped), 123.6 (q, $^1J_{\text{C-F}} = 270.8$ Hz), 122.1, 116.2, 110.8, 58.1, 53.3, 29.8, 28.4, 23.7; ^{19}F NMR (376 MHz, CDCl_3): δ -62.6; HRMS (ESI) Calcd for $\text{C}_{25}\text{H}_{23}\text{NOF}_3$ [$\text{M} + \text{H}$] $^+$ 410.1732, found 410.1732.

1-(2-(1-Benzylazepan-2-yl)-5-(trifluoromethyl)phenyl)ethan-1-one (3he):

Light yellow oil (48.4 mg, 64%; eluent: hexane/EtOAc = 50/1). R_f 0.52 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.13 (d, $J = 8.6$ Hz, 1H), 7.70-7.68 (m, 2H), 7.25-7.15 (m, 5H), 4.23-4.21 (m, 1H), 3.51 (d, $J = 13.8$ Hz, 1H), 3.45 (d, $J = 13.8$ Hz, 1H), 2.99-2.79 (m, 2H), 2.53 (s, 3H), 1.97-1.82 (m, 3H), 1.73-1.47 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 201.6, 151.5, 139.7, 138.7, 129.1, 128.6, 128.3 (q, $^2J_{\text{C-F}} = 32.3$ Hz), 128.1, 127.2 (q, $^3J_{\text{C-F}} = 3.3$ Hz), 126.7, 124.3 (q, $^3J_{\text{C-F}} = 3.7$ Hz), 123.8 (q, $^1J_{\text{C-F}} = 270.7$ Hz), 64.7, 59.3, 50.3, 35.4, 30.3, 29.1, 27.2, 26.4; ^{19}F NMR (376 MHz, CDCl_3): δ -62.5; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{25}\text{NOF}_3$ [$\text{M} + \text{H}$] $^+$ 376.1888, found 376.1885.

1-(2-(1-(Benzyl(ethyl)amino)ethyl)-5-(trifluoromethyl)phenyl)ethan-1-one (3hf):

Light yellow oil (40.5 mg, 58%; eluent: hexane/EtOAc = 30/1). R_f 0.42 (hexane/EtOAc = 10/1); ^1H NMR (500 MHz, CDCl_3): δ 7.80 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.62 (s, 1H), 7.28-7.19 (m, 5H), 4.50 (q, J = 6.6 Hz, 1H), 3.52 (d, J = 17.3 Hz, 1H), 3.45 (d, J = 17.2 Hz, 1H), 2.62-2.45 (m, 5H), 1.37 (d, J = 6.5 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 202.4, 148.7, 141.1, 139.9, 128.7 (two signals overlapped), 128.2, 128.1, 126.8, 126.7 (q, $^3J_{\text{C-F}}$ = 3.7 Hz), 123.8 (q, $^1J_{\text{C-F}}$ = 270.7 Hz), 123.4 (q, $^3J_{\text{C-F}}$ = 3.7 Hz), 55.2, 54.3, 43.6, 30.5, 16.2, 11.0; ^{19}F NMR (376 MHz, CDCl_3): δ -62.5; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{23}\text{NOF}_3$ $[\text{M} + \text{H}]^+$ 350.1732, found 350.1729.

1-(2-(1-(Benzyl(butyl)amino)butyl)-5-(trifluoromethyl)phenyl)ethan-1-one

(3hg): Light yellow oil (35.7 mg, 44%; eluent: hexane/EtOAc = 60/1). R_f 0.65 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, d_6 -acetone): δ 7.94 (s, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.28-7.19 (m, 5H), 4.53 (dd, J = 8.8, 5.5 Hz, 1H), 3.69 (d, J = 13.9 Hz, 1H), 3.42 (d, J = 13.9 Hz, 1H), 2.62 (s, 3H), 2.57-2.50 (m, 1H), 2.36-2.29 (m, 1H), 2.03-1.94 (m, 1H), 1.89-1.80 (m, 1H), 1.39-1.04 (m, 6H), 0.91 (t, J = 7.3 Hz, 3H), 0.75 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 202.3, 145.8, 142.1, 140.3, 128.8, 128.6 (q, $^2J_{\text{C-F}}$ = 32.7 Hz), 128.5, 128.1, 126.7, 126.4 (q, $^3J_{\text{C-F}}$ = 3.7 Hz), 123.8 (q, $^1J_{\text{C-F}}$ = 270.3 Hz), 123.6 (q, $^3J_{\text{C-F}}$ = 3.7 Hz), 59.1,

54.7, 50.0, 32.8, 30.6, 28.7, 20.5, 19.8, 14.3, 13.9; ^{19}F NMR (376 MHz, CDCl_3): δ – 62.6; HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{31}\text{NOF}_3$ $[\text{M} + \text{H}]^+$ 406.2358, found 406.2361.

Transformation of Product 3aa (Scheme 2.16)

1-(2-(1-Benzylpyrrolidin-2-yl)phenyl)-2-diazoethan-1-one (9): To a solution of LiHMDS (1.0 M, 2.49 mL) in 5.0 mL THF was added 1-(2-(1-benzylpyrrolidin-2-yl)phenyl)ethan-1-one (**3aa**, 642 mg, 2.30 mmol) in THF (4.6 mL) over 1 min at – 78 °C. The resulting mixture was stirred at the same temperature for 30 min, followed by the addition of trifluoroethyl trifluoroacetate (541.1 mg, 2.76 mmol) over 2–3 min. After additional stirring for 3 h, the reaction mixture was warmed to room temperature, stirred overnight and then poured into a separatory funnel together with Et_2O (20 mL) and sat. NH_4Cl (20 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layer was washed with brine, dried over MgSO_4 , and concentrated under reduced pressure. The residue was placed in a dry 50 mL 3-necked round-bottomed flask under a nitrogen atmosphere and dissolved in acetonitrile (9.3 mL). To this solution was added water (0.02 mL) and NEt_3 (0.23 mL), followed by the dropwise addition of *p*-acetamidobenzenesulfonyl azide (402.5 mg, 1.68 mmol) in acetonitrile (9.3 mL). After stirring at room temperature for 24 h, the mixture was poured into a separatory funnel with Et_2O (20 mL). The organic layer was washed with 5% NaOH aqueous solution (3 x 10 mL), water (3 x 10 mL), and brine. The combined organic layer was dried over MgSO_4 and concentrated under reduced pressure. Silica gel chromatography (eluent: hexane/ EtOAc = 8/1–1/1) of the crude product afforded the desired product as a yellow oil (127.4 mg, 32%).

based on recovered **3aa**) along with recovery of **3aa** (275.3 mg).

R_f 0.67 (hexane/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3): δ 8.01 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.35-7.19 (m, 7H), 5.59 (brs, 1H), 3.85 (brs, 1H), 3.79 (d, J = 13.1 Hz, 1H), 3.11-3.06 (m, 2H), 2.44-2.35 (m, 1H), 2.21 (q, J = 8.9 Hz, 1H), 1.89-1.61 (m, 3H); ^{13}C NMR (100 MHz, CD_3CN): δ 191.2, 143.9, 140.7, 139.8, 132.1, 129.5 (2C), 129.1 (2C), 128.6, 127.7, 127.5, 66.0, 58.9, 54.0, 36.3, 23.4; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_3\text{O}$ $[\text{M} + \text{H}]^+$ 306.1606, found 306.1602.

1'-Benzylspiro[indene-1,2'-pyrrolidin]-3(2H)-one (10): A solution of 1-(2-(1-benzylpyrrolidin-2-yl)phenyl)-2-diazoethan-1-one (**9**, 127.4 mg, 0.42 mmol) in dichloromethane (20 mL) was added dropwise to a suspension of $\text{Rh}_2(\text{OAc})_4$ in dichloromethane (9.3 mg, 0.02 mmol, 42 mL) at room temperature over a period of 6 h using a syringe pump. The resulting mixture was stirred for additional 20 h and then concentrated under reduced pressure. Silica gel chromatography (eluent: hexane/EtOAc = 12/1) of the crude product afforded the desired product as a light yellow oil (78.7 mg, 68%).

R_f 0.24 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.75 (t, J = 7.1 Hz, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.3 Hz, 1H), 7.30-7.21 (m, 5H), 3.35 (d, J = 13.0 Hz, 1H), 3.17-3.09 (m, 2H), 2.93 (d, J = 18.7 Hz, 1H), 2.51-2.47 (m, 2H), 2.28-2.21 (m, 1H), 2.08-1.90 (m, 3H); ^{13}C NMR (100 MHz, CD_3CN): δ 204.7, 159.1, 140.9, 138.5, 136.1, 129.7, 129.2, 129.1, 127.7, 126.0, 123.2, 70.5, 53.7, 51.9, 43.1, 42.1, 22.4; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{20}\text{NO}$ $[\text{M} + \text{H}]^+$ 278.1545, found 278.1545.

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Chapter 3. Cobalt-Catalyzed Tandem Radical Cyclization/C–C

Coupling Initiated by Directed C–H Activation

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3.1 Introduction

Transition metal-catalyzed 1,2-dicarbofunctionalization of unactivated alkenes with organometallic reagents and organic (pseudo)halides represents a powerful transformation in organic synthesis.¹ This transformation generates two C–C bonds in a single step and could rapidly build molecular complexity from simple and readily available building blocks.

One common method for olefin dicarbofunctionalization is the integrated Heck carbometallation/cross-coupling, which combines the direct cross-coupling and Heck reaction into one synthetic platform (Scheme 3.1).² Oxidative addition, carbometallation, transmetalation and reductive elimination constitute the four elementary steps of the integrated reaction.

Scheme 3.1. Integrated Heck carbometallation/cross-coupling

Another method for olefin dicarbofunctionalization is the transition metal-catalyzed tandem radical addition/cross-coupling reaction. The reaction can proceed via a three-component intermolecular process³ or a two-component cyclization/cross-coupling process using tethered olefins as the substrates.

In terms of the three-component coupling process, in 2003, Oshima and co-workers reported cobalt-catalyzed 1,2-dicarbofunctionalization of 1,3-dienes with alkyl halides and $\text{Me}_3\text{SiCH}_2\text{MgCl}$ using a combination of CoCl_2 and dppe (Scheme 3.2).^{3a} The reaction involves the generation of an alkyl radical species from the alkyl halide via SET from a low-valent cobalt species. Addition of the alkyl radical species to the conjugated diene followed by radical rebound with the oxidized cobalt species would afford a π -allylcobalt complex. Subsequent transmetalation and reductive elimination would give the difunctionalized product along with regeneration of the low-valent cobalt species.

Scheme 3.2. Cobalt-catalyzed three-component coupling between 1,3-dienes, alkyl halides and $\text{Me}_3\text{SiCH}_2\text{MgCl}$

Proposed mechanism:

In terms of the two-component tandem radical cyclization/cross-coupling, olefin-tethered organohalides are commonly used as the substrates. A typical mechanistic pathway for this type of reaction includes the generation of an initiating radical species from the tethered halo-alkene via single electron reduction by an organotransition metal species, radical cyclization, rebound of the resulting radical with the transition metal species, and reductive elimination (Scheme 3.3).

Scheme 3.3. Transition metal-catalyzed tandem radical cyclization/C–C coupling

The cobalt-catalyzed radical cyclization/cross-coupling of tethered halo-alkenes has proved to be very successful. In 2001, Oshima and co-workers reported the synthesis of various arymethyl-substituted heterocycles via Co-catalyzed arylative radical cyclization of tethered halo-alkenes with aryl Grignard reagents (Scheme 3.4a).⁴ Using a cobalt–diamine catalyst system, they later demonstrated a highly diastereoselective tandem radical cyclization/arylation process for the short total synthesis of the synthetic prostaglandin AH13205 (Scheme 3.4b).⁵ Using 1-(trimethylsilyl)ethenylmagnesium bromide and 2-(trimethylsilyl)ethynylmagnesium bromide as coupling partners, they also achieved alkenylative and alkynylative radical cyclization of tethered halo-alkenes.⁶ The scope of the cobalt-catalyzed sequential cyclization/coupling was further extended to organosilylmethyl and alkyl-substituted alkynyl Grignard reagents with the aid of NHC ligands.⁷

Scheme 3.4. Co-catalyzed tandem radical cyclization/arylation of tethered halo-alkenes

Scheme 3.5. Ni-catalyzed tandem radical cyclization/arylation of tethered haloalkenes

In 2005, Nakamura and coworkers reported the synthesis of lactol derivatives via Fe-catalyzed tandem cyclization/arylation between olefin-tethered iodoacetals and arylzinc reagents (Scheme 3.6a).¹¹ Later, a variety of 3-aryl(methyl)-substituted heterocycles were synthesized by Kang and coworkers via Fe-catalyzed tandem cyclization/Kumada cross-coupling of iodo-alkenes with aryl Grignard reagents (Scheme 3.6b).¹²

Scheme 3.6. Fe-catalyzed tandem radical cyclization/arylation of tethered haloalkenes

a) Nakamura (2005)

b) Kang (2015)

Olefin dicarbofunctionalization via tandem cyclization/cross-coupling has also been achieved using olefin-tethered organometallic reagents and organic halides. In 2014, Fu and coworkers described Ni-catalyzed enantioselective cyclization/cross-coupling of olefin-tethered aryl-(9-BBN) reagents with alkyl halides using a chiral diamine as the ligand (Scheme 3.7a).¹³ In the same year, Cu-catalyzed vicinal diarylation of olefin-tethered aryl-(9-BBN) with aryl iodides was achieved by Brown and coworkers (Scheme 3.7b).¹⁴ Later, the reaction was rendered enantioselective using CuBr/BenzP* as the chiral catalyst (Scheme 3.7c).¹⁵ Unlike the above-discussed tandem reactions involving radical cyclization, these reactions should proceed via migratory insertion of the tethered alkene into an arylnickel or arylcopper species as the enantioselectivity-determining step. In 2017, Giri and coworkers reported Cu-catalyzed cyclization/cross-coupling of (hetero)aryl iodides with olefin-tethered alkyl/arylzinc reagents generated in situ from the corresponding alkyl/aryl halides and Zn (Scheme 3.7d).¹⁶ This reaction was proposed to proceed through radical cyclization to afford a C(sp³)-Cu species, which undergoes cross-coupling with the aryl iodide to furnish the desired product.

Scheme 3.7. Tandem cyclization/C–C coupling of olefin-tethered organometallic reagents

a) Fu (2014)

b) Brown (2014)

c) Brown (2015)

d) Giri (2015)

Tandem radical cyclization/C–C coupling has also been achieved via reductive cross-coupling between two electrophiles using zinc as the reductant. The first Ni-catalyzed reductive dicarbofunctionalization of tethered halo-alkenes was achieved by Peng and coworkers using aryl iodides as the coupling partners.¹⁷ A series of linear-fused perhydrofuro[2,3-*b*]furan(pyran) and [5,5]/[6,5]/[5,6]-spiroketal

skeletons were built using this method (Scheme 3.8a and Scheme 3.8b). More recently, Diao and coworkers broadened the scope of such tandem transformations using bromo-alkenes and (hetero)aryl bromides.¹⁸ A series of pharmaceutically important pyrrolidine, piperidine, and tetrahydrofuran derivatives were synthesized by this methodology (Scheme 3.8c).

Scheme 3.8. Ni-catalyzed reductive dicarbofunctionalization of tethered halo-alkenes

Over the last several years, transition metal-mediated, directing group-assisted arene C–H alkylation with alkyl (pseudo)halides has been developed using both noble (Pd¹⁹, Ru²⁰) and earth-abundant, cost-effective first-row transition metals (Mn²¹, Fe²², Co²³, Ni²⁴). For the latter cases, the reactions are generally considered to involve chelation-assisted arene C–H metalation followed by SET from the resulting metalacycle to the alkyl halide to afford an alkyl radical. As the support for the

radical mechanism, radical clock experiments using 6-bromohex-1-ene were reported to afford a mixture of ring-closing and direct alkylation products.^{21a, 22b-d, 23d, 24e-f} The ratio of these two products proved highly dependent on the arene substrate and the catalytic system used. For example, the (quinolinyl)amino-nickel-catalyzed C-2 alkylation of 1-(pyridin-2-yl)-1*H*-indole afforded the cyclized product as the exclusive product (Scheme 3.9a).^{24e} The nickel-catalyzed C–H alkylation of 2-pyrimidyl anilines afforded a near equimolar mixture of the cyclized and uncyclized products (Scheme 3.9b).^{24d} The cobalt-catalyzed, N–H imine-directed reaction exclusively afforded the direct alkylation product (Scheme 3.9c).^{23f} Besides the use of 6-bromohex-1-ene as the mechanistic probe, these first-row transition metal-catalyzed C–H activation systems have not been proactively utilized for tandem radical cyclization/C–C coupling.

Scheme 3.9. Transition metal-catalyzed, directed C–H alkylation with 6-bromohex-1-ene

We reasoned that the chemoselectivity between the cyclization and the direct alkylation could be controlled by a tether group (Z) causing Thorpe-Ingold effect²⁵ thus enabling selective tandem radical cyclization/C–C coupling. Based on this assumption, we have achieved a cobalt-catalyzed tandem radical cyclization/cross-coupling between tethered bromo-alkenes and aryl N–H imines initiated by N–H imine-directed C–H activation (Scheme 3.10).²⁶ With the assistance of a cobalt–NHC catalyst and a Grignard reagent, this reaction allows for the construction of a variety of benzylated pyrrolidines and related cyclic products in reasonably good yields at room temperature.

Scheme 3.10. Co-catalyzed tandem radical cyclization/cross-coupling initiated by imine-directed C–H activation

3.2 Results and Discussion

We initiated the present study by optimizing conditions for the reaction between *N*-allyl-*N*-(2-bromoethyl)-*p*-toluenesulfonamide (**1a**, 0.3 mmol) and pivalophenone N–H imine (**2a**, 0.2 mmol) (Table 3.1). The Co–**L1**–*t*-BuCH₂MgBr system we previously used for the *ortho*-alkylation of pivalophenone N–H imines^{23f} promoted

the reaction moderately to produce the desired product **3aa** in 44% yield (entry 1). The desired radical cyclization/arylation product was formed together with several byproducts arising from the direct *ortho*-C–H alkylation (**3aa'**, 6%), *ortho*-C–H neopentylation (**4**, 20%) and dehydrobrominative/reductive cyclization (**5** and **6**, 22% combined yield). We also observed a trace amount (2%) of the tandem radical cyclization/neopentylation product (**7**). These side reactions proved persistent regardless of the reaction conditions. Nonetheless, we were able to improve the yield of **3aa** by replacing the *i*-Pr groups of **L1** with more hindered secondary groups (**L2**–**L5**) (entries 2–5). Particularly, **3aa** was formed in more than 60% yield using NHCs containing 3-pentyl and cyclohexylethyl *N*-substituents. On the other hand, the use of *N*-primary or tertiary alkyl-substituted ligands proved detrimental to the present reaction (entries 6 and 7). Benzofused analogues of **L1** and **L4** afforded comparable yields of **3aa** (entries 8 and 9). Other types of ligands such as phosphines and *N,N'*-diaryl-substituted NHCs failed to promote the present reaction (entries 10–17). With **L5** as the ligand, the yield of **3aa** was further increased to 74% by reducing the concentration of **2a** from 0.2 M to 0.08 M (entry 18). In agreement with the radical cyclization mechanism, **L5** did not induce any enantiomeric excess in **3aa**. It should be noted that replacing **1a** with its chloro- or iodo analogue largely shut down the desired reaction (entries 19 and 20). The chloro-analogue was largely recovered presumably because of the sluggishness of the C–Cl bond cleavage. On the other hand, the iodo-analogue predominantly underwent cyclization to afford large amounts of byproducts **5**–**7**.

Table 3.1. Optimization of reaction conditions^a

entry	ligand	yield (%) ^b				
		3aa	3aa'	4	5+6	7
1	L1 • HBF_4	44	6	20	22	2
2	L2 • HCl	54	5	11	21	5
3	L3 • HBF_4	45	5	11	24	4
4	L4 • HBF_4	64	5	9	21	6
5	L5 • HBF_4	68	7	8	19	5
6	L6 • HBF_4	16	0	7	30	6
7	L7 • HCl	5	0	13	29	2
8	L8 • HBr	51	7	10	24	5
9	L9 • HBr	62	6	5	22	11
10	IMes• HCl	0	0	0	61	7
11	SIMes• HCl	0	0	2	31	9
12	IPr• HCl	0	0	3	39	13
13	SIPr• HCl	0	0	4	27	17
14 ^c	PPh_3	0	0	3	41	3
15 ^c	PCy_3	0	0	7	51	1
16	dppe	0	0	1	28	4
17	2,2'-bipyridine	0	0	10	30	1
18 ^d	L5 • HBF_4	74	6	4	13	6
19 ^e	L5 • HBF_4	2	0	21	24	0
20 ^f	L5 • HBF_4	1	0	1	44	18

L1• HBF_4 (R = *i*-Pr)
L2• HCl (R = Cy)
L3• HBF_4 (R = *sec*-Bu)
L4• HBF_4 (R = 3-pentyl)
L6• HBF_4 (R = Et)
L7• HCl (R = 1-admantyl)

L5• HBF_4

L8• HBr (R = *i*-Pr)
L9• HBr (R = 3-pentyl)

^a The reaction was performed using 0.2 mmol of **2a** ($c = 0.2$ M) and 0.3 mmol of **1a**. ^b

The yield was determined by GC using *n*-tridecane as the internal standard. For **5** and **6**, the combined yield is reported because of the overlap of their GC peaks. In a typical

reaction (entry 18), the ratio of **5** and **6** was determined to be 2:1 based on ^1H NMR analysis of the chromatographically separated sample. ^c 20 mol % ligand was used. ^d The reaction was performed at 0.08 M. ^e Chloro analogue of **1a** was used. ^f Iodo analogue of **1a** was used.

Having established the optimized conditions (Table 3.1, entry 18), the scope of N–H imines was explored using **1a** as the reaction partner (Scheme 3.11). A series of *para*-substituted pivalophenone N–H imines engaged in the reaction to yield the products **3ab–3ag** in moderate to good yields. Imines containing *m*-methyl, *m*-methoxy, *m*-chloro, or *m*-trifluoromethyl group underwent exclusive alkylation at the less hindered *ortho* positions to give the products **3ah–3ak** in moderate to good yields. On the other hand, 3-fluoro or 3,4-methylenedioxy group directed the C–H activation to take place preferentially in its proximity, albeit with low regioselectivities (see **3al** and **3am**). While *ortho*-methyl-substituted pivalophenone N–H imine was totally unreactive for the present reaction, the one with an *ortho*-fluorine group afforded the product **3ao** in moderate yield. The reaction of 2-naphthyl imine occurred exclusively at the less hindered *ortho*-position to give **3ap** in 68% yield. 2-Thienyl imine also took part in the present reaction to give **3aq** in a moderate yield. Besides pivalophenone N–H imine, phenyl *n*-butyl, phenyl isopropyl and benzophenone N–H imine were also viable substrates, yielding the products **3ar–3at** in moderate yields. In contrast, acetophenone-derived *N*-PMP imine was entirely unreactive for the present reaction (see **3au**). It should be noted that the synthesis of **3aa** could be carried out on a 5 mmol scale with a similar yield as the one obtained in a 0.2 mmol scale reaction.

Scheme 3.11. Reaction of **1a** with various N–H imines^a

^a The reaction was performed on a 0.2 mmol scale under the conditions in Table 3.1, entry 18. ^b The major regioisomer is shown (rr = regioisomer ratio). ^c The product was isolated in the form of ketone after acidic hydrolysis.

Next, the reaction of **2a** with various tethered bromo-alkenes was examined (Table 3.2). Modification of the allyl group of **1a** with crotyl, methallyl, 1-buten-3-yl,

and cyclohexen-3-yl groups allowed the synthesis of the cyclization/arylation products **3ba–3ea** in reasonable yields (entries 1-4). For the tandem reaction of the *N*-crotyl substrate, a moderate diastereoselectivity (1.4:1) was achieved during the arylation step (entry 1). The reaction of *N*-(1-buten-3-yl) substrate preferentially gave the *cis*-isomer as the major product with a diastereomer ratio of 2:1 (entry 3). As a result of *cis*-fusing cyclization and diastereoselective arylation, the reaction of *N*-(cyclohexen-3-yl) substrate exclusively gave the bicyclic product **3ea** as a single diastereomer (entry 4). NTs-tethered bromo-alkenes bearing substituted bromoethyl groups were also amenable substrates for the present reaction, affording the 2,4- or 3,4-disubstituted pyrrolidines **3fa–3ha** in moderate yields (entries 5-7). Consistent with previous pyrrolidine-forming radical cyclization reactions,^{18, 27} *cis*-isomers were preferentially formed in these reactions, which could be explained by the Beckwith-Houk model shown in Figure 3.1.²⁸ The ring closure of an NTs-tethered radical is likely to proceed via a chair-like transition state. For the 1-substituted bromo-alkene **1h**, equatorial substitution at C1 is favorable, thus leading to the preferential formation of the *cis*-3,4-disubstituted pyrrolidine product **3ha**. On the other hand, for bromo-alkenes substituted at C2 and C4 positions, equatorial substitutions would cause unfavorable interactions with the *N*-tosyl group. Thus, the C2 and C4-substituents would prefer to occupy the axial positions to afford the *cis*-disubstituted products **3da**, **3fa**, and **3ga**. Besides NTs-tethered substrates, the substrate with an *N*-Ph group also smoothly took part in the reaction to give **3ia** in good yield (entry 8). Moreover, the present tandem cyclization/arylation reaction also allowed the synthesis of benzylated tetrahydrofuran and indane derivatives from the corresponding acetal oxygen-tethered bromo-alkene and 1-bromo-2-(but-3-en-1-yl)benzene substrates (entries 9 and 10). It should be noted that several byproducts

were observed for the low-yielding examples (entries 1, 2, 4). The products **3ba** and **3ea** were formed together with significant amounts of dehydrobrominative and/or reductive cyclization products (Scheme 3.12a and Scheme 3.12c),²⁹ while **3ca** was accompanied by a similar amount of the direct alkylation product (Scheme 3.12b). These problems could be rationalized by the sluggishness of the secondary alkylation of the crotyl- and cyclohexen-3-yl-bearing substrates (see **3ba** and **3ea**) and the reluctance of the radical cyclization of the methallyl-bearing substrate (see **3ca**).

Table 3.2. Reaction of various bromo-alkenes with **2a**^a

entry	bromo-alkene	product	yield (%) ^b
1 ^c			3ba 46 (1.4:1)
2			3ca 46
3			3da 61 (2.0:1)
4			3ea 31
5			3fa 66 (5.6:1)
6			3ga 62 (5.0:1)
7			3ha 52 (3.0:1)
8			3ia 62
9			3ja 80 (1.7:1)
10			3ka 41

^a The reaction was performed on a 0.2 mmol scale under the conditions in Table 3.1, entry 18. ^b The data in the parentheses represents the diastereomer ratio determined by ¹H NMR. For entries 3-7, the relative configuration of the major diastereomer (shown) was determined by NOESY analysis. ^c The *E/Z* ratio of the bromo-alkene was 5.3:1.

Figure 3.1. Beckwith-Houk model to account for the *cis*-diastereoselectivity.

Scheme 3.12. Details of low yielding reactions

Examples of unsuccessful attempts on tandem radical cyclization/arylation between different bromo-alkenes and **2a** are summarized in Scheme 3.13. The

reaction of 6-bromohex-1-ene (**1l**) predominantly gave the direct alkylation product in 65% yield, along with a small amount (< 10%) of the ring-closing alkylation product (Scheme 3.13a). The NTs-tethered substrate with a 3,3-dimethylallyl group (**1m**) afforded a small amount (6%) of the direct C–H alkylation product, together with a substantial amount (79%) of dehydrobrominative cyclization product (Scheme 3.13b). The reaction of *N*-cinnamyl substrate **1n** afforded neither the desired tandem cyclization/arylation product nor the direct C–H alkylation product but produced small amounts of dehydrobrominative cyclization (11%) and reductive cyclization¹² (4%) products (Scheme 3.13c). The reaction of *N*-(cyclohex-1-enyl)methyl substrate **1o** did not give any desired product but produced a small amount (14%) of direct C–H alkylation product along with significant amounts of dehydrobrominative cyclization^{29c} and reductive cyclization products (68% in total) (Scheme 3.13d). The reaction of the *N*-homoallyl substrate **1p** predominantly gave the direct alkylation product in 43% yield, together with minor amounts of piperidine (21%) and azepane (5%) cyclization/C–C coupling products (Scheme 3.13e). For NTs-tethered bromoalkenes bearing 3,3-dimethylallyl, cinnamyl and (cyclohex-1-enyl)methyl groups, the unsuccessful tandem reaction may be ascribed to the failure of C–C coupling between the cyclized radical and the cyclometalated cobalt species (vide infra) owing to the steric hindrance (for **1m** and **1o**) or the electronic nature (for **1n**, the radical should be more stable compared with those involved in successful cases) of the radical.

Scheme 3.13. Unsuccessful attempts on tandem radical cyclization/C–C coupling^a

^a The reaction was performed on a 0.2 mmol scale under the conditions in Table 3.1, entry 18. The yields were determined by GC using *n*-tridecane as the internal standard.

The present radical cyclization/arylation reaction could be combined with radical decomposition of the pivaloyl N–H imine group to afford benzonitrile derivatives.^{23f} Thus, the cyclization products **3aa**, **3af** and **3ao** were readily converted to the corresponding *ortho*-pyrrolidinylmethyl benzonitriles under copper-catalyzed aerobic conditions (Scheme 3.14).³⁰

Scheme 3.14. Imine-to-nitrile conversion

On the basis of our previous studies on the N–H imine- and *N*-aryl imine-directed C–H functionalization reactions,^{23c, 23f, 31} we propose a catalytic cycle for the present cobalt-catalyzed tandem radical cyclization/C–C coupling reaction as shown in Scheme 3.15. A magnesium alkylideneamide species **2**•MgBr, generated from the imine **2** and the Grignard reagent, would undergo C–H cyclometalation with a low-valent alkylcobalt species **A**, generated from the cobalt precatalyst and the Grignard reagent, to afford a cobaltacycle species **B**. SET from **B** to the bromo-alkene **1** would result in a pair of oxidized cobaltacycle and alkyl radical (**C**). Subsequent 5-*exo-trig* cyclization and transmetalation of the intermediate **C** would give the intermediate **D**. After a radical rebound and C–C reductive elimination of the resulting intermediate **E**, the alkylation product **3**•MgBr would be formed along with regeneration of the species **A**. It should be noted that the model reaction was not significantly affected by the addition of TEMPO (50% yield of **3aa**) or α -cyclopropylstyrene (51% yield of **3aa**) (Scheme 3.16), which might suggest the absence of a free radical and fast radical recombination of the radical pair.

Scheme 3.15. Proposed catalytic cycle

Scheme 3.16. Controlled reaction in the presence of additives

As suggested from Table 3.1, the desired catalytic cycle can be interrupted by several side reactions at different steps. Thus, the intermediate **C** can undergo premature radical recombination to afford the direct *ortho*-C–H alkylation product

3aa'. The intermediate **E** may undergo aryl-neopentyl reductive elimination to afford the *ortho*-C–H neopentylation product **4** as well as the dehydrobrominative and reductive cyclization products **5** and **6**. Moreover, competitive reaction of the low-valent cobalt species **A** with the bromo-alkene **1** would afford the radical cyclization/neopentylation product **7**.

3.3 Conclusion

In summary, we have demonstrated a cobalt-catalyzed two-component dicarbofunctionalization of bromo-alkenes via a tandem process of N–H imine-directed C–H activation and 1,5-radical cyclization. Promoted by a cobalt–NHC catalyst and a Grignard reagent, the present reaction enables the synthesis of a range of benzylated pyrrolidines and related cyclic products under mild reaction conditions. The reaction features a good functional group tolerance on the aryl imine and also allows various variations on the bromo-alkene substrate. Considering the vast scope of conventional radical cyclization reactions,³² we expect that the present tandem process could be used for the construction of more complicated polycyclic systems.

3.4 Experimental Section

Materials. Unless otherwise noted, commercial reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. THF were distilled over Na/benzophenone. Anhydrous CoBr₂ (> 98%) were purchased from Adrich and used as received. Grignard reagents were prepared from the corresponding alkyl halides and magnesium turnings in anhydrous THF, and titrated before use.

Preparation of Starting Materials

Preparation of Bromo-Alkenes

6-Bromohex-1-ene (**1n**) was purchased from Alfa Aesar and used as received. Bromo-alkenes **1a**,³³ **1c**,³⁴ **1e**,^{29a} **1f**,¹⁸ **1g**,¹⁸ **1h**,¹⁸ **1i**,¹⁶ **1k**,³⁵ **1m**,³⁶ **1n**,³⁶ **1o**,^{29c} **1p**³⁷ were prepared according to the literature procedures,^{16, 18, 29c, 33, 38} and their spectral data showed good agreement with the literature data.

N-(But-2-en-1-yl)-4-methylbenzenesulfonamide: To a stirred suspension of *p*-toluenesulfonamide (2.83 g, 16.5 mmol) and potassium carbonate (2.28 g, 16.5 mmol) in acetone (15 mL) was added crotyl bromide (1.54 mL, 15.0 mmol, *E/Z* = 5.7/1). After heating at reflux for 30 h, the mixture was cooled to room temperature, poured onto water (~30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. Silica gel

chromatography (eluent: hexane/EtOAc = 5/1) of the crude product afforded the title compound as a mixture of *E/Z* isomers (*E/Z* = 5.7/1 as indicated by ¹H NMR) as a white solid (2.01 g, 59%).

R_f 0.32 (Hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃, *E* isomer): δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 5.60-5.51 (m, 1H), 5.35-5.25 (m, 1H), 4.66 (poor-splitting triplet, *J* = 5.8 Hz, 1H), 3.49 (t, *J* = 6.1 Hz, 2H), 2.41 (s, 3H), 1.58 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃, *E* isomer): δ 142.9, 136.8, 129.3, 129.0, 126.9, 125.5, 44.9, 21.1, 17.2; HRMS (ESI) Calcd for C₁₁H₁₆NO₂S [M + H]⁺ 226.0902, found 226.0904.

***N*-(2-Bromoethyl)-*N*-(but-2-en-1-yl)-4-methylbenzenesulfonamide (1b):** To a solution of *N*-(but-2-en-1-yl)-4-methylbenzenesulfonamide (2.01 g, 8.9 mmol) in acetonitrile (36 mL) was added dibromoethane (7.68 mL, 89.2 mmol) and cesium carbonate (4.36 g, 13.4 mmol). After stirring at 80 °C for 17 h, the mixture was filtered and the filtrate was concentrated in vacuo. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude mixture afforded the title compound as a mixture of *E/Z* isomers (*E/Z* = 5.3/1 as indicated by ¹H NMR) as a light yellow oil (1.95 g, 66%).

R_f 0.25 (Hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃, *E* isomer): δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.72-5.58 (m, 1H), 5.34-5.23 (m, 1H), 3.74 (d, *J* = 6.8 Hz, 2H), 3.49-3.37 (m, 4H), 2.43 (s, 3H), 1.67 (dd, *J* = 6.5, 1.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃, *E* isomer): δ 143.6, 136.5, 131.3, 129.8, 127.2, 125.5, 51.3, 48.6, 29.4, 21.5, 17.7; HRMS (ESI) Calcd for C₁₃H₁₉NO₂S⁸¹Br [M + H]⁺ 334.0299, found 334.0302.

***N*-(2-Bromoethyl)-*N*-(but-3-en-2-yl)-4-methylbenzenesulfonamide (1d):**

Prepared from *N*-(but-3-en-2-yl)-4-methylbenzenesulfonamide³⁹ (4.21 g, 18.7 mmol) using the same procedure as described for **1b**. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) afforded the title compound as a yellow oil (3.72 g, 60%).

R_f 0.30 (Hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.72 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 5.62-5.54 (m, 1H), 5.15-5.07 (m, 2H), 4.55-4.49 (m, 1H), 3.59-3.52 (m, 1H), 3.49-3.31 (m, 3H), 2.43 (s, 3H), 1.18 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 143.6, 137.2 (two signals overlapped), 129.8, 127.1, 117.4, 54.5, 45.1, 30.7, 21.5, 17.2; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_2\text{S}^{81}\text{Br}$ $[\text{M} + \text{H}]^+$ 334.0299, found 334.0301.

3-(2-Bromo-1-ethoxyethoxy)-3-methylbut-1-ene (1j): Prepared from *N*-bromosuccinimide (1.78 g, 10.0 mmol), ethyl vinyl ether (0.96 mL, 10.0 mmol) and 2-methylbut-3-en-2-ol (5 mL) according to the literature procedure.^{38a} Kugelrohr distillation (4 mbar, 100 °C) afforded the title compound as a colorless oil (1.80 g, 76%).

R_f 0.58 (Hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 5.94 (dd, J = 17.6, 10.8 Hz, 1H), 5.21-5.14 (m, 2H), 4.71 (t, J = 5.5 Hz, 1H), 3.61-3.50 (m, 2H), 3.38-3.34 (m, 1H), 3.30-3.26 (m, 1H), 1.36 (s, 3H), 1.33 (s, 3H), 1.20 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 143.3, 114.1, 96.6, 76.5, 60.2, 33.0, 26.9, 26.0, 15.1; HRMS (ESI) Calcd for $\text{C}_9\text{H}_{18}\text{O}_2^{81}\text{Br}$ $[\text{M} + \text{H}]^+$ 239.0470, found 239.0477.

Preparation of Aryl Imines

Pivalophenone imines **2a–2q** shown below were prepared from the corresponding aryl nitriles and *t*-BuMgCl according to the literature procedure,⁴⁰ and purified by distillation. Imines **2r** and **2s** were prepared from benzonitrile and alkylolithium reagents according to the literature procedure.⁴¹ Benzophenone imine **2t** was purchased from TCI and used as received. *N*-PMP imine **2u** was prepared from acetophenone and *p*-anisidine according to the literature procedures⁴² and purified by recrystallization. Spectral data of known imines showed good agreement with the literature data.^{23f, 43} Characterization data of new imines are shown below.

1-(2-Fluorophenyl)-2,2-dimethylpropan-1-imine (2o): Light yellow oil; ¹H NMR (300 MHz, CDCl₃): δ 9.27 (brs, 1H), 7.35-7.28 (m, 1H), 7.15-7.05 (m, 3H), 1.22 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 185.5, 157.7 (d, ¹J_{C-F} = 246.4 Hz), 129.5 (d, ³J_{C-F} = 7.8 Hz), 128.5, 123.5 (d, ⁴J_{C-F} = 3.3 Hz), 115.6 (d, ²J_{C-F} = 22.1 Hz, 2C overlapped), 40.4, 27.7; ¹⁹F NMR (282 MHz, CDCl₃): δ -113.1, -113.5; HRMS (ESI) Calcd for C₁₁H₁₅NF [M + H]⁺ 180.1189, found 180.1194.

2,2-Dimethyl-1-(thiophen-2-yl)propan-1-imine (2q): Yellow oil; ^1H NMR (300 MHz, CDCl_3): δ 9.39 (brs, 1H), 7.39-7.33 (m, 2H), 7.04 (dd, $J = 5.0, 3.8$ Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 180.0, 142.9, 127.8, 127.2, 126.8, 39.9, 28.4; HRMS (ESI) Calcd for $\text{C}_9\text{H}_{14}\text{NS}$ $[\text{M} + \text{H}]^+$ 168.0847, found 168.0850.

Preparation of N-Heterocyclic Carbene Precursors

L1•HBF₄, **L3•HBF₄**, **L4•HBF₄**, **L5•HBF₄** and **L6•HBF₄** were prepared via the reaction of the corresponding *N,N'*-dialkylethylenediamines, triethyl orthoformate and ammonium tetrafluoroborate according to the patent procedure.⁴⁴ *N*¹,*N*²-Diethylethane-1,2-diamine and *N*¹,*N*²-diisopropylethane-1,2-diamine were purchased from Alfa Aesar. *N*¹,*N*²-di-*sec*-Butylethane-1,2-diamine and *N*¹,*N*²-di(pentan-3-yl)ethane-1,2-diamine were prepared from ethylenediamine and corresponding ketones via reductive amination according to the literature procedure.⁴⁵ *N*¹,*N*²-Bis((*S*)-1-cyclohexylethyl)ethane-1,2-diamine was prepared from glyoxal and (*S*)-1-cyclohexylethylamine according to the literature procedure.⁴⁶ **L2•HCl** and **L7•HCl** were purchased from Combi-Blocks and Strem, respectively. **L8•HBr** and **L9•HBr** were prepared from benzimidazole and corresponding alkyl bromides according to the literature procedure.⁴⁷ Shown below are the procedure and the characterization data for new NHC precursors.

1,3-Di-*sec*-butyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate (L3•HBF₄; a 1:1 mixture of diastereomers): Prepared according to the modified patent procedure.⁴⁴ The crude *N*¹,*N*²-di-*sec*-butylethane-1,2-diamine (0.40 g, 2.3 mmol) prepared from ethylenediamine (0.68 mL, 10.0 mmol) and butan-2-one (2.42 mL, 27.0 mmol) was mixed with triethyl orthoformate (0.39 mL, 2.3 mmol) and ammonium tetrafluoroborate (267.6 mg, 2.6 mmol). The mixture was heated at 120 °C for 18 h and cooled to room temperature. Silica gel chromatography (eluent: CH₂Cl₂/MeOH = 50/1) of the crude mixture afforded the title compound as a yellow oil (516 mg, 19% in two steps).

*R*_f 0.33 (CH₂Cl₂/MeOH = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.16 (s, 1H), 3.98-3.91 (m, 2H), 3.89-3.82 (m, 2H), 3.80-3.71 (m, 2H), 1.70-1.51 (m, 4H), 1.30 (d, *J* = 6.7 Hz, 6H), 0.90 (t, *J* = 7.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 155.94, 155.76, 56.12, 56.10, 44.36, 44.03, 26.87, 26.86, 18.08, 10.23, 10.15; HRMS (ESI) Calcd for C₁₁H₂₄BN₂F₄ [*M* + *H*]⁺ 271.1969, found 271.1975. The pairs of ¹³C NMR signals with close chemical shifts and similar intensities indicated that the compound was obtained as a ca. 1:1 mixture of diastereomers.

1,3-Di(pentan-3-yl)-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate (L4•HBF₄): White solid (2.43 g, 54% in two steps; eluent: CH₂Cl₂/MeOH = 10/1; prepared from ethylenediamine (1.0 mL, 15.0 mmol) and pentan-3-one (4.3 mL, 40.5 mmol) as described for L3•HBF₄). *R*_f 0.22 (CH₂Cl₂/MeOH = 10/1); m.p. 68.8-

70.3 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.40 (s, 1H), 3.85 (s, 4H), 3.67-3.60 (m, 2H), 1.71-1.51 (m, 8H), 0.93 (t, $J = 7.4$ Hz, 12H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.6, 62.2, 43.4, 24.9, 10.2; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{28}\text{N}_2\text{F}_4\text{B}$ $[\text{M} + \text{H}]^+$ 299.2282, found 299.2284.

N^1,N^2 -Bis((*S*)-1-cyclohexylethyl)ethane-1,2-diamine: Prepared from glyoxal (0.92 mL, 8.0 mmol, 40 wt.%) and (*S*)-1-cyclohexylethylamine (2.38 mL, 16.0 mmol) according to the literature procedure.⁴⁵ Silica gel chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$) of the crude mixture afforded the title compound as an orange oil (1.56 g, 70% in two steps).

R_f 0.28 ($\text{DCM}/\text{MeOH} = 10/1$); $[\alpha]_{\text{D}}^{25} = +20.9$ ($c = 0.68$ in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 2.81-2.72 (m, 2H), 2.61-2.53 (m, 2H), 2.43-2.37 (m, 2H), 1.75-1.65 (m, 10H), 1.35-0.94 (m, 20H); ^{13}C NMR (100 MHz, CDCl_3): δ 57.8, 47.4, 42.9, 29.8, 28.1, 26.7, 26.6, 26.4, 16.9; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{37}\text{N}_2$ $[\text{M} + \text{H}]^+$ 281.2957, found 281.2961.

1,3-Bis((*S*)-1-cyclohexylethyl)-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate ($\text{L5} \cdot \text{HBF}_4$): Prepared from N^1,N^2 -bis((*S*)-1-cyclohexylethyl)ethane-1,2-diamine (1.56 g, 5.6 mmol), triethyl orthoformate (0.93 mL, 5.6 mmol) and ammonium

tetrafluoroborate (641.3 mg, 6.1 mmol) using the same procedure as described for **L3**•HBF₄. Silica gel chromatography (eluent: CH₂Cl₂/MeOH = 10/1) of the crude mixture afforded a residue, which was washed with a mixture of diethyl ether/ethyl acetate (10/1) to afford the title compound as a white solid (1.20 g, 57%).

R_f 0.24 (DCM/MeOH = 10/1); m.p. 148.5-150.8 °C; $[\alpha]_D^{25} = +50.4$ ($c = 0.54$ in CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 8.17 (s, 1H), 4.00-3.89 (m, 2H), 3.87-3.76 (m, 2H), 3.64-3.57 (m, 2H), 1.79-1.76 (m, 4H), 1.68-1.66 (m, 4H), 1.54-1.51 (m, 2H), 1.48-1.39 (m, 2H), 1.31 (d, $J = 6.8$ Hz, 6H), 1.27-1.12 (m, 6H), 1.09-0.93 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 156.3, 59.4, 44.7, 40.1, 29.5, 28.7, 25.7 (two signals overlapped), 25.6, 15.9; HRMS (ESI) Calcd for C₁₉H₃₆N₂BF₄ [M + H]⁺ 379.2908, found 379.2906.

1,3-Di(pentan-3-yl)-1H-benzo[d]imidazol-3-ium bromide (L9•HBr): Prepared according to the modified literature procedure.⁴⁷ A mixture of benzimidazole (1.18 g, 10.0 mmol) and K₂CO₃ (1.52 g, 11.0 mmol) was suspended in CH₃CN (6 mL) and stirred at room temperature for 1 h. To the suspension was added 3-bromopentane (3.73 mL, 30.0 mmol) and the resulting mixture was stirred under reflux for 24 h. A second portion of 3-bromopentane (3.73 mL, 30.0 mmol) was added and the stirring continued for 6 d under reflux. After removing the volatiles in vacuo, CH₂Cl₂ (50 mL) was added to the residue and the resulting suspension was filtered over Celite. Silica gel chromatography (eluent: CH₂Cl₂/MeOH = 20/1) of the filtrate afforded a residue, which was washed with ethyl acetate to afford the title compound as a white solid (1.19 g, 34%).

R_f 0.15 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$); m.p. 269.6-272.3 °C; ^1H NMR (300 MHz, CDCl_3): δ 11.77 (s, 1H), 7.81-7.75 (m, 2H), 7.65-7.59 (m, 2H), 4.79-4.69 (m, 2H), 2.39-2.24 (m, 4H), 2.23-2.09 (m, 4H), 0.85 (t, $J = 7.3$ Hz, 12H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.5, 131.3, 126.9, 113.9, 64.2, 27.5, 10.6; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{28}\text{N}_2^{81}\text{Br}[\text{M} + \text{H}]^+$ 341.1415, found 341.1410.

General Procedure and Characterization Data

2,2-Dimethyl-1-(2-((1-tosylpyrrolidin-3-yl)methyl)phenyl)propan-1-imine (3aa;

5 mmol-scale reaction): In a 100 mL Schlenk tube were placed 1,3-bis((*S*)-1-cyclohexylethyl)-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate (**L5**• HBF_4 , 189 mg, 0.50 mmol), 2,2-dimethyl-1-phenylpropane-1-imine (**2a**, 806 mg, 5.0 mmol), *N*-allyl-*N*-(2-bromoethyl)-4-methylbenzenesulfonamide (**1a**, 2.39 g, 7.5 mmol), CoBr_2 (109 mg, 0.50 mmol), and THF (55.9 mL). The resulting solution was cooled to 0 °C and a THF solution of *t*- BuCH_2MgBr (1.51 M, 6.6 mL, 10.0 mmol) was added. After stirring at room temperature for 12 h, the mixture was quenched by sat. NH_4Cl (25 mL). The resulting mixture was extracted with EtOAc (3 x 25 mL) and the combined organic layer was dried over MgSO_4 and concentrated under reduced pressure. Silica gel chromatography (eluent: hexane/EtOAc/ $\text{Et}_3\text{N} = 80/40/1$) of the crude product afforded the title compound as a light yellow solid (1.43 g, 72%).

R_f 0.12 (hexane/EtOAc/ $\text{Et}_3\text{N} = 30/10/1$); m.p. 120.4-123.1 °C; ^1H NMR (400 MHz, CDCl_3): δ 9.18 (brs, 1H), 7.69 (d, $J = 8.2$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.26-7.22 (m, 1H), 7.17 (t, $J = 7.5$ Hz, 1H), 7.12 (d, $J = 7.7$ Hz, 1H), 7.02 (d, $J = 7.4$ Hz, 1H), 3.40-3.34 (m, 2H), 3.17 (q, $J = 8.5$ Hz, 1H), 2.88 (t, $J = 8.6$ Hz, 1H), 2.52-2.27

(m, 3H), 2.43 (s, 3H), 1.89-1.82 (m, 1H), 1.49-1.38 (m, 1H), 1.16 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ 190.2, 143.3, 141.4, 135.6, 133.9, 129.6, 129.1, 127.8, 127.4, 126.4, 125.6, 53.0, 47.3, 40.4, 39.9, 36.6, 31.2, 28.6, 21.4; HRMS (ESI) Calcd for $\text{C}_{23}\text{H}_{31}\text{N}_2\text{O}_2\text{S}$ $[\text{M} + \text{H}]^+$ 399.2106, found 399.2102.

The product was determined to be racemic based on HPLC analysis. HPLC conditions: (CHIRALCEL OD (Φ 0.46 cm x 25 cm), *n*-hexane/2-isopropanol = 85/15, flow rate 0.5 mL/min, detection at 254 nm, t_{R} = 20.3 min and 21.8 min.

General procedure for a small-scale (0.20 mmol) reaction: In a 10 mL Schlenk tube were placed 1,3-bis((*S*)-1-cyclohexylethyl)-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate (**L5**• HBF_4 , 7.6 mg, 0.020 mmol), N–H imine substrate (0.20 mmol) and bromo-alkene substrate (0.30 mmol), a freshly prepared THF solution of CoBr_2 (0.10 M, 0.20 mL, 0.020 mmol), and THF (2.04 mL). The resulting solution was cooled to 0 °C and a THF solution of *t*- BuCH_2MgBr (1.51 M, 0.26 mL, 0.40 mmol) was added. After stirring at room temperature for 12 h, the mixture was quenched by sat. NH_4Cl (1 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layer was dried over MgSO_4 and concentrated in vacuo. Silica gel chromatography of the crude product was performed using a mixture of hexane, EtOAc, and Et_3N (typical ratio = 90/30/1 or 80/40/1) as an eluent.

2,2-Dimethyl-1-(4-methyl-2-((1-tosylpyrrolidin-3-yl)methyl)phenyl)propan-1-imine (3ab): Light yellow oil (56.8 mg, 69%; eluent: hexane/EtOAc/ Et_3N =

90/30/1). R_f 0.17 (hexane/EtOAc/Et₃N = 30/10/1); ¹H NMR (400 MHz, CDCl₃): δ 9.12 (brs, 1H), 7.69 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 8.1 Hz, 1H), 6.92-6.90 (m, 2H), 3.41-3.33 (m, 2H), 3.18 (q, J = 8.5 Hz, 1H), 2.86 (t, J = 8.6 Hz, 1H), 2.47-2.27 (m, 3H), 2.43 (s, 3H), 2.32 (s, 3H), 1.89-1.82 (m, 1H), 1.48-1.37 (m, 1H), 1.15 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 190.5, 143.3, 138.6, 137.5, 135.5, 134.0, 129.7, 129.6, 127.5, 126.3 (2C overlapped), 53.0, 47.3, 40.5, 39.9, 36.5, 31.2, 28.6, 21.5, 21.1; HRMS (ESI) Calcd for C₂₄H₃₃N₂O₂S [M + H]⁺ 413.2263, found 413.2258.

1-(4-Methoxy-2-((1-tosylpyrrolidin-3-yl)methyl)phenyl)-2,2-dimethylpropan-1-imine (3ac): Silica gel chromatography (eluent: hexane/EtOAc/Et₃N = 80/40/1) of the crude product afforded the title compound as a mixture with a minor amount of 4-methoxy-2-((1-tosylpyrrolidin-3-yl)methyl)benzonitrile as a light yellow oil (55.3 mg). The yield was determined to be 59% based on the total weight and the ¹H NMR analysis of the mixture.

R_f 0.23 (hexane/EtOAc/Et₃N = 20/20/1); ¹H NMR (400 MHz, CDCl₃): δ 9.14 (brs, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.4 Hz, 1H), 6.71 (dd, J = 8.4, 2.5 Hz, 1H), 6.66 (d, J = 2.5 Hz, 1H), 3.80 (s, 3H), 3.40-3.34 (m, 2H), 3.21-3.14 (m, 1H), 2.88 (t, J = 8.6 Hz, 1H), 2.49-2.27 (m, 3H), 2.44 (s, 3H), 1.90-1.83 (m, 1H), 1.50-1.40 (m, 1H), 1.15 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 190.2, 158.9, 143.3, 137.4, 134.0, 133.8, 129.6, 127.6, 127.4, 114.8, 110.6, 55.2, 53.0, 47.3,

40.6, 39.8, 36.7, 31.2, 28.6, 21.5; HRMS (ESI) Calcd for $C_{24}H_{33}N_2O_3S$ $[M + H]^+$ 429.2212, found 429.2214.

2,2-Dimethyl-1-(2-((1-tosylpyrrolidin-3-yl)methyl)-4-

(trifluoromethoxy)phenyl)propan-1-imine (3ad): White solid (66.3 mg, 69%; eluent: hexane/EtOAc/Et₃N = 90/30/1). *R_f* 0.17 (hexane/EtOAc/Et₃N = 30/10/1); m.p. 118.5-121.5 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.08 (brs, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.09-7.03 (m, 2H), 6.96 (s, 1H), 3.41-3.36 (m, 2H), 3.18 (q, *J* = 8.6 Hz, 1H), 2.93-2.80 (m, 1H), 2.54-2.32 (m, 3H), 2.44 (s, 3H), 1.93-1.79 (m, 1H), 1.51-1.40 (m, 1H), 1.16 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 189.0, 148.5, 143.4, 139.7, 138.4, 133.8, 129.6, 128.0, 127.4, 121.3, 120.3 (q, ¹*J*_{C-F} = 255.9 Hz), 118.1, 52.8, 47.3, 40.6, 39.5, 36.4, 31.0, 28.4, 21.4; ¹⁹F NMR (376 MHz, CDCl₃): δ -57.8; HRMS (ESI) Calcd for $C_{24}H_{30}N_2O_3SF_3$ $[M + H]^+$ 483.1929, found 483.1928.

1-(4-Fluoro-2-((1-tosylpyrrolidin-3-yl)methyl)phenyl)-2,2-dimethylpropan-1-

imine (3ae): Light yellow oil (63.6 mg, 76%; eluent: hexane/EtOAc/Et₃N = 80/40/1). *R_f* 0.11 (hexane/EtOAc/Et₃N = 30/10/1); ¹H NMR (400 MHz, CDCl₃): δ 9.08 (brs, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.01 (dd, *J* = 8.2, 5.9 Hz, 1H),

6.88 (td, $J = 8.3$, 2.5 Hz, 1H), 6.81 (dd, $J = 10.0$, 2.5 Hz, 1H), 3.40-3.34 (m, 2H), 3.18 (q, $J = 8.5$ Hz, 1H), 2.86 (t, $J = 8.3$ Hz, 1H), 2.51-2.27 (m, 3H), 2.44 (s, 3H), 1.90-1.83 (m, 1H), 1.49-1.38 (m, 1H), 1.14 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 189.3, 161.9 (d, $^1J_{\text{C-F}} = 245.6$ Hz), 143.4, 138.6, 137.4, 133.8, 129.6, 128.2, 127.4, 115.6 (d, $^2J_{\text{C-F}} = 21.1$ Hz), 112.7 (d, $^2J_{\text{C-F}} = 21.1$ Hz), 52.9, 47.2, 40.6, 39.6, 36.5, 31.1, 28.4, 21.5; ^{19}F NMR (282 MHz, CDCl_3): δ -102.2; HRMS (ESI) Calcd for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_2\text{FS}$ $[\text{M} + \text{H}]^+$ 417.2012, found 417.2013.

1-(4-Chloro-2-((1-tosylpyrrolidin-3-yl)methyl)phenyl)-2,2-dimethylpropan-1-

imine (3af): Yellow oil (63.1 mg, 73%; eluent: hexane/EtOAc/ Et_3N = 90/30/1). R_f 0.13 (hexane/EtOAc/ Et_3N = 30/10/1); ^1H NMR (400 MHz, CDCl_3): δ 9.22 (brs, 1H), 7.70 (d, $J = 8.2$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.16 (dd, $J = 8.2$, 1.9 Hz, 1H), 7.10 (d, $J = 1.8$ Hz, 1H), 6.98 (d, $J = 8.2$ Hz, 1H), 3.41-3.34 (m, 2H), 3.18 (q, $J = 8.5$ Hz, 1H), 2.87 (t, $J = 8.4$ Hz, 1H), 2.49-2.28 (m, 3H), 2.44 (s, 3H), 1.90-1.83 (m, 1H), 1.49-1.38 (m, 1H), 1.14 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 189.2, 143.4, 139.5, 137.8, 133.8, 133.6, 129.7, 128.9, 127.8, 127.4, 125.9, 52.9, 47.2, 40.5, 39.6, 36.3, 31.0, 28.4, 21.5; HRMS (ESI) Calcd for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_2\text{SCl}$ $[\text{M} + \text{H}]^+$ 433.1717, found 433.1722.

2,2-Dimethyl-1-(3-((1-tosylpyrrolidin-3-yl)methyl)-[1,1'-biphenyl]-4-yl)propan-

1-imine (3ag): White solid (47.5 mg, 50%; eluent: hexane/EtOAc/Et₃N = 90/30/1). *R_f* 0.13 (hexane/EtOAc/Et₃N = 30/10/1); m.p. 139.8-142.8 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.12 (brs, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.56-7.54 (m, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.41-7.36 (m, 2H), 7.33 (s, 1H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 1H), 3.43-3.36 (m, 2H), 3.19 (q, *J* = 8.5 Hz, 1H), 2.92 (t, *J* = 8.4 Hz, 1H), 2.59-2.37 (m, 3H), 2.42 (s, 3H), 1.93-1.85 (m, 1H), 1.54-1.45 (m, 1H), 1.20 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 190.1, 143.3, 140.8, 140.4 (2C overlapped), 136.2, 133.9, 129.6, 128.8, 127.7, 127.6, 127.5, 127.0 (2C overlapped), 124.4, 53.1, 47.3, 40.6, 39.9, 36.6, 31.2, 28.6, 21.5; HRMS (ESI) Calcd for C₂₉H₃₅N₂O₂S [M + H]⁺ 475.2419, found 475.2419.

2,2-Dimethyl-1-(5-methyl-2-((1-tosylpyrrolidin-3-yl)methyl)phenyl)propan-1-

imine (3ah): Light yellow oil (51.5 mg, 62%; eluent: hexane/EtOAc/Et₃N = 90/30/1). *R_f* 0.16 (hexane/EtOAc/Et₃N = 30/10/1); ¹H NMR (400 MHz, CDCl₃): δ 9.05 (brs, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.82 (s, 1H), 3.39-3.33 (m, 2H), 3.17 (q, *J* = 8.5 Hz, 1H), 2.86 (t, *J* = 8.6 Hz, 1H), 2.47-2.28 (m, 3H), 2.43 (s, 3H), 2.30 (s, 3H), 1.88-1.81 (m, 1H), 1.48-1.39 (m, 1H), 1.16 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 190.5, 143.3, 141.4, 135.2, 133.9, 132.5, 129.6, 129.0, 128.6, 127.4, 126.9, 53.0, 47.3, 40.4, 40.0, 36.2, 31.2, 28.6, 21.5, 20.9; HRMS (ESI) Calcd for C₂₄H₃₃N₂O₂S [M + H]⁺ 413.2263, found 413.2264.

1-(5-Methoxy-2-((1-tosylpyrrolidin-3-yl)methyl)phenyl)-2,2-dimethylpropan-1-imine (3ai): Light yellow solid (54.5 mg, 64%; eluent: hexane/EtOAc/Et₃N = 80/40/1). *R_f* 0.11 (hexane/EtOAc/Et₃N = 30/10/1); m.p. 79.6-82.4 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.10 (brs, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.79 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.55 (d, *J* = 2.0 Hz, 1H), 3.78 (s, 3H), 3.38-3.33 (m, 2H), 3.17 (q, *J* = 8.5 Hz, 1H), 2.86 (t, *J* = 8.4 Hz, 1H), 2.43 (s, 3H), 2.41-2.27 (m, 3H), 1.88-1.81 (m, 1H), 1.48-1.39 (m, 1H), 1.16 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 190.0, 157.1, 143.3, 142.3, 133.8, 130.1, 129.6, 127.6, 127.4, 113.1, 112.2, 55.2, 52.9, 47.2, 40.3, 40.1, 35.8, 31.1, 28.6, 21.4; HRMS (ESI) Calcd for C₂₄H₃₃N₂O₃S [M + H]⁺ 429.2212, found 429.2208.

1-(5-Chloro-2-((1-tosylpyrrolidin-3-yl)methyl)phenyl)-2,2-dimethylpropan-1-imine (3aj): Light yellow solid (66.6 mg, 77%; eluent: hexane/EtOAc/Et₃N = 90/30/1). *R_f* 0.17 (hexane/EtOAc/Et₃N = 30/10/1); m.p. 94.8-97.8 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.11 (brs, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.22 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 7.02 (s, 1H), 3.39-3.32 (m, 2H), 3.16 (q, *J* = 8.5 Hz, 1H), 2.88 (t, *J* = 7.6 Hz, 1H), 2.49-2.28 (m, 3H), 2.44 (s, 3H), 1.88-1.81 (m, 1H), 1.49-1.38 (m, 1H), 1.16 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 188.7, 143.4, 142.7, 134.3, 133.8, 131.5, 130.5, 129.6, 128.0, 127.4, 126.4,

52.8, 47.2, 40.5, 39.8, 36.1, 31.1, 28.4, 21.5; HRMS (ESI) Calcd for $C_{23}H_{30}N_2O_2SCl$ $[M + H]^+$ 433.1717, found 433.1712.

2,2-Dimethyl-1-(2-((1-tosylpyrrolidin-3-yl)methyl)-5-

(trifluoromethyl)phenyl)propan-1-imine (3ak): Light yellow solid (46.4 mg, 50%; eluent: hexane/EtOAc/Et₃N = 80/20/1). *R_f* 0.16 (hexane/EtOAc/Et₃N = 30/10/1); m.p. 137.4-140.4 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.15 (brs, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.28-7.26 (m, 2H), 3.41-3.33 (m, 2H), 3.17 (q, *J* = 8.4 Hz, 1H), 2.98-2.85 (m, 1H), 2.60-2.28 (m, 3H), 2.44 (s, 3H), 1.90-1.81 (m, 1H), 1.57-1.43 (m, 1H), 1.17 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 188.6, 143.4, 141.8, 140.1, 133.8, 129.7, 128.2 (q, ²*J*_{C-F} = 32.5 Hz), 127.5, 127.1, 124.7 (q, ³*J*_{C-F} = 3.6 Hz), 123.8 (q, ¹*J*_{C-F} = 271.9 Hz), 123.5, 52.8, 47.2, 40.6, 39.6, 36.5, 31.1, 28.4, 21.5; ¹⁹F NMR (282 MHz, CDCl₃): δ -62.5; HRMS (ESI) Calcd for $C_{24}H_{30}N_2O_2F_3S$ $[M + H]^+$ 467.1980, found 467.1978.

1-(3-Fluoro-2-((1-tosylpyrrolidin-3-yl)methyl)phenyl)-2,2-dimethylpropan-1-imine (3al) and 1-(5-fluoro-2-((1-tosylpyrrolidin-3-yl)methyl)phenyl)-2,2-dimethylpropan-1-imine (3al'): Obtained as an inseparable mixture as a yellow oil (60.8 mg, 73%; eluent: hexane/EtOAc/Et₃N = 90/30/1). The ratio of **3al** and **3al'** was

determined to be 2.3:1 by ^1H NMR integrations of characteristic signals at 6.83 (d, H^* in **3al**) and 6.76 (dd, H^* in **3al'**) ppm. ^{13}C NMR was assigned according to DEPT135 and HMQC spectra.

R_f 0.15 (hexane/EtOAc/ Et_3N = 30/10/1).

3al: ^1H NMR (300 MHz, CDCl_3): δ 9.11 (brs, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.17 (td, J = 7.9, 5.5 Hz, 1H), 7.01-6.95 (m, 1H), 6.83 (d, J = 7.4 Hz, 1H), 3.40-3.32 (m, 2H), 3.17 (q, J = 8.5 Hz, 1H), 2.94-2.85 (m, 1H), 2.50-2.29 (m, 3H), 2.43 (s, 3H), 1.89-1.74 (m, 1H), 1.54-1.38 (m, 1H), 1.14 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 189.0, 161.4 (d, $^1J_{\text{C-F}}$ = 244.6 Hz), 143.3, 134.0, 131.5, 129.6, 127.5 (d, $^3J_{\text{C-F}}$ = 8.3 Hz), 127.4, 123.6 (d, $^2J_{\text{C-F}}$ = 15.3 Hz), 122.3, 114.8 (d, $^2J_{\text{C-F}}$ = 23.1 Hz), 53.2, 47.3, 40.5 (quaternary carbon of *t*-Bu), 39.5 (d, $^4J_{\text{C-F}}$ = 1.8 Hz, tertiary carbon on pyrrolidine ring), 31.0, 30.6, 28.5, 21.5; ^{19}F NMR (282 MHz, CDCl_3) δ -113.4.

3al': ^1H NMR (300 MHz, CDCl_3): δ 9.11 (brs, 1H), 7.71-7.68 (m, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.10 (dd, J = 8.6, 5.5 Hz, 1H), 6.95-6.92 (m, 1H), 6.76 (dd, J = 8.9, 2.5 Hz, 1H), 3.40-3.32 (m, 2H), 3.17 (q, J = 8.5 Hz, 1H), 2.94-2.85 (m, 1H), 2.50-2.29 (m, 3H), 2.43 (s, 3H), 1.89-1.74 (m, 1H), 1.54-1.38 (m, 1H), 1.16 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 188.9, 160.3 (d, $^1J_{\text{C-F}}$ = 245.1 Hz), 143.4, 133.9, 131.5, 130.7 (d, $^3J_{\text{C-F}}$ = 8.0 Hz), 129.6, 127.4, 123.6 (d, $^3J_{\text{C-F}}$ = 15.3 Hz), 114.8 (d, $^2J_{\text{C-F}}$ = 19.4 Hz), 113.5 (d, $^2J_{\text{C-F}}$ = 21.2 Hz), 52.9, 47.2, 40.5 (quaternary carbon of *t*-Bu), 40.0 (tertiary carbon on pyrrolidine ring), 35.9, 31.1, 28.5, 21.5; ^{19}F NMR (282 MHz, CDCl_3): δ -113.3.

HRMS (ESI) Calcd for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_2\text{SF}$ $[\text{M} + \text{H}]^+$ 417.2012, found 417.2013.

2,2-Dimethyl-1-(4-((1-tosylpyrrolidin-3-yl)methyl)benzo[d][1,3]dioxol-5-yl)propan-1-imine (3am) and 2,2-dimethyl-1-(6-((1-tosylpyrrolidin-3-yl)methyl)benzo[d][1,3]dioxol-5-yl)propan-1-imine (3am'): Obtained as an inseparable mixture as a yellow oil (48.4 mg, 55%; eluent: hexane/EtOAc/Et₃N = 80/40/1). The ratio of **3am** and **3am'** was determined to be 1.1:1 by ¹H NMR integrations of characteristic signals at 6.66 (d, **3am**) and 6.57 (s, **3am'**) ppm.

R_f 0.24 (hexane/EtOAc/Et₃N = 20/20/1).

3am: ¹H NMR (400 MHz, CDCl₃): δ 9.22 (brs, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.33-7.30 (m, 2H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 8.8 Hz, 1H), 5.95 (s, 2H), 3.40-3.31 (m, 2H), 3.21-3.14 (m, 1H), 2.91 (t, *J* = 7.9 Hz, 1H), 2.47-2.25 (m, 3H), 2.43 (s, 3H), 1.89-1.78 (m, 1H), 1.52-1.40 (m, 1H), 1.14 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 189.8, 146.3, 145.3, 143.3, 135.6, 134.0, 129.6, 127.4, 119.7, 118.5, 106.1, 100.7, 53.1, 47.3, 40.5, 38.8, 31.4, 31.1, 28.6, 21.5.

3am': ¹H NMR (400 MHz, CDCl₃): δ 9.22 (brs, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.33-7.30 (m, 2H), 6.57 (s, 1H), 6.51 (s, 1H), 5.93 (dd, *J* = 7.0, 1.3 Hz, 2H), 3.40-3.31 (m, 2H), 3.21-3.14 (m, 1H), 2.84 (t, *J* = 8.8 Hz, 1H), 2.47-2.25 (m, 3H), 2.44 (s, 3H), 1.89-1.78 (m, 1H), 1.52-1.40 (m, 1H), 1.15 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 189.6, 147.2, 146.1, 143.2, 134.5, 133.9, 129.6, 129.4, 127.4, 108.9, 106.7, 101.2, 52.9, 47.3, 40.2, 36.3, 31.4, 31.1, 28.7, 21.5.

HRMS (ESI) Calcd for C₂₄H₃₁N₂O₄S [M + H]⁺ 443.2005, found 443.2001.

1-(3,5-Difluoro-2-((1-tosylpyrrolidin-3-yl)methyl)phenyl)-2,2-dimethylpropan-1-one (3an): Instead of applying the typical workup procedure, the reaction mixture was quenched by the addition of HCl (3 M, 1.0 mL) and stirred for 1 h. The resulting mixture was neutralized with NaOH (3 M, 1.0 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over MgSO₄ and concentrated in vacuo. Silica gel chromatography (eluent: hexane/EtOAc = 5/1) of the crude product afforded the title compound as a white solid (46.7 mg, 54%).

R_f 0.17 (hexane/EtOAc = 5/1); m.p. 102.5-104.7 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.69 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 6.77-6.72 (m, 1H), 6.61-6.59 (m, 1H), 3.37-3.31 (m, 2H), 3.18-3.11 (m, 1H), 2.90 (t, J = 8.6 Hz, 1H), 2.45-2.26 (m, 3H), 2.42 (s, 3H), 1.81-1.74 (m, 1H), 1.51-1.41 (m, 1H), 1.14 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 211.7, 161.4 (dd, ¹ J_{C-F} = 248.5 Hz, ³ J_{C-F} = 11.5 Hz), 160.5 (dd, ¹ J_{C-F} = 248.6 Hz, ³ J_{C-F} = 12.4 Hz), 143.4 (dd, ³ J_{C-F} = 7.2, 4.5 Hz), 143.3, 133.9, 129.6, 127.5, 119.8 (dd, ² J_{C-F} = 17.3 Hz, ⁴ J_{C-F} = 4.2 Hz), 108.1 (dd, ² J_{C-F} = 22.4 Hz, ⁴ J_{C-F} = 3.7 Hz), 104.2 (dd, ² J_{C-F} = 26.9, 24.8 Hz), 53.0, 47.2, 44.9, 39.4, 30.6, 29.7, 27.2, 21.5; ¹⁹F NMR (282 MHz, CDCl₃): δ -109.3 (d, ⁴ J_{F-F} = 8.5 Hz), -111.2 (d, ⁴ J_{F-F} = 8.7 Hz); HRMS (ESI) Calcd for C₂₃H₂₈NO₃SF₂ [M + H]⁺ 436.1758, found 436.1754.

1-(2-Fluoro-6-((1-tosylpyrrolidin-3-yl)methyl)phenyl)-2,2-dimethylpropan-1-imine (3ao): Obtained as a mixture of imine *E/Z* isomers as a light yellow oil (33.3

mg, 40%; eluent: hexane/EtOAc/Et₃N = 90/30/1). The ratio of the isomers was determined to be 5.6:1 by ¹H NMR integrations. ¹³C NMR signals were assigned according to DEPT135 and HMQC spectra. For the minor isomer, ¹³C NMR signals were not assigned due to their weakness and significant overlap with that of the major isomer.

R_f 0.13 (hexane/EtOAc/Et₃N = 30/10/1).

Major isomer: ¹H NMR (300 MHz, CDCl₃): δ 9.33 (brs, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.25-7.17 (m, 1H), 6.96-6.90 (m, 2H), 3.41-3.33 (m, 2H), 3.22-3.13 (m, 1H), 2.98-2.78 (m, 1H), 2.57-2.29 (m, 3H), 2.44 (s, 3H), 1.94-1.78 (m, 1H), 1.50-1.37 (m, 1H), 1.16 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 186.3, 158.0 (d, ¹*J*_{C-F} = 246.6 Hz), 143.3, 138.3, 133.7, 129.6, 129.0 (2C overlapped), 127.4, 124.5 (d, ⁴*J*_{C-F} = 8.4 Hz), 113.3 (d, ²*J*_{C-F} = 22.5 Hz), 53.0-52.7 (m), 47.2-47.1 (m), 40.4 (quaternary carbon of *t*-Bu), 39.8-39.6 (m), 36.3, 31.0, 28.6, 21.4; ¹⁹F NMR (376 MHz, CDCl₃): δ -105.1.

Minor isomer: ¹H NMR (300 MHz, CDCl₃): δ 9.33 (brs, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.25-7.17 (m, 1H), 7.15-7.11 (m, 1H), 7.04-7.01 (m, 1H), 3.41-3.33 (m, 2H), 3.22-3.13 (m, 1H), 2.98-2.78 (m, 1H), 2.57-2.29 (m, 3H), 2.44 (s, 3H), 1.94-1.78 (m, 1H), 1.50-1.37 (m, 1H), 1.16 (s, 9H); ¹⁹F NMR (376 MHz, CDCl₃): δ -100.0.

HRMS (ESI) Calcd for C₂₃H₃₀N₂O₂FS [M + H]⁺ 417.2012, found 417.2017.

2,2-Dimethyl-1-(3-((1-tosylpyrrolidin-3-yl)methyl)naphthalen-2-yl)propan-1-

imine (3ap): Light yellow solid (61.2 mg, 68%; eluent: hexane/EtOAc/Et₃N = 90/30/1). *R_f* 0.12 (hexane/EtOAc/Et₃N = 30/10/1); m.p. 138.3-141.3 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.20 (brs, 1H), 7.79-7.75 (m, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.58 (s, 1H), 7.51-7.44 (m, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.43-3.38 (m, 2H), 3.20 (q, *J* = 8.5 Hz, 1H), 2.95 (t, *J* = 8.8 Hz, 1H), 2.69-2.57 (m, 2H), 2.48-2.44 (m, 1H), 2.44 (s, 3H), 1.94-1.86 (m, 1H), 1.56-1.47 (m, 1H), 1.21 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 190.3, 143.3, 139.8, 133.9 (2C overlapped), 132.6, 131.1, 129.6, 127.6 (two signals overlapped), 127.5, 127.2, 126.4, 126.1, 125.1, 53.0, 47.3, 40.7, 39.6, 37.0, 31.2, 28.6, 21.5; HRMS (ESI) Calcd for C₂₇H₃₃N₂O₂S [M + H]⁺ 449.2263, found 449.2269.

2,2-Dimethyl-1-(3-((1-tosylpyrrolidin-3-yl)methyl)thiophen-2-yl)propan-1-one

(3aq): Yellow solid (39.4 mg, 49%; eluent: hexane/EtOAc = 20/3; prepared as described for **3an**). *R_f* 0.15 (hexane/EtOAc = 5/1); m.p. 99.7-102.5 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 5.0 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 5.0 Hz, 1H), 3.41-3.35 (m, 1H), 3.32 (dd, *J* = 9.6, 7.2 Hz, 1H), 3.22-3.15 (m, 1H), 2.92-2.85 (m, 2H), 2.82-2.77 (m, 1H), 2.48-2.39 (m, 1H), 2.43 (s, 3H), 1.92-1.84 (m, 1H), 1.56-1.46 (m, 1H), 1.34 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 200.9, 148.2, 143.2, 134.0, 131.9, 130.2, 129.6, 128.0, 127.5, 52.9, 47.4, 44.7, 39.4, 33.4, 31.2, 27.8, 21.5; HRMS (ESI) Calcd for C₂₁H₂₈NO₃S₂ [M + H]⁺ 406.1511, found 406.1512.

1-(2-((1-Tosylpyrrolidin-3-yl)methyl)phenyl)pentan-1-one (3ar): Light yellow oil (44.9 mg, 56%; eluent: hexane/EtOAc = 20/3; prepared as described for **3an**). R_f 0.17 (hexane/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3): δ 7.69 (d, J = 8.2 Hz, 2H), 7.64 (dd, J = 7.7, 1.0 Hz, 1H), 7.38 (td, J = 7.5, 1.3 Hz, 1H), 7.32-7.27 (m, 3H), 7.12 (d, J = 7.5 Hz, 1H), 3.42-3.37 (m, 1H), 3.29 (dd, J = 9.7, 7.2 Hz, 1H), 3.19-3.13 (m, 1H), 2.93 (dd, J = 9.7, 7.8 Hz, 1H), 2.85 (t, J = 7.4 Hz, 2H), 2.84-2.80 (m, 1H), 2.72 (dd, J = 13.1, 7.6 Hz, 1H), 2.45-2.35 (m, 1H), 2.43 (s, 3H), 1.89-1.82 (m, 1H), 1.64 (app. quintet, J = 7.5 Hz, 2H), 1.54-1.46 (m, 1H), 1.37 (app. sextet, J = 7.4 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 204.6, 143.2, 139.7, 137.8, 134.0, 131.4, 131.2, 129.6, 128.9, 127.5, 126.4, 52.8, 47.3, 41.4, 40.2, 36.9, 31.2, 26.5, 22.4, 21.5, 13.9; HRMS (ESI) Calcd for $\text{C}_{23}\text{H}_{30}\text{NO}_3\text{S}$ $[\text{M} + \text{H}]^+$ 400.1946, found 400.1949.

2-Methyl-1-(2-((1-Tosylpyrrolidin-3-yl)methyl)phenyl)propan-1-one (3as): Light yellow oil (18.3 mg, 24%; eluent: hexane/EtOAc = 20/3; prepared as described for **3an**). R_f 0.17 (hexane/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3): δ 7.69 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 7.7 Hz, 1H), 7.37 (td, J = 7.5, 1.3 Hz, 1H), 7.32-7.28 (m, 3H), 7.14 (d, J = 7.6 Hz, 1H), 3.43-3.28 (m, 3H), 3.19-3.13 (m, 1H), 2.94 (dd, J = 9.7, 7.8 Hz, 1H), 2.77-2.64 (m, 2H), 2.43 (s, 3H), 2.41-2.36 (m, 1H), 1.89-1.82 (m, 1H),

1.56-1.46 (m, 1H), 1.13 (d, $J = 5.5$ Hz, 3H), 1.11 (d, $J = 5.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 208.7, 143.2, 139.8, 137.8, 134.0, 131.3, 131.0, 129.6, 128.2, 127.5, 126.3, 52.8, 47.4, 40.2, 38.5, 36.9, 31.2, 21.5, 18.7 (two signals overlapped); HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{28}\text{NO}_3\text{S}$ $[\text{M} + \text{H}]^+$ 386.1790, found 386.1786.

Phenyl(2-((1-tosylpyrrolidin-3-yl)methyl)phenyl)methanimine (3at): Yellow oil (33.5 mg, 40%; eluent: hexane/EtOAc/ Et_3N = 80/40/1). R_f 0.47 (hexane/EtOAc/ Et_3N = 20/20/1); ^1H NMR (300 MHz, CDCl_3): δ 9.41 (brs, 1H), 7.64-7.57 (m, 3H), 7.48-7.43 (m, 1H), 7.39-7.26 (m, 7H), 7.20 (d, $J = 7.3$ Hz, 1H), 7.15 (d, $J = 7.5$ Hz, 1H), 3.29-3.20 (m, 2H), 3.15-3.06 (m, 1H), 2.71 (t, $J = 8.6$ Hz, 1H), 2.43 (s, 3H), 2.43-2.41 (m, 2H), 2.27-2.16 (m, 1H), 1.78-1.68 (m, 1H) 1.36-1.26 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 178.4, 143.3, 140.4, 138.3, 136.6, 133.9, 131.0, 129.8, 129.6, 129.1, 128.5, 128.2, 127.9, 127.4, 126.6, 52.8, 47.2, 39.8, 36.2, 31.1, 21.5; HRMS (ESI) Calcd for $\text{C}_{25}\text{H}_{27}\text{N}_2\text{O}_2\text{S}$ $[\text{M} + \text{H}]^+$ 419.1793, found 419.1790.

2,2-Dimethyl-1-(2-(1-(1-tosylpyrrolidin-3-yl)ethyl)phenyl)propan-1-imine (3ba): Light yellow oil (38.2 mg, 46%; eluent: hexane/EtOAc/ Et_3N = 90/30/1; d.r. = 1.4:1 as determined by ^1H NMR). The relative configuration could not be determined based on 2D COSY and NOESY analysis. ^{13}C NMR signals were assigned according to DEPT135 and HMQC spectra.

R_f 0.16 (hexane/EtOAc/Et₃N = 30/10/1).

Major isomer: ¹H NMR (400 MHz, CDCl₃): δ 9.21 (brs, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.28-7.25 (m, 1H), 7.19-7.12 (m, 2H), 6.98 (d, J = 7.6 Hz, 1H), 3.60 (dd, J = 9.3, 7.6 Hz, 1H, H¹), 3.38-3.20 (m, 1H, H²), 3.16-3.06 (m, 1H, H^{2'}), 2.85 (t, J = 9.4 Hz, 1H, H^{1'}), 2.45 (s, 3H, Me of Ts), 2.40-2.34 (m, 1H, H⁵), 2.30-2.24 (m, 1H, H⁴), 1.52-1.49 (m, 1H, H³), 1.43-1.38 (m, 1H, H^{3'}), 1.19-1.16 (m, 12H, Me + *t*-Bu); ¹³C NMR (100 MHz, CDCl₃): δ 190.4, 143.3, 141.6, 140.7, 134.0, 129.7, 128.3, 127.4, 126.5, 126.2, 125.5, 52.3 (C¹), 47.7 (C²), 46.5 (C⁴), 40.4 (quaternary carbon of *t*-Bu), 39.5 (C⁵), 30.4 (C³), 28.8 (Me of *t*-Bu), 21.5 (Me and Me of Ts).

Minor isomer: ¹H NMR (400 MHz, CDCl₃): δ 9.21 (brs, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.32-7.29 (m, 2H), 7.28-7.25 (m, 1H), 7.19-7.12 (m, 2H), 7.01 (d, J = 7.7 Hz, 1H), 3.38-3.20 (m, 2H), 3.16-3.06 (m, 1H), 2.64 (t, J = 9.5 Hz, 1H), 2.43 (s, 3H, Me of Ts), 2.40-2.34 (m, 2H), 2.30-2.24 (m, 1H), 2.09-2.03 (m, 1H), 1.19-1.16 (m, 12H, Me + *t*-Bu); ¹³C NMR (100 MHz, CDCl₃): δ 190.1, 143.3, 141.5, 140.8, 133.7, 129.6, 128.3, 127.5, 126.6, 126.2, 125.6, 52.0, 47.9, 45.8, 40.3 (quaternary carbon of *t*-Bu), 39.5, 30.3, 29.0 (Me of *t*-Bu), 21.5 (Me and Me of Ts).

HRMS (ESI) Calcd for C₂₄H₃₃N₂O₂S [M + H]⁺ 413.2263, found 413.2261.

2,2-Dimethyl-1-(2-((3-methyl-1-tosylpyrrolidin-3-yl)methyl)phenyl)propan-1-

imine (3ca): Light yellow oil (38.3 mg, 46%; eluent: hexane/EtOAc/Et₃N = 100/25/1). R_f 0.21 (hexane/EtOAc/Et₃N = 30/10/1); ¹H NMR (400 MHz, CDCl₃): δ 9.13 (brs, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.26-7.23 (m, 1H),

7.19 (td, $J = 7.4, 1.3$ Hz, 1H), 7.14 (d, $J = 7.6$ Hz, 1H), 6.99 (d, $J = 7.4$ Hz, 1H), 3.41(td, $J = 9.2, 3.1$ Hz, 1H), 3.27-3.20 (m, 2H), 3.08 (d, $J = 9.4$ Hz, 1H), 2.57-2.50 (m, 2H), 2.42 (s, 3H), 1.79-1.72 (m, 1H), 1.59-1.54 (m, 1H), 1.13 (s, 9H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 191.1, 143.3, 142.1, 134.1 (two signals overlapped), 129.6 (two signals overlapped), 127.6, 127.4, 126.8, 126.0, 59.4, 46.3, 43.3, 42.5, 40.6, 38.1, 28.6, 23.2, 21.5; HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{33}\text{N}_2\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 413.2263, found 413.2262.

2,2-Dimethyl-1-(2-((2-methyl-1-tosylpyrrolidin-3-yl)methyl)phenyl)propan-1-

imine (3da): Light yellow oil (50.7 mg, 61%; eluent: hexane/EtOAc/ Et_3N = 90/30/1; d.r. = 2.0:1 as determined by ^1H NMR). *Cis*-relative configuration was assigned for the major isomer based on 2D COSY and NOESY analysis, which showed NOE correlations between H^1 and H^4 as well as between $\text{H}^5/\text{H}^{5'}$ and Me at the α -position of NTs. ^{13}C NMR was assigned according to DEPT135 and HMQC spectra.

R_f 0.15 (hexane/EtOAc/ Et_3N = 30/10/1).

Major isomer: ^1H NMR (400 MHz, CDCl_3): δ 9.20 (brs, 1H), 7.71 (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.1$ Hz, 2H), 7.24-7.20 (m, 1H), 7.15 (t, $J = 7.4$ Hz, 1H), 7.07 (d, $J = 7.6$ Hz, 1H), 7.04-7.00 (m, 1H), 3.90-3.83 (m, 1H, H^1), 3.49-3.44 (m, 1H, H^2), 2.99-2.93 (m, 1H, $\text{H}^{2'}$), 2.57 (dd, $J = 14.3, 4.9$ Hz, 1H, H^5), 2.43 (s, 3H, Me of Ts), 2.34 (dd, $J = 14.2, 9.9$ Hz, 1H, $\text{H}^{5'}$), 1.95-1.88 (m, 1H, H^4), 1.78-1.60 (m, 2H, $\text{H}^3 + \text{H}^{3'}$), 1.19 (d, $J = 6.6$ Hz, 3H, Me), 1.16 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, CDCl_3): δ 190.3, 143.2, 141.5, 135.6, 135.0, 129.6, 128.8, 127.8, 127.3, 126.5, 125.6,

58.0 (C¹), 47.1 (C²), 43.2 (C⁴), 40.4 (quaternary carbon of *t*-Bu), 32.8 (C⁵), 28.7 (Me of *t*-Bu), 28.6 (C³), 21.5 (Me of Ts), 17.5 (Me).

Minor isomer: ¹H NMR (400 MHz, CDCl₃): δ 9.20 (brs, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.34-7.32 (m, 2H), 7.24-7.20 (m, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.04-7.00 (m, 2H), 3.41-3.29 (m, 3H), 2.51-2.45 (m, 1H), 2.44 (s, 3H, Me of Ts), 2.08-1.95 (m, 2H), 1.78-1.60 (m, 2H), 1.34 (d, *J* = 6.3 Hz, 3H, Me), 1.11 (s, 9H, *t*-Bu); ¹³C NMR (100 MHz, CDCl₃): δ 190.1, 143.2, 141.3, 135.6, 135.3, 129.6, 129.3, 127.7, 127.4, 126.5, 125.6, 61.7, 48.4, 47.7, 40.4 (quaternary carbon of *t*-Bu), 36.6, 29.5, 28.5 (Me of *t*-Bu), 22.0 (Me), 21.5 (Me of Ts).

HRMS (ESI) Calcd for C₂₄H₃₃N₂O₂S [M + H]⁺ 413.2263, found 413.2267.

2,2-Dimethyl-1-(2-(1-tosyloctahydro-1*H*-indol-4-yl)phenyl)propan-1-imine

(3ea): Light yellow oil (26.9 mg, 31%; eluent: hexane/EtOAc/Et₃N = 100/20/1). The relative configuration was confirmed as above based on 2D COSY and NOESY analysis, which showed NOE correlations between H¹, H³ and H⁴. ¹³C NMR was assigned according to DEPT135 and HMQC spectra.

*R*_f 0.21 (hexane/EtOAc/Et₃N = 30/10/1); ¹H NMR (400 MHz, CDCl₃): δ 9.14 (brs, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.0 Hz, 1H), 7.17-7.11 (m, 2H), 6.97 (d, *J* = 7.3 Hz, 1H), 3.77-3.72 (m, 1H, H¹), 3.51 (t, *J* = 9.0 Hz, 1H, H²), 2.97-2.91 (m, 1H, H^{2'}), 2.73 (dt, *J* = 13.0, 4.0 Hz, 1H, H⁴), 2.42 (s, 3H), 2.11-2.00 (m, 2H), 1.83 (dt, *J* = 13.4, 3.1 Hz, 1H, H³), 1.76-1.66 (m, 2H), 1.53-1.47 (m, 1H), 1.45-1.38 (m, 2H), 1.34-1.27 (m, 1H), 1.15 (s, 9H); ¹³C NMR (100 MHz,

CDCl₃): δ 190.1, 143.1, 141.0, 139.8, 135.4, 129.7, 127.5, 127.4, 127.1, 126.4, 125.6, 60.4 (C¹), 46.8 (C²), 43.4 (C⁴), 41.1 (C⁵), 40.4 (quaternary carbon of *t*-Bu), 29.9 (C⁸), 29.7 (C⁷), 28.7 (Me of *t*-Bu), 26.3 (C⁶), 24.4 (C³), 21.5 (Me of Ts); HRMS (ESI) Calcd for C₂₆H₃₅N₂O₂S [M + H]⁺ 439.2419, found 439.2422.

2,2-Dimethyl-1-(2-((5-methyl-1-tosylpyrrolidin-3-yl)methyl)phenyl)propan-1-

imine (3fa): The title compound (d.r. = 5.6:1 as determined by ¹H NMR) was isolated together with an unknown impurity as a light yellow oil (59.1 mg in total; eluent: hexane/EtOAc/Et₃N = 100/25/1 to 90/30/1). The combined yields of the two diastereomers were determined to be 66% based on GC analysis. *Cis*-relative configuration was assigned for the major isomer based on 2D COSY and NOESY analysis, which showed the NOE correlation between H² and H⁴ as well as the lack of interaction between H² and H⁵/H^{5'} and between H⁴ and Me at the α -position of NTs. ¹³C NMR signals were assigned according to DEPT135 and HMQC spectra.

*R*_f 0.19 (hexane/EtOAc/Et₃N = 30/10/1).

¹H NMR (400 MHz, CDCl₃, major diastereomer): δ 9.00 (brs, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.01-6.98 (m, 2H), 3.58-3.46 (m, 2H, H¹ + H²), 2.98 (app. t, *J* = 10.7 Hz, 1H, H^{1'}), 2.46-2.38 (m, 3H, H³, H⁵, H^{5'}), 2.41 (s, 3H, Me of Ts), 2.05-1.99 (m, 1H, H^{3'}), 1.79-1.64 (m, 1H, H⁴), 1.37 (d, *J* = 6.1 Hz, 3H, Me), 1.14 (s, 9H, *t*-Bu); ¹³C NMR (100 MHz, CDCl₃, major diastereomer): δ 190.2, 143.2, 141.3, 135.5, 135.1, 129.6, 128.8,

127.8, 127.3, 126.3, 125.6, 56.8 (C²), 54.3 (C¹), 41.2 (C³), 40.4 (quaternary carbon of *t*-Bu), 39.2 (C⁴), 35.9 (C⁵), 28.6 (Me of *t*-Bu), 22.7 (Me), 21.4 (Me of Ts).

HRMS(ESI) Calcd for C₂₄H₃₃N₂O₂S [M + H]⁺ 413.2263, found 413.2266.

1-(2-((5-Benzyl-1-tosylpyrrolidin-3-yl)methyl)phenyl)-2,2-dimethylpropan-1-

imine (3ga): Light yellow oil (60.8 mg, 62%; eluent: hexane/EtOAc/Et₃N = 100/25/1 to 90/30/1; d.r. = 5.0:1 as determined by ¹H NMR). *Cis*-relative configuration was assigned for the major isomer based on 2D COSY and NOESY analysis, which showed the NOE correlation between H² and H⁴ and the lack of interactions between H² and H⁵/H^{5'} and between H⁴ and H⁶/H^{6'}. ¹³C NMR was assigned according to HMQC spectra.

R_f 0.21 (hexane/EtOAc/Et₃N = 30/10/1); ¹H NMR (400 MHz, CDCl₃, major diastereomer): δ 8.92 (brs, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.35-7.27 (m, 4H), 7.24-7.13 (m, 5H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 3.77-3.70 (m, 1H, H²), 3.53 (dd, *J* = 11.5, 6.7 Hz, 1H, H¹), 3.41 (dd, *J* = 13.1, 3.5 Hz, 1H, H⁶), 2.89-2.77 (m, 2H, H^{1'} + H^{6'}), 2.43 (s, 3H, Me of Ts), 2.41-2.27 (m, 2H, H⁵ + H^{5'}), 1.82-1.77 (m, 1H, H³), 1.56-1.51 (m, 1H, H⁴), 1.33-1.28 (m, 1H, H^{3'}), 1.12 (s, 9H, *t*-Bu); ¹³C NMR (100 MHz, CDCl₃, major diastereomer): δ 190.2, 143.4, 141.3, 138.0, 135.4, 135.0, 129.7, 129.5, 128.7, 128.4, 127.8, 127.4, 126.4, 126.3, 125.6, 62.1 (C²), 54.6 (C¹), 42.9 (C⁶), 40.4 (quaternary carbon of *t*-Bu), 39.3 (C⁴), 38.2 (C³), 35.6 (C⁵), 28.6 (Me of *t*-Bu), 21.5 (Me of Ts); HRMS (ESI) Calcd for C₃₀H₃₇N₂O₂S [M + H]⁺ 489.2576, found 489.2579.

2,2-Dimethyl-1-(2-((4-methyl-1-tosylpyrrolidin-3-yl)methyl)phenyl)propan-1-

imine (3ha): Light yellow oil (42.6 mg, 52%; eluent: hexane/EtOAc/Et₃N = 90/30/1; d.r. = 3.0:1 as determined by ¹H NMR). *Cis*-relative configuration was assigned for the major isomer based on 2D COSY and NOESY analysis, which showed the NOE correlation between H⁵ and Me. ¹³C NMR was assigned according to DEPT135 and HMQC spectra.

R_f 0.15 (hexane/EtOAc/Et₃N = 30/10/1).

Major isomer: ¹H NMR (400 MHz, CDCl₃): δ 9.23 (brs, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.24-7.22 (m, 1H), 7.18 (td, *J* = 7.4, 1.1 Hz, 1H), 7.14-7.08 (m, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 3.40-3.35 (m, 1H, H²), 3.24-3.20 (m, 1H, H¹), 3.09-3.02 (m, 2H, H^{1'} + H^{2'}), 2.59-2.53 (m, 1H, H⁵), 2.43 (s, 3H, Me of Ts), 2.34-2.24 (m, 2H, H⁴ + H^{5'}), 2.23-2.17 (m, 1H, H³), 1.18 (s, 9H, *t*-Bu), 0.80 (d, *J* = 7.0 Hz, 3H, Me); ¹³C NMR (100 MHz, CDCl₃): δ 190.4, 143.3, 141.5, 135.6, 134.2, 129.6, 129.2, 127.9, 127.4, 126.5, 125.7, 54.5 (C²), 50.6 (C¹), 42.9 (C⁴), 40.4 (quaternary carbon of *t*-Bu), 35.6 (C³), 31.5 (C⁵), 28.7 (Me of *t*-Bu), 21.5 (Me of Ts), 13.3 (Me).

Minor isomer: ¹H NMR (400 MHz, CDCl₃): δ 9.23 (brs, 1H), 7.68-7.66 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.24-7.22 (m, 1H), 7.18 (td, *J* = 7.4, 1.1 Hz, 1H), 7.14-7.08 (m, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 3.51 (dd, *J* = 9.7, 7.4 Hz, 1H), 3.40-3.35 (m, 1H), 2.95-2.90 (m, 1H), 2.79 (t, *J* = 9.2 Hz, 1H), 2.68 (dd, *J* = 14.4, 4.6 Hz, 1H), 2.43 (s, 3H, Me of Ts), 2.39-2.34 (m, 1H), 1.90-1.83 (m, 1H), 1.80-1.72 (m, 1H), 1.17 (s, 9H, *t*-Bu), 0.89 (d, *J* = 6.3 Hz, 3H, Me); ¹³C NMR (100 MHz, CDCl₃): δ 190.2, 143.3,

141.3, 135.5, 133.9, 129.6, 129.0, 127.9, 127.4, 126.4, 125.7, 54.6, 53.2, 46.9, 40.4 (quaternary carbon of *t*-Bu), 39.0, 35.9, 28.6 (Me of *t*-Bu), 21.5 (Me of Ts), 16.3 (Me).

HRMS (ESI) Calcd for $C_{24}H_{33}N_2O_2S$ $[M + H]^+$ 413.2263, found 413.2262.

2,2-Dimethyl-1-(2-((1-phenylpyrrolidin-3-yl)methyl)phenyl)propan-1-imine

(3ia): Light yellow oil (39.5 mg, 62%; eluent: hexane/EtOAc = 100/3/1). R_f 0.45 (hexane/EtOAc/Et₃N = 30/10/1); 1H NMR (400 MHz, CDCl₃): δ 9.20 (brs, 1H), 7.30 (d, J = 3.8 Hz, 2H), 7.23-7.18 (m, 3H), 7.07 (d, J = 7.6 Hz, 1H), 6.65 (t, J = 7.3 Hz, 1H), 6.52 (d, J = 8.4 Hz, 2H), 3.42-3.36 (m, 2H), 3.28 (q, J = 8.2 Hz, 1H), 2.99 (t, J = 8.0 Hz, 1H), 2.72-2.58 (m, 3H), 2.14-2.07 (m, 1H), 1.77-1.67 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, CDCl₃): δ 190.5, 147.7, 141.6, 136.4, 129.2, 129.0, 127.8, 126.3, 125.4, 115.4, 111.4, 53.1, 47.2, 40.4, 39.9, 37.3, 31.5, 28.7; HRMS (ESI) Calcd for $C_{22}H_{29}N_2$ $[M + H]^+$ 321.2331, found 321.2331.

1-(2-((5-Ethoxy-2,2-dimethyltetrahydrofuran-3-yl)methyl)phenyl)-2,2-

dimethylpropan-1-imine (3ja): Light yellow oil (50.8 mg, 80%; eluent: hexane/EtOAc/Et₃N = 100/10/1; d.r. = 1.7:1 as determined by 1H NMR). The relative configuration could not be assigned based on 2D COSY and NOESY analysis. ^{13}C NMR signals were assigned according to DEPT135 and HMQC spectra.

R_f 0.19 (hexane/EtOAc/Et₃N = 100/10/1).

Major isomer: ¹H NMR (400 MHz, CDCl₃): δ 9.31 (brs, 1H), 7.24-7.21 (m, 2H), 7.19-7.13 (m, 1H), 7.03 (t, J = 7.1 Hz, 1H), 4.98 (d, J = 4.8 Hz, 1H, H¹), 3.79-3.66 (m, 1H, H⁵), 3.45-3.32 (m, 1H, H^{5'}), 2.65-2.58 (m, 1H, H⁴), 2.43-2.35 (m, 1H, H^{4'}), 2.31-2.22 (m, 1H, H³), 1.92-1.88 (m, 1H, H²), 1.78-1.72 (m, 1H, H^{2'}), 1.36 (s, 3H, Me), 1.22 (s, 9H, *t*-Bu), 1.14 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.08 (s, 3H, Me); ¹³C NMR (100 MHz, CDCl₃): δ 190.5, 141.6, 136.4, 129.5, 127.8, 126.2, 125.4, 101.6 (C²), 83.5 (C¹), 62.1 (C⁶), 47.2 (C⁴), 40.3 (quaternary carbon of *t*-Bu), 38.6 (C³), 34.0 (C⁵), 29.4 (Me), 28.8 (Me of *t*-Bu), 23.7 (Me), 15.2 (OCH₂CH₃).

Minor isomer: ¹H NMR (400 MHz, CDCl₃) δ 9.31 (brs, 1H), 7.24-7.21 (m, 2H), 7.19-7.13 (m, 1H), 7.03 (t, J = 7.1 Hz, 1H), 5.02 (t, J = 5.3 Hz, 1H, H¹), 3.79-3.66 (m, 1H, H⁵), 3.45-3.32 (m, 1H, H^{5'}), 2.65-2.58 (m, 1H, H⁴), 2.43-2.35 (m, 1H, H^{4'}), 2.31-2.22 (m, 1H, H³), 2.11-2.04 (m, 1H, H²), 1.78-1.72 (m, 1H, H^{2'}), 1.26 (s, 3H, Me), 1.22 (s, 12H, Me + *t*-Bu), 1.18 (t, J = 7.2 Hz, 3H, OCH₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 190.3, 141.6, 136.4, 129.4, 127.7, 126.3, 125.4, 102.8 (C²), 82.7 (C¹), 63.3 (C⁶), 49.4 (C⁴), 40.3 (quaternary carbon of *t*-Bu), 38.8 (C³), 34.2 (C⁵), 28.8 (Me), 27.8 (Me of *t*-Bu), 23.0 (Me), 15.3 (OCH₂CH₃).

HRMS (ESI) Calcd for C₂₀H₃₂NO₂ [M + H]⁺ 318.2433, found 318.2433.

1-(2-((2,3-Dihydro-1H-inden-1-yl)methyl)phenyl)-2,2-dimethylpropan-1-imine

(3ka): Light yellow oil (24.0 mg, 41%; eluent: hexane/EtOAc/Et₃N = 100/10/1). R_f 0.35 (hexane/EtOAc/Et₃N = 100/10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.68 (brs,

1H), 7.37 (d, $J = 7.5$ Hz, 1H), 7.31 (td, $J = 7.5, 1.1$ Hz, 1H), 7.25-7.21 (m, 1H), 7.20-7.14 (m, 2H), 7.07-7.01 (m, 2H), 6.89-6.78 (m, 1H), 3.50-3.43 (m, 1H), 2.99-2.77 (m, 3H), 2.68-2.62 (m, 1H), 2.24-2.16 (m, 1H), 1.83-1.75 (m, 1H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 190.1, 146.4, 144.0, 141.8, 136.6, 129.5, 127.6, 126.7, 126.2, 125.8, 125.3, 124.7, 123.7, 46.1, 40.4, 38.6, 32.2, 31.0, 28.7; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{26}\text{N}$ $[\text{M} + \text{H}]^+$ 292.2065, found 292.2063.

Product Transformation

2-((1-Tosylpyrrolidin-3-yl)methyl)benzonitrile (8aa): 2,2-Dimethyl-1-(2-((1-tosylpyrrolidin-3-yl)methyl)phenyl)propan-1-imine (**3aa**, 177 mg, 0.44 mmol) was dissolved in DMF (2.2 mL) and then transferred into a 10 mL Schlenk tube containing a stir bar, followed by the addition of $\text{Cu}(\text{OAc})_2$ (8.1 mg, 0.044 mmol) and DMF (2.2 mL). After stirring under oxygen atmosphere at 80 °C for 12 h, the mixture was concentrated and silica gel chromatography (eluent: hexane/EtOAc = 2/1) of the residue afforded the title compound as a white solid (127.6 mg, 84%).

R_f 0.22 (hexane/EtOAc = 3/1); m.p. 120.4-123.1 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.69 (d, $J = 8.2$ Hz, 2H), 7.60 (d, $J = 7.7$ Hz, 1H), 7.51 (t, $J = 7.7$ Hz, 1H), 7.33-7.30 (m, 3H), 7.22 (d, $J = 7.8$ Hz, 1H), 3.44-3.38 (m, 1H), 3.34 (dd, $J = 9.7, 7.1$ Hz, 1H), 3.24-3.18 (m, 1H), 2.94 (dd, $J = 9.7, 7.7$ Hz, 1H), 2.85-2.74 (m, 2H), 2.50-2.39 (m, 1H), 2.44 (s, 3H), 1.94-1.86 (m, 1H), 1.59-1.49 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 143.5 (two signals overlapped), 133.6, 133.0, 132.9, 129.8, 129.7, 127.4, 127.1, 117.8, 112.3, 52.5, 47.2, 39.6, 37.3, 30.9, 21.5; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_2\text{S}$ $[\text{M} + \text{H}]^+$ 341.1324, found 341.1329.

4-Chloro-2-((1-tosylpyrrolidin-3-yl)methyl)benzonitrile (8af): Light yellow oil (75.8 mg, 81%; eluent: hexane/EtOAc = 3/1; prepared from **3af** on a 0.25 mmol scale as described for **8aa**). R_f 0.31 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 7.71 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.3 Hz, 1H), 7.35-7.30 (m, 3H), 7.20 (d, J = 1.9 Hz, 1H), 3.44-3.36 (m, 2H), 3.27-3.21 (m, 1H), 2.93 (dd, J = 9.8, 7.6 Hz, 1H), 2.81-2.71 (m, 2H), 2.49-2.38 (m, 1H), 2.45 (s, 3H), 1.96-1.88 (m, 1H), 1.59-1.49 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 145.4, 143.6, 139.5, 134.1, 133.6, 130.0, 129.7, 127.6, 127.4, 117.0, 110.8, 52.4, 47.1, 39.4, 37.2, 30.9, 21.5; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{SCl}$ $[\text{M} + \text{H}]^+$ 375.0934, found 375.0932.

2-Fluoro-6-((1-tosylpyrrolidin-3-yl)methyl)benzonitrile (8ao): White solid (64.3 mg, 64%; eluent: hexane/EtOAc = 2/1; prepared from **3ao** on a 0.28 mmol scale as described for **8aa**). R_f 0.33 (hexane/EtOAc = 3/1); m.p. 118.2-120.3 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.69 (d, J = 8.2 Hz, 2H), 7.50 (td, J = 8.0, 5.9 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.07 (t, J = 8.6 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 3.44-3.38 (m, 1H), 3.33 (dd, J = 9.8, 7.1 Hz, 1H), 3.24-3.17 (m, 1H), 2.93 (dd, J = 9.8, 7.6 Hz, 1H), 2.84-2.74 (m, 2H), 2.49-2.38 (m, 1H), 2.43 (s, 3H), 1.95-1.87 (m, 1H), 1.59-1.49 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.6 (d, $^1J_{\text{C-F}}$ = 257.6 Hz), 145.8, 143.6, 134.5 (d, $^3J_{\text{C-F}}$ = 8.9 Hz), 133.6, 129.7, 127.4, 125.4 (d, $^3J_{\text{C-F}}$ = 3.3 Hz), 114.3 (d, $^2J_{\text{C-F}}$ =

19.5 Hz), 113.0, 101.7 (d, $^2J_{C-F} = 14.8$ Hz), 52.4, 47.1, 39.4, 37.2, 30.9, 21.5; ^{19}F NMR (282 MHz, CDCl_3): δ -105.1; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{SF}$ $[\text{M} + \text{H}]^+$ 359.1230, found 359.1228.

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Chapter 4. Cobalt-Catalyzed Directed *ortho*-Methylation of Arenes with Methyl Tosylate

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ivAbstract

4.1 Introduction

The methyl group is prevalent in biologically active natural products and pharmaceutical compounds (Figure 4.1). The introduction of a methyl group to a drug can improve its biological and physical properties.¹ In an extreme example, simply replacing a C–H bond in a biaryl amide compound **A** with a C–Me bond results in a 208-fold boost in potency as a p38 α MAP3 kinase inhibitor (Scheme 4.1).² This effect is called the “magic methyl effect”.

Figure 4.1. Small-molecule drugs containing a carbon-bound methyl group.

Scheme 4.1. An example of magic methyl effect

Another attractive means to improve the efficacy of drugs is the introduction of deuterium atoms. Indeed, there is a growing interest in deuterated drug candidates.³ Replacing hydrogen atom(s) in a small-molecule drug with deuterium can lead to improved pharmacokinetic, metabolic and toxicological properties owing to the stronger C–D bond, while maintaining the original efficacy and selectivity of the drug. Indeed, a number of deuterated drug candidates, including those containing CD₃ groups instead of CH₃ groups (Figure 4.2), are now in clinical trials.

Figure 4.2. Examples of CD₃-bearing compounds in clinical trials.

In light of the magic methyl effect and the deuteration effect, the development of efficient methods for methylation, which also allow facile introduction of a CD₃ group, is highly desirable. Over the last few decades, methylation methods via transition metal-catalyzed cross-coupling between aryl (pseudo)halides and methyl nucleophiles have been extensively developed for the synthesis of methylated arenes. As exemplified in Scheme 4.2, a variety of methylmetals such as Me₃Al,⁴ Me₂Zn,⁵

MeMgBr ,⁶ and MeLi ⁷ have been utilized in such methylation reactions. In the last example, deuterated methyllithium was generated in-situ from CD_3I and $t\text{-BuLi}$.

Scheme 4.2. Methylation via transition metal-catalyzed cross-coupling

The major drawback of the above cross-coupling reactions is the use of air- and moisture-sensitive methylmetal reagents, which would require strict procedures for the reaction setup. To overcome such limitations, in 2016, Liao and coworkers reported Ni-catalyzed reductive coupling between aryl halides and methyl iodide.⁸ Notably, trideuteriomethylation can be realized using readily available and cost-effective CD_3I as the CD_3 source (Scheme 4.3).

Scheme 4.3. Methylation via Ni-catalyzed reductive cross-coupling

As an atom- and step-economical alternative to the transition metal-catalyzed cross-coupling, direct C–H methylation of an arene is attractive. A traditional method for direct C–H methylation involves *ortho*-lithiation of an arene followed by subsequent trapping of the resulting aryllithium with a methyl electrophile such as methyl iodide, as exemplified in Scheme 4.4.⁹ However, the *ortho*-lithiation approach requires a stoichiometric amount of the air- and moisture sensitive organolithium reagent and is also limited in viable *ortho*-directing groups.

Scheme 4.4. Methylation via *ortho*-lithiation

Given the limitation of the *ortho*-lithiation approach, transition metal-catalyzed direct C–H methylation reactions, especially those involving directing group-assisted C–H activation, have emerged as efficient and selective methods for the introduction of methyl groups to arenes. As discussed below, not only methyl electrophiles but also methyl nucleophiles can be used as the methyl sources in these reactions.

Despite its high toxicity, methyl iodide is the most frequently used methyl electrophile for C–H methylation (Scheme 4.5). In 1984, Tremont and coworkers described Pd-mediated stoichiometric C–H methylation of acetanilide with methyl iodide (Scheme 4.5a).¹⁰ Inspired by this seminal work, Youn and coworkers

developed Pd-catalyzed *ortho*-methylation of acetanilides at room temperature using AgOAc and Cu(OTf)₂ as the co-oxidants (Scheme 4.5b).¹¹ In 2011, Chen and coworkers reported an isolated example of Pd-catalyzed C(sp²)-H methylation of picolinamide (PA)-protected benzylamine with methyl iodide using O₂ as the sole oxidant (Scheme 4.5c).¹² In addition to palladium, nickel has been used by Chatani and coworkers to achieve 8-AQ-directed C-H methylation of aromatic amides with MeI in-situ generated from equal equivalents of MeOTs and NaI (Scheme 4.5d).¹³

Scheme 4.5. Transition metal-catalyzed C(sp²)-H methylation with MeI

Besides methyl iodide, phenyltrimethylammonium salts can also be used as the

methyl electrophile. In 2016, Chatani and coworkers reported the first use of PhMe_3NI or PhMe_3NBr for Ni-catalyzed, 8-AQ-directed C–H methylation of aromatic amides (Scheme 4.6).¹⁴ No arylation product was detected in these reactions.

Scheme 4.6. Ni-catalyzed $\text{C}(\text{sp}^2)$ –H methylation with PhMe_3NI

Apart from methyl electrophiles, methyl nucleophiles such as methyltin, methylboron and methyl Grignard reagents have also been extensively used in oxidative C–H methylation reactions. In 2006, Yu and coworkers reported Pd-catalyzed C–H methylation of 2-aryl/benzyl oxazolines and pyridines with Me_4Sn using $\text{Cu}(\text{OAc})_2$ /benzoquinone/air as the co-oxidants (Scheme 4.7).¹⁵ Due to the toxicity associated with the methyltin reagent, the development of other environmentally benign methyl nucleophiles is highly desirable.

Scheme 4.7. Pd-catalyzed C–H methylation with Me_4Sn

Because of its low toxicity and excellent air- and moisture-stability, methylboron reagents can be attractive methylating agents for C–H methylation. In 2006, Yu and

coworkers reported Pd-catalyzed, pyridine-directed C–H methylation of arenes using methylboroxine and methylboronic acid as the methyl sources (Scheme 4.8a).¹⁶ MeB(OH)₂ has also been used in a series of Pd-catalyzed C–H methylation reactions assisted by other directing groups such as benzoic acid (Scheme 4.8b),¹⁷ sulfonamide¹⁸ and 2-pyridylsufinyl.¹⁹ In 2013, Yu and coworkers disclosed Pd-catalyzed, monoprotected amino acid (MPAA)-mediated *ortho*-C–H methylation of a phenylacetic acid and a benzoic acid with MeBF₃K (Scheme 4.8c).²⁰ Later, Sanford and coworkers achieved Pd-catalyzed, pyridine or amide-directed methylation of arenes under a much milder condition with the assistance of a combination of MeBF₃K and MnF₃.²¹

Scheme 4.8. Pd-catalyzed C–H methylation with methylboron reagents

Methyl Grignard reagent is another methyl nucleophile widely used in the

transition metal-catalyzed C–H methylation. In 2011, Nakamura and coworkers reported Co-catalyzed methylation of *N*-methyl-1-naphthamide with MeMgCl in the presence of a Lewis basic DMPU ligand (Scheme 4.9a).²² The reaction proceeds efficiently at room temperature using air as the sole oxidant. Later, the research groups of Ackermann²³ and Nakamura²⁴ demonstrated the use of MeMgBr in Fe- and Mn-catalyzed C–H methylation reactions using *vic*-dihaloalkane as the oxidant (Scheme 4.9b and Scheme 4.9c). It is interesting that the Mn-catalyzed methylation of *N*-(1-naphthyl)-2-picolinamide selectively occurs at the pyridine ring, which is suggestive of the lack of bidentate chelation in this reaction.

Scheme 4.9. Transition-metal catalyzed C–H methylation with MeMgX

The weakly nucleophilic trimethylaluminum reagent has also been used in C–H methylation reactions in recent years. In 2015, Nakamura and coworkers reported Fe-catalyzed, PA- or 8-AQ-directed C–H methylation of anilides and carboxamides

using AlMe_3 or its air-stable adduct ($\text{DABCO} \cdot 2\text{AlMe}_3$) as the methyl sources (Scheme 4.10a).²⁵ In contrast to the Mn-catalyzed reaction (Scheme 4.9c), the Fe-catalyzed C–H methylation of *N*-(1-naphthyl)-2-picolinamide selectively occurs at the naphthalene ring via bidentate chelation. One year later, the same group achieved Fe-catalyzed C–H methylation of a series of aromatic carbonyl compounds with a combination of tridentate $\text{NMe}_2\text{-TP}$ ligand and Me_3Al reagent (Scheme 4.10b).²⁶ In 2016, Xu and coworkers disclosed Co-catalyzed, 8-AQ-directed monomethylation of carboxamides with AlMe_3 (Scheme 4.10c).²⁷ The selectivity for monomethylation can be explained by the destabilizing repulsion between the newly introduced methyl group and the dimethylaluminum moiety.

Scheme 4.10. Transition metal-catalyzed C–H methylation with AlMe_3

a) Nakamura (2015)

b) Nakamura (2016)

c) Xu (2016)

As demonstrated by Nakamura and coworkers, MeZnCl is also a viable reagent for Fe-catalyzed methylation of 3-methyl-*N*-(quinol-8-yl)benzamide (Scheme 4.11).²⁸ The methylation reagent was in-situ generated from MeMgBr and ZnCl_2 .

Scheme 4.11. Fe-catalyzed C–H methylation with MeZnCl

Apart from methyl electrophiles and nucleophiles, other methyl sources such as peroxides are also used in directing group-assisted C–H methylation reactions. In 2008, Li and coworkers reported the unprecedented use of dicumyl peroxide (DCP) in Pd-catalyzed C–H methylation of 2-phenylpyridine and acetanilide derivatives (Scheme 4.12a).²⁹ DCP not only serves as a methyl donor but also as a hydrogen acceptor in this reaction. Later, DCP was used by Chatani³⁰ and Lu³¹ in Ni- and Co-catalyzed C–H methylation of aromatic amides with the assistance of 8-aminoquinoline and 2-pyridinyl isopropyl (PIP) directing groups, respectively (Scheme 4.12b and Scheme 4.12c). On the basis of radical trapping experiments, a methyl radical species is likely to be involved in both the reactions.

Scheme 4.12. Transition-metal catalyzed C–H methylation with DCP

Shi and coworkers demonstrated directed C–H methylation using a mixed anhydride as the methylating agent (Scheme 4.13).³² Thus, Rh(I)-catalyzed reaction of 2-arylpyridine with an equimolar mixture of acetic acid and pivalic anhydride afforded

the corresponding *ortho*-methylation product in good yield. The reaction was proposed to involve oxidative addition of an in-situ-formed mixed anhydride to a rhodacycle, decarbonylation of the acetyl-Rh species, and reductive elimination.

Scheme 4.13. Rh-catalyzed methylation of (*m*-tolyl)pyridine with a mixed anhydride

Despite the significant progress made in the area of C–H methylation, the major limitations associated with the currently available methylation methods cannot be neglected. For example, methylmetals are generally sensitive to air and moisture, and their deuterated analogues are either unavailable or available only at a high cost. On the other hand, the reactions involving methyl electrophiles often require noble metals or harsh reaction conditions (high temperature, strong base/acid and oxidants). Therefore, the development of new C–H methylation methods with cost-effective earth-abundant metal catalysts and convenient methylating reagents is still an important task.

Given the above background and our previous studies on cobalt-catalyzed directed C–H alkylation using alkyl halides (*cf.* Chapter 1), we became interested in the development of a directed C–H methylation method using a cobalt catalyst. Here, we have found that methyl tosylate serves as a readily available and efficient methylating agent for cobalt-catalyzed $\text{C}(\text{sp}^2)\text{--H}$ methylation of arenes bearing nitrogen directing groups (Scheme 4.14).³³ The reaction is achieved using a cobalt–N-heterocyclic carbene (NHC) catalyst in combination with a neopentyl Grignard reagent at room temperature. Using CD_3OTs instead of MeOTs , the reaction also

allows facile incorporation of a CD₃ group into arenes.

Scheme 4.14. Cobalt-catalyzed directed *ortho*-methylation of arenes with MeOTs

4.2 Results and Discussion

In the early stage of our study, we explored the methylation of acetophenone-derived imine **1a** with methyl tosylate (1.5 equiv) using a catalytic system consisting of CoBr₂ (10 mol %), ligand (10 mol %), and *t*BuCH₂MgBr (2 equiv) (Table 4.1). The NHC preligands **L1**•HBF₄ and **L2**•HBr, which we previously employed for the *ortho*-alkylation,³⁴ promoted the methylation slightly to afford the monomethylation product **2a** together with small amounts of dimethylation product **2a'** and *ortho*-neopentylation product **2a''** (entries 1 and 2). In order to improve the catalytic performance, we modified the *N*-substituents of **L2**•HBr. To our delight, moderate yields of **2a** could be achieved using cyclohexyl and *sec*-butyl analogues of **L2**•HBr (entries 3 and 4). On the other hand, neither *N*-primary nor tertiary alkyl-substituted ligands afforded better yields (entries 5 and 6). A naphtho-analogue of **L2**•HBr showed comparable activity to **L3**•HCl and **L4**•HBr (entry 7). We also tested other types of ligands such as phosphines and *N,N'*-diaryl-substituted NHCs. However, they exhibited poorer performance for the present reaction (entries 8-18). With **L7**•

HBr as the preligand, we next screened different cobalt salts. Co(acac)₃ showed a similar performance as CoBr₂, whereas other cobalt salts gave lower yields (entries 19-23).

Table 4.1. Initial results of ligand and precatalyst screening for the methylation of acetophenone-derived imine **1a**

entry	ligand	yield (%) ^b		
		2a	2a'	2a''
1	L1 • HBF_4	12	1	12
2	L2 • HBr	17	2	2
3	L3 • HCl	44	2	4
4	L4 • HBr	45	3	3
5	L5 • HBr	24	3	3
6	L6 • HCl	0	0	0
7	L7 • HBr	48	3	3
8	PPh_3	4	0	4
9	PCy_3	5	0	0
10	dppe	16	0	0
11	dppp	14	0	3
12	dppf	0	0	2
13	2,2'-bpy	6	0	3
14	1,10-phenanthroline	5	0	0
15	IMes• HCl	6	0	0
16	SIMes• HCl	6	0	0
17	IPr• HCl	7	0	0
18	SIPr• HCl	3	0	0
19 ^c	L7 • HBr	34	4	1
20 ^d	L7 • HBr	21	3	2
21 ^e	L7 • HBr	37	4	2
22 ^f	L7 • HBr	45	5	0
23 ^g	L7 • HBr	28	4	0

^a The reaction was performed on a 0.2 mmol scale ($c = 0.2$ M). ^b The yield was determined by GC using *n*-tridecane as the internal standard. ^c CoCl_2 was used. ^d CoI_2 was used. ^e $\text{Co}(\text{acac})_2$ was used. ^f $\text{Co}(\text{acac})_3$ was used. ^g $\text{Co}(\text{OAc})_2$ was used.

As the reaction of **1a** was complicated by the issue of mono- and di-methylation,

we decided to use 3-methylacetophenone-derived imine **1b** for further optimization, using Co(acac)₃ as the catalyst (Table 4.2). Unlike the case of **1a**, **L1**•HBF₄ and **L2**•HBr displayed modest activity, promoting methylation of the less hindered *ortho* position of **1b** to afford the product **2b** in near 50% yields (entries 1 and 2). As expected from the above screening (Table 4.1), **L3**•HCl and **L4**•HBr further improved the yield to 56% and 63%, respectively (entries 3 and 4), while **L5**•HBr and **L6**•HCl performed poorly (entries 5 and 6). The naphtho-fused preligand **L7**•HBr was slightly less effective than **L4**•HBr, affording **2b** in 58% yield (entry 7). With **L4**•HBr as the preligand, a comparable yield was obtained by replacing Co(acac)₃ with CoBr₂ (entry 8). By increasing the amounts of MeOTs and *t*-BuCH₂MgBr to 2 equiv and 2.7 equiv, respectively, the yield of **2b** was further improved to 80% (entry 9). Besides methyl tosylate, methyl mesylate and trimethyl phosphate could also be used as methylating agents for the present reaction (entries 10 and 11). Methyl iodide, on the other hand, was too reactive toward the Grignard reagent, thus affording the desired product only in 5% yield (entry 12).

Table 4.2. Methylation of imine **1b** with methyl tosylate or related methylating agents^a

<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>L1•HBF₄</p> </div> <div style="text-align: center;"> <p>L2•HBr (R = <i>i</i>-Pr) L3•HCl (R = Cy) L4•HBr (R = <i>sec</i>-Bu) L5•HBr (R = Et) L6•HCl (R = <i>t</i>-Bu)</p> </div> <div style="text-align: center;"> <p>L7•HBr</p> </div> </div>				
Entry	MeX	NHC•HX	yield ^b [%]	
			2b	2b'
1	MeOTs	L1•HBF₄	47	4
2	MeOTs	L2•HBr	47	1
3	MeOTs	L3•HCl	56	3
4	MeOTs	L4•HBr	63	2
5	MeOTs	L5•HBr	22	2
6	MeOTs	L6•HCl	1	0
7	MeOTs	L7•HBr	58	1
8 ^c	MeOTs	L4•HBr	64	2
9 ^d	MeOTs	L4•HBr	80	2
10	MeOMs	L4•HBr	52	1
11	(MeO) ₃ P=O	L4•HBr	59	3
12	Mel	L4•HBr	5	1

^a The reaction was performed using 0.2 mmol of **1b** (*c* = 0.2 M) and 0.3 mmol of MeX. ^b The yield was determined by GC using *n*-tridecane as the internal standard. ^c CoBr₂ was used. ^d 2 equiv of MeOTs and 2.7 equiv of *t*-BuCH₂MgBr were used.

Having established the Co/**L4** catalytic system (Table 4.2, entry 9), we explored the scope of aryl *N*-PMP imines (Table 4.3). For *meta*-substituted acetophenone imines, the methylation occurred exclusively at the less hindered position to give the methylated products **2b-2f** in good yields. Similarly, 2-naphthylimine underwent exclusive C–H activation at the less hindered 3-position (see **2g**). Methylation of imines derived from 1-tetralone and 4-chromanone also took place smoothly,

affording the corresponding products **2h–2k** in moderate to good yields. The synthesis of **2i** could be carried out on a 5 mmol scale without any decrease in the yield. For *para*-phenyl and methoxy-substituted imines, the monomethylation product could be obtained as the major product using lower amounts of MeOTs (1.5 equiv) and *t*-BuCH₂MgBr (2 equiv). However, nonnegligible amounts of dimethylation products were also obtained for these reactions (see **2l** and **2m**). Besides the acetophenone imines, imines derived from propiophenone and butyrophenone also participated in the reaction to preferentially afford monomethylated products (see **2n** and **2o**). Furthermore, imines derived from indole-3-carbaldehyde and indole-3-ethanone also proved to be amenable substrates, affording the C2-methylation products **2p** and **2q**, respectively, in moderate yields.

For the *para*-phenyl-substituted imine, the dimethylation product **2l'** was predominantly formed using large excess amounts of MeOTs (4 equiv) and *t*-BuCH₂MgBr (5.3 equiv). Imines with *para*- or *meta*-fluorine substituents were identified to have greater tendency for dimethylation, yielding the products **2r–2t** as the major products. An impressive example of this kind of substrates is the 3,5-difluoro-substituted imine, which underwent facile dimethylation even with 2.5 equiv of MeOTs (see **2t**). Unlike other *meta*-substituents that impeded the *ortho*-C–H activation due to the steric effect, the *meta*-fluorine substituent would rather promote methylation at its proximity, which might be rationalized by the secondary directing effect of fluorine atoms.

Table 4.3. Scope of aryl *N*-PMP imines^a

^a The methylated products were isolated in the form of imine or ketone (after hydrolysis). The imine products existed as *E/Z* mixtures. ^b 3 equiv of MeOTs and 4 equiv of *t*-BuCH₂MgBr were used. ^c The regioselectivity was 94:6 (major isomer shown). ^d 1.5 equiv of MeOTs and 2 equiv of *t*-BuCH₂MgBr were used. ^e The yield of *ortho*-dimethylation product (GC) is shown in the parentheses. ^f 4 equiv of MeOTs and 5.3 equiv of *t*-BuCH₂MgBr were used. ^g 2.5 equiv of MeOTs and 3.3 equiv of *t*-

BuCH₂MgBr were used.

Next, we explored the *ortho*-methylation of a series of 2-arylpyridine substrates (Table 4.4). For 2-arylpyridines bearing a *meta*-substituent on the aryl ring, the methylation exclusively took place at the less hindered positions (see **4a-4c**). The reaction of parent 2-phenylpyridine gave approximately equal amounts of mono- and di-methylation products **4e** and **4f**. Although attempts were made to achieve selective mono- or dimethylation, only partial success was obtained. When the reaction was performed using 1.5 equiv MeOTs and 2 equiv *t*-BuCH₂MgBr, **4e** was obtained in 47% yield along with a minor amount of **4f** (19%). Using large excess MeOTs (4 equiv) and *t*-BuCH₂MgBr (5.3 equiv), **4f** was obtained in 55% yield along with a minor amount of **4e** (12%). Consistent with the imine-directed methylation (see **2s** in Table 4.3), the reaction of 2-(3-fluorophenyl)pyridine predominantly gave **4g** as the major product via facile dimethylation. Exclusive monomethylation was achieved for a 2-arylpyridine derivative bearing a 3-methyl group on the pyridine ring (see **4h**). Dimethylation was facilitated by a 2-pyrimidine directing group. Thus, the reaction of 2-phenylpyrimidine preferentially gave the dimethylation product **4i** as the major product (59%) along with a small amount of monomethylation product (9%). The yield of **4i** was further improved to 75% using increased amounts of MeOTs (4 equiv) and *t*-BuCH₂MgBr (5.3 equiv). Note that 2-heteroarylpyridines bearing thiophene and indole moieties were also amenable to the present reaction (see **4j** and **4k**). Besides 2-pyridine directing group, pivaloyl N-H imine also served as a good directing group for the present reaction (see **4l**).³⁵

Table 4.4. Methylation of arenes with other directing groups^a

^a The reaction was performed under the conditions shown in Table 4.3. ^b 4 equiv of MeOTs and 5.3 equiv of *t*-BuCH₂MgBr were used.

In light of the growing interest in deuterated drug candidates in recent years, we tried to extend the present C–H methylation method to C–H trideuteriomethylation using CD₃OTs instead of MeOTs. CD₃OTs can be easily prepared from deuterated methanol and tosyl chloride. A series of arenes were selected to react with CD₃OTs under otherwise identical conditions, thus affording the corresponding trideuteriomethylation products in comparable yields (Table 4.5).

Table 4.5. Trideuteriomethylation of selected arene substrates^a

^a The reaction was performed under the conditions shown in Table 4.3 using CD₃OTs instead of MeOTs.

To gain insight into the present reaction, we performed several preliminary mechanistic experiments (Scheme 4.15). First, we conducted a blank reaction between methyl tosylate and *t*-BuCH₂MgBr. As observed by ¹H NMR, methyl tosylate was fully consumed within 2 h and the formation of MeBr was confirmed by the signal at $\delta = 2.61$ (Scheme 4.15a). The same phenomena were observed for methyl mesylate and methyl phosphate. Based on these control experiments, we are tempted to conclude that the actual methylating agent for the present reaction is methyl bromide. Second, we attempted the C–H methylation of **1b** in the presence of stoichiometric amounts of radical scavengers (Scheme 4.15b). The methylation of **1b** was significantly inhibited by the addition of TEMPO, which might suggest SET-type activation of methyl bromide. Third, we explored the competition reaction of **1b** with a 1:1 mixture of methyl tosylate and *n*-octyl bromide or cyclohexyl bromide (Scheme 4.15c). There was no significant chemoselectivity between the methylation and alkylation, which may be interpreted in favor of SET, rather than inner-sphere oxidative addition, for the C–Br cleavage of MeBr. Finally, competitive methylation

reactions between 3-methyl-substituted and 3-trifluoromethyl-substituted imines **1b** and **1c** preferentially produced the methylation product of the latter (Scheme 4.15d). Similar trend was observed for the competitive reaction between *meta*-substituted 2-phenylpyrine derivatives **3a** and **3b**. These results may appear somewhat contradictory to the results in Table 4.3 (**2b**, 81%; **2c**: 68%) and Table 4.4 (**4a**, 78%; **4b**, 33%), where higher yields were obtained with the electron-rich, 3-methylated arene substrates. However, we noted that the substrates **1c** and **3b** underwent unidentified competitive decompositions under the methylation conditions. Thus, we consider that the results of the competition experiments point to the higher propensity of the electron-deficient arene toward cyclometalation.

Scheme 4.15. Control experiments

On the basis of previous reports of cobalt-catalyzed directed C–H alkylation (*cf.* Chapter 1) and the above-mentioned mechanistic experiments, we propose a catalytic cycle for the present cobalt-catalyzed directed *ortho*-methylation of arenes as shown in Scheme 4.16. An organocobalt species **A**, generated from the cobalt precatalyst and the Grignard reagent, would undergo cyclometalation of the imine to give a

cobaltacycle species **B**. SET from the cobalt center to an in-situ formed methyl bromide would generate a pair of oxidized cobaltacycle and methyl radical (**C**), which would undergo radical rebound to give an intermediate **D**. Subsequently, reductive elimination of **D** would give the methylated arene product. Transmetalation of the resulting cobalt bromide species with the Grignard reagent would regenerate the low-valent cobalt species **A**.

Scheme 4.16. Proposed catalytic cycle for the cobalt-catalyzed directed *ortho*-methylation of arenes with methyl tosylate

4.3 Conclusion

In summary, we have developed a cobalt-catalyzed directed *ortho*-methylation of arenes using readily available methyl tosylate as the methylating reagent. A catalytic system comprised of $Co(acac)_3$, N,N' -di(2-butyl) benzimidazolium bromide, and

neopentyl Grignard reagent promoted the methylation directed by different nitrogen directing groups including *N*-aryl imine, N–H imine, and 2-pyridyl groups. The present reaction system also allows facile C–H trideuteriomethylation of arenes with CD₃OTs. The Grignard reagent not only serves as a base and a reductant, but also acts as a bromide donor to convert methyl tosylate into the actual methylating agent, i.e., methyl bromide.

4.4 Experimental Section

Materials. Unless otherwise noted, commercial reagents were purchased from Sigma-Aldrich, Alfa Aesar, or other commercial suppliers and were used as received. Co(acac)₃ was purchased from Alfa Aesar and used as received. 1,3-Dicyclohexyl-1*H*-benzo[*d*]imidazol-3-ium chloride (**L3•HCl**) and 1,3-*di-tert*-butyl-1*H*-benzo[*d*]imidazol-3-ium chloride (**L6•HCl**) were purchased from Strem Chemicals, while other imidazolium and imidazolinium salts were prepared according to the literature procedure.³⁶ THF was distilled over Na/benzophenone. Methylating agents except CD₃OTs (prepared using the method reported by Poulter³⁷) were purchased from TCI, Sigma-Aldrich or Merck and used as received. Grignard reagents were prepared from the corresponding alkyl halides and magnesium turnings in anhydrous THF and titrated before use.

Preparation of Starting Materials

Preparation of *N*-PMP imines

All *N*-PMP (*p*-methoxyphenyl) imines **1a–1t** were prepared according to the literature procedures,³⁸ and purified by recrystallization or distillation. Spectral data for these known compounds (except **1j**) showed good agreement with the literature

data.³⁹ **(*E*)-7-Methoxy-*N*-(4-methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-imine (1j):**

Yellow solid; R_f 0.36 (hexane/EtOAc/Et₃N = 100/10/1); m.p. 81.8-84.0 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.84 (d, J = 2.7 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.95 (dd, J = 8.4, 2.8 Hz, 1H), 6.92-6.88 (m, 2H), 6.78-6.73 (m, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 2.83 (t, J = 6.1 Hz, 2H), 2.53 (t, J = 6.4 Hz, 2H), 1.89 (quintet, J = 6.3 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 165.8, 158.2, 155.8, 144.7, 134.9, 133.8, 129.8, 120.8, 118.9, 114.3, 108.5, 55.5 (2C), 29.7, 29.2, 23.3; HRMS (ESI) Calcd for C₁₈H₂₀NO₂ [M + H]⁺ 282.1494, found 282.1494.

Preparation of other substrates

2-Arylpyridine derivatives **3a–3k** except commercially available **3e** were prepared according to the literature procedure.⁴⁰ Spectral data for these compounds showed good agreement with the literature data.^{40b, 41} N–H imine **3l** was prepared from 3-methylbenzonitrile and *t*-BuMgCl according to the literature procedure,⁴² and purified by distillation. Spectral data for **3l** showed good agreement with the literature data.⁴³

Preparation of New N-Heterocyclic Carbene Precursors

1,3-Di-*sec*-butyl-1H-benzo[*d*]imidazol-3-ium bromide (L4•HBr**; a 1:1 mixture of diastereomers):** Prepared according to the procedure reported by Huynh and coworkers.^{36b} A mixture of benzimidazole (2.00 g, 16.9 mmol) and K₂CO₃ (2.60 g, 18.8 mmol) was suspended in CH₃CN (10.0 mL) and stirred at room temperature for 1 h. To the suspension was added 2-bromobutane (5.54 mL, 50.8 mmol) and the resulting mixture was stirred under reflux for 24 h. A second portion of 2-bromobutane (5.54 mL, 50.8 mmol) was added and the mixture was stirred for an additional 3 d under reflux. After removing the volatiles in vacuo, CH₂Cl₂ (50 mL)

was added to the residue and the resulting suspension was filtered over Celite. Silica gel chromatography (eluent: CH₂Cl₂/MeOH = 100/2–100/5) of the filtrate afforded a residue, which was washed with ethyl acetate to afford the title compound as a white powder (3.40 g, 65%).

R_f 0.55 (CH₂Cl₂/MeOH = 3/1); m.p. 170.0–173.0 °C; ¹H NMR (400 MHz, CDCl₃): δ 11.62 (s, 1H), 7.79–7.75 (m, 2H), 7.65–7.61 (m, 2H), 5.02–4.91 (m, 2H), 2.34–2.21 (m, 2H), 2.20–2.10 (m, 2H), 1.85 (d, J = 6.8 Hz, 6H), 0.92 (td, J = 7.3, 2.2 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 141.37, 141.34, 130.85, 130.84, 126.89 (two signals overlapped), 113.86, 113.84, 57.85, 57.82, 29.06, 29.00, 20.30, 20.27, 10.66, 10.59; HRMS (ESI) Calcd for C₁₅H₂₄N₂Br [M+ H]⁺ 311.1123, found 311.1127. The pairs of ¹³C NMR signals with close chemical shifts and similar intensities indicated that the compound was obtained as a ca. 1:1 mixture of diastereomers.

1,3-Diisopropyl-1*H*-naphtho[2,3-*d*]imidazol-3-ium bromide (L7•HBr): White solid (3.80 g, 93%; prepared on a 12.3 mmol scale using the procedure described for L4•HBr). R_f 0.48 (CH₂Cl₂/MeOH = 3/1); m.p. 235.7–236.5 °C; ¹H NMR (400 MHz, CDCl₃): δ 11.67 (s, 1H), 8.22 (s, 2H), 8.10–8.06 (m, 2H), 7.67–7.63 (m, 2H), 5.30 (septet, J = 6.8 Hz, 2H), 1.94 (d, J = 6.8 Hz, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 143.9, 131.3, 129.7, 128.2, 127.1, 111.4, 52.4, 22.0; HRMS (ESI) Calcd for C₁₇H₂₂N₂Br [M+ H]⁺ 333.0966, found 333.0964.

Cobalt-Catalyzed Directed Arene C–H Methylation with Methyl Tosylate

Typical Procedure: 1-(2,5-Dimethylphenyl)-*N*-(4-methoxyphenyl)ethan-1-imine (2b). In a 10 mL Schlenk tube were placed (*E*)-*N*-(4-methoxyphenyl)-1-(*m*-tolyl)ethan-1-imine (**1b**, 47.9 mg, 0.20 mmol), 1,3-*di-sec*-butyl-1*H*-benzo[*d*]imidazol-3-ium bromide (**L4**•HBr, 6.2 mg, 0.020 mmol), Co(acac)₃ (7.1 mg, 0.020 mmol), methyl tosylate (74.5 mg, 0.40 mmol, 2 equiv) and THF (0.55 mL). The resulting solution was cooled to 0 °C and a THF solution of *t*-BuCH₂MgBr (1.18 M, 0.45 mL, 0.53 mmol, 2.7 equiv) was added. After stirring at room temperature for 12 h, the mixture was quenched by sat. NH₄Cl (1 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL), and the combined organic layer was dried over MgSO₄ and concentrated in vacuo. Silica gel chromatography (eluent: hexane/EtOAc/Et₃N = 100/2/1–100/10/1) of the crude product afforded the title compound as a light yellow oil (41.1 mg, 81%), which existed as a mixture of imine *E/Z* isomers. The ratio of the isomers was determined to be 61:39 by ¹H NMR integrations of characteristic signals at 3.82 and 3.69 ppm.

Major isomer: *R_f* 0.21 (hexane/EtOAc/Et₃N = 100/10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.18 (s, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.08 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.94–6.90 (m, 2H), 6.82–6.78 (m, 2H), 3.82 (s, 3H), 2.43 (s, 3H), 2.35 (s, 3H), 2.16 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 170.4, 156.0, 144.4, 141.8, 135.2, 130.8, 130.1, 129.2, 127.7, 120.6, 114.3, 55.5, 29.4, 20.9, 19.6.

Minor isomer: *R_f* 0.34 (hexane/EtOAc/Et₃N = 100/10/1); ¹H NMR (400 MHz, CDCl₃): δ 6.95–6.88 (m, 3H), 6.64–6.59 (m, 4H), 3.69 (s, 3H), 2.43 (s, 3H), 2.28 (s, 3H), 1.98 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 170.2, 155.9, 143.4, 139.3, 134.9,

131.6, 129.9, 128.8, 127.4, 122.4, 113.5, 55.2, 29.4, 21.1, 19.2.

HRMS (ESI) Calcd for $C_{17}H_{20}NO$ $[M + H]^+$ 254.1545, found 254.1548.

***N*-(4-Methoxyphenyl)-1-(2-methyl-5-(trifluoromethyl)phenyl)ethan-1-imine**

(2c): The reaction was performed using 3 equiv of methyl tosylate and 4 equiv of *t*-BuCH₂MgBr. Silica gel chromatography (eluent: hexane/EtOAc/Et₃N = 100/1/1–100/10/1) of the crude product afforded the title compound as a yellow oil (41.7 mg, 68%), which existed as a mixture of imine *E/Z* isomers. The ratio of the isomers was determined to be 67:33 by ¹H NMR integrations of characteristic signals at 3.83 and 3.69 ppm.

Major isomer: *R_f* 0.36 (hexane/EtOAc/Et₃N = 100/10/1); ¹H NMR (300 MHz, CDCl₃): δ 7.62 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.83 (s, 3H), 2.53 (s, 3H), 2.20 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 168.8, 156.3, 143.7, 142.3, 139.2, 131.4, 128.3 (q, ²*J*_{C-F} = 32.4 Hz), 125.1 (q, ³*J*_{C-F} = 3.7 Hz), 124.1 (q, ¹*J*_{C-F} = 270.2 Hz), 124.0 (q, ³*J*_{C-F} = 3.6 Hz), 120.5, 114.4, 55.5, 21.0, 20.1; ¹⁹F NMR (300 MHz, CDCl₃): δ -62.4.

Minor isomer: *R_f* 0.20 (hexane/EtOAc/Et₃N = 100/10/1); ¹H NMR (300 MHz, CDCl₃): δ 7.39-7.34 (m, 2H), 7.14 (d, *J* = 7.9 Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 8.7 Hz, 2H), 3.69 (s, 3H), 2.46 (s, 3H), 2.08 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 168.3, 156.2, 142.9, 139.9, 137.3, 130.8, 128.0 (q, ²*J*_{C-F} = 32.4 Hz), 124.7 (q, ³*J*_{C-F} = 3.6 Hz), 124.0 (two signals overlapping, q, ¹*J*_{C-F} = 270.1 Hz and q, ³*J*_{C-F} = 3.5 Hz (partially overlapped)), 122.1, 113.7, 55.2, 29.1, 19.7; ¹⁹F NMR (300 MHz,

CDCl₃): δ -62.4. HRMS (ESI) Calcd for C₁₇H₁₇NOF₃ [M + H]⁺ 308.1262, found 308.1259.

1-(5-Chloro-2-methylphenyl)ethan-1-one (2d): The reaction was performed according to the typical procedure, and then quenched by the addition of HCl (3 N, 1 mL). After stirring for 1 h, the resulting mixture was extracted with Et₂O (3 x 10 mL). The combined organic layer was dried over MgSO₄ and concentrated in vacuo. Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a colorless oil (18.8 mg, 56%).

R_f 0.48 (hexane/EtOAc = 10/1); ¹H NMR (500 MHz, CDCl₃): δ 7.64 (d, *J* = 2.2 Hz, 1H), 7.34 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 2.57 (s, 3H), 2.48 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 200.4, 139.0, 136.6, 133.3, 131.4, 131.3, 129.1, 29.5, 20.9; HRMS (ESI) Calcd for C₉H₁₀OCl [M + H]⁺ 169.0420, found 169.0420.

1-(4,5-Dimethoxy-2-methylphenyl)ethan-1-one (2e):⁴⁴ White solid (27.9 mg, 72%; eluent: hexane/EtOAc = 5/1; prepared as described for **2d**). *R_f* 0.30 (hexane/EtOAc = 3/1); m.p. 75.0-78.0 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.24 (s, 1H), 6.69 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.55 (s, 3H), 2.52 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 199.5, 151.6, 146.3, 133.5, 129.5, 114.6, 113.3, 56.2, 55.9, 29.4, 21.8; HRMS (ESI) Calcd for C₁₁H₁₅O₃ [M + H]⁺ 195.1021, found 195.1025.

1-(3-Methyl-9H-fluoren-2-yl)ethan-1-one (2f): White solid (33.0 mg, 74%; eluent: hexane/EtOAc = 10/1; prepared as described for **2d**). R_f 0.29 (hexane/EtOAc = 10/1); m.p. 99.8-102.8 °C; ^1H NMR (500 MHz, CDCl_3): δ 7.90 (s, 1H), 7.82 (d, J = 7.4 Hz, 1H), 7.64 (s, 1H), 7.58 (d, J = 7.4 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.36 (td, J = 7.4, 1.2 Hz, 1H), 3.92 (s, 2H), 2.65 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 201.3, 144.9, 144.6, 140.6, 140.3, 137.8, 135.9, 127.7, 127.0, 126.2, 125.2, 123.2, 120.6, 36.6, 29.6, 22.2; HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{15}\text{O}$ $[\text{M} + \text{H}]^+$ 223.1123, found 223.1118.

1-(3-Methylnaphthalen-2-yl)ethan-1-one (2g):⁴⁵ Prepared as described for **2d**. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded a mixture of the title compound and its minor regioisomer (1-(1-methylnaphthalen-2-yl)ethan-1-one) as a light yellow solid (30.0 mg, 81%). The ratio of the regioisomers was determined to be 94:6 by ^1H NMR integrations of characteristic signals at 2.71 and 2.80 ppm.

R_f 0.39 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.24 (s, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.65 (s, 1H), 7.57-7.53 (m, 1H), 7.50-7.46 (m, 1H), 2.71 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 201.4, 136.3, 134.8, 134.6, 131.0, 130.6, 130.0, 128.5, 128.2, 126.9, 125.9, 29.4, 21.8; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{13}\text{O}$ $[\text{M} + \text{H}]^+$ 185.0966, found 185.0964.

8-Methyl-3,4-dihydronaphthalen-1(2H)-one (2h):⁴⁶ Colorless oil (21.6 mg, 67%; eluent: hexane/EtOAc = 50/1; prepared as described for **2d** using 1.5 equiv of methyl tosylate and 2 equiv of *t*-BuCH₂MgBr). *R_f* 0.39 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.30 (t, *J* = 7.6 Hz, 1H), 7.11-7.08 (m, 2H), 2.95 (t, *J* = 6.1 Hz, 2H), 2.65 (t, *J* = 6.6 Hz, 2H), 2.64 (s, 3H), 2.08 (quintet, *J* = 6.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 200.2, 145.7, 141.5, 132.2, 131.2, 130.4, 126.7, 41.0, 31.0, 23.3, 23.0; HRMS (ESI) Calcd for C₁₁H₁₃O [M + H]⁺ 161.0966, found 161.0961.

5-Methoxy-8-methyl-3,4-dihydronaphthalen-1(2H)-one (2i):⁴⁶ Colorless oil (31.4 mg, 83%; eluent: hexane/EtOAc = 10/1; prepared as described for **2d**). *R_f* 0.37 (hexane/EtOAc = 10/1); ¹H NMR (500 MHz, CDCl₃): δ 7.04 (d, *J* = 8.2 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 3.84 (s, 3H), 2.89 (t, *J* = 6.2 Hz, 2H), 2.62 (t, *J* = 6.7 Hz, 2H), 2.56 (s, 3H), 2.07 (quintet, *J* = 6.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 200.6, 154.8, 134.2, 132.3, 131.8, 130.0, 113.7, 55.7, 40.8, 23.6, 22.5, 22.4; HRMS (ESI) Calcd for C₁₂H₁₅O₂ [M + H]⁺ 191.1072, found 191.1068.

Preparative scale synthesis of 2i: In a 100 mL Schlenk tube equipped with a stir bar were placed (*E*)-5-methoxy-*N*-(4-methoxyphenyl)-3,4-dihydronaphthalen-1(2H)-imine (**1i**, 1.41 g, 5.0 mmol), 1,3-di-*sec*-butyl-1*H*-benzo[*d*]imidazol-3-ium bromide (**L4**•HBr, 156 mg, 0.50 mmol), Co(acac)₃ (178 mg, 0.50 mmol), methyl tosylate (1.86 g, 10.0 mmol, 2 equiv) and THF (17.1 mL). The resulting solution was cooled

at 0 °C and a THF solution of *t*-BuCH₂MgBr (1.7 M, 7.9 mL, 13.5 mmol, 2.7 equiv) was added. After stirring at room temperature for 12 h, the mixture was quenched by the addition of HCl (3 N, 25.0 mL). After stirring for 1 h, the resulting mixture was extracted with Et₂O (4 x 25 mL). The combined organic layer was dried over MgSO₄ and concentrated in vacuo. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded **2i** as a light yellow oil (0.80 g, 84%).

7-Methoxy-8-methyl-3,4-dihydronaphthalen-1(2H)-one (2j):⁴⁷ White solid (20.8 mg, 55%; eluent: hexane/EtOAc = 30/1; prepared as described for **2d**). *R*_f 0.32 (hexane/EtOAc = 10/1); m.p. 43.9-46.9 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.06 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 3.83 (s, 3H), 2.88 (t, *J* = 6.1 Hz, 2H), 2.63 (t, *J* = 6.6 Hz, 2H), 2.52 (s, 3H), 2.05 (quintet, *J* = 6.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 200.8, 156.6, 137.3, 132.4, 129.7, 126.4, 115.0, 56.1, 41.1, 30.4, 23.2, 13.2; HRMS (ESI) Calcd for C₁₂H₁₅O₂ [M + H]⁺ 191.1072, found 191.1068.

5-Methylchroman-4-one (2k): Light yellow oil (20.0 mg, 62%; eluent: hexane/EtOAc = 30/1; prepared as described for **2d**). *R*_f 0.27 (hexane/EtOAc = 10/1); ¹H NMR (500 MHz, CDCl₃): δ 7.30 (t, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 4.48 (t, *J* = 6.4 Hz, 2H), 2.80 (t, *J* = 6.4 Hz, 2H), 2.64 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 193.3, 162.9, 142.2, 134.5, 124.6, 119.9, 115.8, 66.4, 39.3, 22.9; HRMS (ESI) Calcd for C₁₀H₁₁O₂ [M + H]⁺ 163.0759, found 163.0756.

1-(3-Methyl-[1,1'-biphenyl]-4-yl)ethan-1-one (2l): White solid (20.6 mg, 49%; eluent: hexane/EtOAc = 40/1; prepared as described for **2d** using 1.5 equiv of methyl tosylate and 2 equiv of *t*-BuCH₂MgBr). *R_f* 0.34 (hexane/EtOAc = 10/1); m.p. 60.2-63.2 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.80 (d, *J* = 7.8 Hz, 1H), 7.63-7.60 (m, 2H), 7.50-7.44 (m, 4H), 7.41-7.37 (m, 1H), 2.62 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 201.1, 144.2, 140.0, 139.3, 136.1, 130.8, 130.3, 128.9, 128.0, 127.2, 124.3, 29.5, 22.0; HRMS (ESI) Calcd for C₁₅H₁₅O [M + H]⁺ 211.1123, found 211.1119.

1-(4-Methoxy-2-methylphenyl)ethan-1-one (2m):⁴⁸ Colorless oil (13.8 mg, 42%; eluent: hexane/EtOAc = 20/1; prepared as described for **2d** using 1.5 equiv of methyl tosylate and 2 equiv of *t*-BuCH₂MgBr). *R_f* 0.27 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.75 (d, *J* = 8.7 Hz, 1H), 6.77-6.74 (m, 2H), 3.85 (s, 3H), 2.57 (s, 3H), 2.55 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 199.5, 161.9, 142.2, 132.5, 130.0, 117.5, 110.6, 55.3, 29.1, 22.6; HRMS (ESI) Calcd for C₁₀H₁₃O₂ [M + H]⁺ 165.0916, found 165.0920.

N-(4-methoxyphenyl)-1-(*o*-tolyl)propan-1-imine (2n): Silica gel chromatography (eluent: hexane/EtOAc/Et₃N = 100/1/1) of the crude product afforded the title compound as a light yellow oil (33.6 mg, 66%), which existed as a mixture of imine

E/Z isomers. The ratio of the isomers was determined to be 75:25 by ^1H NMR integrations of characteristic signals at 3.68 and 3.82 ppm.

Major isomer: R_f 0.19 (hexane/EtOAc/Et₃N = 100/10/1); ^1H NMR (400 MHz, CDCl₃): δ 7.15-7.09 (m, 2H), 7.05-7.00 (m, 2H), 6.63-6.58 (m, 4H), 3.68 (s, 3H), 2.70 (q, J = 7.3 Hz, 2H), 2.02 (s, 3H), 1.21 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, CDCl₃): δ 174.0, 155.8, 143.6, 138.9, 133.5, 130.1, 127.8, 127.4, 125.2, 122.2, 113.4, 55.2, 35.3, 19.8, 10.4.

Minor isomer: R_f 0.26 (hexane/EtOAc/Et₃N = 100/10/1); ^1H NMR (400 MHz, CDCl₃): δ 7.31-7.21 (m, 4H), 6.93-6.89 (m, 2H), 6.81-6.77 (m, 2H), 3.82 (s, 3H), 2.57 (q, J = 7.6 Hz, 2H), 2.46 (s, 3H), 0.94 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, CDCl₃): δ 175.1, 155.9, 144.2, 140.2, 135.3, 130.8, 128.3, 127.1, 125.6, 120.4, 114.3, 55.5, 35.3, 26.9, 11.3.

HRMS (ESI) Calcd for C₁₇H₂₀NO $[\text{M} + \text{H}]^+$ 254.1545, found 254.1549.

***N*-(4-methoxyphenyl)-1-(*o*-tolyl)butan-1-imine (2o):** Silica gel chromatography (eluent: hexane/EtOAc/Et₃N = 100/1/1) of the crude product afforded the title compound as a light yellow oil (34.5 mg, 65%), which existed as a mixture of *E/Z* isomers. The ratio of the isomers was determined to be 71:29 by ^1H NMR integrations of characteristic signals at 3.68 and 3.82 ppm.

R_f 0.29 (hexane/EtOAc/Et₃N = 100/10/1).

Major isomer: ^1H NMR (400 MHz, CDCl₃): δ 7.15-7.08 (m, 2H), 7.05-7.00 (m, 2H), 6.63-6.57 (m, 4H), 3.68 (s, 3H), 2.65 (t, J = 7.7 Hz, 2H), 2.02 (s, 3H), 1.71-1.66 (m, 2H), 1.02 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl₃): δ 173.1, 155.8, 143.6, 138.9, 133.5, 130.1, 127.8, 127.4, 125.2, 122.2, 113.4, 55.2, 44.3, 20.2, 19.4, 14.0.

Minor isomer: ^1H NMR (400 MHz, CDCl_3): δ 7.32-7.30 (m, 1H), 7.28-7.21 (m, 3H), 6.93-6.89 (m, 2H), 6.80-6.76 (m, 2H), 3.82 (s, 3H), 2.55-2.51 (m, 2H), 2.47 (s, 3H), 1.42-1.33 (m, 2H), 0.79 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 174.1, 155.9, 144.2, 140.4, 135.2, 130.9, 128.3, 127.1, 125.5, 120.3, 114.2, 55.4, 35.6, 19.9, 19.8, 14.2.

HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{22}\text{NO}$ $[\text{M} + \text{H}]^+$ 268.1701, found 268.1703.

1-(1,2-Dimethyl-1H-indol-3-yl)-N-(4-methoxyphenyl)ethan-1-imine (2p): Silica gel chromatography (eluent: hexane/EtOAc/ Et_3N = 90/30/1) of the crude product afforded the title compound as a brown solid (33.6 mg, 57%), which existed as a mixture of *E/Z* isomers. The ratio of the isomers was determined to be 87:13 by ^1H NMR integrations of characteristic signals at 2.74 and 2.59 ppm.

R_f 0.24 (hexane/EtOAc = 3/1).

Major isomer: ^1H NMR (400 MHz, CDCl_3): δ 7.92 (d, $J = 7.7$ Hz, 1H), 7.32 (d, $J = 8.1$ Hz, 1H), 7.24-7.13 (m, 2H), 6.94-6.90 (m, 2H), 6.83-6.80 (m, 2H), 3.83 (s, 3H), 3.72 (s, 3H), 2.74 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.6, 155.5, 145.3, 138.4, 136.6, 126.5, 122.4, 121.3, 121.0, 120.4 (two signals overlapping), 114.3, 109.0, 55.5, 29.5, 21.3, 12.3.

Minor isomer: ^1H NMR (400 MHz, CDCl_3): δ 7.56 (d, $J = 7.7$ Hz, 1H), 7.24-7.13 (m, 3H), 6.69-6.66 (m, 2H), 6.63-6.60 (m, 2H), 3.69 (s, 3H), 3.52 (s, 3H), 2.59 (s, 3H), 1.86 (s, 3H).

HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 293.1654, found 293.1661.

(E)-1-(1,2-dimethyl-1H-indol-3-yl)-N-(4-methoxyphenyl)methanimine (2q):

Silica gel chromatography (eluent: hexane/EtOAc/Et₃N = 90/30/1) of the crude product afforded the title compound as a mixture with minor amount of anisidine as a light yellow solid (33.2 mg). The yield was determined to be 59% based on the total weight and the ¹H NMR analysis of the mixture.

R_f 0.33 (hexane/EtOAc = 3/1); ¹H NMR (500 MHz, CDCl₃): δ 8.73 (s, 1H), 8.51-8.47 (m, 1H), 7.32-7.24 (m, 3H), 7.23-7.20 (m, 2H), 6.95-6.92 (m, 2H), 3.84 (s, 3H), 3.72 (s, 3H), 2.65 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 157.1, 152.8, 147.4, 142.1, 137.2, 125.9, 122.3, 121.8, 121.6, 121.4, 114.3, 111.4, 108.7, 55.5, 29.6, 10.7; HRMS (ESI) Calcd for C₁₈H₁₉N₂O [M + H]⁺ 279.1497, found 279.1495.

1-(3,5-Dimethyl-[1,1'-biphenyl]-4-yl)-N-(4-methoxyphenyl)ethan-1-imine (2l'):

The reaction was performed using 4 equiv of methyl tosylate and 5.3 equiv of *t*-BuCH₂MgBr. After treatment with 3 N HCl (1.0 mL) for 1 h, the reaction mixture was neutralized with 3 N NaOH (2.0 mL) and then extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over MgSO₄ and concentrated in vacuo. Silica gel chromatography (eluent: hexane/EtOAc/Et₃N = 100/2/1–100/5/1) of the crude product afforded the title compound as a light yellow oil (33.0 mg, 50%), which existed as a mixture of *E/Z* isomers. The ratio of the isomers was determined to be 61:39 by ¹H NMR integrations of characteristic signals at 3.69 and 3.84 ppm.

Major isomer: *R_f* 0.26 (hexane/EtOAc/Et₃N = 100/10/1); ¹H NMR (400 MHz,

CDCl₃): δ 7.45-7.31 (m, 5H), 7.17 (s, 2H), 6.71-6.68 (m, 2H), 6.66-6.63 (m, 2H), 3.69 (s, 3H), 2.42 (s, 3H), 2.24 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 169.7, 156.3, 143.0, 141.1, 140.5, 140.4, 133.6, 128.7, 127.3, 126.9, 126.2, 121.8, 113.5, 55.2, 28.6, 20.1.

Minor isomer: *R_f* 0.19 (hexane/EtOAc/Et₃N = 100/10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.59-7.53 (m, 5H), 7.30 (s, 2H), 6.96-6.93 (m, 2H), 6.87-6.83 (m, 2H), 3.84 (s, 3H), 2.42 (s, 6H), 2.15 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 171.4, 156.2, 144.0, 140.9, 140.6, 138.4, 134.0, 128.7, 127.2, 127.1, 126.7, 120.7, 114.4, 55.5, 21.3, 19.3.

HRMS (ESI) Calcd for C₂₃H₂₄NO [M + H]⁺ 330.1858, found 330.1859.

1-(4-Fluoro-2,6-dimethylphenyl)-N-(4-methoxyphenyl)ethan-1-imine (2r): The reaction was performed using 3 equiv of methyl tosylate and 4 equiv of *t*-BuCH₂MgBr. Silica gel chromatography (eluent: hexane/EtOAc/Et₃N = 100/1/1–100/10/1) of the crude product afforded the title compound as a light yellow oil (46.3 mg, 85%), which existed as a mixture of *E/Z* isomers. The ratio of the isomers was determined to be 56:44 by ¹H NMR integrations of characteristic signals at 3.70 and 3.83 ppm.

R_f 0.17 (hexane/EtOAc/Et₃N = 100/10/1).

Major isomer: ¹H NMR (400 MHz, CDCl₃): δ 6.66-6.60 (m, 6H), 3.70 (s, 3H), 2.37 (s, 3H), 2.16 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 169.0, 161.9 (d, ¹*J*_{C-F} = 244.0 Hz), 156.3, 142.9, 135.6 (d, ³*J*_{C-F} = 8.3 Hz), 135.1 (d, ⁴*J*_{C-F} = 3.2 Hz), 121.6, 114.3 (d, ²*J*_{C-F} = 15.4 Hz), 113.5, 55.2, 28.6, 20.0 (d, ⁴*J*_{C-F} = 1.2 Hz); ¹⁹F NMR (400 MHz,

CDCl_3): δ - 115.5.

Minor isomer: ^1H NMR (400 MHz, CDCl_3): δ 6.95-6.91 (m, 2H), 6.83-6.80 (m, 2H), 6.77 (d, $J = 9.5$ Hz, 2H), 3.83 (s, 3H), 2.34 (s, 6H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 170.8, 161.8 (d, $^1J_{\text{C-F}} = 243.5$ Hz), 156.2, 143.8, 137.9 (d, $^4J_{\text{C-F}} = 2.7$ Hz), 136.1 (d, $^3J_{\text{C-F}} = 8.4$ Hz), 120.6, 114.4, 114.1 (d, $^2J_{\text{C-F}} = 21.0$ Hz), 55.5, 21.4, 19.2 (d, $^4J_{\text{C-F}} = 1.3$ Hz); ^{19}F NMR (400 MHz, CDCl_3): δ - 115.7.

HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{19}\text{NOF}$ $[\text{M} + \text{H}]^+$ 272.1451, found 272.1454.

1-(3-Fluoro-2,6-dimethylphenyl)-N-(4-methoxyphenyl)ethan-1-imine (2s): The reaction was performed using 4 equiv of methyl tosylate and 5.3 equiv of *t*-BuCH₂MgBr, and worked up as described for **2I'**. Silica gel chromatography (eluent: hexane/EtOAc/Et₃N = 100/2/1–100/10/1) of the crude product afforded the title compound as a light yellow oil (36.6 mg, 67%), which existed as a mixture of *E/Z* isomers. The ratio of the isomers was determined to be 60:40 by ^1H NMR integrations of characteristic signals at 3.70 and 3.83 ppm.

Major isomer: R_f 0.17 (hexane/EtOAc/Et₃N = 100/10/1); ^1H NMR (400 MHz, CDCl_3): δ 6.95-6.91 (m, 2H), 6.66-6.61 (m, 4H), 3.70 (s, 3H), 2.37 (s, 3H), 2.12 (s, 3H), 2.09 (d, $J = 1.5$ Hz, 3H, partially overlapped); ^{13}C NMR (75 MHz, CDCl_3): δ 168.4 (d, $^4J_{\text{C-F}} = 1.8$ Hz), 159.5 (d, $^1J_{\text{C-F}} = 241.8$ Hz), 156.3, 142.8, 141.1 (d, $^4J_{\text{C-F}} = 3.6$ Hz), 128.5 (two signals overlapping, d, $^3J_{\text{C-F}} = 8.0$ Hz and d, $^3J_{\text{C-F}} = 3.6$ Hz (partially overlapped)), 121.5, 120.4 (d, $^2J_{\text{C-F}} = 17.4$ Hz), 114.2 (d, $^2J_{\text{C-F}} = 22.5$ Hz), 113.6, 55.2, 28.4, 19.3, 12.3 (d, $^3J_{\text{C-F}} = 4.4$ Hz); ^{19}F NMR (75 MHz, CDCl_3): δ - 119.7.

Minor isomer: R_f 0.25 (hexane/EtOAc/Et₃N = 100/10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.02 (dd, J = 8.3, 5.4 Hz, 1H), 6.89-6.77 (m, 5H), 3.83 (s, 3H), 2.31 (s, 3H), 2.26 (d, J = 2.1 Hz, 3H), 2.09 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 170.3 (d, $^4J_{C-F}$ = 2.7 Hz), 159.7 (d, $^1J_{C-F}$ = 241.2 Hz), 156.3, 143.6, 143.4 (d, $^4J_{C-F}$ = 3.8 Hz), 128.9 (d, $^3J_{C-F}$ = 3.7 Hz), 128.7 (d, $^3J_{C-F}$ = 8.2 Hz), 120.8 (d, $^2J_{C-F}$ = 16.6 Hz, partially overlapped), 120.7, 114.4, 114.1 (d, $^2J_{C-F}$ = 22.4 Hz), 55.5, 21.3, 18.6, 11.1 (d, $^3J_{C-F}$ = 4.8 Hz); ¹⁹F NMR (75 MHz, CDCl₃): δ -120.5;

HRMS (ESI) Calcd for C₁₇H₁₉NOF [M + H]⁺ 272.1451, found 272.1459.

1-(3,5-Difluoro-2,6-dimethylphenyl)-N-(4-methoxyphenyl)ethan-1-imine (2t):

The reaction was performed using 2.5 equiv of methyl tosylate and 3.3 equiv of *t*-BuCH₂MgBr. Silica gel chromatography (eluent: hexane/EtOAc/Et₃N = 100/1/1) of the crude product afforded the title compound as a light yellow oil (42.9 mg, 74%), which existed as a mixture of *E/Z* isomers. The ratio of the isomers was determined to be 57:43 by ¹H NMR integrations of characteristic signals at 3.71 and 3.83 ppm.

Major isomer: R_f 0.27 (hexane/EtOAc/Et₃N = 100/10/1); ¹H NMR (300 MHz, CDCl₃): δ 6.68-6.59 (m, 5H), 3.71 (s, 3H), 2.36 (s, 3H), 2.04 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 167.1 (t, $^4J_{C-F}$ = 2.3 Hz), 159.1 (dd, $^1J_{C-F}$ = 244.5 Hz, $^3J_{C-F}$ = 12.8 Hz), 156.5, 142.7, 142.4 (t, $^3J_{C-F}$ = 4.9 Hz), 121.3, 116.1 (dd, $^2J_{C-F}$ = 13.5 Hz, $^4J_{C-F}$ = 7.5 Hz), 113.7, 102.5 (t, $^2J_{C-F}$ = 26.3 Hz), 55.2, 28.3, 11.9 (dd, J values were small and could not be clearly determined); ¹⁹F NMR (300 MHz, CDCl₃): δ -115.1.

Minor isomer: R_f 0.42 (hexane/EtOAc/Et₃N = 100/10/1); ¹H NMR (300 MHz, CDCl₃): δ 6.97-6.91 (m, 2H), 6.85-6.80 (m, 2H), 6.76 (t, J = 9.6 Hz, 1H), 3.83 (s,

3H), 2.21 (s, 6H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 169.2 (t, $^4J_{\text{C-F}} = 3.4$ Hz), 159.2 (dd, $^1J_{\text{C-F}} = 243.8$ Hz, $^3J_{\text{C-F}} = 12.8$ Hz), 156.5, 144.4 (t, $^3J_{\text{C-F}} = 5.3$ Hz), 143.2, 120.7, 116.6 (dd, $^2J_{\text{C-F}} = 13.1$ Hz, $^4J_{\text{C-F}} = 7.9$ Hz), 114.4, 102.4 (t, $^2J_{\text{C-F}} = 26.3$ Hz), 55.5, 21.3, 10.8 (dd, $^3J_{\text{C-F}} = 1.9$ Hz, $^5J_{\text{C-F}} = 1.1$ Hz); ^{19}F NMR (300 MHz, CDCl_3): δ -116.2.

HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{18}\text{NOF}_2$ $[\text{M} + \text{H}]^+$ 290.1356, found 290.1350.

2-(2,5-Dimethylphenyl)pyridine (4a):⁴⁹ Colorless oil (28.6 mg, 78%; eluent: hexane/EtOAc = 10/1). R_f 0.17 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.69 (ddd, $J = 4.8, 1.7, 1.0$ Hz), 7.73 (td, $J = 7.7, 1.8$ Hz, 1H), 7.40 (dt, $J = 7.8, 1.0$ Hz), 7.25-7.22 (m, 2H), 7.17 (d, $J = 7.8$ Hz, 1H), 7.11 (dd, $J = 7.8, 1.3$ Hz, 1H), 2.36 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.1, 149.2, 140.2, 135.9, 135.3, 132.4, 130.6, 130.2, 128.9, 124.1, 121.5, 20.9, 19.7; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{14}\text{N}$ $[\text{M} + \text{H}]^+$ 184.1126, found 184.1125.

2-(2-Methyl-5-(trifluoromethyl)phenyl)pyridine (4b):⁵⁰ Colorless oil (15.6 mg, 33%; hexane/EtOAc = 10/1). R_f 0.23 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.72 (ddd, $J = 4.8, 1.7, 1.0$ Hz, 1H), 7.79 (td, $J = 7.7, 1.8$ Hz, 1H), 7.66 (s, 1H), 7.55 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.43-7.39 (m, 2H), 7.30 (ddd, $J = 7.6, 4.9, 1.1$ Hz), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.6, 149.5, 140.9, 140.1, 136.4,

131.2, 128.4 (q, $^2J_{\text{C-F}} = 32.4$ Hz), 126.5 (q, $^3J_{\text{C-F}} = 3.7$ Hz), 124.9 (q, $^3J_{\text{C-F}} = 3.7$ Hz), 124.2 (q, $^1J_{\text{C-F}} = 270.3$ Hz), 124.0, 122.2, 20.3; ^{19}F NMR (400 MHz, CDCl_3): δ -62.3; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{11}\text{NF}_3$ $[\text{M} + \text{H}]^+$ 238.0844, found 238.0847.

2-(3-Methylnaphthalen-2-yl)pyridine (4c):¹⁶ White solid (28.2 mg, 64%; eluent: hexane/EtOAc = 10/1). R_f 0.21 (hexane/EtOAc = 10/1); m.p. 69.0-71.8 °C; ^1H NMR (500 MHz, CDCl_3): δ 8.74 (ddd, $J = 4.9, 1.5, 0.9$ Hz), 7.87 (s, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.80-7.77 (m, 2H), 7.74 (s, 1H), 7.51-7.42 (m, 3H), 7.29 (ddd, $J = 7.5, 4.9, 1.0$ Hz), 2.51 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.0, 149.2, 139.4, 136.2, 133.8, 133.4, 131.9, 128.8, 128.7, 127.9, 126.9, 126.3, 125.4, 124.2, 121.7, 20.8; HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{14}\text{N}$ $[\text{M} + \text{H}]^+$ 220.1126, found 220.1121.

2-(2-Methylnaphthalen-1-yl)pyridine (4d):⁵¹ Light yellow solid (27.3 mg, 62%; eluent: hexane/EtOAc = 10/1). R_f 0.42 (hexane/EtOAc = 3/1); m.p. 81.5-84.5 °C; ^1H NMR (300 MHz, CDCl_3): δ 8.82 (d, $J = 4.7$ Hz, 1H), 7.87-7.80 (m, 3H), 7.43-7.28 (m, 6H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 159.0, 149.8, 136.7, 136.2, 133.4, 132.4, 132.0, 128.7, 128.1, 127.8, 126.1, 125.6, 125.3, 124.8, 121.9, 20.2; HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{14}\text{N}$ $[\text{M} + \text{H}]^+$ 220.1126, found 220.1126.

2-(*o*-Tolyl)pyridine (4e)^{41c} and 2-(2,6-dimethylphenyl)pyridine (4f):⁵² Silica gel chromatography (eluent: hexane/EtOAc = 15/1) of the crude product afforded the title compounds **4e** (12.4 mg, 37%) and **4f** (12.2 mg, 33%) as colorless oils.

4e: R_f 0.49 (hexane/EtOAc = 3/1); ^1H NMR (300 MHz, CDCl_3): δ 8.70 (ddd, $J = 4.9$, 1.7, 0.9 Hz, 1H), 7.74 (td, $J = 7.7$, 1.8 Hz, 1H), 7.41-7.38 (m, 2H), 7.31-7.22 (m, 4H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.1, 149.2, 140.4, 136.1, 135.7, 130.7, 129.6, 128.2, 125.8, 124.1, 121.6, 20.2; HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_{12}\text{N}$ [$\text{M} + \text{H}$]⁺ 170.0970, found 170.0965.

4f: R_f 0.46 (hexane/EtOAc = 3/1); ^1H NMR (300 MHz, CDCl_3): δ 8.72 (d, $J = 4.6$ Hz, 1H), 7.76 (td, $J = 7.6$, 1.2 Hz, 1H), 7.28-7.17 (m, 3H), 7.10 (d, $J = 7.4$ Hz, 2H), 2.04 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 159.9, 149.7, 140.5, 136.2, 135.7, 127.8, 127.5, 124.4, 121.6, 20.1; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{14}\text{N}$ [$\text{M} + \text{H}$]⁺ 184.1126, found 184.1134.

2-(2,6-Dimethylphenyl)pyridine (4f): Colorless oil (22.0 mg, 60%; eluent: hexane/EtOAc = 10/1; prepared from **4e** using the typical procedure).

2-(3-Fluoro-2,6-dimethylphenyl)pyridine (4g): Colorless oil (23.0 mg, 57%; eluent: hexane/EtOAc = 15/1). R_f 0.19 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.73 (ddd, J = 4.9, 1.6, 0.9 Hz, 1H), 7.78 (td, J = 7.7, 1.8 Hz, 1H), 7.28 (ddd, J = 7.6, 5.0, 1.1 Hz, 1H), 7.21 (dt, J = 7.8, 1.0 Hz, 1H), 7.05 (dd, J = 8.3, 5.6 Hz, 1H), 6.96 (t, J = 8.9 Hz, 1H), 2.00 (s, 3H), 1.95 (d, J = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 159.7 (d, $^1J_{\text{C-F}}$ = 240.4 Hz), 158.8 (d, $^4J_{\text{C-F}}$ = 3.0 Hz), 149.8, 142.1 (d, $^3J_{\text{C-F}}$ = 4.3 Hz), 136.4, 131.2 (d, $^4J_{\text{C-F}}$ = 3.6 Hz), 128.2 (d, $^3J_{\text{C-F}}$ = 8.3 Hz), 124.4, 123.0 (d, $^2J_{\text{C-F}}$ = 16.8 Hz), 122.0, 114.3 (d, $^2J_{\text{C-F}}$ = 22.7 Hz), 19.6, 11.9 (d, $^3J_{\text{C-F}}$ = 4.6 Hz); ^{19}F NMR (300 MHz, CDCl_3): δ -120.5; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{13}\text{NF}$ $[\text{M} + \text{H}]^+$ 202.1032, found 202.1028.

2-(4-Methoxy-2-methylphenyl)-3-methylpyridine (4h): Light yellow oil (25.6 mg, 60%; eluent: hexane/EtOAc = 5/1). R_f 0.29 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 8.50-8.48 (m, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.17 (dd, J = 7.6, 4.8 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 8.82-6.78 (m, 2H), 3.83 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 159.4, 159.1, 146.6, 137.6, 137.1, 133.0, 131.8, 129.6, 122.0, 115.5, 111.0, 55.2, 19.6, 19.1; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{16}\text{NO}$ $[\text{M} + \text{H}]^+$ 214.1232, found 214.1229.

2-(2,6-Dimethylphenyl)pyrimidine (4i):⁴⁹ Light yellow oil (27.7 mg, 75%; eluent: hexane/EtOAc = 5/1; prepared according to the typical procedure using 4 equiv of methyl tosylate and 5.3 equiv of *t*-BuCH₂MgBr). *R_f* 0.29 (hexane/EtOAc = 3/1); ¹H NMR (500 MHz, CDCl₃): δ 8.88 (d, *J* = 4.9 Hz, 2H), 7.27 (t, *J* = 5.0 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 2H), 2.08 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 168.5, 157.1, 139.0, 135.3, 128.4, 127.6, 118.8, 19.8; HRMS (ESI) Calcd for C₁₂H₁₃N₂ [M + H]⁺ 185.1079, found 185.1083.

2-(3-Methylthiophen-2-yl)pyridine (4j): Light yellow oil (10.5 mg, 30%; eluent: hexane/EtOAc = 50/1; prepared according to the typical procedure using 4 equiv of methyl tosylate and 5.3 equiv of *t*-BuCH₂MgBr). *R_f* 0.32 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.63 (d, *J* = 4.5 Hz, 1H), 7.71 (td, *J* = 7.8, 1.6 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 5.0 Hz, 1H), 7.15 (dd, *J* = 6.9, 5.1 Hz, 1H), 6.93 (d, *J* = 5.0 Hz, 1H), 2.51 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 153.5, 149.6, 138.1, 136.4, 135.3, 132.1, 125.6, 121.3, 121.2, 16.1; HRMS (ESI) Calcd for C₁₀H₁₀NS [M + H]⁺ 176.0534, found 176.0537.

2-Methyl-1-(pyridin-2-yl)-1H-indole (4k):⁴⁹ Colorless oil (28.3 mg, 68%; eluent: hexane/EtOAc = 20/1). *R_f* 0.28 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃):

δ 8.67 (ddd, $J = 4.9, 1.9, 0.7$ Hz, 1H), 7.89 (td, $J = 7.7, 1.9$ Hz, 1H), 7.57-7.53 (m, 1H), 7.43 (dt, $J = 8.0, 0.8$ Hz, 1H), 7.39-7.35 (m, 1H), 7.32 (ddd, $J = 7.5, 4.9, 1.0$ Hz, 1H), 7.15-7.10 (m, 2H), 6.42 (t, $J = 1.0$ Hz, 1H), 2.47 (d, $J = 0.9$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 151.5, 149.5, 138.2, 137.1, 136.8, 128.7, 121.8, 121.5, 120.8, 120.6, 119.7, 110.2, 103.3, 14.0; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_2$ $[\text{M} + \text{H}]^+$ 209.1079, found 209.1072.

1-(2,5-Dimethylphenyl)-2,2-dimethylpropan-1-imine (4l): Colorless oil (20.6 mg, 54%; eluent: hexane/EtOAc/Et₃N = 100/10/1). R_f 0.17 (hexane/EtOAc/Et₃N = 100/10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.08 (d, $J = 7.8$ Hz, 1H), 7.02 (d, $J = 8.3$ Hz, 1H), 6.83 (s, 1H), 2.30 (s, 3H), 2.18 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 190.7, 141.7, 134.3, 130.5, 130.4, 128.3, 126.5, 40.6, 28.5, 20.9, 19.6; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{20}\text{N}$ $[\text{M} + \text{H}]^+$ 190.1596, found 190.1591.

***N*-(4-Methoxyphenyl)-1-(5-methyl-2-(methyl- d_3)phenyl)ethan-1-imine (2b- d_3):**

Prepared as described for **2b** using CD_3OTs . Silica gel chromatography (eluent: hexane/EtOAc/Et₃N = 100/2/1–100/5/1) of the crude product afforded the title compound as a light yellow oil (41.3 mg, 81%), which existed as a mixture of *E/Z* isomers. The ratio of the isomers was determined to be 61:39 by ^1H NMR integrations of characteristic signals at 3.82 and 3.69 ppm.

Major isomer: R_f 0.17 (hexane/EtOAc/Et₃N = 100/10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.18 (s, 1H), 7.12 (d, J = 7.7 Hz, 1H), 7.08 (dd, J = 7.7, 1.2 Hz, 1H), 6.94-6.90 (m, 2H), 6.82-6.78 (m, 2H), 3.82 (s, 3H), 2.35 (s, 3H), 2.15 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 169.2, 155.6, 144.2, 141.5, 134.6, 130.7, 129.9, 129.0, 127.8, 120.4, 114.4, 55.3, 29.1, 20.6, 18.5 (septet, J = 19.3 Hz).

Minor isomer: R_f 0.30 (hexane/EtOAc/Et₃N = 100/10/1); ¹H NMR (400 MHz, CDCl₃): δ 6.95-6.88 (m, 3H), 6.64-6.59 (m, 4H), 3.69 (s, 3H), 2.43 (s, 3H), 2.28 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 169.4, 155.3, 143.5, 139.2, 134.5, 131.4, 129.2, 128.7, 127.5, 121.7, 113.6, 55.0, 29.1, 20.9, ~18.5 (not obvious due to overlap).

HRMS (ESI) Calcd for C₁₇H₁₇D₃NO [M + H]⁺ 257.1733, found 257.1733.

1-(4,5-Dimethoxy-2-(methyl-*d*₃)phenyl)ethan-1-one (2e-*d*₃): White solid (25.4 mg, 64%; eluent: hexane/EtOAc = 5/1; prepared as described for **2e** using CD₃OTs). R_f 0.30 (hexane/EtOAc = 3/1); m.p. 73.0-75.9 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.25 (s, 1H), 6.70 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.55 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 199.5, 151.5, 146.2, 133.4, 129.4, 114.5, 113.2, 56.1, 55.8, 29.4, 21.0 (septet, J = 19.5 Hz); HRMS (ESI) Calcd for C₁₁H₁₂D₃O₃ [M + H]⁺ 198.1209, found 198.1209.

5-Methoxy-8-(methyl-*d*₃)-3,4-dihydronaphthalen-1(2H)-one (2i-*d*₃): Light yellow

oil (31.1 mg, 81%; eluent: hexane/EtOAc = 30/1; prepared as described for **2i** using CD₃OTs). *R_f* 0.38 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.04 (d, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 3.84 (s, 3H), 2.90 (t, *J* = 6.2 Hz, 2H), 2.62 (t, *J* = 6.6 Hz, 2H), 2.07 (quintet, *J* = 6.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 200.6, 154.8, 134.2, 132.2, 131.9, 130.0, 113.7, 55.7, 40.8, 23.5, 22.4, 21.7 (septet, *J* = 19.2 Hz, partially overlapped); HRMS (ESI) Calcd for C₁₂H₁₂D₃O₂ [M + H]⁺ 194.1260, found 194.1256.

(*E*)-*N*-(4-methoxyphenyl)-1-(1-methyl-2-(methyl-*d*₃)-1*H*-indol-3-yl)methanimine

(2q-*d*₃**):** Prepared as described for **2q** using CD₃OTs. Silica gel chromatography (eluent: hexane/EtOAc/Et₃N = 90/30/1) of the crude product afforded the title compound as a mixture with minor amount of anisidine as a light yellow solid (30.6 mg). The yield was determined to be 53% based on the total weight and the ¹H NMR analysis of the mixture.

R_f 0.31 (hexane/EtOAc = 3/1); ¹H NMR (500 MHz, CDCl₃): δ 8.72 (s, 1H), 8.51-8.48 (m, 1H), 7.31-7.24 (m, 3H), 7.23-7.20 (m, 2H), 6.95-6.92 (m, 2H), 3.84 (s, 3H), 3.72 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 157.1, 152.9, 147.4, 142.0, 137.2, 125.9, 122.2, 121.8, 121.6, 121.4, 114.3, 111.4, 108.7, 55.5, 29.6, 9.9 (septet, *J* = 19.7 Hz); HRMS (ESI) Calcd for C₁₈H₁₆D₃N₂O [M + H]⁺ 282.1686, found 282.1682.

2-(5-Methyl-2-(methyl-*d*₃)phenyl)pyridine (4a-*d*₃): Colorless oil (25.5 mg, 68%; eluent: hexane/EtOAc = 10/1; prepared as described for **4a** using CD₃OTs). *R_f* 0.23 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.69 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.73 (td, *J* = 7.7, 1.8 Hz, 1H), 7.39 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.25-7.22 (m, 2H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.11 (dd, *J* = 7.8, 1.2 Hz, 1H), 2.36 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 160.1, 149.2, 140.3, 135.9, 135.3, 132.3, 130.6, 130.2, 128.9, 124.1, 121.5, 20.9, 19.0 (septet, *J* = 19.3 Hz); HRMS (ESI) Calcd for C₁₃H₁₁D₃N [M + H]⁺ 187.1315, found 187.1312.

2-(Methyl-*d*₃)-1-(pyridin-2-yl)-1*H*-indole (4k-*d*₃): Colorless oil (27.2 mg, 64%; eluent: hexane/EtOAc = 20/1; prepared as described for **4k** using CD₃OTs). *R_f* 0.23 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.66 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.89 (td, *J* = 7.7, 1.9 Hz, 1H), 7.57-7.53 (m, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.40-7.36 (m, 1H), 7.31 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.14-7.10 (m, 2H), 6.42 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 151.5, 149.5, 138.1, 137.1, 136.7, 128.7, 121.8, 121.5, 120.7, 120.6, 119.7, 110.2, 103.3, 13.2 (septet, *J* = 19.5 Hz); HRMS (ESI) Calcd for C₁₄H₁₀D₃N₂ [M + H]⁺ 212.1267, found 212.1273.

Control Experiments

Reaction of methyl tosylate with *t*-BuCH₂MgBr (Scheme 4.15a): Methyl tosylate (37 mg, 0.20 mmol) and THF (0.79 mL) were placed in a Schlenk tube. To the

mixture was added a THF solution of *t*-BuCH₂MgBr (0.96 M, 0.21 mL, 0.20 mmol). The resulting mixture was stirred at room temperature for 2 h. Then 1,1,2,2-tetrachloroethane (21.0 μ L, 0.20 mmol) was added, and the mixture was diluted with CDCl₃ (1 mL), followed by filtration through a short pad of Celite. A part (0.1 mL) of the filtrate was transferred to an NMR tube and further diluted with CDCl₃ (0.5 mL) to record ¹H NMR spectrum, which confirmed formation of methyl bromide (δ = 2.61 ppm) and disappearance of methyl tosylate. The rest was treated with sat. NH₄Cl (1 mL), and then subjected to GC analysis to again confirm full consumption of methyl tosylate. The same procedure was also applied to methyl mesylate and trimethyl phosphate, and ¹H NMR spectra of their reactions again indicated the formation of methyl bromide (δ = 2.52 and 2.51 ppm for the reactions of MeOMs and (MeO)₃PO, respectively).

Methylation of 1b in the presence of radical scavenger (Scheme 4.15b): The reaction of **1b** was performed on a 0.2 mmol scale according to the typical procedure, except that TEMPO (0.2 mmol, 1 equiv) was placed in the Schlenk tube together with the reactants and the catalysts. The quenched reaction mixture was analyzed by GC using *n*-tridecane as the internal standard to determine the yields of **2b** and **2b'**.

Competition between methyl tosylate and alkyl bromide (Scheme 4.15c): The reaction of **1b** was set up on a 0.2 mmol scale according to the typical procedure except for the following change: Instead of using 0.4 mmol (2 equiv) of methyl tosylate, 0.2 mmol (1 equiv) each of methyl tosylate and alkyl bromide (n -octyl bromide or cyclohexyl bromide) were placed in the Schlenk tube. The quenched reaction mixture was analyzed by GC using n -tridecane as the internal standard to determine the yields of **2b** and **2b-R**.

Competition between **1b and **1c** (Scheme 4.15d):** A mixture of **1b** and **1c** (0.2 mmol each) was subjected to methylation according to the typical procedure. The quenched reaction mixture was analyzed by GC using n -tridecane as the internal standard to determine the yields of the methylated products **2b** and **2c**.

Competition between 3a and 3b (Scheme 4.15e): A mixture of **3a** and **3b** (0.2 mmol each) was subjected to methylation according to the typical procedure. The quenched reaction mixture was analyzed by GC using *n*-tridecane as an internal standard to determine the yields of the methylated products **4a** and **4b**.

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Chapter 5 Conclusion

During the past four years, I mainly worked on the low-valent cobalt-catalyzed, directing group-assisted *ortho*-C–H alkylation of arenes via radical processes. With the assistance of cobalt–NHC catalysts and Grignard reagents, I have realized the *ortho*-C–H alkylation of aryl imines and 2-arylpyridines using various electrophiles such as 2-bromobenzyl-protected secondary amines, tethered bromo-alkenes and methyl tosylate (Scheme 5.1). These reactions commonly involve a radical species generated from the single electron transfer between a cobaltacycle species and the electrophile.

Scheme 5.1. Cobalt-catalyzed directed arene C–H alkylation via radical processes

In Chapter 2, I have developed a cobalt-catalyzed C(sp²)-H/C(sp³)-H coupling reaction between an aryl *N*-PMP imine and a secondary amine bearing *N*-(2-bromobenzyl) group (Scheme 5.1a). Promoted by a Co-SIPr-*sec*-BuMgBr system, the reaction allows for *ortho*- α -aminoalkylation of the imine under mild reaction conditions. The reaction features a merger of directed C-H activation and 1,5-hydrogen atom transfer. Moreover, the utility of the C(sp²)-H/C(sp³)-H coupling reaction has been demonstrated by a two-step synthesis of a spirocyclic compound from the alkylation product.

In Chapter 3, I have demonstrated a cobalt-catalyzed tandem radical cyclization/C-C coupling reaction between an NTs-tethered bromo-alkene and an aryl *N*-H imine (Scheme 5.1b). Promoted by a cobalt-NHC catalyst and a neopentyl Grignard reagent, the reaction allows for the introduction of a pyrrolidinylmethyl group to the *ortho* position of the imine. The reaction is considered to proceed via *N*-H imine-directed C-H activation, single electron transfer and 1,5-radical cyclization as key steps.

In Chapter 4, I have developed a cobalt-catalyzed *ortho*-methylation of arenes using methyl tosylate as a readily available and convenient methylation agent (Scheme 5.1c). A catalytic system comprised of Co(acac)₃, *N,N'*-di(2-butyl)benzimidazolium bromide, and neopentyl Grignard reagent promoted the methylation directed by different nitrogen directing groups such as *N*-aryl imine, *N*-H imine, and 2-pyridyl groups. Using CD₃OTs instead of MeOTs, the reaction also allows facile incorporation of a CD₃ group into arenes. Mechanistic studies demonstrate that methyl bromide is the actual methylating agent in the methylation reaction and a SET mechanism is responsible for the activation of MeBr.

Overall, this thesis research has led to significant advancement in directed *ortho*-

C–H alkylation of arenes using earth-abundant cobalt catalysts. Several modified cobalt–NHC–Grignard systems have been formulated to promote the desired alkylation reactions. Notably, I have demonstrated that cobalt-catalyzed directed arene C–H activation can be integrated with either a 1,5-HAT or a radical cyclization process in a single catalytic cycle to achieve novel C(sp²)–C(sp³) bond-forming reactions.

In light of the robustness of the cobalt–NHC–Grignard systems in the cobalt-catalyzed arene C–H alkylation reactions, future work could be focused on other types of cobalt-catalyzed C–H functionalizations such as allylation and propargylation. A SET process between the cobaltacycle and corresponding electrophiles can also be expected. Furthermore, inspired by the cobalt-catalyzed two-component alkylarylation of alkenes discussed in Chapter 3, future work could be focused on exploring more challenging three-component alkylarylation of alkenes with alkyl halides and aryl Grignard reagents. As shown in Scheme 5.1, a catalytic cycle involving SET, radical addition, radical rebound, transmetalation and reductive elimination can be proposed.

Scheme 5.1. Cobalt-catalyzed alkylarylation of alkenes with alkyl halides and aryl Grignard reagents

Proposed mechanism: