COBALT-CATALYZED CHELATION-ASSISTED C–C BOND FORMATION *via* C–H BOND ACTIVATION GAO KE 2013

NANYANG TECHNOLOGICAL UNIVERSITY

COBALT-CATALYZED CHELATION-ASSISTED C–C BOND FORMATION *via* C–H BOND ACTIVATION

GAO KE

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2013

COBALT-CATALYZED CHELATION-ASSISTED C–C BOND FORMATION *via* C–H BOND ACTIVATION

GAO KE

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

A thesis submitted to the Nanyang Technological University

in partial fulfillment of the requirement for the degree of

Doctor of Philosophy

2013

Acknowledgements

I would like to express my deep gratitude to Nanyang Assistant Professor Naohiko Yoshikai, my research supervisor, for his patient guidance, enthusiastic encouragement and useful critiques of my four years' research work.

I would like to thank Mr. Pin-Sheng Lee, Dr. Fujita Takeshi and Mr. Chong Long, who made great contributions to the cobalt-catalyzed alkenylation reaction and arylation reaction.

I wish to extend my thanks to all of Dr. Yoshikai's group members for their help and friendship over the four years.

I would like to thank Ms. Ee-Ling Goh in the NMR laboratory, Ms. Wen-Wei Zhu in the GC and Mass spectrometry laboratory, and all the other support staffs at CBC.

I also would like to thank Nanyang Technological University for providing me the research scholarship.

Finally, I would like to extend my gratitude to my family for their unfailing support. I also want to express my thanks to my wife, Mrs. Xiaoman Ma and daughter, Ms. Xinqi Gao for their love, understanding and encouragement over the past years.

TABLE OF CONTENTS

List of Abbreviations

δ	chemical shift (ppm)
°C	degree centigrade
Ac	acetyl
aq	aqueous
Ad	adamantyl
Ar	aryl (substituted aromatic ring)
*n*Bu	*n*-butyl
*t*Bu	*tert*-butyl
cod	1,5-cyclooctadiene
coe	cyclooctene
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
d	doublet
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
h	hour
H	hydrogen
HRMS	High Resolution Mass Spectrometry
Hz	hertz
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
J	coupling constants
m	multiplet
M	concentration (mol/L)

M^+	parent ion peak (mass spectrum)
Me	methyl
mg	milligram
MHz	megahertz
min	minute(s)
mL	milliliter
mmol	millimole
mol %	mole percent
m.p.	melting point
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Ph	phenyl
Phen	1,10-phenanthroline
PMP/*p*-An	*p*-methoxyphenyl
ppm	parts per million
*i*Pr	isopropyl
q	quartet
rt	room temperature
s	singlet
sat	saturated
t	triplet
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
p-TsOH	*p*-toluenesulfonic acid

Abstract

During the past decades, transition metal-catalyzed chelation-assisted C–H bond functionalization has been developed as an efficient and regioselective synthetic strategy. While this chemistry has met with significant success with expensive second-row transition metals, catalysis with cheaper first-row transition metals could lead to the development of cost-effective alternative catalysts as well as the discovery of new reactions.

This thesis describes the development of cobalt-based catalysts for chelation-assisted C–H bond functionalization reactions. A serials of C–C bond forming reactions, including alkenylation, alkylation, and arylation, have been achieved on aromatic substrates bearing pyridine or imine directing groups. The cobalt catalysts not only serve as mild and less expensive alternatives to noble metal catalysts for existing reactions, but also show unique reactivities and selectivities and thus enable transformations that were previously difficult to achieve.

Chapter 1. Introduction

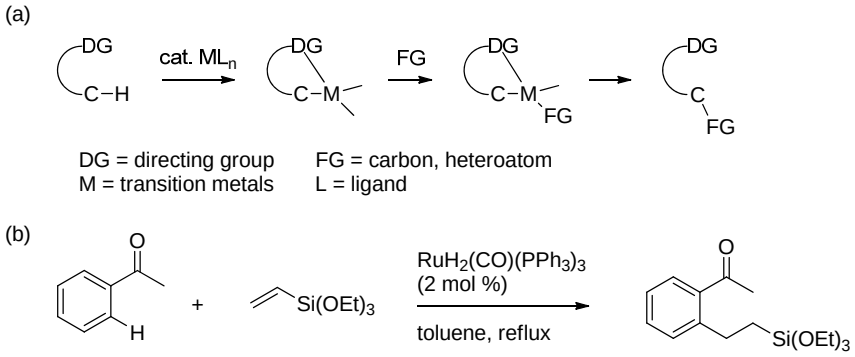
1.1 Development of chelation-assisted C–H bond functionalization: from second-row to first-row transition metals

The development of efficient and selective methods for the synthesis of bulk and fine chemicals with minimal environmental impact represents a fundamentally important challenge in the field of synthesis and catalysis. In this respect, synthetic chemists are now fully aware of the power and potential of so-called C–H functionalization reactions, which allow direct conversion of ubiquitous carbon–hydrogen bonds into new carbon–carbon or carbon–heteroatom bonds. This common perception has developed throughout significant developments of a variety of preparatively useful catalytic C–H bond functionalization methods and their applications in target-oriented chemical synthesis, which have been made possible over the past few decades.[1]

To achieve C–H bond functionalization in a practically useful manner, issues regarding reactivity and selectivity need to be addressed. Thus, a catalyst or a reagent must be reactive enough to cleave an inert C–H bond, and also selective toward a specific C–H bond among others in the reactant. One of the most effective and well-practiced approaches to address reigoselectivity is the use of a heteroatom directing group. With the coordination of a suitable heteroatom functional group, a transition metal catalyst is capable of cleaving the proximal C–H bond, a process called cyclometalation or chelation-assisted C–H activation. The resulting metalacycle intermediate could thus be transformed into a C–H functionalization product through carbon–carbon or carbon–heteroatom bond formation (Scheme 1.1a). One of the earliest and most successful implementations of this concept was reported by Murai group in 1993, who developed a ruthenium-catalyzed *ortho*-alkylation reaction of aromatic ketones with olefins (Scheme 1.1b).[2] Following this breakthrough, a number of catalytic systems have been developed for chelation-assisted C–H bond

functionalization reactions including alkylation,[1b,d,f,3,4] alkenylation,[1d,f,5] arylation[1g,f,6] and many other carbon–carbon and carbon–heteroatom bond formations.[1e,g,7]

Scheme 1.1. Transition Metal-Catalyzed Chelation-Assisted C–C/C–X Bond Formation *via* C–H Bond Activation



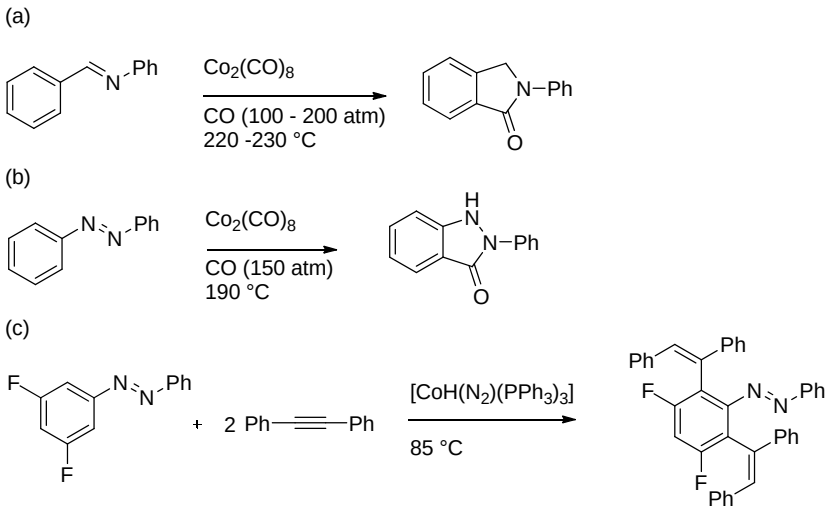
Despite the significant progress, the majority of catalytic systems developed thus far have been based on noble transition metals, e.g., ruthenium, rhodium, and palladium in particular.[1d,f,8] In contrast, the first-row transition metals have been rather underutilized regardless of their low cost and the fact that most of them have been used for stoichiometric cyclometalation.[9] Indeed, until 2010, only a limited number of examples have been known for chelation-assisted C–H functionalization using first-row transition metal catalysts.[10] Besides cobalt catalysis, representative examples include manganese-catalyzed addition of 2-arylimidazoles to aldehydes by Kuninobu and Takai[10a] and iron-catalyzed oxidative arylation of 2-arylpyridines and aryl imines with arylzinc reagents by Nakamura.[10b,c]

With this background in mind, we asked ourselves two questions: First, is it possible to emulate the known reactivity of a noble metal catalyst using a first-row metal to achieve a similar C–H functionalization reaction? Second, is it possible to find new reactivity and selectivity of a first-row metal and thus achieve a C–H functionalization reaction that has been unknown or difficult with noble metal catalysts? In addressing these questions, we became interested in the potential of cobalt catalysts because of the reasons discussed in the next section.

1.2 Catalytic and stoichiometric C–H activation by cobalt complexes

To the best of our knowledge, cobalt was the first metal to be used in chelation-assisted C–H bond functionalization. In 1950s, Murahashi reported on *ortho*-carbonylation reactions of Schiff base and azobenzene using $Co_2(CO)_8$ under high pressure of CO, affording phthalimidine and indazolone derivatives (Scheme 1.2a,b).[11a] This seminal study, however, was followed by only sporadical reports in the following decades. In 1994, Kisch and coworkers reported $CoH(N_2)(PPh_3)_3$ catalyzed alkenylation reaction of an azobenzene with diphenylacetylene to afford a *trans*-addition product (Scheme 1.2c).[12] In addition, in 1997, Brookhart reported that a Cp*Co(I) complex activates simple benzene C–H bonds and thus promotes H/D exchange between pentadeuteriobenzene and ethylene, and catalyzes hydroacylation of olefins with aromatic and aliphatic aldehydes.[13a] The same complex was demonstrated to catalyze a hydroacylation reaction of olefins.[13b,c]

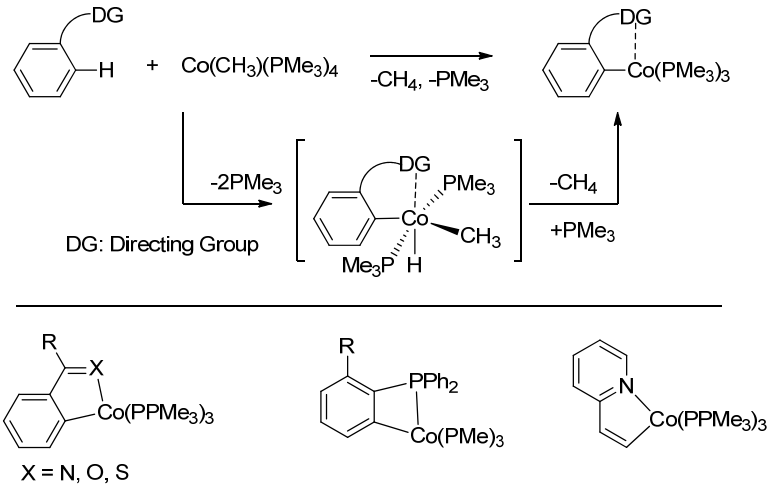
Scheme 1.2. Cobalt-Catalyzed Directed C–H Bond Functionalization



Besides the catalytic examples above, a series of studies have been performed on stoichiometric cyclometalation using well-defined cobalt complexes. In 1993, Klein and coworkers reported a methylcobalt(I)–phosphine complex $MeCo(PMe_3)_4$ underwent cyclometalation of azobenzene under mid conditions.[14a] The mechanism of the reaction has

not been clarified yet, but it is proposed to involve oxidative addition of the *ortho* C–H bond to the cobalt(I) center, followed by C–H reductive elimination of methane. The same cobalt complex has been demonstrated to undergo cyclometalation of some aromatic and olefin substrates bearing nitrogen, oxygen, sulfur, and phosphorus directing groups (Scheme 1.3).[14] However, none of these stoichiometric cyclometalation reactions have been exploited in a catalytic manner.

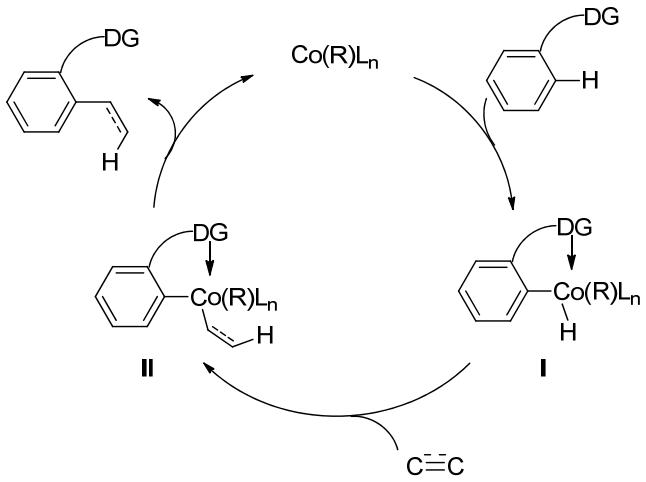
Scheme 1.3. Cyclometalation of Methylcobalt(I) Complex



1.3 Design and summary of thesis research

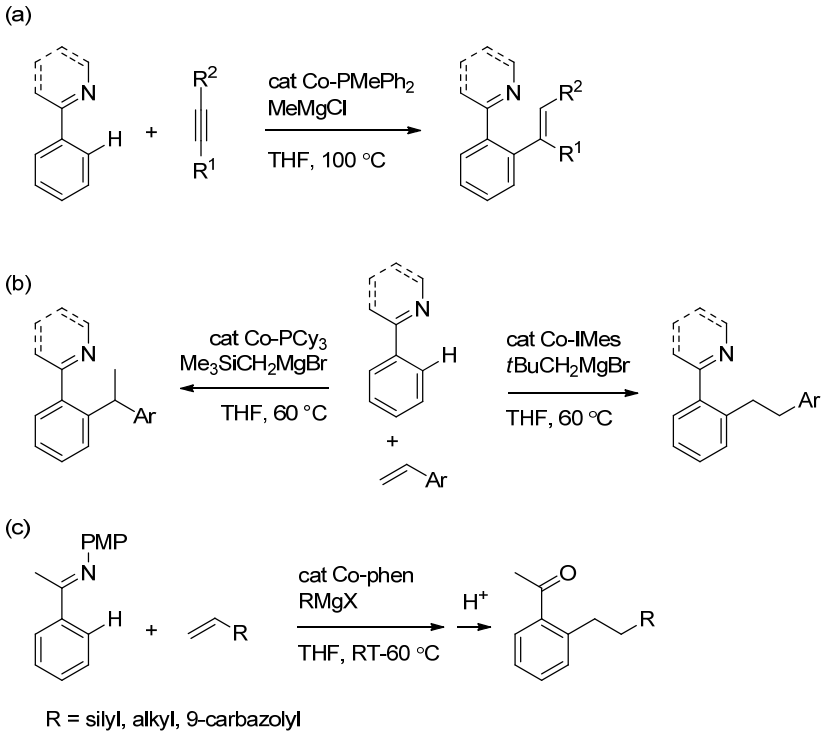
With the aforementioned background in mind, we conjectured the potential use of cobalt complexes for catalytic C–H bond functionalization. In particular, the stoichiometric cyclometalation reactions of the methylcobalt(I)–phosphine complex reported by Klein and coworkers attracted our attention. Thus, we envisaged that cobalt complexes bearing appropriate alkyl groups and phosphine ligands could serve as competent catalysts for chelation-assisted C-H bond functionalization (Scheme 1.4). We propose that alkylcobalt species would undergo oxidative addition of *ortho* C–H bond to generate intermediate **I**, followed by migratory insertion of unsaturated molecules into Co–H bond. Reductive elimination of intermediate **II** gives the product and regenerates of the alkylcobalt species.

Scheme 1.4. Proposed Mechanism I



With this proposed mechanism, we embarked on a series of research projects on cobalt-catalyzed, chelation-assisted addition of C–H bonds to C–C multiple bonds, which will be discussed in detail in the following chapters. In Chapter 2, we report that a Co–$PMePh_2$ catalyst, in combination with MeMgCl, promoted alkenylation reaction of 2-arylpyridine derivatives with internal alkynes (Scheme 1.5a). Following this initial discovery, we extended the cobalt catalysis to chelation-assisted hydroarylation to olefins. In Chapter 3, we report a cobalt-catalyzed addition reaction of 2-arylpyridines to styrene derivatives, where the regioselectivity of C–C bond formation can be controlled by choice of the supporting ligands (Scheme 1.5b). In Chapter 4, we describe an *ortho*-alkylation reaction of aromatic ketimines with vinylsilanes and simple olefins using a cobalt–phenanthroline catalyst (Scheme 1.5c).

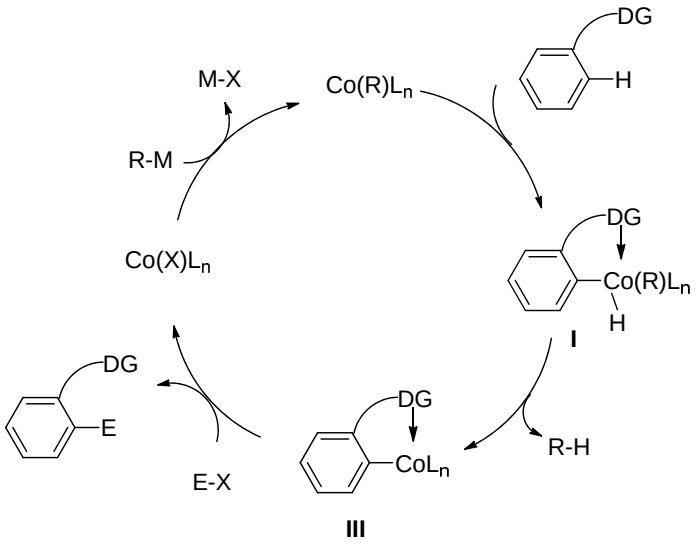
Scheme 1.5. Cobalt-Catalyzed Addition of 2-Phenylpyridine and Ketimines to Unsaturated Compounds



Beside the unsaturated molecular as coupling partners, we are interested whether electrophiles could be coupling partners for cobalt-catalyzed C–H bond functionalization. Cobalt-catalyzed cross-coupling of aryl metallic reagents with aryl and alkyl halides have been well developed.[15] For example: In 2003, Knochel reported cobalt-catalyzed cross-coupling between heteroaryl chlorides with aromatic Grignard reagents.[16] One year later, Oshima reported a similar reaction in the present of $Co(acac)_2$.[17] In 2009, Nakamura and coworker reported a cobalt-catalzyed cross-coupling reaction between aryl and heteroaryl halides with aromatic Grignard reagents.[18] In 2006, Oshima and coworker reported cobalt-catalyzed the cross-coupling between primary alkyl haldies with aromatic Grignard reagents.[19] Later on, Cahiez and coworkers reported cobalt-catalyzed cross-coupling reaction between primary and secondary alkyl bromides with aromatic Grignard reagents.[20]

Based on aforementioned background, we formulated another possible catalytic cycle for cobalt-catalyzed chelation-assisted C–H bond functionalization with electrophiles (Scheme 1.6). Cyclometalation of an aromatic substrate with an organocobalt species may generate a cobaltacycle **III** while liberating a hydrocarbon byproduct R–H. The intermediate **III** may then be intercepted by an electrophile (E–X) to afford an *ortho*-functionalized product and a cobalt salt species. Transmetalation of the cobalt salt species with an organometallic reagent would regenerate the organocobalt species.

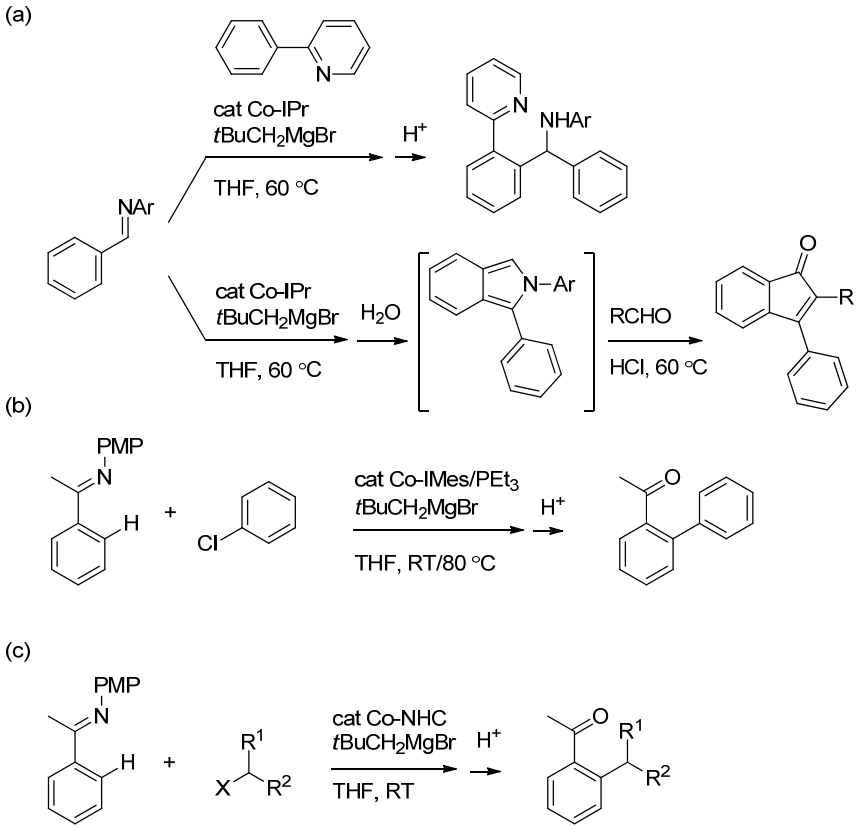
Scheme 1.6. Proposed Mechanism II



Along with this hypothesis, we have developed a series of cobalt-catalyzed *ortho* C–H functionalization reactions using electrophilic reactants. In Chapter 5, we report a Co-IPr catalyst, in combination with *t*BuCH$_2$MgBr, promoted addition reaction of 2-arylpyridines to *N*-aryl aldimines (Scheme 1.7a). The same catalytic system allowed the self-coupling reaction of an aldimine to afford an isoindole derivative, which is further reacted with an aldehyde to afford an indenone product (Scheme 1.7b). In Chapter 6, we describe an *ortho*-arylation reaction of aromatic imines with aryl chlorides using the Co–IMes and Co–PEt$_3$ catalytic systems. In Chapter 7, we report a Co–NHC-catalyzed *ortho*-

alkylation of aromatic imines with primary and secondary alkyl chlorides and bromides at room temperature (Scheme 1.7c).

Scheme 1.7. Cobalt-Catalyzed Directing-Assisted C–H Bond Functionalization of 2-Phenylpyridines and Imines



Throughout our research in the last four years, cobalt has emerged as a promising metal for catalytic C–H bond functionalization reactions. The cobalt/ligand/Grignard ternary catalytic systems not only served as competent catalysts for known C–H bond functionalization reactions catalyzed by second-row transition metal complexes, but also led us to discover some unprecedented phenomena, i.e., ligand-controlled regioselectivity switching and alkylation of secondary alkyl halides.

1.4 References

(1) For recent reviews, see: (a) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960-9009. (b) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (c) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45,* 814. (d) Colby, D. A.; Bergmann, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (e) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (f) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.

(2) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

(3) For selected examples of chelation-assisted alkylation reactions with olefins, see: (a) Jun, C.-H.; Hong, J.-B.; Kim, Y.-H.; Chung, K.-Y. *Angew. Chem. Int. Ed.* **2000**, *39*, 3440. (b) Lim, S.-G.; Ahn, J.-A.; Jun, C.-H. *Org. Lett.* **2004**, *6*, 4687. (c) Martinez, R.; Chevalier, R.; Darses, S.; Genet, J.-P. *Angew. Chem. Int. Ed.* **2006**, *45*, 8232. (d) Martinez, R.; Simon, M.-O.; Chevalier, R.; Pautigny, C.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2009**, *131*, 7887. (e) Kakiuchi, F.; Kochi, T.; Mizushima, E.; Murai, S. *J. Am. Chem. Soc.* **2010**, *132*, 17741.

(4) For selected examples of chelation-assisted alkylation reactions with alkyl haldies, see: (a) Ackerman, L. *Chem. Commun.* **2010**, *46*, 4866. (b) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 6097. (c) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6045. (d) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 6629. (e) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.

(5) For selected examples of chelation-assisted alkenylation reactions, see: (a) Satoh, T.; Nishinaka, Y.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 615. (b) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379. (c) Pham, M. V.; Ye, B. H.; Cramer, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 10610. (d) Ackermann, L. *Acc. Chem. Rev.* **2013**, 10.1021/ar3002798.

(6) For selected examples of chelation-assisted arylation reactions, see: (a) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579. (b) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 112. (c) Ackermann, L.;

Althammer, A.; Born, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 2619. (d) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (e) Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem. Int. Ed.* **2008**, *47*, 9462.

(7) (a) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, 886. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(8) For iridium-catalyzed reactions, see: (a) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Org. Lett.* **2009**, *11*, 1821. (b) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556. (c) Satoh, T.; Nishinaka, Y.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 615.

(9) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087.

(10) (a) Kuninobu, Y.; Nishina, Y.; Takeuchi, T.; Takai, K. *Angew. Chem. Int. Ed.* **2007**, *46,* 6518. (b) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858. (c) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925.

(11) (a) Murahashi, S. *J. Am. Chem. Soc.* **1955**, *77*, 6403. (b) Murahashi, S.; Horiie, S. *J. Am. Chem. Soc.* **1956**, *78*, 4816.

(12) (a) Halbritter, G.; Knoch, F.; Wolski, A.; Kisch, H. *Angew. Chem. Int. Ed.* **1994**, *33*, 1603. (b) Halbritter, G.; Knoch, F.; Kisch, H. *J. Organomet. Chem.* **1995**, *492,* 87. (c) Dürr. U.; Kisch, H. *Synlett* **1997**, 1335.

(13) For C–H addition to olefins/alkynes without chelation assistance, see: (a) Lenges, C. P.; Brookhart, M.; Grant, B. E. *J. Organomet. Chem.* **1997**, *528*, 199. (b) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 3165. (c) Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 6965.

(14) (a) Klein, H.-F.; Helwig, M.; Koch, U.; Floerke, U.; Haupt, H.-J. *Naturforsh*. **1993**, *48b*, 778. (b) Klein, H.-F.; Lemke, U.; Lemke, M.; Brand, A. *Organometallics* **1998**, *17*, 4196. (c) Klein, H.-F.; Beck, R.; Flörke, U.; Haupt, H.-J. *Eur. J. Inorg. Chem.* **2003**, 853. (d) Klein, H.-F.; Camadanli, S.; Beck, R.; Leukel, D.; Flörke, U. *Angew. Chem. Int. Ed.* **2005**, *44*, 975. (e) Beck, R.; Frey, M.; Camadanli, S.; Klein, H.-F. *Dalton Trans.* **2008**, 4981. (f) Camadanli, S.; Beck, R.; Flörke, U.; Klein, H.-F. *Dalton Trans.* **2008**, 5701. (g) Beck, R.; Sun, H. J.; Li, X. Y.; Camadanli, S.; Klein, H.-F. *Eur. J. Inorg. Chem.* **2008**, 3253.

(15) (a) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435. (b) Gosmini, C.; Bégouin, J.-M.; Moncomble, A. *Chem. Commun.*, **2008**, 3221.

(16) Korn, T. J.; Cahiez, G.; Knochel, P. *Synlett* **2003**, *12*, 1892.

(17) Ohmiya, H.; Yorimitu, H.; Oshima, K. *Chem. Lett.* **2004**, *33*, 1240.

(18) Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 11949.

(19) Ohmiya, H.; Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 2207.

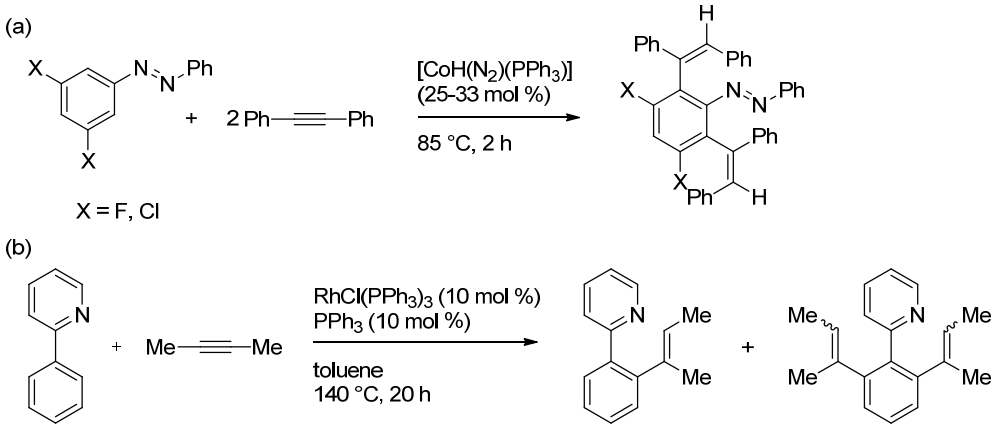
(20) Cahiez, G.; Chaboche, C.; Duplais, C.; Moyeux, A. *Org. Lett.* **2009**, *11*, 277.

Chapter 2. Cobalt-Catalyzed Alkenylation of 2-Arylpyridines with Alkynes

2.1 Introduction

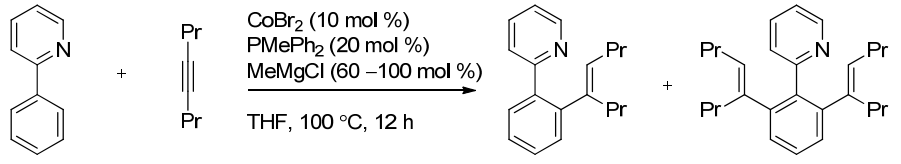
Over the past decades, transition metal-catalyzed C–C bond formation *via* chelation-assisted C–H bond activation has emerged as a powerful strategy for organic synthesis.[1] Among these reactions, addition of an aromatic C–H bond across a C–C triple bond represents a straightforward and atom-economical method for the C–H alkenylation. In 1994, Kisch and coworkers reported a pioneering work on cobalt-catalyzed *ortho*-alkenylation with an internal alkyne (Scheme 2.1a).[2] In the presence of [$CoH(N_2)(PPh_3)$], an azobenzene derivative reacted with diphenylacetylene to afford a dialkenylation product in a *trans*-addition manner. This seminal study, however, has not been followed by further investigation. In the meantime, second-row transition metals such as ruthenium and rhodium emerged as suitable catalysts for *ortho*-alkenylation reactions.[1a,e,h,3] In 2001, Lim and Kang reported a $RhCl(PPh_3)_3$-catalyzed alkenylation reaction of 2-arylpyridine derivatives with internal alkynes at 140 °C (Scheme 2.1b).[3a] The scope of the rhodium catalysis was further extended to aryl imines by Jun and coworkers.[3b] Compared to costly second-row transition metals, first-row transition metals, regardless of their ready availability,[4] have been used only sporadically in the chelation-assisted C–H alkenylation and other types of C–H functionalization reactions.[2,5,6]

Scheme 2.1. Cobalt- and Rhodium-Catalyzed Chelation-Assisted Alkenylation of Arenes with Alkynes



As discussed in Chapter 1, Klein and coworkers reported cyclometalation reactions of a methylcobalt(I)-phosphine complex. With this and the afore-mentioned studies of Kisch,[7] we envisaged that cobalt complexes bearing appropriate alkyl groups and phosphine ligands could be competent catalysts for chelation-assisted C-H bond functionalization. With this idea in mind, we embarked on a research program on cobalt-catalyzed, chelation-assisted addition of C–H bonds across C–C triple bonds. In this chapter, we report a cobalt-catalyzed addition reaction of 2-arylpyridine derivatives to unactivated internal alkynes (Scheme 2.2), which affords trisubstituted olefins in high stereoselectivity through *cis*-addition of the *ortho* C–H bond across the C–C triple bond.

Scheme 2.2. Cobalt-Catalyzed *ortho*-Alkenylation of 2-Phenylpyridine with Internal Alkyne



1a **2a** (2.5 equiv) **3aa** 4% **4aa** 83%

2.2 Results and discussion

We chose 2-phenylpyridine (**1a**) and 4-octyne (**2a**) as model substrates for the optimization of reaction conditions. After screening several parameters such as cobalt precatalysts, ligands, and reducing agents, we found that a cobalt catalyst generated in situ from $CoBr_2$ (10 mol %), $PMePh_2$ (20 mol %), and MeMgCl (100 mol %) promoted the reaction at 100 °C in THF for 12 h to give a monoalkenylation product **3aa** and a dialkenylation product **4aa** in 4% and 83% yield, respectively (Scheme 2.2 and Table 2.1, entry 1). The *syn*-stereochemistry of the product was confirmed by nuclear Overhauser effect experiments. The reaction produced a trace amount of an *ortho*-methylation product as detected by GC and GC/MS. Notably, the amount of MeMgCl could be reduced to 60 mol % without significant decrease in the product yield after 12 h, while the rate of the reaction became slightly lower (entry 2). When the amount of MeMgCl was reduced to 50 mol %, the reaction became even more sluggish (entry 3). While it is well known that a low-valent cobalt complex catalyzes cyclotrimerization of alkynes,[8] only a trace amount of a cyclotrimerization product of **2a** was detected under the standard conditions.

Table 2.1. Cobalt-Catalyzed Reaction of 2-Phenylpyridine (**1a**) with 4-Octyne (**2a**)[a]

entry	Ligand	RMgX (mol %)	yield (%)[b]	
			3aa	**4aa**
1	$PMePh_2$	MeMgCl (100)	3[29](4)	77[45](83)
2	$PMePh_2$	MeMgCl (60)	4[45]	76[31]
3	$PMePh_2$	MeMgCl (50)	54	19
4	PMe_2Ph	MeMgCl (100)	45	34
5	PPh_3	MeMgCl (100)	36	0
6	PCy_3	MeMgCl (100)	2	0
7	$PMePh_2$	*n*BuMgBr (100)	41	20
8	$PMePh_2$	*i*PrMgBr (100)	29	36
9	$PMePh_2$	*t*BuMgCl (100)	19	0
10	$PMePh_2$	$(CH_3)_3CCH_2MgBr$ (100)	42	9
11	$PMePh_2$	*n*BuLi (100)	13	0
12	$PMePh_2$	Et_2Zn (100)	16	0

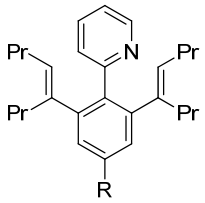
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (2.5 equiv), $CoBr_2$ (10 mol %), ligand (20 mol %), RMgX (100 mol %), THF, 100 ºC, 12h. [b] Determined by GC using *n*-tridecane as an internal standard. In brackets and parentheses are shown yields at 1 h and isolated yields, respectively.

Under otherwise identical conditions, other monophosphine ligands gave lower catalytic activities (entries 4-6). In the presence of PMe_2Ph, the reaction afforded products **3aa** and **4aa** in 45% and 34% yield, respectively (entry 4). PPh_3 was only moderately effective, affording the product **3aa** in 36% yield (entry 5). Bulky ligands such as PCy_3 afforded only a trace amount of **3aa** (entry 6). Bidentate phosphines (dppe, dppp, dppf, etc) completely shut down the reaction. As for the reducing agent, other alkyl Grignard reagents such as *n*-butyl, isopropyl, *t*-butyl, and neopentylmagnesium halides were much less effective (entries 7-10). When *n*-BuLi was used as a reducing agent, the monoalkenylation product **3aa** (13%) was accompanied by a large amount of an *ortho*-butylation product (ca. 40%) as determined by GC analysis (entry 11). Diethylzinc also served as a reducing agent to afford the monoalkenylation product in 16% yield (entry 12). Other reducing agents such

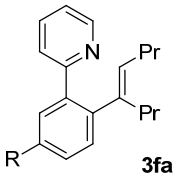
as DIBAL-H and Zn dust did not promote the reaction at all. Other cobalt sources such as $CoCl_2$, $Co(acac)_2$, $Co(acac)_3$ gave inferior results. Other transition metal precatalysts, including first-row transition metals (e.g., Mn, Fe, Ni, Cu, Ru, Rh, Pd, and Ir salts) did not catalyze the reaction under otherwise identical conditions.

With the optimized conditions in hand, we investigated the scope and limitation of the present reaction. First, various 2-arylpyridines and similar substrates were allowed to react with 4-octyne (Chart 2.1). Both electron-donating and electron-withdrawing groups at the *para*-position of arylpyridines (MeO, Me_2N, F, and CF_3) were tolerated, as demonstrated by the formation of the corresponding dialkenylated products **4ba**–**4ea** in good yields. Arylpyridines bearing *meta*-substituents (Me, CF_3, and OTBS) reacted at the less hindered position to afford monoalkenylation products **3fa**–**3ha** in moderate to good yields of 57–62%. A methyl group at the 3-position of the pyridine ring also prevented dialkenylation to afford the monoalkenylation product **3ia** in 75% yield. An *ortho*-methyl group significantly slowed down the reaction to afford the product **3ja** in 35% yield. The reaction of benzo[*h*]quinoline under the modified conditions employing $P(4\text{-}MeOC_6H_4)_3$ and neopentylmagnesium bromide afforded the product **3ka** in 68% yield. In this case, isomerization of the olefin moiety was observed to a small extent (*E*/*Z* = 90:10). Heteroarenes such as pyrrole and thiophene also participated in the reaction albeit in modest yields (**4la** and **3ma**). A pyrazolyl group, though not as good as a pyridyl group, also served as a directing group to afford a mixture of mono- (**3na**) and dialkenylation (**4na**) products in 46% and 39% yields, respectively.

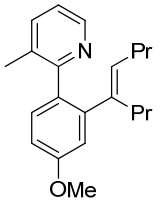
Chart 2.1. Scope of Arylpyridines[a]



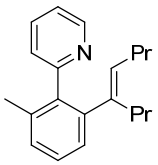
4ba (R = OMe), 80%
4ca (R = NMe_2), 86%
4da (R = F), 83%
4ea (R = CF_3), 74%



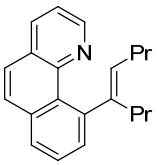
3fa (R = Me), 62%
3ga (R = CF_3), 57%
3ha (R = OTBS), 55%



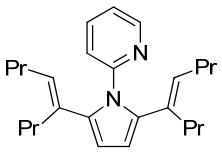
3ia, 75%



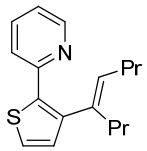
3ja, 35%



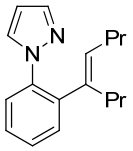
3ka,68%[b]



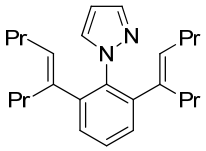
4la, 68%



3ma, 42%



+



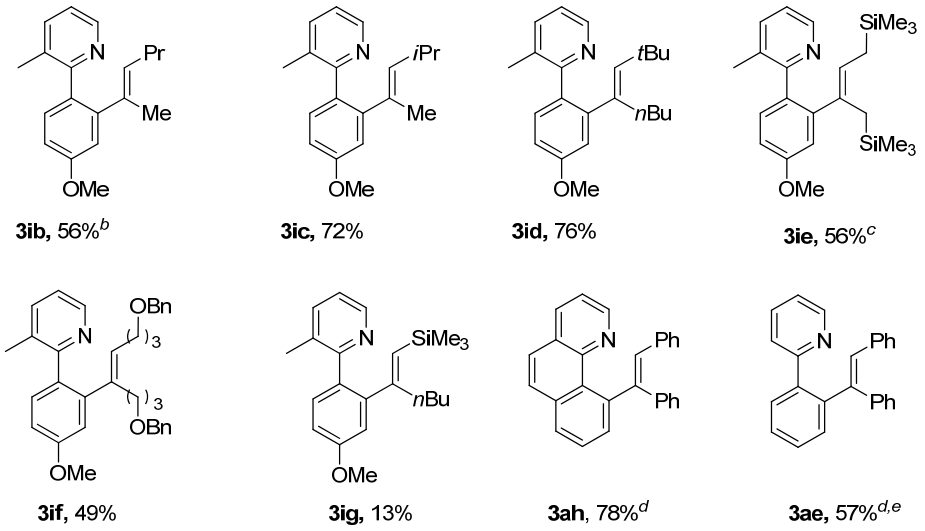
3na, 46% **4na,** 39%

[a] Reaction was performed under the conditions shown in entry 1, Table 1 using either 2.5 equiv (for dialkenylation) or 1.5 equiv (for monoalkenylation) of alkyne for 12-24 h. E/Z ratio was >99:1 unless otherwise indicated. [b] $P(4\text{-}MeOC_6H_4)_3$ (20 mol %) and tBuCH$_2$MgBr (100 mol %) was used instead of $PMePh_2$ and MeMgCl, and the reaction was performed at 60 °C, E/Z ratio = 90:10.

Chart 2.2 illustrates the scope of internal alkynes. Internal aliphatic alkynes bearing methyl and primary, secondary, and tertiary alkyl groups participated in the reaction to afford alkenylated products **3ib**, **3ic**, and **3id** in moderate to good yields. The unsymmetrical alkynes underwent C–C bond formation preferentially at the less sterically hindered position. 2-Hexyne reacted with a modest regioselectivity of 71:29 (**3ia**), while the regioselectivity was excellent when a bulkier substituent such as secondary or tertiary group was used (see **3ic** and **3id**). Trimethylsilyl and benzyloxy groups were tolerated (see **3ie** and **3if**), although isomerization of the olefin moiety was observed. A silyl-substituted

alkyne reacted sluggishly to afford the alkenylation product **3ig** in 13% yield. The reaction of diphenylacetylene under the modified conditions (*vide supra*) allowed monoalkenylation of benzo[*h*]quinoline and 2-phenylpyridine in 78% and 57% yields, respectively (see **3ah** and **3kh**). Notably, terminal alkynes such as phenyacetylene and 1-octyne failed to participate in the alkenylation reaction, which is probably because the acidic proton of terminal alkynes consumed the Grignard reagent.

Chart 2.2. Scope of Alkynes[a]

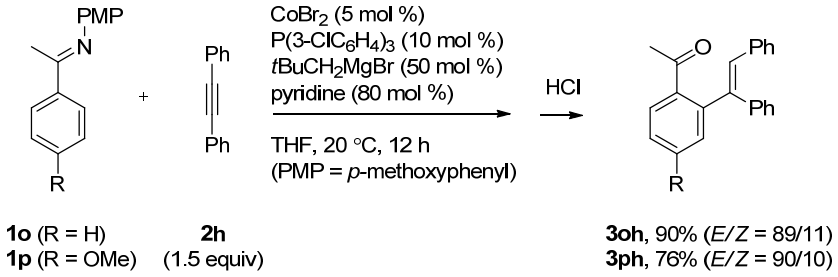


[a] Reaction was performed under the conditions shown in Table 1, entry 1 using 1.5 equiv (for monoalkenylation) of alkyne for 12-24 h. *E/Z* ratio was >99:1 unless otherwise indicated. [b] Major regioisomer is shown (ratio = 71:29). [c] *E/Z* = 16:84. [d] P(4-MeOC$_6$H$_4$)$_3$ (20 mol %) and *t*BuCH$_2$MgBr (100 mol %) was used instead of PMePh$_2$ and MeMgCl, and the reaction was performed at 60 °C. [e] *E/Z* = 84:16.

The CoBr$_2$/PMePh$_2$/MeMgCl catalytic system failed to promote the reaction of aryl ketimines **1o** and **1p** with diphenylacetylene **2h**. However, after further optimization of reaction conditions, an alternative catalytic system consisting of CoBr$_2$ (5 mol %), P(3-ClC$_6$H$_4$)$_3$ (10 mol %), *t*BuCH$_2$MgBr (50 mol %), and pyridine (80 mol %) promoted the

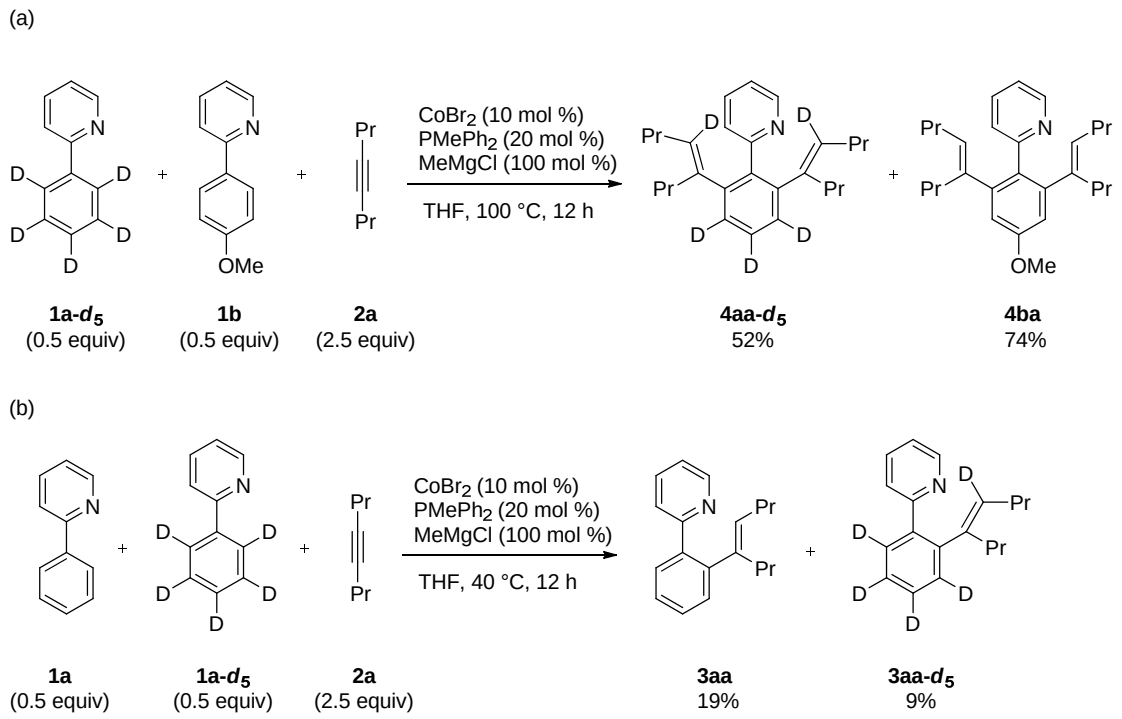
desired reaction of ketimine **1o** and **1p** with diphenylacetylene **2h** at room temperature (Scheme 2.3). Upon hydrolysis, the corresponding ketones **3oh** and **3ph** were obtained in good yields and stereoselectivities (*E*/*Z* = ca. 9/1).

Scheme 2.3. Cobalt-Catalyzed Alkenylation of Ketimines with Internal Alkyne



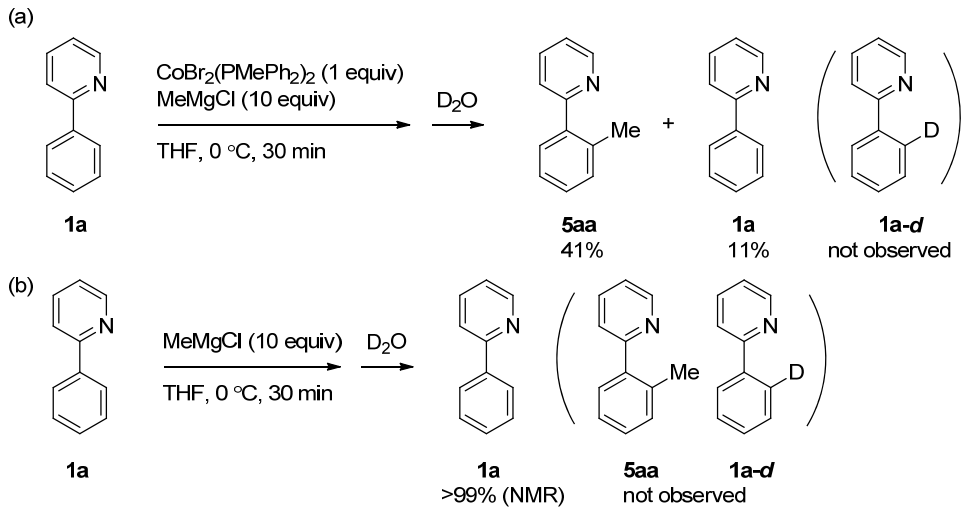
In order to gain insight into the reaction mechanism, deuterium-labeling experiments were performed. First, the reaction of a 1:1 mixture of **1a-*d*$_5$** and **1b** with 4-octyne did not cause H/D crossover to afford **4aa-*d*$_5$** and **4ba** in 52% and 74% yield, respectively (Scheme 2.4a). This result clearly indicates that the reaction does not involve deprotonation of the *ortho* C–H bond by MeMgCl or a putative methylcobalt species generated from the cobalt precatalyst and MeMgCl. Second, a competitive reaction of **1a** and **1a-*d*$_5$** with 4-octyne was performed at 40 °C and quenched at the early stage, which afforded a mixture of alkenylated product **3aa** and **3aa-*d*$_5$** in 19% and 9% yields, respectively (Scheme 2.4b). The intermolecular kinetic isotope effect value of 2.1 suggests that C–H bond cleavage is the first irreversible step of the reaction.[9]

Scheme 2.4. Deuterium-Labeling Experiments



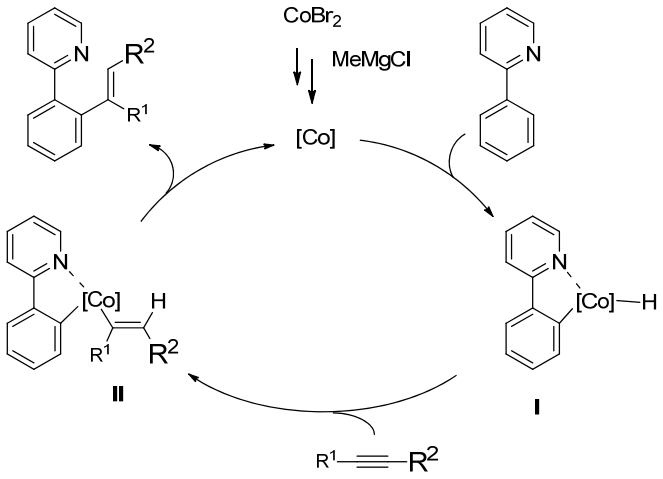
Finally, a stoichiometric reaction of **1a**, $CoBr_2(PMePh_2)_2$ (1 equiv), and MeMgCl (10 equiv) was performed at 0 °C for 30 min, which afforded an *ortho*-methylation product **5aa** in 41% yield (Scheme 2.5a). Note that the reaction did not afford either the *ortho*-methylation product or the *ortho*-deuteration product in the absence of $CoBr_2(PMePh_2)_2$ (Scheme 2.5b). Although the mechanism of the methylation reaction is not clear, this phenomenon suggests that C–H bond cleavage is a rather facile step.

Scheme 2.5. Stoichiometric Reactions



The nature of the in-situ generated cobalt catalyst is unclear at this moment. In light of the necessity of a larger amount (>40 mol %) of the Grignard reagent than required for reduction of cobalt(II) to cobalt(0) (Table 2.1), we speculate that the reaction involves an organocobalt(0)ate species as a catalytically active species.[10] A plausible catalytic cycle may include the following steps (Scheme 2.6). The cobalt species undergoes chelation-assisted oxidative addition of **1a** to form a cobaltacycle intermediate **I**,[11,12] followed by migratory insertion the alkyne into the Co–H bond. Reductive elimination of the resulting alkenyl(aryl)cobalt intermediate gives the monoalkenylation product and regenerates the active cobalt species. The dialkenylation product should be obtained through a similar process. The regioselectivity observed for unsymmetrical alkynes may be explained by the preference of the cobalt center to avoid steric repulsion during the alkyne insertion step.

Scheme 2.6. Plausible Catalytic Cycle



2.3 Conclusion

In summary, we have developed an efficient cobalt-catalyzed alkenylation reaction of a 2-arylpyridine with an unactivated internal alkyne through chelation-assisted C–H bond activation. The reaction affords a trisubstituted olefin in a moderate to good yield with excellent regio- and stereoselectivity. The present work has demonstrated that the reactivity of a rhodium(I) catalyst can be emulated by a cobalt catalyst generated from an appropriate combination of a ligand and a reducing agent. Further extension of this work would lead to a variety of directed C–H bond functionalization reactions using cobalt catalysts.

2.4 Experimental section

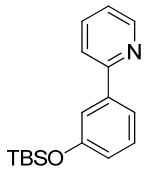
Materials and Methods

General. All reactions dealing with air- or moisture-sensitive compound were performed by standard Schlenk techniques in oven-dried reaction vessels under nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. Flash chromatography was performed as described by Still et al.,[13] using 40–63 μm silica gel (Si 60, Merck). ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on JEOL ECA-400 (400 MHz) or Bruker AV-400 (400 MHz) NMR spectrometers. ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and $CHCl_3$ (77.0 ppm), respectively. Gas chromatographic (GC) analysis was performed on a Shimadzu GC-2010 system equipped with an FID detector and a capillary column, DB-5 (Agilent J&W, 0.25 mm i.d. x 30 m, 0.25 μm film thickness). High-resolution mass spectra (HRMS) were obtained with a Q-Tof Premier LC HR mass spectrometer.

Materials. Unless otherwise noted, commercial reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. Anhydrous cobalt(II) bromide was purchased from Alfa Aesar (99% or 99.99%) or Aldrich (99%), and was used as received. THF was distilled over Na/benzophenone. Grignard reagents except MeMgCl (purchased from Aldrich) were prepared from the corresponding halides and magnesium turnings in anhydrous THF and titrated before use. $CoBr_2(PMePh_2)_2$ was prepared according to the literature procedure.[14]

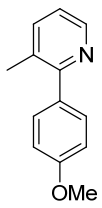
Preparation of Substrates for Cobalt-Catalyzed Hydroarylation

Preparation of Arylpyridine Derivatives.



2-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)pyridine (1h): The title compound was prepared by silylation of 3-(pyridin-2-yl)phenol [15] (428 mg, 2.5 mmol) with *tert*-butyldimethylchlorosilane (452.2 mg, 3 mmol) and imidazole (255.2 mg, 3.75 mmol) in CH_2Cl_2 (10 mL). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as colorless oil (428 mg, 60%).

R_f 0.53 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.24 (s, 6H), 1.01 (s, 9H), 6.89 (dd, *J* = 2.3 Hz, 7.8 Hz, 1H), 7.22 (t, *J* = 5.9 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.48-7.49 (m, 1H), 7.58 (dd, *J* = 0.9 Hz, 7.8Hz, 1H), 7.67-7.74 (m, 2H), 8.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.1, 18.4, 25.9, 118.9, 120.2, 120.78, 120.82, 122.3, 129.9, 136.9, 141.2, 149.8, 156.3, 157.4; HRMS (ESI) Calcd for $C_{17}H_{24}NOSi$ $[M + H]^+$ 286.1627, found 286.1628.



2-(4-Methoxyphenyl)-3-methylpyridne (1i): The title compound was prepared by nickel-catalyzed cross-coupling reaction of 2-bromo-3-methylpyridine (1.11 mL, 10 mmol) and 4-methoxyphenylmagnesium bromide (0.86 M in THF, 17 mL, 15 mmol) according to the procedure developed by Mongin et al.[16] Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a yellow solid (1.3 g, 70%).

R_f 0.15 (hexane/EtOAc = 5/1); m.p. 50-51 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.03(s, 3H), 3.46(s, 3H), 6.68-6.71 (m, 2H), 7.75-7.79 (m, 1H), 7.17(d, J = 7.8 Hz, 1H), 7.23-7.25(m, 2H), 8.23-8.24(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 54.4, 112.8, 121.0, 129.7, 129.9, 132.4, 137.8, 146.2, 157.4, 158.7; HRMS (ESI) Calcd for $C_{13}H_{14}NO$ $[M + H]^+$ 200.1075, found 200.1070.

The following 2-arylpyridine derivatives were prepared by a similar procedure as described above, and their spectral data showed good agreement with the literature data: 2-(4-methoxyphenyl)pyridine (**1b**), [17] *N*,*N*-dimethyl-4-(pyridin-2-yl)aniline (**1c**), [18] 2-(4-fluorophenyl)pyridine (**1d**),[16] 2-(4-(trifluoromethyl)phenyl)pyridine (**1e**), [19] 2-(*m*-tolyl)pyridine (**1f**), [20] 2-(3-(trifluoromethyl)phenyl)pyridine (**1g**), [21] 2-(*o*-tolyl)pyridine (**1i**),[17] 2-(thiophen-2-yl)pyridine (**1l**),[22] and 2-(phenyl-d_5)pyridine (**1a**-d_5).[23]

2-(1*H*-pyrrol-1-yl)pyridine (**1j**) was prepared according to the literature procedure.[24]

Preparation of Alkynes.

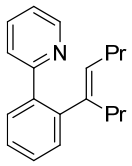
2,2-Dimethyloct-3-yne (**2d**),[25] 1,4-bis(trimethylsilyl)but-2-yne (**2e**),[26] and 1-trimethylsilyl-1-hexyne (**2g**)[27] were prepared according to the literature procedures.

1,8-Bis(benzyloxy)oct-4-yne (2h): To a THF solution of oct-4-yne-1,8-diol (0.70 g, 5 mmol, prepared according to the literature procedure[28]) in THF (20 mL) was added NaH (360 mg, 15 mmol) portionwise at 0 °C. After stirring for 10 min, benzyl bromide (1.3 mL, 11 mmol) was added. The resulting mixture was stirred for 2 h. Water (10 mL) was added to the reaction mixture at 0 °C. The resulting mixture was extracted with ether (10 mL x 3)

and the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 25/1) afforded the title compound as a colorless oil (1.02 mg, 63%).

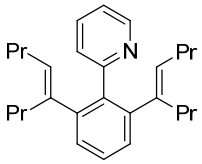
R_f 0.52 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79-1.75 (m, 4 H), 2.26 (t, J = 6.9 Hz, 4 H), 3.54 (t, J = 6.3 Hz, 4 H), 4.50 (s, 4 H), 7.29-7.26 (m, 2 H), 7.34-7.33 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.58, 29.20, 68.96, 72.92, 79.75, 127.50, 127.58, 128.34, 138.55; HRMS (ESI) Calcd for $C_{22}H_{27}O_2$ $[M + H]^+$ 323.2011, found 323.2010.

A Typical Procedure: In a Schlenk tube were placed $CoBr_2$ (6.6 mg, 0.03 mmol), $PMePh_2$ (11 μL, 0.06 mmol), 2-phenylpyridine (43 μL, 0.3 mmol), and THF (0.65 mL). To the mixture was added a THF solution of MeMgCl (3.0 M, 0.1 mL, 0.3 mmol) dropwise at 0 °C. After stirring for 30 min, 4-octyne (110 μL, 0.75 mmol) was added. The resulting mixture was stirred at 100 °C for 12 h, and then allowed to room temperature, diluted with ether (1 mL), and quenched by saturated aqueous solution of NH_4Cl (1 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 100/1) to afford (*E*)-2-(2-(oct-4-en-4-yl)phenyl)pyridine (**3aa**, 7.1 mg, 4%) and 2-(2,6-di((*E*)-oct-4-en-4-yl)phenyl)pyridine (**4aa**, 96.9 mg, 83%) as colorless oils.

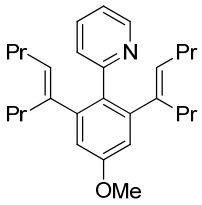


3aa: R_f 0.44 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (t, J = 7.3 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H), 1.13-1.19 (m, 2H), 1.37-1.42 (m, 2H), 1.86 (t, J = 7.8 Hz, 2H), 2.05-2.11 (m, 2H), 5.48 (t, J = 7.3 Hz, 1H), 7.16-7.19 (m, 1H), 7.19-7.24 (m, 1H), 7.32-

7.36 (m, 2H), 7.51-7.62 (m, 3H), 8.67 (d, J = 4.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.2, 21.8, 23.0, 30.5, 33.6, 121.6, 124.5, 127.0, 128.2, 130.0, 130.4, 131.9, 135.6, 138.7, 141.6, 143.6, 149.5, 159.9. HRMS (ESI) Calcd for $C_{19}H_{24}N$ $[M + H]^+$ 266.1909, found 266.1908.



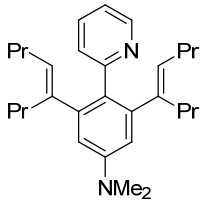
4aa: R_f 0.74 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (t, J = 7.3 Hz, 6H), 0.81 (t, J = 7.4 Hz, 6H), 1.14-1.29 (m, 8H), 1.76 (t, J = 7.4 Hz, 4H), 1.91-1.96 (m, 4H), 5.30 (t, J = 7.3 Hz, 2H), 7.08-7.11 (m, 3H), 7.20-7.24 (m, 2H), 7.53 (m, 1H), 8.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.2, 21.6, 22.9, 30.4, 33.3, 121.1, 126.4, 127.2, 128.2, 131.6, 134.8, 137.4, 141.0, 144.1, 148.5, 160.2; HRMS (ESI) Calcd for $C_{27}H_{38}N$ $[M + H]^+$ 376.3004, found 376.3007. The stereochemistry of the olefin moiety was assigned by a NOESY measurement.



2-(4-Methoxy-2,6-di((*E*)-oct-4-en-4-yl)phenyl)pyridine (4ba): The typical procedure was applied to 2-(4-methoxyphenyl)pyridine (**1b**, 55.6 mg, 0.3 mmol) and 4-octyne (110 μL, 0.75 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a yellow oil (97.2 mg, 80%).

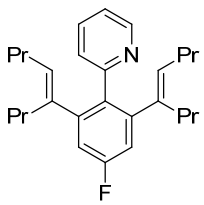
R_f 0.68 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.73 (t, J = 7.3 Hz, 6H), 0.80 (t, J = 7.3 Hz, 6H), 1.14-1.28 (m, 8H), 1.74 (t, J = 7.3 Hz, 4H), 1.90-1.95 (m, 4H), 5.32 (t,

J = 7.3 Hz, 2H), 6.66 (s, 2H), 7.05-7.08 (m, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.51 (m, 1H), 8.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 14.0, 21.4, 22.7, 30.1, 33.0, 113.3, 120.6, 126.5, 130.3, 131.3, 134.5, 140.8, 145.4, 148.3, 158.0, 159.8. HRMS (ESI) calcd for $C_{28}H_{40}NO$ $[M + H]^+$: 406.3110, found 406.3111.



***N,N*-Dimethyl-3,5-di((*E*)-oct-4-en-4-yl)-4-(pyridin-2-yl)aniline (4ca):** The typical procedure was applied to *N,N*-dimethyl-4-(pyridin-2-yl)amine (**1c**, 59.5 mg, 0.3 mmol) and 4-octyne (110 μL, 0.75 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as yellow oil (108.2 mg, 86%).

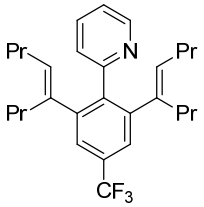
R_f 0.72 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (t, *J* = 7.3 Hz, 6H), 0.81 (t, *J* = 7.3 Hz, 6H), 1.16-1.30 (m, 8H), 1.75 (t, *J* = 8.2 Hz, 4H), 1.92-1.97 (m, 4H), 2.97 (s, 6H), 5.34 (t, *J* = 7.4 Hz, 2H), 6.49 (s, 2H), 7.02-7.06 (m, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.48 (m, 1H), 8.51 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.3, 21.7, 22.9, 30.4, 33.5, 40.8, 112.6, 120.5, 126.8, 126.9, 130.8, 134.6, 142.0, 145.0, 148.4, 149.4, 160.7. HRMS (ESI) calcd for $C_{29}H_{43}N_2$ $[M + H]^+$: 419.3426, found 419.3421.



2-(4-Fluoro-2,6-di((*E*)-oct-4-en-4-yl)phenyl)pyridine (4da): The typical procedure was applied to 2-(4-fluorophenyl)pyridine (**1d**, 52 mg, 0.3 mmol) and 4-octyne (110 μL, 0.75

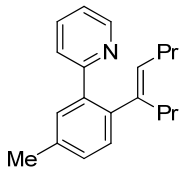
mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a yellow oil (97.9 mg, 83%).

R_f 0.71 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (t, J = 7.3 Hz, 6H), 0.79 (t, J = 7.3 Hz, 6H), 1.13-1.27 (m, 8H), 1.74 (t, J = 7.3 Hz, 4H), 1.89-1.95 (m, 4H), 5.31 (t, J = 7.3 Hz, 2H), 6.82 (d, J = 9.6 Hz, 1H), 7.08-7.11 (m, 1H), 7.17 (d, J = 7.8 Hz, 1H), 7.53 (m, 1H), 8.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 14.2, 21.6, 22.8, 30.3, 33.1, 114.7 (d, J = 83.9Hz), 121.3, 126.5, 132.3, 133.6, 134.9, 140.2, 146.4 (d, J = 66.3 Hz), 148.6, 159.4, 160.3, 162.8. HRMS (ESI) calcd for $C_{27}H_{37}FN$ $[M + H]^+$: 394.2910, found 394.2912.



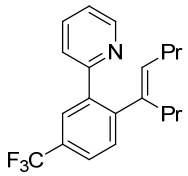
2-(4-Trifluoromethyl-2,6-di((*E*)-oct-4-en-4-yl)phenyl)pyridine (4ea): The typical procedure was applied to 2-(4 (trifluoromethyl)phenyl)pyridine (**1e**, 67 mg, 0.3 mmol) and 4-octyne (110 μL, 0.75 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a yellow oil (98.5 mg, 74%).

R_f 0.75 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.73 (t, J = 7.3 Hz, 6H), 0.80 (t, J = 7.3 Hz, 6H), 1.11-1.26 (m, 8H), 1.75 (t, J = 7.3 Hz, 4H), 1.90-1.96 (m, 4H), 5.32 (t, J = 7.3 Hz, 2H), 7.12-7.15 (m, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.34 (s, 2H), 7.57 (m, 1H), 8.55 (d, J = 4.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 14.2, 21.6, 22.8, 30.3, 33.1, 114.7 (d, J = 83.9Hz), 121.3, 126.5, 132.3, 133.6, 134.9, 140.2, 146.4 (d, J = 66.3 Hz), 148.6, 159.4, 160.3, 162.8. HRMS (ESI) calcd for $C_{28}H_{37}F_3N$ $[M + H]^+$: 444.2878, found 444.2876.



(*E*)-2-(5-Methyl-2-(oct-4-en-4-yl)phenyl)pyridine (3fa): The typical procedure was applied to 2-(*m*-tolyl)pyridine (**1f**, 49 μL, 0.3 mmol) and 4-octyne (66 μL, 0.45 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a yellow oil (48.2 mg, 62%).

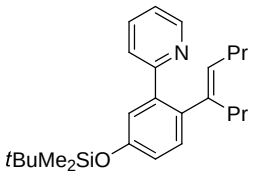
R_f 0.45 (hexane/EtOAc = 5/1);^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H), 1.12-1.18 (m, 2H), 1.36-1.41 (m, 2H), 1.85 (t, *J* = 8.0 Hz, 2H), 2.04-2.10 (m, 2H), 2.38 (s, 3H), 5.45 (t, *J* = 7.3 Hz, 1H), 7.11-7.19 (m, 3H), 7.40 (s, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.59 (m, 1H), 8.66 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.2, 21.2, 21.8, 23.0, 30.6, 33.7, 121.6, 124.5, 129.0, 130.4, 130.7, 131.7, 135.5, 136.7, 138.5, 140.8, 141.4, 149.5, 160.0. HRMS (ESI) calcd for $C_{20}H_{26}N$ $[M + H]^+$: 280.2065, found 280.2064.



(*E*)-2-(2-(Oct-4-en-4-yl)-5-(trifluoromethyl)phenyl)pyridine (3ga): The typical procedure was applied to 2-(3-(trifluoromethyl)phenyl)pyridine (**1g**, 54 μL, 0.3 mmol) and 4-octyne (66 μL, 0.45 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a yellow oil (56.9 mg, 57%).

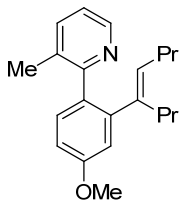
R_f 0.67 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H), 1.10-1.17 (m, 2H), 1.35-1.43 (m, 2H), 1.87 (t, *J* = 7.8 Hz, 2H), 2.06-

2.12 (m, 2H), 5.51 (t, *J* = 7.3 Hz, 1H), 7.21-7.26 (m, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.52-7.58 (m, 2 H), 7.64 (m, 1H), 7.84 (s, 1H), 8.69 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 21.8, 22.9, 30.6, 33.4, 122.3, 124.4, 125.0, 125.8, 127.2, 129.2, 129.5, 130.9, 133.2, 135.9, 139.3, 140.7, 147.2, 149.8, 158.5. HRMS (ESI) calcd for $C_{20}H_{23}F_3N$ $[M + H]^+$: 334.1783, found 334.1785.



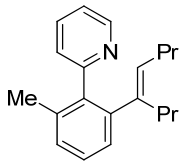
(*E*)-2-(5-(*tert*-butyldimethylsilyloxy)-2-(oct-4-en-4-yl)phenyl)pyridine (3ha): The typical procedure was applied to 2-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)pyridine (**1h**, 87 μL, 0.3 mmol) and 4-octyne (66 mL, 0.45 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded the title compound as a yellow oil (65.0 mg, 55%).

R_f 0.46 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.21 (d, *J* = 0.9 Hz, 6H), 0.71 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.98 (d, *J* = 0.9 Hz, 9H), 1.11-1.17 (m, 2H), 1.34-1.40 (m, 2H), 1.81 (t, *J* = 7.8 Hz, 2H), 2.06-2.08 (m, 2H), 5.42 (t, *J* = 7.3 Hz, 1H), 6.79 (dd, *J* = 1.8 Hz, 8.2 Hz, 1H), 7.04-7.09 (m, 2H), 7.17 (t, *J* = 5.9 Hz, 1H), 7.50 (dd, *J* = 0.9 Hz, 7.8Hz, 1 H), 7.59 (t, *J* = 7.8 Hz, 1H), 8.65 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.2, 14.1, 14.2, 18.3, 21.8, 23.0, 25.9, 30.6, 33.8, 119.5, 121.4, 121.6, 124.4, 131.4, 135.6, 136.8, 139.9, 141.2, 149.5, 154.6, 159.8. HRMS (ESI) calcd for $C_{25}H_{38}NOSi$ $[M + H]^+$: 396.2723, found 396.2722.



(*E*)-2-(4-Methoxy-2-(oct-4-en-4-yl)phenyl)-3-methylpyridine(3ia): The typical procedure was applied to 2-(4-methoxyphenyl)-3-methylpyridine (**1i**, 56 μL, 0.3 mmol) and 4-octyne (66 μL, 0.45 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a yellow oil (94.4 mg, 75%).

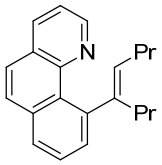
R_f 0.53 (hexane/EtOAc = 5/1);^{1}H NMR (400 MHz, $CDCl_3$): δ 0.73 (t, *J* = 7.3 Hz, 3H), 0.80 (t, *J* = 7.3 Hz, 3H), 1.16-1.28 (m, 4H), 1.77 (t, *J* = 7.3 Hz, 2H), 1.93-1.98 (m, 2H), 2.07 (s, 3H), 3.83 (s, 3H), 5.36 (t, *J* = 7.3 Hz, 1H), 6.79 (d, *J* = 2.3 Hz, 1H), 6.83 (dd, *J* = 2.8 Hz, 8.2Hz, 1H), 7.08-7.13 (m, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 8.43 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 14.2, 19.6, 21.9, 22.9, 30.4, 32.7, 55.4, 111.4, 115.5, 122.0, 130.4, 131.3, 131.8, 132.1, 137.5,141.1, 145.2, 146.4, 159.1, 160.0. HRMS (ESI) calcd for $C_{21}H_{28}NO$ $[M + H]^+$: 310.2171, found 310.2170.



(*E*)-2-(2-Methyl-6-(oct-4-en-4-yl)phenyl)pyridine (3ja): The typical procedure was applied to 2-(*o*-tolyl)pyridine (**1j**, 49 μL, 0.3 mmol) and 4-octyne (66 μL, 0.45 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a yellow oil (29.1 mg, 35%).

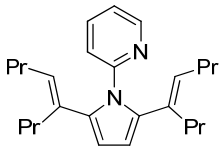
R_f 0.52 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (t, *J* = 7.4 Hz, 3H), 0.80 (t, *J* = 7.5 Hz, 3H), 1.16-1.25 (m, 4H), 1.78 (bs, 2H), 1.90-1.95 (m, 2H), 2.09 (s, 3H), 5.26

(t, J = 7.4 Hz, 1H), 7.06 (d, J = 7.3 Hz, 1H), 7.15-7.29 (m, 5H), 7.64 (m, 1H), 8.65 (d, J = 4.6 Hz, 1H). HRMS (ESI) calcd for $C_{20}H_{26}N$ $[M + H]^+$: 280.2065, found 280.2061.



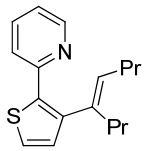
(*E*)-10-(Oct-4-en-4-yl)benzo[*h*]quinoline(3ka): The procedure for the generation of the cobalt catalyst was modified by using P(4-$MeOC_6H_4$)$_3$ (21.1 mg, 0.06 mmol) and neopentylmagnesium bromide (0.69 M in THF, 0.43 mL, 0.3 mmol) instead of $PMePh_2$ and MeMgCl, respectively. The reaction of benzo[*h*]quinoline (53.8 mg, 0.3 mmol) and 4-octyne (66 μL, 0.45 mmol) gave the title compound as a yellow oil (58.3 mg, 68%) after purification by silica gel chromatography (eluent: hexane/EtOAc = 200/1).

R_f 0.37 (hexane/EtOAc = 50/1);^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (t, J = 7.3 Hz, 3H), 1.09 (t, J = 7.3 Hz, 3H), 1.20-1.29 (m, 2H), 1.54-1.63 (m, 2H), 2.17-2.37 (m, 1H), 2.34-2.41 (m, 1H), 2.80-2.88 (m, 1H), 5.38 (t, J = 7.3 Hz, 1H), 7.42-7.46 (m, 2H), 7.60 (t, J = 3.2 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.80-7.85 (m, 2H), 8.12 (dd, J = 1.8 Hz,7.8 Hz, 1H), 8.93 (dd, J = 1.8 Hz, 4.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 14.6, 22.2, 22.3, 30.6, 35.7, 121.0, 124.7, 125.7, 127.3, 127.4, 127.5, 128.8, 129.0, 131.2, 135.0, 135.3, 144.5, 147.2, 147.6, 147.7. HRMS (ESI) calcd for $C_{21}H_{24}N$ $[M + H]^+$: 290.1909, found 290.1907.



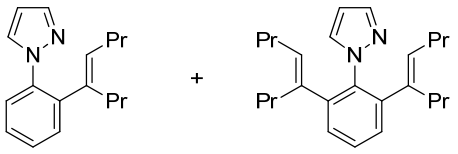
2-(2,5-Di((*E*)-oct-4-en-4-yl)-1H-pyrrol-1-yl)pyridine(4la): The typical procedure was applied to 2-(1*H*-pyrrol-1-yl)pyridine (**1l**, 41 μL, 0.3 mmol) and 4-octyne (110 μL, 0.75 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 100/1) of the crude product afforded the title compound as s yellow oil (74.1 mg, 68%).

R_f 0.78 (hexane/EtOAc = 5/1);^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75 (t, *J* = 7.3 Hz, 6H), 0.79 (t, *J* = 7.3 Hz, 6H), 1.12-1.21 (m, 4H), 1.26-1.35 (m, 4H), 1.90-1.97 (m, 8H), 5.16 (t, *J* = 7.3 Hz, 1H), 6.08 (s, 2H), 7.08 (d, *J* = 8.2 Hz, 1H), 7.20 (m, 1H), 7.66 (m, 1H), 8.51 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ. 14.0, 14.2, 22.1, 22.9, 30.4, 33.1, 108.2, 122.2, 123.5, 131.3, 132.2, 137.3, 137.5, 148.8, 154.0. HRMS (ESI) calcd for $C_{25}H_{37}N_2$ $[M + H]^+$: 365.2957, found 365.2960.



(*E*)-2-(3-(Oct-4-en-4-yl)thiophen-2-yl)pyridine(3ma): The typical procedure was applied to 2-(thiophen-2-yl)pyridine (**1m**, 48.4 mg, 0.3 mmol) and 4-octyne (66 μL, 0.45 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product to afford the title compound as yellow oil (33.8 mg, 42%).

R_f 0.53 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, *J* = 7.3 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H), 1.29-1.35 (m, 2H), 1.38-1.45 (m, 2H), 2.12-2.18 (m, 2H), 2.28 (t, *J* = 8.2 Hz, 2H), 5.52 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 5.5 Hz, 1H), 7.01-7.10 (m, 1H), 7.26 (t, *J* = 4.6 Hz, 1H), 7.57 (m, 1H), 7.71 (m, 1H), 8.55 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 14.4, 22.1, 22.9, 30.5, 33.9, 121.4, 121.6, 126.0, 131.6, 131.7, 136.1, 136.5, 138.2, 143.2, 149.5, 153.5. HRMS (ESI) calcd for $C_{17}H_{22}NS$ $[M + H]^+$: 272.1473, found 272.1472.

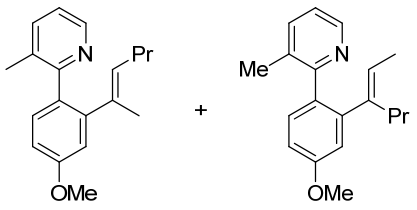


3na **4na**

(*E*)-1-(2-(Oct-4-en-4-yl)phenyl)-1*H*-pyrazole (3na) and 1-(2,6-di((*E*)-oct-4-en-4-yl)phenyl)-1*H*-pyrazole (4na): The typical procedure was applied to 1-phenyl-1*H*-pyrazole (**1n**, 41 μL, 0.3 mmol) and 4-octyne (110 μL, 0.75 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded a mixture of the title compounds as a yellow oil (77.3 mg, 46% yield for **3na** and 39% yield for **4na** as determined by ^{1}H NMR). A pure sample of each compound was obtained by further chromatographic purification.

3na: R_f 0.52 (hexane/EtOAc = 5/1);^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (t, *J* = 7.3 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H), 1.08-1.16 (m, 2H), 1.39-1.48 (m, 2H), 1.71 (t, *J* = 7.3 Hz, 2H), 2.08-2.14 (m, 2H), 5.30 (t, *J* = 7.3 Hz, 1H), 6.36 (t, *J* = 2.3 Hz, 1H), 7.25-7.26 (d, *J* = 2.8 Hz, 1H), 7.28-7.37 (m, 2H), 7.49 (dd, *J* = 1.8 Hz, 7.5 Hz, 1H), 7.68 (dd, *J* = 2.3 Hz, 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.2, 21.8, 23.0, 30.5, 32.0, 106.5, 125.8, 127.8, 131.0, 131.3, 132.2, 128.3, 139.1, 140.0, 140.3. HRMS (ESI) calcd for $C_{17}H_{23}N_2$ $[M + H]^+$: 255.1861, found 255.1865.

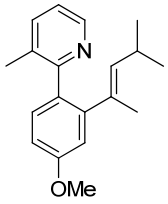
4na: R_f 0.79 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75 (t, *J* = 7.3 Hz, 6H), 0.91 (t, *J* = 7.3 Hz, 6H), 1.12-1.18 (m, 4H), 1.34-1.40 (m, 4H), 1.65 (t, *J* = 7.3 Hz, 4H), 2.00-2.06 (m, 4H), 5.41 (t, *J* = 7.3 Hz, 1H), 6.30 (t, *J* = 1.8 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 2.3 Hz, 1H), 7.58 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 21.8, 23.0, 30.4, 31.7, 105.6, 128.1, 129.4, 131.4, 132.5, 139.3, 139.6, 142.3. HRMS (ESI) calcd for $C_{25}H_{37}N_2$ $[M + H]^+$: 365.2957, found 365.2961.



3ib **3ib'**

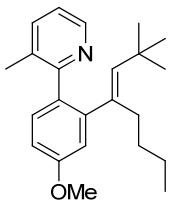
(*E*)-2-(2-(Hex-2-en-2-yl)-4-methoxyphenyl)-3-methylpyridine (3ib): The typical procedure was applied to 2-(4-methoxyphenyl)-3-methylpyridine (**1i**, 56 μL, 0.3 mmol) and 2-hexyne (**2b**, 51 μL, 0.45 mmol). Silica gel chromatography of the crude product afforded a mixture of the title compound and its minor regiosiomer, (*E*)-2-(2-(hex-2-en-3-yl)-4-methoxyphenyl)-3-methylpyridine (**3ib'**) as a yellow oil (47.6 mg, 56%, ratio = 71:29 as determined by ^{1}H NMR).

R_f 0.44 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71 (t, *J* = 7.3 Hz, 3H, **3ib'**), 0.73 (t, *J* = 7.3 Hz, 3H, **3ib**), 1.11-1.19 (m, 2H ,**3ib** and **3ib'**), 1.59 (d, *J* = 6.9 Hz, 3H, **3ib'**), 1.64 (d, *J* = 0.9 Hz, 3H, **3ib**), 1.73 (t, *J* = 7.8 Hz, 2H, **3ib'**), 1.85-1.91 (m, 2H, **3ib**), 2.05 (s, 3H, **3ib**), 2.06 (s, 3H, **3ib'**), 3.83 (s, 3H, **3ib** and **3ib'**), 5.22 (dt, *J* = 7.3, 1.4 Hz, 1H, **3ib**), 5.47 (q, *J* = 6.9 Hz, 1H, **3ib'**), 6.76-6.84 (m, 2H, **3ib** and **3ib'**), 7.08-7.16 (m, 2H, **3ib** and **3ib'**), 7.43-7.47 (m, 1H, **3ib** and **3ib'**), 8.44 (m, 1H, **3ib** and **3ib'**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 14.0, 14.1, 17.3, 19.5, 19.6, 21.6, 22.5, 30.6, 32.3, 55.5, 111.6, 111.8, 113.9, 115.5, 121.8, 122.0, 130.5, 130.8, 131.7, 131.9, 132.0, 132.2, 135.0, 137.5, 137.6, 142.3, 145.3, 146.1, 146.45, 146.53. HRMS (ESI) calcd for $C_{19}H_{24}NO$ $[M + H]^+$: 282.1858, found 282.1856.



(*E*)-2-(4-Methoxy-2-(4-methylpent-2-en-2-yl)phenyl)-3-methylpyridine (3ic): The typical procedure was applied to 2-(4-methoxyphenyl)-3-methylpyridine (**1i**, 56 μL, 0.3 mmol) and 4-methylpent-2-yne (**2c**, 52 μL, 0.45 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 8/1) of the crude product afforded the title compound as a yellow oil (60.9 mg, 72%).

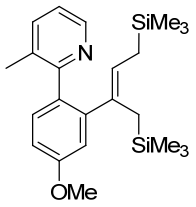
R_f 0.44 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70 (d, J = 6.4 Hz, 6H), 1.69 (d, J = 1.4 Hz, 3H), 2.04 (s, 3H), 2.33-2.39 (m, 1H), 3.82 (s, 3H), 4.93 (dd, J = 1.4 Hz, 9.2 Hz, 1H), 6.80-6.84 (m, 2H), 7.07-7.10 (m, 1H), 7.16 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 6.8 Hz, 1H), 8.43 (d, J = 3.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 19.4, 22.4, 27.6, 55.4, 111.8, 113.7, 121.8, 130.7, 131.9, 132.0, 132.1, 137.4, 139.4, 145.9, 146.4, 159.2, 160.2. HRMS (ESI) calcd for $C_{19}H_{24}NO$ $[M + H]^+$: 282.1858, found 282.1860. The stereochemistry of the olefin moiety was assigned by a NOESY measurement.



(*E*)-2-(2-(2,2-dimethyloct-3-en-4-yl)-4-methoxyphenyl)-3-methylpyridine (3id): The typical procedure was applied to 2-(4-methoxyphenyl)-3-methylpyridine (**1i**, 56 μL, 0.3 mmol) and 2,2-dimethyloct-3-yne (**2d**, 80 μL, 0.45 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 5/1) of the crude product afforded the title compound as a yellow oil (77.2 mg, 76%).

R_f 0.45 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (t, J = 6.9 Hz, 3H), 0.99 (s, 9H), 1.12-1.19 (m, 4H), 1.90 (bs, 2H), 2.10 (s, 3H), 3.84 (s, 3H), 5.32 (s, 1H), 6.77 (d, J =2.8 Hz, 1H), 6.83 (dd, J = 2.8 Hz, 8.3 Hz, 1H), 7.11 (t, J = 2.8 Hz, 1H), 7.13 (s, 1H),

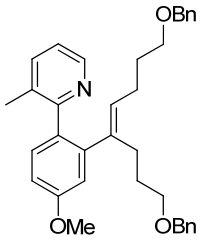
7.47 (d, J = 7.3 Hz, 1H), 8.43 (d, J = 4.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 19.7, 23.2, 31.1, 31.15, 31.20, 32.7, 55.4, 111.3, 115.7, 122.0, 130.3, 131.8, 132.2, 137.5, 140.9, 141.0, 146.1, 146.3, 159.0, 159.9. HRMS (ESI) calcd for $C_{23}H_{32}NO$ $[M + H]^+$: 338.2484, found 338.2484. The stereochemistry of the olefin moiety was assigned by a NOESY measurement.



(*Z*)-2-(2-(1,4-Bis(trimethylsilyl)but-2-en-2-yl)-4-methoxyphenyl)-3-methylpyridine (3ie):

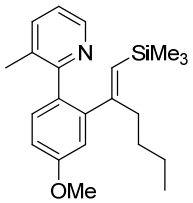
The typical procedure was applied to 2-(4-methoxyphenyl)-3-methylpyridine (**1i**, 56 μL, 0.3 mmol) and 1,4-bis(trimethylsilyl)but-2-yne (**2e**, 112 μL, 0.45 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded a mixture of the title compound and its *E*-stereoisomer (*E*/*Z* = 16/84 as determined by GC and 1H NMR analysis as a yellow oil (65.3 mg, 55%).

R_f 0.50 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$, major isomer): δ -0.19 (s, 9H), -0.07 (s, 9H), 1.21 (s, 2H), 1.37 (d, J = 8.2 Hz, 2H), 2.09 (s, 3H), 3.83 (s, 3H), 5.41 (t, J = 8.7 Hz, 1H), 6.78-6.82 (m, 2H), 7.07-7.12 (m, 2H), 7.45 (m, 1H), 8.45 (dd, J = 1.4 Hz, 4.6Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, major isomer): δ -1.31, -0.60, 19.9, 20.1, 21.8, 55.5, 111.4, 116.0, 122.0, 123.7, 130.5, 132.0, 132.2, 137.5, 137.7, 146.6, 146.9, 159.1, 160.2. HRMS (ESI) calcd for $C_{23}H_{36}NOSi_2$ $[M + H]^+$: 398.2335, found 398.2335.



(*E*)-2-(2-(1,8-bis(benzyloxy)oct-4-en-4-yl)-4-methoxyphenyl)-3-methylpyridine (3if): The typical procedure was applied to 2-(4-methoxyphenyl)-3-methylpyridine (**1i**, 56 μL, 0.3 mmol) and 1,8-di(benzyloxy)oct-4-yne (**2f**, 140 μL, 0.45 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 5/1~1/1) of the crude product afforded the title compound as a yellow oil (76.3 mg, 49%).

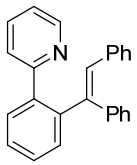
R_f 0.13 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52-1.59 (m, 4H), 1.96 (t, *J* = 7.3 Hz, 2H), 2.08 (s, 3H), 2.09-2.15 (m, 2H), 3.32 (t, *J* = 6.0 Hz, 2H), 3.36 (t, *J* = 6.9 Hz, 2H), 3.83 (s, 3H), 4.40 (s, 2H), 4.43 (s, 2H), 5.39 (t, *J* = 7.4 Hz, 1H), 6.79 (d, *J* = 1.8Hz, 1H), 6.86 (dd, *J* = 1.8 Hz, 8.7 Hz, 1H), 7.10-7.15 (m, 2H), 7.26-7.36 (m, 10H), 7.46 (d, *J* =7.7 Hz, 1H), 8.43 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 24.8, 27.1, 28.6, 29.8, 55.4, 69.9, 70.1, 72.8, 73.0, 76.9, 77.2, 77.6, 111.7, 115.5, 122.1, 127.5, 127.6, 127.7, 127.8, 128.4, 130.5, 130.9, 131.7, 132.2, 137.7, 138.7, 138.8, 141.0, 144.7, 146.4, 159.1, 159.8. HRMS (ESI) calcd for $C_{35}H_{40}NO_3$ $[M + H]^+$: 522.3008, found 522.3005.



(*E*)-2-(4-methoxy-2-(1-(trimethylsilyl)hex-1-en-2-yl)phenyl)-3-methylpyridine (3ig): The typical procedure was applied to 2-(4-methoxyphenyl)-3-methylpyridine (**1i**, 56 μL, 0.3 mmol) and hex-1-yn-1-yltrimethylsilane (**2g**, 88 μL, 0.45 mmol). Silica gel

chromatography (eluent : hexane/EtOAc = 10/1-5/1) of the crude product afforded the title compound as a yellow oil (14.2 mg, 13%).

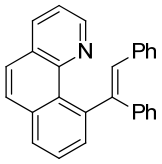
R_f 0.45 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 9H), 0.76 (t, *J* = 7.4 Hz, 3H), 1.12-1.18 (m, 4H), 1.82 (t, *J* = 6.9Hz, 2H), 2.10 (s, 3H), 3.85 (s, 3H), 5.43 (s, 1H), 6.81 (d, *J* =2.3 Hz, 1H), 6.85 (dd, *J* = 2.7 Hz, 8.2 Hz, 1H), 7.11-7.15 (m, 2H), 7.47 (d, *J* = 7.3 Hz, 1H), 8.43 (d, *J* = 4.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.17, 14.1, 19.7, 23.0, 31.6, 36.1, 55.5, 111.9, 114.9, 122.1, 130.4, 130.7, 130.9, 132.2, 137.6, 146.4, 146.5, 159.2, 159.6, 159.9. HRMS (ESI) calcd for $C_{22}H_{36}NOSi$ $[M + H]^+$: 354.2253, found 354.2249. The stereochemistry of the olefin moiety was assigned by a NOESY measurement.



(*E*)-2-(2-(1,2-diphenylvinyl)phenyl)pyridine (3ae): The procedure for the generation of the cobalt catalyst was modified by using P(4-$MeOC_6H_4$)$_3$ (21.1 mg, 0.06 mmol) and neopentylmagnesium bromide (0.69 M in THF, 0.43 mL, 0.3 mmol) instead of $PMePh_2$ and MeMgCl, respectively. The reaction of 2-phenylpyridine (43 mL, 0.3 mmol) and diphenylacetylene (80.2 mg, 0.45 mmol) for 24 h gave the title compound as a yellow oil (57.4 mg, 57%) after purification by silica gel chromatography (eluent: hexane/EtOAc = 30/1). The *E*-stereochemistry of the compound was assumed from other cases.

R_f 0.38 (hexane/EtOAc = 5/1);^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (s, 1H), 6.96-7.00 (m, 3H), 7.11-7.23 (m, 8H), 7.28-7.30 (m, 1H), 7.36-7.42 (m, 3H), 7.49 (m, 1H), 7.73 (dd, *J* = 1.4 Hz, 7.8Hz, 1H), 8.38 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.5, 123.7, 127.1, 127.3, 127.4, 128.2, 128.4, 129.0, 129.3, 129.4, 130.4, 130.7, 131.7, 135.4, 137.4, 138.9,

140.8, 142.0, 143.0, 149.2, 158.4. HRMS (ESI) calcd for $C_{25}H_{20}N$ $[M + H]^+$: 334.1596, found 334.1595.



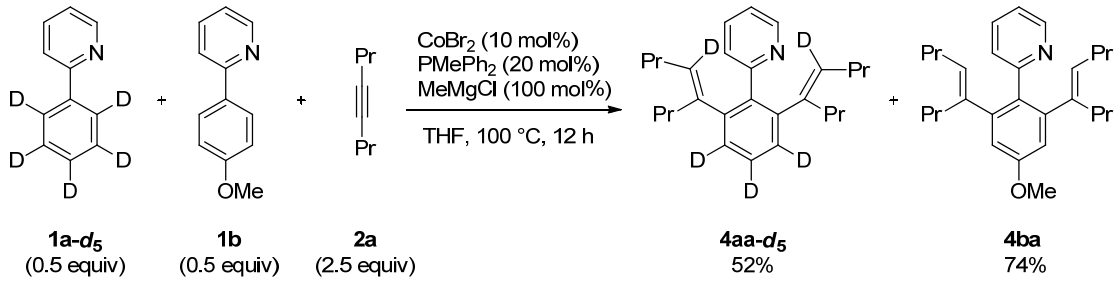
(*E*)-10-(1,2-diphenylvinyl)benzo[h]quinoline (3ah): The procedure for the generation of the cobalt catalyst was modified by using $P(4\text{-}MeOC_6H_4)_3$ (21.1 mg, 0.06 mmol) and neopentylmagnesium bromide (0.69 M in THF, 0.43 mL, 0.3 mmol) instead of $PMePh_2$ and MeMgCl, respectively. The reaction of benzo[*h*]quinoline (53.8 mg, 0.3 mmol) and diphenylacetylene (80.2 mg, 0.45 mmol) for 24 h gave a mixture of the title compound and its minor stereoisomer (ratio = 90/10 as determined by GC and ^{1}H NMR) as a yellow oil (83.3 mg, 78%) after purification by silica gel chromatography (eluent: hexane/EtOAc = 30/1). The *E*-stereochemistry of the major stereoisomer was assumed from other cases.

R_f 0.24 (hexane/EtOAc = 50/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (s, 1H), 7.00-7.43 (m, 11H), 7.63-8.02 (m, 6H), 8.84-8.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.2, 125.8, 126.0, 126.3, 126.6, 127.0, 127.2, 127.4, 127.8, 128.1, 128.4, 129.6, 129.7, 130.9, 131.9, 135.1, 135.2, 138.9, 141.2, 143.1, 146.4, 147.4, 147.6. HRMS (ESI) calcd for $C_{27}H_{20}N$ $[M + H]^+$: 358.1596, found 358.1596.

Deuterium-Labeling Experiments

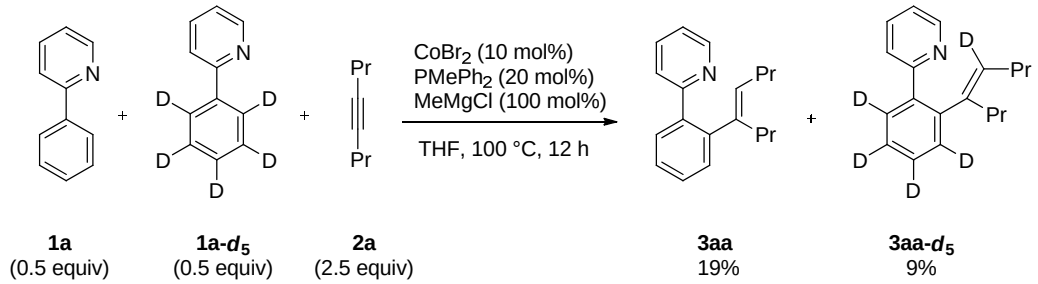
Crossover Experiment: A mixture of **1a**-d_5 (0.15 mmol), **1b** (0.15 mmol), and 4-octyne (0.75 mmol) was subjected to the standard reaction conditions. Purification of the crude mixture by silica gel chromatography (eluent: hexane/EtOAc = 100/1) afforded **4aa**-d_5

(29.9 mg, 52%) and **4ba** (43.9 mg, 74%). ^{1}H NMR analysis of each product indicated that no H/D crossover took place during the reaction.

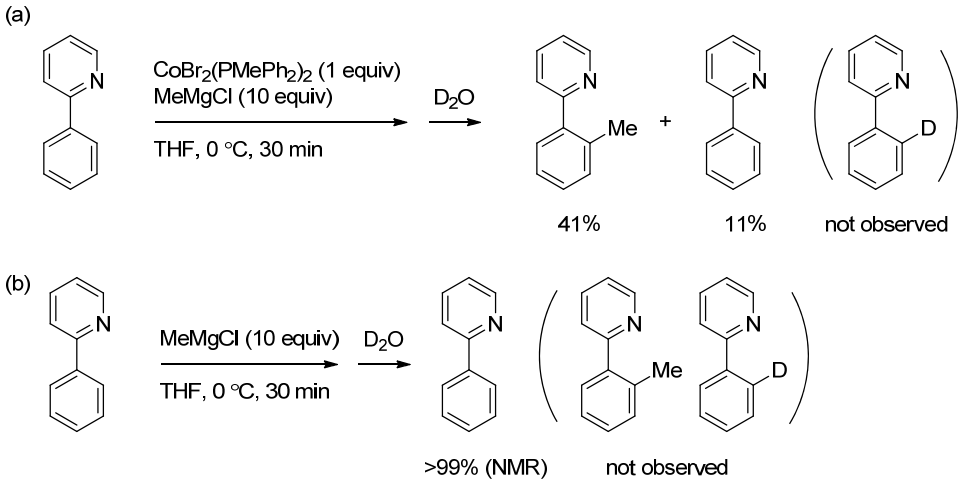


4aa-d_5: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (t, J = 7.3 Hz, 6H), 0.81 (t, J = 7.4 Hz, 6H), 1.14-1.28 (m, 8H), 1.76 (t, J = 7.4 Hz, 4H), 1.93 (t, J = 6.9 Hz, 4H), 7.08-7.12 (m, 1H), 7.20 (d, J = 7.8 Hz, 1H), 7.54 (m, 1H), 8.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.3, 21.7, 22.9, 30.3, 33.3, 121.1, 126.4, 128.5, 128.9, 130.8, 132.2, 134.8, 137.4, 140.8, 144.1, 160.2; HRMS (ESI) Calcd for $C_{27}H_{33}D_5N$ $[M + H]^+$ 381.3318, found 381.3318.

Competition Experiment: A mixture of **1a** (0.15 mmol), **1a**-d_5 (0.15 mmol) and 4-octyne (0.36 mmol) was subjected to the cobalt catalysis under milder conditions (40 °C) for shorter reaction time (2 h) to give a mixture of the monoalkenylation products **3aa** and **3aa**-d_5 (11.1 mg). The yields of **3aa** and **3aa**-d_5 were determined by ^{1}H NMR analysis to be 19% and 9%, respectively, which indicates an intermolecular kinetic isotope effect of 2.1.



Stoichiometric Reaction: To a mixture of 2-phenylpyridine (43 μL, 0.3 mmol) and $CoBr_2(PMePh_2)_2$ (185.8 mg, 0.3 mmol) in THF (2 mL) was added MeMgCl (3.0 M in THF, 1.0 mL, 3 mmol) dropwise at 0 °C. The reaction was stirred at this temperature for 30 min, and then quenched by addition of D_2O. Standard aqueous workup followed by silica gel chromatography afforded 2-(*o*-tolyl)pyridine (20.8 mg, 41%), 2-phenylpyridine (i.e., recovered starting material, 4.9 mg, 11%), and an inseparable mixture of unidentified products (5.3 mg). ^1H NMR analysis of the recovered starting material indicated no deuterium incorporation into the *ortho* position. Note that the reaction performed in the absence of $CoBr_2(PMePh_2)_2$, which was also quenched by D_2O, did not give either the *ortho*-methylation product or the *ortho*-deuteration product.



2.5 References

(1) For recent reviews, see: (a) Colby, D. A.; Bergmann, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. (d) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (e) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (g) Godula, K.; Sames, D *Science* **2006**, *312*, 67. (h) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*. 1077.

(2) Halbritter, G.; Knoch, F.; Wolski, A. Kisch, H. *Angew. Chem. Int. Ed.* **1994**, *33*, 1603.

(3) (a) Lim, Y.-G.; Lee, K.-H.; Koo, B. T.; Kang, J.-B. *Tetrahedron Lett.* **2001**, *42*, 7609. (b) Lim, S.-G.; Jun, H. L.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003**, *5*, 2759. (c) Cheng, K.; Yao, B.; Zhao, J.; Zhang, Y. *Org. Lett.* **2008**, *10*, 5309. (d) Katagiri, T.; Mukai, T.; Satoh, T.; Hirano, K.; Miura, M. *Chem. Lett.* **2009**, *38*, 118.

(4) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087.

(5) For chelation-assisted reactions other than C-H addition to olefins/alkynes, see: (a) Murahashi, S. *J. Am. Chem. Soc.* **1955**, *77*, 6403. (b) Murahashi, S.; Horiie, S. *J. Am. Chem. Soc.* **1956**, *78*, 4816. (c) Kuninobu, Y.; Nishina, Y.; Takeuchi, T.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 6518. (d) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858. (e) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925.

(6) For C-H addition to olefins/alkynes without chelation assistance, see: (a) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 3165. (b) Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 6965. (c) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146. (d) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (e) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170. (f) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 5070. (g) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama,T. *J. Am. Chem. Soc.* **2009**, *131*, 15996.

(7) (a) Klein, H.-F.; Lemke, U.; Lemke, M.; Brand, A. *Organometallics* **1998**, *17*, 4196. (b) Klein, H.-F.; Beck, R.; Flörke, U.; Haupt, H.-J. *Eur. J. Inorg. Chem.* **2003**, 853. (c) Klein, H.-F.; Camadanli, S.; Beck, R.; Leukel, D.; Flörke, U. *Angew. Chem. Int. Ed.* **2005**, *44*, 975. (d) Beck, R.; Frey, M.; Camadanli, S.; Klein, H.-F. *Dalton Trans.* **2008**, 4981. (e) Camadanli, S.; Beck, R.; Flörke, U.; Klein, H.-F. *Dalton Trans.* **2008**, 5701. (f) Beck, R.; Sun, H. J.; Li, X. Y.; Camadanli, S.; Klein, H.-F. *Eur. J. Inorg. Chem.* **2008**, 3253.

(8) (a) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100,* 2901. (b) Vollhardt, K. P. C. *Angew. Chem. Int. Ed.* **1984**, *23*, 539.

(9) Yoshikai, N.; Matsuda, H.; Makamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 15258.

(10) (a) Ohmiya, H.; Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 2207. (b) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374. (c) Kauffmann, T. *Angew. Chem. Int. Ed.* **1996**, *35*, 386.

(11) Klein, H.-F.; Camadanli, S.; Beck, R.; Leudel, D.; Flörke, U. *Angew. Chem. Int. Ed.* **2005**, *44*, 975.

(12) Lenges, C. P.; Brookhart, M.; Grant, B. E. *J. Organomet. Chem.* **1997**, *528*, 199.

(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(14) Drago, R. S.; Stahlbush, J. R.; Kitko, D. J.; Breese, J. *J. Am. Chem. Soc.* **1980**, *102*, 1884.

(15) Terashima, M.; Seki, K.; Yoshida, C.; Ohkura, K.; Kanaoka, Y. *Chem. Pharm. Bull.* **1985**, *33*, 1009.

(16) Mongin, F.; Mojovic, L.; Guillamet, B.; Trécourt, F.; Quéguiner, G. *J. Org. Chem.* **2002,** *67*, 8991.

(17) Ackermann, L.; Althammer, A. *Org. Lett.* **2006,** *8*, 3457.

(18) Gosmini, C.; Bassene-Ernst, C.; Durandetti, M. *Tetrahedron* **2009**, *65*, 6141.

(19) Gosmini, C.; Lasry, S.; Nedelec, J.-Y.; Perichon, J. *Tetrahedron* **1998**, *54*, 1289.

(20) Martinez-Barrasa, V.; Garcia de Viedma, A.; Burgos, C.; Alvarez-Builla, J. *Org. Lett.* **2000**, *2*, 3933.

(21) Billingsley, K. L.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 4695.

(22) Li, J.-H.; Zhu, Q.-M.; Xie, Y.-X. *Tetrahedron* **2006**, *62*, 10888.

(23) (a) Bonnet, V.; Mongin, F.; Trecourt, F.; Queguiner, G.; Knochel, P. *Tetrahedron*, **2002**, *58*, 4429. (b) Thummel, R. P.; Jahng, Y. *J. Org. Chem.* **1987**, *52*, 73.

(24) Ma, H.-C.; Jiang, X.-Z. *J. Org. Chem.* **2007**, *72*, 8943.

(25) McLaughlin, E. C.; Doyle, M. P. *J. Org. Chem.* **2008**, *73*, 4317.

(26) Saeeng, R.; Isobe, M. *Org. Lett.* **2005**, *7*, 1585.

(27) Stang, P. J.; Kitamura, T. *Org. Synth.* Vol. 70 (1992).

(28) von Hirschheydt, T.; Wolfart, V.; Gleiter, R.; Irngartinger, H.; Oeser, T.; Rominger, F.; Eisenträger, F. *J. Chem. Soc., Perkin Trans. 2* **2000**, 175.

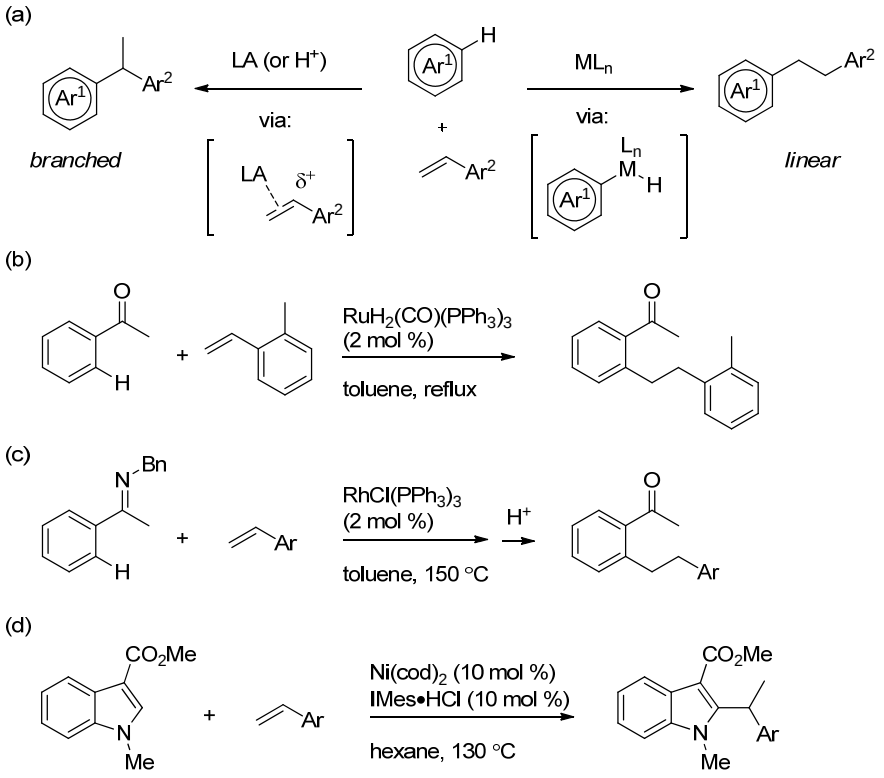
Chapter 3. Cobalt-Catalyzed Alkylation of 2-Arylpyridines with Styrenes

3.1 Introduction

The structural motifs of 1,1- and 1,2-diarylethane derivatives are often found in pharmaceuticals and biologically active compounds.[1] Among the most straightforward approaches to the construction of these structures is the addition of an aromatic C–H bond to a styrene derivative (i.e., hydroarylation). The hydroarylation reactions can be mechanistically categorized into two major types. One is the Friedel-Crafts type reaction promoted by Lewis acid or Brønsted acid, and the other involves transition metal-catalyzed aromatic C–H bond activation (Scheme 3.1a).

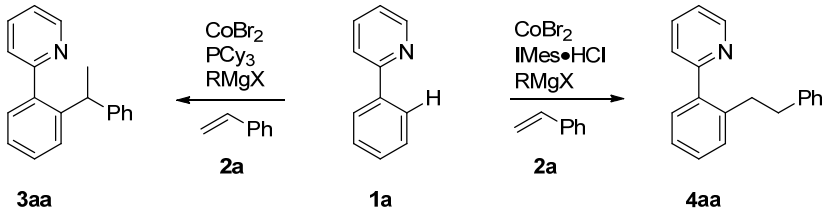
Importantly, these two types of reactions have different substrate scopes and regioselectivity. The Friedel-Crafts reaction is applicable to electron-rich arenes and is always branched-selectivity, because a positive charge builds up on the α-position of styrene upon coordination to Lewis acid.[2] On the other hand, the transition metal-catalyzed C–H bond activation approach typically requires a directing group or other electronic perturbations, and shows preference toward a linear addition product.[3,4] An early example of the linear selectivity can be found in Murai's ruthenium-catalyzed *ortho*-alkylation of acetophenone with 2-methylstyrene (Scheme 3.1b).[4a] The same regioselectivity was observed in the subsequent studies of Darses and coworkers on ruthenium catalysis.[4f,g,h] The linear selectivity is also common in rhodium catalysis. For example, Jun's ketimine-directed alkylation reaction (Scheme 3.1c) and Bergman/Ellman's C2-alkylation reaction of benzimidazole afforded linear adducts as the major products.[4d,e] Until 2010, only limited exceptions to this trend were known.[5] For example, in 2008 Nakao and Hiyama reported nickel-catalyzed addition of azoles and related heterocycles to styrenes that exclusively afford branched products (Scheme 3.1d).[5d]

Scheme 3.1. Hydroarylation Reactions of Styrenes



In light of the aforementioned background, we became interested in addressing two questions. First, is it possible to broaden the scope of branch-selective styrene hydroarylation using transition metal catalysis, and thereby to complement the limitation of the Fredel-Craft chemistry? Second, is it possible to control the regioselectivity of transition metal-catalyzed styrene hydroaylation by a ligand or other factors? These questions and our recent development of a cobalt catalytic system for *ortho* C–H alkenylation of arylpyridines with alkynes (Chapter 2) [6,7] promoted us to explore the possibility of styrene hydroarylation through cobalt-mediate, chelation-assisted C–H bond activation. In this chapter, we report on cobalt–phosphine and cobalt–NHC catalysts for the addition of 2-arylpyridines and imines to styrenes that afford the branched and linear diarylethane derivatives, respectively (Scheme 3.2).

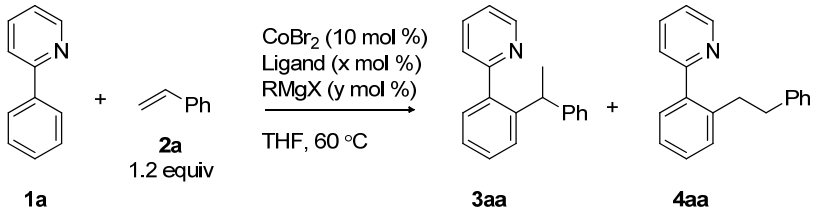
Scheme 3.2. Cobalt-Catalyzed Regioselectivity-Switchable Hydroarylation of Styrene



3.2 Results and discussion

We chose 2-phenylpyridine **1a** and styrene **2a** as model substrates to perform screening of reaction conditions. Selected data are summarized in Table 3.1. After some experiments, we found that a cobalt catalyst generated in situ from $CoBr_2$ (5 mol %), PCy_3 (10 mol %), and Me_3SiCH_2MgCl (50 mol %) promoted the alkylation of **1a** with **2a** in THF at 60 °C to afford the branched product **3aa** in 88% yield with high regioselectivity (*b/l* = 96:4) (entry 1). The yield of product **3aa** was not improved either by increasing the catalyst loading or by changing the Grignard reagent to *t*$BuCH_2MgBr$ (entries 2 and 3). The use of other phosphines such as PPh_3, and XPhos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) were less effective (entries 4 and 5).

Table 3.1. Cobalt-Catalyzed Reaction of 2-Phenylpyridine **1a** with Styrene **2a**[a]



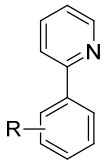
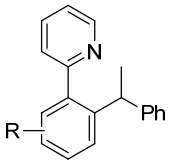
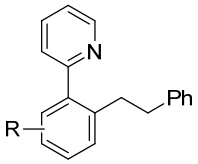
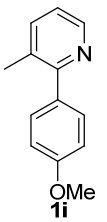
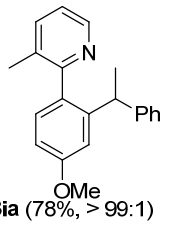
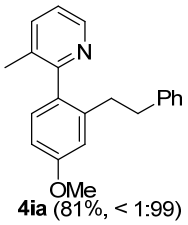
Entry	Ligand (x)	RMgX (y)	Yield (**3aa**:**4aa**)[b]
1	PCy_3 (5)	Me_3SiCH_2MgCl (50)	88% (96:4)[c,d]
2	PCy_3 (10)	Me_3SiCH_2MgCl (80)	81% (98:2)
3	PCy_3 (10)	*t*$BuCH_2MgBr$ (100)	68% (98:2)
4	PPh_3 (20)	*t*$BuCH_2MgBr$ (100)	4% (> 99:1)
5	XPhos (20)	*t*$BuCH_2MgBr$ (100)	42% (96:4)
6	IMes•HCl (10)	*t*$BuCH_2MgBr$ (100)	84% (3:97)[d]
7	IMes•HCl (10)	Me_3SiCH_2MgCl (100)	3% (< 1:99)
8	IPr•HCl (10)	*t*$BuCH_2MgBr$ (100)	2% (< 1:99)
9	IAd•HCl (10)	*t*$BuCH_2MgBr$ (100)	4% (50:50)
10	SIMes•HBF_4 (10)	*t*$BuCH_2MgBr$ (100)	32% (19:81)

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), $CoBr_2$ (10 mol %), ligand, RMgX, THF, 60 ºC, 12 h. [b] Determined by GC using *n*-tridecane as an internal standard. Isolated yield is shown in parenthesis. [c] 5 mol % $CoBr_2$ were used. [d] Isolated yields.

To our surprise, the reaction using a combination of IMes•HCl (1,3-dimesitylimidazolium chloride) and *t*$BuCH_2MgBr$ promoted the reaction but caused a nearly complete switch of the regioselectivity, affording the linear addition product **4aa** in 84% (entry 6).[8] In contrast to the case with PCy_3, the reaction was rather sensitive to the Grignard reagent, and was almost shut down with Me_3SiCH_2MgCl (entry 7). Other commercially available NHC preligands such as IPr•HCl (1,3-bis(2,6-diisopropylphenyl)imidazolium chloride) and IAd•HCl (1,3-bis(1-adamantyl)imidazolium chloride) were much less effective (entries 8 and 9). The reaction with a saturated NHC preligand, SIMes•HBF_4 (1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate), afforded the product in 32% yield but with a lower regioselectivity (*b/l* =19:81) (entry 10).

These two catalytic systems can be applied to various 2-arylpyridine derivatives (Table 3.2). The arylpyridines bearing electron-donating groups at the *meta*- or *para*-position reacted with styrene to afford the desired products in moderate to good yields with regioselectivity greater than 90:10 (entries 1-4). The regioselectivity dropped slightly when a *para*-fluoro group was present (entry 5). As for the arylpyridine bearing an electron-withdrawing trifluoromethyl group, both of the two catalytic systems afforded the branched product with moderate regioselectivity (entry 6). These observations indicate that the reaction pathways leading to the branched and linear products are competing with each other, and that the regioselectivity is not controlled solely by ligands, but also by the nature of the substrates. The Co–PCy_3 catalysis did not promote the reaction of an *ortho*-methyl substituted arylpyridine at all, while the *ortho*-methyl group did not interfere with the Co–IMes catalysis (entry 7). On the other hand, the steric hindrance at the pyridyl ring did not affect the reaction and regioselectivity (entry 8).

Table 3.2. Cobalt-Catalyzed Addition of 2-Phenylpyridine Derivatives to Styrene[a]

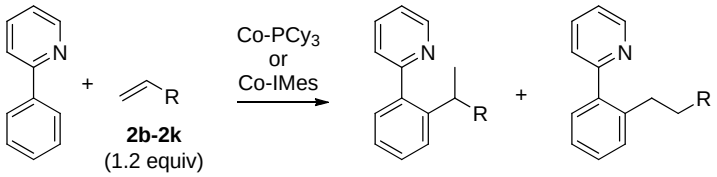
Entry	Substrate	Product (yield, branched:linear ratio)[b]	
		Co-PCy_3 catalysis	Co-IMes catalysis
			
1	**1b** (R = 4-OMe)	**3ba** (82%, 96:4)	**4ba** (74%, 2:98)
2	**1c** (R = 4-NMe_2)	**3ca** (46%, > 99:1)	**4ca** (53%, 1:99)
3	**1d** (R = 3-Me)	**3da** (67%, 97:3)[c]	**4da** (86%, 2:98)
4	**1e** (R = 3-OMe)	**3ea** (67%, > 99:1)	**4ea** (58%, 7:93)
5	**1f** (R = 4-F)	**3fa** (83%, 85:15)	**4fa** (82%, 14:86)[d]
6	**1g** (R = 4-CF_3)	**3ga** (31%, 79:21)	**4ga** (81%, 85:15)
7	**1h** (R = 2-Me)	**3ha** (N.R.)	**4ha** (81%, 1:99)[e]
8	 **1i**	 **3ia** (78%, > 99:1)	 **4ia** (81%, < 1:99)

[a] The reaction was performed with 0.3 mmol of the arene and 0.36 mmol of styrene. Co–PCy_3 catalysis: $CoBr_2$ (10 mol %), PCy_3 (10 mol %), Me_3SiCH_2MgBr (80 mol %), 40-80 °C, 12-72 h; Co–IMes catalysis: $CoBr_2$ (10 mol %), IMes•HCl (10 mol %), *t*$BuCH_2MgBr$ (100 mol %), 40-80 °C, 12-72 h. [b] Isolated yield. Regioselectivity was determined by ^1H NMR or GC. N.R. = No reaction. [c] *t*$BuCH_2MgBr$ was used instead of Me_3SiCH_2MgCl. [d] Dialkylation product was obtained in 18% yield. [e] Loadings of $CoBr_2$, the ligand, and the Grignard reagent were doubled.

Next, the hydroarylation of various styrenes with **1a** was explored and the result is summarized in Table 3.3. Styrenes with electron-donating groups reacted smoothly with 2-phenylpyridine to afford the desired products with good regioselectivity for both catalytic systems (entries 1-5), except that *ortho*-methyl substituted styrene resulted in low yield with the Co–PCy_3 catalysis. Styrenes bearing fluoro groups reacted sluggishly and required doubling of the catalytic loading in some cases to afford the reasonable yields (entries 6-8). 2-Fluorostyrene failed to participate in the reaction under the Co–PCy_3 catalysis. 2-

Vinylnaphthalene reacted with high branched selectivity under the Co–PCy_3 catalysis, while the same substrate showed rather poor regioselectivity with the Co–IMes catalyst (entry 9). The reaction with an aliphatic olefin such as *tert*-butylethylene resulted in low yield of the linear product under both the catalytic systems (entry 10).

Table 3.3. Cobalt-Catalyzed Addition of 2-Phenylpyridine to Various Styrene Derivatives[a]



1a **3** **4**

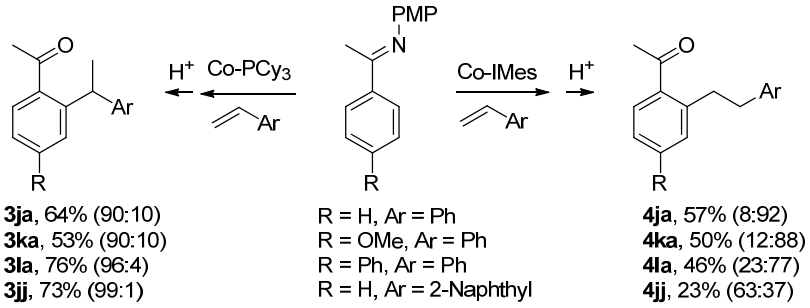
Entry	R	yield (**3**:**4**)[b]	
		Co-PCy_3 catalysis	Co-IMes catalysis
1	**2b** (R = 4-MeC_6H_4)	93% (> 99:1)	69% (1:99)[c]
2	**2c** (R = 3-MeC_6H_4)	87% (99:1)	60% (6:94)[c]
3	**2d** (R = 2-MeC_6H_4)	34% (92:8)[d]	78% (< 1:99)[c]
4	**2e** (R = 4-PhC_6H_4)	80% (99:1)	72% (9:91)
5	**2f** (R = 4-$MeOC_6H_4$)	68% (99:1)	74% (10:90)
6	**2g** (R = 4-FC_6H_4)	86% (94:6)[d]	69% (2:98)
7	**2h** (R = 3-FC_6H_4)	66% (> 99:1)[d]	62% (7:93)[d]
8	**2i** (R = 2-FC_6H_4)	N.R.	84% (2:98)[c]
9	**2j** (R = 2-Naphthyl)	88% (> 99:1)	68% (39:61)
10	**2k** (R = *t*Bu)	7% (< 1:99)	39% (< 1:99)[c]

[a] The reaction was performed with 0.3 mmol of the arene and 0.36 mmol of styrene. Co–PCy_3 catalysis: $CoBr_2$ (10 mol %), PCy_3 (10 mol %), Me_3SiCH_2MgBr (80 mol %), 60 °C, 12-52 h; Co–IMes catalysis: $CoBr_2$ (10 mol %), IMes•HCl (10 mol %), *t*$BuCH_2MgBr$ (100 mol %), 60 °C, 12-48 h. [b] Isolated yield. Regioselectivity was determined by ^1H NMR or GC. N.R. = No reaction. [c] Dialkylation products (5-13%) were obtained. [d] Loadings of $CoBr_2$, the ligand, and the Grignard reagent were doubled.

Both the catalytic systems were also applicable to the addition of arylimines to styrenes. The reaction was sluggish and required a higher catalyst loading of 20 mol % (Scheme 3.3). While the Co–PCy_3 catalysis afforded branched adducts in moderate to good

yields with high regioselectivity (≥ 90:10), the Co–IMes system gave linear adducts with varying yields and regioselectivities.

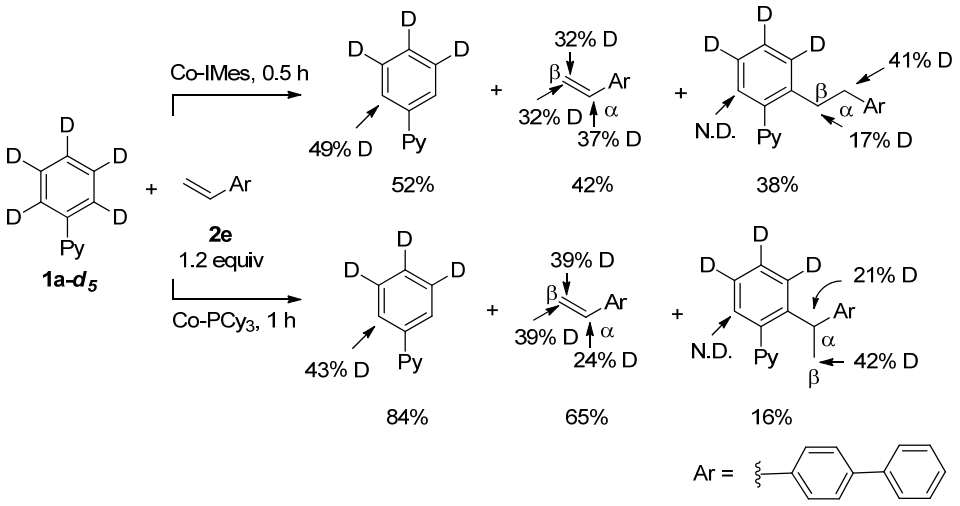
Scheme 3.3. Addition of Imines to Styrenes[a]



[a] The reaction was performed with 0.3 mmol of the imine and 0.36 mmol of the olefin. PMP = *p*-Methoxyphenyl. Co–PCy_3 catalysis: $CoBr_2$ (20 mol %), PCy_3 (20 mol %), Me_3SiCH_2MgBr (160 mol %), 60 °C, 72 h; Co–IMes catalysis: $CoBr_2$ (20 mol %), IMes•HCl (20 mol %), *t*$BuCH_2MgBr$ (200 mol %), 60 °C, 72 h. In parentheses is shown the *b*/*l* ratio.

To gain insight into the reaction mechanism, we performed deuterium-labeling experiments (Scheme 3.4). The reactions of **1a**-d_5 with 4-vinylbiphenyl **2e** were stopped at an early stage for both the Co–PCy_3 and Co–IMes catalytic systems. Judged from ^{1}H NMR of the starting materials and products, the H/D scrambling between **1a**-d_5 and **2e** was observed. The significant decrease of the deuterium content at the *ortho*-position of **1a**-d_5 was detected. Meanwhile, a considerable degree of deuterium incorporation into the α- and β-position of **2e** was observed. We also noted that the deuterium content was higher at β-position than α-position under the Co–PCy_3 catalytic system, while the trend was reversed in the Co–IMes catalytic system.

Scheme 3.4. Deuterium-Labeling Experiments[a]

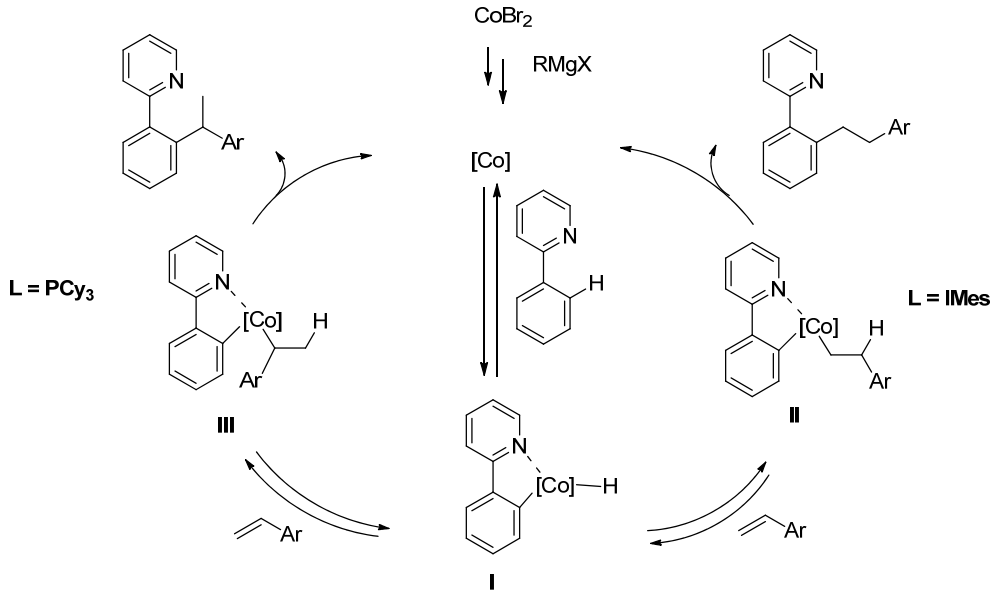


[a] Py = 2-pyridyl; Ar = 4-PhC_6H_4. Co–PCy_3 catalysis: $CoBr_2$ (10 mol %), PCy_3 (10 mol %), Me_3SiCH_2MgCl (80 mol %), 60 °C, 1 h; Co–IMes catalysis: $CoBr_2$ (10 mol %), IMes•HCl (10 mol %), *t*$BuCH_2MgBr$ (100 mol %), 60 °C, 30 min. Deuterium incorporation was determined by ^1H NMR analysis. N.D. = Not determined due to overlapping peaks.

A plausible mechanism of the present reaction would involve the following steps (Scheme 3.5): (1) chelation-assisted oxidative addition of the C–H bond to the cobalt center,[6,9] (2) styrene insertion into the Co–H bond, and (3) reductive elimination of the resulting aryl(alkyl)cobalt species **II** and **III** to generate the corresponding linear and branched products, respectively. We speculate that an organocobalt(0)ate species are involved in the reaction as reactive species.[6,7,10] The observation of H/D scrambling indicates that both the C–H bond oxidative addition and olefin insertion steps are reversible, and that the two insertion pathways are competing with each other. This means that the reductive elimination step would be the rate- and regioselectivity-determining step. We speculate that the branched selectivity in the Co–PCy_3 catalyst is governed by the thermodynamic preference for the benzylcobalt species, which may exist as a pi-benzyl type complex.[5d,11] On the other hand, the linear selectivity in the Co–IMes catalysis may originate from the steric nature of the IMes ligand, which would prefer to avoid steric

congestion around the cobalt center. The regioselectivity should also be affected by substituents on the arene and styrene substrates (e.g. Table 3.2, entry 6).

Scheme 3.5. Plausible Catalytic Cycle.



3.3 Conclusion

In summary, we have developed cobalt–phosphine and cobalt–carbene catalysts for alkylation reaction of 2-arylpyridines with styrenes to afford branched and linear products with high regioselectivity, respectively. The ligand-controlled regioselectivity switch is very rare in hydroarylation reaction.[4g] The inexpensive cobalt catalysts and the relatively mild reaction conditions are also attractive features of the reaction. Further extension of this chemistry to more diverse aromatic and olefinic substrates could significantly broaden the scope of aromatic alkylation reactions.

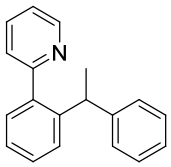
3.4 Experimental section

Materials. Unless otherwise noted, commercial reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. Anhydrous cobalt(II) bromide was purchased from Alfa Aesar (99% or 99.99%) or Aldrich (99%), and was used as received. THF was distilled over Na/benzophenone. Grignard reagents except MeMgCl (purchased from Aldrich) were prepared from the corresponding halides and magnesium turnings in anhydrous THF and titrated before use. The following 2-arylpyridine derivatives were prepared by a similar procedure,[12] and their spectral data showed good agreement with the literature data: 2-(4-methoxyphenyl)pyridine (**1b**),[13] *N*,*N*-dimethyl-4-(pyridin-2-yl)aniline (**1c**),[14] 2-(*m*-tolyl)pyridine (**1d**),[15] 2-(3-methoxyphenyl)pyridine (**1e**),[16] 2-(4-fluorophenyl)pyridine (**1f**),[12] 2-(4-(trifluoromethyl)phenyl)pyridine (**1e**),[17] 2-(3-(trifluoromethyl)phenyl)pyridine (**1g**),[18] 2-(*o*-tolyl)pyridine (**1h**),[13] 2-(4-methoxyphenyl)-3-methylpyridine (**1i**),[6] and 2-(phenyl-d_5)pyridine (**1a**-d_5).[19]

(*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1j**) was prepared from acetophenone and *p*-anisidine according to the literature procedure.[20] 4-Vinylbiphenyl (**2e**) was prepared according to the literature procedure,[21] and its spectral data showed good agreement with the literature data.[22]

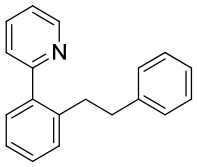
A Typical Procedure for Co–PCy_3 Catalyzed Hydroarylation: In a Schlenk tube were placed $CoBr_2$ (3.3 mg, 0.015 mmol), PCy_3 (4.2 mg, 0.015 mmol), 2-phenylpyridine (43 μL, 0.3 mmol), and THF (0.73 mL). To the mixture was added a THF solution of Me_3SiCH_2MgCl (0.89 M, 0.27 mL, 0.24 mmol) dropwise at 0 °C. After stirring for 30 min, styrene (41 μL, 0.36 mmol) was added. The resulting mixture was stirred at 60 °C for 12 h, and then allowed to room temperature, diluted with ether (1 mL), and quenched by saturated aqueous solution of NH_4Cl (1 mL). The aqueous layer was extracted with ethyl acetate (3

x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 20/1 – 12/1) to afford 2-(2-(1-phenylethyl)phenyl)pyridine (**3aa**, 68.6 mg, 88 %, b:l (branched:linear) = 96:4) as a light yellow oil.

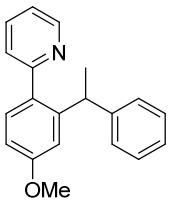


3aa: R_f 0.13 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (d, J = 7.2 Hz, 3H), 4.54 (q, J = 7.2 Hz, 1H), 7.01-7.09 (m, 3H), 7.12-7.21 (m, 4H), 7.25-7.33 (m, 4H), 7.58-7.62 (m, 1H), 8.67-8.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 40.0, 121.8, 124.5, 125.8, 126.1, 127.75, 127.77, 128.2, 128.7, 129.9, 136.2, 140.7, 144.4, 146.7, 149.2, 160.5; HRMS (ESI) Calcd for $C_{19}H_{18}N$ $[M + H]^+$ 260.1439, found 260.1434.

A Typical Procedure for Co–IMes Catalyzed Co–IMes Catalyzed Hydroarylation: In a Schlenk tube were placed $CoBr_2$ (6.6 mg, 0.03 mmol), IMes•HCl (10.2 mg, 0.03 mmol), 2-phenylpyridine (43 μL, 0.3 mmol), and THF (0.62 mL). To the mixture was added a THF solution of *t*$BuCH_2MgBr$ (0.80 M, 0.38 mL, 0.3 mmol) dropwise at 0 °C. After stirring for 30 min, styrene (41 μL, 0.36 mmol) was added. The resulting mixture was stirred at 60 °C for 6 h, and then allowed to room temperature, diluted with ether (1 mL), and quenched by saturated aqueous solution of NH_4Cl (1 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 20/1 – 12/1) to afford 2-(2-phenethylphenyl)pyridine (**4aa**, 65.4 mg, 88 %, b:l = 3:97) as a light yellow oil.

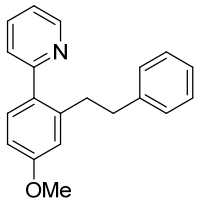


4aa: R_f 0.13 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.75-2.79 (m, 2H), 2.99-3.03 (m, 2H), 7.00 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.18-7.25 (m, 4H), 7.28-7.35 (m, 5H), 7.70 (t, *J* = 7.6 Hz, 1H), 8.75 (d, *J* = 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.6, 38.0, 121.9, 124.2, 125.9, 126.3, 128.38, 128.48, 128.55, 130.0, 130.1, 136.4, 139.9, 140.6, 142.2, 149.2, 160.3; HRMS (ESI) Calcd for $C_{19}H_{18}N$ $[M + H]^+$ 260.1439, found 260.1435.



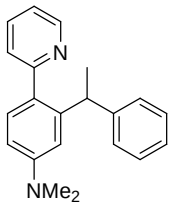
2-(4-Methoxy-2-(1-phenylethyl)phenyl)pyridine (3ba): 2-(4-Methoxyphenyl)pyridine (**1b**, 55.6 mg, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (10 mol % $CoBr_2$, 10 mol % PCy_3, 80 mol % Me_3SiCH_2MgCl, 60 °C, 15 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 10/1) of the crude product afforded the title compound as a light yellow oil (71.0 mg, 82%, b:l = 96:4).

R_f 0.21 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (d, *J* = 7.2 Hz, 3H), 3.78 (s, 3H), 4.59 (q, *J* = 7.2 Hz, 1H), 6.80 (dd, *J* = 8.4 Hz, 2.8 Hz, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 2H), 7.07-7.19 (m, 5H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.58-7.60 (m, 1H), 8.65-8.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 40.0, 55.4, 110.8, 114.0, 121.5, 124.6, 125.8, 127.7, 128.2, 131.2, 133.6, 136.2, 146.0, 146.5, 149.2, 159.8, 160.2; HRMS (ESI) Calcd for $C_{20}H_{20}NO$ $[M + H]^+$ 290.1545, found 290.1549.



2-(4-Methoxy-2-phenethylphenyl)pyridine (4ba): 2-(4-Methoxyphenyl)pyridine (**1b**, 55.6 mg, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % *t*$BuCH_2MgBr$, 60 °C, 15 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 10/1) of the crude product afforded the title compound as a light yellow oil (64.4 mg, 74%, b:l = 2:98).

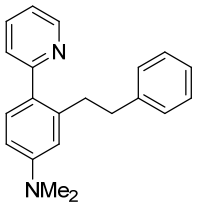
R_f 0.21 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.76-2.80 (m, 2H), 3.00-3.04 (m, 2H), 3.81 (s, 3H), 6.82-6.84 (m, 2H), 7.02 (d, *J* = 7.2 Hz, 2H), 7.13-7.19 (m, 1H), 7.21-7.29 (m, 3H), 7.30-7.31 (m, 2H), 7.67-7.71 (m, 1H), 8.67-8.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.8, 37.9, 55.5, 111.6, 115.6, 121.6, 124.3, 125.9, 128.4, 128.5, 131.3, 133.4, 136.4, 141.6, 142.2, 149.2, 159.7, 160.1. HRMS (ESI) Calcd for $C_{20}H_{20}NO$ $[M + H]^+$ 290.1545, found 290.1542.



***N,N*-dimethyl-3-(1-phenylethyl)-4-(pyridin-2-yl)aniline (3ca):** *N,N*-Dimethyl-4-(pyridin-2-yl)amine (**1c**, 59.5 mg, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (10 mol % $CoBr_2$, 10 mol % PCy_3, 80 mol % Me_3SiCH_2MgCl, 60 °C, 24 h). Silica gel chromatography (eluent: hexane/EtOAc = 15/1) of the crude product afforded the title compound as a yellow oil (42.1 mg, 46%, b:l > 99:1).

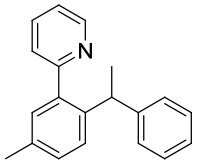
R_f 0.37 (hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (d, *J* = 7.2 Hz, 3H) , 2.94 (s, 6H), 4.64 (q, *J* = 7.2 Hz, 1H), 6.64-6.66 (m, 2H), 7.08-7.10 (m, 3H), 7.14-7.17 (m,

4H), 7.17-7.25 (m, 1H), 7.56-7.58 (m, 1H), 8.64-8.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 40.0, 40.8, 110.5, 111.9, 121.1, 124.6, 125.7, 127.8, 128.2, 129.5, 131.0, 136.1, 145.1, 147.1, 149.2, 150.8, 160.8; HRMS (ESI) Calcd for $C_{20}H_{23}N_2$ $[M + H]^+$ 303.1861, found 303.1860.



***N,N*-dimethyl-3-phenethyl-4-(pyridin-2-yl)aniline (4ca):** *N,N*-Dimethyl-4-(pyridin-2-yl)amine (**1c**, 59.5 mg, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % *t*$BuCH_2MgBr$, 60 °C, 24 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a yellow oil (44.2 mg, 53%, b:l = 1:99).

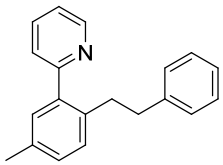
R_f 0.37 (hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.78-2.82 (m, 2H), 2.96 (s, 6H), 3.00-3.08 (m, 2H), 6.62 (d, *J* = 2.4 Hz, 1H), 6.66 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 2H), 7.13- 7.23 (m, 4H), 7.23-7.34 (m, 2H), 7.64-7.69 (m, 1H), 8.66-8.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.3, 38.2, 40.7, 110.6, 114.1, 121.0, 124.1, 125.8, 128.4, 128.5, 129.1, 131.1, 136.2, 140.9, 142.6, 149.1, 150.7, 160.7; HRMS (ESI) Calcd for $C_{20}H_{23}N_2$ $[M + H]^+$ 303.1861, found 303.1864.



2-(5-Methyl-2-(1-phenylethyl)phenyl)pyridine (3da): 2-(*m*-Tolyl)pyridine (**1d**, 49 μL, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (10 mol % $CoBr_2$, 10 mol % PCy_3, 80 mol % *t*$BuCH_2MgBr$, 60 °C, 48 h). Silica gel

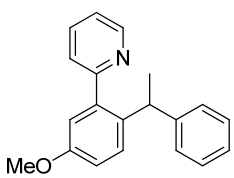
chromatography (eluent: hexane/EtOAc = 40/1 – 10/1) of the crude product afforded the title compound as a light yellow oil (54.0 mg, 67%, b:l = 97:3).

R_f 0.26 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (d, J = 7.2 Hz, 3H), 2.34 (s, 3H), 4.46 (q, J = 7.2 Hz, 1H), 7.04 (d, J = 7.2 Hz, 2H), 7.07-7.09 (m, 1H), 7.11-7.22 (m, 7H), 7.58-7.62 (m, 1H), 8.68-8.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 22.3, 39.7, 121.8, 124.5, 125.7, 127.68, 127.71, 128.2, 129.4, 130.5, 135.6, 136.1, 140.5, 141.3, 146.9, 149.3, 160.5; HRMS (ESI) Calcd for $C_{20}H_{20}N$ $[M + H]^+$ 274.1596, found 274.1598.



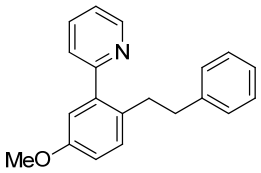
2-(5-Methyl-2-phenethylphenyl)pyridine (4da): 2-(*m*-Tolyl)pyridine (**1d**, 49 μL, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % *t*$BuCH_2MgBr$, 60 °C, 48 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 12/1) of the crude product afforded the title compound as a light yellow oil (70.5 mg, 86%, b:l = 2:98).

R_f 0.26 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.72-2.76 (m, 2H), 2.94-2.98 (m, 2H), 7.00 (d, J = 6.8 Hz, 2H), 7.10-7.24 (m, 7H), 7.32 (d, J = 6.8 Hz, 1H), 7.67-7.71 (m, 1H), 8.68-8.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 35.2, 38.1, 121.8, 124.2, 125.9, 128.4, 128.5, 129.3, 130.0, 130.6, 135.7, 136.3, 136.8, 140.4, 142.3, 149.3, 160.4; HRMS (ESI) Calcd for $C_{20}H_{20}N$ $[M + H]^+$ 274.1596, found 274.1593.



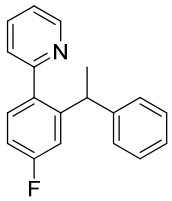
2-(5-Methoxy-2-(1-phenylethyl)phenyl)pyridine (3ea): 2-(*m*-Methoxyl)pyridine (**1e**, 48 μL, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (10 mol % $CoBr_2$, 10 mol % PCy_3, 80 mol % Me_3SiCH_2MgCl, 60 °C, 48 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 15/1) of the crude product afforded the title compound as a light yellow solid (55.8 mg, 67%, b:l > 99:1).

m.p. 83.2-83.9 ºC; R_f 0.17 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68 (d, *J* = 7.2 Hz, 3H), 3.54 (s, 3H), 4.31 (q, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.06-7.11 (m, 1H), 7.17 (d, *J* = 4.4 Hz, 2H), 7.20-7.63 (m, 5H), 7.63-7.65 (m, 1H), 8.66-8.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 38.1, 55.7, 112.5, 121.9, 122.5, 124.3, 125.0, 127.2, 127.4, 127.6, 133.3, 136.0, 142.4, 146.0, 149.3, 158.6, 160.7; HRMS (ESI) Calcd for $C_{20}H_{20}NO$ $[M + H]^+$ 290.1545, found 290.1544.



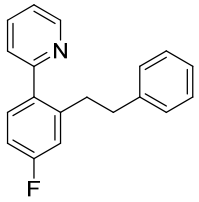
2-(5-Methoxy-2-phenethylphenyl)pyridine (4ea): 2-(*m*-Methoxyl)pyridine (**1e**, 48 μL, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % *t*$BuCH_2MgBr$, 60 °C, 48 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 15/1) of the crude product afforded the title compound as a light yellow oil (47.7 mg, 58%, b:l = 7:93).

R_f 0.17 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.70-2.74 (m, 2H), 2.91-2.95 (m, 2H), 3.82 (s, 3H), 6.89-6.91 (m, 2H), 6.98 (d, *J* = 7.2 Hz, 2H), 7.13-7.32 (m, 6H), 7.72-7.73 (m, 1H), 8.68-8.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.7, 38.2, 55.6, 114.5, 115.1, 122.0, 124.2, 125.9, 128.4, 128.5, 131.2, 132.1, 136.5, 141.5, 142.3, 149.3, 157.9, 160.2; HRMS (ESI) Calcd for $C_{20}H_{20}NO$ $[M + H]^+$ 290.1545, found 290.1548.



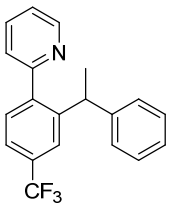
2-(4-Fluoro-2-(1-phenylethyl)phenyl)pyridine (3fa): 2-(4-Fluorophenyl)pyridine (**1f**, 52 mg, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (10 mol % $CoBr_2$, 10 mol % PCy_3, 80 mol % Me_3SiCH_2MgCl, 60 °C, 12 h). Silica gel chromatography (eluent: hexane/EtOAc = 20/1 – 10/1) of the crude product afforded the title compound as a light yellow oil (69.0 mg, 83%, b:l = 85:15).

R_f 0.13 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (d, J = 7.2 Hz, 3H), 4.55 (q, J = 7.2 Hz, 1H), 6.96-7.28 (m, 10H), 7.59-7.63 (m, 1H), 8.66-8.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 40.1, 113.1 (d, $^2J_{C–F}$ = 21 Hz), 114.6 (d, $^2J_{C–F}$ = 22 Hz), 122.0, 124.6, 126.1, 127.7, 128.4, 131.6 (d, $^3J_{C–F}$ = 8 Hz), 136.4, 136.6 (d, $^4J_{C–F}$ = 3 Hz), 145.9, 147.3 (d, $^3J_{C–F}$ = 7 Hz), 149.3, 159.6, 163.1 (d, $^1J_{C–F}$ = 245 Hz); HRMS (ESI) Calcd for $C_{19}H_{17}FN$ $[M + H]^+$ 278.1345, found 278.1343.



2-(4-Fluoro-2-phenethylphenyl)pyridine (4fa): 2-(4-Fluorophenyl)pyridine (**1f**, 52 mg, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % tBuCH$_2$MgBr, 60 °C, 12 h). Silica gel chromatography (eluent: hexane/EtOAc = 20/1 – 10/1) of the crude product afforded an inseparable mixture of the title compound (55.9 mg, 82%, b:l = 14:86) and a dialkylation product (19.3 mg, 18%) as a light yellow oil.

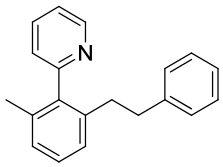
R_f 0.13 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.75-2.79 (m, 2H), 3.00-3.02 (m, 2H), 6.86-7.02 (m, 3H), 7.13-7.33 (m, 7H), 7.68-7.70 (m, 1H), 8.67-8.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.5, 37.6, 113.1 (d, $^2J_{C–F}$ = 21 Hz), 116.6 (d, $^2J_{C–F}$ = 20 Hz), 122.0, 124.3, 126.1, 128.4, 128.5, 131.7 (d, $^3J_{C–F}$ = 9 Hz), 136.5, 136.8 (d, $^4J_{C–F}$ = 3 Hz), 141.7, 142.7,(d, $^3J_{C–F}$ = 7 Hz), 149.3, 159.5, 162.9 (d, $^1J_{C–F}$ = 245 Hz); HRMS (ESI) Calcd for $C_{19}H_{17}FN$ $[M + H]^+$ 278.1345, found 278.1347.



2-(2-(1-Phenylethyl)-4-(trifluoromethyl)phenyl)pyridine (3ga): 2-(4-(Trifluoromethyl)phenyl)pyridine (**1g**, 67 mg, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (10 mol % $CoBr_2$, 10 mol % PCy_3, 80 mol % Me_3SiCH_2MgCl, 40 °C, 15 h). Silica gel chromatography (eluent: hexane/EtOAc = 40/1 – 10/1) of the crude product afforded the title compound as a yellow oil (30.8 mg, 31%, b:l = 79:21).

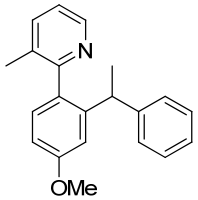
R_f 0.22 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (d, J = 7.2 Hz, 3H), 4.59 (q, J = 7.2 Hz, 1H), 6.95 (d, J = 7.2 Hz, 2H), 7.08-7.11 (m, 2H), 7.14-7.18 (m, 2H), 7.20-7.25 (m, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.62-7.64 (m, 2H), 8.69-8.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 39.9, 122.3, 122.9 (q, $^3J_{C–F}$ = 3.5 Hz), 124.25, 124.34 (q, $^3J_{C–F}$ = 3.7 Hz), 126.0, 127.5, 128.3, 130.6 (q, $^2J_{C–F}$ = 32 Hz), 136.3, 143.9, 145.3, 145.5, 149.2, 158.9. The signal for the carbon atom of the CF_3 group could not be identified due to overlapping with other signals; HRMS (ESI) Calcd for $C_{20}H_{17}F_3N$ $[M + H]^+$ 328.1313, found 328.1310.

The reaction of the same substrates under the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % *t*$BuCH_2MgBr$, 80 °C, 14 h) also afforded the compound **3ga** as the major isomer (79.4 mg, 81%, b:l = 85:15).



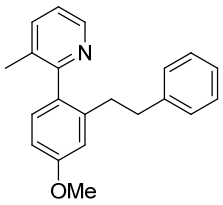
2-(2-Methyl-6-phenethylphenyl)pyridine (4ha): 2-(*o*-Tolyl)pyridine (**1h**, 49 μL, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (20 mol % $CoBr_2$, 20 mol % IMes•HCl, 200 mol % *t*$BuCH_2MgBr$, 60 °C, 12 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light yellow oil (66.6 mg, 81%, b:l = 1:99).

R_f 0.41 (hexane/EtOAc = 15/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.60-2.70 (m, 4H), 6.91 (d, *J* = 6.8 Hz, 2H), 7.11-7.24 (m, 8H), 7.70-7.74 (m, 1H), 8.60-8.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5, 36.2, 37.9, 122.0, 124.8, 125.9, 126.9, 128.0, 128.2, 128.37, 128.41, 136.1, 136.3, 139.8, 140.5, 142.2, 149.7, 159.8; HRMS (ESI) Calcd for $C_{20}H_{20}N$ $[M + H]^+$ 274.1596, found 274.1597.



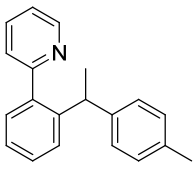
2-(4-Methoxy-2-(1-phenylethyl)phenyl)-3-methylpyridine (3ia): 2-(4-Methoxyphenyl)-3-methylpyridine (**1i**, 56 μL, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (10 mol % $CoBr_2$, 10 mol % PCy_3, 80 mol % Me_3SiCH_2MgCl, 60 °C, 48 h). Silica gel chromatography (eluent: hexane/EtOAc = 15/1) of the crude product afforded the title compound as a light yellow oil (70.1 mg, 78%, b:l > 99:1).

R_f 0.17 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.45 (d, J = 7.2 Hz, 3H), 1.62 (brs, 3H), 3.77 (s, 3H), 4.02 (brs, 1H), 6.84-6.92 (m, 2H), 7.01-7.15 (m, 6H), 7.24-7.28 (m, 1H), 7.57 (brs, 1H), 8.47-8.48 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.8, 21.3, 40.9 (this chemical shift was read from ^{13}C NMR in $CDCl_3$), 55.0, 110.4, 113.0, 122.3, 125.8, 127.2, 128.0, 128.2, 130.0, 131.9, 132.3, 137.7, 145.4, 146.3, 158.7, 158.9. The signal for the benzylic carbon atom was overlapping with the DMSO peaks. It appeared at 40.9 ppm in $CDCl_3$; HRMS (ESI) Calcd for $C_{21}H_{22}NO$ $[M + H]^+$ 304.1701, found 304.1699.



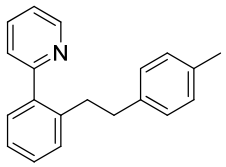
2-(4-Methoxy-2-phenethylphenyl)-3-methylpyridine (4ia): 2-(4-Methoxyphenyl)-3-methylpyridine (**1i**, 56 μL, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % tBuCH$_2$MgBr, 40 °C, 48 h). Silica gel chromatography (eluent: hexane/EtOAc = 10/1 – 8/1) of the crude product afforded the title compound as a light yellow oil (73.3 mg, 81%, b:l < 1:99).

R_f 0.17 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.70 (brs, 4H), 3.81 (s, 3H), 6.81-6.83 (m, 2H), 6.93 (d, J = 7.2 Hz, 2H), 7.10-7.13 (m, 2H), 7.16-7.20 (m, 3H), 7.56 (d, J = 7.6 Hz, 1H), 8.53 (d, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 35.8, 37.3, 55.3, 111.3, 115.0, 122.2, 125.8, 128.27, 128.32, 130.1, 132.0, 132.7, 137.8, 141.1, 142.0, 146.6, 159.25, 159.28; HRMS (ESI) Calcd for $C_{21}H_{22}NO$ $[M + H]^+$ 304.1701, found 304.1700.



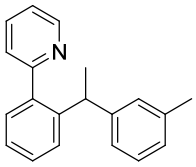
2-(2-(1-*p*-Tolylethyl)phenyl)pyridine (3ab): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 4-methylstyrene (**2b**, 47 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (10 mol % $CoBr_2$, 10 mol % PCy_3, 80 mol % Me_3SiCH_2MgCl, 60 °C, 12 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 12/1) of the crude product afforded the title compound as a yellow oil (76.1 mg, 93%, b:l > 99:1).

R_f 0.29 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71 (d, J = 7.2 Hz, 3H), 2.42 (s, 3H), 4.64 (q, J = 7.2 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.33-7.51 (m, 6H), 7.77-7.81 (m, 1H), 8.84-8.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 22.2, 39.5, 121.8, 124.6, 126.0, 127.6, 127.7, 128.7, 128.9, 129.8, 135.2, 136.2, 140.5, 143.6, 144.6, 149.2, 160.4; HRMS (ESI) Calcd for $C_{20}H_{20}N$ $[M + H]^+$ 274.1596, found 274.1596.



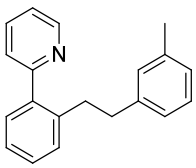
2-(2-(4-Methylphenethyl)phenyl)pyridine (4ab): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 4-methylstyrene (**2b**, 47 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % *t*$BuCH_2MgBr$, 60 °C, 12 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 12/1) of the crude product afforded an inseparable mixture of the title compound (56.6 mg, 69%, b:l = 1:99) and a dialkylation product (10.3 mg, 9%) as a colorless oil.

R_f 0.29 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3H), 2.71-2.75 (m, 2H), 2.97-3.01 (m, 2H), 6.89 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 7.6 Hz, 2H), 7.27-7.35 (m, 6H), 7.69-7.72 (m, 1H), 8.68-8.69 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 35.7, 37.5, 121.9, 124.2, 126.2, 128.26, 128.33, 128.5, 129.9, 130.0, 135.3, 136.4, 139.1, 140.0, 140.6, 149.2, 160.3; HRMS (ESI) Calcd for $C_{20}H_{20}N$ $[M + H]^+$ 274.1596, found 274.1597.



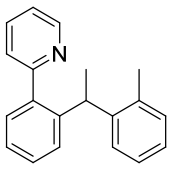
2-(2-(1-*m*-Tolylethyl)phenyl)pyridine: (3ac): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 3-methylstyrene (**2c**, 48 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (10 mol % $CoBr_2$, 10 mol % PCy_3, 80 mol % Me_3SiCH_2MgCl, 60 °C, 12 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 13/1) of the crude product afforded the title compound as a colorless oil (71.1 mg, 87%, b:l = 99:1).

R_f 0.17 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62 (d, J = 7.2 Hz, 3H), 2.30 (s, 3H), 4.56 (q, J = 7.2 Hz, 1H), 6.89-6.91 (m, 2H), 6.97 (d, J = 7.2 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.29-7.42 (m, 5H), 7.66-7.70 (m, 1H), 8.74-8.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 22.2, 33.9, 121.8, 124.6, 124.8, 126.0, 126.6, 127.7, 128.1, 128.56, 128.64, 129.8, 136.1, 137.6, 140.6, 144.5, 146.6, 149.2, 160.5. HRMS (ESI) Calcd for $C_{20}H_{20}N$ $[M + H]^+$ 274.1596, found 274.1599.



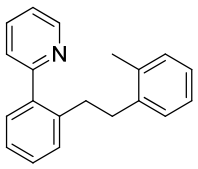
2-(2-(3-Methylphenethyl)phenyl)pyridine (4ac): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 3-methylstyrene (**2c**, 48 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % *t*$BuCH_2MgBr$, 60 °C, 13 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 13/1) of the crude product afforded an inseparable mixture of the title compound (49.6 mg, 60%, b:l = 6:94) and a dialkylation product (5.6 mg, 5%) as a colorless oil.

R_f 0.17 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.71-2.75 (m, 2H), 2.98-3.02 (m, 2H), 6.78-6.96 (m, 2H), 6.95 (d, J = 7.6 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H), 7.22-7.36 (m, 6H), 7.69-7.71 (m, 1H), 8.69-8.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 35.6, 38.0, 121.9, 124.2, 125.4, 126.2, 126.6, 128.3, 128.5, 129.3, 129.9, 130.0, 136.4, 137.9, 140.1, 140.6, 142.1, 149.2, 160.4; HRMS (ESI) Calcd for $C_{20}H_{20}N$ $[M + H]^+$ 274.1596, found 274.1600.



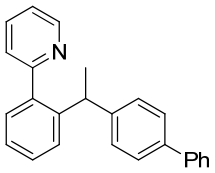
2-(2-(1-o-Tolylethyl)phenyl)pyridine (3ad): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 2-methylstyrene (**2d**, 48 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (20 mol % $CoBr_2$, 20 mol % PCy_3, 160 mol % Me_3SiCH_2MgCl, 60 °C, 48 h). Silica gel chromatography (eluent: hexane/EtOAc = 40/1 – 13/1) of the crude product afforded the title compound as a yellow solid (27.6 mg, 34%, b:l = 92:8).

m.p. 94.8-95.5 ºC; R_f 0.26 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (d, J = 7.2 Hz, 3H), 1.88 (s, 3H), 4.57 (q, J = 7.2 Hz, 1H), 6.95 (d, J = 7.2 Hz, 1H), 7.01-7.22 (m, 5H), 7.25-7.27 (m, 3H), 7.31-7.33 (m, 1H), 7.57-7.63 (m, 1H), 8.66-8.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 21.8, 37.3, 121.8, 124.3, 125.9, 126.0, 126.1, 127.1, 127.6, 128.6, 128.6, 129.9, 130.3, 136.17, 136.24, 140.8, 143.9, 144.8, 149.2, 160.6; HRMS (ESI) Calcd for $C_{20}H_{20}N$ $[M + H]^+$ 274.1596, found 274.1596.



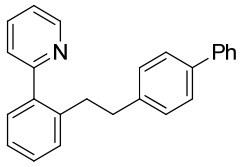
2-(2-(2-Methylphenethyl)phenyl)pyridine (4ad): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 2-methylstyrene (**2d**, 48 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % *t*$BuCH_2MgBr$, 60 °C, 13 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 15/1) of the crude product afforded an inseparable mixture of the title compound (64.1 mg, 78%, b:l < 1:99) and a dialkylation product (15.4 mg, 13%) as a colorless oil.

R_f 0.26 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 3H), 2.72-2.77 (m, 2H), 2.94-2.98 (m, 2H), 6.86-6.95 (m, 1H), 7.03-7.05 (m, 3H), 7.22-7.36 (m, 6H), 7.68-7.72 (m, 1H), 8.67-8.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 34.2, 35.7, 121.9, 124.3, 126.1, 126.3, 127.4, 128.6, 129.1, 130.0, 130.16, 130.22, 136.0, 136.3, 140.2, 140.4, 140.7, 149.3, 160.4; HRMS (ESI) Calcd for $C_{20}H_{20}N$ $[M + H]^+$ 274.1596, found 274.1595.



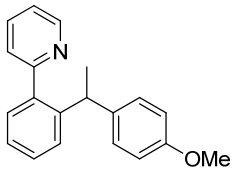
2-(2-(1-(biphenyl-4-yl)ethyl)phenyl)pyridine (3ae): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 4-vinylbiphenyl (**2e**, 64.9 mg, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (10 mol % $CoBr_2$, 10 mol % PCy_3, 80 mol % Me_3SiCH_2MgCl, 60 °C, 17 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 13/1) of the crude product afforded the title compound as a light yellow oil (80.5 mg, 80%, b:l = 99:1).

R_f 0.15 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (d, J = 7.2 Hz, 3H), 4.59 (q, J = 7.2 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.17-7.20 (m, 2H), 7.28-7.31 (m, 3H), 7.37-7.42 (m, 6H), 7.52-7.55 (m, 2H), 7.60-7.64 (m, 1H), 8.69-8.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 39.7, 121.9, 124.6, 126.2, 126.95, 127.11, 127.15, 127.8, 128.2, 128.73, 128.85, 129.9, 136.2, 138.7, 140.7, 141.2, 144.3, 145.9, 149.3, 160.5. HRMS (ESI) Calcd for $C_{25}H_{22}N$ $[M + H]^+$ 336.1752, found 336.1756.



2-(2-(2-(Biphenyl-4-yl)ethyl)phenyl)pyridine (4ae): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 4-vinylbiphenyl (**2e**, 64.9 mg, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % *t*$BuCH_2MgBr$, 60 °C, 12 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 13/1) of the crude product afforded the title compound as a light yellow solid (72.7 mg, 72%, b:l = 9:91).

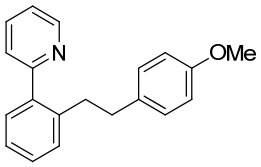
m.p. 108.7-109.3 ºC; R_f 0.15 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.79-2.83 (m, 2H), 3.04-3.08 (m, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.21-7.43 (m, 11H), 7.53-7.55 (m, 2H), 7.67- 7.71 (m, 1H), 8.69-8.71 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.5, 37.7, 121.9, 124.2, 126.3, 126.9, 127.1, 128.2, 128.6, 128.86, 128.92, 130.0, 130.1, 136.4, 138.9, 139.9, 140.6, 141.28, 141.31, 149.2, 160.4. HRMS (ESI) Calcd for $C_{25}H_{22}N$ $[M + H]^+$ 336.1752, found 336.1755.



2-(2-(1-(4-Methoxyphenyl)ethyl)phenyl)pyridine (3af): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 4-methoxylstyrene (**2f**, 48 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (10 mol % $CoBr_2$, 10 mol % PCy_3, 80 mol % Me_3SiCH_2MgCl, 60 °C, 52 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 10/1) of the crude product afforded the title compound as a brown oil (59.2 mg, 68%, b:l = 99:1).

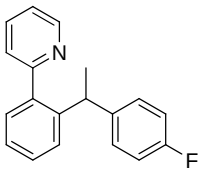
R_f 0.12 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (d, *J* = 7.2 Hz, 3H), 3.72 (s, 3H), 4.47 (q, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 6.8 Hz, 2H), 6.74 (d, *J* = 6.8 Hz, 2H),

7.15-7.35 (m, 6H), 7.60-7.63 (m, 1H), 8.68-8.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 39.1, 55.3, 111.6, 121.8, 124.5, 126.0, 127.6, 128.6 (two signals overlapping), 129.8, 136.2, 138.9, 140.5, 144.7, 149.2, 157.7, 160.5; HRMS (ESI) Calcd for $C_{20}H_{20}NO$ $[M + H]^+$ 290.1545, found 290.1543.



2-(2-(4-Methoxyphenethyl)phenyl)pyridine (4af): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 4-methoxylstyrene (**2f**, 48 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % *t*$BuCH_2MgBr$, 60 °C, 12 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 10/1) of the crude product afforded the title compound as a light yellow oil (63.8 mg, 74%, b:l = 10:90).

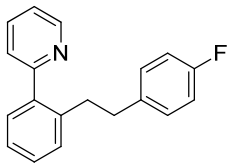
R_f 0.12 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.69-2.73 (m, 2H), 2.96-3.00 (m, 2H), 3.74 (s, 3H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 7.24-7.35 (m, 6H), 7.71-7.73 (m, 1H), 8.68-8.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.8, 37.1, 55.4, 113.8, 121.9, 124.2, 126.3, 128.6, 129.4, 130.0, 130.1, 134.3, 136.4, 140.0, 140.6, 149.3, 157.9, 160.4; HRMS (ESI) Calcd for $C_{20}H_{20}NO$ $[M + H]^+$ 290.1545, found 290.1548.



2-(2-(1-(4-Fluorophenyl)ethyl)phenyl)pyridine (3ag): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 4-fluorostyrene (**2g**, 43 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (20 mol % $CoBr_2$, 20 mol % PCy_3, 160 mol % Me_3SiCH_2MgCl, 60 °C, 52 h). Silica gel

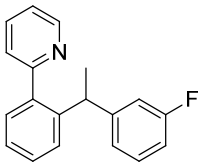
chromatography (eluent: hexane/EtOAc = 40/1 – 15/1) of the crude product afforded the title compound as a yellow oil (71.4 mg, 86% , b:l = 94:6).

R_f 0.39 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (d, J = 7.2 Hz, 3H), 4.54 (q, J = 7.2 Hz, 1H), 6.80-6.85 (m, 2H), 6.93-6.97 (m, 2H), 7.12-7.14 (m, 1H), 7.25-7.35 (m, 5H), 7.63-7.65 (m, 1H), 8.66-8.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 39.3, 114.9 (d, $^2J_{C–F}$ = 21 Hz), 121.9, 124.5, 126.2, 127.5, 128.7, 129.1 (d, $^3J_{C–F}$ = 8 Hz), 129.9, 136.3, 140.6, 142.5 (d, $^4J_{C–F}$ = 3 Hz), 114.2, 149.2, 160.5, 161.2 (d, $^1J_{C–F}$ = 242 Hz). HRMS (ESI) Calcd for $C_{20}H_{17}FN$ $[M + H]^+$ 278.1345, found 278.1343.



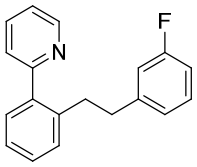
2-(2-(4-Fluorophenethyl)phenyl)pyridine (4ag): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 4-fluorostyrene (**2g**, 43 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % *t*$BuCH_2MgBr$, 60 °C, 12 h). Silica gel chromatography (eluent: hexane/EtOAc = 15/1) of the crude product afforded the title compound as a yellow oil (57.0 mg, 69%, b:l = 2:98).

R_f 0.39 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71-2.75 (m, 2H), 2.98-3.02 (m, 2H), 6.84-6.93 (m, 4H), 7.26-7.33 (m, 6H), 7.70-7.74 (m, 1H), 8.68-8.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.6, 37.1, 115.1 (d, $^2J_{C–F}$ = 21 Hz), 121.9, 124.2, 126.4, 128.6, 129.9 (d, $^3J_{C–F}$ = 8 Hz), 130.0, 130.2, 136.5, 137.7 (d, $^4J_{C–F}$ = 3 Hz), 139.7, 140.6, 149.2, 160.4, 161.4 (d, $^1J_{C–F}$ = 242 Hz); HRMS (ESI) Calcd for $C_{20}H_{17}FN$ $[M + H]^+$ 278.1345, found 278.1343.



2-(2-(1-(3-Fluorophenyl)ethyl)phenyl)pyridine (3ah): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 3-fluorostyrene (**2h**, 43 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (20 mol % $CoBr_2$, 20 mol % PCy_3, 160 mol % Me_3SiCH_2MgCl, 60 °C, 17 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 15/1) of the crude product afforded the title compound as a yellow oil (55.3 mg, 66%, b:l > 99:1).

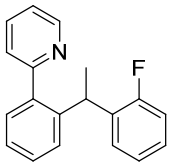
R_f 0.20 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (d, J = 7.2 Hz, 3H), 4.57 (q, J = 7.2 Hz, 1H), 6.74-6.79 (m, 3H), 7.01-7.16 (m, 2H), 7.22-7.37 (m, 5H), 7.61-7.65 (m, 1H), 8.67-8.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 39.7 (d, $^4J_{C–F}$ = 1 Hz), 112.6 (d, $^2J_{C–F}$ = 21 Hz), 114.6 (d, $^2J_{C–F}$ = 21 Hz), 121.9, 123.5 (d, $^4J_{C–F}$ = 3 Hz), 124.5, 126.4, 127.6, 128.8, 129.6 (d, $^3J_{C–F}$ = 8 Hz), 129.9, 136.3, 140.6, 143.7, 149.2, 149.5 (d, $^3J_{C–F}$ = 7 Hz), 160.3, 162.9 (d, $^1J_{C–F}$ = 243 Hz); HRMS (ESI) Calcd for $C_{20}H_{17}FN$ $[M + H]^+$ 278.1345, found 278.1349.



2-(2-(3-Fluorophenethyl)phenyl)pyridine (4ah): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 3-fluorostyrene (**2h**, 43 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (20 mol % $CoBr_2$, 20 mol % IMes•HCl, 200 mol % tBuCH$_2$MgBr, 60 °C, 18 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 15/1) of the crude product afforded the title compound as a pink oil (51.3 mg, 62%, b:l = 7:93).

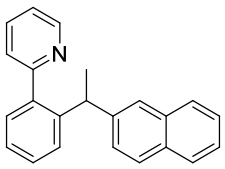
R_f 0.20 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74-2.78 (m, 2H), 3.01-3.03 (m, 2H), 6.67-6.70 (m, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.79-6.82 (m, 1H), 7.11-7.14 (m,

1H), 7.24-7.35 (m, 6H), 7.70-7.74 (m, 1H), 8.69-8.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.3, 37.7 (d, $^4J_{C–F}$ = 1Hz), 112.7 (d, $^2J_{C–F}$ = 21 Hz), 115.3 (d, $^2J_{C–F}$ = 21 Hz), 122.0, 124.15, 124.17, 126.4, 128.6, 129.7 (d, $^3J_{C–F}$ = 8 Hz), 130.0, 130.1, 136.5, 139.5, 140.5, 144.8 (d, $^3J_{C–F}$ = 7 Hz), 149.2, 160.3, 162.9 (d, $^1J_{C–F}$ = 244 Hz); HRMS (ESI) Calcd for $C_{20}H_{17}FN$ $[M + H]^+$ 278.1345, found 278.1342.



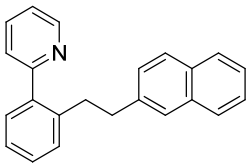
2-(2-(2-Fluorophenethyl)phenyl)pyridine (4ai): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 2-fluorostyrene (**2i**, 43 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % *t*$BuCH_2MgBr$, 60 °C, 12 h). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 15/1) of the crude product afforded an inseparable mixture of the title compound (69.7 mg, 84%, b:l = 2:98) and a dialkylation product (9.3 mg, 8%) as a pink oil.

R_f 0.20 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.79-2.83 (m, 2H), 2.99-3.03 (m, 2H), 6.85-6.95 (m, 3H), 7.01-7.36 (m, 7H), 7.69-7.73 (m, 1H), 8.67-8.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.2 (d, $^3J_{C–F}$ = 6 Hz), 34.0, 115.2 (d, $^2J_{C–F}$ = 22 Hz), 121.9, 124.0 (d, $^4J_{C–F}$ = 3.5 Hz), 124.2, 126.4, 127.7 (d, $^3J_{C–F}$ = 8 Hz), 128.6, 128.9 (d, $^2J_{C–F}$ = 16 Hz), 130.0, 130.2, 130.9 (d, $^3J_{C–F}$ = 5.2 Hz), 136.4, 139.7, 140.7, 149.3, 160.3, 161.3 (d, $^1J_{C–F}$ = 244 Hz); HRMS (ESI) Calcd for $C_{20}H_{17}FN$ $[M + H]^+$ 278.1345, found 278.1341.



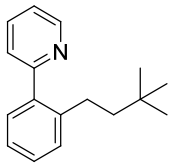
2-(2-(1-(Naphthalen-2-yl)ethyl)phenyl)pyridine (3aj): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 2-vinylnaphthalene (**2j**, 55.5 mg, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (10 mol % $CoBr_2$, 10 mol % PCy_3, 80 mol % Me_3SiCH_2MgCl, 60 °C, 16 h). Silica gel chromatography (eluent: hexane/EtOAc = 40/1 – 15/1) of the crude product afforded the title compound as a light yellow solid (81.9 mg, 88%, b:l > 99:1).

m.p. 96.5-97.3 ºC; R_f 0.19 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (d, J = 7.2 Hz, 3H), 4.69 (q, J = 7.2 Hz, 1H), 7.14-7.21 (m, 3H), 7.27-7.40 (m, 6H), 7.46 (bs, 1H), 7.54-7.59 (m, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.67-7.73 (m, 2H), 8.69-8.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 40.1, 121.9, 124.6, 125.2, 125.4, 125.9, 126.2, 127.3, 127.6, 127.8, 127.85, 127.94, 128.7, 129.9, 132.0, 133.5, 136.3, 140.7, 144.1, 144.2, 149.3, 160.4; HRMS (ESI) Calcd for $C_{23}H_{20}N$ $[M + H]^+$ 310.1596, found 310.1593.



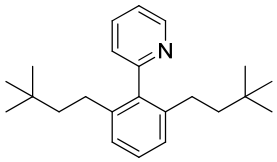
2-(2-(2-(Naphthalen-2-yl)ethyl)phenyl)pyridine (4aj): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 2-vinylnaphthalene (**2j**, 55.5 mg, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % tBuCH$_2$MgBr, 60 °C, 12 h). Silica gel chromatography (eluent: hexane/EtOAc = 40/1 – 15/1) of the crude product afforded the title compound as a colorless oil (63.0 mg, 68%, b:l = 39:61).

R_f 0.19 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91-2.95 (m, 2H), 3.09-3.13 (m, 2H), 7.10-7.41 (m, 10H), 7.61-7.74 (m, 4H), 8.70 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.4, 38.2, 121.9, 124.2, 125.2, 126.0, 126.3, 126.5, 127.5, 127.6, 127.7, 127.9, 128.6, 130.0, 130.2, 132.1, 133.8, 136.4, 139.7, 140.6, 144.1, 149.2, 160.4; HRMS (ESI) Calcd for $C_{23}H_{20}N$ $[M + H]^+$ 310.1596, found 310.1600.

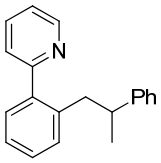


2-(2-(3,3-Dimethylbutyl)phenyl)pyridine (4ak): 2-Phenylpyridine (**1a**, 43 μL, 0.3 mmol) and 2-vinylnaphthalene (**2k**, 46 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (10 mol % $CoBr_2$, 10 mol % IMes•HCl, 100 mol % *t*$BuCH_2MgBr$, 60 °C, 12 h). Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded the title compound and a dialkylation product (2-(2,6-bis(3,3-dimethylbutyl)phenyl)pyridine) as a colorless oil (28.1 mg, 39%) and a white solid (12.3 mg, 13%), respectively.

4ak: R_f 0.30 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (s, 9H), 1.31-1.35 (m, 2H), 2.63-2.68 (m, 2H), 7.23-7.39 (m, 6H), 7.71-7.75 (m, 1H), 8.67-8.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.7, 29.3, 30.7, 46.4, 121.8, 124.3, 125.9, 128.5, 129.9, 130.1, 136.2, 140.5, 141.7, 149.3, 160.5; HRMS (ESI) Calcd for $C_{17}H_{22}N$ $[M + H]^+$ 240.1752, found 240.1756. The spectral data showed good agreement with the literature data.[23]

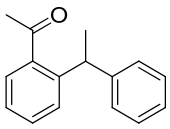


2-(2,6-Bis(3,3-dimethylbutyl)phenyl)pyridine: m.p. 114.5-115.1 ºC; R_f 0.30 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.67 (s, 18H), 1.22-1.35 (m, 4H), 2.25-2.29 (m, 4H), 7.09 (d, J = 7.6 Hz, 2H), 7.22-7.29 (m, 3H), 7.71-7.75 (m, 1H), 8.70-8.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.1, 30.5, 46.3, 53.6, 121.8, 125.4, 126.8, 128.3, 135.8, 140.0, 141.6, 149.5, 160.5; HRMS (ESI) Calcd for $C_{23}H_{34}N$ $[M + H]^+$ 324.2691, found 324.2690.



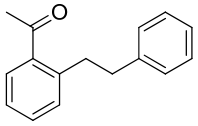
2-(2-(2-Phenylpropyl)phenyl)pyridine: 2-Phenylpyridine (**1a**, 43 µL, 0.3 mmol) and 2-methylstyrene (47 µL, 0.36 mmol) were subjected to the Co–IMes catalysis (20 mol % $CoBr_2$, 20 mol % IMes•HCl, 200 mol % *t*$BuCH_2MgBr$, 60 °C, 48 h). Silica gel chromatography (eluent: hexane/EtOAc = 40/1 – 13/1) of the crude product afforded the title compound as a yellow oil (21.1 mg, 26%, b:l < 1:99).

R_f 0.24 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, *J* = 7.2 Hz, 3H), 2.73-2.79 (m, 1H), 2.89-2.92 (dd, *J* = 13.2 Hz, 8.0 Hz, 1H), 3.11-3.16 (dd, *J* = 13.2 Hz, 6.4 Hz, 1H), 6.90 (d, *J* = 6.8 Hz, 2H), 7.10-7.18 (m, 4H), 7.23-7.30 (m, 5H), 7.70 (t, *J* = 7.6 Hz, 1H), 8.68-8.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 41.4, 42.3, 121.8, 124.4, 126.0, 126.3, 127.1, 128.2, 128.3, 130.0, 131.0, 136.4, 139.0, 140.9, 147.2, 149.2, 160.7; HRMS (ESI) Calcd for $C_{20}H_{20}N$ $[M + H]^+$ 274.1596, found 274.1595.



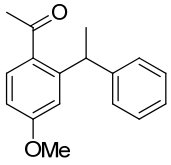
1-(2-(1-Phenylethyl)phenyl)ethanone (3ja): (*E*)-4-Methoxy-*N*-(1-phenylethylidene)aniline (**1j**, 67.6 mg, 0.3 mmol) and styrene (41 µL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (20 mol % $CoBr_2$, 20 mol % PCy_3, 160 mol % Me_3SiCH_2MgCl, 60 °C, 72 h). The reaction was quenched with 3 N HCl (1.0 mL). The resulting mixture was stirred for 3 h at room temperature and extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 150/1) to afford the title compound as a yellow oil (42.9 mg, 64%, b:l = 90:10).

R_f 0.29 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65 (d, J = 6.8 Hz, 3H), 2.40 (s, 3H), 4.92 (q, J = 7.2 Hz, 1H), 7.18-7.22 (m, 3H), 7.27-7.32 (m, 3H), 7.37-7.45 (m, 2H), 7.50-7.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 30.5, 39.8, 125.9, 126.1, 127.8, 128.3, 128.4, 128.6, 131.1, 129.6, 145.4, 146.4, 204.0; HRMS (ESI) Calcd for $C_{16}H_{17}O$ $[M + H]^+$ 225.1279, found 225.1283.



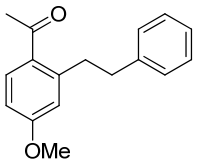
1-(2-Phenethylphenyl)ethanone (4ja): (*E*)-4-Methoxy-*N*-(1-phenylethylidene)aniline (**1j**, 67.6 mg, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (20 mol % $CoBr_2$, 20 mol % IMes•HCl, 200 mol % *t*$BuCH_2MgBr$, 60 °C, 72 h). The reaction was quenched with 3 N HCl (1.0 mL). The resulting mixture was stirred for 3 h at room temperature and extracted with ethyl acetate (3 x 10 mL). The organic layer was dired over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 150/1) to afford the title compound as a light yellow oil (38.6 mg, 57%, b:l = 8:92).

R_f 0.29 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (s, 3H), 2.86-2.90 (m, 2H), 3.13-3.17 (m, 2H), 7.19-7.29 (m, 7H), 7.36-7.40 (m, 1H), 7.65-7.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.9, 36.5, 38.4, 126.0 (two signals overlapping), 126.1, 128.5, 128.8, 129.4, 131.6, 131.7, 138.1, 142.1, 202.1; HRMS (ESI) Calcd for $C_{16}H_{17}O$ $[M + H]^+$ 225.1279, found 225.1276. The spectral data showed good agreement with the literature data.[4b]



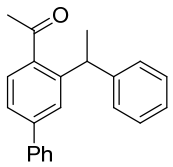
1-(4-Methoxy-2-(1-phenylethyl)phenyl)ethanone (3ka): (*E*)-4-Methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**3k**, 76.6 mg, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (20 mol % $CoBr_2$, 20 mol % PCy_3, 160 mol % Me_3SiCH_2MgCl, 60 °C, 72 h). Silica gel chromatography (eluent: hexane/EtOAc = 100/1 – 15/1) of the crude product afforded the title compound as a yellow oil (42.9 mg, 64%, b:l = 90:10).

R_f 0.25 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, CDCl3): δ 1.58 (d, *J* = 7.2 Hz, 3H), 2.42 (s, 3H), 3.78 (s, 3H), 5.16 (q, *J* = 7.2 Hz, 1H), 6.73 (dd, *J* = 2.4 Hz, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 2.4 Hz, 1H), 7.13-7.28 (m, 5H), 7.62 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 30.0, 39.6, 55.4, 110.1, 115.3, 126.0, 128.2, 128.4, 128.5, 131.7, 146.3, 149.6, 162.0, 201.3; HRMS (ESI) Calcd for $C_{17}H_{19}O_2$ $[M + H]^+$ 255.1385, found 255.1388.



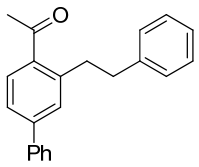
1-(4-Methoxy-2-phenethylphenyl)ethanone (4ka): (*E*)-4-Methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**3k**, 76.6 mg, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (20 mol % $CoBr_2$, 20 mol % IMes•HCl, 200 mol % *t*$BuCH_2MgBr$, 60 °C, 72 h). Silica gel chromatography (eluent: hexane/EtOAc = 100/1 – 15/1) of the crude product afforded the title compound as a light yellow oil (38.1 mg, 50%, b:l = 12:88).

R_f 0.25 (hexane/EtOAc = 10/1); δ 2.53 (s, 3H), 2.85-2.89 (m, 2H), 3.18-3.22 (m, 2H), 3.79 (s, 3H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.77 (dd, *J* = 2.4 Hz, *J* = 8.8 Hz, 1H), 7.16-7.20 (m, 1H), 7.24-7.30 (m, 4H), 7.75 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.4, 37.4, 38.1, 55.5, 111.2, 117.2, 126.0, 128.5, 128.9, 130.0, 132.9, 142.3, 145.9, 162.1, 199.8; HRMS (ESI) Calcd for $C_{17}H_{19}O_2$ $[M + H]^+$ 255.1385, found 255.1381.



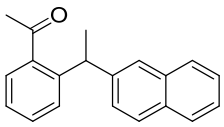
1-(3-(1-Phenylethyl)biphenyl-4-yl)ethanone (3la): (*E*)-*N*-(1-([1,1'-Biphenyl]-4-yl)ethylidene)-4-methoxyaniline (**3l**, 90.4 mg, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (20 mol % $CoBr_2$, 20 mol % PCy_3, 160 mol % Me_3SiCH_2MgCl, 60 °C, 72 h). Silica gel chromatography (eluent: eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a yellow oil (68.6 mg, 76%, b:l = 96:4).

m.p. 55.6-56.5 ºC; R_f 0.31 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, CDCl3): δ 1.66 (d, J = 7.2 Hz, 3H), 2.40 (s, 3H), 5.00 (q, J = 7.2 Hz, 1H), 7.15-7.17 (m, 1H), 7.20-7.27 (m, 4H), 7.35-7.38 (m, 1H), 7.41-7.46 (m, 3H), 7.53-7.58 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 30.5, 39.7, 124.6, 126.1, 127.41, 127.44, 128.1, 128.2, 128.5, 128.9, 129.1, 137.9, 140.5, 143.9, 146.26, 146.30, 203.4; HRMS (ESI) Calcd for $C_{22}H_{21}O$ $[M + H]^+$ 301.1592, found 301.1592.



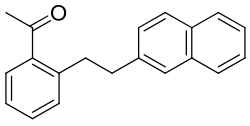
1-(3-Phenethylbiphenyl-4-yl)ethanone (4la): (*E*)-*N*-(1-([1,1'-Biphenyl]-4-yl)ethylidene)-4-methoxyaniline (**3l**, 90.4 mg, 0.3 mmol) and styrene (41 μL, 0.36 mmol) were subjected to the Co–IMes catalysis (20 mol % $CoBr_2$, 20 mol % IMes•HCl, 200 mol % $tBuCH_2MgBr$, 60 °C, 72 h). Silica gel chromatography (eluent: hexane/EtOAc = 100/1 – 15/1) of the crude product afforded the title compound as a light yellow oil (41.7 mg, 46%, b:l = 23:77).

R_f 0.31 (hexane/EtOAc = 10/1); δ 2.40 (s, 3H), 2.91-2.95 (m, 2H), 3.22-3.26 (m, 2H), 7.20-7.29 (m, 5H), 7.38-7.56 (m, 7H), 7.78 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.8, 37.0, 38.4, 124.8, 126.1, 127.4, 128.3, 128.5, 128.9, 129.1, 130.5, 130.6, 136.3, 140.1, 142.1, 143.0, 144.4, 201.4; HRMS (ESI) Calcd for $C_{22}H_{21}O$ $[M + H]^+$ 301.1593, found 301.1592.



1-(2-(1-(Naphthalen-2-yl)ethyl)phenyl)ethanone (3jj): (*E*)-4-Methoxy-*N*-(1-phenylethylidene)aniline (**3j**, 67.6 mg, 0.3 mmol) and 2-vinylnaphthalene (**2j**, 55.5 mg, 0.36 mmol) were subjected to the Co–PCy_3 catalysis (20 mol % $CoBr_2$, 20 mol % PCy_3, 160 mol % Me_3SiCH_2MgCl, 60 °C, 72 h). Silica gel chromatography (eluent: eluent: hexane/EtOAc = 50/1 – 10/1) of the crude product afforded the title compound as a yellow oil (60.1 mg, 73%, b:l = 99:1).

R_f 0.28 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, CDCl3): δ 1.74 (d, J = 7.2 Hz, 3H), 2.43 (s, 3H), 5.11 (q, J = 7.2 Hz, 1H), 7.27-7.31 (m, 2H), 7.37-7.48 (m, 4H), 7.55 (dd, J = 1.2 Hz, J = 6.4 Hz, 1H), 7.70 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.80-7.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 30.6, 39.8, 125.6, 125.8, 126.0, 126.1, 127.6, 127.7, 127.94, 128.00, 128.1, 128.9, 131.2, 132.1, 133.6, 139.3, 143.8, 145.4, 203.8; HRMS (ESI) Calcd for $C_{20}H_{19}O$ $[M + H]^+$ 275.1436, found 275.1440.



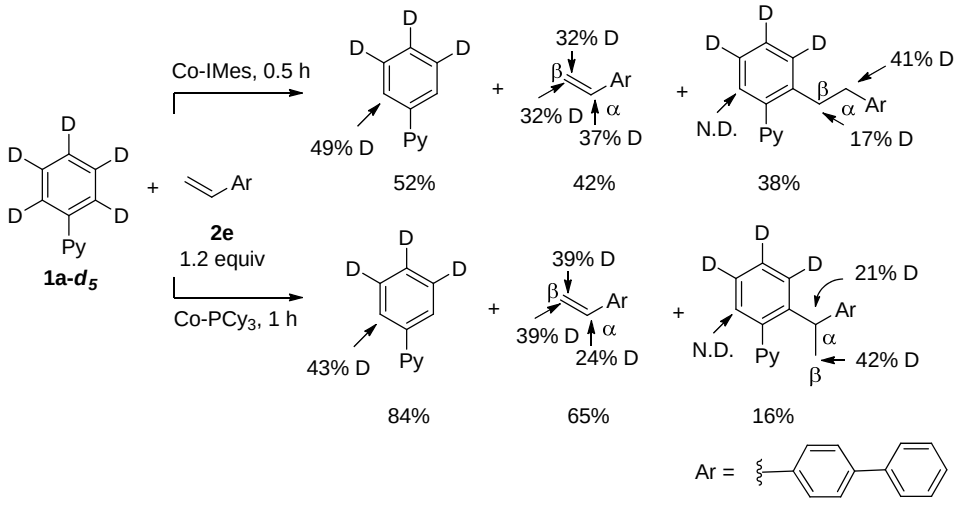
1-(2-(2-(Naphthalen-2-yl)ethyl)phenyl)ethanone (4jj): (*E*)-4-Methoxy-*N*-(1-phenylethylidene)aniline (**3j**, 67.6 mg, 0.3 mmol) and 2-vinylnaphthalene (**2j**, 55.5 mg, 0.36 mmol) were subjected to the Co–IMes catalysis (20 mol % $CoBr_2$, 20 mol % IMes•HCl,

200 mol % *t*BuCH$_2$MgBr, 60 °C, 72 h). Silica gel chromatography (eluent: hexane/EtOAc = 50/1 – 10/1) of the crude product afforded the title compound as a light yellow oil (17.4 mg, 24%, b:l = 63:37).

R_f 0.28 (hexane/EtOAc = 10/1); δ 2.52 (s, 3H), 3.04-3.06 (m, 2H), 3.22-3.26 (m, 2H), 7.24-7.44 (m, 7H), 7.65 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.76-7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.9, 36.6, 38.6, aromatic carbon signals could not be identified due to significant overlap with the signals due to the branched isomer, 203.1; HRMS (ESI) Calcd for $C_{20}H_{19}O$ $[M + H]^+$ 275.1436, found 275.1433.

Deuterium-Labeling Experiments:

A mixture of **1a**-d_5 (0.3 mol) and **2e** (0.36 mmol) was subjected to the standard reaction conditions (Co–PCy$_3$ catalysis: $CoBr_2$ (10 mol %), PCy$_3$ (10 mol %), Me_3SiCH_2MgCl (80 mol %), 60 °C, 1 h; Co–IMes catalysis: $CoBr_2$ (10 mol %), IMes•HCl (10 mol %), *t*BuCH$_2$MgBr (100 mol %), 60 °C, 30 min). Purification of the crude mixture by silica gel chromatography (eluent: hexane/EtOAc = 30/1 – 15/1) afforded the recovered starting materials and the hydroarylation products, which were analyzed by ^{1}H NMR.



3.5 References

(1) (a) D. Lednicer, L. A. Mitscher, The Organic Chemistry of Drug Synthesis, Vol. 1, Wiley, New York, 1977, Chapter 4; (b) D. Lednicer, L. A. Mitscher, The Organic Chemistry of Drug Synthesis Vol. 1, Wiley, New York, 1980, Chapter 2.

(2) For selected examples, see: (a) Kischel, J.; Jovel, I.; Mertins, K.; Zapf, A.; Beller, M. *Org. Lett.* **2006**, *8*, 19. (b) Rueping, M.; Nachtsheim, B. J.; Scheidt, T. *Org. Lett.* **2006**, *8*, 3717. (c) Sun, H.-B.; Li, B.; Hua, R.; Yin, Y. *Eur. J. Org. Chem.* **2006**, 4231. (d) Zhang, Z.; Wang, X.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 3717. (e) Chu, C.-M.; Huang, W.-J.; Liu, J.-T.; Yao, C.-F. *Tetrahedron Lett.* **2007**, *48*, 6881. (f) Wang, M.-Z.; Wong, M.-K.; Che, C.-M. *Chem. Eur. J.* **2008**, *14*, 8353. (g) Das, B.; Krishnaiah, M.; Laxminarayana, K.; Damodar, K.; Kumar, D. N. *Chem. Lett.* **2009**, *38*, 42.

(3) For reviews, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

(4) For selected examples, see: (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (b) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62. (c) Matsumoto, T.; Periana, R. A.; Taube, D. J.; Yoshida, H. *J. Mol. Catal. A* **2002**, *180*, 1. (d) Jun, C.-H.; Moon, C. W.; Hong, J.-B.; Lim, S.-G.; Chung, K.-Y.; Kim, Y.-H. *Chem. Eur. J.* **2002**, *8*, 485. (e) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964. (f) Martinez, R.; Chevalier, R.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 8232. (g) Martinez, R.; Genet, J.-P.; Darses, S. *Chem. Commun.* **2008**, 3855. (h) Martinez, R.; Simon, M.-O.; Chevalier, R.; Pautigny, C.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2009**, *131*, 7887.

(5) (a) Uchimaru, Y. *Chem. Commun.* **1999**, 1133. (b) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170. (c) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 6410. (d) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 4451.

(6) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249.

(7) Ding, Z.-H.; Yoshikai, N. *Org. Lett.* **2010**, *12*, 4180.

(8) For examples of unique reactivities of the IMes ligand in cobalt catalysis, see: (a) Kobayashi, T.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2008**, *130*, 11276. (b) Kobayashi, T.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2009**, *4*, 1078.

(9) (a) Klein, H.-F.; Camadanli, S.; Beck, R.; Leudel, D.; Flörke, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 975. (b) Lenges, C. P.; Brookhart, M.; Grant, B. E. *J. Organomet. Chem.* **1997**, *528*, 199.

(10) (a) Ohmiya, H.; Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 2207. (b) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374. (c) Czaplik, W. M.; Mayer, M.; Jacobi von Wangelin, A. *Synlett* **2009**, 2931.

(11) (a) Galamb, V.; Pályi, G. *J. Chem. Soc. Chem. Commun.* **1982**, 487. (b) Galamb, V.; Pályi, G.; Ungváry, F.; Markó, L.; Boese, R.; Schmid, G. *J. Am. Chem. Soc.* **1986**, *108*, 3344.

(12)Mongin, F.; Mojovic, L.; Guillamet, B.; Trécourt, F.; Quéguiner, G. *J. Org. Chem.* **2002**, *67*, 8991.

(13) Ackermann, L.; Althammer, A. *Org. Lett.* **2006**, *8*, 3457.

(14) Gosmini, C.; Bassene-Ernst, C.; Durandetti, M. *Tetrahedron* **2009**, *65*, 6141.

(15) Martinez-Barrasa, V.; Garcia de Viedma, A.; Burgos, C.; Alvarez-Builla, J. *Org. Lett.* **2000**, *2*, 3933.

(16) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

(17) Gosmini, C.; Lasry, S.; Nedelec, J.-Y.; Perichon, J. *Tetrahedron* **1998**, *54*, 1289.

(18) Billingsley, K. L.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 4695.

(19) (a) Bonnet, V.; Mongin, F.; Trecourt, F.; Queguiner, G.; Knochel, P. *Tetrahedron* **2002**, *58*, 4429. (b) Thummel, R. P.; Jahng, Y. *J. Org. Chem.* **1987**, *52*, 73.

(20) Samec, J. S. M.; Bäckvall, J.-E. *Chem. Eur. J.* **2002**, *8*, 2955.

(21) Jiang, N.; Ragauskas, A. J. *Tetrahedron Lett.* **2006**, *47*, 197.

(22) Lee, P. H.; Lee, S. W.; Seomoon, D. *Org. Lett.* **2003**, *5*, 4963.

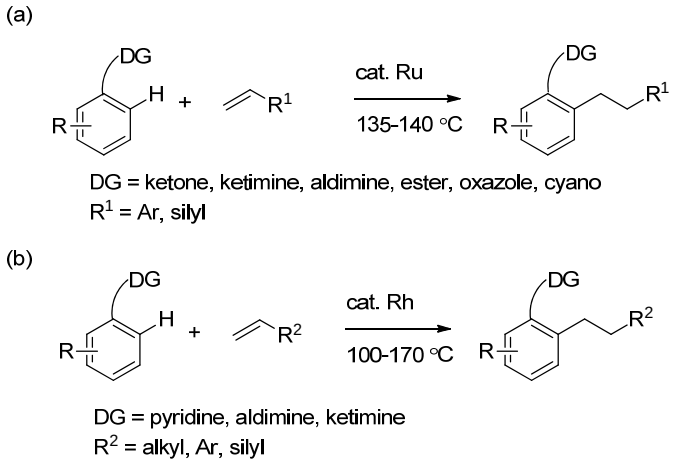
(23) Lim, Y.-G.; Kang, J.-B.; Kim, Y. H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2201.

Chapter 4. Cobalt-Catalyzed Alkylation of Aromatic Imines with Olefins

4.1 Introduction

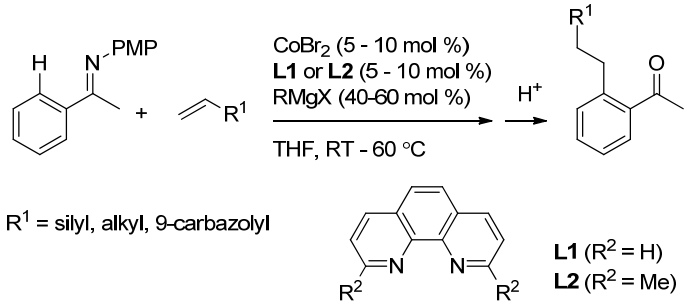
Chelation-assisted alkylation of aromatic C–H bond with olefins offers a straightforward, atom-economic, and regioselective method to introduce alkyl groups onto aromatic compounds.[1] Over the past few decades, a series of catalytic systems, mostly based on ruthenium and rhodium, have been developed for such transformations.[2,3] This area started to evolve with the groundbreaking work of the Murai group on the ruthenium-catalyzed *ortho*-alkylation of aromatic ketones with olefins such as vinylsilanes.[4] The scope of the ruthenium catalysis was further extended by the Murai group and others (Scheme 4.1a).[2] For example, Darses *et al.* reported ruthenium-catalyzed alkylation of ketimines and aldimines with vinylsilanes.[2g,h,i] The ruthenium catalysis typically requires heating up to 140 °C, while Kakiuchi and coworkers recently reported a highly active catalytic system that allows *ortho*-alkylation under room-temperature conditions.[2e] The ruthenium catalysis also suffers from a relatively limited scope of olefins, because it usually works poorly with isomerizable olefins. In the meantime, rhodium-catalyzed *ortho*-alkylation reactions of arylpyridines and aryl imines were developed by groups of Jun and Lim (Scheme 4.1b).[3] While the rhodium catalysis tolerates a broader range of olefins including isomerizable olefins, it also requires high temperatures typically around 100-170 °C. With these precedents in mind, the development of a mild and broad-scope *ortho*-alkylation reaction, preferably with a cheap catalyst, is highly desirable.[5]

Scheme 4.1. Ruthenium- and Rhodium-Catalyzed *ortho*-Alkylation Reactions with Olefins



As discussed in Chapter 2 and 3, we developed cobalt-catalyzed *ortho*-alkenylation and alkylation reactions of arylpyridines and aryl imines with internal alkynes and styrenes, respectively.[6] These reactions feature not only the low cost of the cobalt catalysts but also mild conditions and unique regioselectivity[7,8,9,10] In this chapter, we report that cobalt–phenanthroline (**L1** or **L2**) catalysts efficiently promote an *ortho*-alkylation reaction of aromatic imines with various olefins under mild reaction conditions (Scheme 4.2).[11,12,13]

Scheme 4.2. Cobalt-Catalyzed Alkylation of Aromatic Imines with Olefins

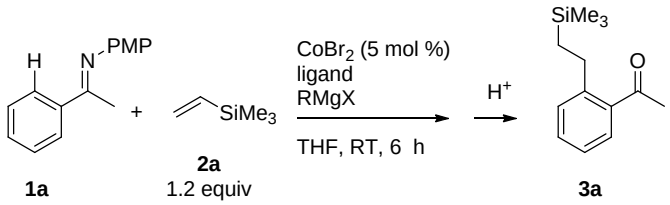


4.2 Results and discussion

In the last two chapters, we demonstrated that an imino group is a viable directing group for cobalt-catalyzed C–H functionalization reactions albeit with limited substrate scopes. Being aware of greater synthetic versatility of the imino group than the pyridyl group, we chose acetophenone imine **1a** and vinyltrimethylsilane **2a** as model substrates

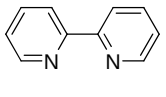
for the *ortho*-alkylation reaction (Table 4.1). After extensive screening of ligands and Grignard reagents, we found that the reaction proceeded smoothly at room temperature in the presence of a cobalt catalyst generated in situ from $CoBr_2$ (5 mol %), phenanthroline (**L1**) (5 mol %), and *t*$BuCH_2MgBr$ (40 mol %) to afford the alkylation product **3a** in 85% yield (entry 1). No dialkylation product was detected in this reaction. A similar level of catalytic activity was achieved using bathophenanthroline instead of **L1** (entry 2), while the use of bipyridine and neocproine **L2** resulted in low yield (entries 3 and 4). Bathophenanthroline performed as efficiently as **L1**, while **L1** was selected as the standard ligand due to its low cost. Other Grignard reagents such as MeMgCl and Me_3SiCH_2MgCl reduced the catalytic activity (entries 5 and 6). Decreasing the amount of Grignard reagent resulted in lower yield (entry 7). Cobalt–phosphine and cobalt–carbene catalysts, which were previously used for alkylation with styrenes, were much less effective (entries 8-10).

Table 4.1. Optimization of Alkylation of Acetophenone Imine **1a** with Vinyltrimethylsilane **2a**[a]

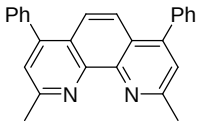


1a **2a** 1.2 equiv **3a**

Entry	Ligand (mol %)	RMgX (mol %)	Yield[b]
1	**L1** (5)	*t*BuCH$_2$MgBr (40)	87% (85%)
2	bathophen (5)	*t*BuCH$_2$MgBr (40)	88%
3	bpy (5)	*t*BuCH$_2$MgBr (40)	19%
4	**L2** (5)	*t*BuCH$_2$MgBr (40)	50%
5	**L1** (5)	MeMgCl (40)	20%
6	**L1** (5)	Me$_3$SiCH$_2$MgCl (40)	67%
7	**L1** (5)	*t*BuCH$_2$MgBr (20)	7%
8	PMe$_2$Ph (10)	MeMgCl (40)	3%
9	PCy$_3$ (5)	Me$_3$SiCH$_2$MgCl (40)	21%
10	IMes•HCl (5)	*t*BuCH$_2$MgBr (40)	20%



bpy



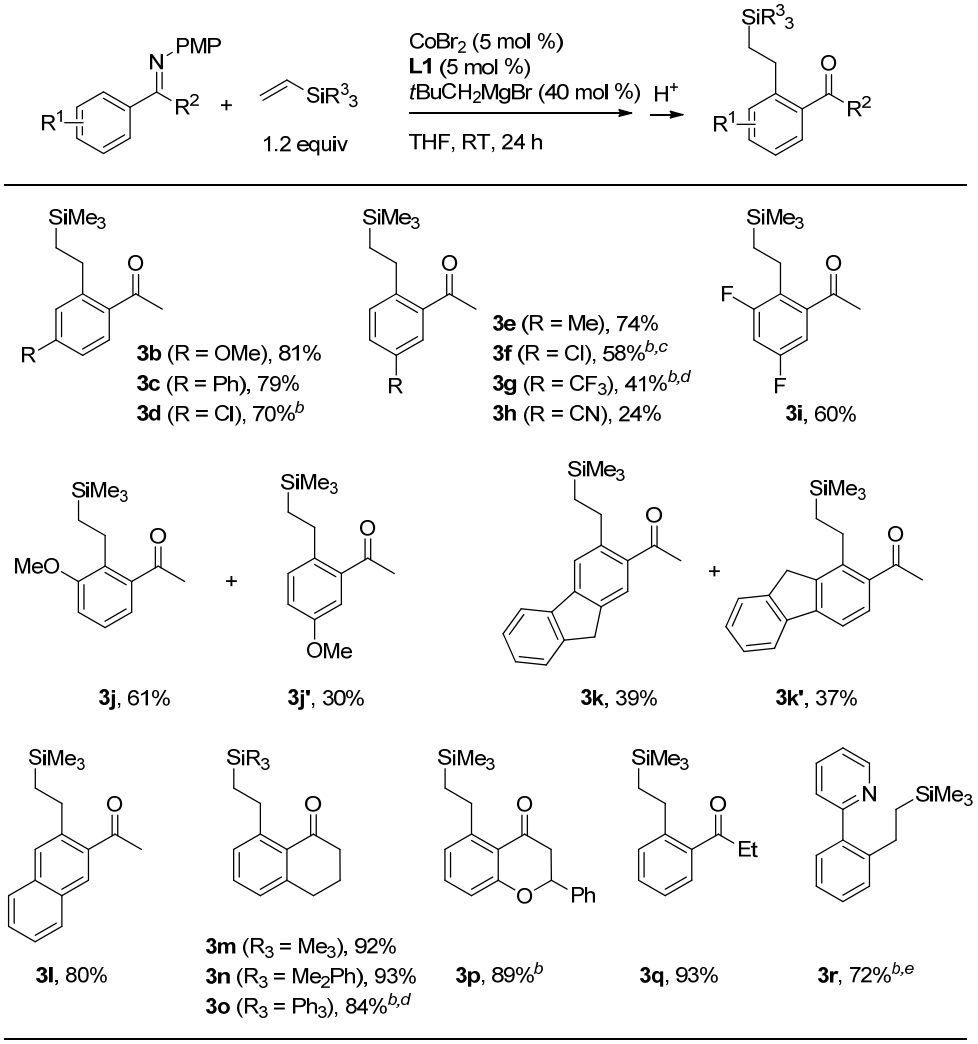
bathophen

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), CoBr$_2$ (5 mol %), ligand, RMgX, THF, RT, 6h. [b] Determined by GC using *n*-tridecane as an internal standard. Isolated yield is shown in parenthesis. IMes•HCl = 1,3-dimesitylimidazolium chloride.

A variety of aryl imines were successfully alkylated with vinylsilane under the optimized conditions (Table 4.2). The reaction showed reasonable compatibility with functional groups including methoxy (**3b**, **3j**), chloro (**3d**, **3f**), fluoro (**3i**), trifluoromethyl (**3g**), and cyano (**3h**). Imines bearing substituents at the *meta*-position reacted exclusively at the less hindered position (**3e**-**3h**), except that the one bearing a *meta*-methoxy group preferentially reacted at the position proximal to the methoxy group (**3j** and **3j'**, regioselectivity = 2:1). This may be attributed to a secondary directing effect of the methoxy group, which has been previously observed in ruthenium- and iridium-catalyzed

reactions.[12c,d,13b,c, 14 , 15] The imine derived from 2-fluorenyl methyl ketone gave an approximately 1:1 mixture of two regioisomers (**3k** and **3k'**), and the acidic proton (pK_a ≈ 22) of the fluorenyl group did not interfere with the reaction.[16] The imine derived from 2-acetonaphthone exclusively afforded the C3-alkylation product **3l**, which was in contrast to the C1 selectivity observed in the ruthenium-catalyzed reaction of 2-acetonaphthone.[13a]

Table 4.2. Scope of Aromatic Imines for Alkylation with Vinylsilanes[a]



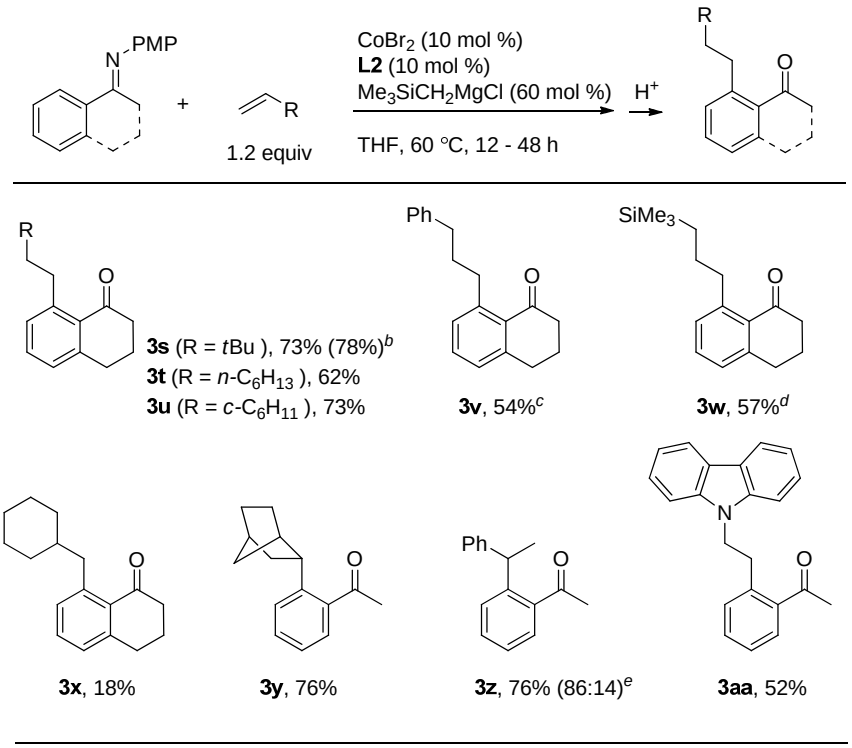
[a] Yields refer to the isolated yields. [b] Catalyst loading was doubled. [c] Reaction time was 36 h. [d] Reaction time was 48 h. [e] Performed at 60 °C.

Imines derived from tetralone, chromanone, and propiophenone participated in the reaction to afford the corresponding alkylation products in excellent yields (**3m-3q**). Besides vinyltrimethylsilane, vinyldimethylphenylsilane and vinyltriphenylsilane also

reacted smoothly to afford the desired products in good yields (**3n** and **3o**), while no alkylation was observed for the reaction with vinyltriethoxysilane. In addition to the imine derivatives, 2-phenylpyridine also smoothly participated in the reaction to afford the alkylation product in 72% yield at 60 °C (**3r**).[17]

We next explored the scope of the olefinic reaction partners. While only a limited amount of desired product (< 30%) was obtained in the reaction of tetralone imine with 3,3-dimethyl-1-butene under the original conditions, a simple modification of the catalytic system allowed *ortho* alkylation with various olefins (Table 4.3). The modified catalytic system with $CoBr_2$ (10 mol %), neocuproine (**L2**, 10 mol %) and Me_3SiCH_2MgCl (60 mol %) afforded the alkylation product **3s** in 73% yield, accompanied by a small amount of *ortho*-trimethylsilylmethylation product (10%).[8c] The replacement of Me_3SiCH_2MgCl with 4-$MeOC_6H_4MgBr$ improved the yield of **3s** to 78% while suppressing the side reaction.

Table 4.3. Addition of aromatic imine to various olefins[a]

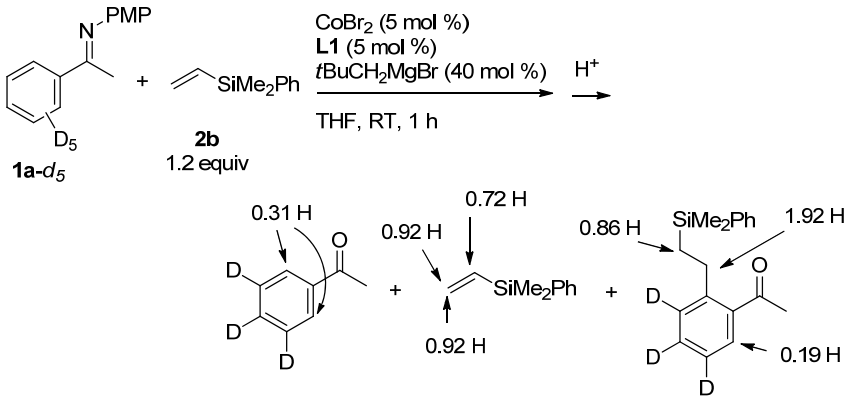


[a] Yields refer to the isolated yields. [b] Yield in parentheses was obtained using 4-$MeOC_6H_4MgBr$ instead of Me_3SiCH_2MgCl. [c] Catalyst loading was doubled. [d] Reaction was performed with the cobalt–**L1** catalyst at RT for 48 h. [e] Branched/linear ratio is shown in parentheses.

Although isomerization of terminal olefins to internal olefins has been reported to take place in the presence of a cobalt catalyst and a Grignard reagent,[18] the present reaction tolerated terminal olefins bearing allylic hydrogens, affording the desired alkylation products in moderate to good yields (**3t**-**3w**). The reaction of exocylic olefin also took place to afford the desired product in low yield (**3x**). An internal olefin such as *trans*-oct-2-ene afforded only a small amount of the alkylation product, while the *cis* isomer was total unreactive. The reaction of norbornene, a strained internal olefin, also took place smoothly to afford the adduct **3y** in 76% yield. The alkylation reaction took place with styrene to afford the branched product as the major product (**3z**).[6b] 9-Vinylcarbazole was, for the first time, used for the *ortho*-alkylation reaction, which afforded the adduct **3aa** in moderate yield.

To probe the mechanism of the reaction, deuterium labeling experiments were performed using pentadeuterated imine **1a**-d_5 and vinyldimethylphenylsilane **2b** under cobalt–**L1** catalyst system (Scheme 4.3). According to the ^{1}H NMR analysis of the recovered starting materials, the deuterium content at the *ortho* position of **1a**-d_5 decreased to 85%, while α- and β-positions of vinylsilane were deuterated in 28% and 8%, respectively. The deuterium distribution in the alkylation product was consistent with those observed in the starting materials. This result is in sharp contrast to the H/D scrambling in the cobalt-catalyzed alkylation with styrene, where significant deuterium incorporation was observed at both α- and β-positions (Chapter 3).[6b]

Scheme 4.3. Deuterium-Labeling Experiment.



In deuterium-labeling experiments performed by Murai's ruthenium-catalyzed *ortho*-alkylation reaction,[13a,f,19] the *ortho* D atom of [D_5]acetophenone and vinylic protons of vinylsilane were nearly completely scrambling at high temperature (135 °C),[13f] while partial H/D scrambling was observed under mild reaction condition using a highly active catalyst.[13f] Our result is similar to the latter set of experiments, indicating that the alkylation reaction may involve reversible C–H bond oxidative addition[20] and olefin insertion[21] steps, while such an equilibrium process may not be significantly faster than the reductive elimination step. The small amount of deuterium incorporation into the β position indicates that the olefin insertion step predominantly generates linear aryl(alkyl)cobalt intermediate.

4.3 Conclusion

In summary, we have developed cobalt–phenanthroline catalysts for *ortho*-alkylation of aromatic imines with various olefins with high regioselectivity under mild conditions. The present cobalt catalysis may serve as an alternative or complementary method to the related reactions catalyzed by rhodium and ruthenium complexes, which typically require high temperature above 100 °C.[11,12,13,17] Further efforts will be focused on mechanistic and synthetic exploration of the cobalt-catalyzed C–H bond functionalization.

4.4 Experimental section

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

Preparation of Aryl Imines

All imines were synthesized by the literature procedures,[22] and purified by silica gel column chromatography (e.g. eluent: hexane/EtOAc/Et_3N = 100/10/2). Spectral data for the following compounds showed good agreement with the literature data:

(*E*)-4-Methoxy-*N*-(1-phenylethylidene)aniline (**1a**)[23]

(*E*)-4-Methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**)[24]

(*E*)-*N*-(1-([1,1'-biphenyl]-4-yl)ethylidene)-4-methoxyaniline (**1c**)[6b]

(*E*)-*N*-(1-(4-Chlorophenyl)ethylidene)-4-methoxyaniline (**1d**)[25]

(*E*)-4-Methoxy-*N*-(1-*m*-tolylethylidene)aniline (**1e**)[25]

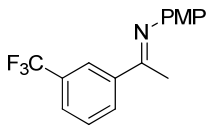
(*E*)-*N*-(1-(3-Chlorophenyl)ethylidene)-4-methoxyaniline (**1f**)[26]

(*E*)-4-Methoxy-*N*-(1-(3-methoxyphenyl)ethylidene)aniline (**1j**)[25]

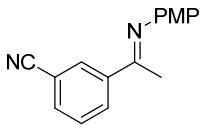
(*E*)-4-Methoxy-*N*-(1-(naphthalen-2-yl)ethylidene)aniline (**1l**)[25]

(*E*)-*N*-(3,4-Dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline (**1m**)[26]

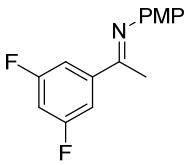
(*E*)-4-Methoxy-*N*-(1-phenylpropylidene)aniline (**1o**)[26]



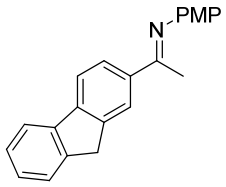
(*E*)-4-Methoxy-*N*-(1-(3-(trifluoromethyl)phenyl)ethylidene)aniline (1g): Yellow liquid; R_f 0.50 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 3.83 (s, 3H), 6.75-6.79 (m, 2H), 6.91-6.95 (m, 2H), 7.55-7.59 (m, 1H), 7.70-7.72 (m, 1H), 8.13-8.15 (m, 1H), 8.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 55.4, 114.3, 120.7, 124.0 (q, $^3J_{C-F}$ = 3.8 Hz), 124.0 (q, $^1J_{C-F}$ = 274 Hz), 126.8 (q, $^3J_{C-F}$ = 3.8 Hz), 128.8, 130.3, 130.8 (q, $^2J_{C-F}$ = 33 Hz), 140.4, 144.1, 156.2, 164.2; HRMS (ESI) Calcd for $C_{16}H_{15}F_3NO$ $[M+H]^+$ 294.1106, found 294.1108.



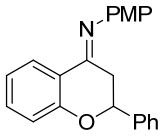
(*E*)-3-(1-(4-Methoxyphenylimino)ethyl)benzonitrile (1h): Yellow solid; R_f 0.33 (hexane/EtOAc = 3/1); m.p. 88.9-90.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 3.83 (s, 3H), 6.74-6.78 (m, 2H), 6.91-6.95 (m, 2H), 7.56 (app. t, J = 8.0 Hz, 1H), 7.72-7.74 (m, 1H), 8.20 (app. d, J = 7.8 Hz, 1H), 8.27-8.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 55.4, 112.6, 114.3, 118.6, 120.7, 129.2, 130.9, 131.2, 133.4, 140.7, 143.8, 156.3, 163.3; HRMS (ESI) Calcd for $C_{16}H_{15}N_2O$ $[M+H]^+$ 251.1184, found 251.1179.



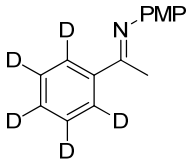
(*E*)-*N*-(1-(3,5-Difluorophenyl)ethylidene)-4-methoxyaniline (1i): Yellow solid; R_f 0.55 (hexane/EtOAc = 3/1); m.p. 100.1-103.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3H), 3.82 (s, 3H), 6.74-6.76 (m, 2H), 6.90-6.93 (m, 3H), 7.48-7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 55.5, 105.4 (t, $^2J_{C-F}$ = 25 Hz), 110.1 (dd, $^2J_{C-F}$ = 19 Hz, $^4J_{C-F}$ = 7.2 Hz), 114.3, 120.7, 140.1 (t, $^3J_{C-F}$ = 8.6 Hz), 143.8, 156.3, 162.9 (dd, $^1J_{C-F}$ = 249 Hz, $^3J_{C-F}$ = 12 Hz), 163.2; HRMS (ESI) Calcd for $C_{15}H_{14}F_2NO$ $[M+H]^+$ 262.1043, found 262.1048.



(*E*)-*N*-(1-(9*H*-fluoren-2-yl)ethylidene)-4-methoxyaniline (1k): Yellow solid; R_f 0.50 (hexane/EtOAc = 3/1); m.p. 183.3-184.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.83 (s, 3H), 3.97 (s, 2H), 6.78-6.80 (m, 2H), 6.91-6.94 (m, 2H), 7.33-7.37 (m, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.58 (d, J = 7.2 Hz, 1H), 7.82-7.85 (m, 2H), 7.96-7.99 (m, 1H), 8.21 (d, J = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.7, 37.1, 55.7, 114.5, 119.7, 120.6, 121.0, 123.9, 125.4, 126.4, 127.1, 127.5, 138.5, 141.3, 143.5, 144.0, 144.3, 145.1, 156.1, 166.1; HRMS (ESI) Calcd for $C_{22}H_{20}NO$ $[M+H]^+$ 314.1545, found 314.1548.

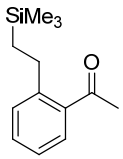


(*E*)-4-methoxy-*N*-(2-phenylchroman-4-ylidene)aniline (1n): Yellow solid; R_f 0.50 (hexane/EtOAc = 3/1); m.p. 135.0-135.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.84 (dd, J = 16.4, 12.0 Hz, 1H), 2.97 (dd, J = 16.4, 2.8 Hz, 1H), 3.79 (s, 3H), 5.17 (dd, J = 12.0, 2.8 Hz, 1H), 6.77-6.79 (m, 2H), 6.91-6.94 (m, 2H), 7.02-7.07 (m, 2H), 7.35-7.41 (m, 6H), 8.22 (dd, J = 8.0, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.1, 55.7, 78.5, 114.5, 117.9, 121.72, 121.78, 121.84, 126.39, 126.48, 128.7, 128.9, 133.0, 139.8, 143,4, 156.5, 158.6, 159.8; HRMS (ESI) Calcd for $C_{22}H_{20}NO_2$ $[M+H]^+$ 330.1494, found 330.1490.



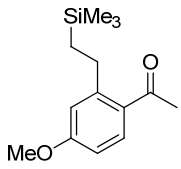
(*E*)-4-Methoxy-*N*-(1-(pentadeuteriophenyl)ethylidene)aniline (1a-d_5): Yellow solid; R_f 0.49 (hexane/EtOAc = 3/1); m.p. 188.3-188.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 3.82 (s, 3 H), 6.74-6.77 (m, 2H), 6.90-6.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 55.5, 114.2, 120.7, 144.8, 155.9, 165.7 (signals for the deuterated benzene ring are missing due to coupling with the deuterium atoms); MS (EI, 70 V): *m*/*z* (relative abundance) 230 (M^+, 66), 215 (100), 100 (50).

Typical Procedure A. Cobalt–Phenanthroline Catalyzed *ortho*-Alkylation with Vinylsilane: In a Schlenk tube were placed $CoBr_2$ (3.3 mg, 0.015 mmol), 1,10-phenanthroline (2.7 mg, 0.015 mmol), (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (67.6 mg, 0.3 mmol), and THF (0.75 mL). To the mixture was added a THF solution of $(CH_3)_3CCH_2MgBr$ (0.80 M, 0.15 mL, 0.12 mmol) dropwise at 0 °C. After stirring for 30 min, vinyltrimethylsilane (53 μL, 0.36 mmol) was added. The resulting mixture was stirred at room temperature for 6 h. The reaction was quenched by the addition of 3 N HCl (1.5 mL). The resulting mixture was stirred at room temperature for 3 h, and then extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 30/1) to afford 1-(2-(2-(trimethylsilyl)ethyl)phenyl)ethanone (**3a**, 46.8 mg, 71 %) as a light brown oil.



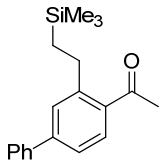
3a: R_f 0.47 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 9H), 0.82-0.87 (m, 2H), 2.60 (s, 3H), 2.84-2.88 (m, 2H), 7.24-7.31 (m, 2H), 7.41 (td, J = 8.0, 1.2 Hz, 1H), 7.65 (dd, J = 8.0, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 19.7, 28.6, 30.1, 125.6, 129.4, 130.7, 131.7, 137.6, 146.1, 202.3; HRMS (ESI) Calcd for $C_{13}H_{21}OSi$ $[M + H]^+$

221.1362, found 221.1364. The ^{1}H and ^{13}C spectra of the product showed good agreement with the literature data.[13b]



1-(4-Methoxy-2-(2-(trimethylsilyl)ethyl)phenyl)ethanone (3b): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**, 76.3 mg, 0.30 mmol) and vinyltrimethylsilane (53 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 6/1) of the crude product afforded the title compound as a light brown oil (60.5 mg, 81%).

R_f 0.36 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 9H), 0.78-0.82 (m, 2H), 2.54 (s, 3H), 2.87-2.91 (m, 2H), 3.84 (s, 3H), 6.73 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 19.3, 29.4, 29.5, 55.5, 110.5, 116.2, 129.5, 132.9, 150.1, 162.3, 199.8; HRMS (ESI) Calcd for $C_{14}H_{23}O_2Si$ $[M + H]^+$ 251.1467, found 251.1463. The ^{1}H and ^{13}C spectra of the product showed good agreement with the literature data.[27]

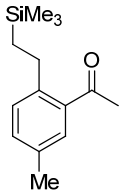


1-(3-(2-(Trimethylsilyl)ethyl)biphenyl-4-yl)ethanone (3c): The typical procedure A was applied to (*E*)-*N*-(1-(biphenyl-4-yl)ethylidene)-4-methoxyaniline (**1c**, 90.4 mg, 0.30 mmol) and vinyltrimethylsilane (53 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a colorless oil (70.1 mg, 79%).

R_f 0.42 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.09 (s, 9H), 0.87-0.91 (m, 2H), 2.63 (s, 3H), 2.94-2.98 (m, 2H), 7.38-7.42 (m, 1H), 7.46-7.50 (m, 3H), 7.52 (d, *J* = 1.6 Hz, 1H), 7.63-7.65 (m, 2H), 7.76 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 19.7, 28.9, 30.0, 124.3, 127.4, 128.2, 129.1, 129.5, 130.4, 136.0, 140.4, 144.5, 147.0, 201.5; HRMS (ESI) Calcd for $C_{19}H_{25}OSi$ $[M + H]^+$ 297.1675, found 297.1678.

1-(4-Chloro-2-(2-(trimethylsilyl)ethyl)phenyl)ethanone (3d): The typical procedure A was applied to (*E*)-*N*-(1-(4-chlorophenyl)ethylidene)-4-methoxyaniline (**1d**, 77.9 mg, 0.30 mmol) and vinyltrimethylsilane (53 μL, 0.36 mmol) with 10 mol % catalyst loading. Silica gel chromatography (eluent: hexane/EtOAc = 100/1) of the crude product afforded the title compound as a light brown oil (53.3 mg, 70%).

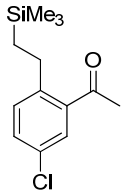
R_f 0.47 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.08 (s, 9H), 0.80-0.85 (m, 2H), 2.59 (s, 3H), 2.83-2.87 (m, 2H), 7.24 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 19.4, 28.6, 30.0, 125.8, 130.7, 131.1, 135.7, 137.7, 148.5, 201.0; HRMS (ESI) Calcd for $C_{13}H_{20}{}^{35}ClOSi$ $[M + H]^+$ 255.0972, found 255.0967. The ^{1}H and ^{13}C spectra of the product showed good agreement with the literature data.[13d]



1-(5-Methyl-2-(2-(trimethylsilyl)ethyl)phenyl)ethanone (3e): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-*m*-tolylethylidene)aniline (**1e**, 71.8 mg, 0.30 mmol)

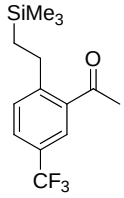
and vinyltrimethylsilane (53 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 100/1) of the crude product afforded the title compound as a colorless oil (51.7 mg, 74%).

R_f 0.52 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 9H), 0.77-0.81 (m, 2H), 2.36 (s, 3H), 2.56 (s, 3H), 2.77-2.81 (m, 2H), 7.16 (d, J = 8.0 Hz, 1H), 7.20 (dd, J = 8.0, 1.2 Hz, 1H), 7.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 19.7, 21.1, 28.1, 30.0, 129.8, 130.6, 132.3, 135.1, 137.6, 142.9, 202.4; HRMS (ESI) Calcd for $C_{14}H_{23}OSi$ $[M + H]^+$ 235.1518, found 235.1513.



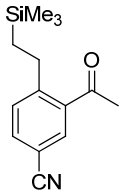
1-(5-Chloro-2-(2-(trimethylsilyl)ethyl)phenyl)ethanone (3f): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-(3-chlorophenyl)ethylidene)aniline (**1f**, 77.9 mg, 0.30 mmol) and vinyltrimethylsilane (53 μL, 0.36 mmol) with 10 mol % catalyst loading. Silica gel chromatography (eluent: hexane/EtOAc = 100/1) of the crude product afforded the title compound as a light yellow oil (44.4 mg, 58%).

R_f 0.74 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 9H), 0.75-0.79 (m, 2H), 2.56 (s, 3H), 2.76-2.80 (m, 2H), 7.21 (d, J = 8.0 Hz, 1H), 7.34 (dd, J = 8.0, 2.4 Hz, 1H), 7.56 (d, J =2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 19.6, 28.0, 30.0, 129.0, 131.3, 131.5, 132.1, 139.0, 144.3, 200.9; HRMS (ESI) Calcd for $C_{13}H_{20}{}^{35}ClOSi$ $[M + H]^+$ 255.0972, found 255.0976.



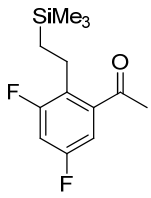
1-(5-(Trifluoromethyl)-2-(2-(trimethylsilyl)ethyl)phenyl)ethanone (3g): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-(3-(trifluoromethyl)phenyl)ethylidene)aniline (**1g**, 77 μL, 0.30 mmol) and vinyltrimethylsilane (53 μL, 0.36 mmol) with 10 mol % catalyst loading. Silica gel chromatography (eluent: hexane/EtOAc = 100/1) of the crude product afforded the title compound as a colorless oil (35.1 mg, 41%).

R_f 0.63 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 9H), 0.78-0.82 (m, 2H), 2.61 (s, 3H), 2.84-2.88 (m, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 19.6, 28.6, 30.0, 124.3 (q, $^1J_{C\text{-}F}$ = 271 Hz), 125.9 (q, $^3J_{C\text{-}F}$ = 3 Hz), 128.0 (q, $^3J_{C\text{-}F}$ = 3 Hz), 128.2 (q, $^2J_{C\text{-}F}$ = 23 Hz), 131.3, 138.0, 150.1, 201.0; HRMS (ESI) Calcd for $C_{14}H_{20}F_3OSi$ $[M + H]^+$ 289.1236, found 289.1233.



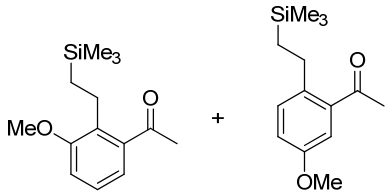
3-Acetyl-4-(2-(trimethylsilyl)ethyl)benzonitrile (3h): The typical procedure A was applied to (*E*)-3-(1-(4-methoxyphenylimino)ethyl)benzonitrile (**1h**, 75.1 mg, 0.30 mmol) and vinyltrimethylsilane (53 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a light yellow solid (17.3 mg, 24%).

m.p. 49.4-50.3 °C; R_f 0.28 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 9H), 0.76-0.80 (m, 2H), 2.59 (s, 3H), 2.83-2.87 (m, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.65 (dd, J = 8.0, 2.0 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.7, 19.5, 28.9, 30.0, 109.9, 118.4, 131.7, 132.7, 134.5, 138.5, 151.5, 200.2; HRMS (ESI) Calcd for $C_{14}H_{20}NOSi$ $[M + H]^+$ 246.1314, found 246.1314.



1-(3,5-Difluoro-2-(2-(trimethylsilyl)ethyl)phenyl)ethanone (3i): The typical procedure A was applied to (*E*)-*N*-(1-(3,5-difluorophenyl)ethylidene)-4-methoxyaniline (**1i**, 78.4 mg, 0.3 mmol) and vinyltrimethylsilane (53 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a light yellow oil (46.5 mg, 60%).

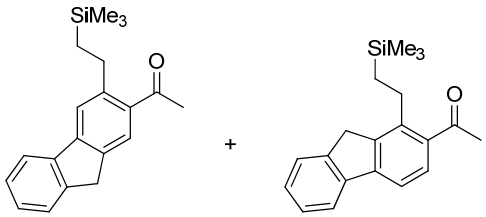
R_f 0.52 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 9H), 0.75-0.79 (m, 2H), 2.46 (s, 3H), 2.71-2.76 (m, 2H), 6.89 (ddd, J = 9.6, 8.4, 2.4 Hz, 1H), 7.09 (ddd, J = 8.4, 2.4, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.7, 18.7, 19.9 (d, $^3J_{C–F}$ = 5 Hz), 30.2, 106.6 (dd, $^2J_{C–F}$ = 28, 25 Hz), 111.4 (dd, $^2J_{C–F}$ = 22 Hz, $^4J_{C–F}$ = 4 Hz), 128.9 (dd, $^3J_{C–F}$ = 16 Hz, $^4J_{C–F}$ = 4 Hz), 140.4 (t, $^3J_{C–F}$ = 6 Hz), 160.3 (dd, $^1J_{C–F}$ = 246 Hz, $^3J_{C–F}$ = 13 Hz), 161.6 (dd, $^1J_{C–F}$ = 247 Hz, $^3J_{C–F}$ = 11 Hz), 200.2 (t, $^4J_{C–F}$ = 2 Hz); HRMS (ESI) Calcd for $C_{13}H_{19}F_2OSi$ $[M + H]^+$ 257.1173, found 257.1172.



1-(3-Methoxy-2-(2-(trimethylsilyl)ethyl)phenyl)ethanone (3j) and 1-(5-methoxy-2-(2-(trimethylsilyl)ethyl)phenyl)ethanone (3j'): The typical procedure A was applied to (*E*)-3-methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**, 76.3 mg, 0.30 mmol) and vinyltrimethylsilane (53 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compounds as light yellow oils (**3j**, 45.6 mg, 61%; **3j'**, 22.4 mg, 30%).

3j: R_f 0.36 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 9H), 0.75-0.79 (m, 2H), 2.54 (s, 3H), 2.71-2.75 (m, 2H), 3.84 (s, 3H), 6.94 (d, J = 8.0 Hz, 1H), 7.12 (dd, J = 8.0, 0.8 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 18.1, 20.9, 30.8, 55.9, 113.0, 120.3, 126.2, 133.8, 139.9, 157.9, 203.3; HRMS (ESI) Calcd for $C_{14}H_{23}O_2Si$ $[M + H]^+$ 251.1467, found 251.1464.

3j': R_f 0.27 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 9H), 0.75-0.79 (m, 2H), 2.56 (s, 3H), 2.73-2.77 (m, 2H), 3.82 (s, 3H), 6.94 (dd, J = 8.4, 2.8 Hz, 1H), 7.12 (d, J = 2.8 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 19.8, 27.6, 30.1, 55.6, 114.9, 116.8, 131.6, 137.7, 138.6, 157.3, 202.3; HRMS (ESI) Calcd for $C_{14}H_{23}O_2Si$ $[M + H]^+$ 251.1467, found 251.1467.

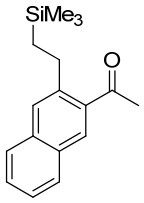


1-(3-(2-(Trimethylsilyl)ethyl)-9*H*-fluoren-2-yl)ethanone (3k) and 1-(1-(2-(trimethylsilyl)ethyl)-9*H*-fluoren-2-yl)ethanone (3k'): The typical procedure A was applied to (*E*)-*N*-(1-(9*H*-fluoren-2-yl)ethylidene)-4-methoxyaniline (**1k**, 94.0 mg, 0.30 mmol) and vinyltrimethylsilane (53 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 100/1) of the crude product afforded the title compounds **3k** and **3k'** as a light yellow solid and a light brown solid, respectively (**3k**, 36.5 mg, 39%; **3k'**, 33.9 mg, 37%).

3k: m.p. 83.7-84.3 °C; R_f 0.37 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.10 (s, 9H), 0.88-0.92 (m, 2H), 2.64 (s, 3H), 2.95-2.99 (m, 2H), 3.90 (s, 2H), 7.35-7.41 (m, 2H), 7.57 (d, J = 7.2 Hz, 1H), 7.67 (s, 1H), 7.83-7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.5, 20.0, 29.1, 30.1, 36.8, 120.8, 121.9, 125.4, 126.3, 127.1, 127.8, 135.8, 140.2, 140.9,

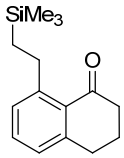
144.7, 145.1, 145.7, 201.9; HRMS (ESI) Calcd for $C_{20}H_{25}OSi$ $[M + H]^+$ 309.1675, found 309.1675.

3k': m.p. 82.4-83.8 °C; R_f 0.44 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.14 (s, 9H), 0.85-0.89 (m, 2H), 2.64 (s, 3H), 2.95-2.99 (m, 2H), 3.88 (s, 2H), 7.36-7.41 (m, 2H), 7.60 (d, *J* = 6.8 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 18.1, 25.5, 30.2, 35.8, 117.0, 120.9, 125.3, 127.1, 127.9, 129.7, 135.2, 141.2, 142.9, 143.1, 144.2, 144.9, 201.7; HRMS (ESI) Calcd for $C_{20}H_{25}OSi$ $[M + H]^+$ 309.1675, found 309.1674.



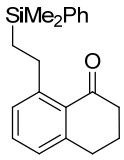
1-(3-(2-(Trimethylsilyl)ethyl)naphthalen-2-yl)ethanone (3l): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-(naphthalen-2-yl)ethylidene)aniline (**1l**, 82.6 mg, 0.30 mmol) and vinyltrimethylsilane (53 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light yellow solid (65.1 mg, 80%).

m.p. 48.8-49.8 °C; R_f 0.41 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.09 (s, 9H), 0.87-0.91 (m, 2H), 2.71 (s, 3H), 3.02-3.07 (m, 2H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.69 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 8.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 19.5, 28.7, 29.9, 126.0, 127.2, 128.2, 128.5, 128.6, 130.5, 131.0, 135.0, 136.5, 142.3, 201.9; HRMS (ESI) Calcd for $C_{17}H_{23}OSi$ $[M + H]^+$ 271.1518, found 271.1521.



8-(2-(Trimethylsilyl)ethyl)-3,4-dihydronaphthalen-1(2*H*)-one (3m): The typical procedure A was applied to (*E*)-*N*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline (**1m**, 75.4 mg, 0.30 mmol) and vinyltrimethylsilane (53 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a light brown oil (68.3 mg, 92%).

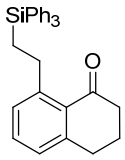
R_f 0.55 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 9H), 0.79-0.84 (m, 2H), 2.07 (quintet, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 6.4 Hz, 2H), 2.94 (t, *J* = 6.0 Hz, 2H), 2.99-3.03 (m, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 19.2, 23.1, 29.9, 31.3, 41.3, 126.8, 129.3, 130.5, 132.6, 146.0, 149.4, 200.1; HRMS (ESI) Calcd for $C_{15}H_{23}OSi$ $[M + H]^+$ 247.1518, found 247.1516. The ^{1}H and ^{13}C spectra of the product showed good agreement with the literature data.[13b]



8-(2-(Dimethyl(phenyl)silyl)ethyl)-3,4-dihydronaphthalen-1(2*H*)-one (3n): The typical procedure A was applied to (*E*)-*N*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline (**1m**, 75.4 mg, 0.30 mmol) and vinyldimethylphenylsilane (**2n**, 66 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a light yellow oil (85.7 mg, 93%).

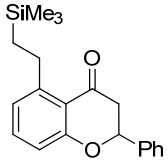
R_f 0.50 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.41 (s, 6H), 1.11-1.15 (m, 2H), 2.09 (quintet, *J* = 6.4 Hz, 2H), 2.67 (t, *J* = 6.4 Hz, 2H), 2.96 (t, *J* = 6.4 Hz, 2H), 3.06-3.11 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.38-7.41 (m, 3H), 7.60-7.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -2.9, 18.1, 23.1, 29.9, 31.3, 41.3, 126.9,

127.9, 128.9, 129.3, 130.6, 132.6, 133.8, 139.7, 146.0, 149.0, 200.0; HRMS (ESI) Calcd for $C_{20}H_{25}OSi$ $[M + H]^+$ 309.1675, found 309.1675.



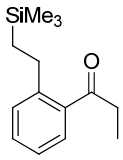
8-(2-(Triphenylsilyl)ethyl)-3,4-dihydronaphthalen-1(2*H*)-one (3o): The typical procedure A was applied to (*E*)-*N*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline (**1m**, 75.4 mg, 0.30 mmol) and vinyltriphenylsilane (**2o**, 103.3 mg, 0.36 mmol) with 10 mol % catalyst loading. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a light brown solid (109.2 mg, 84%).

m.p. 108.8-109.6 °C; R_f 0.23 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78-1.83 (m, 2H), 2.10 (quintet, *J* = 6.4 Hz, 2H), 2.69 (t, *J* = 6.4 Hz, 2H), 2.97 (t, *J* = 6.4 Hz, 2H), 3.24-3.29 (m, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.41-7.48 (m, 9H), 7.70-7.72 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ15.6, 23.1, 30.2, 31.3, 41.3, 127.0, 128.0, 129.4, 129.5, 130.7, 132.7, 135.5, 136.0, 146.1, 148.6, 200.0; HRMS (ESI) Calcd for $C_{30}H_{29}OSi$ $[M + H]^+$ 433.1988, found 433.1990.



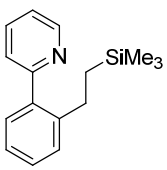
2-Phenyl-5-(2-(trimethylsilyl)ethyl)chroman-4-one (3p): The typical procedure was applied to (*E*)-4-methoxy-*N*-(2-phenylchroman-4-ylidene)aniline (**1p**, 98.8 mg, 0.3 mmol) and vinyltrimethylsilane (53 μL, 0.36 mmol) with 10 mol % catalyst loading. Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a light yellow oil (86.5 mg, 89%).

R_f 0.61 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 9H), 0.79-0.86 (m, 2H), 2.87 (dd, *J* = 16.4, 2.8 Hz, 1H), 2.94-3.17 (m, 3H), 5.43 (dd, *J* = 13.6, 2.8 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.91 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.34-7.59 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 18.8, 29.7, 46.5, 78.9, 116.1, 118.7, 123.6, 126.2, 128.8, 129.0, 135.2, 139.2, 150.2, 163.1, 193.2; HRMS (ESI) Calcd for $C_{20}H_{25}O_2Si$ $[M + H]^+$ 325.1624, found 325.1622.



1-(2-(2-(Trimethylsilyl)ethyl)phenyl)propan-1-one (3q): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-phenylpropylidene)aniline (**1q**, 71.7 mg, 0.30 mmol) and vinyltrimethylsilane (53 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a light yellow oil (65.4 mg, 93%).

R_f 0.72 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 9H), 0.82-0.87 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H), 2.79-2.83 (m, 2H), 2.92 (q, *J* = 7.2 Hz, 2H), 7.25 (td, *J* = 7.6, 1.2 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.40 (td, *J* = 7.2, 1.6 Hz, 1H), 7.55 (dd, *J* = 8.0, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 8.7, 19.8, 28.2, 35.5, 125.6, 128.0, 130.4, 131.1, 138.5, 145.2, 206.0; HRMS (ESI) Calcd for $C_{14}H_{23}OSi$ $[M + H]^+$ 235.1518, found 235.1514. The ^{1}H NMR spectrum showed good agreement with the literature data.[11a]

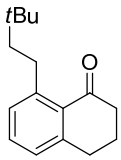


2-(2-(2-(Trimethylsilyl)ethyl)phenyl)pyridine (3r): The typical procedure A was applied to 2-phenylpyridine (**1m**, 43 μL, 0.3 mmol) and vinyltrimethylsilane (53 μL, 0.36 mmol)

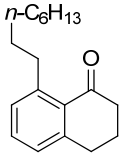
with 10 mol % catalyst loading at 60 °C. Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light brown oil (54.8 mg, 72%).

R$_f$ 0.31 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.10 (s, 9H), 0.70-0.74 (m, 2H), 2.70-2.75 (m, 2H), 7.25-7.29 (m, 2H), 7.34-7.40 (m, 3H), 7.41 (dd, *J* = 6.8, 0.8 Hz, 1H), 7.76 (td, *J* = 7.6, 1.6 Hz, 1H), 8.71 (dd, *J* = 4.8, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.8, 19.4, 27.5, 121.8, 124.3, 125.8, 128.6, 129.4, 129.9, 136.3, 139.9, 143.7, 149.3, 160.5; HRMS (ESI) Calcd for $C_{16}H_{22}NSi$ $[M + H]^+$ 256.1522, found 256.1524. The ^{1}H and ^{13}C NMR spectra showed good agreement with the literature data.[17b]

Typical Procedure B. Cobalt–Neocuproine-Catalyzed *ortho*-Alkylation with Olefin: In a Schlenk tube were placed $CoBr_2$ (6.6 mg, 0.030 mmol), neocuproine (6.2 mg, 0.030 mmol), (*E*)-*N*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline (**1m**, 75.4 mg, 0.30 mmol), and THF (0.70 mL). To the mixture was added a THF solution of Me_3SiCH_2MgCl (0.89 M, 0.20 mL, 0.18 mmol) dropwise at 0 °C. After stirring for 30 min, 3,3-dimethyl-1-butene (46 μL, 0.36 mmol) was added. The resulting mixture was stirred at 60 °C for 24 h. The reaction was cooled to room temperature and then quenched by the addition of 3 N HCl (1 mL). The resulting mixture was stirred at room temperature for 3 h, and then extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 50/1) to afford 8-(3,3-dimethylbutyl)-3,4-dihydronaphthalen-1(2*H*)-one (**3s**, 73%) as a light yellow oil, which contained an *ortho*-trimethylsilylmethylation product (8-((trimethylsilyl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one, 10%) as an inseparable byproduct as judged from GC/GCMS and ^{1}H NMR analysis. The title compound was obtained in 78% yield by using $MeOC_6H_4MgBr$ instead of Me_3SiCH_2MgCl.

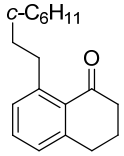


3s: R_f 0.36 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (s, 9H), 1.41-1.46 (m, 2H), 2.07 (quintet, *J* = 6.0 Hz, 2H), 2.64 (t, *J* = 6.0 Hz, 2H), 2.94 (t, *J* = 6.0 Hz, 2H), 2.98-3.02 (m, 2H), 7.07-7.10 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 29.5, 30.88, 30.93, 31.3, 41.3, 46.1, 126.8, 130.1, 131.0, 132.5, 146.0, 147.2, 200.1; HRMS (ESI) Calcd for $C_{16}H_{23}O$ $[M + H]^+$ 231.1749, found 231.1752. The ^{1}H and ^{13}C NMR spectra showed good agreement with the literature data.[11c]



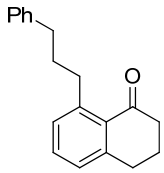
8-Octyl-3,4-dihydronaphthalen-1(2*H*)-one (3t): The typical procedure B was applied to (*E*)-*N*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline (**1m**, 75.4 mg, 0.3 mmol) and 1-octene (57 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound (62%) as a light brown oil, which contained the *ortho*-trimethylsilylmethylation byproduct (12%) as judged from GC/GCMS and ^{1}H NMR analysis.

R_f 0.44 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.27-1.36 (m, 8H), 1.38-1.42 (m, 2H), 1.51-1.57 (m, 2H), 2.04-2.17 (m, 2H), 2.64 (t, *J* = 6.4 Hz, 2H), 2.94 (t, *J* = 6.4 Hz, 2H), 2.99-3.03 (m, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 22.9, 23.1, 29.6, 29.7, 30.2, 31.3, 31.7, 32.1, 35.6, 41.3, 126.9, 130.0, 131.1, 132.4, 146.0, 146.5, 200.2; HRMS (ESI) Calcd for $C_{18}H_{27}O$ $[M + H]^+$ 259.2062, found 259.2063.



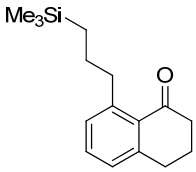
8-(2-Cyclohexylethyl)-3,4-dihydronaphthalen-1(2*H*)-one (3u): The typical procedure B was applied to (*E*)-*N*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline (**1m**, 75.4 mg, 0.3 mmol) and vinylcyclohexane (50 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound (68%) as a light yellow oil, which contained the *ortho*-trimethylsilylmethylation byproduct (9%) as judged from GC/GCMS and ^{1}H NMR analysis.

R_f 0.44 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96-1.02 (m, 2H), 1.15-1.28 (m, 3H), 1.38-1.46 (m, 3H), 1.64-1.74 (m, 3H), 1.82 (brd, J = 12.4 Hz, 2H), 2.04-2.10 (m, 2H), 2.64 (t, J = 6.8 Hz, 2H), 2.94 (t, J = 6.4 Hz, 2H), 3.00-3.04 (m, 2H), 7.08 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 26.6, 27.0, 31.4, 33.1, 33.5, 38.4, 39.6, 41.3, 126.9, 130.0, 131.1, 132.4, 146.0, 147.0, 200.2; HRMS (ESI) Calcd for $C_{18}H_{25}O$ $[M + H]^+$ 257.1905, found 257.1911.



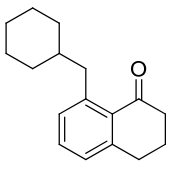
8-(3-Phenylpropyl)-3,4-dihydronaphthalen-1(2*H*)-one (3v): The typical procedure B was applied to (*E*)-*N*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline (**1m**, 75.4 mg, 0.3 mmol) and allylbenzene (48 μL, 0.36 mmol) with 20 mol % catalyst laoding. Silica gel chromatography (eluent: hexane/EtOAc = 200/1) of the crude product afforded the title compound (54%) as a light brown oil, which contained the *ortho*-trimethylsilylmethylation byproduct (9%) as judged from GC/GCMS and ^{1}H NMR analysis.

R_f 0.44 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91-1.95 (m, 2H), 2.04-2.18 (m, 2H), 2.66 (t, *J* = 6.4 Hz, 2H), 2.75 (t, *J* = 8.0 Hz, 2H), 2.96 (d, *J* = 6.0 Hz, 2H), 3.07-3.11 (m, 2H), 7.08-7.11 (m, 2H), 7.16-7.20 (m, 1H), 7.22-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 31.3, 33.2, 35.4, 36.3, 41.3, 125.7, 127.1, 128.4, 128.6, 130.0, 131.1, 132.4, 142.9, 145.9, 146.1, 200.2; HRMS (ESI) Calcd for $C_{19}H_{21}O$ $[M + H]^+$ 265.1592, found 265.1595.



8-(3-(Trimethylsilyl)propyl)-3,4-dihydronaphthalen-1(2*H*)-one (3w): The typical procedure A was applied to (*E*)-*N*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline (**1m**, 75.4 mg, 0.3 mmol) and allyltrimethylsilane (57 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 100/1) of the crude product afforded the title compound as a light brown oil (44.1 mg, 57%).

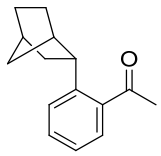
R_f 0.63 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ -0.02 (s, 9H), 0.60-0.64 (m, 2H), 1.55-1.59 (m, 2H), 2.08 (quintet, *J* = 6.4 Hz, 2H), 2.64 (t, *J* = 6.4 Hz, 2H), 2.95 (t, *J* = 6.0 Hz, 2H), 3.01-3.05 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.4, 17.4, 23.2, 26.2, 31.4, 39.4, 41.3, 127.0, 130.2, 131.2, 132.32, 146.0, 146.2, 200.1; HRMS (ESI) Calcd for $C_{16}H_{25}OSi$ $[M + H]^+$ 261.1675, found 261.1672.



8-(Cyclohexylmethyl)-3,4-dihydronaphthalen-1(2*H*)-one (3x): The typical procedure B was applied to (*E*)-*N*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline (**1m**, 75.4

mg, 0.3 mmol) and methylenecyclohexane (43 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 150/1) of the crude product afforded the title compound (18%), which contained the *ortho*-trimethylsilylmethylation byproduct (11%) as judged from GC/GCMS and ^{1}H NMR analysis.

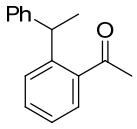
R_f 0.50 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96-1.02 (m, 2H), 1.15-1.18 (m, 3H), 1.44-1.54 (m, 1H), 1.60-1.72 (m, 5H), 2.03-2.11 (m, 2H), 2.60-2.66 (m, 2H), 2.91 (d, J = 6.4 Hz, 2H), 2.91-2.97 (m, 2H), 7.03 (d, J = 7.2 Hz, 1H), 7.10 (d, J = 6.8 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 26.6, 26.9, 31.4, 33.6, 39.2, 41.5, 43.2, 125.0, 127.1, 131.3, 131.9, 144.7, 146.1, 200.3; HRMS (ESI) Calcd for $C_{18}H_{25}O$ $[M + H]^+$ 243.1749, found 243.1745.



1-(2-(Bicyclo[2.2.1]heptan-2-yl)phenyl)ethanone (3y): The typical procedure B was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1a**, 67.6 mg, 0.3 mmol) and norbornene (33.9 mg, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a colorless oil (48.8 mg, 76%), which contained the *ortho*-trimethylsilylmethylation byproduct (10%) as judged from GC/GCMS and ^{1}H NMR analysis.

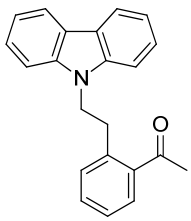
R_f 0.49 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23-1.30 (m, 2H), 1.38-1.42 (m, 1H), 1.47-1.52 (m, 1H), 1.55-1.61 (m, 3H), 1.80-1.84 (m, 1H), 2.33-2.37 (m, 2H), 2.56 (s, 3H), 3.18-3.21 (m, 1H), 7.19-7.23 (m, 1H), 7.38-7.42 (m, 2H), 7.49 (dd, J = 7.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.9, 30.7, 30.9, 36.9, 37.2, 40.5, 42.8, 43.7, 125.3, 126.6, 128.2, 131.0, 139.5, 146.4, 204.0; HRMS (ESI) Calcd for $C_{15}H_{19}O$ $[M + H]^+$

215.1436, found 215.1435. The ^{1}H and ^{13}C NMR spectra showed good agreement with the literature data.[11c]



1-(2-(1-Phenylethyl)phenyl)ethanone (3z): The typical procedure B was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1a**, 67.6 mg, 0.3 mmol) and styrene (41 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a colorless oil (51.3 mg, 76%, b/l = 86/14).

R_f 0.44 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (d, J = 7.2 Hz, 3H), 2.38 (s, 3H), 4.90 (q, J = 7.2 Hz, 1H), 7.15-7.20 (m, 3H), 7.24-7.29 (m, 3H), 7.34-7.41 (m, 2H), 7.49 (dd, J = 6.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 30.5, 39.7, 125.9, 126.1, 127.8, 128.2, 128.4, 128.6, 131.1, 139.6, 145.3, 146.4, 204.0; HRMS (ESI) Calcd for $C_{16}H_{17}O$ $[M + H]^+$ 225.1279, found 225.1280. The ^{1}H and ^{13}C NMR spectra showed good agreement with the literature data.[6b]



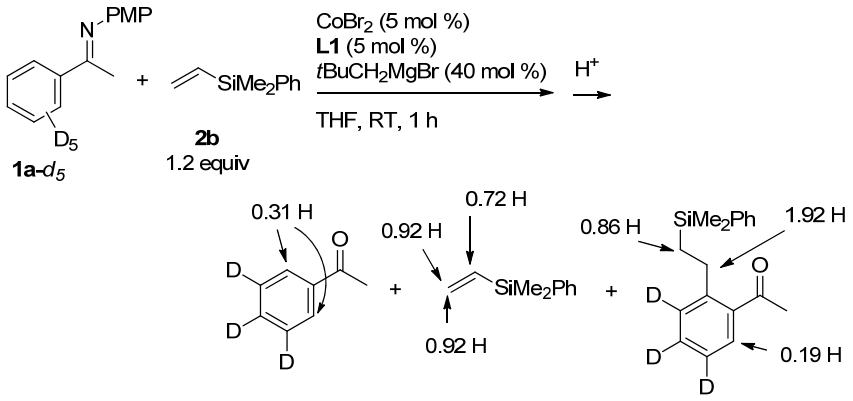
1-(2-(2-(9*H*-Carbazol-9-yl)ethyl)phenyl)ethanone (3aa): The typical procedure B was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1a**, 67.6 mg, 0.3 mmol) and 9-vinylcarbazole (69.6 mg, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a white solid (48.9 mg, 52%).

m.p. 160.8-161.6 °C; R_f 0.21 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 3H), 3.36 (t, J = 7.6 Hz, 2H), 4.64 (t, J = 7.6 Hz, 2H), 7.10-7.12 (m, 1H), 7.22 (t, J = 7.6

Hz, 2H), 7.29-7.32 (m, 2H), 7.48 (td, J = 6.8, 1.2 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.74-7.76 (m, 1H), 8.11 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 34.3, 44.8, 109.1, 118.9, 120.4, 123.0, 125.8, 126.9, 130.0, 132.1, 132.6, 137.9, 139.2, 140.6, 201.8; HRMS (ESI) Calcd for $C_{22}H_{20}NO$ $[M + H]^+$ 314.1545, found 314.1542.

Deuterium-Labeling Experiment:

A mixture of **1a**-d_5 (0.3 mol) and vinyldimethylphenylsilane (0.36 mmol) was subjected to the typical procedure A for 30 min. Purification of the crude mixture by silica gel chromatography (eluent: hexane/EtOAc = 150:1) afforded the recovered starting materials and the alkylation product, which were analyzed by ^{1}H NMR (see attached spectra). Note that the isolated yields of the recovered starting materials (acetophenone, 20%; vinylsilane, 34%) may not reflect the actual yields because of their volatility.



4.5 References

(1) For recent reviews, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (c) Kakiuchi, F. Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (d) Kuninobu, Y. Takai, K. *Chem Rev.* **2011**, *111*, 1938. (e) Lyons, T. W. Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (f) Sun, C. L.; Li, B. J.; Shi, Z. J. *Chem. Commun.* **2010**, *46*, 677. (g) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (h) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792.

(2) For ruthenium catalysis, see: (a) Kakiuchi, F.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, 111. (b) Sonoda, M.; Kakiuchi, F.; Kamatani, A.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, 109. (c) Kakiuchi, F.; Sato, T.; Tsujimoto, T.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1998**, 1053. (d) Kakiuchi, F.; Sato, T.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1999**, 19. (e) Kakiuchi, F.; Sonoda, M.; Tsujimoto, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1999**, 1083. (f) Kakiuchi, F.; Ohtaki, H.; Sonoda, M.; Chatani, N.; Murai, S. *Chem. Lett.* **2001**, 918. (g) Martinez, R.; Chevalier, R.; Darses, S.; Genet, J. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 8232. (h) Martinez, R.; Genet, J.-P.; Darses, S. *Chem. Commun.* **2008**, 3855. (i) Martinez, R.; Simon, M. O.; Chevalier, R.; Pautigny, C.; Genet, J. P.; Darses, S. *J. Am. Chem. Soc.* **2009**, *131*, 7887. (j) Kakiuchi, F.; Kochi, T.; Mizushima, E.; Murai, S. *J. Am. Chem. Soc.* **2010**, *132*, 17741.

(3) For rhodium catalysis, see: (a) Jun, C. H.; Hong, J. B.; Kim, Y. H.; Chung, K. Y. *Angew. Chem. Int. Ed.* **2000**, *39*, 3440. (b) Lim, Y. G.; Han, J. S.; Yang, S. S.; Chun, J. H. *Tetrahedron Lett.* **2001**, *42*, 4853. (c) Jun, C. H.; Moon, C. W.; Hong, J. B.; Lim, S. G.; Chung, K. Y.; Kim, Y. H. *Chem. Eur. J.* **2002**, *8*, 485. (d) Lim, Y. G.; Han, J. S.; Koo, B. T.; Kang, J. B. *J. Mol. Catal. A: Chem.* **2004**, *209*, 41. (e) Lim, S. G.; Ahn, J. A.; Jun, C. H. *Org. Lett.* **2004**, *6*, 4687. (f) Vo-Thanh, G.; Lahrache, H.; Loupy, A.; Kim, I. J.; Chang, D. H.; Jun, C. H. *Tetrahedron* **2004**, *60*, 5539. (g) Yoon, J. H.; Park, Y. J.; Lee, J. H.; Yoo, J.; Jun, C. H. *Org. Lett.* **2005**, *7*, 2889. (h) Lim, Y. G.; Koo, B. T. *Tetrahedron Lett.* **2005**, *46*, 7997.

(4) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

(5) (a) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087. (b) Nakamura, E. Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061. (c) Sun, C.-L.; Li, B.-J. Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (d) Nakamura, E.; Sato, K. *Nat. Mater.* **2011**, *10*, 158.

(6) (a) Gao, K.; Lee, P. S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249. (b) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 400.

(7) For earlier studies, see: a) Murahashi, S. *J. Am. Chem. Soc.* **1955**, *77*, 6403. (b) Murahashi, S.; Horiie, S. *J. Am. Chem. Soc.* **1956**, *78*, 4816. (c) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 3165. (d) Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 6965. (e) Funk, J. K.; Yennawar, H.; Sen, A. *Helv. Chim. Acta* **2006**, 89, 1687. (f) Bolig, A. D.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, *129*, 14544.

(8) (a) Ding, Z.; Yoshikai, N. *Org. Lett.* **2010**, *12*, 4180. (b) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428. (c) Li, B.; Wu, Z.-H.; Gu, Y.-F.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2011**, *50*, 1109.

(9) Yoshikai N. *Synlett* **2011**, 1047.

(10) Reviews on cobalt-catalyzed C–C bond formations: (a) Yorimitsu, H.; Oshima, K. *Pure Appl. Chem.* **2006**, *78*, 441. (b) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537. (c) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435.

(11) For rhodium catalysis, see: (a) Jun, C. H.; Hong, J. B.; Kim, Y. H.; Chung, K. Y. *Angew. Chem. Int. Ed.* **2000**, *39*, 3440. (b) Lim, Y. G.; Han, J. S.; Yang, S. S.; Chun, J. H. *Tetrahedron Lett.* **2001**, *42*, 4853. (c) Jun, C. H.; Moon, C. W.; Hong, J. B.; Lim, S. G.; Chung, K. Y.; Kim, Y. H. *Chem. Eur. J.* **2002**, *8*, 485. (d) Lim, Y. G.; Han, J. S.; Koo, B. T.; Kang, J. B. *J. Mol. Catal. A: Chem.* **2004**, *209*, 41. (e) Lim, S. G.; Ahn, J. A.; Jun, C. H. *Org. Lett.* **2004**, *6*, 4687. (f) Vo-Thanh, G.; Lahrache, H.; Loupy, A.; Kim, I. J.; Chang, D. H.; Jun, C. H. *Tetrahedron* **2004**, *60*, 5539. (g) Yoon, J. H.; Park, Y. J.; Lee, J. H.; Yoo, J.; Jun, C. H. *Org. Lett.* **2005**, *7*, 2889. (h) Lim, Y. G.; Koo, B. T. *Tetrahedron Lett.* **2005**, *46*, 7997.

(12) For ruthenium catalysis, see: (a) Kakiuchi, F.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, 111. (b) Kakiuchi, F.; Sato, T.; Tsujimoto, T.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1998**, 1053. (c) Martinez, R.; Chevalier, R.; Darses, S.; Genet, J. P. *Angew. Chem. Int.*

Ed. **2006**, *45*, 8232. (d) Martinez, R.; Simon, M. O.; Chevalier, R.; Pautigny, C.; Genet, J. P.; Darses, S. *J. Am. Chem. Soc.* **2009**, *131*, 7887.

(13) For *ortho*-alkylation of aromatic ketones, see ref 4 and 12c, d, and the following papers: (a) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62. (b) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *J. Organomet. Chem.* **1995**, *504*, 151. (c) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117. (d) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616. (e) Martinez, R.; Genet, J. P.; Darses, S. *Chem. Commun.* **2008**, 3855. (f) Kakiuchi, F.; Kochi, T.; Mizushima, E.; Murai, S. *J. Am. Chem. Soc.* **2010**, *132*, 17741.

(14) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Synlett* **2010**, 97.

(15) A *m*-methoxy group did not cause such a directing effect in the Rh-catalyzed *ortho*-alkylation of aromatic aldimines (see ref 11b).

(16)Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006.

(17) (a) Lim, Y. G.; Kim, Y. H.; Kang, J. B. *J. Chem. Soc. Chem. Commun.* **1994**, 2267. (b) Lim, Y. G.; Kang, J. B.; Kim, Y. H. *J. Chem. Soc. Perkin Trans. 1* **1996**, 2201.

(18) Kobayashi, T.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2009**, *4*, 1078.

(19) Note that Brookhart and coworkers also studied H/D scrambling in *ortho*-alkylation of aromatic ketones with vinylsilane under Rh catalysis (see ref 13d). In contrast to the Murai-type and our systems, their system caused H/D scrambling not only at the *ortho* positions but also at the *meta*- and *para* positions.

(20) Klein, H. F.; Camadanli, S.; Beck, R.; Leukel, D.; Florke, U. *Angew. Chem.* **2005**, *117*, 997; *Angew. Chem. Int. Ed.* **2005**, *44*, 975.

(21) Lenges, C. P.; Brookhart, M.; Grant, B. E. *J. Organomet. Chem.* **1997**, *528*, 199.

(22) (a) Mrsic, N.; Panella, L.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *J. Am. Chem. Soc.* **2009**, *131*, 8358. (b) Gautier, F.-M.; Jones, S.; Martin, S. J. *Org. Biomol. Chem.* **2009**, *7*, 229.

(23) Samec, J. S. M.; Ell, A. H.; Bäckvall, J.-E. *Chem. Eur. J.* **2005**, *11*, 2327.

(24) Imamoto, T.; Iwadate, N.; Yoshida, K. *Org. Lett.* **2006**, *8*, 2289.

(25) Moessner, C.; Bolm, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 7564.

(26) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem. Int. Ed.* **2009**, *48*, 2925.

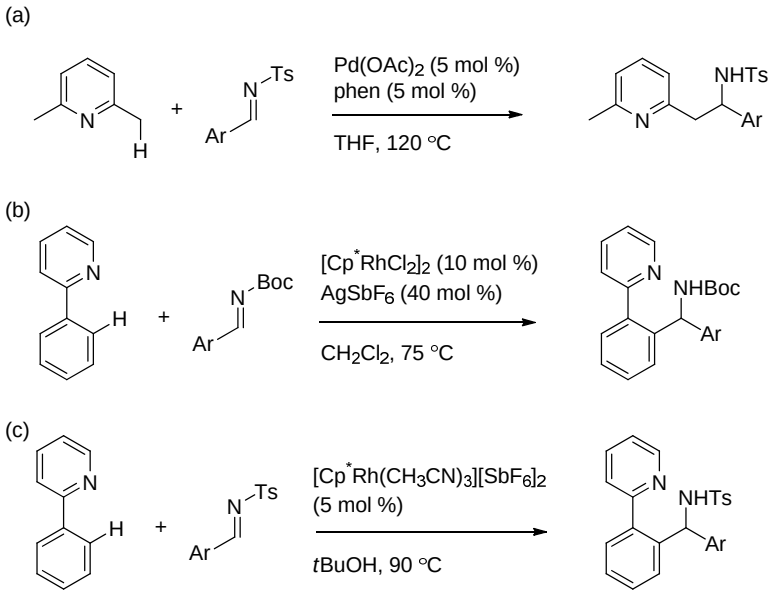
(27) Harris, P. W. R.; Woodgate, P. D. *J. Organomet. Chem.* **1997**, *530*, 211.

Chapter 5. Cobalt-Catalyzed Addition of 2-Arylpyridines to Aryl Aldimines and Self-Coupling of Aryl Aldimines

5.1 Introduction

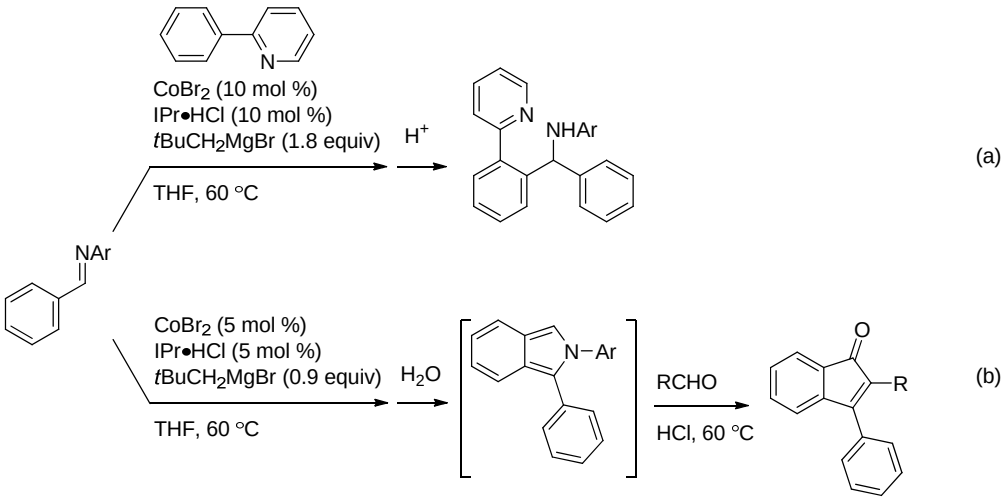
Transition metal-catalyzed addition of C–H bond to olefins and alkynes have been well documented as highly atom-economic protocols to introduce alkyl and alkenyl group onto aromatic rings.[1] On the other hand, analogous C–H bond functionalization reactions *via* addition to polar C–O and C–N multiple bonds have been relatively limited. Such reactions may serve as an alternative strategy for nucleophilic addition of preformed organometallic reagents.[2] Thus, various polar unsaturated compounds such as aldehydes,[3] ketones,[4] carbon dioxide,[5] imines,[6] isocyanates[7] and nitriles[8] have been used as reaction partners for such reactions. Among these reactions, the addition to imines represents a powerful method for the synthesis of α-branched amine. Only three examples of direct addition to aryl aldimines *via* C–H bond functionalization have been known before 2012. In 2010, Xia and Huang reported the first palladium-catalyzed benzylic addition of 2-methylpyridine derivatives to *N*-tosyl imines (Scheme 5.1a).[6e] The groups of Bergman/Ellman and Shi independently reported the synthesis of diarylmethylamine derivatives by rhodium(III)-catalyzed addition of 2-arylpyridines to aryl aldimines (Scheme 5.1b,c).[6a,c] In Bergman and Ellman's work, $[Cp^*RhCl_2]_2$ in combination with $AgSbF_6$ was used as the catalyst for addition reaction to *N*-Boc imines. In Shi's work, a cationic Rh(III) complex $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ and an *N*-tosylimine were used as the catalyst and substrate, respectively.

Scheme 5.1. Addition of 2,6-Lutidine and 2-Phenylpyridine to Aryl Aldimines



As discussed in the previous three chapters, we have demonstrated that low-valent cobalt species generated under reductive conditions serves as an efficient catalyst for *ortho*-alkenylation and alkylation reactions through chelation-assisted C–H bond activation.[9,10] With these previous works in mind, we wondered whether a putative cobaltacycle species generated through *ortho* C–H activation would serve as an aryl donor to a polar unsaturated substrate. Thus, in this chapter we report that a cobalt–NHC catalyst, in combination with a Grignard reagent promotes a chelation-assisted addition reaction of 2-arylpyridines to aryl aldimines to afford diarylmethylamine products (Scheme 5.2a).[6a,b] Furthermore, the same catalytic system also allows the self-coupling of aryl aldimine to afford isoindole derivatives,[11] which are unstable in air, but it can be intercepted by an aldehyde to afford indenone derivatives in a regiocontrolled manner (Scheme 5.2b).

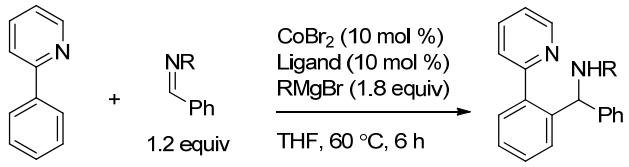
Scheme 5.2. Cobalt-Catalyzed Addition of 2-Arylpyridines to Aldimines and Self-Coupling of Aldimines



5.2 Results and discussion

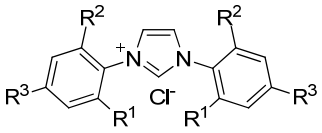
Our initial study focused on the reaction of 2-phenylpyridine **1a** with *N*-phenyl benzaldimine **2a** (Table 5.1). After extensive screening of ligands and Grignard reagents, a cobalt catalyst generated from $CoBr_2$ (10 mol %), IPr•HCl (10 mol %), and *t*$BuCH_2MgBr$ (1.8 equiv) promoted the addition reaction to afford diarylmethylamine **3a** in 84% yield at 60 °C (entry 1). A similar result was obtained by using *N*-*p*-methoxyphenyl benzaldimine **2b** in the presence of $CoCl_2$ (entry 2). Other less sterically hindered NHC preligands were less effective (entries 3-5). Phosphine and phenanthroline derivatives did not promote the reaction at all. Less Grignard reagents resulted in lower yield. The choice of Grignard reagent turned out to be critical as other Grignard reagents such as MeMgCl, *n*BuMgBr, *i*PrMgBr, and Me_3SiCH_2MgCl afforded the desired product in low yields (entries 6-9). Addition of the Grignard reagent to the aldimine substrate was not observed. The imines bearing Boc and Ts groups, which were used in rhodium-catalyzed reaction (Scheme 5.1b,c),[6a,c] did not participate in this reaction.

Table 5.1. Screening of Reaction Conditions[a]



1a **2a** (R = Ph) **2b** (R = 4-MeOC$_6$H$_4$) **3a,b**

Entry	imine	Ligand	RMgX	Yield (%)[b]
1	**2a**	IPr•HCl	*t*BuCH$_2$MgBr	84[c]
2	**2b**	IPr•HCl	*t*BuCH$_2$MgBr	81[d]
3	**2a**	IMes•HCl	*t*BuCH$_2$MgBr	21
4	**2a**	**L1**	*t*BuCH$_2$MgBr	< 1
5	**2a**	**L2**	*t*BuCH$_2$MgBr	< 1
6	**2a**	IPr•HCl	MeMgCl	14
7	**2a**	IPr•HCl	*n*BuMgBr	2
8	**2a**	IPr•HCl	*i*PrMgBr	2
9	**2a**	IPr•HCl	Me$_3$SiCH$_2$MgCl	4



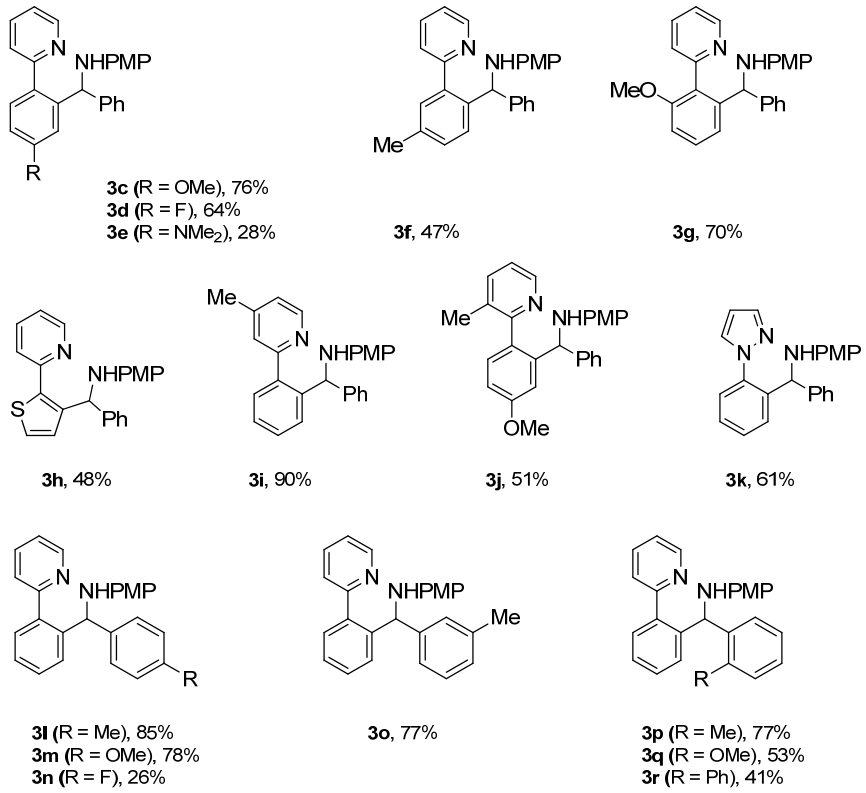
IPr•HCl (R^1 = R^2 = *i*Pr, R^3 = H)
IMes•HCl (R^1 = R^2 = R^3 = Me)
L1 (R^1 = Me, R^2 = R^3 = H)
L2 (R^1 = R^2 = H, R^3 = Ph)

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), $CoBr_2$ (10 mol %), ligand, RMgX, THF, 60 °C, 6 h. [b] Determined by GC using *n*-tridecane as an internal standard. [c] Isolated yield. [d] $CoCl_2$ was used instead of $CoBr_2$. The reaction time was 24 h.

A series of arylpyridines and aldimines smoothly participated in the reaction to afford diarylmethylamine products (Chart 5.1). Various *para*-substituted arylpyridines afforded adducts in moderated to good yields (**3c**-**3e)**. The C–H bond functionalization occurred at the less hindered position of a *meta*-methyl substituted arylpyridine (**3f**). An *ortho*-methoxy group did not cause any inhibition of the reaction. 2-(2-Thienyl)pyridine afforded the adduct with **2b** in a moderate yield (**3h**). A methyl group at the *para*-position of pyridine did not affect the reaction, while a 3-methyl group slowed down the reaction (**3i** and **3j**). A pyrazolyl group also served as a directing group for the arylation reaction to afford the adduct **3k** in good yield. Electron-rich aldimines reacted smoothly with **1a** to

afford adducts **3l** and **3m** in good yields. An aldimine bearing *para*-fluoro group reacted rather sluggishly (**3n**). The reaction tolerated *ortho*-substituted benzaldimine derivatives (**3p**-**3r**).

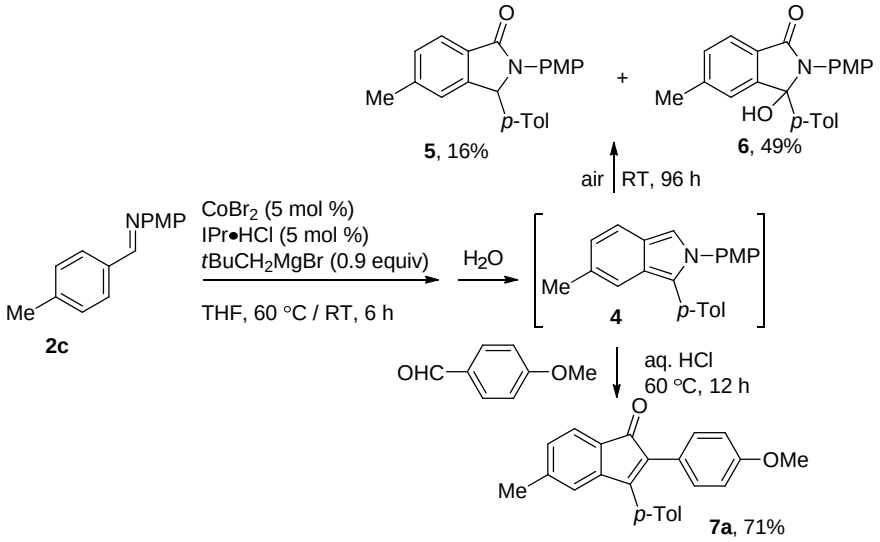
Chart 5.1. Addition of 2-Arylpyridines Derivatives to Aryl Aldimines[a]



[a] Reaction conditions: 2-arylpyridine (0.3 mmol), aldimine (0.36 mmol), $CoCl_2$ (10 mol %), IPr•HCl (10 mol %), *t*BuCH_2MgBr (1.8 equiv), THF, 60 °C, 14-48 h. PMP = *p*-methoxyphenyl.

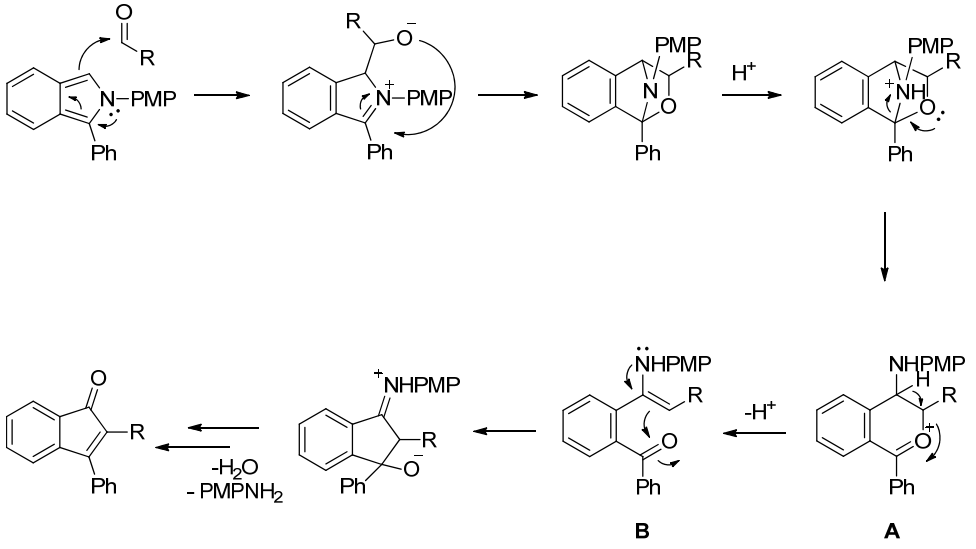
When the reaction was performed in the absence of 2-phenylpyridine **1a**, aldimine **2a** underwent a self-coupling reaction (Scheme 5.3). Thus, after quenching and aqueous workup of the reaction under air, isoindolinones **5** and **6** were isolated in 16% and 49% yields, respectively. Although isoindole **4** was observed as an intermediate for products **5** and **6** by GC-MS analysis, it could not be isolated due to its low stability toward oxidation.[12] The self-coupling reaction took place even at room temperature. When the resulting mixture was treated with *p*-anisaldehyde under acidic conditions, indenone **7a** was obtained in 71% yield.

Scheme 5.3. Self-Coupling of Aryl Aldimine



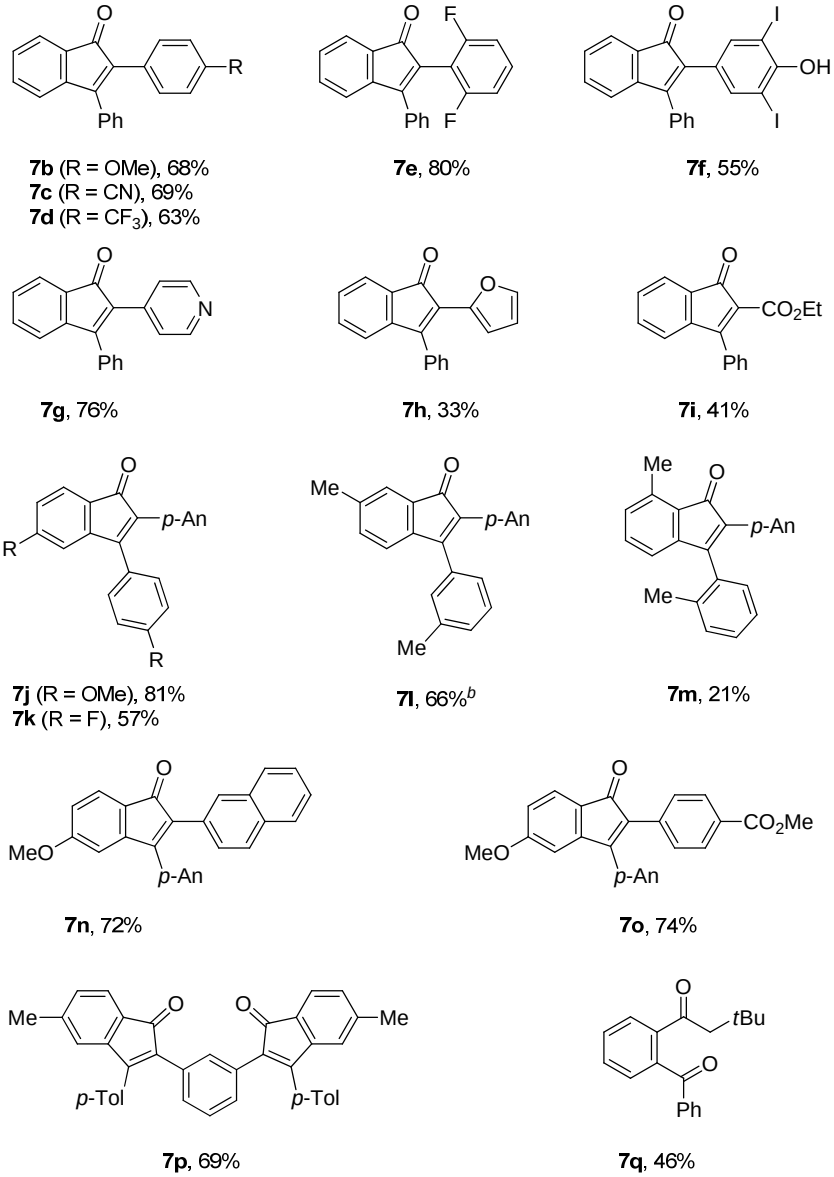
The formation of indenone may be explained by a reaction pathway similar to the one proposed for the reaction of isobenzofuran and benzaldehyde (Scheme 5.4).[13] It may involve the following steps: 1) nucleophilic addition of an isoindole derivative to an aldehyde, 2) intramolecular nucleophilic attack of the alkoxide to the iminium group, 3) ring-opening of the resulting hemiaminal to form intermediate **A**, 4) ring-opening of intermediate **A** and elimination of proton affords intermediate **B**, 5) intramolecular aldol reaction and dehydration affords an indenole product.

Scheme 5.4. Proposed Mechanism for the Formation of Indenone



The present condensation reaction allows regioselective preparation of 2,3-diaryl indenones that are not easily accessible by other transition metal-catalyzed indenone synthesis (Chart 5.2).[14] Various functional groups such as cyano, trifluromethyl, iodo, flouro, hydroxyl and ester as well as heterocylcles of pyridine and furan were tolerated (**7b**-**7p**). Note that the reaction of ethyl glyoxylate proceeded smoothly to afford the indenone **7i** in moderate yield. 3-Methylbenzaldehyde imine underwent the condensation reaction to afford the less sterically congested indenone with a modest level of regioselectivity (2.7:1) (**7l**). Twofold condensation of isophthaldehyde afforded the bis-indenone product **7p** in 69% yield. The reaction of pivalaldehyde afforded a diketone **7q** rather than an indenone derivative, which supported the participation of the intermediate **B** in the proposed mechanism.

Chart 5.2. Indenone Synthesis *via* Self-Coupling of Aldimines with Aldehyde[a]

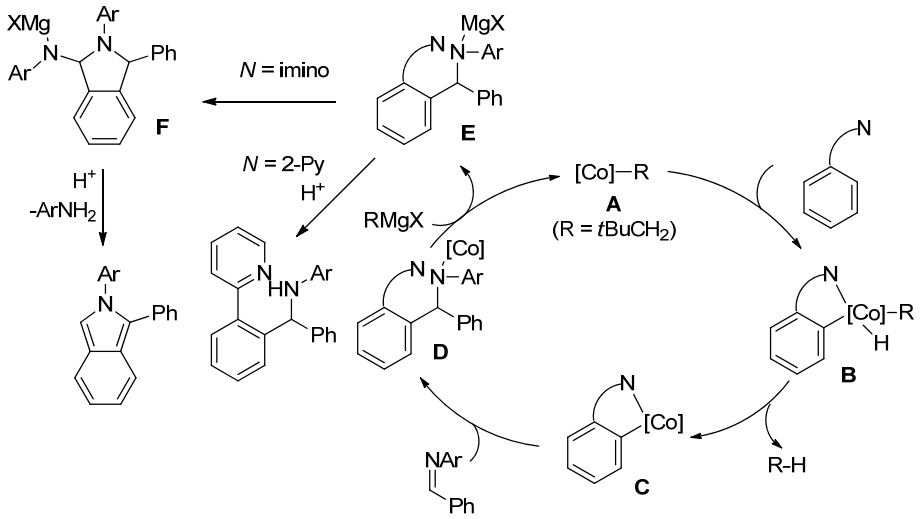


[a] The reactions were performed on 0.6-1.2 mmol scale. [b] Regioselectivity was 2.7:1.

Because the present reaction requires a stoichiometric amount of Grignard reagent, the mechanism should be different from the one proposed for cobalt-catalyzed *ortho* C–H functionalization with alkyne or olefin,[10] as well as the one proposed for the rhodium-catalyzed reaction of 2-arylpyridines with aldimines.[6a,c] We suggest a mechanism analogous to the one proposed for rhodium(I)-catalyzed *ortho*-carboxylation of 2-arylpyridines with carbon dioxide by Iwasawa *et al.* (Scheme 5.5).[5] We hypothesize that a neopentylcobalt species **A** would be generated from the cobalt precatalyst with

neopentylmagnesium bromide. Oxidative addition of the C–H bond to this active species **A** results in an intermediate **B**, which would undergo reductive elimination of neopentane to give an intermediate **C**.[15] Nucleophilic attack of **C** to the aldimine and subsequent transmetalation of the resulting species **D** and Grignard reagent would afford the magnesium amide **E** and regenerate catalytic species **A**. When the directing group is an imino group, the magnesium amide **E** would undergo intramolecular addition to the C=N bond to give an aminal intermediate **F**, which subsequently undergoes deamination by acidic workup to afford an isoindole.

Scheme 5.5. Possible Catalytic Cycle



5.3 Conclusion

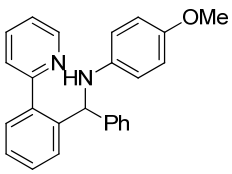
In summary, we have demonstrated that a Co–NHC catalytic system allows chelation-assisted functionalization of arenes with a polar C=N bond. Thus, a variety of diarylmethylamines were obtained through coupling of 2-arylpyridines with aryl aldimines. The same catalytic system also promotes self-coupling of the aryl aldimines to afford isoindoles, which could be further transformed to indenones *via* condensation with aldehydes. The latter reaction serves as a unique method for the regiocontrolled synthesis

of 2,3-diarylindenones derivatives. Further efforts will be focused on expansion of the scope of reaction partners and investigation of the mechanism.

5.4 Experimental section

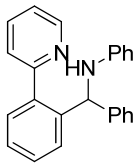
Materials. Unless otherwise noted, commercial reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. Anhydrous cobalt(II) bromide (>99%) was purchased from Alfa Aesar, and was used as received. THF was distilled over Na/benzophenone. Grignard reagents except MeMgCl (purchased from Aldrich) were prepared from the corresponding halides and magnesium turnings in anhydrous THF and titrated before use. The 2-arylpyridine derivatives were prepared by nickel-catalyzed cross-coupling according to the procedure reported by Mongin *et al*.[16] The aldimines were prepared by condensation of the corresponding aldehydes and aniline or *p*-anisidine in EtOH.

A Typical Procedure for Alkenylation Product: In a Schlenk tube were placed $CoCl_2$ (3.9 mg, 0.03 mmol), IPr•HCl (12.8 mg, 0.03 mmol), 2-phenylpyridine (**1a**, 43 μL, 0.3 mmol), and THF (0.64 mL). To the mixture was added a THF solution of $(CH_3)_3CCH_2MgBr$ (0.63 M, 0.86 mL, 0.54 mmol) dropwise at 0 °C. After stirring for 30 min, (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 76.1 mg, 0.36 mmol) was added. The resulting mixture was stirred at 60 ˚C for 24 h, and then diluted with ether (1 mL), and quenched by saturated aqueous solution of NH_4Cl (1 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 10/1/0.1) to afford **4-methoxy-*N*-(phenyl(2-(pyridin-2-yl)phenyl)methyl)aniline** (**3b**, 89.0 mg, 81 %) as a red oil.



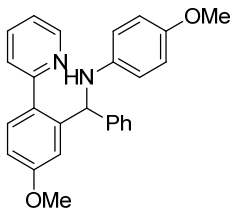
3b: R_f 0.17 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (s, 3H), 4.28 (brs, 1H), 5.88 (s, 1H), 6.51 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 7.13-7.22 (m, 7H),

7.36-7.40 (m, 3H), 7.53-7.59 (m, 2H), 8.65 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8, 59.7, 114.6, 114.8, 122.0, 124.4, 126.9, 127.4, 127.7, 128.2, 128.4, 128.9, 130.2, 136.4, 140.5, 141.2, 141.8, 143.1, 149.1, 152.0, 159.7. HRMS (ESI) Calcd for $C_{25}H_{23}N_2O$ $[M + H]^+$ 367.1810, found 367.1812.



***N*-(Phenyl(2-(pyridin-2-yl)phenyl)methyl)aniline (3a):** The typical procedure was applied to 2-phenylpyridine (**1a**, 43 μL, 0.30 mmol) and (*E*)-*N*-benzylideneaniline (**2a**, 65.2 mg, 0.36 mmol) with $CoBr_2$ (6.6 mg, 0.03 mmol) at 60 ºC for 6 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 10/1/0.1) of the crude product afforded the title compound (**3a**, 84.3 mg, 84 %) as a yellow oil.

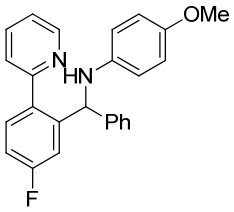
R_f 0.15 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.56 (brs, 1H), 6.01 (s, 1H), 6.58(d, J = 8.0 Hz, 2H), 6.70 (t, J = 7.2 Hz, 1H), 7.11-7.23 (m, 9H), 7.39-7.44 (m, 3H), 7.55-7.59 (m, 2H), 8.66-8.67 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 59.0, 113.5, 117.4, 122.0, 124.3, 127.0, 127.4, 127.7, 128.2, 128.4, 128.9, 129.2, 130.3, 136.4, 140.5, 141.0, 142.9, 147.4, 149.1, 159.6. HRMS (ESI) Calcd for $C_{24}H_{21}N_2$ $[M + H]^+$ 337.1705, found 337.1709.



4-Methoxy-*N*-((5-methoxy-2-(pyridin-2-yl)phenyl)(phenyl)methyl)aniline (3c): The typical procedure was applied to 2-(4-methoxyphenyl)pyridine (**1c**, 55.6 mg, 0.30 mmol) and (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 76.1 mg, 0.36 mmol) for 14 h. Silica gel

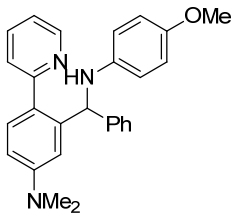
chromatography (eluent: hexane/EtOAc/Et_3N = 10/1/0.1 ~ 5/1/0.1) of the crude product afforded the title compound as a dark brown oil (90.4 mg, 76%).

R_f 0.15 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.79 (s, 3H), 4.28 (brs, 1H), 5.92 (s, 1H), 6.51-6.53 (m, 2H), 6.70-6.72 (m, 2H), 6.89 (dd, *J* = 2.8Hz, *J* =8.4 Hz,1H), 7.12-7.26 (m, 8H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.53-7.57 (m, 1H), 8.61-8.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4, 55.8, 59.7, 112.2, 114.1, 114.7, 114.8, 121.7, 124.4, 127.0, 127.7, 128.4, 131.6, 133.2, 136.3, 141.8, 142.9, 143.0, 149.1, 152.1, 159.5, 160.0. HRMS (ESI) Calcd for $C_{26}H_{25}N_2O_2$ $[M + H]^+$ 397.1916, found 397.1921.



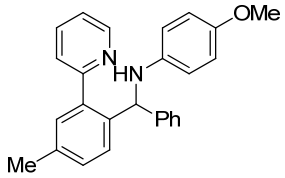
***N*-((5-fluoro-2-(pyridin-2-yl)phenyl)(phenyl)methyl)-4-methoxyaniline (3d):** The typical procedure was applied to 2-(4-fluorophenyl)pyridine (**1d**, 52.0 mg, 0.30 mmol) and (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 76.1 mg, 0.36 mmol) for 14 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 10/1/0.1) of the crude product afforded the title compound as a dark brown oil (73.3 mg, 64%).

R_f 0.15 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (s, 3H), 4.12 (brs, 1H), 5.88 (s, 1H), 6.51-6.53 (m, 2H), 6.70-6.72 (m, 2H), 7.03-7.09 (m, 4H), 7.16-7.21 (m, 4H), 7.32-7.36 (m, 2H), 7.55-7.59 (m, 1H), 8.62-8.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.9, 59.7, 114.3 (d, $^2J_{C\text{-}F}$ = 21Hz), 114.8, 114.90 (d, $^2J_{C\text{-}F}$ = 20Hz), 114.91, 122.2, 124.5, 127.3, 127.8, 128.6 (two signals overlapping), 132.1 (d, $^3J_{C\text{-}F}$ = 8 Hz), 136.5, 141.5, 142.5, 144.1 (d, $^3J_{C\text{-}F}$ = 7 Hz), 149.2, 152.3, 158.9, 163.3 (d, $^1J_{C\text{-}F}$ = 246 Hz). HRMS (ESI) Calcd for $C_{25}H_{22}FN_2O$ $[M + H]^+$ 385.1716, found 385.1719.



3-(((4-Methoxyphenyl)amino)(phenyl)methyl)-*N*,*N*-dimethyl-4-(pyridin-2-yl)aniline (3e): The typical procedure was applied to *N*,*N*-dimethyl-4-(pyridin-2-yl)aniline (**1e**, 59.5 mg, 0.30 mmol) and (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 76.1 mg, 0.36 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 6/1/0.1 ~ 5/1/0.1) of the crude product afforded the title compound as a brown solid (34.2 mg, 28%).

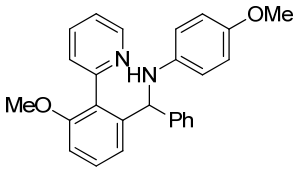
m.p. 125.0-126.1 ºC; R_f 0.12 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92 (s, 6H), 3.70 (s, 3H), 4.37 (brs, 1H), 5.92 (s, 1H), 6.49-6.52 (m, 2H), 6.69 (m, 3H), 6.82 (d, *J* = 2.4Hz, 1H), 7.09-7.18 (m, 7H), 7.26-7.31 (m, 1H), 7.52-7.54 (m, 1H), 8.57-8.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.6, 55.9, 60.1, 111.2, 112.4, 114.7, 114.8, 121.2, 124.3, 126.7, 127.7, 128.3, 128.9, 131.4, 136.2, 142.1, 142.2, 143.5, 149.0, 150.9, 152.0, 160.1. HRMS (ESI) Calcd for $C_{27}H_{28}N_3O$ $[M + H]^+$ 410.2232, found 410.2230.



4-Methoxy-*N*-((4-methyl-2-(pyridin-2-yl)phenyl)(phenyl)methyl)aniline (3f): The typical procedure was applied to 2-(*m*-tolyl)pyridine (**1f**, 49 μL, 0.30 mmol) and (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 76.1 mg, 0.36 mmol) for 16 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 10/1/0.1) of the crude product afforded the title compound as a brown oil (53.9 mg, 47%).

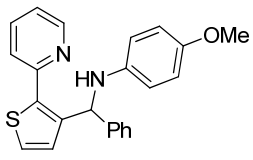
R_f 0.25 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.71 (s, 3H), 4.26 (brs, 1H), 5.77 (s, 1H), 6.47-6.49 (m, 2H), 6.68-6.71 (m, 2H), 7.13-7.22 (m, 9H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.54-7.58 (m, 1H), 8.63-8.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ 21.2, 55.9, 59.5, 114.6, 114.8, 122.0, 124.3, 126.9, 127.8, 128.2, 128.4, 129.6, 130.9, 136.3, 137.0, 138.3, 140.4, 141.8, 143.3, 149.2, 152.0, 159.7. HRMS (ESI) Calcd for $C_{26}H_{25}N_2O$ $[M + H]^+$ 381.1967, found 381.1969.



4-Methoxy-*N*-((3-methoxy-2-(pyridin-2-yl)phenyl)(phenyl)methyl)aniline (3g): The typical procedure was applied to 2-(2-methoxyphenyl)pyridine (**1g**, 52 μL, 0.30 mmol) and (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 76.1 mg, 0.36 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 10/1/0.1 ~ 3/1/0.1) of the crude product afforded the title compound as a dark brown oil (83.4 mg, 70%).

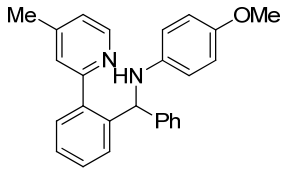
R_f 0.06 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (s, 3H), 3.72 (s, 3H), 4.10 (brs, 1H), 5.31 (s, 1H), 6.43-6.46 (m, 2H), 6.66-6.69 (m, 2H), 6.91 (d, *J* =8.0 Hz,1H), 6.96 (d, *J* = 7.6 Hz, 1H), 7.04-7.06 (m, 2H), 7.13-7.18 (m, 5H), 7.34 (t, *J* = 6.0 Hz, 1H), 7.51-7.53 (m, 1H), 8.62 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.88, 55.91, 60.2, 110.1, 114.6, 114.8, 120.0, 122.0, 126.2, 127.1, 127.8, 128.4, 129.6, 129.7, 135.8, 141.9, 142.9, 143.0, 149.4, 152.0, 156.3, 157.3. HRMS (ESI) Calcd for $C_{26}H_{25}N_2O_2$ $[M + H]^+$ 397.1916, found 397.1920.



4-Methoxy-*N*-(phenyl(2-(pyridin-2-yl)thiophen-3-yl)methyl)aniline (3h): The typical procedure was applied to 2-(thiophen-2-yl)pyridine (**1h**, 48.4 mg, 0.30 mmol) and (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 76.1 mg, 0.36 mmol) for 24 h. Silica gel

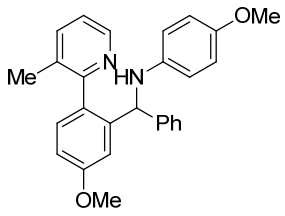
chromatography (eluent: hexane/EtOAc/Et_3N = 10/1/0.1 ~ 7/1/0.1) of the crude product afforded the title compound as a dark brown solid (56.3 mg, 48%).

m.p. 104.1-105.9 ºC; R_f 0.33 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (s, 3H), 4.25 (brs, 1H), 6.17 (s, 1H), 6.51-6.53 (m, 2H), 6.69-6.72 (m, 2H), 7.01 (d, *J* = 5.2 Hz, 1H), 7.15-7.18 (m, 1H), 7.26 (t, *J* = 6.8 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.61-7.63 (m, 1H), 8.63-8.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8, 57.0, 114.7, 114.9, 122.0, 122.5, 126.2, 127.3, 127.5, 128.7, 129.6, 136.9, 139.4, 141.5, 141.9, 142.9, 149.7, 152.2, 152.8. HRMS (ESI) Calcd for $C_{23}H_{21}N_2OS$ $[M + H]^+$ 373.1375, found 373.1376.



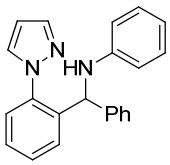
4-Methoxy-*N*-((2-(4-methylpyridin-2-yl)phenyl)(phenyl)methyl)aniline (3i): The typical procedure was applied to 4-methyl-2-phenylpyridine (**1i**, 50.8 mg, 0.30 mmol) and (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 76.1 mg, 0.36 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 6/1/0.1) of the crude product afforded the title compound as a brown solid (76.5 mg, 67%).

m.p. 126.4-127.3 ºC; R_f 0.20 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.71 (s, 3H), 4.26 (brs, 1H), 5.85 (s, 1H), 6.48-6.51 (m, 2H), 6.69-6.72 (m, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.16-7.21 (m, 5H), 7.35-7.41 (m, 4H), 7.49-7.51 (m, 1H), 8.48 (dd, *J* = 0.6 Hz, *J* = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 55.8, 59.6, 114.6, 114.8, 123.8, 126.9, 127.3, 127.7, 128.2, 128.4, 128.7, 130.2, 131.5, 136.9, 140.4, 141.2, 141.8, 143.2, 149.5, 152.0, 156.7. HRMS (ESI) Calcd for $C_{26}H_{25}N_2O$ $[M + H]^+$ 381.1967, found 381.1962.



4-Methoxy-*N*-((5-methoxy-2-(3-methylpyridin-2-yl)phenyl)(phenyl)methyl)aniline (3j): The typical procedure was applied to 2-(4-methoxyphenyl)-3-methylpyridine (**1j**, 56 μL, 0.30 mmol) and (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 76.1 mg, 0.36 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 6/1/0.1) of the crude product afforded the title compound as a yellow oil (62.6 mg, 51%).

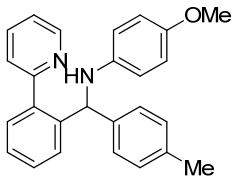
R_f 0.16 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 4.32 (brs, 1H), 5.40 (s, 1H), 6.52 (brs, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 6.85 (dd, *J* = 2.4 Hz, *J* = 8.4 Hz, 1H), 6.93 (brs, 2H), 7.08-7.13 (m, 5H), 7.19-7.23 (m, 1H), 7.34 (dd, *J* = 0.4 Hz, *J* = 8.0 Hz, 1H), 8.45-8.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 55.5, 55.9, 60.8, 111.9, 114.7, 114.8, 122.4, 124.9, 127.1, 127.7, 128.4, 129.2, 130.7, 132.4, 132.9, 138.0, 141.9, 142.3, 146.5, 152.1, 158.8, 159.7. HRMS (ESI) Calcd for $C_{27}H_{27}N_2O_2$ $[M + H]^+$ 411.2073, found 411.2076.



***N*-((2-(1H-pyrazol-1-yl)phenyl)(phenyl)methyl)aniline (3k):** The typical procedure was applied to 1-phenyl-1*H*-pyrazole (**1k**, 40 μL, 0.30 mmol) and (*E*)-*N*-benzylideneaniline (**2b**, 65.2 mg, 0.36 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 15/1/0.1 ~ 10/1/0.1) of the crude product afforded the title compound as a light yellow oil (59.3 mg, 61%).

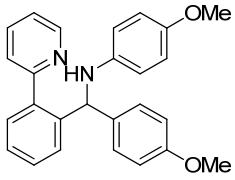
R_f 0.42 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.35 (brs, 1H), 5.85 (s, 1H), 6.30 (t, *J* = 2.0 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 2H), 6.72 (t, *J* = 7.2 Hz, 1H), 7.08-7.10 (m,

2H), 7.12-7.16 (m, 2H), 7.21-7.25 (m, 4H), 7.35 (dt, *J* = 1.6 Hz, *J* = 7.2 Hz, 1H), 7.41 (dt, *J* = 1.6 Hz, *J* = 7.2 Hz, 1H), 7.44 (dt, *J* = 1.6 Hz, *J* = 7.2 Hz, 1H), 7.69 (dd, *J* = 1.6 Hz, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.6, 106.5, 113.6, 117.8, 127.2, 127.5, 127.6, 128.2, 128.59, 128.62, 129.26, 129.31, 131.2, 138.9, 139.5, 140.7, 142.1, 147.0. HRMS (ESI) Calcd for $C_{22}H_{20}N_3$ $[M + H]^+$ 326.1657, found 326.1658.



4-Methoxy-*N*-((2-(pyridin-2-yl)phenyl)(p-tolyl)methyl)aniline (3l): The typical procedure was applied to 2-phenylpyridine (**1a**, 43 μL, 0.30 mmol) and (*E*)-4-methoxy-*N*-(4-methylbenzylidene)aniline (**2l**, 81.1 mg, 0.36 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 7/1/0.1) of the crude product afforded the title compound as a dark red solid (97.3 mg, 85%).

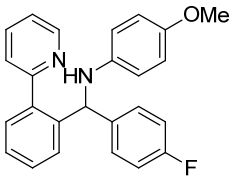
m.p. 89.3-91.6 ºC; R_f 0.25 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 3.69 (s, 3H), 4.21 (brs, 1H), 5.83 (s, 1H), 6.48-6.50 (m, 2H), 6.69-6.71 (m, 2H), 7.02 (s, 4H), 7.18-7.23 (m, 2H), 7.33-7.39 (m, 3H), 7.53-7.56 (m, 2H), 8.62-8.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 55.8, 59.3, 114.6, 114.7, 122.0, 124.3, 127.2, 127.6, 128.0, 128.8, 129.1, 130.1, 136.3, 136.5, 140.1, 140.4, 141.3, 141.8, 149.1, 151.9, 159.6. HRMS (ESI) Calcd for $C_{26}H_{25}N_2O$ $[M + H]^+$ 381.1967, found 381.1970.



4-Methoxy-*N*-((4-methoxyphenyl)(2-(pyridin-2-yl)phenyl)methyl)aniline (3m): The typical procedure was applied to 2-phenylpyridine (**1a**, 43 μL, 0.30 mmol) and (*E*)-4-

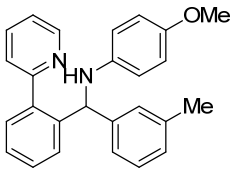
methoxy-*N*-(4-methoxybenzylidene)aniline (**2m**, 86.9 mg, 0.36 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 10/1/0.1 - 5/1/0.1) of the crude product afforded the title compound as a dark brown oil (92.8 mg, 78%).

R_f 0.13 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.75 (s, 3H), 4.22 (brs, 1H), 5.83 (s, 1H), 6.51 (d, *J* = 9.2 Hz, 2H), 6.71-6.75 (m, 4H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.15-7.20 (m, 2H), 7.35-7.40 (m, 3H), 7.56-7.60 (m, 2H), 8.65 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 55.8, 59.0, 113.7, 114.6, 114.7, 121.9, 124.3, 127.2, 127.8, 128.8 (two signals overlapping), 130.1, 135.3, 136.3, 140.4, 141.3, 141.8, 149.1, 151.9, 158.5, 159.7. HRMS (ESI) Calcd for $C_{26}H_{25}N_2O_2$ $[M + H]^+$ 397.1916, found 397.1918.



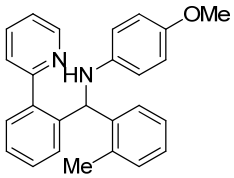
***N*-((4-Fluorophenyl)(2-(pyridin-2-yl)phenyl)methyl)-4-methoxyaniline (3n):** The typical procedure was applied to 2-phenylpyridine (**1a**, 43 μL, 0.30 mmol) and (*E*)-*N*-(4-fluorobenzylidene)-4-methoxyaniline (**2n**, 82.5 mg, 0.36 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 10/1/0.1 - 7/1/0.1) of the crude product afforded the title compound as a brown oil (30.4 mg, 26%).

R_f 0.17 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (s, 3H), 4.25 (brs, 1H), 5.83 (s, 1H), 6.47-6.49 (m, 2H), 6.69-6.71 (m, 2H), 6.86 (t, *J* = 8.8 Hz, 2H), 7.06-7.09 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.17-7.20 (m, 1H), 7.36-7.38 (m, 3H), 7.46-7.49 (m, 1H), 7.54-7.58 (m, 1H), 8.61-8.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.9, 59.0, 114.7, 114.9, 115.2 (d, $^2J_{C\text{-}F}$ = 21 Hz), 121.1, 124.3, 127.5, 128.2, 129.0, 129.3 (d, $^3J_{C\text{-}F}$ = 8 Hz), 130.3, 136.5, 138.9 (d, $^4J_{C\text{-}F}$ = 3 Hz), 140.5, 141.1, 141.6, 149.1, 152.2, 159.7, 161.8 (d, $^1J_{C\text{-}F}$ = 244 Hz). HRMS (ESI) Calcd for $C_{25}H_{22}FN_2O$ $[M + H]^+$ 385.1716, found 385.1718.



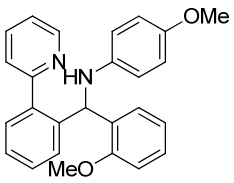
4-Methoxy-*N*-((2-(pyridin-2-yl)phenyl)(m-tolyl)methyl)aniline (3o): The typical procedure was applied to 2-phenylpyridine (**1a**, 43 μL, 0.30 mmol) and (*E*)-4-methoxy-*N*-(3-methylbenzylidene)aniline (**2o**, 81.1 mg, 0.36 mmol) for 13 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 7/1/0.1) of the crude product afforded the title compound as a dark red oil (87.8 mg, 77%).

R_f 0.20 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H), 3.71 (s, 3H), 4.21 (brs, 1H), 5.82 (s, 1H), 6.50-6.52 (m, 2H), 6.70-6.72 (m, 2H), 6.93 (s, 1H), 6.93 (d, *J* = 6.8 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.16-7.21 (m, 2H), 7.36-7.40 (m, 3H), 7.53-7.58 (m, 2H), 8.65-8.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 55.8, 59.7, 114.6, 114.8, 122.0, 124.4, 124.8, 127.3, 127.7, 128.1, 128.3, 128.4, 128.9, 130.1, 136.3, 137.9, 140.5, 141.3, 141.9, 143.0, 149.1, 152.0, 159.7. HRMS (ESI) Calcd for $C_{26}H_{25}N_2O$ $[M + H]^+$ 381.1967, found 381.1962.



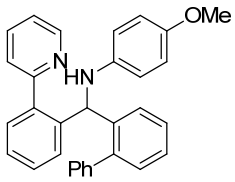
4-Methoxy-*N*-((2-(pyridin-2-yl)phenyl)(o-tolyl)methyl)aniline (3p): The typical procedure was applied to 2-phenylpyridine (**1a**, 43 μL, 0.30 mmol) and (*E*)-4-methoxy-*N*-(2-methylbenzylidene)aniline (**2p**, 81.1 mg, 0.36 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 10/1/0.1 - 5/1/0.1) of the crude product afforded the title compound as a light yellow solid (88.3 mg, 77%).

m.p. 120.0-121.3 ºC; R_f 0.19 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (s, 3H), 3.71 (s, 3H), 4.07 (brs, 1H), 5.85 (s, 1H), 6.44-6.46 (m, 2H), 6.70-6.72 (m, 2H), 7.05-7.06 (m, 1H), 7.10-7.15 (m, 2H), 7.14-7.17 (m, 2H), 7.25-7.27 (m, 1H), 7.36-7.39 (m, 2H), 7.43-7.46 (m, 2H), 7.50-7.52 (m, 1H), 8.60 (d, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 55.8, 56.7, 114.1, 114.8, 121.9, 124.0, 126.0, 127.1, 127.4, 127.6, 128.2, 128.7, 130.0, 130.5, 136.2, 136.3, 139.9, 140.8, 140.9, 141.8, 149.2, 151.9, 159.5. HRMS (ESI) Calcd for $C_{26}H_{25}N_2O$ $[M + H]^+$ 381.1967, found 381.1972.



4-Methoxy-*N*-((2-methoxyphenyl)(2-(pyridin-2-yl)phenyl)methyl)aniline (3q): The typical procedure was applied to 2-phenylpyridine (**1a**, 43 μL, 0.30 mmol) and (*E*)-4-methoxy-*N*-(2-methoxybenzylidene)aniline (**2q**, 86.9 mg, 0.36 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 10/1/0.1 - 5/1/0.1 – 3/1/0.1) of the crude product afforded the title compound as a dark brown oil (62.9 mg, 53%).

R_f 0.13 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.52 (s, 3H), 3.70 (s, 3H), 4.22 (brs, 1H), 5.99 (s, 1H), 6.43-6.45 (m, 2H), 6.66-6.69 (m, 2H), 6.72 (d, J = 8.0 Hz, 1H), 6.84 (t, J = 7.2 Hz, 1H), 7.14-7.18 (m, 2H), 7.25-7.27 (m, 2H), 7.32-7.34 (m, 2H), 7.39-7.41 (m, 2H), 7.54-7.58 (m, 1H), 8.61-8.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.1, 55.3, 55.9, 110.6, 114.5, 114.8, 120.6, 121.8, 124.1, 127.2, 128.0, 128.21, 128.24, 128.6, 130.0, 130.9, 136.0, 140.76, 140.79, 141.9, 149.2, 151.9, 156.9, 159.7. HRMS (ESI) Calcd for $C_{26}H_{25}N_2O_2$ $[M + H]^+$ 397.1916, found 397.1911.

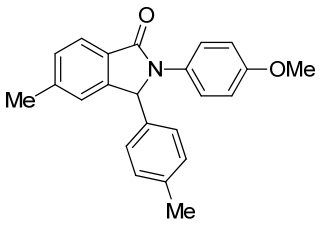


***N*-([1,1'-Biphenyl]-2-yl(2-(pyridin-2-yl)phenyl)methyl)-4-methoxyaniline (3r):** The typical procedure was applied to 2-phenylpyridine (**1a**, 43 μL, 0.30 mmol) and (*E*)-*N*-([1,1'-biphenyl]-2-ylmethylene)-4-methoxyaniline (**2r**, 103.4 mg, 0.36 mmol) for 48 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 10/1/0.1 - 7/1/0.1) of the crude product afforded the title compound as a light yellow solid (46.7 mg, 35%).

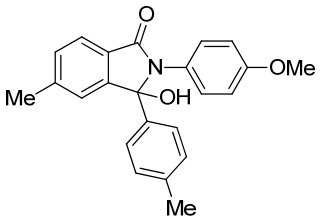
m.p. 142.1-143.1 ºC; R_f 0.16 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (s, 3H), 4.22 (brs, 1H), 5.69 (s, 1H), 6.40-6.42 (m, 2H), 6.66-6.68 (m, 2H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.2 Hz, 2H), 6.99-7.01 (m, 1H), 7.12-7.16 (m, 3H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.24-7.27 (m, 3H), 7.28-7.32 (m, 2H), 7.34-7.47 (m, 2H), 7.47-7.49 (m, 1H), 8.27-8.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8, 57.0, 114.5, 114.7, 121.6, 123.5, 126.9, 127.0, 127.3, 127.6, 128.0, 128.3, 128.4, 128.7, 129.1, 130.1, 130.4, 135.9, 139.9, 140.7, 140.8, 141.0, 141.5, 141.9, 149.0, 151.9, 159.0. HRMS (ESI) Calcd for $C_{31}H_{27}N_2O$ $[M + H]^+$ 443.2123, found 443.2127.

A Typical Procedure for Isoindolone Product: In a Schlenk tube were placed $CoBr_2$ (6.6 mg, 0.03 mmol), IPr•HCl (12.8 mg, 0.03 mmol), (*E*)-4-methoxy-*N*-(1-(*p*-tolyl)ethylidene)aniline (**2l**, 67.6 mg, 0.3 mmol), and THF (0.64 mL). To the mixture was added a THF solution of $(CH_3)_3CCH_2MgBr$ (0.63 M, 0.86 mL, 0.54 mmol) dropwise at 0 °C. After stirring for 30 min, (*E*)-4-methoxy-*N*-(1-(*p*-tolyl)ethylidene)aniline (**2l**, 67.6 mg, 0.3 mmol) was added. The resulting mixture was stirred at 60 ˚C for 6 h, and then diluted with ether (1 mL), and quenched by H_2O (1 mL), added ethyl acetate (3 mL) and stayed for 4 days. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude

product was purified by silica gel chromatography (eluent: hexane/EtOAc = 5/1 ~ 3/1 ~1/1) to afford **2-(4-methoxyphenyl)-5-methyl-3-(p-tolyl)isoindolin-1-one** (**5**, 16.3 mg, 16 %) as a pale solid and **3-hydroxy-2-(4-methoxyphenyl)-5-methyl-3-(p-tolyl)isoindolin-1-one** (6, 52.8 mg, 49%) as a pale solid.



2-(4-Methoxyphenyl)-5-methyl-3-(p-tolyl)isoindolin-1-one (5): m.p. 161.3-162.4 ºC; R_f 0.29 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.38 (s, 3H), 3.75 (s, 3H), 5.91 (s, 1H), 6.82 (d, J = 8.8 Hz, 2H), 7.01 (s, 1H), 7.04-7.09 (m, 4H), 7.28 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 22.1, 55.5, 66.0, 114.3, 123.5, 123.9, 124.8, 127.3, 129.0, 129.7, 129.9, 130.9, 135.0, 138.3, 143.2, 146.4, 157.1, 168.1. HRMS (ESI) Calcd for $C_{23}H_{22}NO_2$ $[M + H]^+$ 344.1651, found 344.1650.

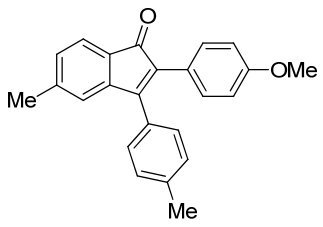


3-Hydroxy-2-(4-methoxyphenyl)-5-methyl-3-(p-tolyl)isoindolin-1-one (6): m.p. 208.8-210.1 ºC; R_f 0.16 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H), 2.34 (s, 3H), 3.68 (s, 3H), 6.82 (d, J = 9.2 Hz, 2H), 7.05-7.07 (m, 3H), 7.21 (d, J = 8.4 Hz, 2H), 7.32-7.36 (m, 3H), 7.44 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.1, 21.8, 55.6, 92.4, 114.0, 123.3, 123.5, 126.5, 128.0, 129.4 (two signals

overlapping), 129.7, 130.5, 137.4, 137.7, 143.8, 150.6, 157.6, 166.8. HRMS (ESI) Calcd for $C_{23}H_{22}NO_3$ $[M + H]^+$ 360.1600, found 360.1596.

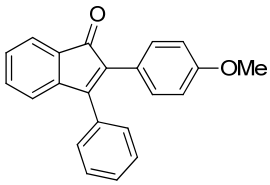
Synthesis of Indenones via Self-Coulpling of Aldimines (Scheme 5.2 and Chart 5.2)

A Typical Procedure: 2-(4-methoxyphenyl)-5-methyl-3-(*p*-tolyl)-1*H*-inden-1-one (7a). In a Schlenk tube were placed $CoBr_2$ (6.6 mg, 0.03 mmol), IPr•HCl (12.8 mg, 0.03 mmol), (*E*)-4-methoxy-*N*-(1-(*p*-tolyl)ethylidene)aniline (**2c**, 67.6 mg, 0.3 mmol), and THF (0.71 mL). To the mixture was added a THF solution of $(CH_3)_3CCH_2MgBr$ (0.68 M, 0.79 mL, 0.54 mmol) dropwise at 0 °C. After stirring for 30 min, (*E*)-4-methoxy-*N*-(1-(*p*-tolyl)ethylidene)aniline (**2c**, 67.6 mg, 0.3 mmol) was added. The resulting mixture was stirred at room temperature for 12 h, and then added 0.3 mL H_2O and 4-methoxybenzaldehyde (73 μL, 0.6 mmol) under N_2 and stirred at room temperature for 1 h, added HCl (3M, 1 mL) to the resulting mixture and stirred at 60 ºC for 12 h. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 50/1) to afford the title compound as a red solid(72.0 mg, 71% based on **2c**).



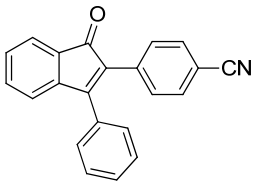
7a: m.p. 173.5-174.3 ºC; R_f 0.40 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.42 (s, 3H), 3.80 (s, 3H), 6.82 (d, J = 8.8 Hz, 2H), 6.94 (s, 1H), 7.05 (d, J = 7.2 Hz, 1H), 7.23-7.27 (m, 4H), 7.29 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 22.3, 55.3, 113.8, 122.4, 123.0, 123.6, 128.6 (two signals

overlapping), 128.7, 129.7, 130.3, 131.4, 132.1, 139.3, 144.4, 146.2, 153.8, 159.2, 196.9. HRMS (ESI) Calcd for $C_{24}H_{21}O_2$ $[M + H]^+$ 341.1542, found 341.1540.



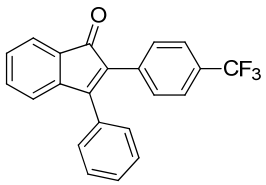
2-(4-Methoxyphenyl)-3-phenyl-1*H*-inden-1-one (7b): The typical procedure was applied to (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 126.8 mg, 0.60 mmol) and 4-methoxybenzaldehyde (73 μL, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a light red solid (64.0 mg, 68%).

m.p. 116.8-117.5 ºC; R_f 0.47 (hexane/EtOAc = 8/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 6.81 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.24-7.28 (m, 3H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.39-7.44 (m, 5H), 7.57 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4, 113.8, 121.1, 123.0, 123.3, 128.7, 128.8, 129.0, 129.3, 130.9, 131.5, 132.1, 133.2, 133.6, 145.7, 154.0, 159.4, 197.2. HRMS (ESI) Calcd for $C_{22}H_{17}O$ $[M + H]^+$ 313.1229, found 313.1226.



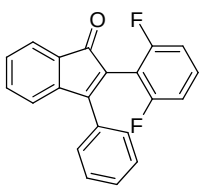
4-(1-Oxo-3-phenyl-1*H*-inden-2-yl)benzonitrile (7c): The typical procedure was applied to (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 126.8 mg, 0.60 mmol) and 4-cyanobenzaldehyde (78.7 mg, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 25/1) of the crude product afforded the title compound as a red solid (63.6 mg, 69%).

m.p. 139.1-139.9 ºC; R_f 0.27 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, J = 7.2 Hz, 1H), 7.34-7.37 (m, 4H), 7.38-7.41 (m, 2H), 7.43-7.47 (m, 3H), 7.53 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.2, 119.0, 122.1, 123.5, 128.5, 129.3, 129.9, 130.2, 130.5 (two signals overlapping), 130.7, 132.0, 132.1, 134.0, 135.9, 144.7, 158.0, 195.6. HRMS (ESI) Calcd for $C_{22}H_{14}NO$ $[M + H]^+$ 308.1075, found 308.1078.



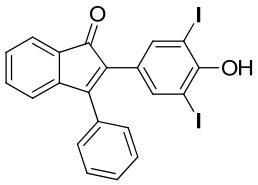
3-Phenyl-2-(4-(trifluoromethyl)phenyl)-1*H*-inden-1-one (7d): The typical procedure was applied to (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 126.8 mg, 0.60 mmol) and 4-trifluoromethylbenzaldehyde (82 μL, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 100/1) of the crude product afforded the title compound as a light red oil (66.3 mg, 63%).

R_f 0.53 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, J = 7.2 Hz, 1H), 7.31-7.35 (m, 1H), 7.36-7.42 (m, 5H), 7.43-7.46 (m, 3H), 7.52 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.9, 123.5, 124.4 (q, $^1J_{C\text{-}H}$ =248 Hz), 125.2 (q, $^3J_{C\text{-}H}$ =4.0 Hz), 128.4 (q, $^2J_{C\text{-}H}$ =30 Hz), 128.6, 129.3, 129.7, 130.0, 130.2, 130.4, 130.8, 132.4, 133.9, 134.7, 145.0, 157.3, 196.0. HRMS (ESI) Calcd for $C_{22}H_{14}F_3O$ $[M + H]^+$ 351.0997, found 351.0999.



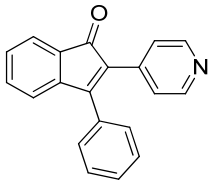
2-(2,6-Difluorophenyl)-3-phenyl-1*H*-inden-1-one (7e): The typical procedure was applied to (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 126.8 mg, 0.60 mmol) and 2,6-difluorobenzaldehyde (65 μL, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a yellow solid (76.6 mg, 80%).

m.p. 133.3-134.5 ºC; R_f 0.50 (hexane/EtOAc = 8/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (t, *J* = 7.2 Hz, 2H), 7.25-7.30 (m, 2H), 7.32-7.36 (m, 1H), 7.40-7.44 (m, 6H), 7.63 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.2 (t, $^3J_{C\text{-}F}$ = 10 Hz), 111.7 (dd, $^3J_{C\text{-}F}$ = 6 Hz, $^2J_{C\text{-}F}$ = 19 Hz), 122.0, 123.5, 127.8, 128.9, 129.6, 130.1, 130.4 (t, $^3J_{C\text{-}F}$ = 10 Hz), 131.5, 132.6, 133.5, 144.8, 144.8, 160.1, 161.0 (dd, $^3J_{C\text{-}F}$ = 7 Hz, $^1J_{C\text{-}F}$ = 249 Hz), 194.4. HRMS (ESI) Calcd for $C_{21}H_{13}F_2O$ $[M + H]^+$ 319.0934, found 319.0933.



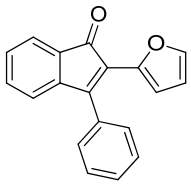
2-(4-Methoxyphenyl)-3-phenyl-1*H*-inden-1-one (7f): The typical procedure was applied to (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 126.8 mg, 0.60 mmol) and 3,5-diiodo-4-hydroxybenzaldehyde (224.3 mg, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 3/1) of the crude product afforded the title compound as a dark red solid (91.5 mg, 55%).

m.p. 177.2-178.4 ºC; R_f 0.55 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (brs, 1H), 7.13 (d, *J* = 4.8 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.36-7.39 (m, 3H), 7.46-7.47 (m, 3H), 7.57 (d, *J* = 6.8 Hz, 1H), 7.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 81.9, 121.7, 123.3, 127.2, 128.5, 128.8, 129.2, 129.5, 130.0, 130.6, 132.2, 133.9, 140.7, 145.0, 153.2, 156.0, 196.1. HRMS (ESI) Calcd for $C_{21}H_{13}I_2O_2$ $[M + H]^+$ 550.9005, found 550.9000.



3-Phenyl-2-(pyridin-4-yl)-1*H*-inden-1-one (7g): The typical procedure was applied to (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 126.8 mg, 0.60 mmol) and 4-pyridinecaboxaldehyde (56 μL, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 5/1) of the crude product afforded the title compound as an orange solid (64.9 mg, 76%).

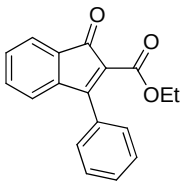
m.p. 131.3-132.5 ºC; R_f 0.20 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-7.18 (m, 3H), 7.34-7.37 (m, 3H), 7.40 (dd, *J* = 1.2 Hz, *J* = 7.6 Hz, 1H), 7.43-7.47 (m, 3H), 7.61 (dd, *J* = 0.8 Hz, *J* = 7.2 Hz, 1H), 8.49 (d, *J* = 2.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.2, 123.5, 124.4, 128.4, 129.3, 129.7, 130.0, 130.2, 130.8, 132.0, 133.9, 138.9, 144.7, 149.8, 158.7, 195.4. HRMS (ESI) Calcd for $C_{20}H_{14}NO$ $[M + H]^+$ 284.1075, found 284.1078.



2-(Furan-2-yl)-3-phenyl-1*H*-inden-1-one (7h): The typical procedure was applied to (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 126.8 mg, 0.60 mmol) and furfural (50 μL, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a dark red solid (27.3 mg, 33%).

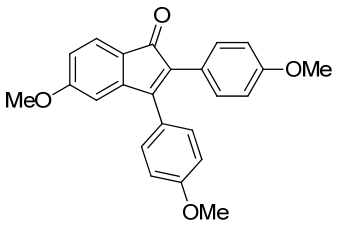
m.p. 92.3-93.7 ºC; R_f 0.55 (hexane/EtOAc = 8/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.43-6.44 (m, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 3.2 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 1.6 Hz, 1H), 7.32 (td, *J* = 0.8 Hz, *J* = 7.6 Hz, 1H), 7.47-7.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.7, 112.7, 121.7, 122.1, 123.2, 128.4, 128.8, 128.9, 129.4, 131.0,

133.2, 134.0, 143.1, 146.6, 147.3, 150.9, 195.2. HRMS (ESI) Calcd for $C_{19}H_{13}O_2$ $[M + H]^+$ 273.0916, found 273.0916.



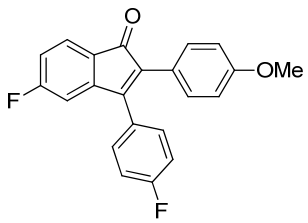
Ethyl 1-oxo-3-phenyl-1*H*-indene-2-carboxylate (7i): The typical procedure was applied to (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 126.8 mg, 0.60 mmol) and ethyl glyoxalate solution 50% in toluene (120 μL, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1 ~ 10/1) of the crude product afforded the title compound as a yellow solid (34.0 mg, 41%).

m.p. 84.0-84.8 ºC; R_f 0.20 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, J = 7.2 Hz, 3H), 4.20 (q, J = 6.8 Hz, 2H), 7.19-7.21 (m, 1H), 7.39-7.42 (m, 2H), 7.50-7.54 (m, 5H), 7.59-7.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 61.1, 123.6, 124.6, 128.3, 128.6, 130.6 (two signals overlapping) 130.7, 131.2, 131.7, 133.7, 143.3, 163.2, 165.1, 192.3. HRMS (ESI) Calcd for $C_{18}H_{15}O_3$ $[M + H]^+$ 279.1021, found 279.1019.



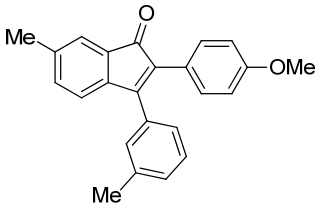
5-Methoxy-2,3-bis(4-methoxyphenyl)-1*H*-inden-1-one (7j): The typical procedure was applied to (*E*)-4-methoxy-*N*-(4-methoxybenzylidene)aniline (**2d**, 144.8 mg, 0.60 mmol) and 4-methoxybenzaldehyde (73 μL, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 15/1 – 5/1) of the crude product afforded the title compound as an orange solid (94.9 mg, 81%).

m.p. 169.4-170.1 ºC; R_f 0.21 (hexane/EtOAc = 8/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 6.63 (dd, *J* = 2.0 Hz, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 2.0Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 9.2 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 55.4, 55.8, 110.0, 110.3, 113.7, 114.3, 123.7, 123.8, 124.7, 125.2, 130.3, 131.4, 132.7, 148.2, 151.7, 159.2, 160.3, 164.4, 195.7. HRMS (ESI) Calcd for $C_{24}H_{21}O_4$ $[M + H]^+$ 373.1440, found 373.1439.



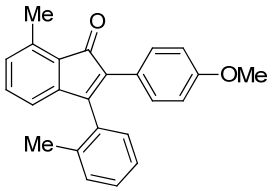
5-Fluoro-3-(4-fluorophenyl)-2-(4-methoxyphenyl)-1*H*-inden-1-one (7k): The typical procedure was applied to (*E*)-*N*-(4-fluorobenzylidene)-4-methoxyaniline (**2e**, 137.6 mg, 0.60 mmol) and 4-methoxybenzaldehyde (73 μL, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a light red solid (59.6 mg, 57%).

m.p. 180.4-181.3 ºC; R_f 0.38 (hexane/EtOAc = 8/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 6.78-6.83 (m, 3H), 6.87-6.92 (m, 1H), 7.13 (t, *J* = 7.6Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.34-7.38 (m, 2H), 7.52-7.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4, 109.8 (d, $^2J_{C\text{-}F}$ = 26 Hz), 114.0, 114.4 (d, $^2J_{C\text{-}F}$ = 23 Hz), 116.4 (d, $^2J_{C\text{-}F}$ = 21 Hz), 122.7, 125.0 (d, $^3J_{C\text{-}F}$ = 9 Hz), 126.6 (d, $^4J_{C\text{-}F}$ = 3 Hz), 128.7 (d, $^4J_{C\text{-}F}$ = 3 Hz), 130.6 (d, $^3J_{C\text{-}F}$ = 9 Hz), 131.5, 133.6, 148.9 (d, $^3J_{C\text{-}F}$ = 9 Hz), 150.6, 159.7, 162.3 (d, $^1J_{C\text{-}F}$ = 249 Hz), 166.7 (d, $^1J_{C\text{-}F}$ = 253 Hz), 195.2. HRMS (ESI) Calcd for $C_{22}H_{15}F_2O_2$ $[M + H]^+$ 349.1040, found 349.1042.



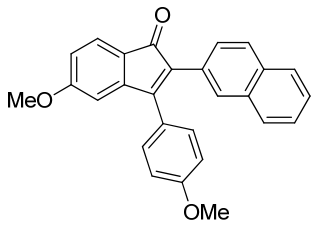
2-(4-Methoxyphenyl)-6-methyl-3-(m-tolyl)-1*H*-inden-1-one (7l): The typical procedure was applied to (*E*)-4-methoxy-*N*-(3-methylbenzylidene)aniline (**2c**, 135.2 mg, 0.60 mmol) and 4-methoxybenzaldehyde (73 μL, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a dark red solid (67.1 mg, 66%).

m.p. 104.1-105.9 ºC; R_f 0.48 (hexane/EtOAc = 8/1); ^{1}H NMR (400 MHz, $CDCl_3$, major isomer): δ 2.36 (s, 3H), 2.37 (s, 3H), 3.79 (s, 3H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 7.6 Hz, 1H), 7.10-7.16 (m, 2H), 7.17-7.26 (m, 3H), 7.28 (s, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 21.6, 55.3, 113.7 (two signals overlapping), 121.0, 123.5, 124.1, 125.8, 128.6, 129.0, 130.0, 131.2, 131.28, 131.33, 133.5, 138.6, 139.0, 143.0, 154.5, 159.2, 197.6. HRMS (ESI) Calcd for $C_{24}H_{21}O_2$ $[M + H]^+$ 341.1542, found 341.1537.



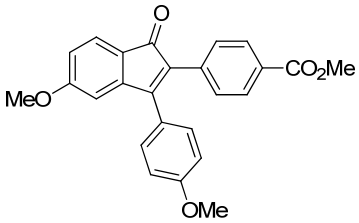
2-(4-Methoxyphenyl)-7-methyl-3-(o-tolyl)-1*H*-inden-1-one (7m): The typical procedure was applied to (*E*)-4-methoxy-*N*-(2-methylbenzylidene)aniline (**2g**, 135.2 mg, 0.60 mmol) and 4-methoxybenzaldehyde (73 μL, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 100/1) of the crude product afforded the title compound as a light red oil(21.7 mg, 21%).

R_f 0.45 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.64 (s, 3H), 3.78 (s, 3H), 6.62 (d, *J* = 7.2 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.26-7.36 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.5, 20.1, 55.3, 113.8, 119.1, 124.1, 126.4, 126.9, 128.4, 128.8, 130.6, 131.0, 132.06, 132.14, 133.1, 133.4, 136.0, 137.8, 146.8, 153.4, 159.3, 198.5. HRMS (ESI) Calcd for $C_{24}H_{21}O_2$ $[M + H]^+$ 341.1542, found 341.1537.



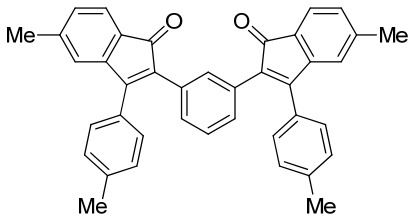
5-Methoxy-3-(4-methoxyphenyl)-2-(naphthalen-2-yl)-1*H*-inden-1-one (7n): The typical procedure was applied to (*E*)-4-methoxy-*N*-(4-methoxybenzylidene)aniline (**2d**, 144.8 mg, 0.60 mmol) and 2-naphthaldehyde (93.7 mg, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1 – 5/1) of the crude product afforded the title compound as a red solid (84.2 mg, 72%).

m.p. 59.6-60.8 ºC; R_f 0.18 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3H), 3.85 (s, 3H), 6.69 (dd, *J* = 2.0 Hz, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 2.0Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.23 (dd, *J* = 2.0 Hz, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.44-7.47 (m, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.76-7.78 (m, 1H), 7.80-7.82 (m, 1H), 7.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4, 55.9, 110.4, 110.7, 114.4, 124.0, 124.9, 125.0, 126.1, 126.4, 127.5, 127.6, 127.7, 128.6, 128.9, 129.9, 130.5, 132.8, 133.0, 133.4, 148.0, 153.4, 160.6, 164.5, 195.3. HRMS (ESI) Calcd for $C_{27}H_{21}O_3$ $[M + H]^+$ 393.1491, found 393.1496.



Methyl 4-(5-methoxy-3-(4-methoxyphenyl)-1-oxo-1*H*-inden-2-yl)benzoate (7o): The typical procedure was applied to (*E*)-4-methoxy-*N*-(4-methoxybenzylidene)aniline (**2d**, 144.8 mg, 0.60 mmol) and methyl 4-formylbenzoate (98.5 mg, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1 – 3/1) of the crude product afforded the title compound as an orange solid (88.7 mg, 74%).

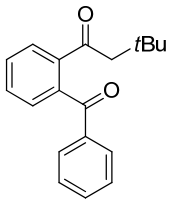
m.p. 114.3-115.6 ºC; R_f 0.30 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.825 (s, 3H), 3.833 (s, 3H), 3.88 (s, 3H), 6.68 (dd, *J* = 2.4 Hz, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 2.0Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.8 Hz 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.2, 55.5, 55.9, 110.8, 111.0, 114.5, 123.8, 124.4, 125.0, 129.0, 129.4, 130.1, 130.3, 132.1, 136.3, 147.5, 154.8, 160.8, 164.5, 167.1, 194.6. HRMS (ESI) Calcd for $C_{25}H_{21}O_5$ $[M + H]^+$ 401.1389, found 401.1386.



2,2'-(1,3-Phenylene)bis(5-methyl-3-(*p*-tolyl)-1*H*-inden-1-one) (7p): In a Schlenk tube were placed $CoBr_2$ (13.2 mg, 0.06 mmol), IPr•HCl (23.6 mg, 0.06 mmol), (*E*)-4-methoxy-*N*-(1-(*p*-tolyl)ethylidene)aniline (**2c**, 135.2 mg, 0.6 mmol), and THF (1.42 mL). To the mixture was added a THF solution of $(CH_3)_3CCH_2MgBr$ (0.68 M, 1.58 mL, 1.08 mmol) dropwise at 0 °C. After stirring for 30 min, (*E*)-4-methoxy-*N*-(1-(*p*-tolyl)ethylidene)aniline (**2c**, 135.2 mg, 0.6 mmol) was added. The resulting mixture was stirred at room temperature

for 12 h, and then added 0.6 mL H_2O and isophthalaldehyde (26.8 mg, 0.2 mmol) under N_2 and stirred at room temperature for 1 h, added HCl (3M, 2 mL) to the resulting mixture and stirred at 100 ºC for 12 h. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 3/1) to afford the title compound as a dark red solid (75.3 mg, 69%).

m.p. 193.4-194.5 ºC; R_f 0.15 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 6H), 2.40 (s, 6H), 7.00 (s, 2H), 7.06 (d, J = 7.2 Hz, 2H), 7.09-7.12 (m, 3H), 7.21-7.26 (m, 8H), 7.32 (s, 1H), 7.44 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 22.3, 122.7, 123.1, 127.9, 128.7 (two signals overlapping), 129.0, 129.4, 129.6, 129.9, 131.2, 131.8, 132.6, 139.5, 144.3, 145.9, 155.3, 196.2. HRMS (ESI) Calcd for $C_{40}H_{31}O_2$ $[M + H]^+$ 543.2324, found 543.2325.



1-(2-Benzoylphenyl)-3,3-dimethylbutan-1-one (7q): The typical procedure was applied to (*E*)-*N*-benzylidene-4-methoxyaniline (**2b**, 63.4 mg, 0.30 mmol) and pivalaldehyde (65 μL, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 20/1 ~ 5/1) of the crude product afforded the title compound as a red oil (39.0 mg, 46%).

R_f 0.20 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 9H), 2.75 (s, 2H), 7.39-7.42 (m, 3H), 7.50-7.54 (m, 1H), 7.55-7.59 (m, 2H), 7.72-7.74 (m, 2H), 7.82-7.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.8, 31.7, 51.5, 128.5, 128.7, 129.0, 129.6, 129.8, 131.7, 133.0, 137.6, 139.9, 141.0, 198.0, 201.3. HRMS (ESI) Calcd for $C_{19}H_{21}O_2$ $[M + H]^+$ 281.1542, found 281.1545.

5.5 References

(1) For selected recent reviews, see: (a) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (b) Nakao, Y. *Synthesis* **2011**, 3209. (c) Colby, A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212. (e) Rossi, R.; Bellina, F.; Lessi, M. *Synthesis* **2010**, 4131. (f) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147. (g) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

(2) Colby, D. A.; Tsai, A. S.; Bergman R. G.; Ellman, J. A. *Acc. Chem. Res*. **2012**, *45*, 814.

(3) (*a*) Fukumoto, Y.; Sawada, K.; Hagihara, M.; Chatani N.; Murai, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2779. (b) Li, B.-J. Shi, Z.-J. *Chem. Sci.* **2011**, *2*, 488. (c) Kuninobu, Y.; Nishina, Y.; Nakagawa, C.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 12376. (d) Kuninobu, Y.; Fujii,Y.; Matsuki, T.; Nishina, Y.; Takai, K. *Org. Lett.* **2009**, *11*, 2711. (e) Kuninobu, Y.; Nishina, Y.; Takeuchi, T.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 6518. (f) Basle,O.; Bidange, J.; Shuai, Q.; Li, C. J. *Adv. Synth. Catal.* **2010**, *352*, 1145. (g) Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009**, *11*, 3120. (h) Yang, L.; Correia, C. A.; Li, C.-J. *Adv. Synth. Catal.* **2011**, *353*, 1269. (i) Li, Y.; Zhang, X.-S.; Chen, K.; He, K.-H.; Pan, F.; Li, B.-J.; Shi, Z.-J. *Org. Lett.* **2012**, *14*, 636.

(4) (a) Shibata, T.; Hashimoto, Y. K.; Otsuka, M.; Tsuchikama, K.; Endo, K. *Synlett* **2011**, 2075; (b) Tsuchikama, K.; Hashimoto, Y.; Endo, K.; Shibata, T. *Adv. Synth. Catal.* **2009**, *351*, 2850.

(5) Mizuno, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 1251.

(6) Arylation of C–N multiple bonds: (a) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133,* 1248. (b) Tauchert, M. E.; Incarvito, C. D.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 1482. (c) Li, Y.; Li, B.-J.; Wang, W.-H.; Huang, W. P.; Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2115. (d) Li, Y.; Zhang, X.-S.; Li, H.; Wang, W.-H.; Chen, K.; Li, B.-J.; Shi, Z.-J. *Chem. Sci.* **2012**, *3*, 1634. (e) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650.

(7) (a) Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430. (b) Hong, P.; Yamazaki, H.; Sonogashira, K.; Hagihara, N. *Chem. Lett.* **1978**, 535. (c) Kuninobu, Y.; Kikuchi, K.; Tokunaga, Y.; Nishina, Y.; Takai, K. *Tetrahedron* **2008**, *64*, 5974. (d) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202.

(8) Zhou, C. Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302.

(9) Yoshikai, N. *Synlett* **2011**, 1047.

(10) (a) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249. (b) Ding, Z.; Yoshikai, N. *Org. Lett.* **2010**, *12*, 4180. (c) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 400. (d) Gao, K.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 6888, (e) Ding, Z.; Yoshikai, N. *Synthesis* **2011**, 2561, (f) Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 17283.

(11) For recent examples of transition metal-catalyzed preparation of isoindoles, see: (a) Ohmura, T.; Kijima, A.; Suginome, M. *Org. Lett.* **2011**, *13*, 1238. (b) Sole, D.; Serrano, O. *J. Org. Chem.* **2010**, *75,* 6267. (c) Shimizu, H.; Igarashi, T.; Murakami, M. *Bull. Korean Chem. Soc.* **2010**, *31*, 1461. (d) Sole, D.; Serrano,O. *Org. Biomol. Chem.* **2009**, *7*, 3382. (e) Ohmura, T.; Kijima, A.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 6070. (f) Heugebaert, T. S. A.; Stevens, C. V. *Org. Lett.* **2009**, *11*, 5018.

(12) For autoxidation of isoindoles, see: (a) Kricka, L. J.; Vernon, J. M. *J. Chem. Soc. C*, **1971**, 2667. (b) Ahmed, M.; Kricka, L. J.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 71. (c) Ahmed, I.; Cheeseman, G. W. H.; Jaques, B. *Tetrahedron* **1979**, *35*, 1145. (d) Stobaugh, J. F.; Repta, A. J.; Sternson, L. A. *J. Org. Chem.* **1984**, *49*, 4306. (e) Kreher, R. P.; Sewarteross, G.; Vogt, G. *Chem. Ber.* **1992**, *125,* 183.

(13) Kuninobu, Y.; Matsuki, T.; Takai, K. *Org. Lett.* **2010**, *12*, 2948.

(14) For recent examples, see: (a) Miura, T.; Murakami, M. *Org. Lett.* **2005**, *7*, 3339. (b) Harada, Y.; Nakanishi, J.; Fujihara, H.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 5766. (c) Tsukamoto, H.; Kondo, Y. *Org. Lett.* **2007**, *9*, 4227. (d) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141.

(15) (a) Klein, H. F.; Camadanli, S.; Beck, R.; Leukel, D.; Florke, U. *Angew. Chem, Int. Ed.* **2005**, *44*, 975. (b) Klein, H. F.; Helwig, M.; Koch, U.; Florke, U.; Haupt, H. J. *Z. Naturforsch. B*, **1993**, *48*, 778.

(16) (a) Mongin, F.; Mojovic, L.; Guillamet, B.; Trécourt, F.; Quéguiner, G. *J. Org. Chem.* **2002**, *67*, 8991. (b) Rebstock, A.-S.; Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron* **2003**, *59*, 4973.

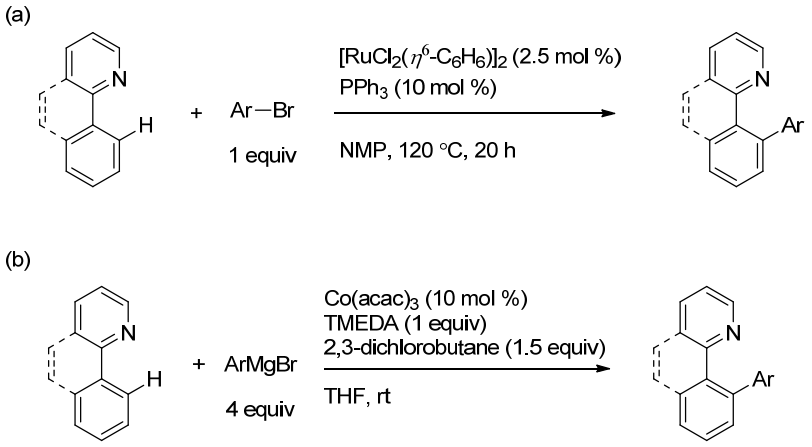
Chapter 6. Cobalt-Catalyzed *ortho*-Arylation of Aromatic Imines with Aryl Chlorides

6.1 Introduction

The synthesis of biaryl compounds have heavily relied on transition metal-catalyzed cross-coupling between halogenated arenes and metalated arenes.[1] Regardless of its high reliability, the conventional cross-coupling is not ideal in terms of atom- and step economy, because the process requires two prefunctionalized starting materials and inevitably generates metal salt as the byproduct. In recognition of such problems, synthetic chemists have extensively developed new methods for the direct arylation of arenes based on various strategies including chelation-assisted C–H bond activation.[2] One of the earliest examples of this kind is a ruthenium-catalyzed *ortho*-arylation reaction of 2-arylpyridine derivatives with aryl bormides reported by Oi and Inoue in 2001 (Scheme 6.1a).[3a] The ruthenium catalysis was later applied to aryl imines and azole derivatives by themselves and Ackermann et al.[3] Besides this, a variety of catalytic systems based on second-row transition metals, such as palladium[4] and rhodium[5] have been developed for directed C–H arylation reactions.

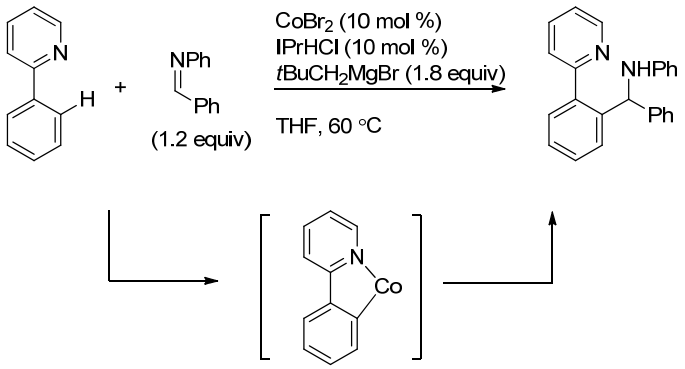
Recent studies have demonstrated the feasibility of directed C–H arylation using first-row transition metal catalysts.[6] Nakamura and coworkers develop a series of iron-catalyzed oxidative arylation of 2-arylpyridines and aryl imines with arylzinc or aryl Grginard reagents at a temperature as low as 0 °C.[7] Wang and Shi demonstrated that $Co(acac)_3$ serves as an efficient catalyst for a similar reaction of 2-arylpyridines with aryl Grignard reagents at room temperature (Scheme 6.1b).[8] Despite the relatively mild reaction conditions, the requirement of a large amount of arylmetal reagents is still the major drawback in these reactions.

Scheme 6.1. Ruthenium- and Cobalt-Catalyzed Arylation of 2-Arylpyridines



As discussed in the previous chapter, we have developed a cobalt-catalyzed *ortho* C–H bond functionalization reaction of 2-arylpyridine with an aromatic aldimine (Scheme 6.2).[9] The proposed mechanism for this reaction involves a cobaltacycle species[10] that serves as a nucleophilic aryl donor to the aldimine. In addition, aryl chlorides were used as an electrophile in cobalt-catalyzed cross-coupling reaction.[11] We hypothesized that the putative cobaltacycle species would also be intercepted by an aryl halide, thus affording an *ortho*-arylation product.[12] In this chapter, we report on a cobalt-catalyzed *ortho*-arylation reaction of aromatic imines with aryl chlorides under mild room temperature conditions.[13,14,15,16,17]

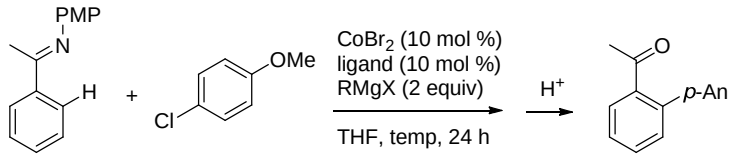
Scheme 6.2. Cobalt-Catalyzed Addition of 2-Phenylpyridine to Benzaldimine



6.2 Results and discussion

We selected acetophenone imine **1a** and 4-chloroanisole **2a** as model substrates for C–H/C–Cl biaryl coupling (Table 6.1). The Co–IPr–*t*BuCH$_2$MgBr catalytic system, which was used for the reaction of 2-arylpyridines with aldimines[9], afforded the desired biaryl product **3aa** in 3% yield (entry 1). In contrast, the use of IMes•HCl instead of IPr•HCl significantly improved the yield of **3aa** to 65% along with a byproduct arising from cross-coupling of **2a** and *t*BuCH$_2$MgBr in 17% yield (entry 2). When 4-bromoanisole was used instead of **2a**, the cross-coupling product of 4-bromoanisole with the Grignard reagent was mainly obtained. Neopentylmagnesium bromide seemed to be critical for the reaction, as other Grignard reagents such as Me$_3$SiCH$_2$MgCl, EtMgBr, *i*PrMgBr, and PhMgBr were much less effective under otherwise identical conditions (entries 3-6). The product yield decreased at higher reaction temperature of 80 °C (entry 7).

Table 6.1. Screening of Reaction Conditions[a]



1a **2a** **3aa**

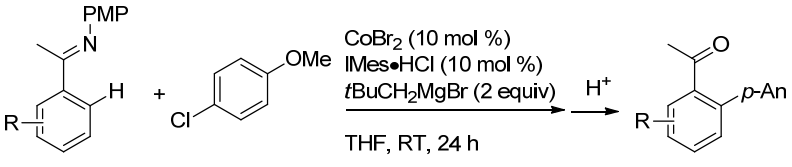
entry	ligand (mol%)	RMgX	temp (°C)	yield (%)[b]
1	IPr•HCl (10)	*t*BuCH$_2$MgBr	25	3
2	IMes•HCl (10)	*t*BuCH$_2$MgBr	25	65[c]
3	IMes•HCl (10)	Me$_3$SiCH$_2$MgCl	25	0
4	IMes•HCl (10)	EtMgBr	25	0
5	IMes•HCl (10)	*i*PrMgBr	25	1
6	IMes•HCl (10)	PhMgBr	25	6
7	IMes•HCl (10)	*t*BuCH$_2$MgBr	80	41
8[d]	PEt$_3$ (30)	*t*BuCH$_2$MgBr	80	63[c]
9[d]	PMe$_3$ (30)	*t*BuCH$_2$MgBr	80	35
10[d]	PPh$_3$ (30)	*t*BuCH$_2$MgBr	80	< 1
11[d]	PCy$_3$ (30)	*t*BuCH$_2$MgBr	80	17

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $CoBr_2$ (10 mol %), ligand, RMgX, THF, 24 h. PMP = *p*-An = 4-$MeOC_6H_4$. [b] Determined by GC using *n*-tridecane as an internal standard. [c] Isolated yield. [d] 0.36 mmol of **2a** was used.

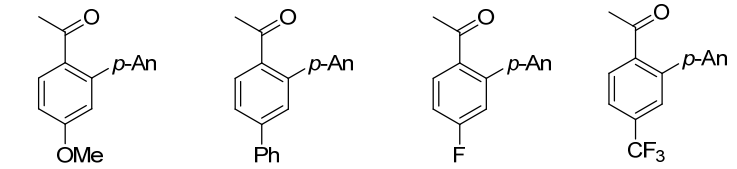
Other ligands including mono- and bidentate phosphines and phenanthroline derivatives were less effective at room temperature. A comparable reaction efficiency was observed with PEt_3 ligand (30 mol %) at 80 °C, affording the desired product in 63% yield (entry 8). Other monodentate phosphines such as PMe_3, PPh_3, and PCy_3 were much less effective (entries 9-11). Note that the Co–PEt_3 catalytic system did not produce the cross-coupling product between **2a** and neopentylmagnesium bromide.

With the two efficient catalytic systems in hand, we explored the scope of aromatic imines (Table 6.2). Imines bearing groups such as methoxy, phenyl, and fluoro group at the *para*-position afforded the desired products in good yields (**3ba-3da**). An imine with a trifluoromethyl group at the *para*-position failed to react under the Co–IMes catalytic system, but afforded the desired product **3ea** in 20% yield under the Co–PEt_3 system. An imine bearing a *meta*-methyl group was arylated exclusively at the less hindered position (**3fa**). A poor regioselectivity (56:44) was observed for 2-acetonaphthone-derived imine (**3ga**). Imines bearing 3,4-methylenedioxy and *meta*-fluoro groups reacted at the proximity position (**3ha** and **3ia**), presumably because they caused secondary directing effect or stabilized the *meta*-carbon bond of the cyclometated intermediate.[18,19,20] An imine derived from 3,5-difluoroacetophenone afforded both the monoarylation product **3ja** and the diarylation product **4ja** in 34% and 25% yield, respectively. Imines derived from propiophenone, tetralone, and indole-3-carbaldehyde also afforded the corresponding arylation products in moderate to good yields (**3ka-3ma**).

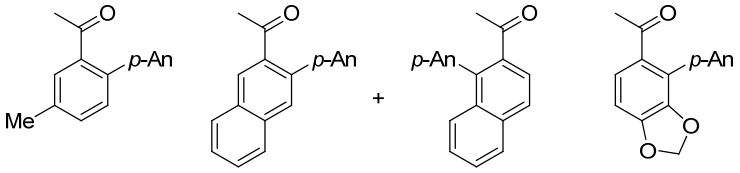
Table 6.2. Scope of Aryl Imines[a]



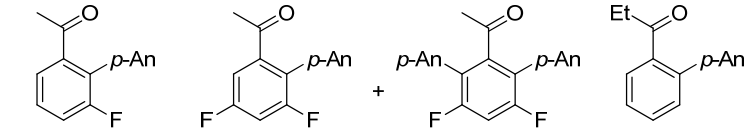
1 **2a** **3**



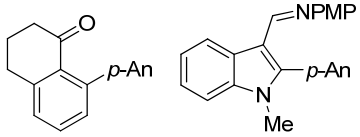
3ba, 79% **3ca**, 61% **3da**, 66% **3ea**, 20%[b]



3fa, 53%[b] **3ga** + **3ga'**, 66% (56:44)[c] **3ha**, 68%



3ia, 46% **3ja**, 34% **4ja**, 25% **3ka**, 48%



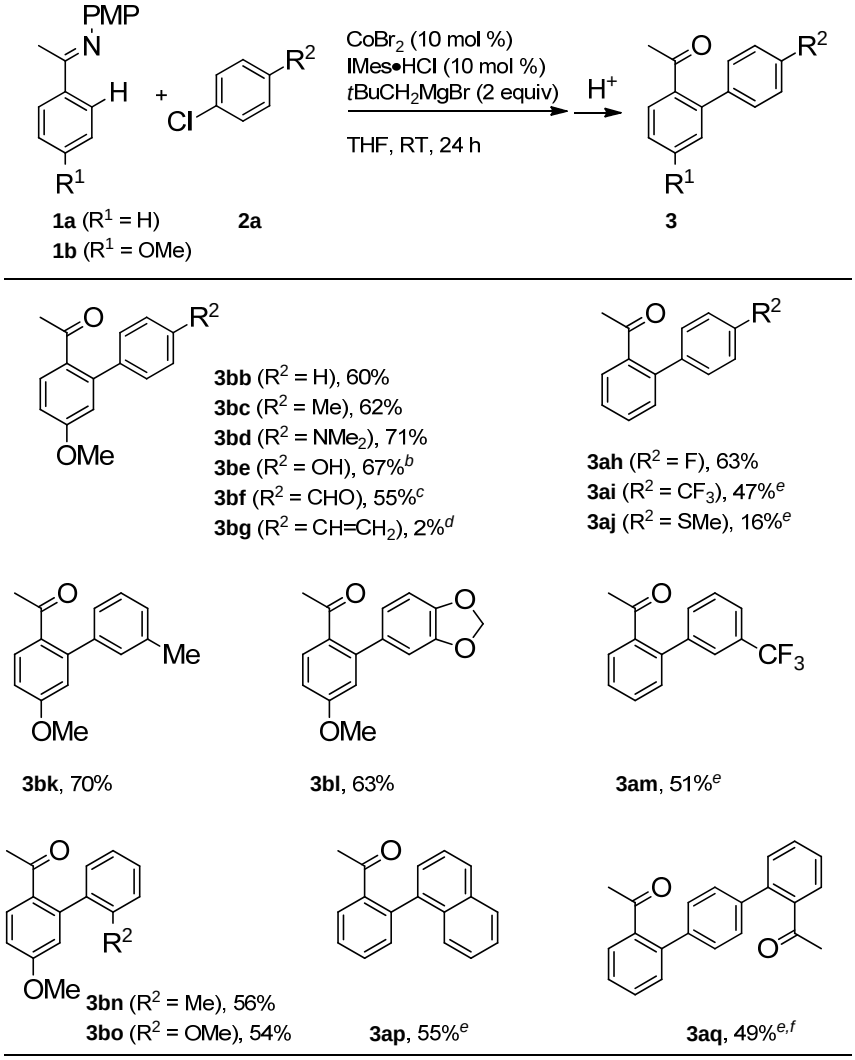
3ia, 36% **3ma**, 87%[d]

[a] The reaction was performed on a 0.3 mmol scale. [b] The reaction was performed under the Co–PEt_3 system (Table 6.1, entry 8). [c] The product ratio was determined by ^{1}H NMR. [d] The product was isolated without acidic hydrolysis.

A variety of aryl chlorides were also explored as summarized in Table 6.3. The Co–IMes catalytic system allowed the reaction to take place smoothly with aryl chlorides bearing various groups such as dimethyamino, siloxy, acetal, and fluoro groups at the *para*-

position (**3bb-3ah**). 4-Chlorobenzotrifluoride afforded the coupling product with **1a** in moderate yield under the Co–PEt_3 catalyst system (**3ai**). The reactions of *p*-chlorostyrene and *p*-chlorothioanisole were rather sluggish presumably due to coordination of the vinyl and thioether moieties to the catalyst (**3bg** and **3aj**). The reaction also tolerated the *meta*- and *ortho*-substituted aryl chlorides to afford the corresponding products in moderate to good yields (**3bk-3bo**). 1-Chloronaphthalene reacted under the Co–PEt_3 system to afford the product **3ap** in moderate yield. Two-fold C–H/C–Cl coupling was achieved on *p*-dichlorobenzene under the Co-PEt_3 system, affording the teraryl product **3aq** in 49% yield.

Table 6.3. Scope of Aryl Chlorides[a]

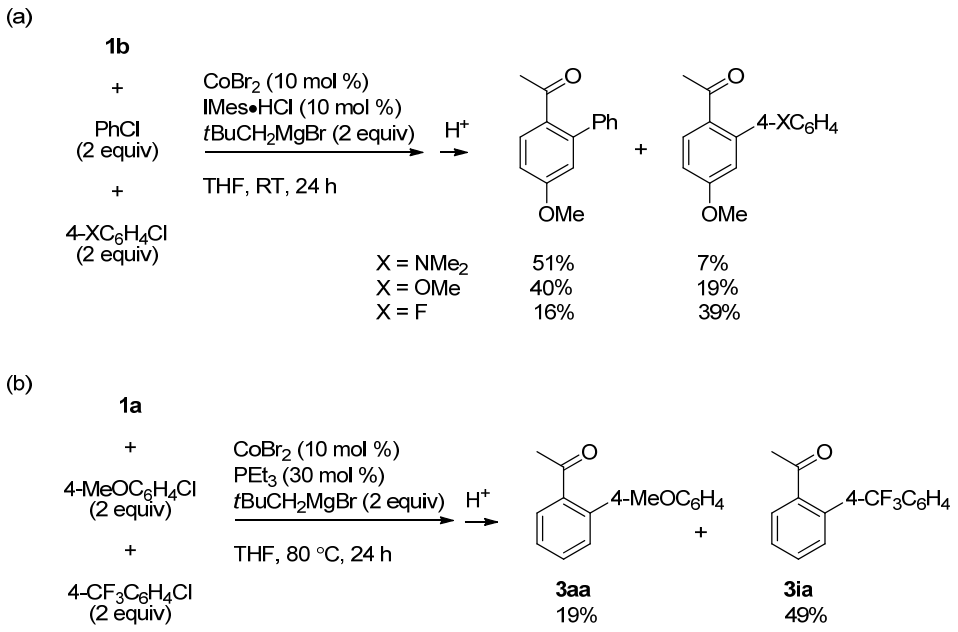


[a] The reaction was performed on a 0.3 mmol scale. [b] 4-chloro-1-*tert*-butyldimethylsilyloxybenzene was used and the siloxy group was removed by acidic hydrolysis. [c] 2-(4-chlorophenyl)-1,3-

dioxolane was used and the acetal group was removed by acidic hydrolysis. [d] GC yield. [e] The reaction was performed under the Co–PEt_3 system. [f] The reaction conditions: **1a** (0.66 mmol), **2q** (0.3 mmol), $CoBr_2$ (10 mol %), PEt_3 (30 mol %), *t*$BuCH_2MgBr$ (3 equiv), THF, 80 °C, 24 h.

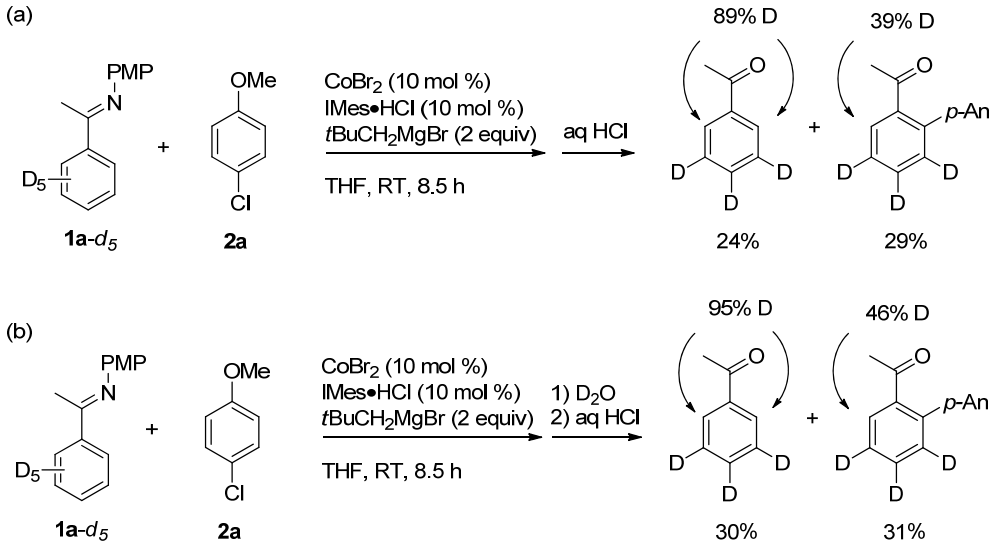
To gain insight of the nature of the C–Cl bond activation step, we performed competition experiments with several electronically different aryl chlorides under the both catalytic systems. The competition reactions of **1b** with chlorobenzene and an aryl chloride bearing a dimethylamino, methoxy, or fluoro group were performed under the Co–IMes catalytic system, where the more electron-deficient aryl chloride always reacted preferentially (Scheme 6.3a). Likewise, the competition reaction of **1a** with *p*-chloroanisole and *p*-chlorobenzotrifluoride under the Co–PEt_3 system preferentially afforded the arylation product of the latter (Scheme 6.3b). These results indicate that the electron-poor aryl chloride exhibits higher reactivity towards the putative cobaltacycle intermediate (Scheme 6.2).

Scheme 6.3. Competition Experiments



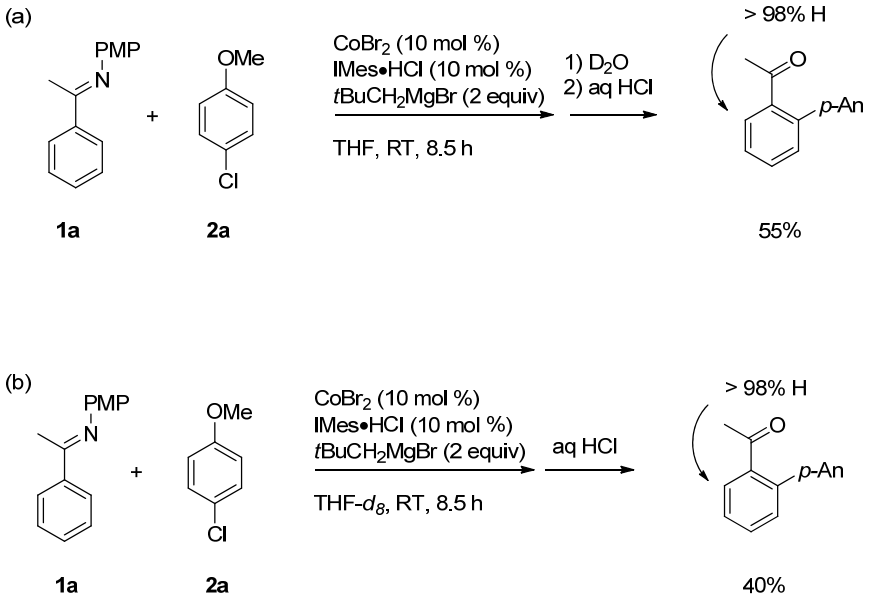
To gain more insight into the mechanism, deuterium-labeling experiments were performed using pentadeuterated imine **1a**-d_5 and 4-chloroanisole **2a** under the Co–IMes catalytic system (Scheme 6.4). The reaction was quenched with either aqueous HCl or D_2O (followed by aq HCl) to probe the distribution of deuterium atoms in both the recovered acetophenone and the arylation product. In either case, the deuterium content at the *ortho*-position of acetophenone decreased slightly (89% D and 95% D for Scheme 6.4a and Scheme 6.4b, respectively). In contrast, a significant decrease of the deuterium content was observed in the arylation product (39% D and 46% D for Scheme 6.4a and Scheme 6.4b, respectively). These results suggest that the reaction goes through reversible C–H bond cleavage.

Scheme 6.4. Deuterium-Labeling Experiments



To probe the source of the hydrogen atom incorporated into the *ortho* position of the arylation product, we examined the reaction of imine **1a** with 4-chloroanisole **2a**, which was quenched with D_2O or performed in THF-d_8 (Scheme 6.5). In neither case did we observe deuterium incorporation into the arylation product. Thus, although the results in Scheme 6.4 indicate a reversible cleavage of the *ortho* C–H bond, the detail of the mechanism remains elusive.

Scheme 6.5. Attempts on Identification of the Origin of H/D Exchange



6.3 Conclusion

In summary, we have developed Co–IMes and Co–PEt_3 catalytic systems for *ortho*-arylation of aromatic imines with aryl chlorides. The Co–IMes system allows the reaction to take place at room temperature, while the Co–PEt_3 system complements the scope of the Co–IMes system. We will make efforts on the development of broadly applicable catalytic systems and the mechanism investigation of the C–H/C–Cl coupling.

6.4 Experimental section

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

Preparation of Starting Materials

All imines were synthesized according to the literature procedures,[21] and purified by silica gel column chromatography (e.g. eluent: hexane/EtOAc/Et_3N = 100/10/2). Spectral data for the following compounds showed good agreement with the literature data: (*E*)-4-Methoxy-*N*-(1-phenylethylidene)aniline (**1a**)[22]

(*E*)-4-Methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**)[23]

(*E*)-*N*-(1-([1,1'-Biphenyl]-4-yl)ethylidene)-4-methoxyaniline (**1c**)[24]

(*E*)-*N*-(1-(4-Fluorophenyl)ethylidene)-4-methoxyaniline (**1d**)[25]

(*E*)-4-Methoxy-*N*-(1-(4-(trifluoromethyl)phenyl)ethylidene)aniline (**1e**)[25]

(*E*)-4-Methoxy-*N*-(1-*m*-tolylethylidene)aniline (**1f**)[25]

(*E*)-4-Methoxy-*N*-(1-(naphthalen-2-yl)ethylidene)aniline (**1g**)[25]

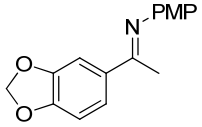
(*E*)-*N*-(1-(3-Fluorophenyl)ethylidene)-4-methoxyaniline (**1i**)[26]

(*E*)-*N*-(1-(3,5-Difluorophenyl)ethylidene)-4-methoxyaniline **(1j)**[26]

(*E*)-4-Methoxy-*N*-(1-phenylpropylidene)aniline (**1k**)[26]

(*E*)-*N*-(3,4-Dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline (**1l**)[26]

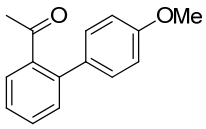
(*E*)-4-Methoxy-*N*-((1-methyl-1*H*-indol-3-yl)methylene)aniline (**1m**)[27]



(*E*)-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)ethylidene)-4-methoxyaniline (1h): Yellow solid; R_f 0.50 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 3.81 (s, 3H), 6.01 (s, 2H), 6.73 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 55.4, 101.4, 107.2, 107.6, 114.2, 120.8, 121.9, 134.3, 144.7, 147.9, 149.4, 155.8, 164.4; HRMS (ESI) Calcd for $C_{16}H_{16}NO_3$ $[M+H]^+$ 270.1130, found 270.1132.

tert-Butyl(4-chlorophenoxy)dimethylsilane (**2e**) and 2-(4-chlorophenyl)-1,3-dioxolane (**2h**) were synthesized according to the literature procedures.[28,29]

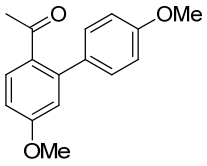
Cobalt-Catalyzed ortho-Arylation of Aryl Imines



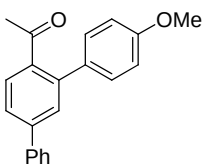
1-(4'-Methoxy-[1,1'-biphenyl]-2-yl)ethanone (3aa)

Typical Procedure A: In a Schlenk tube were placed $CoBr_2$ (6.6 mg, 0.03 mmol), IMes•HCl (10.2 mg, 0.03 mmol), (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (67.6 mg, 0.3 mmol), 4-chloroanisole (75 μL, 0.60 mmol), and THF (0.51 mL). To the mixture was added a THF solution of *t*BuCH$_2$MgBr (1.23 M, 0.49 mL, 0.60 mmol) dropwise at 0 °C. The resulting mixture was stirred at room temperature for 24 h. The reaction 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 extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 40/1–30/1) to afford the desired product **3aa** as a yellow oil (44.1 mg, 65 %). The ^{1}H and ^{13}C NMR spectra of the product showed good agreement with the literature data.[3b]

Typical Procedure B: In a Schlenk tube were placed $CoBr_2$ (6.6 mg, 0.03 mmol), PEt_3 (1.0 M, 0.09 mL, 0.09 mmol), (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (67.6 mg, 0.3 mmol), 4-chloroanisole (44 μL, 0.36 mmol), and THF (0.42 mL). To the mixture was added a THF solution of *t*BuCH$_2$MgBr (1.23 M, 0.49 mL, 0.6 mmol) dropwise at 0 °C. The resulting mixture was stirred at 80 °C for 24 h. The reaction was allowed to room temperature and then quenched by the addition of 3 N HCl (1.0 mL). The resulting mixture was stirred at room temperature for 1 h, and then extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 40/1–30/1) to afford the desired product **3aa** as a yellow oil (**3aa**, 43.1 mg, 63 %).



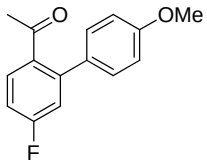
1-(4',5-Dimethoxybiphenyl-2-yl)ethanone (3ba): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**, 76.6 mg, 0.30 mmol) and 4-chloroanisole (**2a**, 75 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as an orange oil (60.5 mg, 79%). The ^{1}H and ^{13}C NMR spectra showed good agreement with the literature data.[3b]



1-(4''-Methoxy-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3ca): The typical procedure A was applied to (*E*)-*N*-(1-([1,1'-biphenyl]-4-yl)ethylidene)-4-methoxyaniline (**1c**, 90.4 mg, 0.30 mmol) and 4-chloroanisole (**2a**, 75 μL, 0.60 mmol). Silica gel chromatography (eluent:

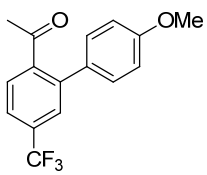
hexane/EtOAc = 10/1) of the crude product afforded the title compound as a yellow oil (55.3 mg, 61%).

R_f 0.23 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H) , 3.85 (s, 3H), 6.98 (app. d, J = 8.7 Hz, 2H), 7.32 (app. d, J = 8.7 Hz, 2H), 7.37-7.39 (m, 1H), 7.43-7.47 (m, 2H), 7.59-7.67 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.4, 55.3, 114.1, 125.6, 127.2, 128.0, 128.7, 128.85, 128.94, 130.0, 133.0, 139.4, 139.9, 140.8, 143.5, 159.6, 204.6; HRMS (ESI) Calcd for $C_{21}H_{19}O_2$ $[M + H]^+$ 303.1385, found 303.1386.



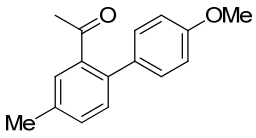
1-(5-Fluoro-4'-methoxybiphenyl-2-yl)ethanone (3da): The typical procedure A was applied to (*E*)-*N*-(1-(4-fluorophenyl)ethylidene)-4-methoxyaniline (**1d**, 73.0 mg, 0.30 mmol) and 4-chloroanisole (**2a**, 75 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a brown oil (48.5 mg, 66%).

R_f 0.25 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (s, 3H), 3.86 (s, 3H), 6.97 (app.d, J = 8.7 Hz, 2H), 7.03-7.09 (m, 2H), 7.25 (app.d, J = 8.7 Hz, 2H), 7.54-7.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.3, 55.3, 114.0 (d, $^2J_{C–F}$ = 22 Hz), 114.2, 116.9 (d, $^2J_{C–F}$ = 26 Hz), 129.9, 130.5 (d, $^3J_{C–F}$ = 9.6 Hz), 131.9, 136.9, 143.1 (d, $^3J_{C–F}$ = 9 Hz), 159.9, 163.6 (d, $^1J_{C–F}$ = 253 Hz) 203.6; HRMS (ESI) Calcd for $C_{15}H_{14}FO_2$ $[M + H]^+$ 245.0978, found 245.0979.



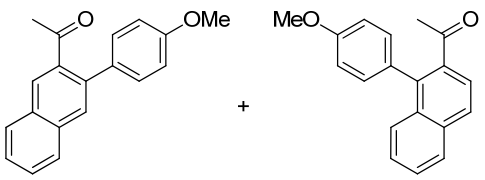
1-(4'-Methoxy-5-(trifluoromethyl)biphenyl-2-yl)ethanone (3ea): The typical procedure B was applied to (*E*)-4-methoxy-*N*-(1-(4-(trifluoromethyl)phenyl)ethylidene)aniline (**1e**, 88.0 mg, 0.30 mmol) and 4-chloroanisole (**2a**, 75 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a yellow oil (17.8 mg, 20%).

R_f 0.27 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 3H), 3.87 (s, 3H), 6.99 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.59-7.65 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.3, 55.4, 114.4, 123.6 (q, $^1J_{C–F}$ = 274 Hz), 123.8 (q, $^3J_{C–F}$ = 3.8 Hz), 126.9 (q, $^3J_{C–F}$ = 3.8 Hz), 128.2, 130.0, 131.4, 132.4 (q, $^2J_{C–F}$ = 33 Hz), 140.5, 143.8, 160.1, 204.3; HRMS (ESI) Calcd for $C_{16}H_{14}F_3O_2$ $[M + H]^+$ 295.0946, found 295.0942.



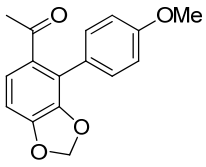
1-(4'-Methoxy-4-methylbiphenyl-2-yl)ethanone (3fa): The typical procedure B was applied to (*E*)-4-methoxy-*N*-(1-(*m*-tolyl)ethylidene)aniline (**1f**, 71.8 mg, 0.30 mmol) and 4-chloroanisole (**2a**, 75 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a brown oil (38.1 mg, 53%).

R_f 0.31 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00 (s, 3H), 2.40 (s, 3H), 3.84 (s, 3H), 6.94 (d, J = 8.2 Hz, 2H), 7.23-7.27 (m, 3H), 7.29-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 30.4, 55.3, 114.1, 128.2, 129.9, 130.1, 131.4, 132.9, 136.9, 137.3, 140.7, 159.3, 205.6; HRMS (ESI) Calcd for $C_{16}H_{17}O_2$ $[M + H]^+$ 241.1229, found 241.1228.



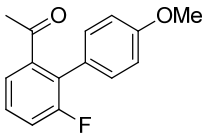
1-(3-(4-Methoxyphenyl)naphthalen-2-yl)ethanone (3ga) and 1-(1-(4-methoxyphenyl)naphthalen-2-yl)ethanone (3ga'): The typical procedure B was applied to (*E*)-4-methoxy-*N*-(1-(naphthalen-2-yl)ethylidene)aniline (**1g**, 82.6 mg, 0.30 mmol) and 4-chloroanisole (**2a**, 75 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded an inseparable mixture of the title compounds as a yellow oil (55.4 mg, 61%). The ratio of the regioisomers was determined to be 57:43 by ^{1}H NMR integrations of characteristic singlet signals at 1.95 and 2.11 ppm. Furthermore, **3ga** was assigned as the major regioisomer on the basis of a characterisic singlet signal at 8.05 ppm.

R_f 0.23 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.11 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 6.97-7.00 (m, 2H), 7.02-7.05 (m, 2H), 7.26-7.29 (m, 2H), 7.33-7.37 (m, 2H), 7.41-7.46 (m, 1H), 7.49-7.57 (m, 3H), 7.64 (d, J = 8.7 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.80 (s, 1H), 7.84-7.92 (m, 4H), 8.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.4, 30.8, 55.3 (overlapped), 114.0, 114.1, 124.3, 126.5, 126.6, 127.1, 127.1, 127.6, 127.7, 127.8, 128.0, 128.3, 128.6, 129.0, 130.0, 130.2, 131.5, 131.7, 132.2, 133.1, 134.1, 134.4, 136.9, 138.1, 138.3, 139.4, 159.3, 159.6, 204.6, 205.2; HRMS (ESI) Calcd for $C_{19}H_{17}O_2$ $[M + H]^+$ 277.1229, found 277.1230.



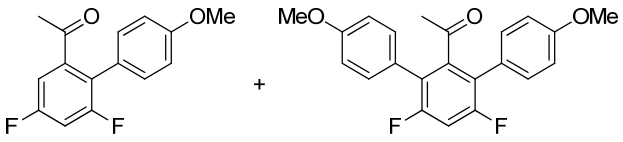
1-(4-(4-Methoxyphenyl)benzo[*d*][1,3]dioxol-5-yl)ethanone (3ha): The typical procedure B was applied to (*E*)-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)ethylidene)-4-methoxyaniline (**1h**, 80.8 mg, 0.30 mmol) and 4-chloroanisole (**2a**, 75 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a yellow solid (55.1 mg, 68%).

m.p. 118.0-121.1 °C; R_f 0.12 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01 (s, 3H), 3.84 (s, 3H), 6.01 (s, 2H), 6.81 (d, J = 7.8 Hz, 1H), 6.97 (app.d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.2 Hz, 1H) 7.30 (app.d, J = 9.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.2, 55.2, 101.5, 106.9, 114.0, 122.5, 123.7, 126.5, 130.5, 134.9, 145.5, 149.5, 159.5, 202.2; HRMS (ESI) Calcd for $C_{16}H_{15}O_4$ $[M + H]^+$ 271.0970, found 271.0967.



1-(6-Fluoro-4'-methoxybiphenyl-2-yl)ethanone (3ia): The typical procedure A was applied to (*E*)-*N*-(1-(3-fluorophenyl)ethylidene)-4-methoxyaniline (**1i**, 80.8 mg, 0.30 mmol) and 4-chloroanisole (**2a**, 75 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a light yellow oil (33.4 mg, 46%).

R_f 0.25 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 3H), 3.85 (s, 3H), 6.98 (d, J = 8.7 Hz, 2H), 7.23-7.27 (m, 3H), 7.31-7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.3, 55.2, 114.1, 118.0 (d, $^2J_{C–F}$ = 23 Hz) 123.3 (d, $^3J_{C–F}$ = 3.8 Hz), 125.5, 127.4 (d, $^2J_{C–F}$ = 16 Hz), 128.7 (d, $^3J_{C–F}$ = 8.6 Hz), 131.1, 143.4, 159.5 (d, $^1J_{C–F}$ = 249 Hz), 159.8, 203.6; HRMS (ESI) Calcd for $C_{15}H_{14}FO_2$ $[M + H]^+$ 245.0978, found 245.0973.

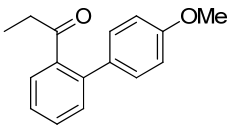


1-(4,6-Difluoro-4'-methoxybiphenyl-2-yl)ethanone (3ja) and (*E*)-*N*-(1-(4',6'-Difluoro-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)ethylidene)-4-methoxyaniline (4ja): The typical procedure A was applied to (*E*)-*N*-(1-(3,5-difluorophenyl)ethylidene)-4-methoxyaniline (**1j**, 78.4 mg, 0.30 mmol) and 4-chloroanisole (**2a**, 75 μL, 0.60 mmol).

Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the monoarylation product **3ja** (26.9 mg, 34%) and the diarylation product **4ja** (33.5 mg, 25%) as a yellow oil and a yellow solid, respectively.

3ja: R_f 0.25 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H), 3.85 (s, 3H), 6.96-7.02 (m, 3H), 7.05-7.08 (m, 1H), 7.21-7.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.2, 55.3, 106.1 (t, $^2J_{C–F}$ = 26 Hz), 110.5 (dd, $^2J_{C–F}$ = 22 Hz, $^4J_{C–F}$ = 4 Hz) 114.2, 123.8 (dd, $^2J_{C–F}$ = 17 Hz, $^4J_{C–F}$ = 4 Hz), 124.6, 131.2, 144.0 (dd, $^3J_{C–F}$ = 7.7, 6.7 Hz), 159.8 (dd, $^1J_{C–F}$ = 251 Hz, $^3J_{C–F}$ = 12 Hz), 159.9, 161.6 (dd, $^1J_{C–F}$ = 252 Hz, $^3J_{C–F}$ = 12 Hz), 202.1; HRMS (ESI) Calcd for $C_{15}H_{13}F_2O_2$ $[M + H]^+$ 263.0884, found 263.0885.

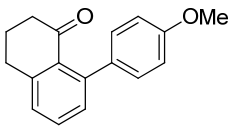
4ja: m.p. 130.0-133.0 °C; R_f 0.25 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 3H), 3.73 (s, 3H), 3.86 (s, 6H), 6.14 (app. d, J = 6.9 Hz, 2H), 6.74 (app. d, J = 6.9 Hz, 2H), 6.96-7.01 (m, 5H), 7.35 (d, J = 8.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 55.3, 55.4, 104.4 (t, $^2J_{C–F}$ = 27 Hz), 113.5, 114.1, 119.8, 123.2 (d, $^2J_{C–F}$ = 22.1 Hz), 125.4, 131.7, 143.3, 144.8 (t, $^3J_{C–F}$ = 3.9 Hz), 159.3, 158.1 (dd, $^1J_{C–F}$ = 249.1 Hz, $^3J_{C–F}$ = 12.4 Hz), 159.3, 168.4; HRMS (ESI) Calcd for $C_{29}H_{26}F_2NO_3$ $[M + H]^+$ 474.1881, found 474.1878.



1-(4'-Methoxybiphenyl-2-yl)propan-1-one (3ka): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-phenylpropylidene)aniline (**1k**, 71.8 mg, 0.30 mmol) and 4-chloroanisole (**2a**, 75 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a yellow oil (34.8 mg, 48%).

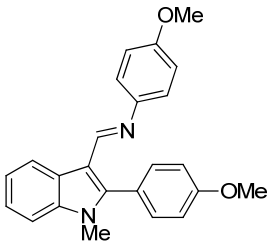
R_f 0.23 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J = 7.3 Hz, 3H), 2.27 (q, J = 7.3 Hz, 2H), 3.85 (s, 3H), 6.96 (app.d, J = 8.7 Hz, 2H), 7.26 (app.d, J = 9.2 Hz, 2H), 7.35-7.38 (m, 2H), 7.42-7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.6, 36.1, 55.3,

114.1, 127.0, 127.5, 129.9, 130.0, 130.3, 132.9, 139.5, 141.0, 159.4, 209.2; HRMS (ESI) Calcd for $C_{16}H_{17}O_2$ $[M + H]^+$ 241.1229, found 241.1228.



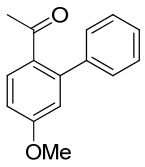
8-(4-Methoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (3la): The typical procedure A was applied to (*E*)-*N*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline (**1l**, 75.4 mg, 0.30 mmol) and 4-chloroanisole (**2a**, 75 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 20/1–10/1) of the crude product afforded the title compound as a light brown solid (27.5 mg, 36%).

m.p. 94.4-96.3 °C; R_f 0.20 (hexane/EtOAc = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13-2.16 (m, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 3.01 (t, *J* = 6.4 Hz, 2H), 3.85 (s, 3H), 6.92 (app. d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.17 (app. d, *J* = 8.8 Hz, 2H), 7.23 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 30.7, 40.5, 55.2, 113.2, 127.8, 129.3, 130.4, 131.2, 131.7, 135.0, 143.5, 145.6, 158.4, 198.7; HRMS (ESI) Calcd for $C_{17}H_{17}O_2$ $[M + H]^+$ 253.1229, found 253.1231.

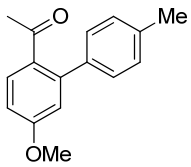


(*E*)-4-Methoxy-*N*-((2-(4-methoxyphenyl)-1-methyl-1*H*-indol-3-yl)methylene)aniline (3ma): The typical procedure A was applied to (*E*)-4-methoxy-*N*-((1-methyl-1*H*-indol-3-yl)methylene)aniline (**1m**, 72.3 mg, 0.30 mmol) and 4-chloroanisole (**2a**, 75 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 3/1) of the crude product afforded the title compound as a yellow solid (96.3 mg, 87%).

m.p. 175.0-178.0 °C; R_f 0.33 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.61 (s, 3H), 3.78 (s, 3H), 3.86 (s, 3H), 6.86 (app.d, J = 9.2 Hz, 2H), 7.02 (app.d, J = 9.2 Hz, 2H), 7.12 (app.d, J = 9.2 Hz, 2H), 7.30-7.37 (m, 5H), 8.39 (s, 1H), 8.70-8.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.9, 55.4, 55.5, 109.3, 113.0, 114.0, 114.2, 121.8, 121.9, 122.1, 122.8, 123.2, 125.5, 132.2, 137.6, 146.4, 147.1, 154.4, 157.1, 160.2; HRMS (ESI) Calcd for $C_{24}H_{23}N_2O_2$ $[M + H]^+$ 371.1760, found 371.1763.



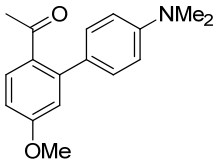
1-(5-Methoxy-[1,1'-Biphenyl]-2-yl)ethanone (3bb): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**, 76.6 mg, 0.30 mmol) and chlorobenzene (**2b**, 61 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 20/1–10/1) of the crude product afforded the title compound as a yellow oil (40.8 mg, 60%). The ^{1}H and ^{13}C NMR spectra of the product showed good agreement with the literature data.[25]



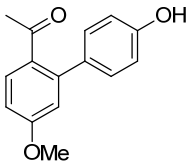
1-(5-Methoxy-4'-methyl-[1,1'-biphenyl]-2-yl)ethanone (3bc): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**, 76.6 mg, 0.30 mmol) and 4-chlorotoluene (**2c**, 71 μL, 0.6 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 20/1–10/1) of the crude product afforded the title compound as a yellow oil (44.9 mg, 62%).

R_f 0.20 (hexane/EtOAc = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (s, 3H), 2.41 (s, 3H), 3.86 (s, 3H), 6.85 (d, J = 2.4 Hz, 1H), 6.91 (dd, J = 8.4, 2.4 Hz, 1H), 7.23 (app. s, 4H), 7.62

(d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 30.2, 55.4, 112.5, 115.5, 128.6, 129.3, 130.6, 133.2, 137.8, 138.1, 143.4, 161.3, 203.0; HRMS (ESI) Calcd for $C_{16}H_{17}O_2$ $[M + H]^+$ 241.1229, found 241.1227.



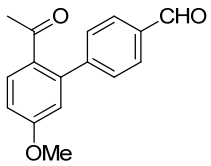
1-(4'-(Dimethylamino)-5-methoxy-[1,1'-biphenyl]-2-yl)ethanone (3bd): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**, 76.6 mg, 0.30 mmol) and 4-chloro-*N*,*N*-dimethylaniline (**2d**, 93.3 mg, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 20/1–11/1) of the crude product afforded the title compound as a light yellow oil (57.5 mg, 71%). The ^{1}H and ^{13}C NMR spectra of the product showed good agreement with the literature data.[30]



1-(4'-Hydroxy-5-methoxy-[1,1'-biphenyl]-2-yl)ethanone (3be): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**, 76.6 mg, 0.30 mmol) and *tert*-butyl(4-chlorophenoxy)dimethylsilane (**2e**, 0.15 mL, 0.60 mmol). The silyl ether moiety of the product was deprotected during the acidic hydrolysis, and silica gel chromatography (eluent: hexane/EtOAc = 11/1-4/1–1/1) of the crude product afforded the title compound as a brown oil (48.9 mg, 67%).

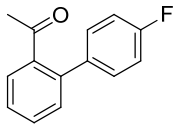
m.p. 93.0-96.0 °C; R_f 0.40 (hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H), 3.87 (s, 3H), 6.85-6.91 (m, 4H), 7.05 (br, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.2, 55.5, 112.4, 115.6, 115.7, 130.0, 130.7,

132.8, 132.9, 143.5, 156.4, 161.6, 204.9; HRMS (ESI) Calcd for $C_{15}H_{15}O_3$ $[M + H]^+$ 243.1021, found 243.1021.



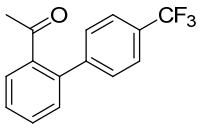
2'-Acetyl-5'-methoxy-[1,1'-biphenyl]-4-carbaldehyde (3bf): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**, 76.6 mg, 0.30 mmol) and 2-(4-chlorophenyl)-1,3-dioxolane (**2f**, 88 μL, 0.60 mmol). The acetal moiety of the product was hydrolyzed during the acidic hydrolysis, and silica gel chromatography (eluent: hexane/EtOAc = 30/1–10/1–5/1) of the crude product afforded the title compound as a yellow solid (42.1 mg, 55%).

m.p. 93.0-96.0 °C; R_f 0.18 (hexane/EtOAc = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3H), 3.88 (s, 3H), 6.82 (d, J = 2.8 Hz, 1H), 6.96 (dd, J = 8.8, 2.8 Hz, 1H), 7.47 (app. d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 1H), 7.92 (app. d, J = 8.4 Hz, 2H), 10.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.8, 55.5, 113.0, 116.2, 129.3, 129.7, 131.3, 132.0, 135.4, 142.4, 147.8, 161.6, 191.8, 200.8; HRMS (ESI) Calcd for $C_{16}H_{15}O_3$ $[M + H]^+$ 255.1021, found 255.1019.

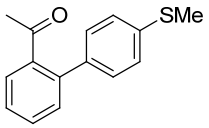


1-(4'-Fluoro-[1,1'-biphenyl]-2-yl)ethanone (3ah): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**, 76.6 mg, 0.30 mmol) and 1-chloro-4-fluorobenzene (**2h**, 64 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1–10/1) of the crude product afforded the title compound as a light yellow oil (40.8 mg, 63%).

R_f 0.31 (hexane/EtOAc = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H), 7.09-7.14 (m, 2H), 7.29-7.32 (m, 2H), 7.35 (dd, J = 7.6, 0.8 Hz, 1H), 7.42 (td, J = 7.6, 1.2 Hz, 1H), 7.50 (dd, J = 7.6, 1.6 Hz, 1H), 7.55 (td, J = 7.2, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.4, 115.5, 115.7, 127.8 (d, $^2J_{C–F}$ = 35 Hz), 130.3, 130.4 (d, $^3J_{C–F}$ = 8 Hz), 130.8, 136.8 (d, $^4J_{C–F}$ = 4 Hz), 139.3, 140.7, 162.6 (d, $^1J_{C–F}$ = 246 Hz), 204.5; HRMS (ESI) Calcd for $C_{14}H_{12}FO$ $[M + H]^+$ 215.0872, found 215.0874.



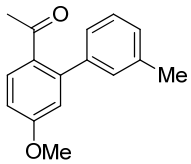
1-(4'-(Trifluoromethyl)-[1,1'-biphenyl]-2-yl)ethanone (3ai): The typical procedure B was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1a**, 67.6 mg, 0.30 mmol) and 4-chlorobenzotriflouride (**2i**, 48 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 40/1–30/1) of the crude product afforded the title compound as a brown oil (37.5 mg, 47%). The ^{1}H and ^{13}C NMR spectra of the product showed good agreement with the literature data.[30]



1-(4'-(Methylthio)-[1,1'-biphenyl]-2-yl)ethanone (3aj): The typical procedure B was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1a**, 67.6 mg, 0.3 mmol) and 4-chlorothioanisole (**2j**, 47 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as an orange oil (17.3 mg, 24%).

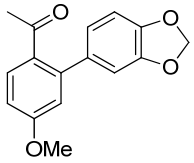
R_f 0.31 (hexane/EtOAc = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H), 2.53 (s, 3H), 7.25-7.31 (m, 4H), 7.36-7.42 (m, 2H), 7.49-7.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

15.5, 30.5, 126.4, 127.4, 127.9, 129.2, 130.2, 130.8, 137.3, 138.7, 139.9, 140.8, 204.9; HRMS (ESI) Calcd for $C_{15}H_{15}OS$ $[M + H]^+$ 243.0844, found 243.0849.



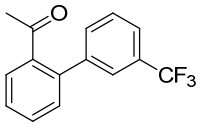
1-(5-Methoxy-3'-methyl-[1,1'-biphenyl]-2-yl)ethanone (3bk): The typical procedure A was applied to (*E*)-4-methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**, 76.6 mg, 0.30 mmol) and 3-chlorotoluene (**2k**, 71 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 20/1–11/1) of the crude product afforded the title compound as a light yellow oil (50.6 mg, 70%).

R_f 0.28 (hexane/EtOAc = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 3H), 2.40 (s, 3H), 3.87 (s, 3H), 6.85 (d, *J* = 2.4 Hz, 1H), 6.92 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.16 (s, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 30.2, 55.4, 112.6, 115.5, 125.9, 128.4, 128.6, 129.4, 130.6, 133.2, 138.2, 141.1, 143.5, 161.3, 202.9; HRMS (ESI) Calcd for $C_{16}H_{17}O_2$ $[M + H]^+$ 241.1229, found 241.1231.

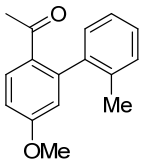


1-(2-(Benzo[*d*][1,3]dioxol-5-yl)-4-methoxyphenyl)ethanone (3bl): The typical procedure A was applied to (*E*)-3-methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**, 76.6 mg, 0.30 mmol) and 5-chlorobenzo[*d*][1,3]dioxole (**2l**, 70 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 20/1–10/1) of the crude product afforded the title compound as a yellow solid (51.2 mg, 63%).

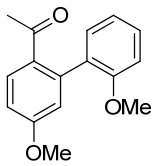
m.p. 74.4-77.0 °C; R_f 0.22 (hexane/EtOAc = 8/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H), 3.85 (s, 3H), 6.01 (s, 2H), 6.75 (dd, J = 8.0, 0.8 Hz, 1H), 6.81–6.85 (m, 3H), 6.89 (dd, J = 8.4, 2.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.2, 55.4, 101.3, 108.4, 109.1, 112.5, 115.5, 122.5, 130.6, 133.2, 134.9, 142.9, 147.5, 147.8, 161.3, 202.8; HRMS (ESI) Calcd for $C_{16}H_{15}O_4$ $[M + H]^+$ 271.0970, found 271.0970.



1-(3'-(Trifluoromethyl)-[1,1'-biphenyl]-2-yl)ethanone (3am): The typical procedure B was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1a**, 67.6 mg, 0.3 mmol) and 3-chlorobenzotrifluoride (**2m**, 49 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 40/1–30/1) of the crude product afforded the title compound as a yellow oil (40.3 mg, 51%). The ^{1}H and ^{13}C NMR spectra showed good agreement with the literature data.[31]

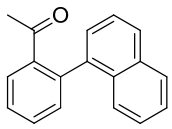


1-(5-Methoxy-2'-methyl-[1,1'-biphenyl]-2-yl)ethanone (3bn): The typical procedure A was applied to (*E*)-3-methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**, 76.6 mg, 0.30 mmol) and 2-chlorotoluene (**2n**, 70 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 20/1–11/1) of the crude product afforded the title compound as a yellow oil (40.5 mg, 56%). The ^{1}H and ^{13}C NMR spectra showed good agreement with the literature data.[3b]



1-(2',5-Dimethoxy-[1,1'-biphenyl]-2-yl)ethanone (3bo): The typical procedure A was applied to (*E*)-3-methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (**1b**, 76.6 mg, 0.30 mmol) and 2-chloroanisole (**2o**, 76 μL, 0.60 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 20/1–5/1) of the crude product afforded the title compound as a dark brown oil (41.3 mg, 54%).

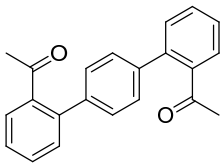
R_f 0.17 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 3H), 3.73 (s, 3H), 3.85 (s, 3H), 6.82 (d, *J* = 2.4 Hz, 1H), 6.89-6.93 (m, 2H), 7.05 (td, *J* = 7.2, 0.8 Hz, 1H), 7.26 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.37 (td, *J* = 7.8, 2.0 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.7, 55.1, 55.3, 110.5, 112.3, 116.6, 121.0, 129.3, 130.0, 130.2 (two signals overlapping), 133.1, 139.4, 155.8, 161.5, 200.8; HRMS (ESI) Calcd for $C_{16}H_{17}O_3$ $[M + H]^+$ 257.1178, found 257.1178.



1-(2-(Naphthalen-1-yl)phenyl)ethanone (3ap): The typical procedure B was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1a**, 67.6 mg, 0.3 mmol) and 1-chloronaphthalene (contain 15% of 2-chloronaphthalene) (**2p**, 49 μL, 0.36 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 40/1–30/1) of the crude product afforded a mixture of the title compound and its regioisomer arising from 2-chloronaphthalene (1-(2-(naphthalen-2-yl)phenyl)ethanone) as a brown oil (40.5 mg, 55%, 83:17 by ^{1}H NMR).

R_f 0.38 (hexane/EtOAc = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80 (s, 3H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 6.8 Hz, 2H), 7.47-7.55 (m, 3H), 7.57 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.77 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.90-7.93 (m, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 29.7, 125.3, 125.6, 126.1, 126.5, 127.3, 127.8, 128.26, 128.30, 128.32, 130.8, 131.6, 131.8, 133.5, 138.6, 139.0, 141.2, 203.2; HRMS (ESI) Calcd for $C_{18}H_{15}O$ $[M + H]^+$ 247.1123, found 247.1120.



1-(2-(Naphthalen-1-yl)phenyl)ethanone (3aq): The typical procedure B was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1a**, 148.7 mg, 0.66 mmol) and 1,4-dichlorobenzene (**2q**, 44.1 mg, 0.30 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1–3/1) of the crude product afforded mixture of the title compound as a brown solid (46.5 mg, 55%). The ^1H and ^{13}C NMR spectra showed good agreement with the literature data.[32]

6.5 References

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. (b) *Modern Arylation Methods*; Ackermann, L. Ed.; Wiley-VCH: Weinheim, 2009.

(2) For selected reviews, see: (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (b) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57. (c) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211. (d) Bouffard, J.; Itami, K. *Top. Curr. Chem.* **2010**, *292*, 231. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (g) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792.

(3) For selected examples of ruthenium-catalyzed direct arylation with aryl halides, see: (a) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.***2001**, *3*, 2579. (b) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783. (c) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123. (d) Ackermann, L.; Althammer, A.; Born, R. *Tetrahedron* **2008**, *64*, 6115.

(4) For selected examples of palladium-catalyzed direct arylation with aryl halides, see: (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem. Int. Ed.* **1997**, *36*, 1740. (b) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345. (c) Kametani, Y.; satoh, T.; Miura, M.; Nomura, M.; *Tetrahedron Lett.* **2000**, *41*, 2655. (d) Daugulis, O.; G. Zaitsev, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 4046. (e) Lazareva, A.; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211. (f) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879.

(5) For selected examples of rhodium-catalyzed direct arylation with aryl halides, see: (a) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 112. (b) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669. (c) Oi, S.; Watanabe, S.-I.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665.

(6) (a) Sun, C. L.; Li, B. J.; Shi, Z. J. *Chem. Rev.* **2011**, *111*, 1293. (b) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061. (c) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087.

(7) (a) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858. (b) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925.

(c) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Synlett* **2010**, 313. (d) Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 7672. (e) Yoshikai, N.; Asako, S.; Yamakawa, T.; Ilies, L.; Nakamura, E. *Chem. Asian J.* **2011**, *6*, 3059. (f) Ilies, L.; Kobayashi, M.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2012**, *354*, 593.

(8) Li, B.; Wu, Z.-H.; Gu, Y.-F.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2011**, *50*, 1109.

(9) Gao, K.; Yoshikai, N. *Chem. Commun.* **2012**, *48*, 4305.

(10) Klein, H. F.; Camadanli, S.; Beck, R.; Leukel, D.; Florke, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 975.

(11) (a) Korn, T. J.; Cahiez, G.; Knochel, P. *Synlett* **2003**, *12*, 1892. (b) Ohmiya, H.; Yorimitu, H.; Oshima, K. *Chem. Lett.* **2004**, *33*, 1240. (c) Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 11949.

(12) For cobalt-catalyzed *ortho* C–H functionalization with alkyl chlorides, see: Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428.

(13) For direct arylation of aryl imines with aryl nucleophiles, see ref 5 and the following: Tredwell, M. J.; Gulias, M.; Bremeyer, N. G.; Johansson, C. C. C.; Collins, B. S. L.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1076.

(14) For cobalt-catalyzed non-directed C–H arylation reactions with aryl halides, see: (a) Liu, W.; Cao, H.; Xin, J.; Jin, L.; Lei, A. *Chem. Eur. J.* **2011**, *17*, 3588. (b) Li, H.; Sun, C.-L.; Yu, M.; Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Chem. Eur. J.* **2011**, *17*, 3593.

(15) For a review on mild metal-catalyzed C–H bond functionalization, see: Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev*. **2011**, *40*, 4740.

(16) Song, W.; Ackermann, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 8251.

(17) (a) Korn, T. J.; Cahiez, G.; Knochel, P. *Synlett,* **2003**, 1892. (b) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2004**, *33*, 1240.

(18) Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 17283.

(19) (a) Ackermann, L.; Diers, E.; Manvar, A. *Org. Lett.* **2012**, *14*, 1154. (b) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032. (c) Campeau, L. C.; Parisien,

M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (d) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117.

(20) (a) Clot, E.; Megret, C.; Eisenstein, O.; Perutz, R. N. *J. Am. Chem. Soc.* **2009**, *131*, 7817. (b) Clot, E.; Eisenstein, O.; Jasim, N.; Macgregor, S. A.; Mcgrady, J. E.; Perutz, R. N. *Acc. Chem. Res.* **2011**, *44*, 333.

(21) (a) Mrsic, N.; Panella, L.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *J. Am. Chem. Soc.* **2009**, *131*, 8358. (b) Gautier, F.-M.; Jones, S.; Martin, S. J. *Org. Biomol. Chem.* **2009**, *7*, 229.

(22) Samec, J. S. M.; Ell, A. H.; Bäckvall, J.-E. *Chem. Eur. J.* **2005**, *11*, 2327.

(23) Imamoto, T.; Iwadate, N.; Yoshida, K. *Org. Lett.* **2006**, *8*, 2289.

(24) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 400.

(25) Moessner, C.; Bolm, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 7564.

(26) Gao, K.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6888

(27) Tobisu, M.; Yamaguchi, S.; Chatani, N. *Org. Lett.* **2007**, *9*, 3351.

(28) Iwao, M. *J. Org. Chem.* **1990**, *55*, 3622.

(29) Huerta, F. F.; Gómez, C.; Yus, M. *Tetrahedron* **1999**, *55*, 4043.

(30) Hiroshima, S.; Matsumura, D.; Kochi, T.; Kakiuchi, F. *Org. Lett.* **2010**, *12*, 5318.

(31) Lipshutz, B.; Butler, T.; Swift, E. *Org. Lett.* **2008**, *10*, 697.

(32) Salomone, A.; Petrera, M.; Coppi, D. I.; Perna, F. M.; Florio, S.; Capriati, V. *Synlett* **2011**, 1761.

Chapter 7. Cobalt-Catalyzed *ortho*-Alkylation of Aromatic Imines with Primary and Secondary Alkyl Halides

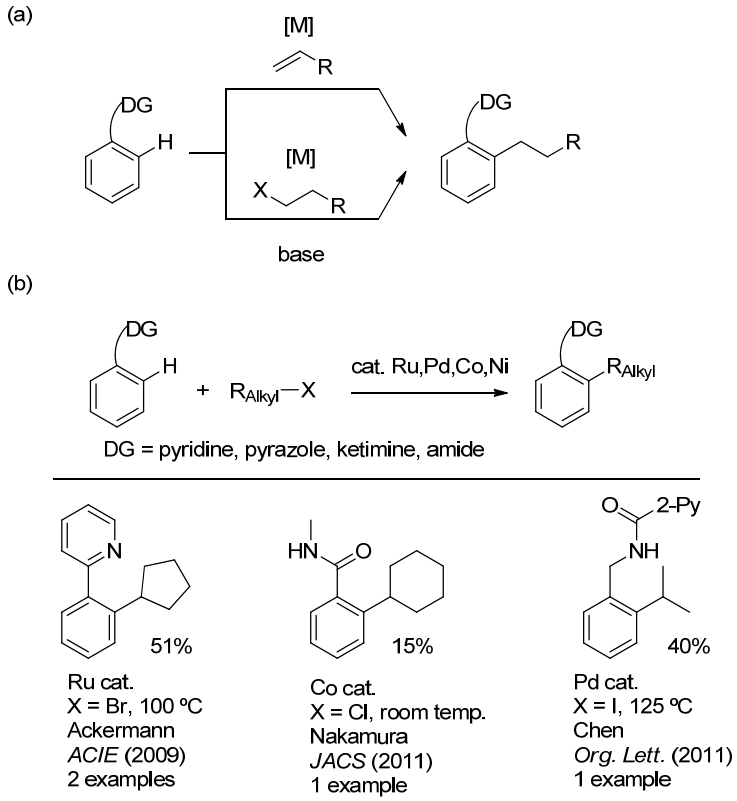
7.1 Introduction

Transition metal-catalyzed, chelation-assisted regioselective C–H bond functionalization to introduce an alkyl group onto an aromatic ring has been well developed. Among these straightforward approaches, two main types of strategies are used according to the different alkyl coupling partners. One is transition metal-catalyzed alkylation with olefins,[1,2] the other one is transition metal-catalyzed alkylation with alkyl halides (Scheme 7.1).[3,4]

Transition metal-catalyzed alkylation with olefins was initialed by Murai et al. in 1993. They reported the groundbreaking work on ruthenium-catalyzed *ortho*-alkylation of aromatic ketones,[5] which laid foundation for the development of a series of catalytic systems for such transformations. However, this strategy has not been very successful to introduce secondary alkyl groups with few exceptions.[6,7] The reasons for this include anti-Markovnikov selectivity with terminal olefins, low reactivity of internal olefins, and isomerization of internal acyclic olefins. On the other hand, transition metal-catalyzed chelation-assisted alkylation with alkyl halides has been developed recently. With this strategy, a variety of primary alkylation reactions have been achieved using transition metals such as ruthenium, palladium, cobalt, and nickel (Scheme 7.1b).[4] Ackermann and coworkers developed ruthenium-catalyzed alkylation of arylpyridines and ketimines with alkyl halides.[4a,e] Yu, Daugulis, and Chen independently developed palladium-catalyzed direct alkylation reactions.[4b,c,f] Nakamura and co-workers reported that a cobalt catalyst promotes *ortho*-alkylation of benzamides with primary alkyl chlorides at room temperature.[4d] In 2013, Chatani and coworkers reported nickel-catalyzed alkylation of benzamides and acylamides with primary alkyl bromides *via* bidentate-chelation

assistance.[4g] Despite the success of alkylation with primary alkyl halides, only a handful of secondary alkylation reactions were achieved.[4a,d,f, 8, 9, 10] For example, in Ackermann's ruthenium chemistry, only two examples of cyclopentylation products were included.[4a] One example of alkylation with chlorocyclohexane was reported in cobalt catalysis.[4d] In Chen's work, only one example of palladium-catalyzed alkylation of isopropyl iodide was included.[4f]

Scheme 7.1. *Ortho*-Alkylation of Arenes with Olefins or Alkyl Halides

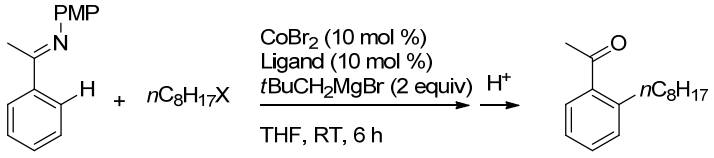


As discussed in Chapter 5 and 6, we have developed cobalt–NHC catalytic systems for *ortho* C–H bond functionalization using aldimines, and aryl chlorides as electrophiles.[2c, 6b,11] Based on these results, we conceived that alkyl halides may serve as good electrophiles for an *ortho*-alkylation reaction of aromatic ketimines. In this chapter, we report that cobalt–NHC catalytic systems promote *ortho*-alkylation of aromatic imines with unactivated primary and secondary alkyl bromides and chlorides at room temperature.

7.2 Results and discussion

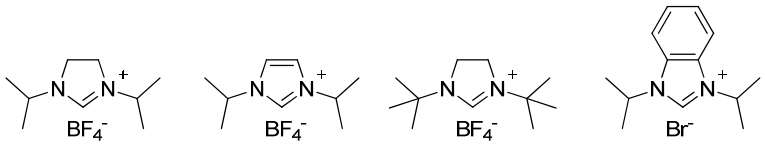
We initially focused on the reaction of acetophenone imine **1** with *n*-octyl chloride (Table 7.1). The Co–IMes–*t*BuCH$_2$MgBr catalytic system, which we used for the *ortho*-arylation reaction (Chapter 6),[11h] afforded the alkylation product **2a** in 38% yield (entry 1). Other common bulky NHC preligands such as IPr•HCl and SIMes•HCl were less effective (entries 2 and 3). After further screening of NHC preligands, we found that the yield could be improved to 64% by using a *N*,*N*'-diisopropylimidazolinium salt **L1** (entry 4). The unsaturated and *t*-butyl analogues **L2** and **L3** were less effective (entries 5 and 6). On the other hand, a benzo-fused analogue **L4** further improved the yield to 82% (entry 7). Neopentylmagnesium bromide performed better than alkyl Grignard reagents such as primary, secondary, and those without β-hydrogen Grignard reagents.

Table 7.1. Screening of Reaction Conditions[a]



1 (1.2-1.5 equiv) **2**

entry	X	Ligand	yield (%)[b]
1	Cl	IMes•HCl	38
2	Cl	IPr•HCl	13
3	Cl	SIMes•HCl	20
4	Cl	**L1**	64
5	Cl	**L2**	38
6	Cl	**L3**	14
7	Cl	**L4**	82[c]
8	Br	**L1**	79[c]
9	Br	**L4**	57
10	I	**L1**	14
11	I	**L4**	6
12[d]	OTs	**L1**	64[c]
13[d]	OTs	**L4**	49[c]



L1 **L2** **L3** **L4**

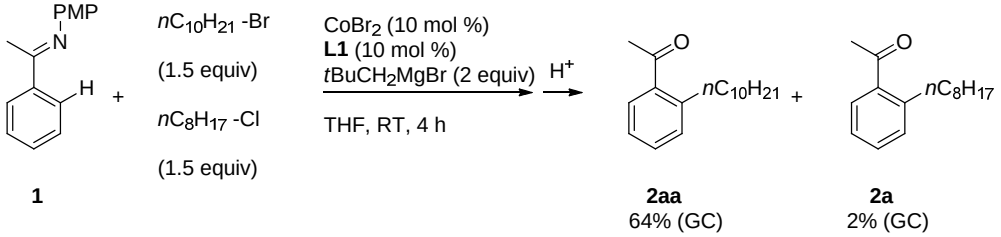
[a] Reaction conditions: **1** (0.3 mmol), $CoBr_2$ (10 mol %), ligand (10 mol %), *t*$BuCH_2MgBr$ (2 equiv), THF, 6 h. PMP = 4-$MeOC_6H_4$. [b] Determined by GC using *n*-tridecane as an internal standard. [c] Isolated yield. [d] Performed at 60 °C.

With the two promising preligands **L1** and **L4**, we examined various leaving groups. *n*-Octyl bromide smoothly participated in the reaction using either **L1** or **L4** (entries 8 and 9). In contrast, *n*-octyl iodide afforded the desired product in low yield but decomposed through dehydrohalogenation (entries 10 and 11). *n*-Octyl tosylate afforded the alkylation product in moderate yield at 60 °C (entries 12 and 13). However, a control experiment using the tosylate and *t*$BuCH_2MgBr$ in the absence of $CoBr_2$ and imine **1**

resulted in substantial displacement of the tosyloxy group with the bromide anion. This result suggests that the alkylation reaction does not take place directly from the alkyl tosylate but involves formation of the alkyl bromide.

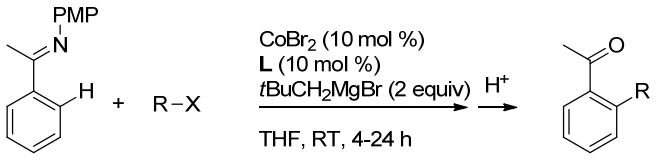
Next, we explored a variety of primary alkyl halides (Table 7.2). The reaction of *n*-hexyl bromide could be performed on a 10 mmol scale in 77% yield (entry 1). Phenethyl chloride and bromide reacted smoothly to afford the alkylation product in good yield (entries 2 and 3). Both 5-bromo-1-pentene and 6-bromo-1-hexene afforded the desired alkylation products, a part of which underwent terminal-to-internal isomerization of the olefin moieties (entries 4 and 5).[12] Chemoselective activation of an alkyl bromide moiety was achieved in the reaction of 1-bromo-4-fluorobutane and 1-bromo-4-chlorobutane (entries 6 and 7). An intermolecular competition reaction of imine **1** with *n*-bromodecane and *n*-chlorooctane mainly afforded the *n*-decylation product **2aa**, which was consistent with the high chemoselectivity observed for 1-bromo-4-chlorobutane (Scheme 7.3). On the other hand, the reaction of 1-bromo-6-tosyloxyhexane afforded a mixture of alkylation products bearing terminal C–OTs and C–Br bonds as the major and minor products, respectively (entry 8). In light of the relatively facile displacement of a tosyloxy group with a bromide anion (*vide supra*), the minor product appears to have formed from the major product. Alkyl chlorides containing aryl fluoride or chloride moiety afforded the desired alkylation products with retention of the aryl-halogen bonds (entries 9 and 10).

Scheme 7.3. Intermolecular Competition of Imine **1** with *n*-Bromodecane and *n*-Chlorooctane



1 **2aa** 64% (GC) **2a** 2% (GC)

Table 7.2. Primary Alkylation of Imine **1**[a]



1 (1.5 equiv) **2**

entry	R-X	L	yield (%)[b]
1[c]	nC_6H_{13}-Br	**L1**	**2b**, 77%
2	Ph, Cl	**L4**	**2c**, 73%
3	Ph, Br	**L1**	**2c**, 82%
4	Br	**L1**	**2d** (R = -$(CH_2)_3CH=CH_2$), 66% **2d'** (R = -$(CH_2)_2CH=CHCH_3$), 6%[d]
5	Br	**L1**	**2e** (R = -$(CH_2)_4CH=CH_2$), 85% **2e'** (R = -$(CH_2)_3CH=CHCH_3$), 12%[d]
6	F, Br	**L1**	**2f** (R = -$(CH_2)_4F$), 73%
7	Cl, Br	**L1**	**2g** (R = -$(CH_2)_4Cl$), 80%
8	TsO, Br	**L1**	**2d** (R = -$(CH_2)_6OTs$), 71% **2d'** (R = -$(CH_2)_6Br$), 18%
9	Cl	**L4**	**2i** (X = F), 77%
10	X	**L4**	**2j** (X = Cl), 61%
11	*t*Bu, Br	**L1**	**2k**, 86%
12	Me_3Si, Br	**L1**	**2l**, 65%
13	O, O, Br	**L4**	**2m** (R = -$(CH_2)_3C(=O)CH_3$), 69%
14[e]	O, N, Br	**L1**	**2n**, 41%[f]
15	Cl, N	**L4**	**2o**, 19%[g]
16	Br	**L1/L4**	complex mixture

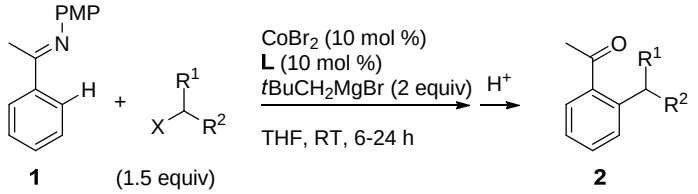
[a] Reaction conditions: **1** (0.3 mmol), $CoBr_2$ (10 mol %), **L** (10 mol %), *t*$BuCH_2MgBr$ (2 equiv), THF. [b] Isolated yield. [c] 10 mmol scale. [d] Obtained as a mixture, and the ratio was determined by ^1H NMR. [e] An additional 1 equiv of *t*$BuCH_2MgBr$ was added at the reaction time of 2 h. [f] Obtained as a mixture with the alkyl bromide and its β-elimination product. [g] Obtained as a mixture with *p*-anisidine.

Neopentyl bromide and trimethylsilylmethyl chloride, which are sterically congested at the β position, smoothly participated in the reaction (entries 11 and 12). An

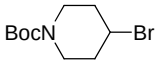
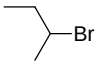
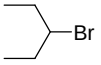
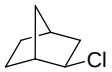
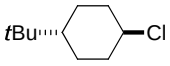
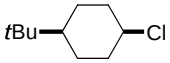
acetal-protected alkyl bromide afforded, after acidic workup, the alkylation product with a ketone moiety (entry 13). A secondary amide moiety was tolerated albeit in a moderate yield (entry 14). The presence of a pyridine moiety in the alkyl chloride made the reaction rather sluggish (entry 15). The reaction of cyclopropylmethyl bromide resulted in a complex mixture (entry 16). Neither alkylation product (i.e., cyclopropylmethylation) nor ring opening product (i.e, homoallylation) was detected in the reaction.

The Co–NHC catalytic system was also applicable to a wide variety of secondary alkyl bromides and chlorides (Table 7.3). Cycloalkyl halides of various ring size, ranging from cyclobutyl bromide/chloride to cyclododecyl chloride, afforded the corresponding alkylation products in moderate to good yields (entries 1-7). The reaction of 4-bromopiperidine bearing a Boc-protecting group afforded the desired product in moderate yield (entry 8). Acyclic secondary alkyl halides were also tolerated. The reaction of isopropyl chloride/bromide and *sec*-butyl bromide proceeded smoothly to afford the corresponding secondary alkylation products along with small amounts of primary isomers under the Co–**L1** system (entries 9-11). The regioselectivity decreased (*i*:*n* = 8:2 or 7:3) when the Co–**L4** system was used (data not shown). The reaction of 3-bromopentane with the Co–**L1** catalyst afforded the 3-pentylation product as the sole product (entry 12). The reaction of *exo*-2-chloronorbornane took place in 82% yield with an *exo/endo* ratio of 90:10 (entry 13). Both *trans*- and *cis*-isomers of 1-chloro-4-*tert*-butylcyclohexane afforded the corresponding alkylation product **2v** with the same *trans/cis* ratio of 79:21 (entries 14 and 15). *tert*-Butyl bromide and chloride failed to participate in the alkylation reaction under either of the Co–**L1** and Co–**L4** systems.

Table 7.3. Secondary Alkylation of Imine **1**[a]



1 (1.5 equiv) **2**

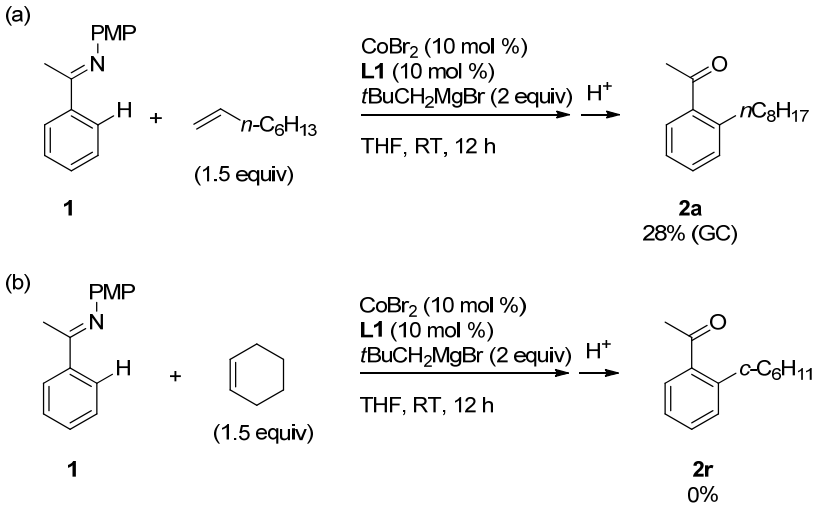
entry	R-X	L	yield (%)[b]
1	*c*-C_4H_7-Cl	**L4**	**2l**, 51%
2	*c*-C_4H_7-Br	**L1**	**2l**, 75%
3[c]	*c*-C_5H_9-Cl	**L1**	**2m**, 78%
4	*c*-C_6H_{11}-Cl	**L4**	**2n**, 73%
5	*c*-C_6H_{11}-Br	**L1**	**2n**, 90%
6	*c*-C_7H_{13}-Cl	**L4**	**2o**, 84%
7[d]	*c*-$C_{12}H_{23}$-Cl	**L1**	**2p**, 65%
8[d]		**L1**	**2q**, 42%
9	*i*-C_3H_7-Cl	**L1**	**2r** (*i:n* = 99;1), 65%[e]
10	*i*-C_3H_7-Br	**L1**	**2r** (*i:n* = 93:7), 68%[e]
11		**L1**	**2s** (*i:n* = 94:6), 56%[e]
12		**L1**	**2t**, 63%
13		**L1**	**2u** (*exo;endo* = 90:10), 82%[e]
14	 (*trans:cis* = 91:9)	**L1**	**2v** (*trans:cis* =79:21), 31%[f]
15	 (*trans:cis* = 4:96)	**L1**	**2v** (*trans:cis* =79:21), 30%[f]

[a] Reaction conditions: **1** (0.3 mmol), $CoBr_2$ (10 mol %), **L** (10 mol %), *t*$BuCH_2MgBr$ (2 equiv), THF. [b] Isolated yield. [c] An additional 1 equiv of *t*$BuCH_2MgBr$ was added at the reaction time of 5 h. [d] 2 equiv of alkyl halide was used. An additional 1 equiv of *t*$BuCH_2MgBr$ was added at the reaction time of 2 h. [e] *i:n* refers to the ratio of the secondary and primary alkylation products, which was determined by ^{1}H NMR. [f] The ratio was determined by GC.

The present catalytic system generally produced olefin byproducts *via* β-elimination of the alkyl halides (e.g., 1-octene and its isomers from *n*-octyl halide). Control

experiments were performed to examine whether olefins were involved in the reaction. The reaction of imine **1** with 1-octene afforded the octylation product in 28% yield (Scheme 7.4a), which was much lower than the yield achieved using *n*-octyl chloride. Cyclohexene was entirely unreactive under the standard conditions (Scheme 7.4b). Thus, the present reaction does not involve olefins as the major source of the alkyl group.

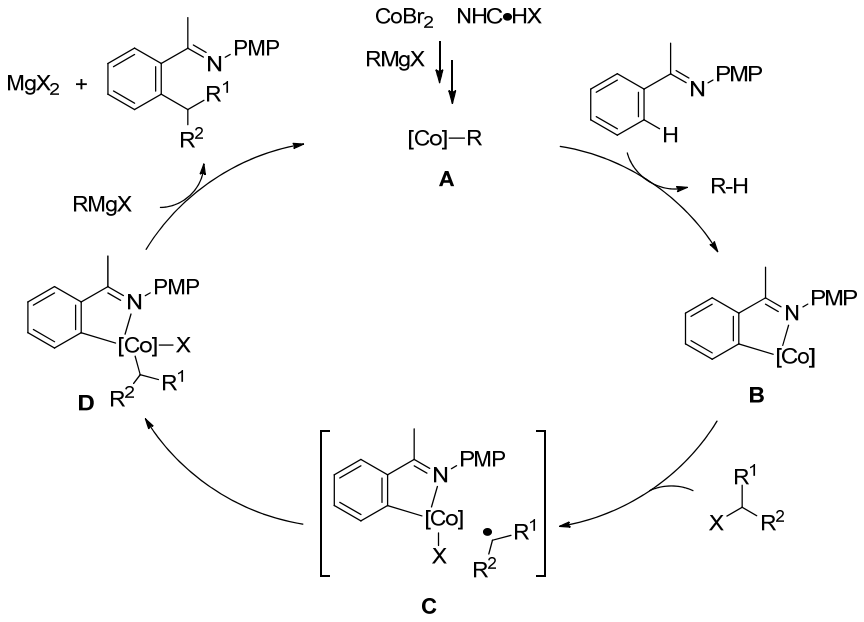
Scheme 7.4. Cobalt-Catalyzed Alkylation of Imine **1** with Alkenes



The stereochemical outcomes in entries 13-15 of Table 7.3 suggest that the present reaction takes place through a catalytic cycle involving a radical process (Scheme 7.5). First, an alkylcobalt species **A** is generated in situ from the cobalt precatalyst, the NHC preligand and the Grignard reagent. The species A undergoes cyclometalation of the imine to afford a cobaltacycle intermediate **B**. Single electron transfer from the intermediate **B** to the alkyl halide affords a pair of a one-electron-oxidized cobaltacycle and an alkyl radical (**C**), which is followed by recombination of the cobalt and the radical centers to afford an intermediate **D**. The single-electron transfer/radical recombination process has been proposed for the cobalt-catalyzed cross-coupling reaction of alkyl halides and aryl Grignard reagents.[13,14] A sequence involving aryl–alkyl reductive elimination and transmetalation with the Grignard reagent affords the alkylation product and regenerates the alkylcoblat species **A**. The

intermediate **D** may also go through a β-hydride elimination/re-insertion process to the C–C bond formation. This would have caused the formation of the primary alkylation product from acyclic secondary halides (Table 7.3, entries 9-11).

Scheme 7.5. Possible Catalytic Cycle

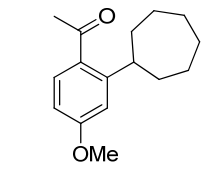


The reaction of 6-bromo-1-hexene did not afford a ring-closing product presumably because of faster recombination of 5-hexenyl radical and the cobalt center than the 5-*exo*-*trig* cyclization.[15] The failure of cyclopropylmethylation may be explained by the rapid ring opening of a cyclopropylmethyl radical,[16] although the reason for the absence of ring opening product is still unclear at present.

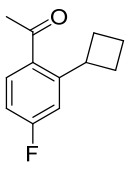
The scope of various aromatic imines was explored as summarized in Chart 7.1. The imines bearing methoxy, fluoro, chloro, and phenyl groups at the *para* position afforded the corresponding products **3**-**6** in moderate to good yields. The reaction of 3-methyl, 2-naphthyl, and 3-fluorenyl imines reacted exclusively at the less hindered position (**7**-**9**). On the other hand, the imine with a methylenedioxy group at the 3,4-position was alkylated at the proximal position in 45% yield with moderate selectivity (**10**:**10'** = 84:16). Imines derived from tetralone and propiophenone smoothly participated in the reaction to

afford the desire products **11** and **12** in 81% and 80% yields, respectively. Heteroarenes such as thiophene and indole rings were tolerated to afford the corresponding products in modest yields (**13** and **14**).

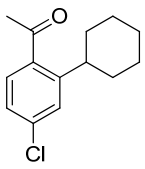
Chart 7.1. Products of Cycloalkylation of Different Imines[a]



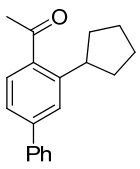
3 (X = Cl, **L4**), 81%[b] **[10 mmol scale]**



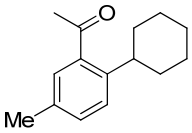
4 (X = Br, **L1**), 53%



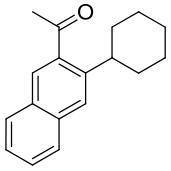
5 (X = Br, **L1**), 65%[c]



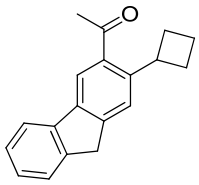
6 (X = Cl, **L1**), 85%[c]



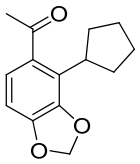
7 (X = Br, **L1**), 81%[c,d]



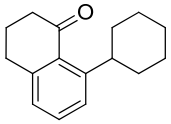
8 (X = Cl, **L4**), 54%



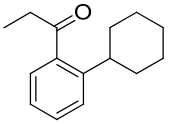
9 (X = Br, **L1**), 78%



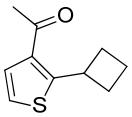
10 (X = Cl, **L4**), 45%[e]



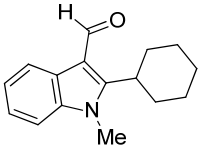
11 (X = Cl, **L4**), 81%



12 (X = Br, **L1**), 80%[c,d]



13 (X = Br, **L1**), 24%



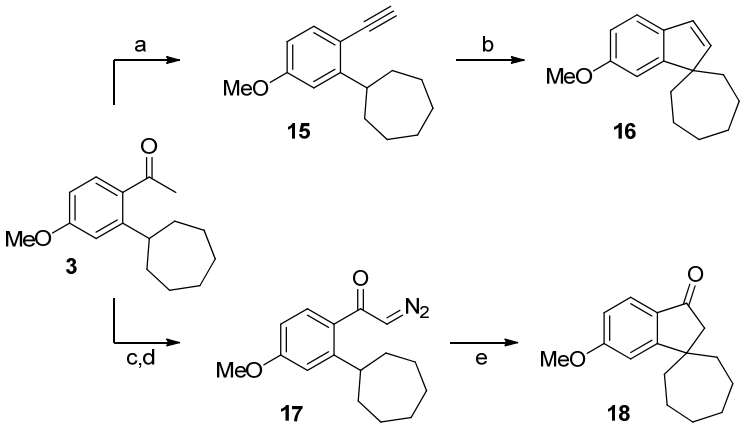
14 (X = Br, **L1**), 45%

[a] The product was obtained after acidic hydrolysis of the reaction of PMP imine (0.3 mmol) under the standard conditions for 24 h. The leaving group and the ligand used are indicated for each case. [b] The reaction time was 6 h. [c] An additional 1 equiv of *t*BuCH$_2$MgBr was added at the reaction time of 2, 4, 5 h. [d] 2 equiv of alkyl halide was used. [e] Obtained as a mixture with a regioisomer **10'** in a ratio of 84:16.

Further transformation of the acetyl group and the newly introduced cycloalkyl group allowed us to construct unique benzo-fused spirocycles (Scheme 7.6). The acetyl group of **3** was converted to an ethynyl group through the formation of enol phosphate and base-mediated elimination. The resulting 1-cycloheptyl-2-ethynylarene **15** underwent platinium-catalyzed carbocyclization[17] to afford indene **16** in 77% yield. In another

example, the acetyl group was converted to a diazo **17**. A subsequent rhodium-catalyzed intramolecular C–H insertion afforded indenone **18** in 27% overall yield.

Scheme 7.6. Transformation of *ortho*-Cycloalkylation Product to Spirocycles[a]



[a] Reaction conditions: a) LDA (1.05 equiv), $ClP(O)(OEt)_2$ (1.1 equiv), THF, –78 °C to rt, then LDA (2.25 equiv), –78 °C to rt, 56%; b) $PtCl_2$ (10 mol %), CuBr (2 equiv), toluene, 100 °C, 77%; c) LiHMDS (1.1 equiv), THF, –78 °C, then $CF_3CO_2CH_2CF_3$ (1.2 equiv), –78 °C to rt; d) 4-acetamidobenzenesulfonyl azide (1.5 equiv), H_2O, Et_3N, MeCN, rt, 75% (two steps); e) $Rh_2(OAc)_4$ (2 mol %), CH_2Cl_2, rt, 36%.

7.3 Conclusion

In summary, we have developed a cobalt–NHC-catalyzed *ortho*-alkylation reaction of aromatic imines with primary and secondary alkyl halides at room temperature. With the wide applicability to alkyl halides, secondary halides in particular, the present work has significantly expanded the scope of *ortho*-alkylation of aromatic compounds. The reaction mechanism appears to involve a combination of cyclometalation and radical processes, which deserves further mechanistic and synthetic studies.

7.4 Experimental section

Materials. Unless otherwise noted, commercial reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. Anhydrous cobalt(II) bromide (> 98%) was purchased from Alfa Aesar and was used as received. Imidazolium and imidazolinium salts except diisopropylbenzimidazolium bromide (**L4**) were purchased from Aldrich or Strem Chemicals and were used as received. THF was distilled over Na/benzophenone. Grignard reagents except MeMgCl (purchased from Aldrich) were prepared from the corresponding halides and magnesium turnings in anhydrous THF and titrated before use.

Preparation of Starting Materials

All imines were synthesized according to the literature procedures,[18] and purified by silica gel column chromatography (e.g. eluent: hexane/EtOAc/Et_3N = 100/10/2). Spectral data for the following compounds showed good agreement with the literature data:

(*E*)-4-Methoxy-*N*-(1-phenylethylidene)aniline[19]

(*E*)-4-Methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline[20]

(*E*)-*N*-(1-(4-Fluorophenyl)ethylidene)-4-methoxyaniline[21]

(*E*)-*N*-(1-([1,1'-Biphenyl]-4-yl)ethylidene)-4-methoxyaniline[6b]

(*E*)-4-Methoxy-*N*-(1-*m*-tolylethylidene)aniline[21]

(*E*)-4-Methoxy-*N*-(1-(naphthalen-2-yl)ethylidene)aniline[21]

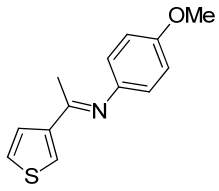
(*E*)-*N*-(1-(9*H*-Fluoren-3-yl)ethylidene)-4-methoxyanilineaniline[2c]

(*E*)-*N*-(1-(Benzo[*d*][1,3]dioxol-5-yl)ethylidene)-4-methoxyaniline[11f]

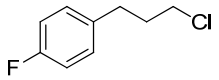
(*E*)-*N*-(3,4-Dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline[6b]

(*E*)-4-Methoxy-*N*-(1-phenylpropylidene)aniline[6b]

(*E*)-4-Methoxy-*N*-((1-methyl-1*H*-indol-3-yl)methylene)aniline[22]

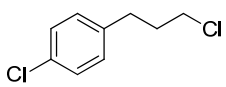


(*E*)-4-Methoxy-*N*-(1-(thiophen-3-yl)ethylidene)aniline: Yellow solid; R_f 0.50 (hexane/EtOAc = 5/1); m.p. 93.6-94.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22 (s, 3H), 3.81 (s, 3H), 6.76 (app. d, *J* = 6.8 Hz, 2H), 7.90 (app. d, *J* = 6.8 Hz, 2H), 7.33 (dd, *J* = 5.2 Hz, 3.2 Hz, 1H), 7.70 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 7.75 (dd, *J* = 2.8 Hz, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 55.4, 114.1, 120.8, 125.7, 126.5, 126.6, 143.8, 144.3, 155.9, 161.2; HRMS (ESI) Calcd for $C_{13}H_{14}NOS$ $[M + H]^+$ 232.0796, found 232.0799.



1-(3-Chloropropyl)-4-fluorobenzene: Chlorination of of 3-(4-fluorophenyl)propan-1-ol (561.0 mg, 3.6 mmol) with triphosgene (534.1 mg, 1.8 mmol) and triethylamine (1.3 mL, 9.1 mmol) in CH_2Cl_2 (20 mL) according to the literature procedure.[23] Silica gel chromatography (eluent: hexane/Et_2O = 50/1) of the crude product afforded the title compound as a colorless oil (528.2 mg, 85%).

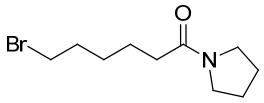
R_f 0.75 (hexane/Et_2O = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04-2.10 (m, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 3.53 (t, *J* = 6.4 Hz, 2H), 6.99 (app. t, *J* = 8.8 Hz, 2H), 7.14-7.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.8, 34.0, 44.0, 115.2 (d, $^2J_{C–F}$ = 21 Hz), 129.8 (d, $^3J_{C–F}$ = 8 Hz), 136.2 (d, $^4J_{C–F}$ = 3 Hz), 161.4 (d, $^1J_{C–F}$ = 243 Hz); HRMS (ESI) Calcd for $C_9H_{11}ClF$ $[M + H]^+$ 173.0533, found 173.0535.



1-Chloro-4-(3-chloropropyl)benzene: Chlorination of of 3-(4-chlorophenyl)propan-1-ol (255.8 mg, 1.5 mmol) with triphosgene (222.6 mg, 0.75 mmol) and triethylamine (0.5 mL,

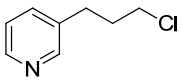
5 mmol) in CH_2Cl_2 (15 mL) according to the literature procedure.[23] Silica gel chromatography (eluent: hexane/Et_2O = 50/1) of the crude product afforded the title compound as a colorless oil (235.0 mg, 83%).

R_f 0.75 (hexane/Et_2O = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01-2.08 (m, 2H), 2.75 (t, *J* = 7.6 Hz, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 7.12 (app. d, *J* = 8.4 Hz, 2H), 7.25 (app. d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.0, 33.8, 43.9, 128.6, 129.9, 131.9, 139.1; HRMS (ESI) Calcd for $C_9H_{11}Cl_2$ $[M + H]^+$ 189.0233, found 189.0238.



6-Bromo-1-(pyrrolidin-1-yl)hexan-1-one: Amidation of of 6-bromohexanoic acid (975.3 mg, 5 mmol) according to a amidation procedure.[24] Silica gel chromatography (eluent: Et_2O) of the crude product afforded the title compound as a light yellow oil (806.0 mg, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39-1.46 (m, 2H), 1.45-1.63 (m, 2H), 1.76-1.84 (m, 4H), 1.85-1.90 (m, 2H), 2.21 (t, *J* = 7.2 Hz, 2H), 3.32-3.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8, 24.2, 25.9, 27.8, 32.4, 33.6, 34.3, 45.4, 46.4, 171.1; HRMS (ESI) Calcd for $C_{10}H_{19}BrNO$ $[M + H]^+$ 248.0655, found 248.0650.



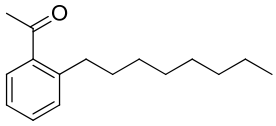
3-(3-Chloropropyl)pyridine: Chlorination of 3-(pyridin-3-yl)propan-1-ol (272.4 mg, 2 mmol) with thionyl chloride (0.2 mL, 2.8 mmol) in CH_2Cl_2 (20 mL) according to a chlorination procedure.[25] Silica gel chromatography (eluent: hexane/Et_2O/Et_3N = 1/1/0.1) of the crude product afforded the title compound as a brown oil (184.0 mg, 60%).

R_f 0.49 (Et_2O/Et_3N = 10/0.1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06-2.13 (m, 2H), 2.80 (t, *J* = 7.6 Hz, 2H), 3.54 (t, *J* = 6.4 Hz, 2H), 7.23 (dd, *J* = 7.2 Hz, 4.4 Hz, 1H), 7.53 (dt, *J* = 7.6

Hz, 2.0 Hz, 1H), 8.47 (d, J = 4.4 Hz, 1H), 8.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 33.4, 43.7, 123.3, 135.8 (two signals overlapping), 147.6, 149.8; HRMS (ESI) Calcd for $C_8H_{11}Cl$ $[M + H]^+$ 156.0583, found 156.0580.

Chlorocyclododecane, *trans*-4-*tert*-butyl-1-chlorocyclohexane and *cis*-4-*tert*-butyl-1-chlorocyclohexane were synthesized according to the literature procedures.[26,27] 1,3-Diisopropylbenzimidazolium bromide (**L4**) was synthesized according to the literature procedure.[28]

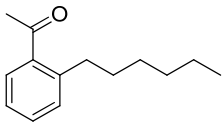
Cobalt-Catalyzed *ortho*-Alkylation of Aryl Imines



Typical Procedure: 1-(2-Octylphenyl)ethanone (2a). In a 10 mL Schlenk tube were placed $CoBr_2$ (6.6 mg, 0.03 mmol), 1,3-diisopropylbenzimidazolium bromide (**L4**, 8.5 mg, 0.03 mmol), (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), 1-chlorooctane (76.5 μL, 0.45 mmol), and THF (0.69 mL). To the mixture was added a THF solution of *t*BuCH$_2$MgBr (1.92 M, 0.31 mL, 0.60 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 6 h, and then quenched by the addition of 3 N HCl (1.0 mL). The resulting mixture was stirred at room temperature for 1-3 h, and then extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 40/1) to afford the title compound as a light yellow oil (57.3 mg, 82%). The reactions of 1-bromooctane and 1-octyl tosylate were performed with the same procedure except for the use of 1,3-diisopropylimidazolinium tetrafluoroborate (**L1**, 7.3 mg, 0.03 mg) instead of **L4** for the both and the reaction

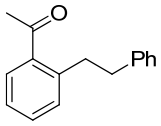
temperature of 60 °C for the latter, affording the title compound in 79% and 64% yields, respectively.

R_f 0.55 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 7.2 Hz, 3H), 1.26-1.35 (m, 10H), 1.53-1.59 (m, 2H), 2.57 (s, 3H), 2.83 (t, J = 8.0 Hz, 2H), 7.22-7.26 (m, 2H), 7.36-7.40 (m, 1H), 7.60-7.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 29.3, 29.4, 29.7, 29.9, 31.9 (two signals overlapping), 34.0, 125.5, 128.9, 131.1, 131.2, 138.0, 142.9, 202.3; HRMS (ESI) Calcd for $C_{16}H_{25}O$ $[M + H]^+$ 233.1905, found 233.1903.



Procedure for 10 mmol-scale Reaction: 1-(2-Hexylphenyl)ethanone (2b). In a 100 mL 2-necked flask were placed $CoBr_2$ (219 mg, 1.0 mmol), **L1** (242 mg, 1.0 mmol), **1** (2.25 g, 10.0 mmol), 1-bromohexane (2.11 mL, 15.0 mmol), and THF (22.3 mL). To the mixture was added a THF solution of *t*BuCH$_2$MgBr (1.82 M, 11.0 mL, 20 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 6 h, and then quenched by the addition of 3N HCl (5 mL). The resulting mixture was stirred for 3 h and then extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded the title compound as a light yellow oil (1.58 g, 77%).

R_f 0.50 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, 3H), 1.28-1.38 (m, 6H), 1.54-1.58 (m, 2H), 2.57 (s, 3H), 2.83 (t, J = 8.0 Hz, 2H), 7.22-7.26 (m, 2H), 7.35-7.39 (m, 1H), 7.60-7.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.6, 29.4, 29.9, 31.7, 31.8, 34.0, 125.5, 128.9, 131.1, 131.2, 138.1, 142.8, 202.3; HRMS (ESI) Calcd for $C_{14}H_{21}O$ $[M + H]^+$ 205.1592, found 205.1594.



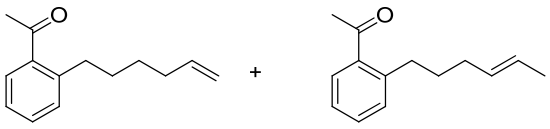
1-(2-Phenethylphenyl)ethanone (2c): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L4** (8.5 mg, 0.03 mmol) and (2-chloroethyl)benzene (59.2 μL, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light yellow oil (48.9 mg, 73%). The ^{1}H and ^{13}C NMR spectra (see attached) showed good agreement with the literature data.[29] The same compound was obtained in 82% yield using **L1** (7.3 mg, 0.03 mmol) and (2-bromoethyl)benzene (61.5 μL, 0.45 mmol) with the reaction time of 24 h.

R_f 0.29 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (s, 3H), 2.96 (t, *J* = 8.0 Hz, 2H), 3.22 (t, *J* = 8.0 Hz, 2H), 7.24-7.35 (m, 7H), 7.44 (td, *J* = 7.5 Hz, 1.3 Hz, 1H), 7.72 (dd, *J* = 7.7 Hz, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 36.3, 38.2, 125.8, 125.9 (two signals overlapping), 128.2, 128.6, 129.2, 131.42, 131.45, 137.8, 141.9, 201.9.

1-(2-(Pent-4-en-1-yl)phenyl)ethanone (2d) and (*E*)-1-(2-(pent-3-en-1-yl)phenyl)ethanone (2d'): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and 5-bromopentane (53.3 μL, 0.45 mmol) for 6 h. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded a mixture of the title compounds as a light yellow oil (40.9 mg, 72%). The ratio of the regioisomers was determined to be 91:8 by ^{1}H NMR integrations of characteristic signals at 5.81-5.88 and 5.33-5.46 ppm.

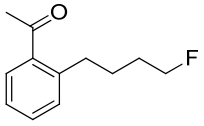
R_f 0.40 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$, major isomer): δ 1.64-1.71 (m, 2H), 2.10-2.15 (m, 2H), 2.57 (s, 3H), 2.86 (t, *J* = 6.0 Hz, 2H), 4.97 (ddt, *J* = 10.2 Hz,

2.0 Hz, 1.1 Hz, 1H), 5.02 (ddt, *J* = 17.1 Hz, 1.7 Hz, 1.6 Hz, 1H), 5.85 (ddt, *J* = 17.0 Hz, 10.3 Hz, 6.6 Hz, 1H), 7.24-7.28 (m, 2H), 7.39 (td, *J* = 7.4 Hz, 1.2 Hz, 1H), 7.64 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer): δ 29.9, 30.9, 33.5, 33.7, 114.6, 125.7, 129.1, 131.2, 131.3, 137.9, 138.6, 142.5, 202.1; HRMS (ESI) Calcd for $C_{13}H_{17}O$ $[M + H]^+$ 189.1279, found 189.1280.



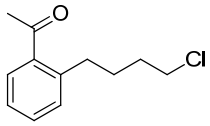
1-(2-(Hex-5-en-1-yl)phenyl)ethanone (2e) and (*E*)-1-(2-(Hex-4-en-1-yl)phenyl)ethanone (2e'): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and 6-bromohexene (60.1 μL, 0.45 mmol) for 6 h. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded a mixture of the title compounds as a yellow oil (58.6 mg, 97%). The ratio of the regioisomers was determined to be 88:12 by ^{1}H NMR integrations of characteristic signals at 5.78-5.85 and 5.40-5.49 ppm.

R_f 0.39 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$, major isomer): δ 1.44-1.50 (m, 2H), 1.55-1.61 (m, 2H), 2.06-2.11 (m, 2H), 2.58 (s, 3H), 2.85 (t, *J* = 7.6 Hz, 2H), 4.94 (ddt, *J* = 10.2 Hz, 2.0 Hz, 1.1 Hz, 1H), 5.00 (ddt, *J* = 17.1 Hz, 1.9 Hz, 1.6 Hz, 1H), 5.81 (ddt, *J* = 17.0 Hz, 10.2 Hz, 6.7 Hz, 1H), 7.24-7.27 (m, 2H), 7.39 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.63 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer): δ 28.9, 29.9, 31.3, 33.6, 33.8, 114.3, 125.6, 129.0, 131.1, 131.2, 137.9, 138.9, 142.7, 202.2; HRMS (ESI) Calcd for $C_{14}H_{19}O$ $[M + H]^+$ 203.1436, found 203.1437.



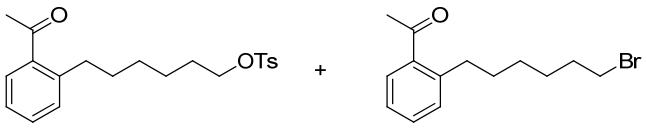
1-(2-(4-Fluorobutyl)phenyl)ethanone (2f): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and 4-fluoro-1-bromobutane (48.3 μL, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light yellow oil (42.5 mg, 73%).

R_f 0.38 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.671.82 (m, 4H), 2.58 (s, 3H), 2.89 (t, J = 7.6 Hz, 2H), 4.46 (dt, $^1J_{C–F}$ = 47.2 Hz, J = 5.6 Hz, 2H), 7.25-7.29 (m, 2H), 7.40 (td, J = 7.4 Hz, J = 1.2 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.3 (d, $^3J_{C–F}$ = 5.2 Hz), 29.8, 30.3 (d, $^2J_{C–F}$ = 19.2 Hz), 33.5, 84.0 (d, $^1J_{C–F}$ = 163 Hz), 125.9, 129.3, 131.2, 131.4, 137.7, 142.3, 201.9; HRMS (ESI) Calcd for $C_{12}H_{16}FO$ $[M + H]^+$ 195.1185, found 195.1185.



1-(2-(4-Chlorobutyl)phenyl)ethanone (2g): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and 4-chloro-1-bromobutane (51.9 μL, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light yellow oil (50.4 mg, 80%).

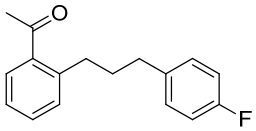
R_f 0.38 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70-1.75 (m, 2H), 1.81-1.86 (m, 2H), 2.58 (s, 3H), 2.87 (t, J = 7.6 Hz, 2H), 3.55 (t, J = 6.8 Hz, 2H), 7.25-7.29 (m, 2H), 7.39 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.9, 29.8, 32.5, 33.2, 44.8, 125.9, 129.3, 131.2, 131.5, 137.6, 142.1, 201.9; HRMS (ESI) Calcd for $C_{12}H_{16}ClO$ $[M + H]^+$ 211.0890, found 211.0887.



6-(2-Acetylphenyl)hexyl 4-methylbenzenesulfonate (2h) and 1-(2-(6-Bromohexyl)phenyl)ethanone (2h'): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and 6-bromohexyl 4-methylbenzenesulfonate (112.3 μL, 0.45 mmol) for 4 h. Silica gel chromatography (eluent: hexane/EtOAc = 20/1 - 5/1) of the crude product afforded the title compounds **2h** and **2h'** as a brown oil (80.4 mg, 71%) and a light yellow oil (15.0 mg, 18%), respectively.

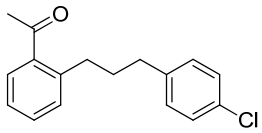
2h: R_f 0.25 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31-1.40 (m, 4H), 1.50-1.53 (m, 2H), 1.62-1.66 (m, 2H), 2.44 (s, 3H), 2.57 (s, 3H), 2.79 (t, *J* = 7.6 Hz, 2H), 4.01 (t, *J* = 6.4 Hz, 2H), 7.21-7.27 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.37 (td, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 7.64 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 25.1, 28.7, 28.9, 29.9, 31.5, 33.8, 70.6, 125.7, 127.8, 129.1, 129.8, 131.1, 131.4, 133.2, 137.7, 142.6, 144.6, 202.1; HRMS (ESI) Calcd for $C_{21}H_{27}O_4S$ $[M + H]^+$ 375.1630, found 375.1632.

2h': R_f 0.59 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41-1.49 (m, 4H), 1.54-1.63 (m, 2H), 1.83-1.90 (m, 2H), 2.84 (s, 3H), 2.84 (t, *J* = 7.6 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 7.24-7.27 (m, 2H), 7.39 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0, 28.8, 29.9, 31.5, 32.7, 33.89, 33.93, 125.7, 129.1, 131.1, 131.3, 137.8, 142.7, 202.1; HRMS (ESI) Calcd for $C_{14}H_{20}BrO$ $[M + H]^+$ 283.0698, found 283.0697.



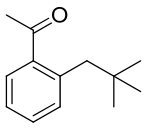
1-(2-(3-(4-Fluorophenyl)propyl)phenyl)ethanone (2i): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L4** (8.5 mg, 0.03 mmol) and 1-(3-chloropropyl)-4-fluorobenzene (77.7 mg, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded the title compound as a light yellow oil (59.2 mg, 77%).

R_f 0.44 (hexane/EtOAc = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85-1.93 (m, 2H), 2.57 (s, 3H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.89 (t, *J* = 7.6 Hz, 2H), 6.96 (t, *J* = 8.4 Hz, 2H), 7.13 -7.17 (m, 2H), 7.23-7.29 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.8, 33.4, 33.7, 35.0, 118.9 (d, $^2J_{C–F}$ = 21 Hz), 125.8, 129.2, 129.6 (d, $^3J_{C–F}$ = 8 Hz), 131.1, 131.4, 137.7, 137.9 (d, $^4J_{C–F}$ = 4 Hz), 142.3, 161.1 (d, $^1J_{C–F}$ = 241 Hz), 202.0; HRMS (ESI) Calcd for $C_{17}H_{18}FO$ $[M + H]^+$ 257.1338, found 257.1342.



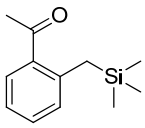
1-(2-(3-(4-Chlorophenyl)propyl)phenyl)ethanone (2j): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L4** (8.5 mg, 0.03 mmol) and 1-chloro-4-(3-chloropropyl)benzene (85.1 mg, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/Et_2O = 50/1 - 25/1) of the crude product afforded the title compound as a light yellow oil (49.9 mg, 61%).

R_f 0.43 (hexane/Et_2O = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82-1.93 (m, 2H), 2.57 (s, 3H), 2.66 (t, *J* = 7.6 Hz, 2H), 2.88 (t, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.22 -7.29 (m, 4H), 7.39 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.66 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.8, 33.2, 33.7, 35.2, 125.9, 128.3, 129.3, 129.8, 131.2, 131.4, 131.5, 137.7, 140.8, 142.3, 202.0; HRMS (ESI) Calcd for $C_{17}H_{18}ClO$ $[M + H]^+$ 273.1045, found 273.1046.



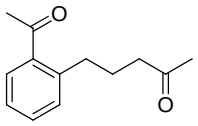
1-(2-Neopentylphenyl)ethanone (2i): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and neopentyl bromide (56.7 μL, 0.45 mmol) for 13 h. Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light yellow oil (49.3 mg, 86%).

R_f 0.67 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (s, 9H), 2.56 (s, 3H), 2.94 (s, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.23-7.27 (m, 1H), 7.35 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.54 (dd, *J* = 7.6 Hz, *J* = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.4, 30.2, 32.6, 44.4, 125.7, 127.9, 130.0, 133.3, 138.5, 140.4, 203.6; HRMS (ESI) Calcd for $C_{13}H_{19}O$ $[M + H]^+$ 191.1436, found 191.1431.



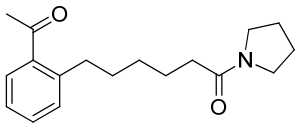
1-(2-((Trimethylsilyl)methyl)phenyl)ethanone (2j): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and chloromethyltrimethylsilane (62.8 μL, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light yellow oil (40.4 mg, 65%).

R_f 0.67 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ -0.05 (s, 9H), 2.56 (s, 3H), 2.62 (s, 2H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 6.8 Hz, 1H), 7.30 (td, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 7.69 (dd, *J* = 7.6 Hz, *J* = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.6, 25.2, 29.5, 123.7, 130.0, 131.0, 131.3, 135.5, 142.3, 201.4; HRMS (ESI) Calcd for $C_{12}H_{19}OSi$ $[M + H]^+$ 207.1205, found 207.1201.



5-(2-Acetylphenyl)pentan-2-one (2k): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L4** (8.5 mg, 0.03 mmol) and 5-chloro-2-pentanone ethylene ketal (67.7 μL, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 20/1 – 5/1) of the crude product afforded the title compound as an orange oil (42.1 mg, 69%).

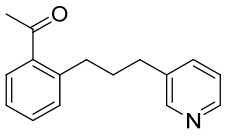
R_f 0.13 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83-1.89 (m, 2H), 2.12 (s, 3H), 2.47 (t, J = 7.6 Hz, 2H), 2.56 (s, 3H), 2.82 (t, J = 7.6 Hz, 2H), 7.24-7.28 (m, 2H), 7.37 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.6, 29.7, 29.8, 33.1, 43.3, 125.9, 129.3, 131.2, 131.5, 137.6, 141.9, 201.9, 208.9; HRMS (ESI) Calcd for $C_{13}H_{17}O_2$ $[M + H]^+$ 205.1229, found 205.1224.



6-(2-Acetylphenyl)-1-(pyrrolidin-1-yl)hexan-1-one (2n): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and 6-bromo-1-(pyrrolidin-1-yl)hexan-1-one (111.7 mg, 0.6 mmol) with the reaction time of 24 h (additional 1 equiv of *t*BuCH$_2$MgBr was added dropwise at the reaction time of 2 h. Silica gel chromatography (eluent: hexane/EtOAc = 2/3) of the crude product afforded a mixture of the title compound (35.4 mg, 41%), 6-bromo-1-(pyrrolidin-1-yl)hexan-1-one, and (*E*)-1-(pyrrolidin-1-yl)hex-4-en-1-one as an orange oil.

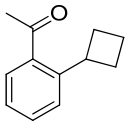
R_f 0.11 (hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38-1.45 (m, 2H), 1.55-1.70 (m, 4H), 1.82-1.87 (m, 2H), 1.90-1.95 (m, 2H), 2.26 (t, J = 8.0 Hz, 2H), 2.56 (s, 3H), 2.83 (t, J = 8.0 Hz, 2H), 3.40 (t, J = 6.8 Hz, 2H), 3.45 (t, J = 6.8 Hz, 2H), 7.23-7.25 (m,

2H), 7.38 (t, J = 7.6 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 24.8, 26.1, 29.5, 29.9, 31.5, 33.9, 34.7, 45.6, 46.6, 125.6, 129.0, 131.2, 131.3, 137.9, 142.6, 171.9, 202.2; HRMS (ESI) Calcd for $C_{18}H_{26}NO_2$ $[M + H]^+$ 288.1964, found 288.1965.



1-(2-(3-(Pyridin-3-yl)propyl)phenyl)ethanone (2o): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L4** (8.5 mg, 0.03 mmol) and 3-(3-chloropropyl)pyridine (70.0 mg, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 5/1/0.1) of the crude product afforded a mixture of the title compound (13.4 mg, 19%) and *p*-anisidine as a brown oil.

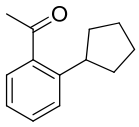
R_f 0.10 (hexane/EtOAc/Et_3N = 5/1/0.1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89-1.95 (m, 2H), 2.57 (s, 3H), 2.69 (t, J = 8.0 Hz, 2H), 2.90 (t, J = 8.0 Hz, 2H), 7.18-7.30 (m, 3H), 7.40 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.51 (dd, J = 7.6 Hz, 1.0 Hz, 1H), 7.68 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 8.43 (d, J = 4.0 Hz, 1H), 8.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 33.0 (two signals overlapping), 33.8, 123.2, 126.0, 129.4, 131.2, 131.5, 135.8, 137.5, 139.9, 147.2, 149.9, 152.8, 201.8; HRMS (ESI) Calcd for $C_{16}H_{18}NO$ $[M + H]^+$ 240.1388, found 240.1386.



1-(2-Cyclobutylphenyl)ethanone (2l): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L4** (8.5 mg, 0.03 mmol) and chlorocyclobutane (41.4 μL, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded the title compound as a light yellow

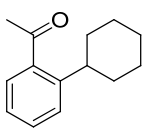
oil (26.5 mg, 51%). The same compound was obtained in 75% yield using **L1** (7.3 mg, 0.03 mmol) and bromocyclobutane (42.4 μL, 0.45 mmol) with the reaction time of 24 h.

R_f 0.45 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69-1.82 (m, 1H), 1.96-2.17 (m, 3H), 2.32-2.38 (m, 2H), 2.54 (s, 3H), 4.02 (m, 1H), 7.21-7.25 (m, 1H), 7.40-7.46 (m, 2H), 7.51 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 29.4, 30.0, 38.1, 125.4, 127.2, 127.8, 131.0, 138.2, 144.9, 203.0; HRMS (ESI) Calcd for $C_{12}H_{15}O$ $[M + H]^+$ 175.1123, found 175.1125.



1-(2-Cyclopentylphenyl)ethanone (2m): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and chlorocyclopentane (46.8 μL, 0.45 mmol) for 24 h, except that additional 1 equiv of *t*BuCH$_2$MgBr was added dropwise to the reaction mixture at the reaction time of 5 h. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded the title compound as a light yellow oil (35.7 mg, 63%). The ^{1}H and ^{13}C NMR spectra (see attached) showed good agreement with the literature data.[30]

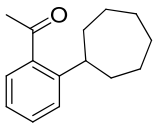
R_f 0.51 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54-1.62 (m, 2H), 1.66-1.71 (m, 2H), 1.78-1.83 (m, 2H), 2.03-2.09 (m, 2H), 2.57 (s, 3H), 3.43-3.48 (m, 1H), 7.19-7.23 (m, 1H), 7.39-7.41 (m, 2H), 7.45 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.8, 30.7, 35.1, 41.5, 125.2, 127.1, 127.3, 130.9, 139.9, 145.2, 204.0.



1-(2-Cyclohexylphenyl)ethanone (2n): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L4** (8.5 mg, 0.03 mmol)

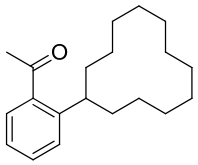
and chlorocyclohexane (53.4 μL, 0.45 mmol) for 12 h. Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a light yellow oil (44.2 mg, 73%). The ^{1}H and ^{13}C NMR spectra (see attached) showed good agreement with the literature data.[30] The same compound was obtained in 90% yield using **L1** (7.3 mg, 0.03 mmol) and bromocyclohexane (74.0 μL, 0.6 mmol) with the reaction time of 6 h (additional 1 equiv of *t*BuCH$_2$MgBr was added dropwise at the reaction time of 2 h).

R_f 0.13 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15-1.21 (m, 1H), 1.39-1.44 (m, 4H), 1.73-1.85 (m, 5H), 2.57 (s, 3H), 3.00-3.07 (m, 1H), 7.20-7.24 (m, 1H), 7.37-7.40 (m, 2H), 7.47 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2, 26.9, 30.8, 34.5, 40.0, 125.3, 127.1, 127.6, 130.9, 139.1, 146.6, 203.8.



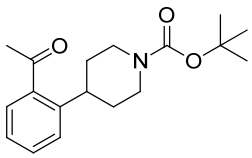
1-(2-Cycloheptylphenyl)ethanone (2o): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L4** (8.5 mg, 0.03 mmol) and chlorocycloheptane (62.2 μL, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded the title compound as a light yellow oil (54.6 mg, 84%).

R_f 0.51 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53-1.71 (m, 8H), 1.76-1.80 (m, 2H), 1.87-1.92 (m, 2H), 2.57 (s, 3H), 3.15-3.20 (m, 1H), 7.17-7.22 (m, 1H), 7.35-7.41 (m, 2H), 7.45 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.4, 27.7, 30.7, 36.9, 41.6, 125.0, 127.37, 127.42, 131.0, 138.2, 148.7, 203.6; HRMS (ESI) Calcd for $C_{15}H_{21}O$ $[M + H]^+$ 217.1592, found 217.1593.



1-(2-Cyclododecylphenyl)ethanone (2p): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and chlorocyclododecane (99.1 μL, 0.45 mmol) for 24 h. To the mixture was added additional 1 equiv of *t*BuCH$_2$MgBr (1.92 M, 0.16 mL, 0.30 mmol) dropwise at the reaction time of 2 h. Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a light yellow oil (55.9 mg, 65%).

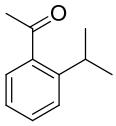
R_f 0.59 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36-1.75 (m, 20H), 1.75-1.82 (m, 2H), 2.56 (s, 3H), 3.39-3.42 (m, 1H), 7.18-7.22 (m, 1H), 7.38-7.43 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.9, 23.0, 23.2, 24.0 (two signals overlapping), 30.8, 31.8, 34.1, 125.1, 126.9, 128.0, 130.6, 140.3, 146.1, 204.2; HRMS (ESI) Calcd for $C_{20}H_{31}O$ $[M + H]^+$ 287.2375, found 287.2377.



***tert*-Butyl 4-(2-acetylphenyl)piperidine-1-carboxylate (2q):** The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and 1-*N*-Boc-4-bromopiperidine (118.9 mg, 0.45 mmol) for 24 h. To the mixture was added additional 1 equiv of *t*BuCH$_2$MgBr (1.92 M, 0.16 mL, 0.30 mmol) dropwise at the reaction time of 2 h. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded the title compound as a brown oil (38.4 mg, 42%).

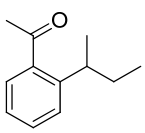
R_f 0.14 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 9H), 1.58-1.63 (m, 2H), 1.77-1.80 (m, 2H), 2.57 (s, 3H), 2.73-2.84 (m, 2H), 3.29 (tt, J = 12.0 Hz, 3.3 Hz, 1H), 4.18-4.23 (brs, 2H), 7.26 (t, J = 7.4 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 7.2 Hz,

1H), 7.57 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.5, 30.4, 33.2, 38.0, 44.5, 79.4, 125.8, 127.2, 128.4, 131.4, 138.4, 145.0, 154.9, 203.0; HRMS (ESI) Calcd for $C_{18}H_{26}NO_3$ $[M + H]^+$ 304.1913, found 304.1916.



1-(2-Isopropylphenyl)ethanone (2r): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and 2-chloropropane (41.0 μL, 0.45 mmol) for 6 h. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded the title compound as a light yellow oil containing a small amount of the *n*-propyl isomer (31.5 mg, 65%). The regioisomer ratio was determined to be 99:1 by ^{1}H NMR analysis. The ^{1}H and ^{13}C NMR spectra showed good agreement with the literature data.[31] The same compound was obtained in 68% yield with the *i*:*n* ratio of 93:7 using 2-bromopropane (42.2 μL, 0.45 mmol) and **L1** (7.3 mg, 0.03 mmol) with the reaction time of 6 h.

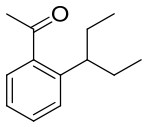
R_f 0.39 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (d, J = 6.8 Hz, 6H), 2.57 (s, 3H), 3.47 (septet, J = 6.8 Hz, 1H), 7.22-7.25 (m, 1H), 7.41-7.43 (m, 2H), 7.48 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 29.2, 30.7, 125.3, 126.5, 127.6, 131.0, 138.9, 147.6, 203.7.



1-(2-(*sec*-Butyl)phenyl)ethanone (2s): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and 2-bromobutane (49.1 μL, 0.45 mmol) for 6 h. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded the title compound as a light yellow

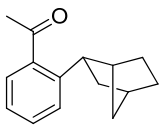
oil containing a small a amount of the *n*-butyl isomer (29.6 mg, 56%). The regioisomer ratio was determined to be 94:6 by ^{1}H NMR analysis.

R_f 0.52 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (t, J = 7.6 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H), 1.53-1.67 (m, 2H), 2.56 (s, 3H), 3.17 (app. sextet, J = 7.0 Hz, 1H), 7.22 (td, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.39-7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.2, 22.0, 30.8, 31.1, 36.2, 125.3, 126.8, 127.3, 130.8, 139.8, 146.4, 203.9; HRMS (ESI) Calcd for $C_{12}H_{17}O$ $[M + H]^+$ 177.1279, found 177.1274.



1-(2-(Pentan-3-yl)phenyl)ethanone (2t): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and 3-bromopentane (74.5 μL, 0.6 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a light yellow oil (36.1 mg, 63%).

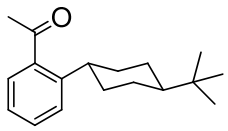
R_f 0.35 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (t, J = 7.4 Hz, 6H), 1.52-1.61 (m, 2H), 1.63-1.72 (m, 2H), 2.54 (s, 3H), 2.94-3.02 (m, 1H), 7.22 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.38-7.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.0, 29.3, 31.1, 43.2, 125.2, 126.9, 127.0, 130.6, 141.2, 144.4, 204.1; HRMS (ESI) Calcd for $C_{13}H_{19}O$ $[M + H]^+$ 191.1436, found 191.1438.



***exo*-1-(2-(Bicyclo[2.2.1]heptan-2-yl)phenyl)ethanone (3u):** The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and *exo*-2-chloronorbornane (55.5 μL, 0.45 mmol) for 24 h. Silica gel

chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light yellow oil containing a small amount of the *endo* isomer (52.6 mg, 82%). The *exo*/*endo* ratio was determined to be 90:10 by ^{1}H NMR integrations of characteristic signals at 3.19 (dd, J = 8.9 Hz, 6.0 Hz) and 3.62-3.68 ppm. The ^{1}H and ^{13}C NMR spectra (see attached) showed good agreement with the literature data.[2c]

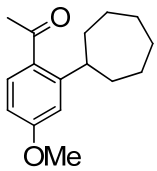
R_f 0.42 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21-1.32 (m, 2H), 1.37-1.43 (m, 1H), 1.47-1.51 (m, 1H), 1.53-1.61 (m, 3H), 1.68-1.86 (m, 1H), 2.35 (d, J = 18.4 Hz, 2H), 2.56 (s, 3H), 3.19 (dd, J = 8.9 Hz, 6.0 Hz, 1H), 7.20 (td, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.36-7.42 (m, 2H), 7.49 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.7, 30.4, 30.6, 36.6, 37.0, 40.2, 42.6, 43.4, 125.0, 126.4, 128.0, 130.7, 139.3, 146.2, 203.7.



***trans*-1-(2-(4-(*tert*-Butyl)cyclohexyl)phenyl)ethanone (2v):** The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L4** (8.5 mg, 0.03 mmol) and *trans*-4-*tert*-butyl-1-chlorocyclohexane (*trans*/*cis* = 91/9, 78.6 mg, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded a mixture of the title compound and the *cis* isomer as a light yellow oil (23.8 mg, 31%). The *trans*/*cis* ratio was determined to be 79:21 by GC. The same compound was obtained in 30% yield with a *trans*/*cis* ratio of 79:21 using *cis*-4-*tert*-butyl-1-chlorocyclohexane (*trans*/*cis* = 4/96, 78.6 mg, 0.45 mmol) and **L4** (8.5 mg, 0.03 mmol) with the reaction time of 24 h.

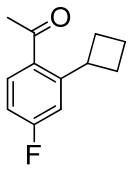
R_f 0.67 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$, *trans* isomer): δ 0.88 (s, 9H), 1.08-1.22 (m, 3H), 1.35-1.48 (m, 2H), 1.79-1.93 (m, 4H), 2.57 (s, 3H), 2.98 (tt, J = 12 Hz, 3.2 Hz, 1H), 7.20-7.24 (m, 1H), 7.37-7.40 (m, 2H), 7.47-7.48 (m, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$, *trans* isomer): δ 27.6, 27.7, 30.8, 32.5, 34.8, 40.0, 47.9, 125.3, 127.0, 127.7, 130.9, 139.3, 146.4, 203.8; HRMS (ESI) Calcd for $C_{18}H_{27}O$ $[M + H]^+$ 259.2062, found 259.2057.



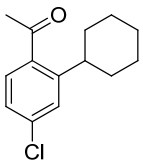
1-(2-Cycloheptyl-4-methoxyphenyl)ethanone (3): The procedure for 10 mmol-scale reaction (see **2b**) was applied to (*E*)-4-methoxy-*N*-(1-(4-methoxyphenyl)ethylidene)aniline (2.55 g, 10.0 mmol), **L4** (283 mg, 1.0 mmol) and chlorocycloheptane (2.07 mL, 15.0 mmol) for 6 h. Silica gel chromatography (eluent: hexane/EtOAc = 30/1-20/1) of the crude product afforded the title compound as a light yellow oil (2.10 g, 85%).

R_f 0.37 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56-1.63 (m, 6H), 1.69-1.78 (m, 4H), 1.87-1.92 (m, 2H), 2.54 (s, 3H), 3.45-3.50 (m, 1H), 3.83 (s, 3H), 6.70 (dd, *J* = 8.8 Hz, *J* = 2.8 Hz, 1H), 6.88 (d, *J* = 2.8 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5, 27.7, 30.0, 36.9, 41.1, 55.2, 109.6, 113.3, 129.9, 131.2, 153.0, 161.9, 201.0; HRMS (ESI) Calcd for $C_{16}H_{23}O_2$ $[M + H]^+$ 247.1698, found 247.1693.



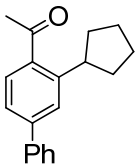
1-(2-Cyclobutyl-4-fluorophenyl)ethanone (4): The typical procedure was applied to (*E*)-*N*-(1-(4-fluorophenyl)ethylidene)-4-methoxyaniline (73.0 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and bromocyclobutane (42.4 μL, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded the title compound as a light yellow oil (30.4 mg, 53%).

R_f 0.43 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77-1.80 (m, 1H), 1.80-1.81 (m, 3H), 1.98-2.39 (m, 2H), 2.53 (s, 3H), 4.04-4.08 (m, 1H), 6.90 (td, J = 8.0 Hz, J = 2.4 Hz, 1H), 7.09 (dd, J = 10.8 Hz, J = 2.4 Hz, 1H), 7.57 (dd, J = 8.8 Hz, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 29.3, 29.8, 38.1, 112.1 (d, $^2J_{C–F}$ = 21 Hz), 114.6 (d, $^2J_{C–F}$ = 21 Hz), 130.9 (d, $^3J_{C–F}$ = 9 Hz), 134.0, 149.2 (d, $^3J_{C–F}$ = 8 Hz), 164.4 (d, $^1J_{C–F}$ = 250 Hz), 200.9; HRMS (ESI) Calcd for $C_{12}H_{14}FO$ $[M + H]^+$ 193.1029, found 193.1032.



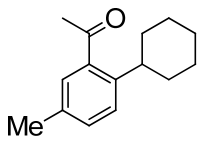
1-(4-Chloro-2-cyclohexylphenyl)ethanone (5): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1**, 67.6 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and bromocyclohexane (74.0 μL, 0.6 mmol) with the reaction time of 24 h (additional 1 equiv of *t*BuCH$_2$MgBr was added dropwise at the reaction time of 2 h. Silica gel chromatography (eluent: hexane/EtOAc = 20/1) of the crude product afforded the title compound as an orange oil (45.9 mg, 65%).

R_f 0.41 (hexane/EtOAc = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23-1.29 (m, 1H), 1.36-1.43 (m, 4H), 1.73-1.83 (m, 5H), 2.55 (s, 3H), 3.08-3.11 (m, 1H), 7.20 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 26.7, 30.6, 34.4, 39.8, 125.5, 127.6, 129.3, 137.0, 137.1, 149.1, 202.2; HRMS (ESI) Calcd for $C_{14}H_{18}ClO$ $[M + H]^+$ 237.1046, found 237.1041.



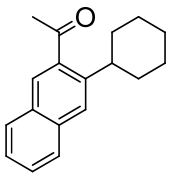
1-(3-Cyclopentyl-[1,1'-biphenyl]-4-yl)ethanone (6): The typical procedure was applied to (*E*)-*N*-(1-([1,1'-biphenyl]-4-yl)ethylidene)-4-methoxyaniline (90.4 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and chlorocyclopentane (46.8 μL, 0.45 mmol) for 24 h, except that additional 1 equiv of *t*BuCH$_2$MgBr was added dropwise at the reaction time of 5 h. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded the title compound as a yellow solid (67.6 mg, 85%).

R_f 0.30 (hexane/EtOAc = 10/1); m.p. 78.5-79.6 ˚C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.65-1.75 (m, 4H), 1.84-1.87 (m, 2H), 2.13-2.15 (m, 2H), 2.62 (s, 3H), 3.07-3.63 (m, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.44-7.49 (m, 3H), 7.58-7.65 (m, 3H), 7.60 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 25.8, 30.5, 35.1, 41.5, 124.0, 126.0, 127.2, 127.8, 128.3, 128.8, 138.3, 140.5, 143.8, 146.2, 203.2; HRMS (ESI) Calcd for $C_{19}H_{21}O$ [M + H]$^+$ 265.1592, found 266.1591.



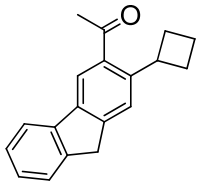
1-(2-Cyclohexyl-5-methylphenyl)ethanone (7): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-(*m*-tolyl)ethylidene)aniline (71.8 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and bromocyclohexane (74 μL, 0.60 mmol) for 24 h, except that additional 1 equiv of *t*BuCH$_2$MgBr was added dropwise at the reaction time of 4 h. Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a light yellow oil (38.1 mg, 53%).

R_f 0.47 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.22-1.29 (m, 1H), 1.34-1.45 (m, 4H), 1.73-1.83 (m, 5H), 2.34 (s, 3H), 2.55 (s, 3H), 2.97-3.01 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 7.27 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 20.8, 26.2, 26.9, 30.7, 34.6, 39.6, 127.0, 128.1, 131.6, 134.8, 139.1, 143.5, 203.9; HRMS (ESI) Calcd for $C_{15}H_{21}O$ [M + H]$^+$ 217.1592, found 217.1593.



1-(3-Cyclohexylnaphthalen-2-yl)ethanone (8): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-(naphthalen-2-yl)ethylidene)aniline (82.6 mg, 0.30 mmol), **L4** (8.5 mg, 0.03 mmol) and chlorocyclohexane (53.4 μL, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded an inseparable mixture of the title compounds as a yellow oil (42.6 mg, 56%).

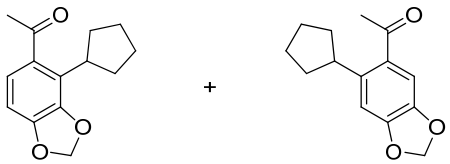
R_f 0.48 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26-1.35 (m, 1H), 1.42-1.55 (m, 4H), 1.78-1.98 (m, 5H), 2.70 (s, 3H), 3.21-3.27 (m, 1H), 7.46 (td, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 7.53 (td, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 7.78 (s, 1H), 7.83 (t, *J* = 8.0 Hz, 2H), 8.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 27.0, 30.6, 34.9, 39.6, 125.7, 125.9, 127.4, 127.6, 128.2, 128.6, 130.6, 134.5, 137.9, 143.7, 203.2; HRMS (ESI) Calcd for $C_{18}H_{21}O$ $[M + H]^+$ 253.1592, found 253.1591.



1-(2-Cyclobutyl-9*H*-fluoren-3-yl)ethanone (9): The typical procedure was applied to (*E*)-*N*-(1-(9*H*-fluoren-3-yl)ethylidene)-4-methoxyanilineaniline (94.0 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and chlorocyclobutane (42.4 μL, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded an inseparable mixture of the title compounds as a light yellow oil (59.2 mg, 75%).

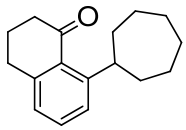
R_f 0.20 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85-1.90 (m, 1H), 2.02-2.19 (m, 1H), 2.14-2.19 (m, 2H), 2.41-2.48 (m, 2H), 2.61 (s, 3H), 3.88 (s, 2H), 4.13-4.18 (m, 1H), 7.35 (t, *J* = 6.8 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.71 (s,

1H), 7.80 (s, 1H), 7.86 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 29.6, 29.9, 36.5, 38.4, 118.4, 120.4, 124.8, 125.1, 126.8, 127.5, 136.5, 139.9, 140.8, 144.30, 144.33, 144.4, 202.6; HRMS (ESI) Calcd for $C_{19}H_{19}O$ $[M + H]^+$ 263.1436, found 263.1435.



1-(4-Cyclopentylbenzo[*d*][1,3]dioxol-5-yl)ethanonene (10) and 1-(6-cyclopentylbenzo[*d*][1,3]dioxol-5-yl)ethanone (10'): The typical procedure was applied to (*E*)-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)ethylidene)-4-methoxyaniline (80.8 mg, 0.30 mmol), **L4** (8.5 mg, 0.03 mmol) and chlorocyclopentane (46.8 μL, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the compound **9** in a pure form (17.2 mg, 25%) as a pale solid and a mixture of **9** and **9'** (13.9 mg, 20%, **9**:**9'** = 64:36 as determined by ^{1}H NMR) as a light yellow liquid. Characterization data of **9** are given below.

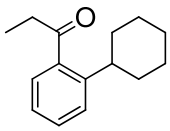
R_f 0.34 (hexane/EtOAc = 10/1); m.p. 65.8-66.9 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60-1.64 (m, 2H), 1.80-1.93 (m, 6H), 2.53 (s, 3H), 3.45-3.54 (m, 1H), 5.98 (s, 2H), 6.68 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.4, 30.4, 31.9, 38.6, 101.0, 105.3, 123.5, 128.4, 134.6, 146.4, 149.7, 201.7; HRMS (ESI) Calcd for $C_{14}H_{17}O_3$ $[M + H]^+$ 233.1178, found 233.1178.



8-Cycloheptyl-3,4-dihydronaphthalen-1(2*H*)-one (11): The typical procedure was applied to (*E*)-*N*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-4-methoxyaniline (75.4 mg, 0.30

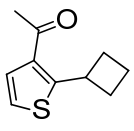
mmol), **L4** (8.5 mg, 0.03 mmol) and chlorocycloheptane (62.2 μL, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a orange oil (59.4 mg, 81%).

R_f 0.45 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55-1.65 (m, 6H), 1.70-1.82 (m, 4H), 1.88-1.91 (m, 2H), 2.03-2.10 (m, 2H), 2.66 (t, *J* = 6.8 Hz, 2H), 2.92 (t, *J* = 6.0 Hz, 2H), 3.84-3.89 (m, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 6.4 Hz, 1H), 7.34 (t, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.9, 27.7, 27.8, 31.2, 37.0, 40.8, 41.3, 125.8, 125.9, 130.3, 132.2, 145.1, 153.2, 200.6; HRMS (ESI) Calcd for $C_{17}H_{23}O$ $[M + H]^+$ 243.1749, found 243.1750.



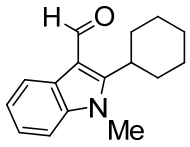
1-(2-Cyclohexylphenyl)propan-1-one (12): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-phenylpropylidene)aniline (71.8 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and bromocyclohexane (74 μL, 0.60 mmol) for 24 h, except that additional 1 equiv of *t*BuCH$_2$MgBr was added dropwise at the reaction time of 2 h. Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a light yellow oil (51.8 mg, 80%).

R_f 0.54 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.2 Hz, 3H), 1.22-1.30 (m, 1H), 1.37-1.44 (m, 4H), 1.73-1.84 (m, 5H), 2.86 (q, *J* = 7.2 Hz, 2H), 2.83-2.89 (m, 1H), 7.19-7.23 (m, 1H), 7.37-7.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.4, 26.2, 26.8, 34.6, 36.3, 40.2, 125.3, 126.7, 127.0, 130.4, 139.6, 146.0, 207.3; HRMS (ESI) Calcd for $C_{15}H_{21}O$ $[M + H]^+$ 217.1592, found 217.1595.



1-(2-Cyclobutylthiophen-3-yl)ethanone (13): The typical procedure was applied to (*E*)-4-methoxy-*N*-(1-(thiophen-3-yl)ethylidene)aniline (69.4 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and bromocyclobutane (42.4 μL, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a light yellow oil (15.1 mg, 24%).

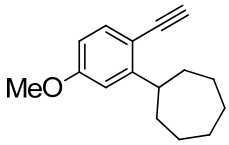
R_f 0.30 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84-1.90 (m, 1H), 1.98-2.12 (m, 3H), 2.48 (s, 3H), 2.49-2.53 (m, 2H), 4.34-4.40 (m, 1H), 7.06 (d, *J* = 5.6 Hz, 1H), 7.35 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 29.8, 31.2, 36.0, 121.1, 129.4, 134.6, 160.3, 193.5; HRMS (ESI) Calcd for $C_{10}H_{13}OS$ $[M + H]^+$ 181.0687, found 181.0692.



2-Cyclohexyl-1-methyl-1*H*-indole-3-carbaldehyde (14): The typical procedure was applied to (*E*)-4-methoxy-*N*-((1-methyl-1*H*-indol-3-yl)methylene)aniline (72.3 mg, 0.30 mmol), **L1** (7.3 mg, 0.03 mmol) and bromocyclohexane (55.3 μL, 0.45 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a brown oil (32.4 mg, 45%).

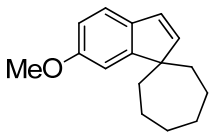
R_f 0.34 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26-1.47 (m, 3H), 1.84-2.05(m, 7H), 3.20-3.26 (m, 1H), 3.80 (s, 3H), 7.28-7.29 (m, 3H), 8.36-8.38 (m, 1H), 10.4 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.8, 27.0, 30.9, 32.9, 37.4, 109.3, 114.0, 121.7, 122.9, 123.2, 126.1, 136.9, 155.2, 184.8; HRMS (ESI) Calcd for $C_{16}H_{20}NO$ $[M + H]^+$ 242.1545, found 242.1545.

Transformation of Cycloalkylation Product 3



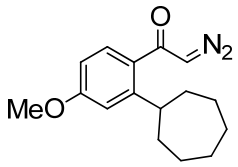
(2-Ethynyl-5-methoxyphenyl)cycloheptane (15): To a solution of LDA prepared at 0 °C from diisopropylamine (148.7 mg, 1.47 mmol) and *n*-butyllithium in hexane (1.6 M, 1.30 mL, 1.47 mmol) in THF (10 mL) was added dropwise a solution of 1-(2-cycloheptyl-4-methoxyphenyl)ethanone (**3**, 350 mg, 1.4 mmol) in THF (5 mL) at –78 ˚C. The resulting mixture was stirred at this temperature for 1 h, followed by the addition of diethyl chlorophosphate (265.7 mg, 1.54 mmol). The reaction mixture was gradually warmed to room temperature, and was added dropwise to a solution of LDA in THF (3.15 mmol, prepared as above) at –78 °C. The resulting mixture was warmed to room temperature over 3 h, quenched with water, and then extracted with hexane (3 x 10 mL). The extract was washed with 1 N HCl (10 mL), water (10 mL), and aqueous $NaHCO_3$ (10 mL). The organic solution was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 10/1) to afford the desired product as a yellow oil (181.7 mg, 56 %).

R_f 0.52 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60-1.66 (m, 6H), 1.70-1.74 (m, 2H), 1.78-1.84 (m, 2H), 1.91-1.96 (m, 2H), 3.18 (s, 1H), 3.20-3.25 (m, 1H), 3.80 (s, 3H), 6.66 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.77 (d, J = 2.4 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5, 27.8, 35.8, 43.8, 55.2, 79.2, 82.6, 110.4, 111.9, 112.8, 134.2, 154.1, 160.1; HRMS (ESI) Calcd for $C_{16}H_{21}O$ $[M + H]^+$ 229.1592, found 229.1593.



6'-Methoxyspiro[cycloheptane-1,1'-indene] (16): In a 10 mL Schlenk tube were placed (2-ethynyl-5-methoxyphenyl)cycloheptane (**14**, 68.5 mg, 0.30 mmol), CuBr (86.1 mg, 0.60 mmol), $PtCl_2$ (8.0 mg, 0.03 mmol) and toluene (3 mL). The resulting mixture was stirred at 100 °C for 24 h. After completion of the reaction, a dark solid in the reaction mixture was removed by filtration through a pad of Celite, followed by washing of the Celite bed with diethyl ether (3 x 5 mL). The combined filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 10/1 – 5/1) to afford the desired product as a yellow oil (53.0 mg, 77 %).

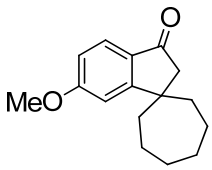
R_f 0.30 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55-1.60 (m, 2H), 1.67-1.79 (m, 6H), 1.81-1.85 (m, 4H), 3.83 (s, 3H), 6.51 (d, J = 5.6 Hz, 1H), 6.59 (d, J = 5.6 Hz, 1H), 6.75 (dd, J = 8.0 Hz, 2.4 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5, 29.9, 36.9, 55.5, 56.8, 108.8, 110.9, 121.3, 127.6, 135.4, 143.8, 156.9, 158.0; HRMS (ESI) Calcd for $C_{16}H_{21}O$ $[M + H]^+$ 229.1592, found 29.1592.



1-(2-Cycloheptyl-4-methoxyphenyl)-2-diazoethanone (17): To a solution of LiHMDS (1.0 M, 1.30 mL) in 10 mL THF was added 1-(2-cycloheptyl-4-methoxyphenyl)ethanone (**3**, 289 mg, 1.2 mmol) in THF (5 mL) over 1 min at –78 ˚C. The resulting was stirred at the same temperature for 30 min, followed by the addition of trifluoroethyl trifluoroacetate (282.3 mg, 1.44 mmol) over 2-3 min. After additional stirring for 3 h, the reaction mixture was allowed to room temperature and then poured into a separatory funnel together with Et_2O (10 mL) and 5% aq. HCl (20 mL). The aqueous layer was extracted with Et_2O (30

mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford a yellow oil. The oil was placed in a dry 50 mL 3-necked round bottom flask under a nitrogen atmosphere and dissolved in acetonitrile (10 mL). To this solution was added water (0.02 mL) and NEt_3 (0.25 mL), followed by the dropwise addition of *p*-acetamidobenzenesulfonyl azide (432.4 mg, 1.8 mmol) in acetonitrile (10 mL). The resulting solution was stirred at ambient temperature for 8 h, and then poured into a separatory funnel with Et_2O (20 mL). The organic layer was washed with 5% NaOH aqueous solution (3 x 20 mL), water (3 x 20 mL), and brine. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 30/1 - 5/1) to afford the desired product as a yellow oil (240.9 mg, 75 %).

R_f 0.30 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53-1.61 (m, 6H), 1.63-1.70 (m, 2H), 1.72-1.77 (m, 2H), 1.87-2.00 (m, 2H), 3.24-3.37 (m, 1H), 3.77 (s, 3H), 5.52 (s, 1H), 6.64 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.2, 27.6, 36.7, 41.3, 55.0, 56.1, 109.8, 113.0, 128.8, 129.1, 151.2, 161.4, 189.6; HRMS (ESI) Calcd for $C_{16}H_{21}N_2O_2$ $[M + H]^+$ 273.1602, found 273.1603.



6'-Methoxyspiro[cycloheptane-1,1'-inden]-3'(2'*H*)-one (18): A solution of 1-(2-cycloheptyl-4-methoxyphenyl)-2-diazoethanone (**16**, 81.7 mg, 0.3 mmol) in dichloromethane (22.5 mL) was added dropwise to a suspension of $Rh_2(OAc)_4$ in dichloromethane (7.5 mL) at room temperature over a period of 6 h using a syringe pump. The resulting mixture was stirred for additional 3 h and then concentrated under reduced

pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 10/1) to afford the desired product as a yellow oil (26.2 mg, 36 %).

R_f 0.32 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56-1.62 (m, 2H), 1.65-1.72 (m, 6H), 1.75-1.79 (m, 2H), 1.90 (t, J = 12.0 Hz, 2H), 2.60 (s, 2H), 3.89 (s, 3H), 6.87 (dd, J = 8.0 Hz, 2.4 Hz, 1H), 6.93 (d, J = 2.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 28.5, 41.9, 45.8, 50.3, 55.6, 107.6, 114.7, 125.1, 128.2, 165.4, 168.2, 204.4. Calcd for $C_{16}H_{21}O_2$ $[M + H]^+$ 245.1542, found 245.1544.

7.5 References

(1) For recent reviews, see: (a) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (c) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (d) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879.

(2) For recent examples, see: (a) Kakiuchi, F.; Kochi, T.; Mizushima, E.; Murai, S. *J. Am. Chem. Soc.* **2010**, *132*, 17741. (b) Ilies, L.; Chen, Q.; Zeng, X.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 5221. (c) Gao, K.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6888.

(3) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866.

(4) (a) Ackermann, L.; Novak, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045. (b) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097. (c) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (d) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428. (e) Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875. (f) Zhao, Y. S.; Chen, G. *Org. Lett.* **2011**, *13*, 4850. (g) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308.

(5) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

(6) Branched-selective reaction with styrene derivatives: (a)Uchimaru, Y. *Chem. Commun.* **1999**, 1133. (b) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 400. (c) Pan, S.; Ryu, N.; Shibata, T. *J. Am. Chem. Soc.* **2012**, *134*, 17474. (d) Lee, P.-S.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 1240.

(7) Reaction of phenol and anisole derivatives with alkyl olefins: (a) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728. (b) Dorta, R.; Togni, A. *Chem. Commun.* **2003**, 760. (c) Kuninobu, Y.; Matsuki, T.; Takai, K. *J. Am. Chem. Soc.* **2009**, *131*, 9914. (d) Oyamada, J.; Hou, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 12828.

(8) For examples of secondary alkylation of heteroarenes without cyclometalation, see: (a) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 616. (b) Ren, P.; Salihu, I.; Scopelliti, R.; Hu, X. *Org. Lett.* **2012**, *14*, 1748.

(9) For *meta*-selective secondary alkylation through cyclometalation process: Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877.

(10) For secondary *ortho*-alkylations based on different strategies, see: (a) Lee, D. H.; Kwon, K. H.; Yi, C. S. *J. Am. Chem. Soc.* **2012**, *134*, 7325. (b) Deng, G. J.; Zhao, L.; Li, C. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278.

(11) (a) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249. (b) Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 17283. (c) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428. (d) Ding, Z.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 4698. (e) Gao, K.; Yoshikai, N. *Chem. Commun.* **2012**, *48*, 4305. (f) Gao, K.; Lee, P. S.; Long, C.; Yoshikai, N. *Org. Lett.* **2012**, *14*, 4234. (g) Song, W.; Ackermann, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8251. (h) Lee, P.-S.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 1240. (i) Yamakawa, T.; Yoshikai, N. *Org. Lett.* **2013**, *15*, 196. (j) Yamakawa, T.; Yoshikai, N. *Tetrahedron* **2013**, *69*, 4459.

(12) Kobayashi, T.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2009**, *4*, 1078.

(13) (a) Ohmiya, H.; Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 2207. (b) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886.

(14) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435.

(15) Even in cross-coupling reactions proposed to involve radical mechanisms, the fate of this radical probe depends on each case. For examples, see: (a) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374. (b) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (c) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun.* **2005**, 4161. (d) Bedford, R. B.; Betham, M.; Bruce, D. W.; Davis, S. A.; Frost, R. M.; Hird, M. *Chem. Commun.* **2006**, 1398. (e) Yasuda, S.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 287. (f) Vechorkin, O.; Proust, V.; Hu, X. *J. Am. Chem. Soc.* **2009**, *131*, 9756.

(16) For examples of cross-couplings involving ring opening of this probe, see ref 16c,d,f and the following: Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773.

(17) Yang, S.; Li, Z.; Han, X.; He, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 3999.

(18) (a) Mrsic, N.; Panella, L.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *J. Am. Chem. Soc.* **2009**, *131*, 8358. (b) Gautier, F.-M.; Jones, S.; Martin, S. J. *Org. Biomol. Chem.* **2009**, *7*, 229.

(19) Samec, J. S. M.; Ell, A. H.; Bäckvall, J.-E. *Chem. Eur. J.* **2005**, *11*, 2327.

(20) Imamoto, T.; Iwadate, N.; Yoshida, K. *Org. Lett.* **2006**, *8*, 2289.

(21) Moessner, C.; Bolm, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 7564.

(22) Tobisu, M.; Yamaguchi, S.; Chatani, N. *Org. Lett.* **2007**, *9*, 3351.

(23) Ayala, C. E.; Villalpando, A.; Nguyen, A. L.; McCandless, G. T.; Kartika, R. *Org. Lett.* **2012**, *14*, 3676.

(24) Paomter, T. O.; Thornton, P. D.; Orestano, M.; Santini, C.; Organ, M. G.; Aubé, J. *Chem. Eur. J.* **2011**, *17*, 9595.

(25) Guthrie, R. W.; Kierstead, R. W.; Mullin, J. G.; Tilley, J. W. Pyridine Compounds Which Are Useful in Treating A Disease State Characterized by An Excess of Platelet Activating Factors. U.S. Patent 4,927,838. May 22, 1990.

(26) Yasuda, M.; Yamasaki, S.; Onishi, Y.; Baba, A. *J. Am. Chem.Soc.* **2004**, *126*, 7186.

(27) Roberts, B. P.; Steel, A. J. *J. Chem. Soc., Perkin Trans. 2.* **1994**, 2411.

(28) Huynh, H. V.; Han, Y.; Ho, J. H. H.; Tan, G. K. *Organometallics.* **2006**, *25*, 3267.

(29) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 62.

(30) Savarin, C. G.; Grisé, C.; Murry, J. A.; Reamer, R. A.; Hughes, D. L. *Org. Lett.* **2007**, *9*, 981.

(31) Cahiez, G.; Luart, D.; Lecomte, F. *Org. Lett.* **2004**, *6*, 4395.

List of Publications

1. Cobalt-Catalyzed Hydroarylation of Alkynes through Chelation-Assisted C–H Bond Activation, Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249.
2. Regioselectivity-Switchable Hydroarylation of Styrenes, Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 400.
3. Cobalt-Phenanthroline Catalysts for the *ortho* Alkylation of Aromatic Imines under Mild Reaction Conditions, Gao, K.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 6888.
4. Cobalt-Catalyzed Arylation of Aldimines *via* Direct C–H Bond Functionalization: Addition of 2-Arylpyridines and Self-Coupling of Aromatic Aldimines, Gao, K.; Yoshikai, N. *Chem. Commun.* **2012**, *48*, 4305.
5. Cobalt-Catalyzed *ortho*-Arylation of Aromatic Imines with Aryl Chlorides, Gao, K.; Lee, P.-S.; Long, C.; Yoshikai, N. *Org. Lett.* **2012**, *14*, 4234.
6. Cobalt-Catalyzed *ortho*-Alkylation of Aromatic Imines with Primary and Secondary Alkyl Halides, Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 9279.