



**NANYANG
TECHNOLOGICAL
UNIVERSITY**

**COBALT-CATALYZED CHELATION-ASSISTED INSERTION OF
C–C MULTIPLE BONDS INTO C(sp²)–H BONDS**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2014

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List of Abbreviations

δ	chemical shift (ppm)
$^{\circ}\text{C}$	degree centigrade
Ac	Acetyl
acac	Acetylacetonate
app.	Apparent
aq	Aqueous
Ar	aryl (substituted aromatic ring)
B3LYP	Becke's three-parameter nonlocal exchange and Lee-Yang-Parr
<i>n</i> Bu	<i>n</i> -butyl
<i>t</i> Bu	<i>tert</i> -butyl
Bn	benzyl
cod	1,5-cyclooctadiene
coe	cyclooctene
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
Cy	cyclohexyl
d	doublet
DMPU	<i>N,N'</i> -dimethylpropyleneurea
DMF	<i>N,N</i> -dimethylformamide

equiv	equivalent
ESI	ElectroSpray Ionization
Et	ethyl
GC	Gas Chromatography
GC-MS	Gas Chromatograph Mass Spectrometer
h	hour
H	hydrogen
HRMS	High Resolution Mass Spectrometry
Hz	hertz
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene
Ipr	1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene
IXyl	1,3-bis(2,6-dimethylphenyl)imidazole-2-ylidene
<i>J</i>	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	<i>N</i> -heterocyclic carbene
NMR	nuclear magnetic resonance
Ph	phenyl
Phen	1,10-phenanthroline
PMP	<i>p</i> -methoxyphenyl
ppm	parts per million
cPr	cyclopropyl
<i>i</i> Pr	isopropyl
q	quartet
rt	room temperature
s	singlet
sat	saturated
t	triplet
Tf	trifluoromethanesulfonyl

TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
THF	tetrahydrofuran
TLC	thin layer chromatography

Abstract

Among transition metal-catalyzed chelation-assisted direct functionalization of C–H bonds to C–C bonds, hydroarylation is particularly attractive because of no waste from starting material. While ruthenium and rhodium complex have been mainly employed as catalysts, quite recently our group have revealed that cobalt catalyst can promote hydroarylation.

In this thesis, I describe chelation-assisted cobalt-catalyzed insertion of C–C multiple bond into C(sp²)–H bond. Chapter 1 describes a brief review of a major developments of insertion of C–C multiple bond into C(sp²)–H bond. Chapter 2 describes aldimine-directed cobalt-catalyzed hydroarylation of aromatic aldimines with alkynes. The obtained *ortho*-alkenylated benzaldehydes are transformed into the corresponding indene and naphthalene derivatives. Chapter 3 describes annulation of α,β -unsaturated imine and alkyne to afford 1,2-dihydropyridine under inexpensive cobalt catalysis. The reaction likely proceeds via olefinic C–H bond alkenylation followed by electrocyclization of the resulting azatriene intermediate. Chapter 4 describes cobalt-catalyzed branched-selective hydroarylation of β -substituted styrenes. The same catalytic system promotes isomerization of allyl, homoallyl, and bishomoallylbenzenes to the corresponding β -substituted styrenes and hydroarylation of the resulting β -substituted styrenes to afford the corresponding 1,1-diarylalkanes.

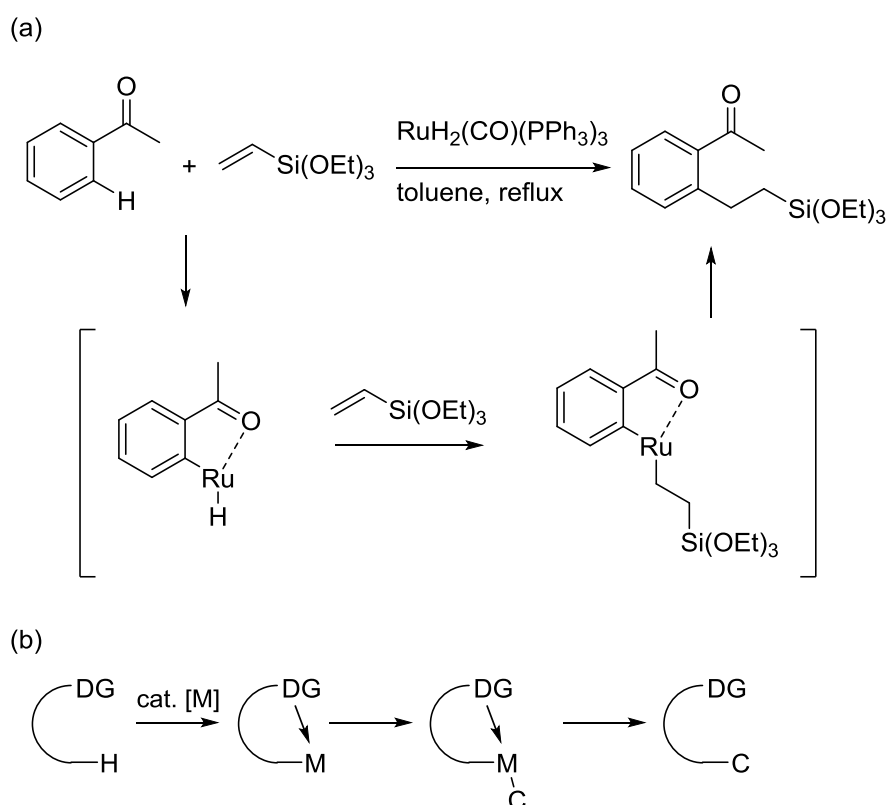
1.1 Directing Groups in Chelation-Assisted C–H Bond Activation

Efficient and selective transformation of simple and readily available starting materials into complex organic molecules with minimum waste is among the most important tasks in synthetic organic chemistry. In this context, direct conversion of ubiquitous C–H bonds to C–C and C–heteroatom bonds, so-called C–H functionalization, has received considerable attention of the synthetic community over the last decades. Such processes allow us to increase molecular complexity without the need for prefunctionalized starting materials such as organic halides and organometallic reagents, which are, for example, used in conventional cross-coupling reactions.¹ However, while the efficiency and regioselectivity of the cross-coupling reaction are ensured by the reactive carbon-halogen and carbon-metal bonds, selective functionalization of a specific C–H bond in an organic molecule is not a trivial task because of the inertness and ubiquity of C–H bonds. Thus, to achieve practically useful C–H functionalization, we always need to address issues of reactivity and selectivity.

One of the most powerful strategies for efficient and selective C–H functionalization relies on the ability of a transition metal complex to promote cleavage of a C–H bond in the proximity of a heteroatom-based functional group and to form a metalacycle complex. While such a process, often called cyclometalation, had been known for a series of transition metals on the periodic table since the early 1960's,² its relevance to catalytic C–H functionalization became particularly clear when Murai and co-workers reported on ruthenium-catalyzed *ortho*-alkylation of aryl ketones with terminal olefins in 1993 (Scheme 1.1a).³ Regardless of the actual mechanistic complexity,⁴ this reaction can be understood by a catalytic cycle consisting of three fundamental reaction steps, that is, oxidative addition of the *ortho*-C–H bond to

ruthenium with the assistance of the coordination of the oxygen atom, migratory insertion of olefin into the Ru–H bond, and reductive elimination of the resulting alkyl(aryl)ruthenium species. This catalytic cycle provided an important implication that appropriate combination of cyclometalation and other elementary reactions could lead to a variety of C–H bond functionalization reactions. Indeed, since this groundbreaking discovery, a huge numbers of C–C bond formation reactions via chelation-assisted C–H bond activation have been reported, which include alkylation,^{5,6} alkenylation,^{7,8} arylation,⁹ and alkynylation (Scheme 1.1b).¹⁰

Scheme 1.1. Transition Metal-Catalyzed Chelation-Assisted C–H Bond Functionalization



1.2 Chelation-Assisted Insertion of C–C Multiple Bonds into C(sp²)–H Bonds

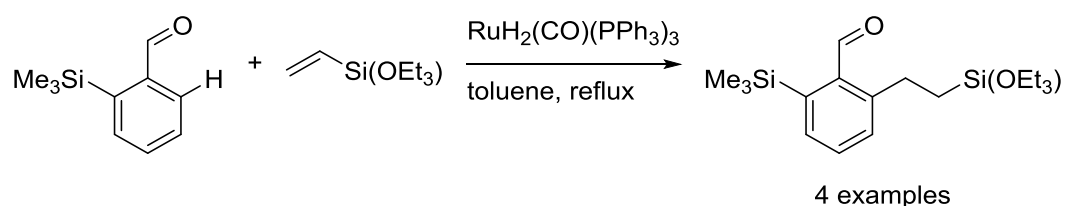
Among directed transformations of C–H bonds into C–C bonds, catalytic insertion of a C–C multiple bond into a C–H bond is highly attractive because the overall process does not produce any byproducts. The Murai reaction (Scheme 1.1a) is important

not only because it represents an archetypal example of such atom-economical transformations but also because it has opened a new approach to aromatic alkylation that complements the classical Friedel–Crafts alkylation. Since the discovery of this reaction, extensive studies have been performed on the development of chelation-assisted insertion of alkenes and alkynes into C(sp²)–H bonds using late transition metal catalysts. The following subsections describe the scope and limitations of such transformations from a few different aspects, which was known as of the time when we embarked on the present study.

1.2.1 Directing Groups

Besides ketone directing groups¹¹ that were used originally in the Murai reaction, a series of directing groups have been used in hydroarylation of alkenes and alkynes. Nitrogen-based directing groups such as pyridines,¹² ketimines,¹³ imidates,¹⁴ hydrazones¹⁵, or imidazoles¹⁶ have been successfully employed in hydroarylation reactions mainly using rhodium catalysts. Other directing groups such as esters¹⁷ and nitriles¹⁸ also proved to serve as directing groups for ruthenium-catalyzed hydroarylation of alkenes. However, despite its potential utility, formyl group has rarely been used as a directing group for hydroarylation (Scheme 1.2)¹⁹ due to the propensity of aldehyde to undergo decarbonylation²⁰ or hydroacylation²¹ in the presence of transition metals.

Scheme 1.2. Aldehyde-Directed Hydroarylation of Olefin

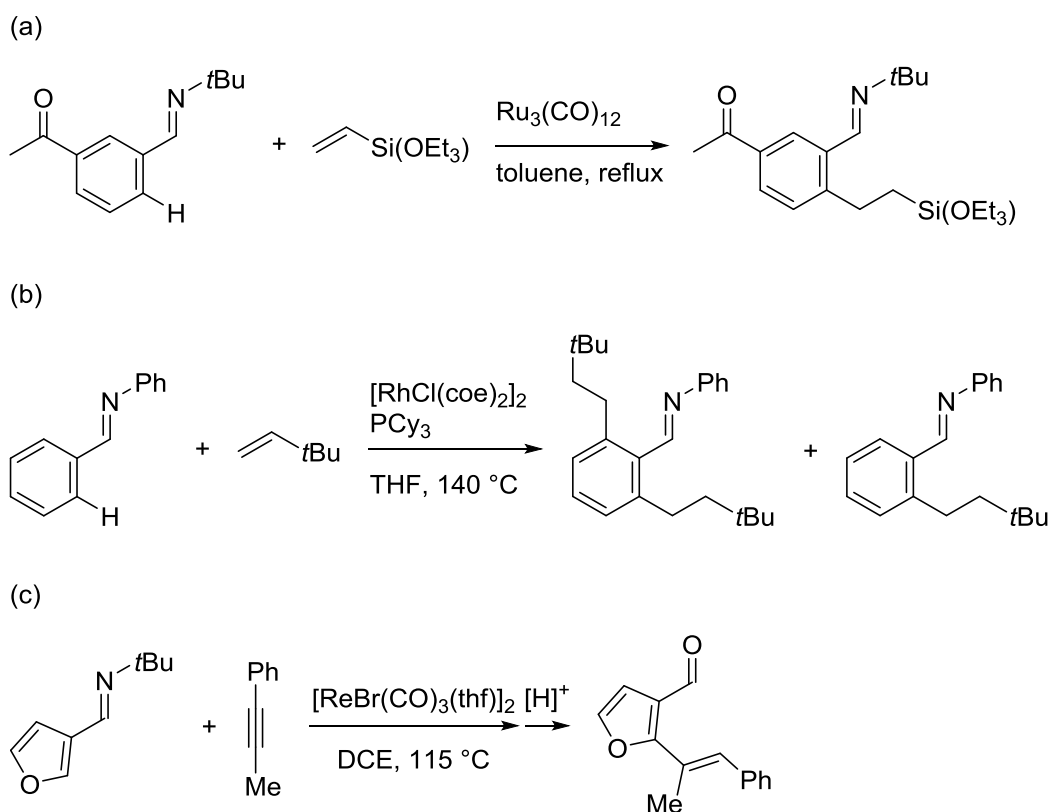


Aldimine, which is readily interconvertible with aldehyde, has also been rarely

Chapter 1

employed as a directing group for hydroarylation. Murai and co-workers reported a few examples of ruthenium-catalyzed hydroarylation of an olefin or an alkyne with an aryl aldimine (Scheme 1.3a).²² Lim and co-workers reported that a rhodium(I) catalyst promotes the addition of an aryl aldimine to an olefin, which tends to produce a dialkylation product even the use of the aldimine as a limiting reagent (Scheme 1.3b).²³ Kuninobu and Takai reported rhenium-catalyzed *ortho*-alkenylation of heteroaryl aldimines with alkynes (Scheme 1.3c).²⁴ Besides a limitation in scope, aldimine-directed hydroarylation is worthwhile to be improved because a transformation of the resulting *ortho*-functionalized aryl aldimine involving both an aldimine and a newly introduced functional group allows a unique synthetic approach to carbocycles.

Scheme 1.3. Aldimine-Directed Catalytic Addition of C–H Bond to C–C Multiple Bonds

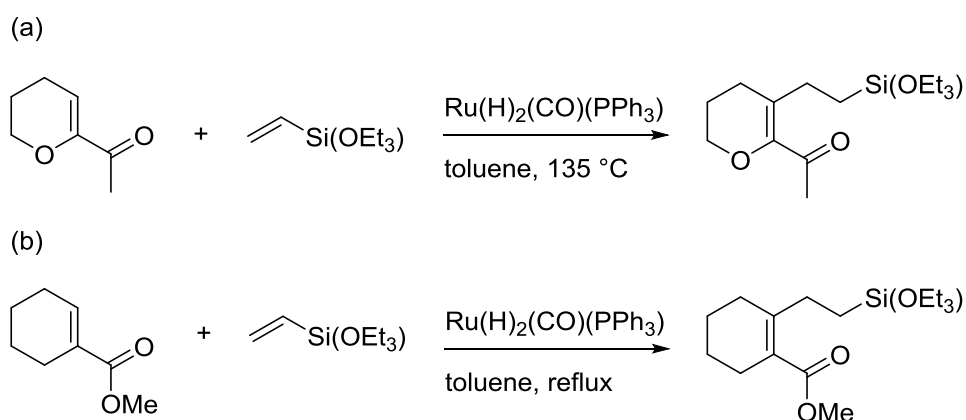


1.2.2 Olefins as C–H Donors

Direct functionalization of olefinic C–H bond allows a stereoselective synthesis

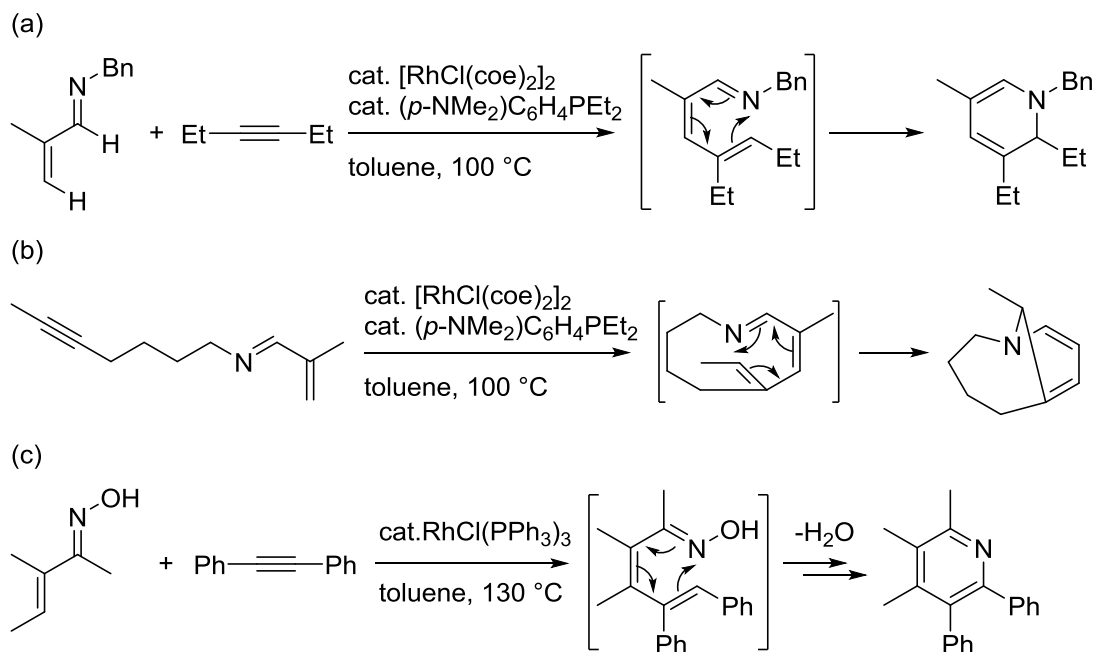
of multi-substituted olefin. Not as extensive as arene functionalization, several examples on direct functionalization of olefinic C–H bond functionalization were reported.²⁵ As a logical extension of the Murai's olefin hydroarylation using acetophenone derivatives,³ the group of Murai²⁶ and Trost²⁷ independently reported on a ruthenium-catalyzed β -alkylation reaction of an α,β -unsaturated ketone or ester to a vinylsilane, which represents the first example of this class of olefinic C–H functionalization (Scheme 1.4).

Scheme 1.4. Addition of Olefinic C–H Bonds to Vinylsilane



Building on Jun's²⁸ and their own²⁹ studies on imine-directed hydroarylation of olefins and alkynes, the group of Bergman and Ellman reported a synthesis of 1,2-dihydropyridine from an α,β -unsaturated imine and an alkyne under rhodium(I) catalysis via olefinic alkenylation/electrocyclization cascade (Scheme 1.5a).^{29,30} They applied the same transformation to an alkyne-tethered α,β -unsaturated imine to afford a bicyclic enamine with bridgehead (Scheme 1.5b).³¹ Cheng also reported a similar cascade reaction of an oxime and an alkyne to afford a pyridine by a sequence of rhodium(I)-catalyzed olefinic alkenylation, electrocyclization, and dehydration. (Scheme 1.5c).³² These facile cascade reactions represent uniqueness of the transformation of olefinic C–H bonds and afford multi-substituted *N*-heterocycles that are not easily accessible with an existing method.

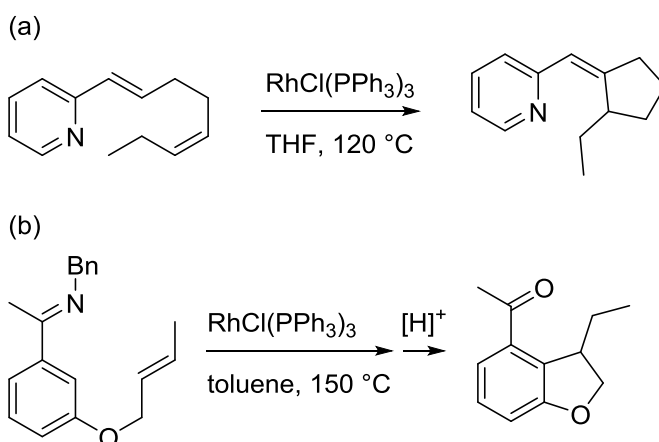
Scheme 1.5. Synthesis of Heterocycles via Olefinic C–H Alkenylation/Cyclization Cascade.



1.2.3 Internal Olefins as C–H Acceptors

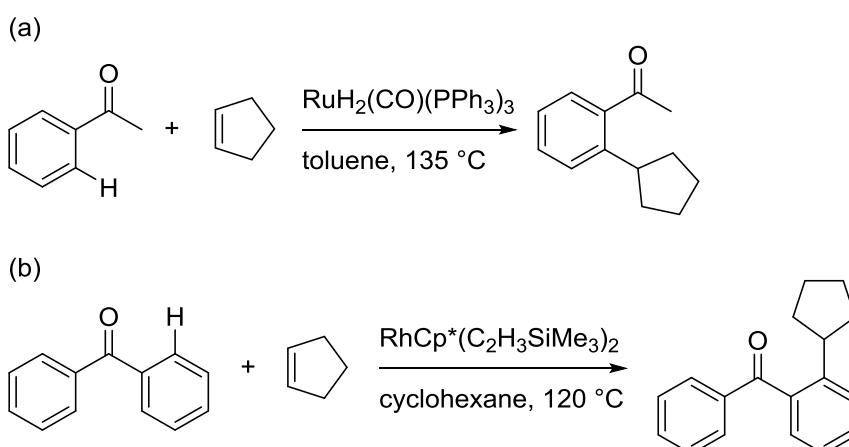
While a significant progress has been made for hydroarylation, there still lies some limitation in scope especially for intermolecular hydroarylation. An internal olefin is rarely used due to its propensity to undergo isomerization under transition metal catalysis and its steric hinderance. Several examples of intramolecular hydroarylation of internal olefin have been reported. Murai and co-workers reported pyridine, oxazole, or imidazole-directed rhodium-catalyzed intramolecular hydroarylation to afford a cyclized product (Scheme 1.6a).³³ The group of Bergman and Ellman reported annulation of aryl imine (Scheme 1.6b).³⁴ Diastereoselective and enantioselective annulation reactions were achieved with the aid of chiral directing group³⁵ and ligand,³⁶ respectively.

Scheme 1.6. Intramolecular Annulation involving C–H Bond Addition to an Internal Olefin



A few examples were reported on intermolecular hydroarylation of internal olefin. Murai reported hydroarylation of cyclopentene with aryl ketones under ruthenium catalysis (Scheme 1.7a).³⁷ Brookhart also reported hydroarylation of cyclopentene with aryl ketone under rhodium catalysis (Scheme 1.7b).³⁸ Hydroarylation of norbornene was achieved³⁷ and was extended to an asymmetric version.^{11e,39}

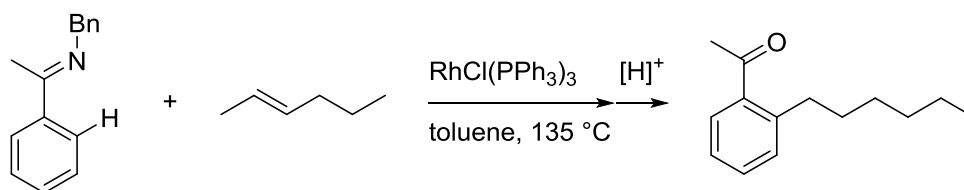
Scheme 1.7. Hydroarylation of Cyclopentene with Aromatic Ketones



A Notable example was reported by Jun and co-workers (Scheme 1.8).⁴⁰ The reaction of (*E*)-2-hexene and aryl ketimine under Wilkinson complex afforded a primary

alkylated aryl ketimine rather than a secondary alkylated product exclusively. This result suggests that isomerization of the stable internal olefin to an unstable but reactive olefin occurs prior to C–C bond formation. However, only limited internal olefins were employed in intermolecular hydroarylation reactions.

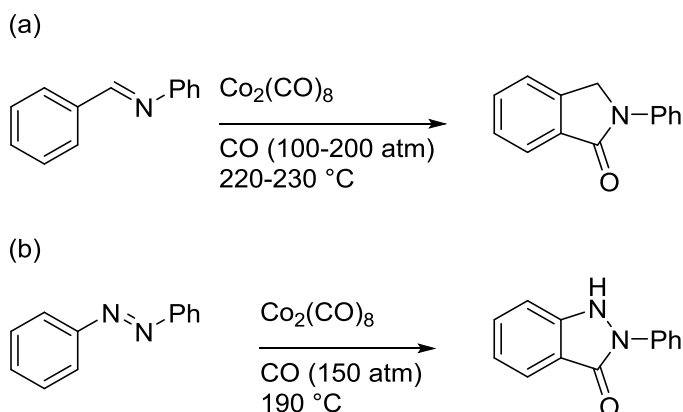
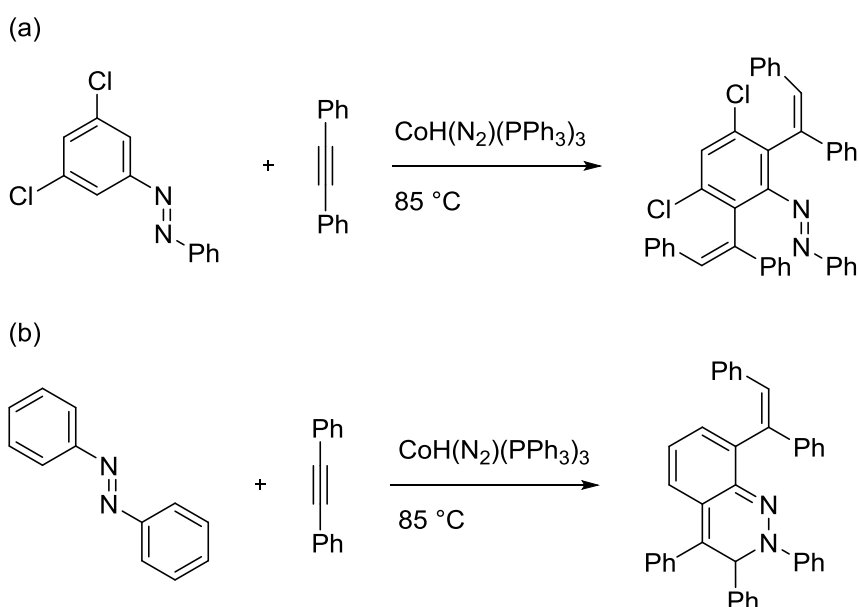
Scheme 1.8. Primary Alkylation of Aryl Ketimine with Internal Olefin



1.3 Cobalt-Mediated/Catalyzed Chelation-Assisted C–H Bond Activation

As discussed above, rhodium and ruthenium were often employed in hydroarylation as metal catalysts. On the other hand, our group has focused on developments of cobalt catalysts in hydroarylation based on early examples of cobalt-catalyzed C–H bond activation reactions and systematic studies on cobalt-mediated cyclometalation.

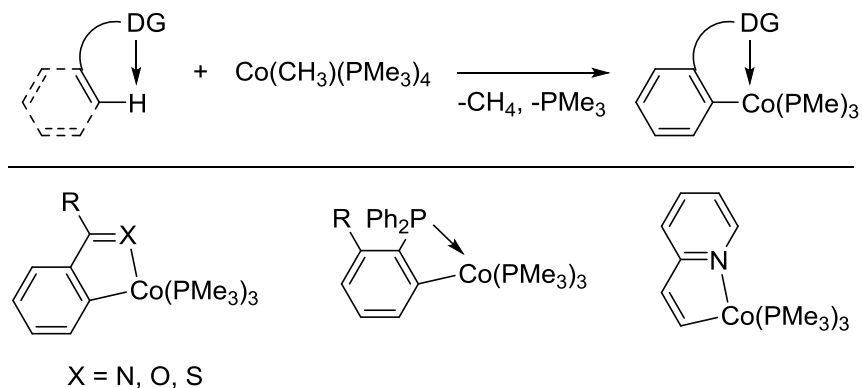
To the best of my knowledge, cobalt is the first metal catalyst in chelation-assisted C–H bond functionalization. Murahashi reported carbonylation of azobenzenes (Scheme 1.9a) and Schiff base (Scheme 1.9b) under high pressure of carbon monoxide with cobalt catalyst in the 1950's.^{41,42} In 1994, Kisch and co-workers reported *ortho*-alkenylation of azobenzenes with diphenylacetylene to afford *ortho*-alkenylated azobenzenes (Scheme 1.10a) or 2,3-dihydrocinnolines after alkenylation/cyclization cascade (Scheme 1.10b).⁴³ Substrates determine whether cyclization occurs or not. These early reports demonstrated the catalytic activity of cobalt complex in chelation-assisted C–H bond functionalization.

Scheme 1.9. Cobalt-Catalyzed Direct Carbonylation of Azobenzene and Schiff Base**Scheme 1.10.** Early Examples of Cobalt-Catalyzed C–H Bond Alkenylation with Alkynes

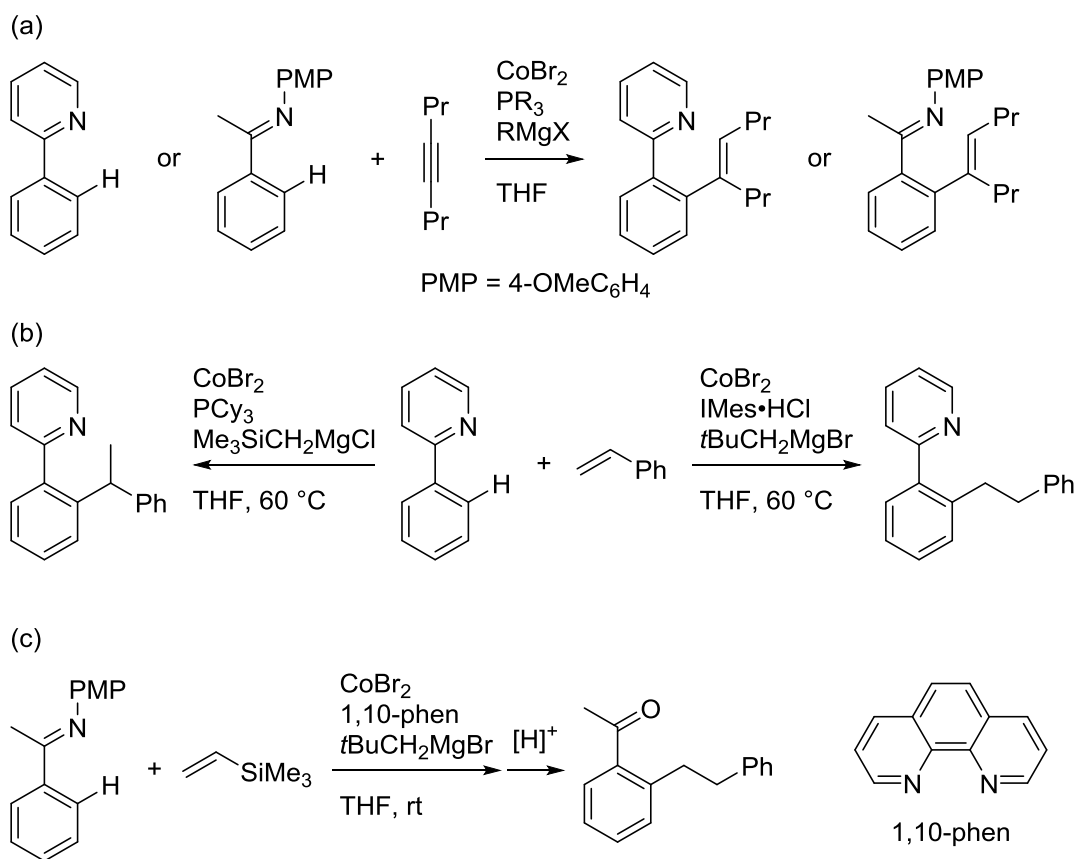
Klein and co-workers reported a series of chelation-assisted cyclometalation reaction with well-defined cobalt complex (Scheme 1.11). In 1993, they reported a methylcobalt(I)–phosphine complex $\text{MeCo}(\text{PMe}_3)_4$ underwent cyclometalation of azobenzene under mild conditions.⁴⁴ Although the actual mechanism has not been elucidated yet, they proposed a following mechanism. The reaction was initiated by oxidative addition of the *ortho*-C–H bond to the cobalt(I) center, followed by reductive elimination of methane. The same cobalt complex also reacts with aromatic and olefinic substrates bearing nitrogen, oxygen, sulfur, and phosphorus directing groups to form the

corresponding cobaltacycles.⁴⁵

Scheme 1.11. Cyclometalation of Methylcobalt (I) Complex.

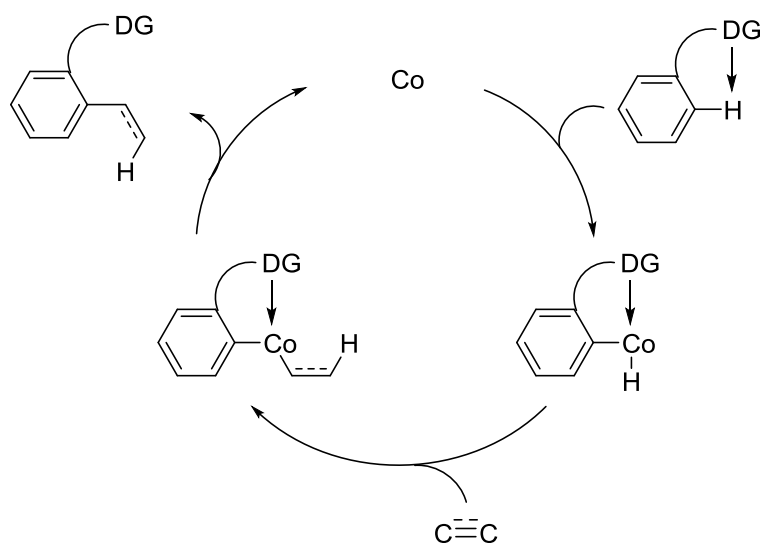


Based on these cyclometalation reaction and early examples of catalytic chelation-assisted C–H bond activation reaction, our group started to develop cobalt-catalyzed chelation-assisted C–H bond functionalization and found that a catalytic system consisting of cobalt(II) bromide, methylmagnesium bromide, and monodentate phosphine ligand efficiently promoted *ortho*-alkenylation of 2-phenylpyridines and aryl ketimines with alkynes (Scheme 1.12a).⁴⁶ Our group also reported regioselectivity-switchable hydroarylation of styrenes with 2-phenylpyridines (Scheme 1.12b).⁴⁷ While a catalytic system prepared from CoBr_2 , $\text{IMes}\cdot\text{HCl}$, and $t\text{BuCH}_2\text{MgBr}$ afforded typical linear adducts, a catalytic system prepared from CoBr_2 , PCy_3 and $\text{Me}_3\text{SiCH}_2\text{MgCl}$ afforded atypical branched-adducts. Our group achieved hydroarylation of vinylsilane with aryl ketimines under a catalytic system consisting of CoBr_2 , 1,10-phenanthroline and $t\text{BuCH}_2\text{MgBr}$ (Scheme 1.12c).⁴⁸

Scheme 1.12. Cobalt-Catalyzed Hydroarylation of C–C Multiple Bonds

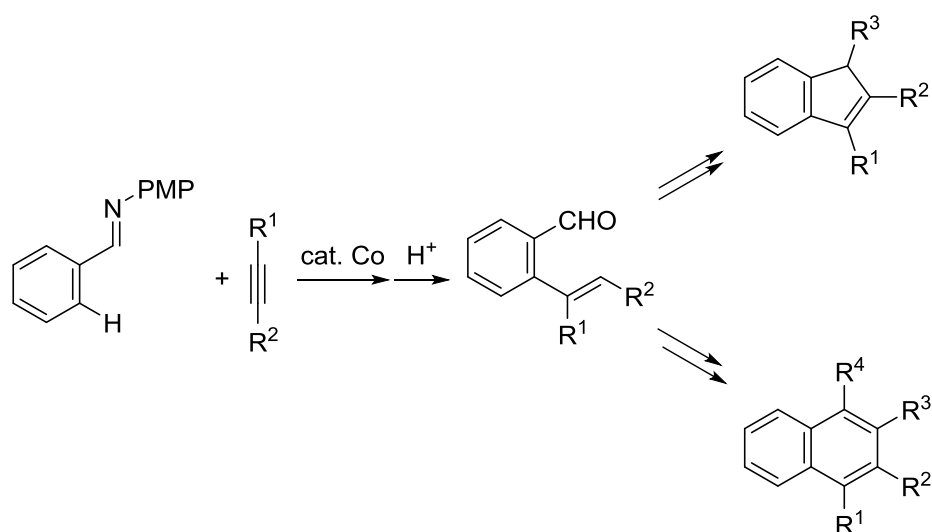
I propose a possible catalytic cycle shown in Scheme 1.13. The cycle begins with oxidative addition of the *ortho*-C–H bond to a catalytic species prepared from cobalt(II) bromide, ligand, and Grignard reagent. Insertion of C–C multiple bonds into the Co–H bond followed by reductive elimination of the resulting diorganocobalt species furnishes an *ortho*-functionalized product and regenerates the catalytic species.

Scheme 1.13. Working Hypothesis for Cobalt-Catalyzed Hydroarylation of C–C Multiple Bonds

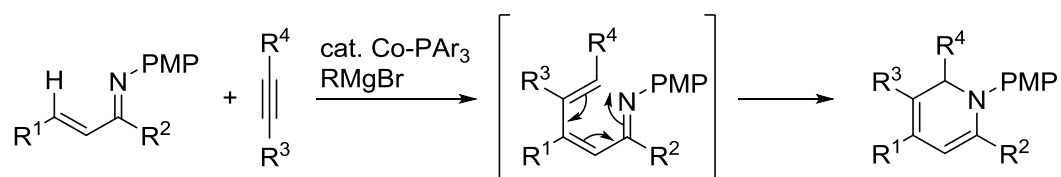


1.4 Scope and Summary of Thesis Research

As the catalytic system prepared from cobalt salt, ligand, and Grignard reagent efficiently promoted hydroarylation of alkynes, styrenes and vinylsilanes, we decided to investigate further scope of our catalytic system, focusing on insertion of C–C multiple bond into C(sp²)–H bond. Chapter 2 describes cobalt-catalyzed hydroarylation of alkynes with aryl aldimines (Scheme 1.14). The catalytic system consisting of cobalt(II) bromide, isopropylmagnesium bromide, and triarylphosphine ligand efficiently promoted simple alkenylation. The obtained *ortho*-alkenylated arylaldehyde, which is not easy to prepare with an existing method, is transformed to carbocycles such as indenes and naphthalenes.

Scheme 1.14. Cobalt-Catalyzed *Ortho*-Alkenylation of Aryl Aldimines with Alkynes

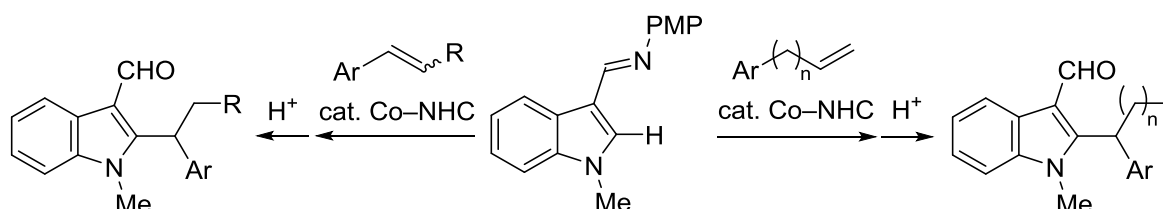
Chapter 3 describes annulation of α,β -unsaturated imines and alkynes under a catalysis prepared from cobalt(II) bromide, isopropylmagnesium bromide, and triarylphosphine ligand (Scheme 1.15). The present reaction likely proceeds via cobalt-catalyzed olefinic C–H bond alkenylation followed by facile 6π -electrocyclization to afford 1,2-dihydropyridines.

Scheme 1.15. Synthesis of 1,2-Dihydropyridines via Olefinic C–H Bond Alkenylation/Cyclization Cascade

Chapter 4 describes cobalt-catalyzed synthesis of 1,1-diarylalkanes from indoles bearing imine at the C3-position and β -substituted styrenes (Scheme 1.16). The present reaction conditions are applicable to non-conjugated arylalkenes such as allylbenzene, homoallylbenzene, and bishomoallylbenzene to afford the corresponding

1,1-diarylalkanes rather than a linear adduct with exclusive regioselectivity. The cobalt catalyst plays a dual role in isomerization and hydroarylation of olefin.

Scheme 1.16. Synthesis of 1,1-Diarylalkanes from Conjugated or Non-Conjugated Aryl Alkenes and 3-Iminoindoles.



Over the last four years, I have developed new cobalt-based catalysts that efficiently promote catalytic addition of aromatic or olefinic C–H bonds to C–C multiple bonds. These catalytic systems serve as alternative catalysts for reactions catalyzed by second-row transition metal catalysts. Furthermore, I found a unique catalytic system that promotes both isomerization and hydroarylation of olefin to afford 1,1-diarylalkanes, which has not been observed with second-row transition metals.

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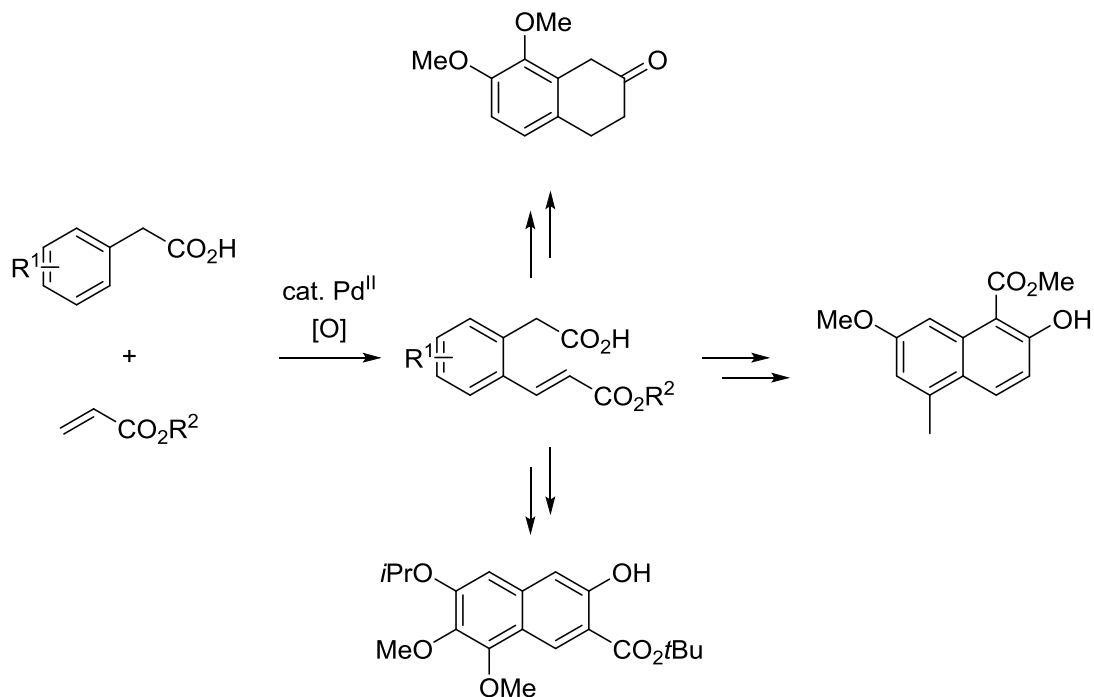
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Cobalt-Catalyzed *Ortho*-Alkenylation of Aryl Aldimines with Alkynes**2.1 Introduction**

Initiated by Murai and co-workers on ruthenium-catalyzed *ortho*-alkylation of aryl ketones with alkenes,¹ chelation-assisted C–C bond formation via C–H bond activation has become a powerful strategy for the regioselective transformation of arenes.² Besides the high regioselectivity of C–H functionalization, this strategy is particularly attractive for the construction of carbo- and heterocycles through intramolecular reaction between the directing group and the newly introduced functional group. This can be achieved by two complementary approaches, that is, (1) simple C–H bond functionalization followed by appropriate functional group interconversion and intramolecular cyclization and (2) direct annulation through sequential C–H bond functionalization/intramolecular cyclization. While the latter direct approach allows straightforward construction of a specific type of carbo- and heterocycles in one shot, the former stepwise approach enables, depending on the versatility of the directing group, construction of a diverse set of cyclic structures in a flexible manner. An illustrative example of the first strategy was reported by Yu and co-workers (Scheme 2.1). They developed a carboxylate-directed Pd(II)-catalyzed oxidative C–H olefination reaction of phenylacetic acid derivatives.³ The thus-obtained *ortho*-alkenylated phenylacetic acid derivatives can be transformed into 2-tetralone and naphthoic acid derivatives.

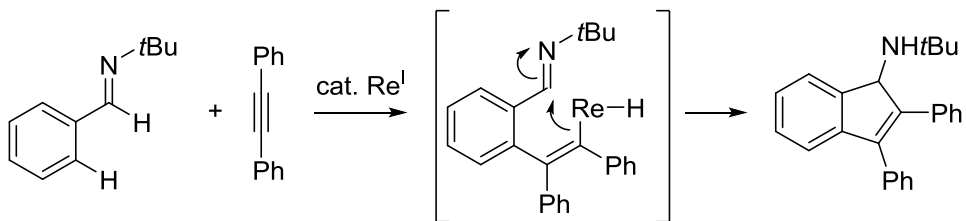
Scheme 2.1. Oxidative Heck Reaction of Phenylacetic Acid and Its Application to Carbocycle Synthesis.



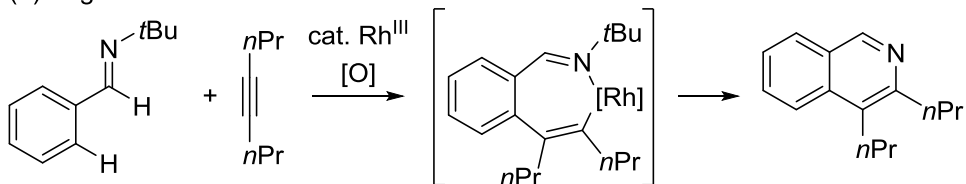
Among numerous examples of the second strategy, two research groups reported on functionalization/annulation reactions using aryl aldimine and alkyne as substrates. Kuninobu, Takai, and co-workers developed a rhenium-catalyzed annulation reaction for the synthesis of indene derivatives (Scheme 2.2a).⁴ The reaction probably involves insertion of alkyne into an arylrhenium species followed by intramolecular nucleophilic attack of the resulting alkenylrhenium species to the C=N bond.⁵ Fagnou and co-workers developed a rhodium-catalyzed oxidative annulation reaction leading to an isoquinoline derivative through C–N reductive elimination of an alkenylrhodium(III) intermediate (Scheme 2.2b).^{6,7,8} While these reactions are mechanistically intriguing and useful for the direct synthesis of indene and isoquinoline derivatives, simple *ortho*-alkenylation of aryl aldimine with alkyne would also be attractive in light of synthetic versatility of the aldimine functionality. Nevertheless, such reactions have rarely been achieved.^{9,10}

Scheme 2.2. Synthesis of Aminoindene and Isoquinoline via *Ortho*-Alkenylation/Cyclization Cascade.

(a) Kuninobu and Takai et al



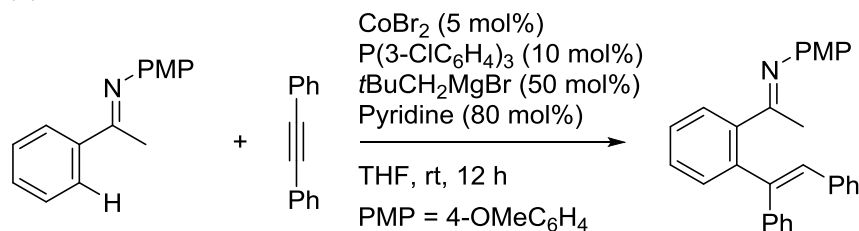
(b) Fagnou et al



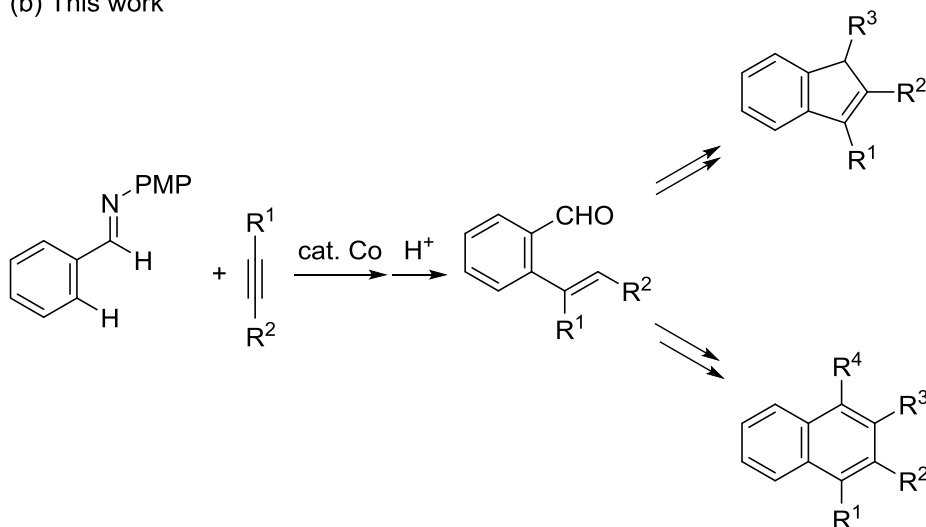
Recently, our group developed a catalytic system consisting of CoBr₂, P(3-ClC₆H₄)₃, neopentylmagnesium bromide, and pyridine, which efficiently promotes an *ortho*-alkenylation reaction of aryl ketimines with alkynes under mild conditions (Scheme 2.3a).¹¹ This and other cobalt-based catalytic systems we have developed for chelation-assisted C–H functionalization^{12,13,14} prompted us to develop a new catalytic system for *ortho*-alkenylation of aldimines with alkynes, which is reported herein (Scheme 2.3b). The reaction affords *ortho*-alkenylated aryl aldehydes in moderate to good yields under mild conditions. Furthermore, the alkenyl and aldehyde functional groups in the product can be utilized for the construction of indene and naphthalene carbocycles.

Scheme 2.3. Cobalt-Catalyzed *Ortho*-Alkenylation of Aryl Imines with Alkynes.

(a) Yoshikai et al



(b) This work

**2.2 Results and Discussion**

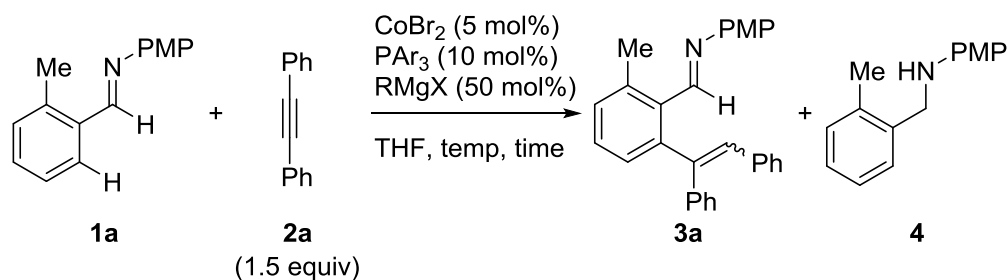
This study has commenced with imine **1a**, derived from 2-methylbenzaldehyde and *p*-anisidine, and diphenylacetylene **2a** as model substrates. Using a catalyst generated from 5 mol% of CoBr_2 , 10 mol% of $\text{P}(3\text{-ClC}_6\text{H}_4)_3$, 50 mol% of neopentylmagnesium bromide and 80 mol% of pyridine, which was effective for the *ortho*-alkenylation of aryl ketimines with alkynes (Scheme 2. 3a),¹¹ the desired *ortho*-alkenylated product **3a** was obtained in 29% yield at room temperature in 3 h (Table 2.1, entry 1). When pyridine was omitted from the catalytic system, the yield was improved to 39% (entry 2). In both cases, a poor mass balance was observed. Thus, the recovery of aldimine **1a** was only 13% and 6% in entries 1 and 2, respectively, for unknown reasons.

Upon brief screening of triarylphosphine ligands, we found that a better mass

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balance was achieved using P(4-MeC₆H₄)₃ instead of P(3-ClC₆H₄)₃. The desired product **3a** was obtained in 26% yield with an *E/Z* ratio of 62:38 determined by ¹H NMR analysis, which was accompanied by the recovered starting material **1a** in 68% yield (entry 3). Raising the temperature to 60 °C slightly improved the yield of **3a** to 44% with a sizable change in the *E/Z* ratio (41:59) with a recovery of **1a** in 48 % yield (entry 4).

Next, a series of Grignard reagents were examined to improve the catalytic activity at 60 °C. Using PhMgBr, **3a** was obtained in 55% yield with an *E/Z* ratio of 25:75 (entry 5). MeMgCl also slightly improved the yield of **3a** (60%, *E/Z* = 17:83; entry 6). In all the cases, formation of a small amount (6%) of amine **4**, which arose from reduction of the C=N bond by Grignard reagent, was observed. The use of *n*BuMgBr afforded **3a** and **4** in 68% and 32% yields, respectively (entry 7). Among the Grignard reagents we screened, *i*PrMgBr showed the highest catalytic activity¹⁴ to afford the desired product **3a** and **4** in 88% and 12% yields, respectively (entry 8). In the latter three cases, the product was obtained as a mixture of *E/Z* (ca. 2:8) isomers. The formation of amine **4** was suppressed by performing the reaction using 20 mol% of the ligand at room temperature for 12 h without significant decrease in the yield of **3a** (entry 9). Notably, these modifications of the reaction conditions had a significant influence on the *E/Z* ratio of **3a** (79:21). The difference of the *E/Z* isomer ratio could be explained as follows. Isomerization of the kinetically favored *E*-isomer to the thermodynamically favored *Z*-isomer was suppressed at lower temperature. Detailed mechanism of isomerization is not clear. The use of P(3-MeC₆H₄)₃ instead of P(4-MeC₆H₄)₃ afforded the desired product **3a** in 87% yield with an *E/Z* ratio of 79:21 (entry 10). Further attempts to improve the stereoselectivity of *E/Z* isomers were unsuccessful.

Table 2.1. Cobalt-Catalyzed *Ortho*-Alkenylation of **1a** with **2a**^a

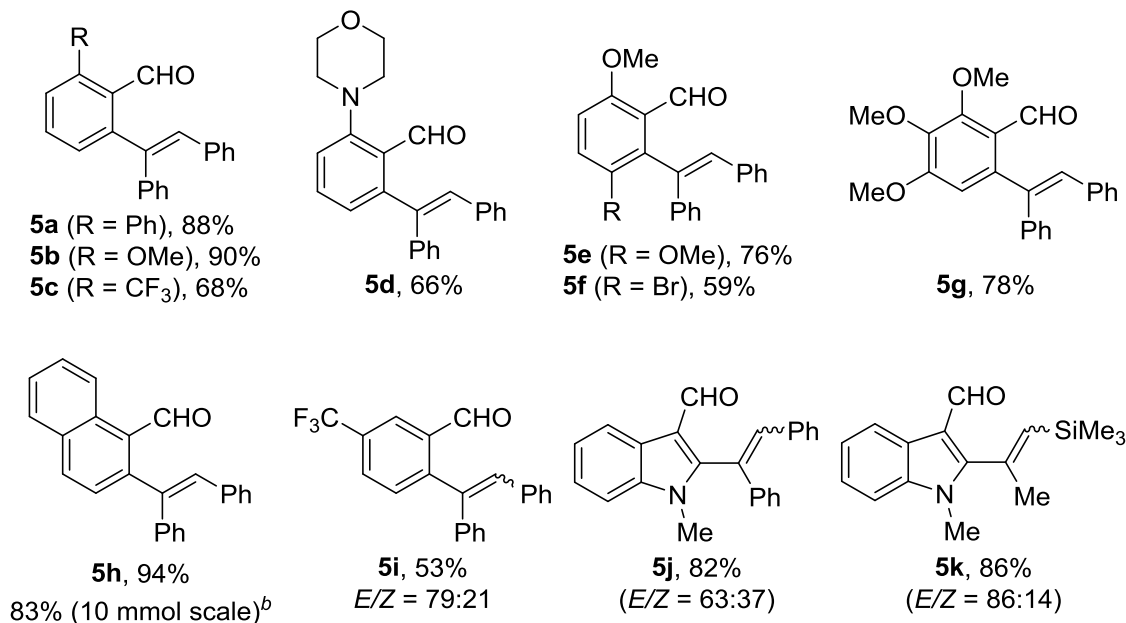
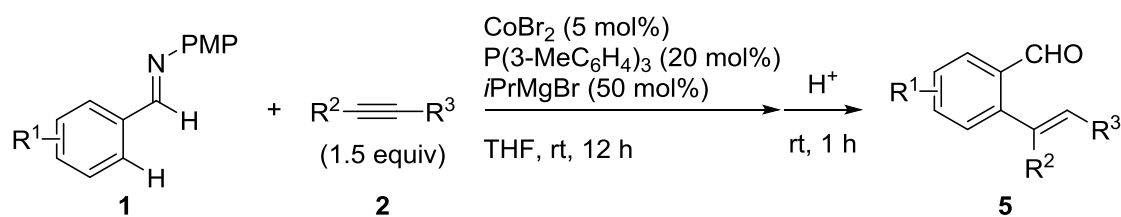
entry	PAr_3	RMgX	temp	time	yield ^b	
					3a (<i>E/Z</i>)	4
1 ^c	$\text{P}(3\text{-ClC}_6\text{H}_4)_3$	<i>t</i> BuCH ₂ MgBr	rt	3 h	29 (N.D.) ^d	0
2	$\text{P}(3\text{-ClC}_6\text{H}_4)_3$	<i>t</i> BuCH ₂ MgBr	rt	3 h	39 (N.D.) ^d	0
3	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	<i>t</i> BuCH ₂ MgBr	rt	3 h	26 (62:38)	0
4	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	<i>t</i> BuCH ₂ MgBr	60	3 h	44 (41:59)	0
5	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	PhMgBr	60	3 h	55 (25:75)	0
6	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	MeMgCl	60	3 h	60 (17:83)	6
7	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	<i>n</i> BuMgBr	60	3 h	68 (22:78)	32
8	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	<i>i</i> PrMgBr	60	3 h	88 (18:82)	12
9 ^e	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	<i>i</i> PrMgBr	rt	12 h	76 (79:21)	2
10 ^e	$\text{P}(3\text{-MeC}_6\text{H}_4)_3$	<i>i</i> PrMgBr	rt	12 h	87 (79:21)	4

^a Reaction was performed on a 0.3 mmol scale. ^b Determined by GC (entries 1 and 2) or ¹H NMR (entries 3-10). ^c Pyridine (80 mol%) was added. ^d N.D. = not determined. ^e 20 mol% of ligand was used.

With the optimized conditions in hand, I explored the scope of the *ortho*-alkenylation reaction (Scheme 2.4). First, a variety of aryl aldimines were subjected to the reaction with diphenylacetylene **1b**. Aryl aldimines bearing phenyl, methoxy, and trifluoromethyl groups at the *ortho*-position smoothly participated in the reaction to afford, upon hydrolysis, the corresponding *ortho*-alkenylated aldehydes **5a-5c** in moderate to high yields. Notably, unlike the case of the model reaction (Table 2.1, entry 10), these alkenylated products were isolated as *E*-isomers with exclusive selectivity. An aldimine bearing morpholino group at the *ortho*-position was also amenable to the reaction.

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Multi-substituted substrates such as 2,5-dimethoxy, 2-methoxy-5-bromo- and 2,3,4-trimethoxy substituted aldimines took part in the reaction to afford the desired *ortho*-alkenylated products **5e**, **5f**, and **5g**, respectively, in good yields. Notably, the C–Br bond of the 2-methoxy-5-bromo-substituted aldimine was tolerated. The reaction of imine derived from 1-naphthaldehyde afforded the desired product **5h** in 94% yield. The same reaction could be performed on a 10 mmol scale without significant decrease in the product yield. When an aryl aldimine bearing trifluoromethyl group at the *meta*-position was used, mono-alkenylation occurred exclusively at the sterically less hindered position to furnish the product **5i** in 53% yield with an *E/Z* ratio of 79:21. C2-alkenylation of imine derived from *N*-methylindole-3-carboxyaldehyde proceeded smoothly to give the product **5j** in 82% yield with an *E/Z* ratio of 63:37. 1-Trimethylsilyl-1-propyne also reacted with the same aldimine to afford the adduct **5k** in 86% yield with an *E/Z* ratio of 86:14. In this case, the C–C bond formation took place at the sterically less hindered acetylenic carbon.^{11,13b,15}

Scheme 2.4. Scope of Cobalt-Catalyzed *Ortho*-Alkenylation of Aldimines with Alkynes ^a

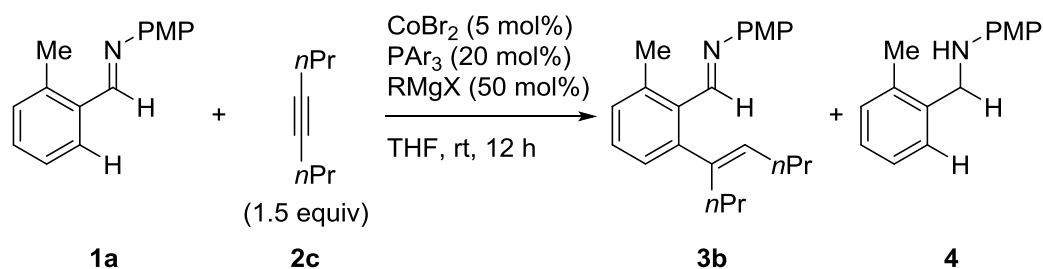
^a The reaction was performed on a 0.3 mmol scale otherwise noted. ^b Reaction was performed on a 10 mmol scale. Reaction time was 24 h.

Upon examination of the reaction of different alkynes, we found that the reaction of aryl imine **1a** and 4-octyne **2e** did not give the desired alkenylation product at all under the standard reaction conditions (Table 2.2, entry 1). Thus, we reexamined reaction conditions for this particular substrate combination. Simply by replacing $\text{P}(3\text{-MeC}_6\text{H}_4)_3$ with $\text{P}(4\text{-MeOC}_6\text{H}_4)_3$, the reaction took place to afford the desired alkenylation product **3b** in 19% yield as an *E*-isomer with exclusively selectivity (entry 2).

Next, we screened a series of Grignard reagents using $\text{P}(4\text{-MeOC}_6\text{H}_4)_3$ as the ligand. $t\text{BuCH}_2\text{MgBr}$ was entirely ineffective (entry 3). Cyclohexylmagnesium bromide and cycloheptylmagnesium bromide gave rise to moderate catalytic activities (entries 4

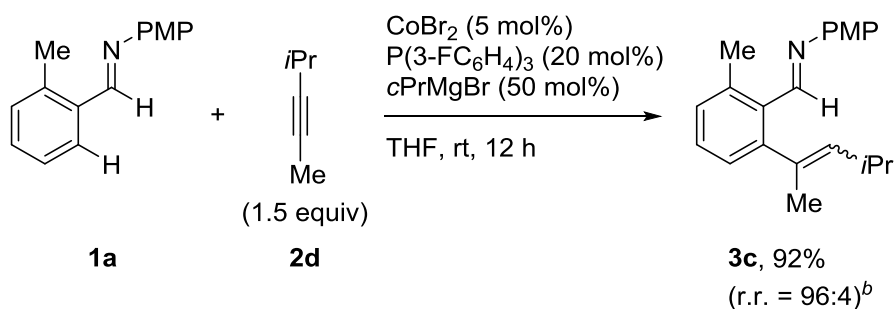
and **5**). The use of cyclopentylmagnesium bromide significantly improved the catalytic activity to afford **3b** in 40 % yield accompanied by the formation of amine **4** in 19% yield (entry 6). The use of cyclopropylmagnesium bromide also improved the catalytic activity to afford **3b** and **4** in 42% and 2% yields, respectively (entry 7). Using cyclopropylmagnesium bromide, we again screened triarylphosphine ligands. While the use of P(3-MeOC₆H₄)₃ or P(3-ClC₆H₄)₃ led to a lower catalytic activity (entries 8 and 9), the use of P(3-FC₆H₄)₃ significantly improved the catalytic activity to afford **3b** in 94% yield (entry 10). Note that, the adduct was isolated as aldimine **3b** because the adduct gave the corresponding aryl aldehyde as well as a cyclized product after acidic hydrolysis.

The reaction of **1a** and **2d** afforded *ortho*-alkenylated aldimine **3c** in 92% yield with a regioisomer ratio of 96:4 under the modified reaction conditions (Scheme 2.5). C–C bond formation dominantly occurred at the sterically less hindered acetylenic carbon. The adduct was isolated as aldimine **3c** due to formations of the corresponding aryl aldehyde and a cyclized product after acidic hydrolysis.

Table 2.2. Hydroarylation of 4-Octyne with Aryl Imine^a

entry	PAr_3	RMgX	yield ^b	
			3b	4
1	$\text{P}(3\text{-MeC}_6\text{H}_4)_3$	<i>i</i> PrMgBr	0	N.D. ^c
2	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	<i>i</i> PrMgBr	19	N.D. ^c
3	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	<i>t</i> BuCH ₂ MgBr	0	N.D. ^c
4	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	<i>c</i> HexMgBr	14	N.D. ^c
5	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	<i>c</i> HeptMgBr	27	9
6	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	<i>c</i> PentMgBr	40	19
7	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	<i>c</i> PrMgBr	42	2
8	$\text{P}(3\text{-MeOC}_6\text{H}_4)_3$	<i>c</i> PrMgBr	7	1
9	$\text{P}(3\text{-ClC}_6\text{H}_4)_3$	<i>c</i> PrMgBr	20	1
10	$\text{P}(3\text{-FC}_6\text{H}_4)_3$	<i>c</i> PrMgBr	83 (94) ^d	1

^a The reaction was performed on a 0.3 mmol scale. ^b Determined by GC (entries 1-4) or ¹H NMR (entries 5-10). ^c N.D. = not determined. ^d Isolated yield.

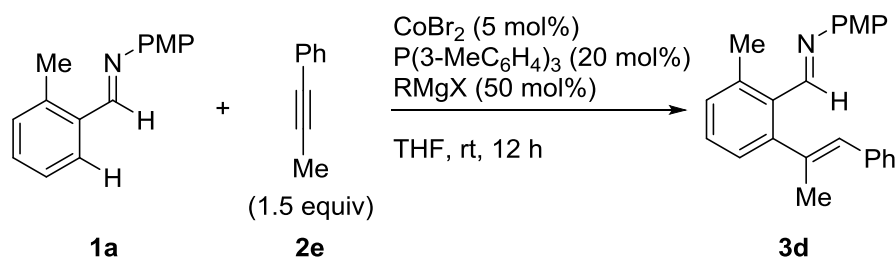
Scheme 2.5. Hydroarylation of 4-Methyl-pent-2-yne **2d** and Aryl Imine **1a**^a

^a The reaction was performed on a 0.3 mmol scale. ^b r.r. = regioisomer ratio.

We further continued the investigation of the scope of alkynes. The reaction of aryl imine **1a** with 1-phenyl-1-propyne **1e** resulted in the formation of an

ortho-alkenylated imine **3d** in less than 1% yield under the standard reaction conditions (Table 2.3, entry 1). Thus we reexamined the reaction conditions for this particular substrate combination. We screened a series of Grignard reagents to improve the catalytic activity. The use of cyclic secondary alkyl Grignard reagents such as cyclopropylmagnesium bromide or cyclohexylmagnesium bromide were ineffective (entries 2 and 3). MeMgCl and TMSCH₂MgCl did not improve the yield of product (entries 4 and 5). The use of *t*BuCH₂MgBr slightly improved the catalytic activity (entry 6). We concluded that hydroarylation of **2e** with **1a** was difficult.

Table 2.3. Attempts of Hydroarylation of 1-Phenyl-1-propyne **2e** with Aryl Imine **1a**^a



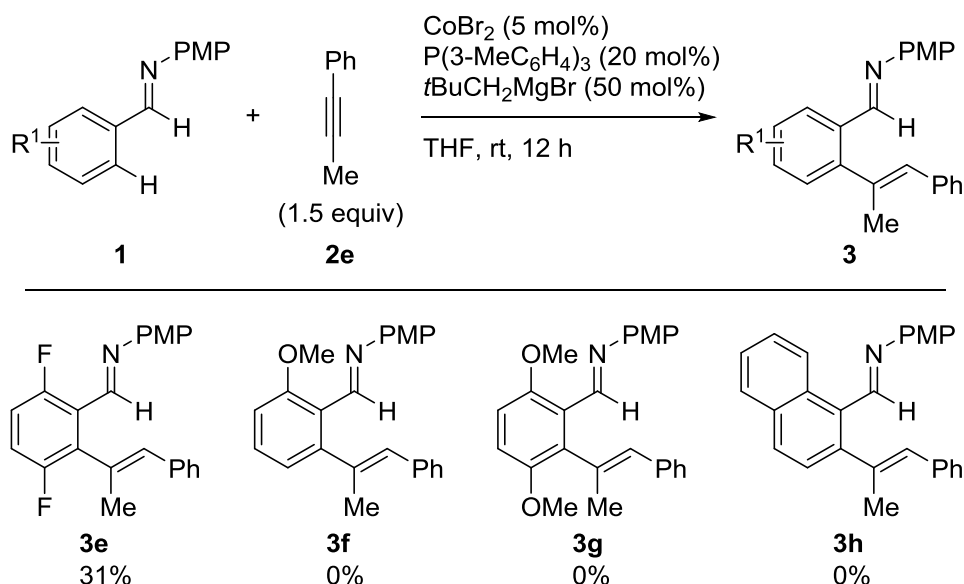
entry	RMgX	yield of 3d ^b
1	<i>i</i> PrMgBr	0.6
2	<i>c</i> PrMgBr	0.8
3	<i>c</i> HexMgBr	0.6
4	MeMgCl	0.6
5	Me ₃ SiCH ₂ MgCl	0.6
6	<i>t</i> BuCH ₂ MgBr	0.9

^a The reaction was performed on a 0.3 mmol scale. ^b Determined by GC using *n*-tridecane as an internal standard.

Next, we investigated a suitable aryl imine for hydroarylation of **2e** using *t*BuCH₂MgBr as the Grignard reagent (Scheme 2.6). Using an aryl imine derived from 2,5-difluorobenzaldehyde, a desired *ortho*-alkenylated imine **3e** was obtained in 31%

yield as a single isomer. 2-methoxy or 2,5-dimethoxy substituted aryl imines failed to take part in the reaction. An imine **1i** derived from 1-naphthaldehyde was also unreactive.

Scheme 2.6. Hydroarylation of 1-Phenyl-1-propyne **2e** with Various Aryl Imines ^a



^a The reaction was performed on a 0.3 mmol scale.

Next, we investigated additives to improve the reaction efficiency of the particular substrate combination of **1i** and **2e** (Table 2.5). While the use of DMPU or NMP as co-solvents gave rise to a poor catalytic activity, the use of TMEDA as a co-solvent slightly increased the yield of **3e** to 55% (entries 1-3). Using 80 mol% of pyridine as an additive,^{11,15a} *ortho*-alkenylated aryl imine **3e** was obtained in an almost quantitative yield (entry 4). The product was isolated without hydrolysis because acidic hydrolysis of the product afforded a mixture of the corresponding aldehyde and a cyclized product.

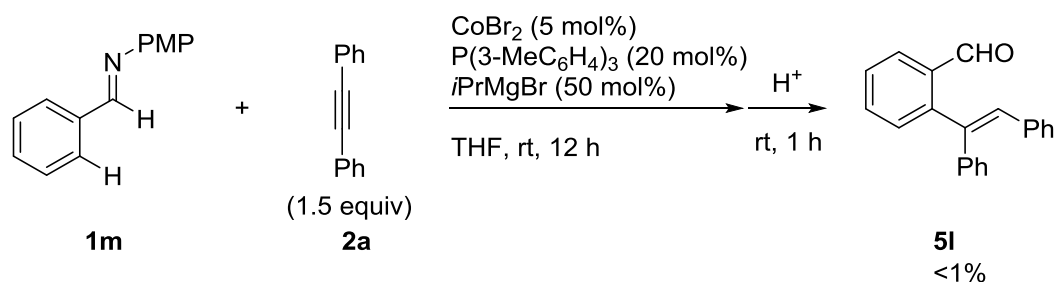
Table 2.5. Screening of Additives for Hydroarylation of 1-Phenyl-1-propyne **2e**^a

entry	additive	Amount	yield of 3e ^b
1	DMPU	Co-solvent (1:1)	20
2	NMP	Co-solvent (1:1)	11
3	TMEDA	Co-solvent (1:1)	55
4	pyridine	80 mol%	84 (97) ^c

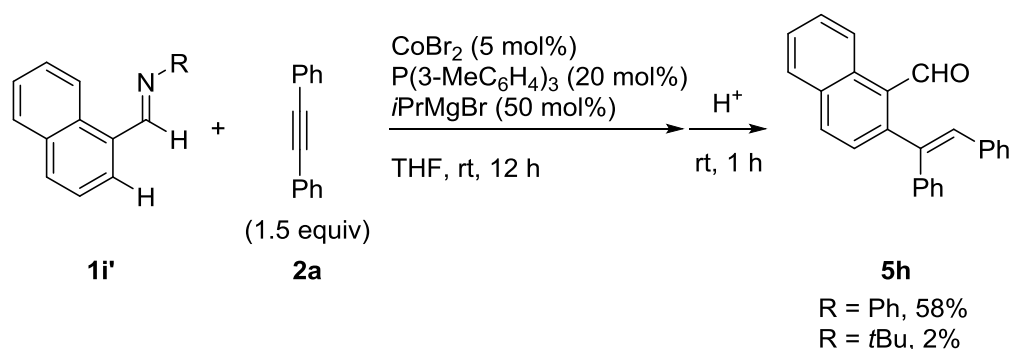
^a The reaction was performed on a 0.3 mmol scale. ^b Determined by GC using *n*-tridecane as an internal standard. ^c Isolated yield.

Rather curiously, the reaction of parent benzaldimine **1m** with diphenylacetylene **2a** under the standard reaction conditions gave only a trace amount of the expected mono-alkenylated product **5l** as judged by GC-MS analysis (Scheme 2.7). The reason for this poor reactivity is not clear at this time. We briefly examined the effect of the substituent on the nitrogen atom of the aldimine (Scheme 2.8). The reaction of 1-naphthaldimine bearing *N*-phenyl or *N*-*tert*-butyl group with diphenylacetylene afforded, upon acidic hydrolysis, the *ortho*-alkenylated product **5h** in 58% and 2% yields, respectively.

Scheme 2.7. Attempts of Hydroarylation of Imine Derived from Benzaldehyde with Diphenylacetylene

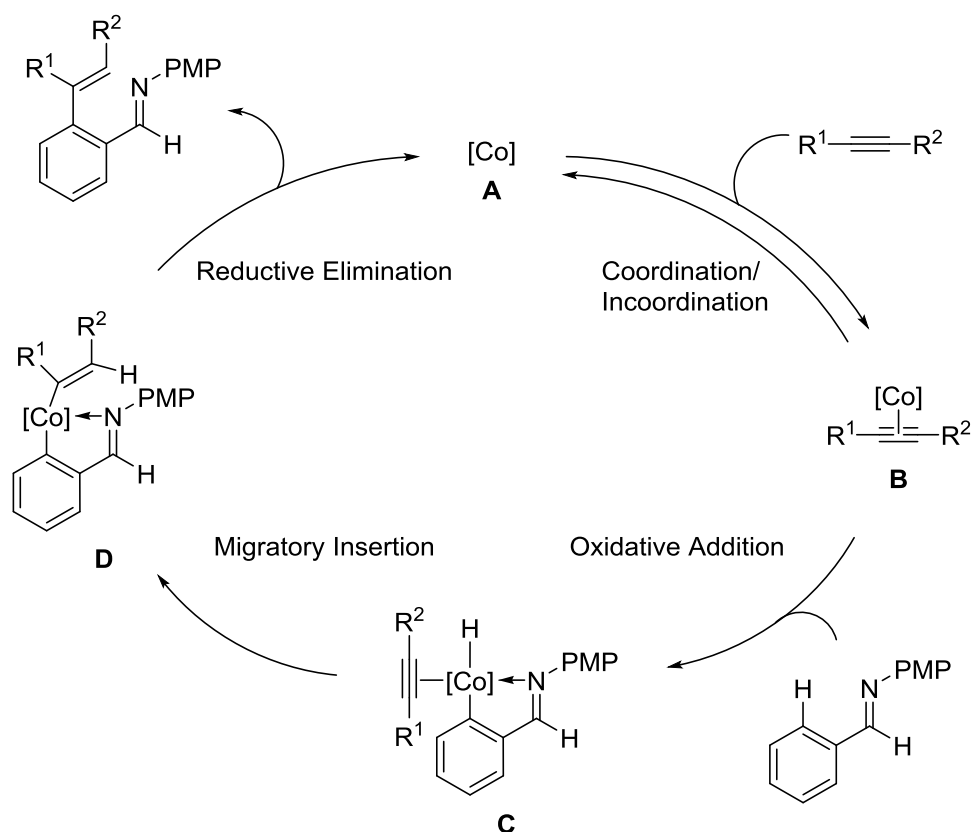


Scheme 2.8. Hydroarylation of Phenyl- or *t*-Butyl Imines with Diphenylacetylene **2a**

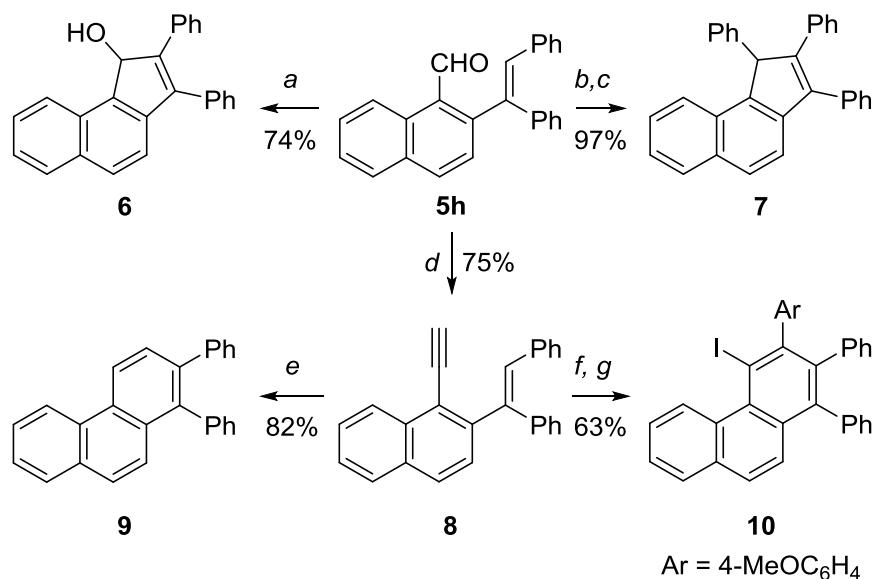


Although I have not performed any particular mechanistic study, I consider that the present reaction involves a catalytic cycle similar to that proposed for the *ortho*-alkenylation reaction of aryl ketimines (Scheme 2.9).¹¹ First, a low-valent cobalt species **A** generated from the cobalt precatalyst and isopropylmagnesium bromide undergoes reversible coordination of an alkyne. Next, the cobalt-alkyne complex **B** undergoes *ortho*-C–H bond activation assisted by the lone pair on nitrogen to form an aryl(hydrido)cobalt species **C**. Migratory insertion of alkyne into the Co–H bond of **C** affords alkenylcobalt species **D**, which undergoes reductive elimination to afford the *ortho*-alkenylated aryl aldimine and regenerates the cobalt species **A**.

Scheme 2.9. Possible Catalytic Cycle



Ortho-alkenylated aryl aldehyde **5h** was transformed into indenes and naphthalenes as shown in Scheme 2.10. BF_3 -mediated cyclization of **5h** afforded an indenol derivative **6** in 74% yield. Addition of PhLi to **5h** followed by BF_3 -mediated cyclization provided an indene derivative **7** in 97% yield over two steps. The formyl group of **5h** was transformed into an ethynyl group with a reagent prepared from trimethylsilyl diazomethane and $n\text{BuLi}$.¹⁶ The obtained terminal alkyne **8** underwent PtCl_2 -catalyzed cyclization to afford a naphthalene derivative **9** in 82% yield.¹⁷ A multi-substituted idonaphthalene derivative **10** was synthesized by the sequence of Sonogashira coupling of terminal alkyne **8** with 4-iodoanisole and NIS-mediated iodocyclization.¹⁸

Scheme 2.10. Transformation of *Ortho*-Alkenylated Aryl Aldehyde **5ia**.

a) BF₃•OEt₂ (2 equiv), CH₂Cl₂, 0 °C; b) PhLi (1.5 equiv), THF, -78 °C; c) BF₃•OEt₂ (2 equiv), CH₂Cl₂, rt; d) Me₃SiCHN₂ (1.2 equiv), BuLi (1.2 equiv), THF, -78 °C to rt; e) PtCl₂ (10 mol%), toluene, 90 °C; f) PdCl₂(PPh₃)₂ (2 mol%), CuI (1 mol%), 4-MeOC₆H₄I (2 equiv), NEt₃, 55 °C; g) NIS (3 equiv), CH₂Cl₂, 50 °C.

2.3 Conclusion

In summary, I have developed cobalt-catalyzed *ortho*-alkenylation of aryl aldimines with internal alkynes. The reaction affords a variety of *ortho*-alkenylated aromatic aldehydes in moderate to excellent yields under mild reaction conditions. The reaction generally takes place with *cis*-stereoselectivity, while significant *E/Z* isomerization is observed in some cases for unknown reasons. The alkenyl and the formyl groups allow for the construction of indene and naphthalene carbocycles.

2.4 Experimental Section**Material and Methods**

General. All reactions dealing with air- and moisture-sensitive compounds were

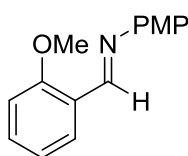
Chapter 2

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 using 40–63 mm silica gel (Si 60, Merck). ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a JEOL ECA-400 (400 MHz) spectrometer, and are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and CHCl_3 (77 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 mm film thickness). High-resolution mass spectra (HRMS) were recorded with a Q-ToF Premier LC HR mass spectrometer.

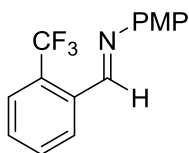
Materials. Unless otherwise noted, commercial reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. Cobalt(II) bromide (99%) were purchased from Aldrich. THF was distilled over Na/benzophenone before use. Grignard reagents except MeMgCl (purchased from Aldrich) were prepared from the corresponding halides and magnesium turnings in anhydrous THF and titrated before use.

General procedure for preparation of aromatic aldimine

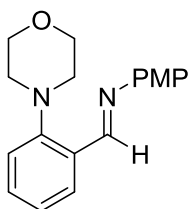
To a solution of aromatic aldehyde (50 mmol) in EtOH (100 mL) was added *p*-anisidine (60 mmol) at room temperature. After stirring for 12 h, the reaction mixture was concentrated under reduced pressure. The crude product was purified by recrystallization or silica gel chromatography. Spectral data of **1a**,¹⁹ **1b**,²⁰ **1h**,²¹ **1i**,²² and **1k**²³ showed good agreement with the literature data.



(E)-4-Methoxy-N-(2-methoxybenzylidene)aniline (1c): Purified by recrystallization from hexane/CH₂Cl₂. Yellow solid (58%); Mp = 43-44 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.83 (s, 3H), 3.90 (s, 3H), 6.91-6.96 (m, 3H), 7.03 (t, *J* = 7.8 Hz, 1H), 7.24 (app. d, *J* = 9.1 Hz, 2H), 7.42 (td, *J* = 8.0 Hz, 1.8 Hz, 1H), 8.14 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.94 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 55.6, 55.7, 111.2, 114.4 (2C), 121.0, 122.5 (2C), 125.1, 127.5, 132.5, 145.8, 154.6, 158.2, 159.5; HRMS (ESI+) Calcd for C₁₅H₁₆NO₂ [M+H]⁺ 242.1181, found 242.1184.

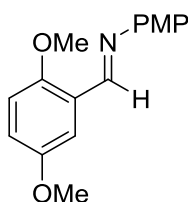


(E)-4-Methoxy-N-(2-(trifluoromethyl)benzylidene)aniline (1d): Purified by silica gel chromatography (eluent: hexane/EtOAc/NEt₃ = 20/1/1). Yellow solid (96%); Mp = 55-56 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.84 (s, 3H), 6.96 (app. d, *J* = 8.7 Hz, 2H), 7.27 (app. d, *J* = 8.7 Hz, 2H), 7.54 (t, *J* = 8.2 Hz, 1H), 7.65 (t, *J* = 7.3 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 8.44 (d, *J* = 7.8 Hz, 1H), 8.84-8.85 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 55.7, 114.7 (2C), 122.7 (2C), 124.5 (q, ¹*J*_{C-F} = 277.8 Hz), 125.9 (q, ³*J*_{C-F} = 5.7 Hz), 128.4, 129.6 (q, ²*J*_{C-F} = 31.6 Hz), 130.5, 132.2, 134.6, 144.6, 154.2, 159.0; HRMS (ESI+) Calcd for C₁₅H₁₃NOF₃ [M+H]⁺ 280.0949, found 280.0950.

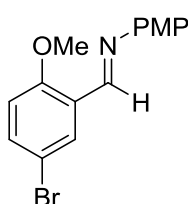


(E)-4-Methoxy-N-(2-morpholinobenzylidene)aniline (1e): Purified by recrystallization from hexane/CH₂Cl₂. Yellow solid (80%); ¹H NMR (400 MHz, CDCl₃): δ 3.02-3.04 (m,

4H), 3.85 (s, 3H), 3.86-3.89 (m, 4H), 6.95 (app. d, $J = 9.2$ Hz, 2H), 7.12 (dd, $J = 8.2, 0.9$ Hz, 1H), 7.17 (t, $J = 7.3$ Hz, 1H), 7.23 (app. d, $J = 11.9$ Hz, 2H), 7.41-7.46 (m, 1H), 8.09 (dd, $J = 7.8, 1.6$ Hz, 1H), 8.87 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 53.7, 55.5, 67.1, 114.4 (2C), 118.8, 122.2 (2C), 123.7, 128.3, 129.8, 131.7, 145.4, 153.3, 156.3, 158.2; HRMS (ESI+) Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 297.1603, found 297.1602.

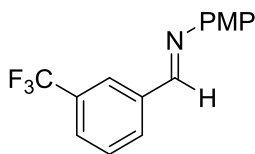


(*E*)-*N*-(2,5-Dimethoxybenzylidene)-4-methoxyaniline (1f): Purified by recrystallization from hexane/EtOAc/ CHCl_3 . Yellow solid (78%); Mp = 76-77 °C; ^1H NMR (400 MHz, CDCl_3): δ 3.83 (s, 3H), 3.86 (s, 3H), 3.86 (s, 3H), 6.88-7.01 (m, 5H), 7.24 (s, 3H), 7.68 (d, $J = 3.2$ Hz, 1H), 8.90 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 55.6, 56.0, 56.4, 110.4, 113.0, 114.5 (2C), 119.6, 122.6 (2C), 125.6, 145.7, 154.0, 154.2, 154.5, 158.3; HRMS (ESI+) Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 272.1287, found 272.1284.

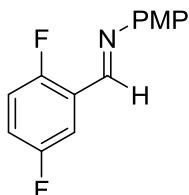


(*E*)-*N*-(5-Bromo-2-methoxybenzylidene)-4-methoxyaniline (1g): Purified by recrystallization from hexane/EtOAc/ CHCl_3 . Yellow solid (59%); Mp = 100-101 °C; ^1H NMR (400 MHz, CDCl_3): δ 3.84 (s, 3H), 3.89 (s, 3H), 6.83 (d, $J = 8.7$ Hz, 1H), 6.93 (app. d, $J = 9.2$, 2H), 7.24-7.26 (m, 2H), 7.50 (dd, $J = 9.2, 2.7$ Hz, 1H), 8.26 (d, $J = 2.7$ Hz, 1H), 8.84 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 55.7, 56.0, 113.1, 113.8, 114.5 (2C), 122.6 (2C), 126.9, 130.0, 134.7, 145.1, 152.8, 158.4, 158.6; HRMS (ESI+) Calcd for

$C_{15}H_{15}NO_2Br$ $[M+H]^+$ 322.0286, found 322.0286.



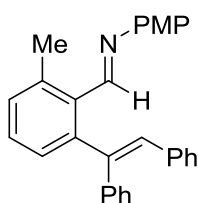
(E)-4-Methoxy-N-(3-(trifluoromethyl)benzylidene)aniline (1j): Purified by silica gel chromatography (eluent: hexane/EtOAc/ NEt_3 = 20/1/1). Dark brown solid (98%); Mp = 42-43 °C; 1H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.94 (app. d, J = 8.7 Hz, 2H), 7.26 (app. d, J = 8.7 Hz, 2H), 7.58 (t, J = 8.2 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 8.05 (d, J = 7.8 Hz, 1H), 8.17 (s, 1H), 8.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.7, 114.7 (2C), 122.6 (2C), 124.2 (q, $^1J_{C-F}$ = 274.0 Hz), 125.3 (q, $^3J_{C-F}$ = 3.8 Hz), 127.5 (q, $^3J_{C-F}$ = 3.8 Hz), 129.4, 131.5 (q, $^2J_{C-F}$ = 32.6 Hz), 131.9, 137.4, 144.3, 156.4, 158.9; HRMS (ESI+) Calcd for $C_{15}H_{13}NOF_3$ $[M+H]^+$ 280.0949, found 280.0952.



(E)-N-(2,5-Difluorobenzylidene)-4-methoxyaniline (1l): Purified by recrystallization from hexane. Yellow solid (70%); Mp = 66-67 °C; 1H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.94 (app. d, J = 9.2 Hz, 2H), 7.08-7.12 (m, 2H), 7.27 (app. d, J = 8.7 Hz, 2H), 7.85-7.89 (m, 1H), 8.74 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.7, 113.6 (dd, $^2J_{C-F}$ = 24.9 Hz), 114.6 (2C), 117.2 (dd, $^2J_{C-F}$, $^3J_{C-F}$ = 24.9 Hz, 8.6 Hz), 119.2 (dd, $^2J_{C-F}$, $^3J_{C-F}$ = 24.9 Hz, 8.6 Hz), 122.7 (2C), 125.6-125.8 (m, 1C), 114.3, 149.9, 158.8 (q, $^1J_{C-F}$ = 248.1 Hz), 159.07, 159.09 (d, $^1J_{C-F}$ = 244.3 Hz); HRMS (ESI+) Calcd for $C_{14}H_{12}NOF_2$ $[M+H]^+$ 248.0887, found 248.0888.

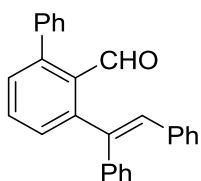
General procedure for cobalt-catalyzed *ortho*-alkenylation of aromatic aldimines with internal alkynes

In a Schlenk tube equipped with a stirrer bar were placed aldimine (0.3 mmol), $P(3\text{-MeC}_6\text{H}_4)_3$ (18.3 mg, 0.06 mmol, 20 mol%), CoBr_2 (0.075 M solution in THF, 0.2 mL, 0.015 mmol, 5 mol%), and THF (0.21 mL). To the mixture was added a THF solution of *i*PrMgBr (1.03 M, 0.14 mL, 0.15 mmol) dropwise at 0 °C. After stirring for 30 min, diphenylacetylene (0.23 M solution in THF, 0.2 mL, 0.45 mmol) was added. The resulting mixture was allowed to room temperature and stirred for 12 h, followed by dilution with THF (1 mL) and quenching with water (0.5 mL) and 1 N HCl (0.5 mL). The resulting mixture was stirred for 1 h and then extracted with EtOAc (4 mL x 3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude product was purified by silica gel chromatography to afford the desired *ortho*-alkenylated aryl aldehyde. Characterization data for the compound **5j** have been reported in the literature.^{9^{ob}}

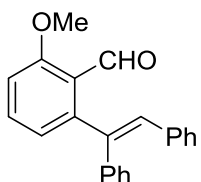


(*E*)-*N*-(2-((*E*)-1,2-Diphenylvinyl)benzylidene)-4-methoxyaniline (3a): The general procedure was applied to (*E*)-*N*-(4-methoxyphenyl)-1-(*o*-tolyl)methanimine **1a** (67.6 mg, 0.3 mmol) and diphenylacetylene **2a** (0.23 M solution in THF, 0.2 mL, 0.45 mmol). The reaction mixture was not treated with aq. HCl (i.e., the imine was not hydrolyzed). The obtained crude product was purified by silica gel chromatography (eluent: hexane/EtOAc/ NEt_3 = 100/1/2) to afford the title compound as a red oil (94.8 mg, 78%) consisting of a 79:21 mixture of alkene *E/Z* isomers as determined by ^1H NMR analysis;

R_f 0.41 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3 , *E*-isomer): δ 2.71 (s, 3H), 3.75 (s, 3H), 6.72-6.77 (m, 4H), 6.99 (d, J = 6.4 Hz, 2H), 7.05-7.13 (m, 5H), 7.22-7.34 (m, 7H), 8.50 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3 , *E*-isomer): δ 22.3, 55.6, 114.2 (2C), 121.9 (2C), 127.1 (2C), 127.3, 127.7, 128.3 (2C), 128.6 (2C), 128.9, 129.4, 129.5 (2C), 130.1, 131.4, 133.6, 137.1, 139.4, 140.9, 142.3, 143.1, 146.1, 158.0, 159.6; HRMS (ESI+) Calcd for $\text{C}_{29}\text{H}_{26}\text{NO}$ $[\text{M}+\text{H}]^+$ 404.2014, found 404.2014.

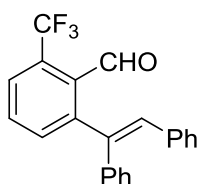


(*E*)-3-(1,2-Diphenylvinyl)-[1,1'-biphenyl]-2-carbaldehyde (5a): The general procedure was applied to (*E*)-1-([1,1'-biphenyl]-2-yl)-*N*-(4-methoxyphenyl)methanimine **1b** (86.2 mg, 0.3 mmol) and diphenylacetylene **2a** (0.23 M solution in THF, 0.2 mL, 0.45 mmol). The obtained crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 25/1) to afford the title compound as a red oil (95.4 mg, 88%); R_f 0.21 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 6.95-6.97 (m, 2H), 7.07-7.15 (m, 4H), 7.22-7.43 (m, 12H), 7.56 (t, J = 7.8 Hz, 1H), 9.78 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 127.1 (3C), 127.6, 128.0, 128.2, 128.39 (2C), 128.42 (2C), 128.8 (2C), 129.4 (2C), 129.9 (2C), 130.7, 131.4, 132.7, 133.8, 137.1, 139.0, 141.2, 142.1, 142.6, 146.0, 192.5; HRMS (ESI+) Calcd for $\text{C}_{27}\text{H}_{21}\text{O}$ $[\text{M}+\text{H}]^+$ 361.1592, found 361.1590.

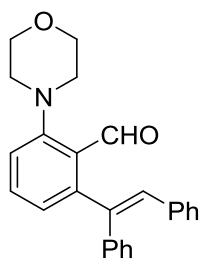


(*E*)-2-(1,2-Diphenylvinyl)-6-methoxybenzaldehyde (5b): The general procedure was applied to (*E*)-1-(2-methoxyphenyl)-*N*-(4-methoxyphenyl)methanimine **1c** (72.4mg, 0.3

mmol) and diphenylacetylene **2a** (0.23 M solution in THF, 0.2 mL, 0.45 mmol). The obtained crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 10/1) to afford the title compound as a red solid (83.7 mg, 90%); Mp = 127-128 °C; R_f 0.13 (hexane/EtOAc = 10/1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 3.95 (s, 3H), 6.82 (d, $J = 7.8$ Hz, 1H), 6.96-7.07 (m, 3H), 7.08-7.14 (m, 4H), 7.22-7.29 (m, 5H), 7.49 (t, $J = 8.2$ Hz, 1H), 10.3 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 56.1, 111.3, 124.0, 124.3, 126.9 (2C), 127.2, 127.7, 128.3 (2C), 128.5 (2C), 128.9, 129.5 (2C), 135.4, 137.1, 140.6, 142.5, 144.5, 162.0, 190.5; HRMS (ESI+) Calcd for $\text{C}_{22}\text{H}_{19}\text{O}_2$ $[\text{M}+\text{H}]^+$ 315.1385, found 315.1389.

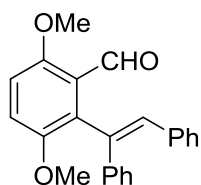


(E)-2-(1,2-Diphenylvinyl)-6-(trifluoromethyl)benzaldehyde (5c): The general procedure was applied to *(E)-N*-(4-methoxyphenyl)-1-(2-(trifluoromethyl)phenyl)methanimine **1d** (83.8mg, 0.3 mmol) and diphenylacetylene **2a** (0.23 M solution in THF, 0.2 mL, 0.45 mmol). The obtained crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 25/1) to afford the title compound as a red solid (71.3 mg, 68%); Mp = 78-79 °C; R_f 0.12 (hexane/EtOAc = 25/1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.88-6.90 (m, 2H), 7.11-7.15 (m, 4H), 7.23-7.34 (m, 4H), 7.46 (d, $J = 7.8$ Hz, 1H), 7.61 (t, $J = 7.8$ Hz, 1H), 7.79 (d, $J = 7.8$ Hz, 1H), 10.7 (q, $J = 2.3$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 126.2 (q, $^3J_{\text{C-F}} = 5.8$ Hz) 127.2 (2C), 127.7, 128.2, 128.5 (2C), 128.8 (2C), 129.5 (2C), 130.3 (q, $^2J_{\text{C-F}} = 32.5$ Hz), 130.5, 132.5, 134.9, 136.1, 136.4, 139.2, 142.0, 143.6, 190.7. The signal of CF_3 carbon could not be identified because of signal overlapping of other peaks; HRMS (ESI+) Calcd for $\text{C}_{22}\text{H}_{16}\text{OF}_3$ $[\text{M}+\text{H}]^+$ 353.1153, found 353.1151.



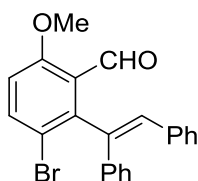
(E)-2-(1,2-Diphenylvinyl)-6-morpholinobenzaldehyde (5d): The

general procedure was applied to (*E*)-*N*-(4-methoxyphenyl)-1-(2-morpholinophenyl)methanimine **1e** (88.9 mg, 0.3 mmol) and diphenylacetylene **2a** (0.23 M solution in THF, 0.2 mL, 0.45 mmol). The obtained crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 25/1) to afford the title compound as a red oil with a mixture of 2-morpholinobenzaldehyde (66% yield as determined by weight and ^1H NMR analysis); R_f 0.17 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 3.02-3.14 (m, 4H), 3.84-3.91 (m, 4H), 6.91-6.93 (m, 3H), 7.07-7.17 (m, 5H), 7.23-7.35 (m, 5H), 7.50 (t, $J = 7.8$ Hz, 1H), 10.2 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 53.9, 67.2, 118.2, 125.7, 127.0 (2C), 127.2, 127.5, 127.8, 128.3 (2C), 128.6 (2C), 129.5 (2C), 129.7, 134.8, 137.0, 140.5, 142.7, 145.9, 154.9, 190.7; HRMS (ESI+) Calcd for $\text{C}_{25}\text{H}_{24}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 370.1807, found 370.1805.

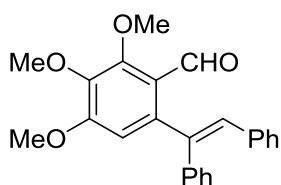


(E)-2-(1,2-Diphenylvinyl)-3,6-dimethoxybenzaldehyde (5e): The general procedure was applied to (*E*)-1-(2,5-dimethoxyphenyl)-*N*-(4-methoxyphenyl)methanimine **1f** (81.4 mg, 0.3 mmol) and diphenylacetylene **2a** (0.23 M solution in THF, 0.2 mL, 0.45 mmol). The obtained crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 15/85) to afford the title compound as a red solid (78.2 mg, 76%); Mp = 118-119; R_f 0.10 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 3.55 (s, 3H), 3.89 (s, 3H), 6.96-7.01 (m, 3H), 7.08-7.15 (m, 4H), 7.19 (s, 1H), 7.23-7.35 (m, 5H), 10.2

(s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 56.4, 56.9, 112.2, 118.4, 124.3, 126.5 (2C), 127.2, 127.6, 128.3 (2C), 128.5 (2C), 128.8 (2C), 130.3, 133.1, 137.3, 142.0, 151.3, 155.5, 1991.1; HRMS (ESI+) Calcd for $\text{C}_{23}\text{H}_{21}\text{O}_3$ $[\text{M}+\text{H}]^+$ 345.1491, found 345.1488.

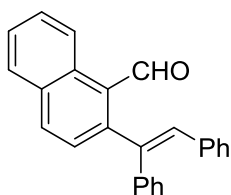


(E)-3-Bromo-2-(1,2-diphenylvinyl)-6-methoxybenzaldehyde (5f): The general procedure was applied to (*E*)-1-(5-bromo-2-methoxyphenyl)-*N*-(4-methoxyphenyl)methanimine **1g** (96.1 mg, 0.3 mmol) and diphenylacetylene **2a** (0.23 M solution in THF, 0.2 mL, 0.45 mmol). The obtained crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 10/1). to afford the title compound as a yellow solid (69.3 mg, 59%) Mp = 138-139 °C; R_f 0.07 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 3.92 (s, 3H), 6.93-6.97 (m, 3H), 7.12-7.15 (m, 3H), 7.21 (s, 1H), 7.25-7.32 (m, 5H), 7.78 (d, J = 9.2 Hz, 2H), 10.1 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 56.3, 113.2, 116.6, 125.7, 126.7 (2C), 127.6, 127.9, 128.5 (2C), 128.7 (2C), 128.9 (2C), 130.6, 136.6, 137.7, 139.0, 140.5, 144.0, 160.5, 190.2; HRMS (ESI+) Calcd for $\text{C}_{22}\text{H}_{18}\text{O}_2\text{Br}$ $[\text{M}+\text{H}]^+$ 393.0490, found 393.0487.

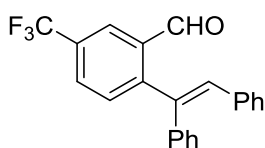


(E)-6-(1,2-Diphenylvinyl)-2,3,4-trimethoxybenzaldehyde (5g): The general procedure was applied to (*E*)-*N*-(4-methoxyphenyl)-1-(2,3,4-trimethoxyphenyl)methanimine **1h** (90.4 mg, 0.3 mmol) and diphenylacetylene **2a** (0.23 M solution in THF, 0.2 mL, 0.45 mmol). The obtained crude product was purified by silica gel chromatography (eluent:

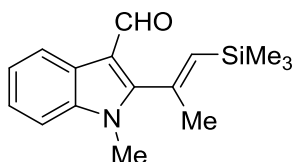
hexane/EtOAc = 9/1) to afford the title compound as a red oil (87.6 mg, 78%); R_f 0.10 (hexane/EtOAc = 10/1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 3.76 (s, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 6.50 (s, 1H), 6.93-6.96 (m, 2H), 7.09-7.13 (m, 4H), 7.26-7.34 (m, 5H), 10.1 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 56.4, 61.4, 62.6, 110.6, 122.5, 126.8 (2C), 127.3, 127.9, 128.4 (2C), 128.6 (2C), 129.2, 129.4 (2C), 136.9, 140.1, 140.2, 142.0, 142.2, 157.0, 158.4, 189.3; HRMS (ESI+) Calcd for $\text{C}_{24}\text{H}_{23}\text{O}_4$ $[\text{M}+\text{H}]^+$ 375.1596, found 375.1599.



(E)-2-(1,2-Diphenylvinyl)-1-naphthaldehyde (5h): The general procedure was applied to (*E*)-*N*-(4-methoxyphenyl)-1-(naphthalen-1-yl)methanimine **1i** (78.4 mg, 0.3 mmol) and diphenylacetylene **2a** (0.23 M solution in THF, 0.2 mL, 0.45 mmol). The obtained crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 50/1) to afford the title compound as a red solid (94.6 mg, 94%) Mp = 130-131 °C; R_f 0.32 (hexane/EtOAc = 10/1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.92-6.94 (m, 2H), 7.03-7.07 (m, 3H), 7.27-7.39 (m, 7H), 7.56-7.61 (m, 1H), 7.67 (t, J = 8.2 Hz, 1H), 7.91 (d, J = 8.2 Hz), 8.08 (d, J = 8.7 Hz, 1H), 9.25 (d, J = 8.7 Hz), 10.5 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 126.3, 127.1 (2C), 127.2, 127.7, 128.2, 128.6 (3C), 128.9 (2C), 129.0, 129.1, 129.4, 129.6 (2C), 131.1, 131.5, 133.6, 135.6, 136.3, 138.7, 142.7, 147.2, 194.5; HRMS (ESI+) Calcd for $\text{C}_{25}\text{H}_{19}\text{O}$ $[\text{M}+\text{H}]^+$ 335.1436, found 335.1432.



(*E*)-2-(1,2-Diphenylvinyl)-5-(trifluoromethyl)benzaldehyde (5i): The general procedure was applied to (*E*)-*N*-(4-methoxyphenyl)-1-(3-(trifluoromethyl)phenyl)methanimine **1j** (83.8 mg, 0.3 mmol) and diphenylacetylene **2a** (0.23 M solution in THF, 0.2 mL, 0.45 mmol). The obtained crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 50/1) to afford the title compound as an orange oil (56.2 mg, 53%) consisting of ca. 79:21 mixture of *E/Z* isomers as determined by ¹H NMR analysis; *R_f* 0.24 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃, *E*-isomer): δ 6.62 (s, 1H), 7.13-7.38 (m, 11H), 7.43 (d, *J* = 8.2 Hz), 7.75 (dd, *J* = 8.2 Hz, 2.3 Hz, 1H), 10.3 (s, 1H); ¹³C NMR (100 MHz, CDCl₃, *E*-isomer): δ 125.2 (q, ³*J*_{C-F} = 3.8 Hz), 128.2, 128.4 (3C), 129.0 (2C), 129.7 (2C), 130.1 (2C), 131.8, 135.3, 135.9, 136.0, 137.4, 139.6, 151.0, 190.7; The signals of the CF₃ carbon and the aromatic carbon next to CF₃ could not be identified because of signal overlapping with other peaks; HRMS (ESI+) Calcd for C₂₂H₁₆OF₃ [M+H]⁺ 353.1153, found 353.1160.

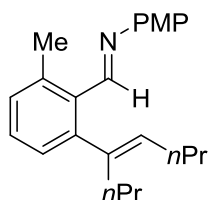


(*E*)-1-Methyl-2-(1-(trimethylsilyl)prop-1-en-2-yl)-1H-indole-3-carbaldehyde (5k):

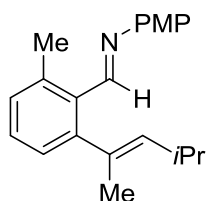
The general procedure was applied to (*E*)-*N*-(4-methoxyphenyl)-1-(1-methyl-1H-indol-3-yl)methanimine **1k** (79.2 mg, 0.3 mmol) and 1-trimethylsilyl-1-propyne **2b** (50.5 mg, 0.45 mmol). The obtained crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 10/1). White solid (89.2 mg, 86%) consisting of ca. 86:14 mixture of *E/Z* isomers as determined by ¹H NMR analysis; Mp = 89-91 °C; *R_f* 0.20 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 0.31 (s, 9H), 2.25 (d, *J* = 0.9 Hz, 3H), 3.70 (s, 3H), 5.94 (d, *J* = 0.9 Hz, 1H),

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7.29-7.36 (m, 3H), 8.37-8.39 (m, 1H), 9.93 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ -0.2 (3C), 23.3, 30.7, 109.7, 113.7, 122.2, 123.2, 123.9, 125.3, 137.0, 140.8, 140.9, 156.9, 186.0; HRMS (ESI+) Calcd for $\text{C}_{16}\text{H}_{22}\text{NOSi}$ $[\text{M}+\text{H}]^+$ 272.1471, found 272.1467.

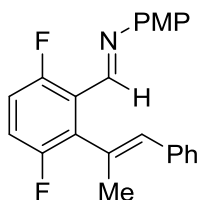


(E)-4-Methoxy-N-(2-methyl-6-((E)-oct-4-en-4-yl)benzylidene)aniline (3b): The general procedure was applied to (*E*)-*N*-(4-methoxyphenyl)-1-(*o*-tolyl)methanimine **1a** (67.6 mg, 0.3 mmol) and 4-octyne **2c** (49.6 mg, 0.45 mmol) using *c*PrMgBr and P(3-FC₆H₄)₃ instead of *i*PrMgBr and P(3-MeC₆H₄)₃, respectively. The reaction mixture was not treated with aq. HCl (i.e., imine was not hydrolyzed). The obtained crude product was purified by silica gel chromatography (eluent: hexane/EtOAc/NEt₃ = 100/0.5/2.5) to afford the title compound as a yellow oil (94.8 mg, 94%); R_f 0.40 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 0.86 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 1.28-1.34 (m, 2H), 1.37-1.43 (m, 2H), 2.16 (q, J = 7.3 Hz, 2H), 2.33-2.37 (m, 2H), 2.66 (s, 3H), 6.92 (app. d, J = 9.2 Hz, 2H), 7.04 (d, J = 7.3 Hz, 1H), 7.13-7.16 (m, 3H), 7.20-7.25 (m, 1H), 8.64 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.1, 14.4, 21.6, 22.1, 23.2, 30.6, 35.0, 55.7, 114.5 (2C), 122.1 (2C), 127.0, 129.0, 130.1, 132.9, 133.0, 138.2, 139.9, 146.0, 147.0, 158.2, 160.7; HRMS (ESI+) Calcd for $\text{C}_{23}\text{H}_{30}\text{NO}$ $[\text{M}+\text{H}]^+$ 336.2327, found 336.2326.



(E)-4-Methoxy-N-(2-methyl-6-((E)-4-methylpent-2-en-2-yl)benzylidene)aniline (3c):

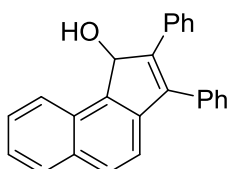
The general procedure was applied to (*E*)-*N*-(4-methoxyphenyl)-1-(*o*-tolyl)methanimine **1a** (67.6 mg, 0.3 mmol) and 4-methylpent-2-yne **2d** (36.9 mg, 0.45 mmol) using *c*PrMgBr and P(3-FC₆H₄)₃ instead of *i*PrMgBr and P(3-MeC₆H₄)₃, respectively. The reaction mixture was not treated with aq. HCl (i.e., imine was not hydrolyzed). The obtained crude product was purified by silica gel chromatography (eluent: hexane/NEt₃ = 100/2.5) to afford the title compound as a yellow oil (89.6 mg, 97%); *R*_f 0.43 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 0.97 (d, *J* = 6.4 Hz, 6H), 1.96 (d, *J* = 1.4 Hz, 3H), 2.62-2.668 (m, 4H), 3.82 (s, 3H), 5.19 (dd, *J* = 9.2 Hz, 1.4 Hz, 1H), 6.91-6.94 (m, 4H), 7.06-7.19 (m, 4H), 7.22-7.25 (m, 1H), 8.61 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 19.1, 22.0, 23.1 (2C), 28.0, 55.7, 114.5 (2C), 122.1 (2C), 126.4, 129.2, 130.0, 132.6, 1332.7, 138.3, 140.4, 145.9, 147.9, 158.2, 160.4; HRMS (ESI+) Calcd for C₂₁H₂₆NO [M+H]⁺ 308.2014, found 308.2016.

**(E)-N-(3,6-Difluoro-2-((E)-1-phenylprop-1-en-2-yl)benzylidene)-4-methoxyaniline**

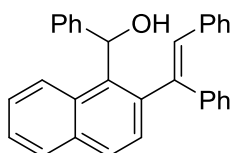
(3e): The general procedure was applied to (*E*)-1-(2,5-difluorophenyl)-*N*-(4-methoxyphenyl)methanimine **1l** (74.2 mg, 0.3 mmol) and 1-phenyl-1-propyne **2e** (52.3 mg, 0.45 mmol) using *t*BuCH₂MgBr instead of *i*PrMgBr and pyridine as an additive (19.0 mg, 0.24 mmol). The reaction mixture was not treated with aq. HCl (i.e., imine was not hydrolyzed). The obtained crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 25/1) to afford the title compound as a red oil (100.3 mg, 92%) consisting of 96:4 mixture of regioisomers as determined by ¹H

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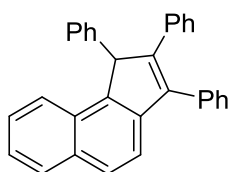
NMR analysis; R_f 0.22 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 2.23 (d, $J = 0.9$ Hz, 3H), 3.80 (s, 3H), 6.44 (d, $J = 0.9$ Hz, 1H), 6.89 (app. d, $J = 9.2$ Hz, 2H), 7.05-7.12 (m, 2H), 7.18 (app. d, $J = 9.2$ Hz, 2H), 7.24-7.39 (m, 6H), 8.59 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.0, 55.7, 114.6 (2C), 115.8 (dd, $J = 25.9$ Hz, 9.6 Hz), 118.1 (dd, $J = 25.9$ Hz, 9.6 Hz), 122.4 (2C), 124.0 (dd, $J = 10.5$ Hz, 3.8 Hz), 127.2, 128.5 (2C), 129.2 (2C), 131.1, 132.6, 134.9 (d, $J = 19.2$ Hz), 137.2, 145.2, 152.8, 155.9 (dd, $J = 240.4$ Hz), 157.8 (dd, $J = 258.7$ Hz, 8.6 Hz), 158.8; HRMS (ESI+) Calcd for $\text{C}_{23}\text{H}_{18}\text{NOF}_2$ $[\text{M}+\text{H}]^+$ 362.1356, found 362.1362.



2,3-Diphenyl-1H-cyclopenta[*a*]naphthalen-1-ol (6): To solution of **5h** (16.7 mg, 0.05 mol) in CH_2Cl_2 was added $\text{BF}_3 \cdot \text{OEt}_2$ (12.7 μL , 0.10 mmol) at 0 °C. After stirring for 10 min, the reaction mixture was quenched with water. The aqueous layer was extracted with EtOAc (1 mL x 3). The combined 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 = 10/1) to afford the title compound as a white solid (12.8 mg, 74%); Mp = 206-207 °C; R_f 0.12 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 6.07 (d, $J = 9.2$ Hz), 7.23-7.31 (m, 4H), 7.35 (d, $J = 8.2$ Hz, 1H), 7.40-7.48 (m, 8H), 7.57 (t, $J = 7.8$ Hz, 1H), 7.82 (d, $J = 8.2$ Hz, 1H), 7.88 (d, $J = 8.2$ Hz, 1H), 8.40 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 77.5, 119.6, 124.4, 125.5, 127.1, 127.5, 128.1, 128.6 (2C), 129.0, 129.2 (2C), 129.4 (2C), 129.5 (2C), 129.7, 130.0, 132.9, 134.1, 135.1, 139.3, 140.0, 141.6, 144.2; HRMS (ESI+) Calcd for $\text{C}_{25}\text{H}_{19}\text{O}$ $[\text{M}+\text{H}]^+$ 335.1436, found 335.1437.



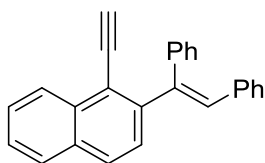
(E)-2-(1,2-Diphenylvinyl)naphthalen-1-yl(phenyl)methanol (7'): To a solution of bromobenzene (23.6 mg, 0.15 mmol) in THF (1.0 mL) was added *n*BuLi (1.6 M in hexane, 94 mL, 0.15 mmol) at $-78\text{ }^{\circ}\text{C}$. After stirring for 20 min, aldehyde **5h** (33.4 mg, 0.098 mol) was added. The reaction mixture was stirred for 90 min and then quenched with water while being allowed to room temperature. The aqueous layer was extracted with EtOAc (1 mL x 3), and the combined 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 = 10/1) to afford the title compound (37.2 mg, 98%) as a white solid. This compound existed as a 55:45 mixture of rotamers as determined by ^1H NMR analysis. Mp = $83\text{--}85\text{ }^{\circ}\text{C}$; R_f 0.24 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 1.46-1.48 (m, 1H, major), 1.94-1.95 (m, 1H, minor), 6.41 (d, $J = 4.1\text{ Hz}$, 1H, minor), 6.53 (d, $J = 3.2\text{ Hz}$, 1H, major), 7.04-7.95 (m, 21H, major, 20H, minor), 8.02 (d, $J = 8.7\text{ Hz}$, 1H, minor); ^{13}C NMR (100 MHz, CDCl_3): peaks of the major and the minor isomers could not be distinguished. δ 72.6, 73.0, 125.87, 125.93, 125.96, 126.01, 126.4, 126.5, 126.7, 127.4, 127.5, 127.6, 127.8, 128.0, 128.07, 128.15, 128.23, 128.4, 128.62, 128.64, 128.80, 128.84, 129.1, 129.2, 129.5, 129.8, 129.9, 130.0, 131.9, 132.1, 134.6, 134.9, 136.1, 136.78, 137.15, 137.9, 138.5, 141.2, 141.5, 142.2, 143.3, 143.5, 143.6; HRMS (ESI+) Calcd for $\text{C}_{31}\text{H}_{25}\text{O}$ $[\text{M}+\text{H}]^+$ 413.1905, found 413.1905.



1,2,3-Triphenyl-1H-cyclopenta[a]naphthalene (7): To a solution of **7'** (19.3 mg, 0.05

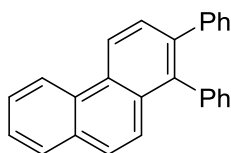
Chapter 2

mmol) in CH_2Cl_2 (0.5 mL) was added $\text{BF}_3 \cdot \text{OEt}_2$ (12.7 μL , 0.10 mmol) at 0 °C and then the reaction mixture was warmed to room temperature. After stirring for 15 min, the reaction mixture was quenched with water. The aqueous layer was extracted with Et_2O (1 mL x 3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent = hexane/ CH_2Cl_2 = 95/5 to 90/10) to afford the title compound as a white solid (18.2 mg, 99%), (97% from **5h** in two steps); Mp = 86-88 °C; R_f 0.40 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 5.41 (s, 1H), 7.06-7.13 (m, 6H), 7.16-7.17 (m, 4H), 7.29 (m, 8H), 7.53 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.84 (t, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 58.2, 119.7, 123.6, 124.8, 126.4, 126.7, 126.8, 127.5, 127.9 (2C), 128.3, 128.6 (2C), 128.8 (4C), 129.0 (2C), 129.56 (2C), 129.62, 129.8 (2C), 132.5, 135.6, 139.7, 140.2, 143.2, 143.7, 148.1; HRMS (ESI+) Calcd for $\text{C}_{31}\text{H}_{22}$ $[\text{M}+\text{H}]^+$ 395.1800, found 395.1804.

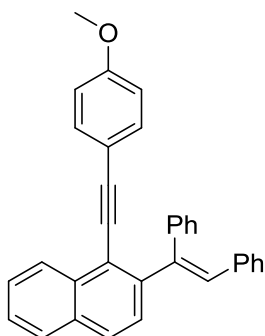


(E)-2-(1,2-Diphenylvinyl)-1-ethynynaphthalene (8): To a solution of diisopropylamine (168 μL , 1.2 mmol) was added *n*-BuLi (1.6 M in hexane, 750 μL , 1.2 mmol) at -78 °C. The resulting mixture was allowed to room temperature, stirred for 15 min, and then cooled again to -78 °C, followed by the addition of trimethylsilyldiazomethane (2.0 M in hexane, 600 μL , 1.2 mmol). After stirring for 45 min, aldehyde **5h** (334 mg, 1.0 mmol) was added. The reaction mixture was stirred for 1 h, warmed to room temperature, and then stirred for additional 10 h before quenching with water. The aqueous layer was extracted with Et_2O (30 mL x 3), and the combined organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude product was

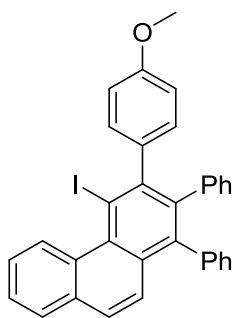
purified by silica gel chromatography (eluent: hexane/ EtOAc = 50/1) to afford the title compound as a white solid (250 mg, 75%); Mp = 83-85 °C; R_f 0.29 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 3.30 (s, 1H), 6.99-7.07 (m, 5H), 7.17 (s, 1H), 7.24-7.34 (m, 6H), 7.52-7.60 (m, 2H), 7.82-7.88 (m, 2H), 8.38 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 80.4, 86.1, 120.0, 126.6, 126.7, 127.2, 127.3 (3C), 127.6, 128.3 (2C), 128.4 (4C), 129.4 (2C), 129.6, 129.9, 132.5, 134.3, 137.4, 141.3, 142.6, 142.9; HRMS (ESI+) Calcd for $\text{C}_{26}\text{H}_{18}$ $[\text{M}+\text{H}]^+$ 331.1487, found 331.1487.



1,2-diphenylphenanthrene (9): A mixture of **8** (33.1 mg, 0.1 mmol) and PtCl_2 (2.9 mg, 0.01 mmol) in toluene (1.0 mL) was stirred at 90 °C for 24 h. The reaction was cooled to room temperature and then quenched with water. The aqueous layer was extracted with EtOAc (1 mL x 3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane) to afford the title compound as a red solid (27.0 mg, 82% yield). Mp = 148-149 °C; R_f 0.28 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.17-7.21 (m, 7H), 7.27-7.32 (m, 3H), 7.57-7.68 (m, 4H), 7.72 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 8.76 (t, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 122.1, 122.8, 125.2, 126.2, 126.66 (2C), 126.71, 127.0, 127.6 (2C), 127.8 (2C), 128.4, 127.5, 129.6, 130.0 (2C), 130.1 (2C), 130.8, 131.5, 131.6, 138.5, 139.3, 139.3, 141.8; HRMS (ESI+) Calcd for $\text{C}_{26}\text{H}_{19}$ $[\text{M}+\text{H}]^+$ 331.1487, found 331.1487.



(E)-2-(1,2-Diphenylvinyl)-1-((4-methoxyphenyl)ethynyl)naphthalene (10'): To a solution of **8** (332 mg, 1.0 mmol) and 4-iodoanisole (470 mg, 2.0 mmol) in NEt₃ (16 mL) were added Pd(PPh₃)₂Cl₂ (14.0 mg, 0.02 mmol) and CuI (2.2 mg, 0.01 mmol). The resulting mixture was stirred at 55 °C for 3 h, followed by quenching with water at room temperature. The aqueous layer was extracted with EtOAc (5 mL x 3), and the combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 25/1) to afford the title compound as a white solid (304 mg, 70% yield). Mp = 65-66 °C; *R_f* 0.23 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 3.78 (s, 3H), 6.77 (d, *J* = 8.7 Hz, 2H), 7.02-7.06 (m, 5H), 7.17-7.33 (m, 7H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.51-7.59 (m, 2H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 8.45 (d, *J* = 8.2 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 54.5, 85.5, 98.9, 114.0 (2C), 115.8, 121.5, 126.6, 126.8, 127.0, 127.1, 127.4 (2C), 127.5, 128.2 (2C), 128.39, 128.43 (2C), 128.5, 128.8, 129.6 (2C), 129.8, 132.7, 133.2 (2C), 134.0, 137.5, 141.6, 142.1, 143.1, 159.7; HRMS (ESI+) Calcd for C₃₃H₂₅O [M+H]⁺ 437.1905, found 437.1907.



4-Iodo-3-(4-methoxyphenyl)-1,2-diphenylphenanthrene (10): To a solution of **10'** (14 mg, 0.03 mmol) in CH_2Cl_2 was added NIS (21 mg, 0.09 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 12 h, followed by quenching with water at room temperature. The aqueous layer was extracted with EtOAc (1 mL x 3), and the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane) to afford the title compound as a white solid (15.2 mg, 90% yield). Mp = 245 °C; R_f 0.40 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 3.75 (s, 3H), 6.73-6.89 (m, 7H), 7.04 (app. d, J = 7.8 Hz, 2H), 7.12-7.25 (m, 5H), 7.35 (d, J = 9.2 Hz, 1H), 7.59-7.61 (m, 3H), 7.81-7.84 (m, 1H), 9.80-9.82 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 55.0, 97.0, 112.7 (2C), 123.7, 124.8, 125.6, 126.6 (3C), 127.4, 127.56 (3C), 127.63, 128.5, 130.8 (2C), 131.0 (3C), 131.5, 132.0 (2C), 132.7, 133.1, 139.1, 139.8, 140.0, 140.1, 140.5, 148.1, 158.2; HRMS (ESI+) Calcd for $\text{C}_{33}\text{H}_{24}\text{IO}$ $[\text{M}+\text{H}]^+$ 563.0870, found 563.0872.

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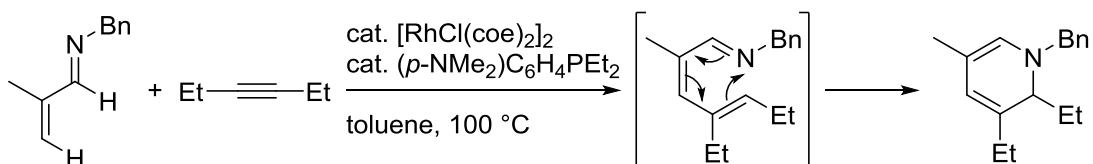
Cobalt-Catalyzed Annulation of α,β -Unsaturated Imines with Alkynes**3.1 Introduction**

Since the groundbreaking work of Murai and co-workers on ruthenium-catalyzed *ortho* C–H bond alkylation of aromatic ketones with olefins, chelation-assisted functionalization of aromatic and heteroaromatic C–H bonds has been a subject of intensive research over the last two decades.¹ While not as extensive as the arene functionalization, chelation-assisted olefinic C–H bond functionalization has also been studied with particular focus on the regio- and stereocontrolled synthesis of multisubstituted olefins via C–H alkylation² and arylation³ reaction as well as regio- and stereocontrolled synthesis of multisubstituted heterocycles via C–H bond alkenylation/cyclization cascades.^{4,5,6}

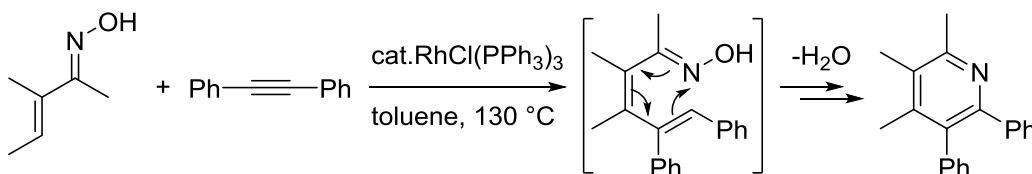
For example, the group of Bergman and Ellman reported a cascade reaction comprising the rhodium(I)-catalyzed olefinic C–H alkenylation of an α,β -unsaturated imine with an alkyne and 6π -electrocyclization of the resulting azatriene intermediate to afford a 1,2-dihydropyridine derivative, which is not easily accessible by other synthetic methods (Scheme 3.1a).^{4a,b} Cheng and co-workers reported a similar cascade reaction using an α,β -unsaturated oxime, an alkyne, and Wilkinson's catalyst (Scheme 3.1b). In this case, sequential olefinic C–H alkenylation, 6π -electrocyclization, and dehydration lead to the formation of a pyridine derivative.^{4c}

Scheme 3.1. Synthesis of Dihydropyridines or Pyridines *via* Olefinic C–H Alkenylation/Electrocyclization Cascade

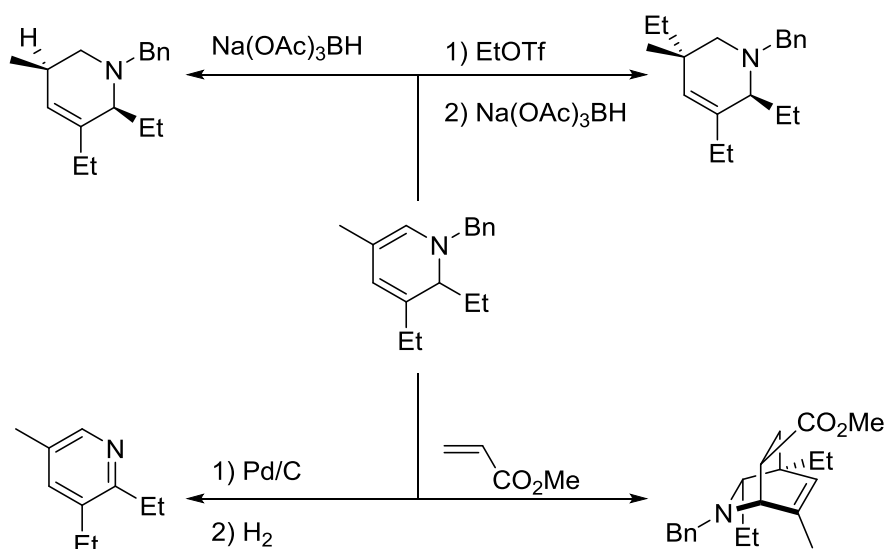
(a) Bergman, Ellman and co-workers



(b) Cheng and co-workers



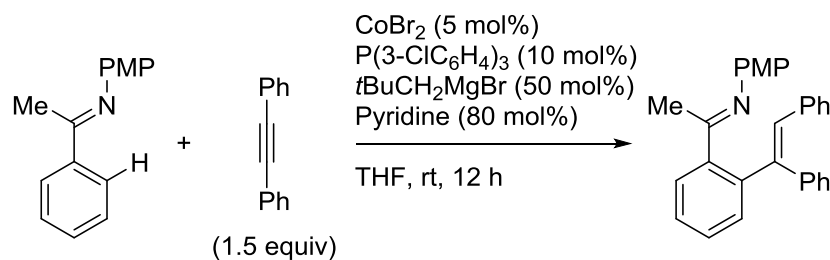
The 1,2-dihydropyridine product obtained by the above Bergman/Ellman's reaction has been demonstrated to serve as a versatile precursor to *N*-heterocycles (Scheme 3.2). For example, tetrahydropyridines can be obtained by reduction with $\text{Na}(\text{OAc})_3\text{BH}^{4a}$ or through a sequence of alkylation with alkyl triflate followed by $\text{Na}(\text{OAc})_3\text{BH}$ reduction.⁷ Poly-substituted pyridines can be synthesized by removal of the benzyl group followed by oxidation.^{4a} Diels-Alder reaction with an electron deficient olefin allows construction of an isoquinuclidine skeleton.⁸

Scheme 3.2. Transformation of 1,2-Dihydropyridine to *N*-Heterocycles

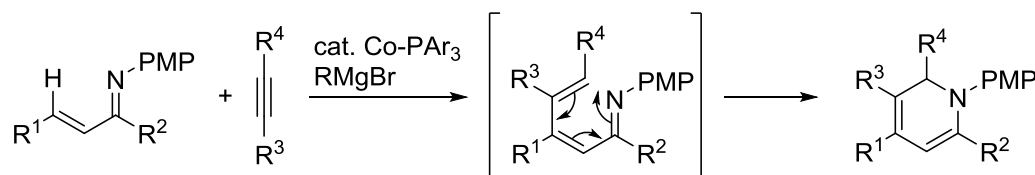
Recently, our group developed a cobalt-catalyzed *ortho*-alkenylation reaction of aryl ketimines with alkynes (Scheme 3.3a).⁹ Because arenes and olefins often show similar reactivity in chelation-assisted C–H functionalization, it is a reasonable idea to extend our catalytic system to olefinic C–H bond activation. Here, we report an annulation reaction of α,β -unsaturated imines and alkynes to afford 1,2-dihydropyridines in the presence of a cobalt–triarylphosphine catalyst (Scheme 3.3b). The reaction represents a rare example of olefinic C–H functionalization reactions catalyzed by first-row transition metal complexes^{3d,10} and features mild reaction conditions and inexpensive catalyst system. The reaction is proposed to proceed through alkenylation of the vinylic C–H bond to form an $\alpha,\beta,\gamma,\delta$ -unsaturated imine, which subsequently undergoes facile 6π -electrocyclization.

Scheme 3.3. Cobalt-Catalyzed C–H Bond Alkenylation with Alkynes

(a) Cobalt-catalyzed aromatic C–H bond activation



(b) This work

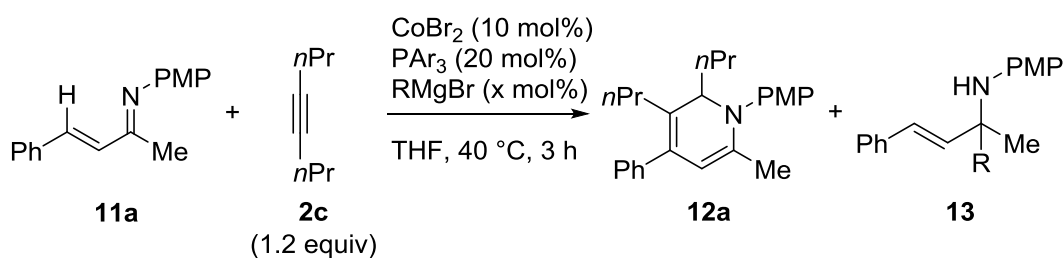
**3.2 Results and Discussion**

The present study began with α,β -unsaturated imine **11a**, derived from benzalacetone and *p*-anisidine, and 4-octyne **2c** as model substrates. The catalytic system consisting of CoBr₂ (10 mol%), P(3-ClC₆H₄)₃ (10 mol%), *t*BuCH₂MgBr (100 mol%), and pyridine (80 mol%), which was effective for *ortho*-alkenylation of aryl ketimines with alkynes,^{9a} promoted the reaction of **11a** and **2c** at 40 °C to afford 1,2-dihydropyridine **12a** in a modest yield of 30% (Table 3.1, entry 1). Removal of pyridine from the catalytic system did not have a significant influence on the yield of **12a** (entry 2). To improve the catalytic activity, we first screened Grignard reagents. Me₃SiCH₂MgCl and MeMgCl, which were effective in several cobalt-catalyzed aromatic C–H bond functionalization reactions,^{9,11} gave poorer results (entries 3 and 4). By contrast, the use of Grignard reagents such as *n*BuMgBr, CyMgBr, and *i*PrMgBr significantly improved the reaction efficiency, affording **12a** in 67%-80% yields (entries 5-7).¹² In these cases, we observed the formation of a small amount of allylic amine **13** (6-8% yields) arising from the Grignard addition to the C=N double bond.

Having identified *i*PrMgBr as the most effective Grignard reagent, we next

examined the effect of triarylphosphines, which eventually revealed that the original ligand, P(3-ClC₆H₄)₃ was optimum. The use of P(4-ClC₆H₄)₃ led to a moderate yield of **12a** (entry 8). P(3-FC₆H₄)₃ and P(4-ClC₆H₄)₃ exhibited slightly poor performances (entries 9 and 10). The electron-withdrawing chloro and fluoro substituents on the phosphine ligand appeared crucial, because PPh₃ gave a much poorer result (entry 11). In all the cases, a small amount but non-negligible amount (6-7%) of **13** was observed. Finally, the formation of **13** could be suppressed by reducing the loading of the Grignard reagent from 60% to 45% without the loss of catalytic activity. The desired 1,2-dihydropyridine **12a** was obtained in 87% yield as determined by ¹H NMR analysis of the crude product. Purification of the crude product on silica gel afforded **12a** in a lower yield of 59% due to partial decomposition (entry 12).

Table 3.1. Cobalt-Catalyzed Annulation of α,β -Unsaturated Imine **1a** and 4-Octyne **2a**^a



entry	PAr ₃	RMgX (x)	yield ^b	
			12a	13
1 ^c	P(3-ClC ₆ H ₄) ₃	<i>t</i> BuCH ₂ MgBr (100)	30	0
2	P(3-ClC ₆ H ₄) ₃	<i>t</i> BuCH ₂ MgBr (100)	29	0
3	P(3-ClC ₆ H ₄) ₃	Me ₃ SiCH ₂ MgCl (100)	8	0
4	P(3-ClC ₆ H ₄) ₃	MeMgCl (100)	22	0
5	P(3-ClC ₆ H ₄) ₃	<i>n</i> BuMgBr (60)	67	6
6	P(3-ClC ₆ H ₄) ₃	CyMgBr (60)	72	7
7	P(3-ClC ₆ H ₄) ₃	<i>i</i> PrMgBr (60)	80	8
8	P(4-ClC ₆ H ₄) ₃	<i>i</i> PrMgBr (60)	45	6
9	P(3-FC ₆ H ₄) ₃	<i>i</i> PrMgBr (60)	71	7
10	P(4-FC ₆ H ₄) ₃	<i>i</i> PrMgBr (60)	75	7
11	PPh ₃	<i>i</i> PrMgBr (60)	22	7
12	P(3-ClC ₆ H ₄) ₃	<i>i</i> PrMgBr (45)	87 (59) ^d	2

^a The reaction was performed on a 0.2 mmol scale. ^b Determined by GC or ¹H NMR. ^c Pyridine

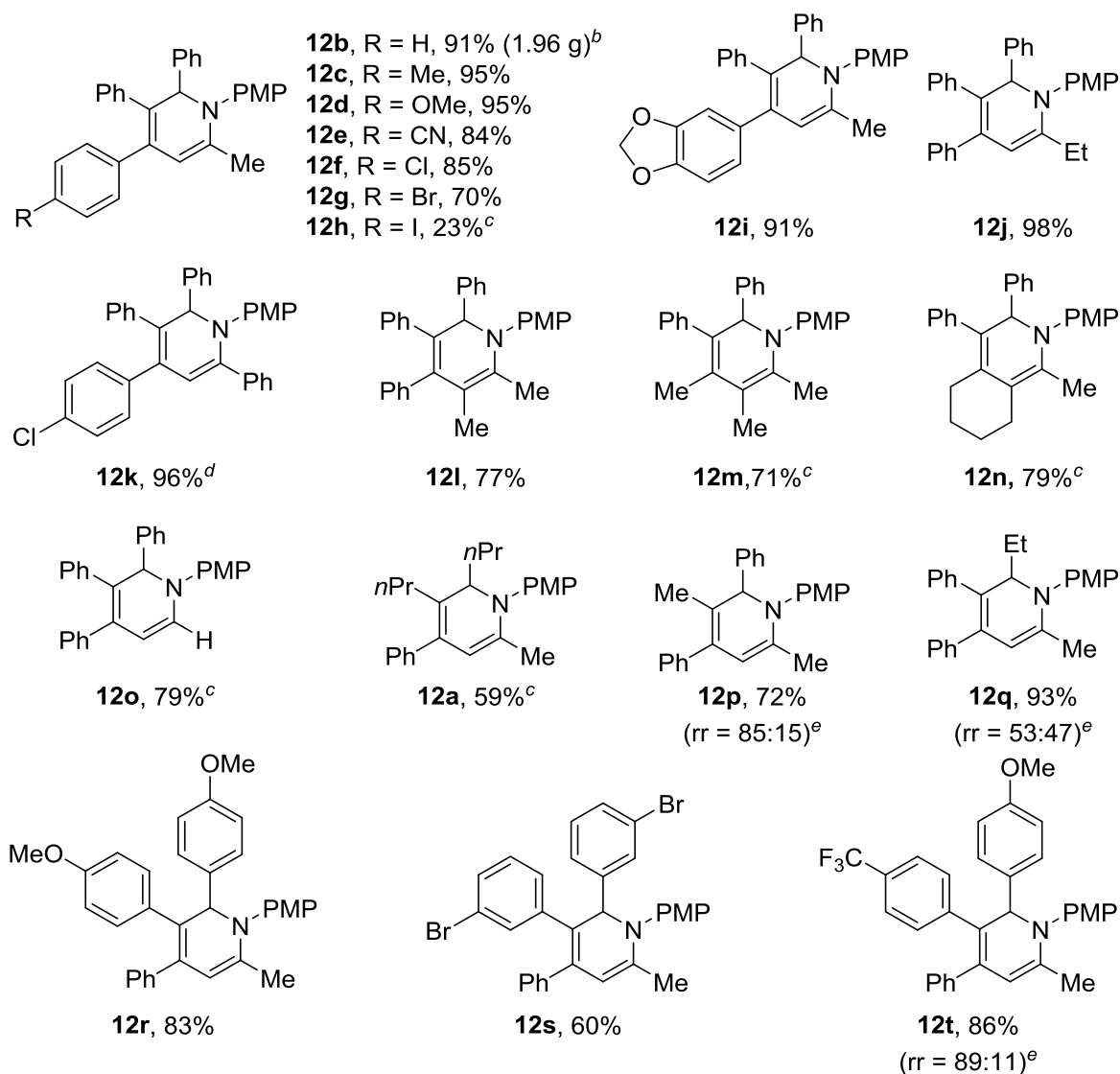
(80 mol %) was added. ^d Isolated yield.

The optimized reaction conditions were applied to a series of α,β -unsaturated imines and alkynes (Scheme 3.4). Firstly, various kinds of imines were subjected to the reaction with diphenylacetylene **2a**. The scalability of the present reaction was demonstrated by the reaction of **1a** on a 5 mmol scale, which afforded the adduct **12b** in 91% yield. Imines derived from benzalacetone derivatives bearing substituents at the *para*-position of the benzene ring participated in the reaction smoothly to afford 1,2-dihydropyridines **12c-12g**. Synthetically useful C–CN, C–Cl, and C–Br bonds could be tolerated. Furthermore, an imine bearing a C–I bond afforded the corresponding annulated product **12g** albeit in a low yield. The reaction tolerated an acetal group to furnish **12i** in 91% yield.

We next investigated imines derived from α,β -unsaturated ketones other than benzalacetone derivatives. An imine derived from (*E*)-1-phenylpent-1-en-3-one smoothly reacted to afford **12j** in 98% yield. The reaction of an imine prepared from a chalcone derivative resulted in selective activation of the olefinic β -C–H bond rather than the aromatic *ortho*-C–H bond, affording the product **12k** in an excellent yield. An imine possessing methyl group at the α -position participated in the reaction smoothly to afford 1,2-dihydropyridine **12l** in 77% yield. An unsaturated imine bearing methyl groups both at the α - and the β -positions delivered the desired product **12m** in 71% yield. A bicyclic 1,2-dihydropyridine **12n** was obtained in 79% yield. A cinnamaldehyde-derived aldimine afforded the desired product **12o** in 79% yield. Note that, while most of the imines **11a-11m** existed as a mixture of *E* and *Z* isomers with respect to the C=N double bond, 1,2-dihydropyridines **12c**, **12d**, **12i**, **12j**, and **12k** were obtained in almost quantitative yields. These results indicate isomerization between the imine *E*- and *Z*-isomers, the former being the suitable conformer for olefinic C–H bond activation.

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We next examined the scope of alkynes using imine **11a** as a reaction partner. With 1-phenyl-1-propyne **2e**, the product was obtained in 72% yield as a mixture of regioisomers in the regioisomer ratio of 85:15. The major regioisomer **12p** arose from C–C bond formation at the 2-position of the alkyne. On the other hand, 1-phenyl-1-butyne **2f** afforded a ca. 1:1 mixture of two regioisomers in an overall yield of 92%. Symmetrical diaryl alkynes bearing 4-methoxy groups or 3-bromo substituents afforded the products **12r** and **12s** in 83% and 60% yields, respectively. An electronically biased alkyne **2i** bearing both 4-trifluorophenyl group at the 2-position and 4-methoxyphenyl at the 1-position provided the desired product **12t** in 86% yield in high regioselectivity (ca. 9:1). The new C–C bond formation dominantly occurred between β -position of α,β -unsaturated imine and acetylenic carbon proximal to the electron-poor aromatic ring. The origin of the regioselectivity is discussed later.

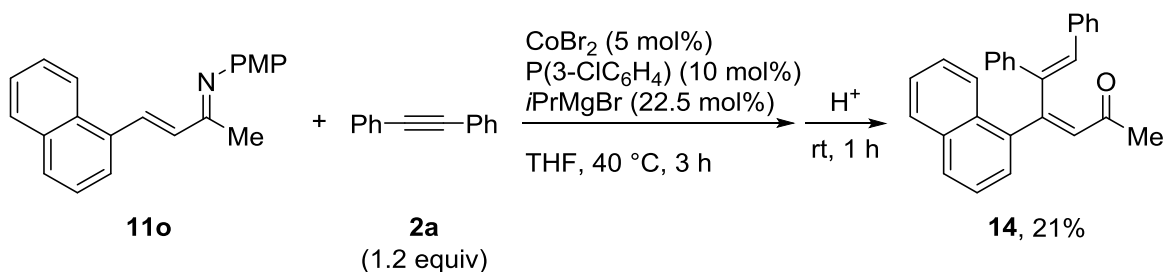
Scheme 3.4. Scope of α,β -Unsaturated Imines and Alkynes^a

^a Unless otherwise noted, the reaction was performed on a 0.2 mmol scale using 5 mol % of CoBr₂, 10 mol % of P(3-ClC₆H₄)₃, and 22.5 mol % of *i*PrMgBr. ^b 5 mmol scale. ^c The reaction was performed with 10 mol % of CoBr₂, 20 mol % of P(3-ClC₆H₄)₃, and 45 mol % of *i*PrMgBr. ^d Obtained as a mixture with a double bond isomer (5:1). ^e r.r. = regioisomer ratio. The major isomer is shown.

The reaction of an imine **11o**, derived from (*E*)-4-(naphthalen-1-yl)but-3-en-2-one and *p*-anisidine, and **2a** afforded, upon hydrolysis,

$\alpha,\beta,\gamma,\delta$ -unsaturated ketone **14** rather than a dihydropyridine derivative (Scheme 3.5). Furthermore, the reaction of **11a** and **2a** afforded the corresponding dienone albeit in less than 1% yield (GC-MS) when quenched by the addition of aqueous HCl with a reaction time of 5 min. These results suggest that the present annulation reaction proceeds in two steps. The first step is a cobalt-catalyzed olefinic C–H bond alkenylation of the α,β -unsaturated imine with the alkyne. The second step is a 6π -electrocyclization of the resulting azatriene intermediate. Note that, the reaction of **11a** and **2a** did not afford the dienone or the corresponding azatriene but afforded **12b** in 36% yield when quenched by addition of water with a reaction time of 5 min. Although I could not confirmed whether the low-valent cobalt species is necessary or not in the electrocyclization step due to a difficulty of isolation of the corresponding azatriene intermediate, the above results may suggest that the low-valent cobalt species is unnecessary for the electrocyclization step.

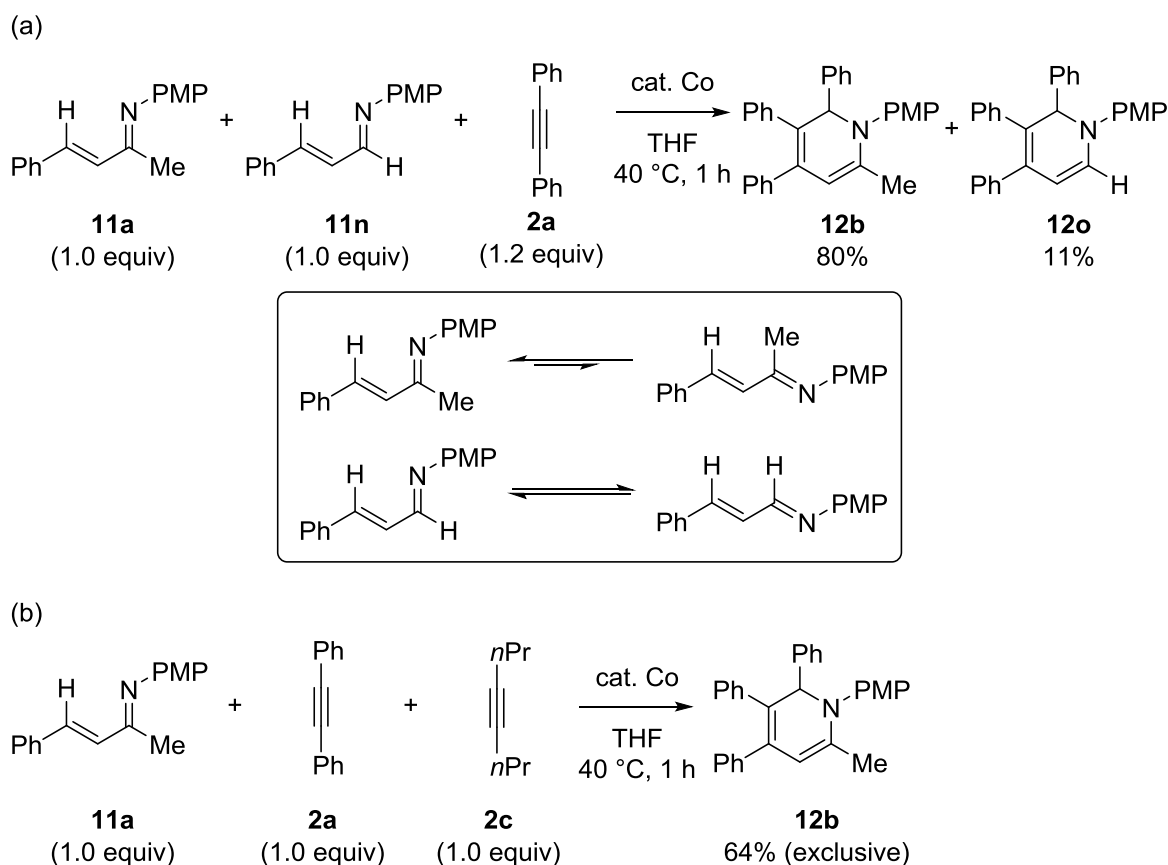
Scheme 3.5. Vinylic C–H Alkenylation of Imine **11o**



Next, we performed two intermolecular competition experiments to examine the relative reactivity of α,β -unsaturated imines (Scheme 3.6). When equimolar amounts of ketimine **11a** and aldimine **11n** were subjected to the reaction with diphenylacetylene **2a**, annulated products **12b** and **12o** were obtained in 80% and 11% yields, respectively (Scheme 3.6a). This result could be explained by conformational preference of imine substrates. Ketimine **11a** should favor *s-cis*-conformation, which is suitable for olefinic C–H bond activation, because the *trans* conformer suffers steric repulsion between the

β -hydrogen atom and the methyl group. On the other hand, aldimine **11n** should not have such conformational preference. Next, competition experiment between 4-octyne **2c** and diphenylacetylene **2a** was performed using **11a**, which exclusively afforded the adduct of the latter alkyne **12b** (Scheme 3.6b). Note that we observed the same chemoselectivity in cobalt-catalyzed *ortho*-alkenylation of aryl ketimine with **2b** and **2a**.^{9b}

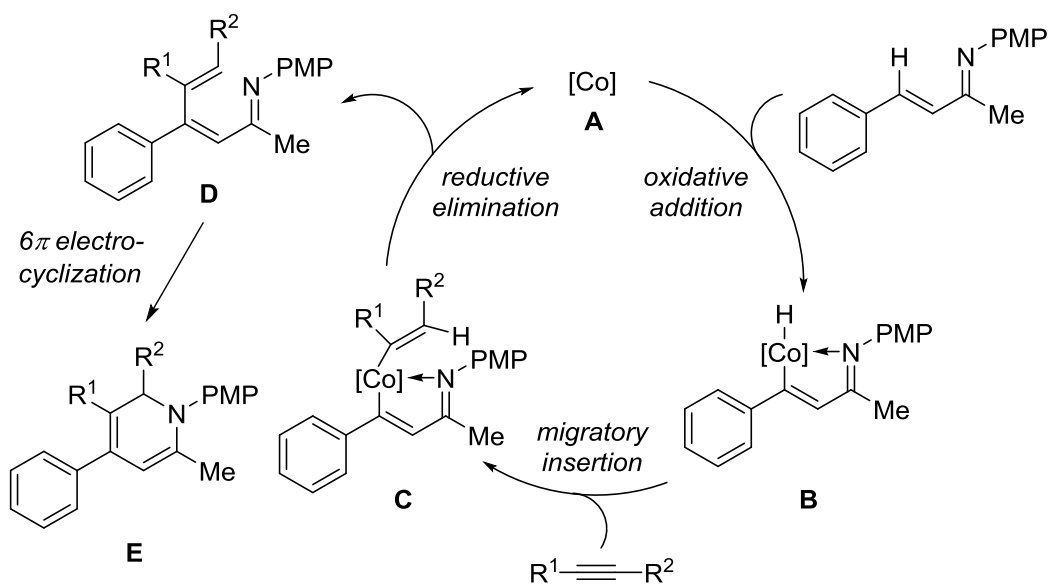
Scheme 3.6. Competition Experiments



On the basis of the above experimental observations, we propose a possible reaction mechanism shown in Scheme 3.7. A low-valent cobalt species **A**, which is generated from CoBr_2 , $\text{P}(\text{3-ClC}_6\text{H}_4)_3$ and $i\text{PrMgBr}$, undergoes oxidative addition of the β -C–H bond to give an alkenyl(hydrido)cobalt species **B**.¹³ As was proposed for the cobalt-catalyzed *ortho*-alkenylation of aryl ketimines with alkynes,^{9b} precoordination of

the alkyne to the cobalt species might occur prior to oxidative addition. Migratory insertion of the alkyne into the Co–H bond of the species **B** affords a dialkenylcobalt species **C**. Reductive elimination of the cobalt species **C** affords azatriene **D** and regenerates the cobalt species **A**. Azatriene **D** then undergoes 6π -electrocyclization to furnish the 1,2-dihydropyridine product **E**. It should be noted that electrocyclization of azatriene often requires high temperature.¹⁴ In the light of this, it is interesting that the putative intermediate **D** is not observed under the present mild conditions except for the case shown in Scheme 3.5. For this case, I speculate that the azatriene intermediate fails to take a proper cyclic conformation for electrocyclization presumably due to steric repulsion of the naphthyl group and its neighboring phenyl group.

Scheme 3.7. Proposed Reaction Mechanism



The regioselectivity of C–C bond formation with unsymmetrical alkynes also deserves some comments. As shown in Scheme 3.4, the reaction of 1-phenyl-1-propyne resulted in preferential C–C bond formation at the position proximal to the methyl group, while 1-phenyl-1-butyne afforded a ca. 1:1 mixture of regioisomers. These selectivities

are likely determined in the migratory insertion step, where the cobalt center would avoid steric repulsion with the larger substituent on the alkyne. The regioselectivity for the unsymmetric diarylalkyne (**2i**) may be ascribed to the electrostatic nature of the putative alkenyl(hydrido)cobalt species (i.e., $\text{Co}(\delta^+)-\text{H}(\delta^-)$). Natural population analysis charges of the acetylenic carbon atoms of **12g** were calculated to be +0.027 (proximal to 4-methoxyphenyl) and -0.014 (proximal to 4-(trifluoromethyl)phenyl) at the B3LYP/6-31G* level. Thus, in the insertion step, cobalt center should prefer to approach the acetylenic carbon proximal to the 4-trifluoromethylphenyl group to fit the electrostatic bias. This speculation corresponds to the observed regioselectivity.

3.3 Conclusion

I have successfully developed a cobalt-catalyzed annulation reaction of α,β -unsaturated imines and internal alkynes to afford 1,2-dihydropyridines. The reaction likely involves alkenylation of the β -position through chelation-assisted activation of the olefinic C–H bond and 6π -electrocyclization of the resulting azatriene intermediate. The features of this catalytic system include the mild reaction conditions, the low cost of the catalyst, and tolerance of a variety of functional groups.

3.4 Experimental Section

Material and Methods

General. All reactions dealing with air- or moisture-sensitive compounds 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.,¹⁵ using 40–63 mm (Si 60, Merck) or 40–50 mm (Silica Gel 60N, Kanto Chemical) silica gel. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on JEOL ECX-400 (400 MHz)

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NMR spectrometers. ^1H 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 mm film thickness). HPLC separation was performed on a JAI LC-9130 NEXT system equipped with a UV detector and JAIGEL-1H (20 mm i.d. x 600 mm) and JAIGEL-2H (20 mm i.d. x 600 mm) columns. High-resolution mass spectra (HRMS) were obtained with a Q-ToF Premier LC HR mass spectrometer.

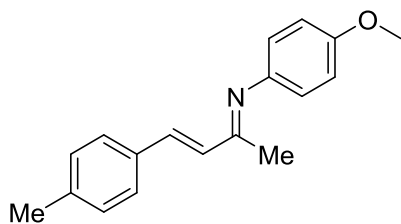
Materials. Unless otherwise noted, reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. Anhydrous cobalt(II) bromide (99%) was purchased from Aldrich and used as received. THF was distilled over Na/benzophenone. Grignard reagents except MeMgCl (purchased from Aldrich) were prepared from the corresponding halides and magnesium turnings in anhydrous THF and titrated before use.

Preparation of Starting Materials

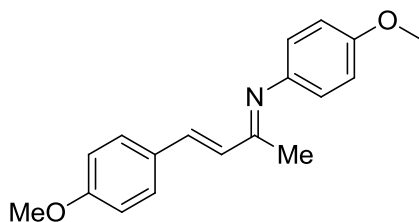
All imines except for **1n** were prepared according to the typical procedure.

Typical Procedure for Preparation of Imines.

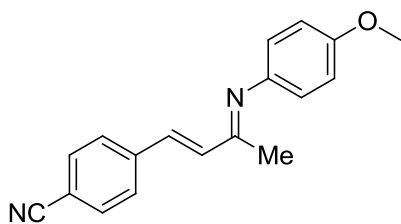
To a solution of α,β -unsaturated carbonyl compounds (20 mmol) and *para*-anisidine (21 mmol) in 20 mL of toluene MS 4A (10 g) was added at room temperature. After 48 h stirring, the reaction mixture was filtered and the resulting crude product was purified by recrystallization from CH_2Cl_2 /hexane, silica gel chromatography, or distillation under reduced pressure. Spectral data for **11a** showed good agreement with the literature data.¹⁶



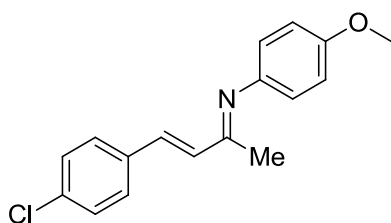
(E)-4-Methoxy-N-((E)-4-(p-tolyl)but-3-en-2-ylidene)aniline (11b): Purified by recrystallization. Yellow solid (53%) consisting of ca. 92:8 mixture of imine *E/Z* isomers as determined by ^1H NMR analysis; Mp = 122–123 °C; ^1H NMR (400 MHz, CDCl_3): δ 2.09 (s, 3H), 2.38 (s, 3H), 3.82 (s, 3H), 6.74 (app. d, $J = 8.7$ Hz, 2H), 6.90 (app. d, $J = 8.7$ Hz, 2H), 6.97 (d, $J = 16.5$ Hz, 1H), 7.14 (d, $J = 16.5$ Hz, 1H), 7.19 (d, $J = 7.8$ Hz, 2H), 7.44 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.0, 21.5, 55.6, 114.3 (2C), 121.3 (2C), 127.5 (2C), 129.8 (2C), 131.2, 133.4, 137.1, 139.3, 144.6, 156.2, 166.6; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{20}\text{NO}$ $[\text{M} + \text{H}]^+$ 266.1545, found 266.1543.



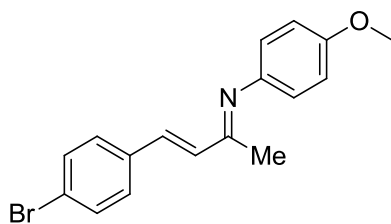
(E)-4-Methoxy-N-((E)-4-(4-methoxyphenyl)but-3-en-2-ylidene)aniline (11c): Purified by recrystallization. Yellow solid (44%) consisting of ca. 83:17 mixture of imine *E/Z* isomers as determined by ^1H NMR analysis; Mp = 145–146 °C; ^1H NMR (400 MHz, CDCl_3): δ 2.07 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 6.75 (app. d, $J = 8.2$ Hz, 2H), 6.89–6.93 (m, 5H), 7.13 (d, $J = 17.0$ Hz, 1H), 7.49 (d, $J = 5.5$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.0, 55.6, 55.7, 114.3 (2C), 114.5 (2C), 121.4 (2C), 128.9, 129.0 (2C), 130.1, 136.8, 144.6, 156.2, 160.6, 166.7; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 282.1494, found 282.1490.



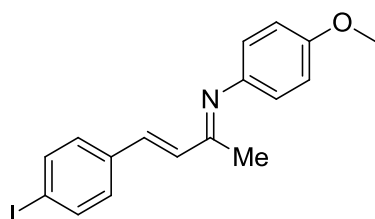
4-((1*E*,3*E*)-3-((4-Methoxyphenyl)imino)but-1-en-1-yl)benzonitrile (11d): Purified by silica gel chromatography (eluent: hexane/EtOAc/NEt₃ = 100/25/5) followed by recrystallization. Orange solid (52%) consisting of ca. 91:9 mixture of imine *E/Z* isomers as determined by ¹H NMR analysis; Mp = 109–111 °C; ¹H NMR (400 MHz, CDCl₃): δ 2.11 (s, 3H), 3.81 (s, 3H), 6.74 (app. d, *J* = 8.7 Hz, 2H), 6.90 (app. d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 17.0 Hz, 1H), 7.14 (d, *J* = 16.5 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 16.2, 55.6, 112.2, 114.4 (2C), 118.9, 121.3 (2C), 127.8 (2C), 132.8 (2C), 134.7, 135.6, 140.7, 144.0, 156.6, 165.7; HRMS (ESI) Calcd for C₁₈H₁₇N₂O [M + H]⁺ 277.1341, found 277.1345.



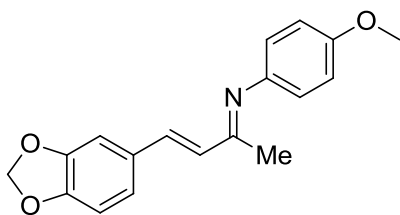
(*E*)-*N*-((*E*)-4-(4-Chlorophenyl)but-3-en-2-ylidene)-4-methoxyaniline (11e): Purified by recrystallization. Yellow solid (68%) consisting of ca. 75:25 mixture of imine *E/Z* isomers as determined by ¹H NMR analysis; Mp = 147–148 °C; ¹H NMR (400 MHz, CDCl₃): δ 2.08 (s, 3H), 3.81 (s, 3H), 6.73 (app. d, *J* = 8.7 Hz, 2H), 6.89 (app. d, *J* = 9.2 Hz, 2H), 6.96 (d, *J* = 16.9 Hz, 1H), 7.10 (d, *J* = 16.5 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.7 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 16.0, 55.6, 114.3 (2C), 121.3 (2C), 128.6 (2C), 129.2 (2C), 132.8, 134.7, 134.9, 135.6, 144.3, 156.4, 166.2; HRMS (ESI) Calcd for C₁₇H₁₇ClNO [M + H]⁺ 286.0999, found 286.0999.



(*E*)-*N*-((*E*)-4-(4-Bromophenyl)but-3-en-2-ylidene)-4-methoxyaniline (11f): Purified by recrystallization. Yellow solid (61%) consisting of ca. 85:15 mixture of imine *E/Z* isomers as determined by ^1H NMR analysis; Mp = 161–163 °C; ^1H NMR (400 MHz, CDCl_3): δ 2.09 (s, 3H), 3.82 (s, 3H), 6.74 (app. d, $J = 8.7$ Hz, 2H), 6.90 (app. d, $J = 8.7$ Hz, 2H), 6.99 (d, $J = 16.9$ Hz, 1H), 7.10 (d, $J = 16.5$ Hz, 1H), 7.40 (d, $J = 8.7$ Hz, 2H), 7.51 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.1, 55.6, 114.3 (2C), 121.3 (2C), 128.9 (2C), 132.1, 132.2 (2C), 132.9, 135.1, 135.7, 144.3, 156.4, 166.2; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{17}\text{BrNO}$ [$\text{M} + \text{H}$] $^+$ 330.0494, found 330.0498.

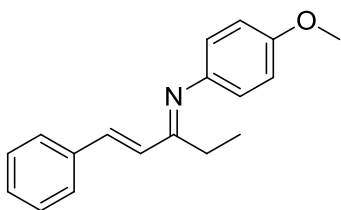


(*E*)-*N*-((*E*)-4-(4-Iodophenyl)but-3-en-2-ylidene)-4-methoxyaniline (11g): Purified by recrystallization. Yellow solid (72%) consisting of ca. 7:3 mixture of imine *E/Z* isomers as determined by ^1H NMR analysis; Mp = 178–180 °C; ^1H NMR (400 MHz, CDCl_3): δ 2.08 (s, 3H), 3.82 (s, 3H), 6.74 (app. d, $J = 7.8$ Hz, 2H), 6.89 (app. d, $J = 8.2$ Hz, 2H), 6.99 (d, $J = 16.5$ Hz, 1H), 7.07 (d, $J = 17.0$ Hz, 1H), 7.71 (d, $J = 7.3$ Hz, 2H), 7.51 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.1, 55.7, 94.9, 114.4 (2C), 121.3 (2C), 122.4, 129.1 (2C), 133.0, 135.9, 138.2 (2C), 144.3, 156.4, 166.2; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{17}\text{INO}$ [$\text{M} + \text{H}$] $^+$ 378.0355, found 378.0351.



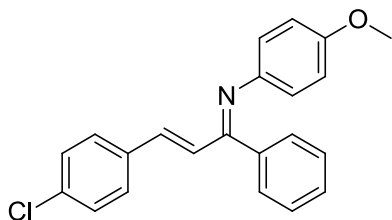
(E)-N-((E)-4-(Benzo[d][1,3]dioxol-5-yl)but-3-en-2-ylidene)-4-methoxyaniline (11h):

Purified by recrystallization. Yellow solid (29%) consisting of ca. 83:17 mixture of imine *E/Z* isomers as determined by ^1H NMR analysis; Mp = 124–125 °C; ^1H NMR (400 MHz, CDCl_3): δ 2.06 (s, 3H), 3.80 (s, 3H), 5.99 (s, 2H), 6.72 (app. d, $J = 9.2$ Hz, 2H), 6.80–6.90 (m, 4H), 6.97 (app. d, $J = 7.8$ Hz, 1H), 7.05–7.09 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.0, 55.6, 101.5, 106.2, 108.7, 114.3 (2C), 121.3 (2C), 123.2, 130.4, 130.7, 136.8, 144.5, 148.5, 148.7, 156.2, 166.5; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{18}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 296.1287, found 296.1283.

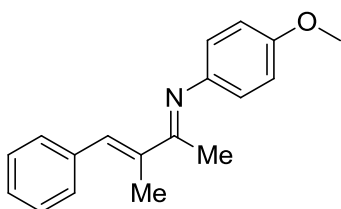


4-Methoxy-N-((E)-1-phenylpent-1-en-3-ylidene)aniline (11i): Purified by distillation under reduced pressure (2.0 mmHg, 220–230 °C) followed by recrystallization from EtOH. Yellow solid (13%) consisting of ca. 3:2 mixture of imine *E/Z* isomers as determined by ^1H NMR analysis; Mp = 99–100 °C; ^1H NMR (400 MHz, CDCl_3): δ 1.13 (t, $J = 7.8$ Hz, 3H, major), 1.32 (t, $J = 7.8$ Hz, 3H, minor), 2.49 (q, $J = 7.8$ Hz, 2H, major), 2.78 (q, $J = 7.3$ Hz, 2H, minor), 3.81 (s, 3H, minor), 3.82 (s, 3H, major), 6.68–6.78 (m, 2H, major, 3H, minor), 6.87–6.91 (m, 3H, major, 2H, minor), 7.10 (d, $J = 16.5$ Hz, 1H, major), 7.22 (d, $J = 16.5$ Hz, 1H, minor), 7.28–7.40 (m, 5H, major, 3H, minor), 7.55, (d, $J = 7.4$ Hz, 2H, minor); ^{13}C NMR (100 MHz, CDCl_3): δ 12.0, 29.3, 55.6, 114.2 (2C), 121.3, 122.0 (2C), 127.6 (2C), 129.0 (2C), 129.4, 136.2, 137.3, 144.2, 156.3, 168.9 (major

isomer), 13.3, 23.0, 55.6, 114.4, 120.6, 127.6, 129.0, 129.2, 130.0, 136.2, 136.9, 144.6, 156.1, 171.8 (minor isomer); HRMS (ESI) Calcd for C₁₈H₂₀NO [M + H]⁺ 266.1545, found 266.1540.

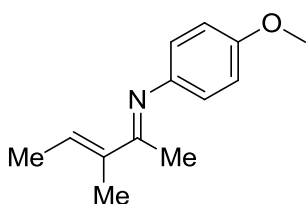


***N*-((*E*)-3-(4-Chlorophenyl)-1-phenylallylidene)-4-methoxyaniline (11j):** Purified by recrystallization. Yellow solid (29%) consisting of a ca. 3:2 mixture of imine *E/Z* isomers as determined by ¹H NMR analysis; Mp = 113–115 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.70 (s, 3H, minor), 3.84 (s, 3H, major), 6.62 (app. d, *J* = 8.8 Hz, 2H, minor), 6.68 (app. d, *J* = 9.1 Hz, 2H, minor), 6.74 (d, *J* = 16.5 Hz, 1H, minor), 6.85 (d, *J* = 16.8 Hz, 1H, major), 6.90–6.96 (m, 5H, major), 7.12–7.14 (m, 2H, minor), 7.21–7.32 (m, 4H, major, 6H, minor), 7.39 (d, *J* = 8.8 Hz, 2H, minor), 7.45–7.49 (m, 3H, major), 7.69–7.72 (m, 2H, major); ¹³C NMR (100 MHz, CDCl₃): δ 55.4, 55.7, 113.8, 114.3 (2C), 122.7 (2C), 123.0, 123.1, 128.5, 128.56 (2C), 128.64, 128.8, 129.1, 129.2 (2C), 129.5 (2C), 130.1, 132.8, 134.5, 134.7, 135.0, 135.3, 135.9, 139.3, 139.7, 139.8, 143.7, 144.3, 156.3, 156.8, 166.9, 168.1. Signals of the major and minor isomers were partially overlapped and could not be distinguished; HRMS (ESI) Calcd for C₂₂H₁₉ClNO [M + H]⁺ 348.1155, found 348.1158.

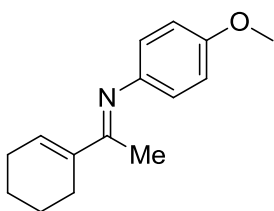


(*E*)-4-Methoxy-*N*-((*E*)-3-methyl-4-phenylbut-3-en-2-ylidene)aniline (11k): Purified by recrystallization. Yellow solid (38%); Mp = 88–89 °C; ¹H NMR (400 MHz, CDCl₃): δ

2.12 (s, 3H), 2.21 (s, 3H), 3.81 (s, 3H), 6.68 (app. d, $J = 11.9$ Hz, 2H), 6.89 (app. d, $J = 11.9$ Hz, 2H), 7.20–7.29 (m, 2H), 7.39–7.40 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.9, 16.6, 55.7, 114.4 (2C), 120.8 (2C), 127.5, 128.4 (2C), 129.7 (2C), 133.9, 137.6, 139.6, 145.4, 156.0, 168.1; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{20}\text{NO}$ $[\text{M} + \text{H}]^+$ 266.1545, found 266.1541.

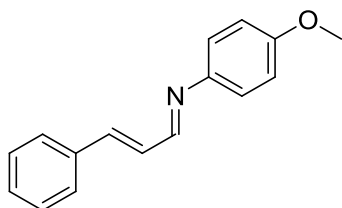


(E)-4-Methoxy-N-((E)-3-methylpent-3-en-2-ylidene)aniline (11l): Purified by distillation under reduced pressure (1.0 mmHg, 100–120 °C). Yellow liquid (10%); ^1H NMR (400 MHz, CDCl_3): δ 1.88 (m, 3H), 1.95 (s, 3H), 1.96 (brs, 3H), 3.79 (s, 3H), 6.29–6.35 (m, 1H), 6.62–6.65 (m, 2H), 6.83–6.87 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.8, 15.0, 16.2, 55.7, 114.3 (2C), 120.8 (2C), 130.7, 138.9, 145.6, 155.8, 167.8; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{18}\text{NO}$ $[\text{M} + \text{H}]^+$ 204.1388, found 204.1384.

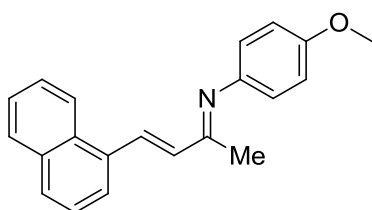


(E)-N-(1-(Cyclohex-1-en-1-yl)ethylidene)-4-methoxyaniline (11m): Purified by distillation under reduced pressure (1.4 mmHg, 170–180 °C) followed by recrystallization from hexane. Yellow solid (13%); Mp = 53–54 °C; ^1H NMR (400 MHz, CDCl_3): δ 1.63–1.72 (m, 4H), 1.93 (s, 3H), 2.26 (m, 2H), 2.44 (m, 2H), 3.79 (s, 3H), 6.49–6.53 (m, 1H), 6.63 (app. d, $J = 8.7$ Hz, 2H), 6.84 (app. d, $J = 9.2$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.9, 22.2, 22.8, 24.9, 26.4, 55.6, 114.2 (2C), 120.8 (2C), 133.6, 139.7, 145.5, 155.7,

167.1; HRMS (ESI) Calcd for $C_{18}H_{20}NO$ $[M + H]^+$ 230.1545, found 230.1540.



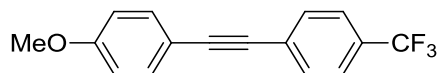
(E)-4-Methoxy-N-((E)-3-phenylallylidene)aniline (11n): To a solution of cinnamaldehyde (6.61 g, 50 mmol) in 100 mL of EtOH *para*-anilidine (6.78 g, 55 mmol) was added at room temperature. After 1 h stirring, the solid was filtered off and washed with EtOH to give a title compound as a yellow solid (9.28 g, 39.1 mmol, 78%). Spectral data showed good agreement with the literature data.¹⁷



(E)-4-Methoxy-N-((E)-4-(naphthalen-1-yl)but-3-en-2-ylidene)aniline (11o): Purified by recrystallization. Yellow solid (54%) consisting of ca. 7:3 mixture of imine *E/Z* isomers as determined by 1H NMR analysis; Mp = 122–124 °C; 1H NMR (400 MHz, $CDCl_3$): δ 2.21 (s, 3H), 3.82 (s, 3H), 6.78 (app. d, $J = 8.7$ Hz, 2H), 6.91 (app. d, $J = 8.7$ Hz, 2H), 7.08 (d, $J = 16.5$ Hz, 1H), 7.49–7.56 (m, 3 H), 7.80 (d, $J = 7.4$ Hz, 1H), 7.86 (d, $J = 8.2$ Hz, 1H), 7.88 (d, $J = 9.2$ Hz, 1H), 7.98 (d, $J = 16.5$ Hz, 1H), 8.19 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3, 55.7, 114.3, 114.4 (2C), 121.4 (2C), 122.1, 123.5, 124.7, 125.9, 126.2, 126.7, 129.4, 131.5, 133.6, 133.9, 135.0, 144.5, 156.4, 166.5; HRMS (ESI) Calcd for $C_{21}H_{20}NO$ $[M + H]^+$ 302.1545, found 302.1544.

1,2-Bis(4-methoxyphenyl)ethyne (**2g**) and 1,2-bis(3-bromophenyl)ethyne (**2h**) were

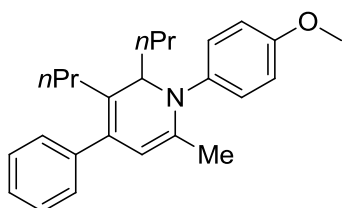
prepared according to the literature procedures.¹⁸



1-Methoxy-4-((4-(trifluoromethyl)phenyl)ethynyl)benzene (2i): To a solution of 1-ethynyl-4-methoxybenzene (335mg, 2.54 mmol) and 1-bromo-4-(trifluoromethyl)benzene (686 mg, 3.05 mmol) in 15 mL of triethylamine PdCl₂(PPh₃)₂ (89 mg, 0.13 mmol) and CuI (13 mg, 0.64 mmol) were added at rt and the reaction mixture was warmed to reflux. After 15 min stirring, the reaction mixture was cooled to rt and sat. NH₄Cl aq. was added and the resulting mixture was stirred for 1 h. the organic layer was separated and the aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine and dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/dichloromethane = 100/3) to afforded the title compound as a white solid (518 mg, 1.88 mmol, 74%). Spectral data showed good accordance with the literature.¹⁹

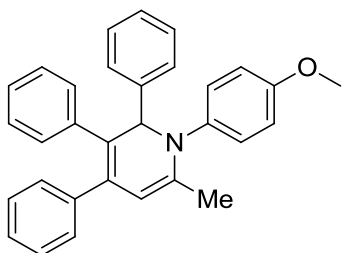
Cobalt-Catalyzed Annulation of α,β -Unsaturated Imine and Alkyne

General Procedure: In a Schlenk tube equipped with a stirrer bar were placed α,β -unsaturated imine (0.20 mmol), alkyne (0.24 mmol), $P(3\text{-ClC}_6\text{H}_4)_3$ (7.3 mg, 0.020 mmol, 10 mol%), CoBr_2 (0.067 M solution in THF, 0.15 mL, 0.010 mmol, 5 mol%) and THF (0.47 mL). To the mixture was added $i\text{PrMgBr}$ (0.89 M in THF, 51 μL , 0.045 mmol, 22.5 mol%) at room temperature. The resulting mixture was stirred at 40 $^\circ\text{C}$ for 3 h, and then quenched with water. The aqueous layer was extracted with ethyl acetate (4 mL x 3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to afford the dihydropyridine derivative.

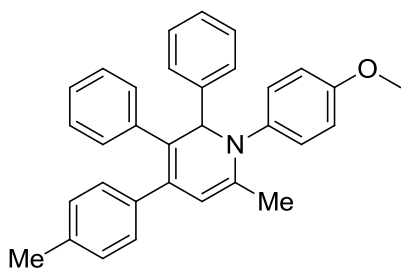
**1-(4-Methoxyphenyl)-6-methyl-4-phenyl-2,3-dipropyl-1,2-dihydropyridine (12b):**

The general procedure was applied to (*E*)-4-methoxy-*N*-((*E*)-4-phenylbut-3-en-2-ylidene)aniline (**11a**, 50.3 mg, 0.20 mmol) and 4-octyne (**2c**, 35.3 μL , 0.24 mmol) with 10 mol% of the catalytic system. Silica gel chromatography (eluent: hexane/ NEt_3 = 100/2) of the crude product afforded the title compound as a red oil (42.3 mg, 59% yield); R_f 0.54 (hexane/ EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 0.61 (t, J = 7.3 Hz, 3H), 1.00 (t, J = 7.3 Hz, 3H), 1.04–1.21 (m, 2H), 1.40–1.54 (m, 2H), 1.60–1.69 (m, 1H), 1.73–1.87 (m, 5H), 2.04–2.13 (m, 1H), 3.79 (s, 3H), 3.91 (m, 1H), 5.43 (s, 1H), 6.82 (app. d, J = 8.7 Hz, 2H), 6.98 (app. d, J = 9.2 Hz, 2H), 7.22–7.24 (m, 3H), 7.30–7.34 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.0, 14.7, 19.5, 19.7, 22.4, 33.2, 33.8, 55.7, 65.0, 111.1, 114.3 (2C), 123.8, 125.4 (2C), 126.3, 128.1 (2C), 129.2 (2C), 130.8, 135.2, 140.8, 141.7, 155.8; **HRMS** (ESI) Calcd for $\text{C}_{25}\text{H}_{32}\text{NO}$

$[M + H]^+$ 362.2484, found 362.2484.

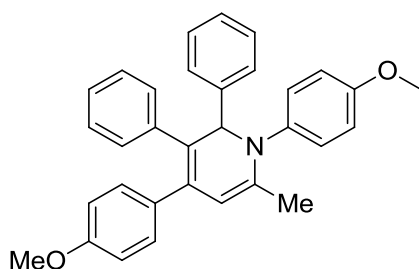


1-(4-Methoxyphenyl)-6-methyl-2,3,4-triphenyl-1,2-dihydropyridine (12b): The reaction was performed in a 25 mL 2-necked flask with (*E*)-4-methoxy-*N*-((*E*)-4-phenylbut-3-en-2-ylidene)aniline (**11a**, 1.26 g, 5.0 mmol), diphenylacetylene (**2a**, 1.07 g, 6.0 mmol), $P(3\text{-ClC}_6\text{H}_4)_3$ (183 mg, 0.5 mmol, 10 mol%), CoBr_2 (0.067 M solution in THF, 3.75 mL, 0.25 mmol, 5 mol%), and *i*PrMgBr (0.89 M in THF, 1.26 mL, 1.13 mmol, 22.5 mol%). Silica gel chromatography (eluent: hexane/EtOAc/ $\text{NEt}_3 = 100/1/2$) of the crude product afforded the title compound as a yellow fluffy solid (1.96 g, 91% yield); Mp = 70–72 °C; R_f 0.47 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 1.88 (s, 3H), 3.79 (s, 3H), 5.41 (s, 1H), 5.50 (s, 1H), 6.83 (d, $J = 7.8$ Hz, 2H), 6.94 (d, $J = 8.2$ Hz, 2H), 6.98–7.03 (m, 3H), 7.08 (d, $J = 7.8$ Hz, 2H), 7.15–7.32 (m, 8H), 7.50 (d, $J = 7.3$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.2, 55.7, 69.9, 108.5, 114.3 (2C), 118.8, 125.7, 126.7, 126.9 (2C), 127.3 (2C), 127.6, 127.9 (2C), 128.2 (2C), 128.4 (2C), 129.6 (2C), 129.7 (2C), 134.1, 139.1, 139.3, 141.1, 141.4, 143.5, 157.0; HRMS (ESI) Calcd for $\text{C}_{31}\text{H}_{28}\text{NO}$ $[M + H]^+$ 430.2171, found 430.2168.



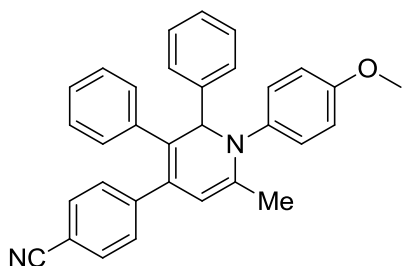
1-(4-Methoxyphenyl)-6-methyl-2,3-diphenyl-4-(*p*-tolyl)-1,2-dihydropyridine (12c):

The general procedure was applied to (*E*)-4-methoxy-*N*-((*E*)-4-(*p*-tolyl)but-3-en-2-ylidene)aniline (**11b**, 53.1 mg, 0.20 mmol) and diphenylacetylene (**2a**, 42.8 mg, 0.24 mmol). Silica gel chromatography (eluent: hexane/EtOAc/NEt₃ = 100/1/2) of the crude product afforded the title compound as a yellow fluffy solid (85.5 mg, 95% yield); Mp = 63–65 °C; *R_f* 0.47 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 1.88 (s, 3H), 2.30 (s, 3H), 3.80 (s, 3H), 5.40 (s, 1H), 5.49 (s, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.99–7.03 (m, 4H), 7.08–7.13 (m, 3H), 7.30–7.34 (m, 3H), 7.51 (d, *J* = 7.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 20.2, 21.4, 55.7, 69.9, 108.7, 114.3 (2C), 118.4, 125.6, 126.9 (2C), 127.3 (2C), 127.5, 127.9 (2C), 128.3 (2C), 128.9 (2C), 129.5 (2C), 129.7 (2C), 134.0, 136.3, 138.4, 138.9, 139.3, 141.2, 143.6, 156.9; HRMS (ESI) Calcd for C₃₂H₃₀NO [M + H]⁺ 444.2327, found 444.2323.



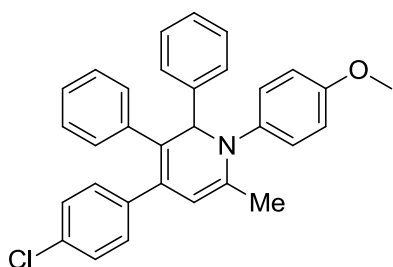
1,4-Bis(4-methoxyphenyl)-6-methyl-2,3-diphenyl-1,2-dihydropyridine (12d): The general procedure was applied to (*E*)-4-methoxy-*N*-((*E*)-4-(4-methoxyphenyl)but-3-en-2-ylidene)aniline (**11c**, 56.3 mg, 0.20 mmol) and diphenylacetylene (**2a**, 42.8 mg, 0.24 mmol). Silica gel chromatography (eluent: hexane/EtOAc/NEt₃ = 100/3/2) of the crude product afforded the title compound as a yellow fluffy solid (87.6 mg, 95% yield); Mp = 64–66 °C; *R_f* 0.20 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 1.88 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 5.39 (s, 1H), 5.48 (s, 1H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 9.2 Hz, 2H), 6.95–7.04 (m, 5H), 7.09 (d, *J* = 9.2 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.26–7.32 (m, 3H), 7.51 (d, *J* = 7.3 Hz, 2H);

^{13}C NMR (100 MHz, CDCl_3): δ 20.2, 55.4, 55.7, 69.9, 108.7, 113.6 (2C), 114.3 (2C), 118.0, 125.6, 126.9 (2C), 127.3 (2C), 127.5, 127.9 (2C), 128.3 (2C), 129.7 (2C), 130.7 (2C), 133.6, 133.7, 138.9, 139.3, 141.3, 143.6, 156.9, 158.5; HRMS (ESI) Calcd for $\text{C}_{32}\text{H}_{30}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 460.2277, found 460.2274.



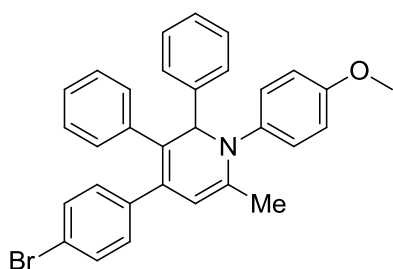
4-(1-(4-Methoxyphenyl)-6-methyl-2,3-diphenyl-1,2-dihydropyridin-4-yl)benzonitrile

(12e): The general procedure was applied to 4-((1*E*,3*E*)-3-((4-methoxyphenyl)imino)but-1-en-1-yl)benzonitrile (**11d**, 55.3 mg, 0.20 mmol) and diphenylacetylene (**2a**, 42.8 mg, 0.24 mmol). Silica gel chromatography (eluent: hexane/EtOAc/ NEt_3 = 100/1/2) of the crude product afforded the title compound as an orange fluffy solid (76.7 mg, 84% yield); Mp = 82–84 °C; R_f 0.24 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 1.89 (s, 3H), 3.79 (s, 3H), 5.30 (s, 1H), 5.50 (s, 1H), 6.83 (d, J = 9.2 Hz, 2H), 6.88–6.90 (m, 2H), 7.03–7.07 (m, 5H), 7.29–7.31 (m, 5H), 7.43–7.47 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.3, 55.7, 70.0, 106.1, 110.1, 114.3 (2C), 119.4, 120.4, 126.4, 127.1 (2C), 127.3 (2C), 127.8, 128.3 (2C), 128.5 (2C), 129.7 (2C), 130.4 (2C), 132.0 (2C), 132.6, 138.8, 140.2, 140.3, 143.0, 146.6, 157.3; HRMS (ESI) Calcd for $\text{C}_{32}\text{H}_{27}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 455.2123, found 455.2125.



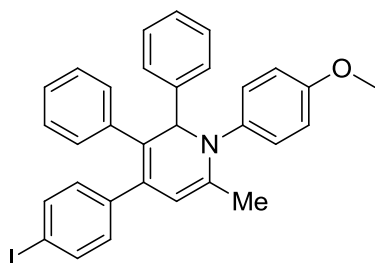
4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-6-methyl-2,3-diphenyl-1,2-dihydropyridine

(12f): The general procedure was applied to (*E*)-*N*-((*E*)-4-(4-chlorophenyl)but-3-en-2-ylidene)-4-methoxyaniline (**11e**, 57.1 mg, 0.20 mmol) and diphenylacetylene (**2a**, 42.8 mg, 0.24 mmol). Silica gel chromatography (eluent: hexane/EtOAc/NEt₃ = 100/1/2) of the crude product afforded the title compound as a yellow fluffy solid (78.9 mg, 85% yield); Mp = 61–63 °C; *R*_f 0.29 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 1.87 (s, 3H), 3.79 (s, 3H), 5.32 (s, 1H), 5.48 (s, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 7.02–7.07 (m, 5H), 7.15 (s, 4H), 7.25–7.32 (m, 3H), 7.47 (d, *J* = 6.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 20.3, 55.7, 69.9, 107.5, 114.3 (2C), 119.1, 126.0, 127.1 (2C), 127.2 (2C), 127.7, 128.1 (2C), 128.36 (2C), 128.41 (2C), 129.7 (2C), 131.0 (2C), 132.4, 132.9, 139.1, 139.5, 139.9, 140.7, 143.3, 157.1; HRMS (ESI) Calcd for C₃₁H₂₇ClNO [M + H]⁺ 464.1781, found 464.1779.

**4-(4-Bromophenyl)-1-(4-methoxyphenyl)-6-methyl-2,3-diphenyl-1,2-dihydropyridine**

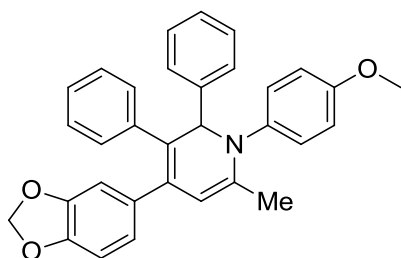
(12g): The general procedure was applied to (*E*)-*N*-((*E*)-4-(4-bromophenyl)but-3-en-2-ylidene)-4-methoxyaniline (**11f**, 66.0 mg, 0.20 mmol) and diphenylacetylene (**2a**, 42.8 mg, 0.24 mmol). Silica gel chromatography (eluent: hexane/EtOAc/NEt₃ = 100/1/2) of the crude product afforded the title compound as a yellow fluffy solid (71.4 mg, 70% yield); Mp = 67–69 °C; *R*_f 0.42 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 1.88 (s, 3H), 3.80 (s, 3H), 5.33 (s, 1H), 5.49 (s, 1H), 6.83 (d, *J* = 9.2 Hz, 2H), 6.93 (d, *J* = 8.2 Hz, 2H), 7.03–7.11 (m, 7H), 7.30–7.32 (m, 5H), 7.47 (d, *J* = 8.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 20.3, 55.7, 69.9, 107.4, 114.3

(2C), 119.2, 120.6, 126.0, 127.1 (2C), 127.2 (2C), 127.7, 128.1 (2C), 128.4 (2C), 129.7 (2C), 131.30 (2C), 131.32 (2C), 133.0, 139.1, 139.6, 140.4, 140.7, 143.3, 157.1; HRMS (ESI) Calcd for $C_{31}H_{27}BrNO$ $[M + H]^+$ 508.1276, found 508.1280.



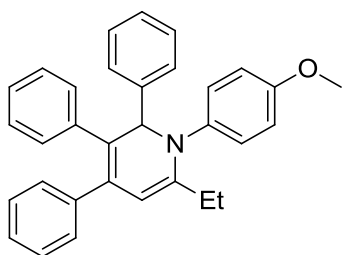
4-(4-Iodophenyl)-1-(4-methoxyphenyl)-6-methyl-2,3-diphenyl-1,2-dihydropyridine

(12h): The general procedure was applied to (*E*)-*N*-((*E*)-4-(4-iodophenyl)but-3-en-2-ylidene)-4-methoxyaniline (**11g**, 75.4 mg, 0.20 mmol) and diphenylacetylene (**2a**, 42.8 mg, 0.24 mmol). Silica gel chromatography (eluent: hexane/ CH_2Cl_2 / NEt_3 = 100/5/2) of the crude product afforded the title compound as a yellow fluffy solid (26.0 mg, 23% yield); Mp = 59–61 °C; R_f 0.44 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, $CDCl_3$): δ 1.88 (s, 3H), 3.79 (s, 3H), 5.32 (s, 1H), 5.48 (s, 1H), 6.83 (app. d, J = 9.2 Hz, 2H), 6.92–6.98 (m, 4H), 7.02–7.08 (m, 5H), 7.30–7.32 (m, 3H), 7.46–7.48 (m, 2H), 7.51 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3, 55.7, 69.9, 92.2, 107.3, 114.3 (2C), 119.1, 126.0, 127.1 (2C), 127.2 (2C), 127.7, 128.1 (2C), 128.4 (2C), 129.7 (2C), 131.6 (2C), 133.0, 137.3 (2C), 139.0, 139.6, 140.7, 141.0, 143.3, 157.1; HRMS (ESI) Calcd for $C_{31}H_{27}INO$ $[M + H]^+$ 556.1137, found 556.1137.



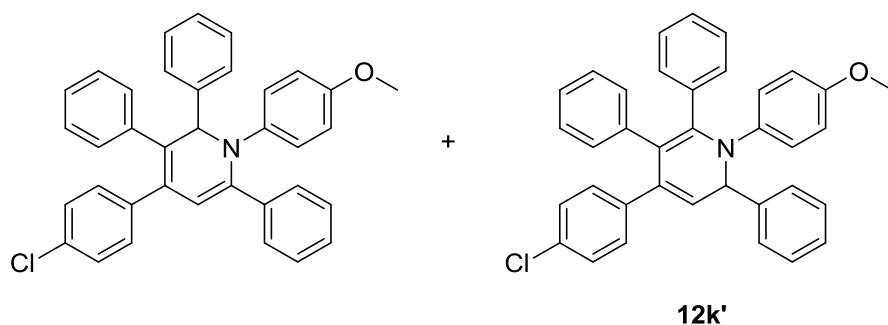
4-(Benzo[*d*][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)-6-methyl-2,3-diphenyl-1,2-dihydro

pyridine (12i): The general procedure was applied to (*E*)-*N*-((*E*)-4-(benzo[*d*][1,3]dioxol-5-yl)but-3-en-2-ylidene)-4-methoxyaniline (**11h**, 59.1 mg, 0.20 mmol) and diphenylacetylene (**2a**, 42.8 mg, 0.24 mmol). Silica gel chromatography (eluent = hexane/EtOAc/NEt₃ = 100/2/2) of the crude product afforded the title compound as a yellow fluffy solid (86.2 mg, 91% yield); Mp = 58–60 °C; *R*_f 0.39 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 1.87 (s, 3H), 3.80 (s, 3H), 5.35 (s, 1H), 5.47 (s, 1H), 5.91 (s, 2H), 6.66 (d, *J* = 8.7 Hz, 1H), 6.72 (dd, *J* = 6.0 Hz, 1.8 Hz, 2H), 6.83 (app. d, *J* = 8.7 Hz, 2H), 6.97–7.09 (m, 7H), 7.29–7.33 (m, 3H), 7.50 (d, *J* = 6.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 20.2, 55.7, 69.8, 101.0, 108.2, 108.5, 110.2, 114.3 (2C), 118.2, 123.1, 125.7, 126.9 (2C), 127.3 (2C), 127.6, 128.0 (2C), 128.3 (2C), 129.6 (2C), 133.7, 135.5, 139.0, 139.2, 141.0, 143.5, 146.4, 147.4, 157.0; HRMS (ESI) Calcd for C₃₂H₂₈NO₃ [M + H]⁺ 474.2069, found 474.2067.



6-Ethyl-1-(4-methoxyphenyl)-2,3,4-triphenyl-1,2-dihydropyridine (12j): The general procedure was applied to 4-methoxy-*N*-((*E*)-1-phenylpent-1-en-3-ylidene)aniline (**11i**, 53.1 mg, 0.20 mmol) and diphenylacetylene (**2a**, 42.8 mg, 0.24 mmol). Silica gel chromatography (eluent: hexane/EtOAc/NEt₃ = 100/1/2) of the crude product afforded the title compound as a yellow fluffy solid (89.2 mg, 98% yield); Mp = 50–52 °C; *R*_f 0.45 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 0.88 (t, *J* = 7.3 Hz, 3H), 2.14–2.30 (m, 2H), 3.79 (s, 3H), 5.47 (s, 1H), 5.56 (s, 1H), 6.82 (d, *J* = 7.8 Hz, 2H), 6.93 (d, *J* = 7.8 Hz, 2H), 6.98–7.03 (m, 3H), 7.14–7.36 (m, 10H), 7.63 (d, *J* = 7.3 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 12.8, 25.9, 55.7, 69.9, 109.3, 114.4 (2C), 118.9, 125.8, 126.4

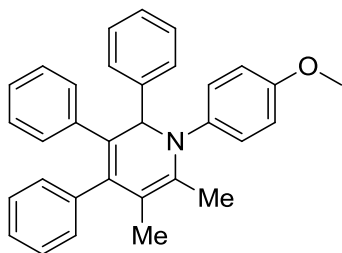
(2C), 126.7, 127.56, 127.62 (2C), 127.9 (2C), 128.2 (4C), 129.6 (2C), 129.7 (2C), 134.1, 139.8, 141.0, 141.5, 143.5, 144.3, 156.8; HRMS (ESI) Calcd for $C_{32}H_{30}NO$ $[M + H]^+$ 444.2327, found 444.2325.



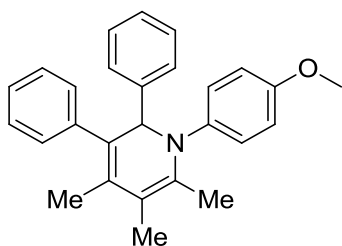
4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-2,3,6-triphenyl-1,2-dihydropyridine (12k)

and 4-(4-chlorophenyl)-1-(4-methoxyphenyl)-2,5,6-triphenyl-1,2-dihydropyridine

(12k'): The general procedure was applied to *N*-((*E*)-3-(4-chlorophenyl)-1-phenylallylidene)-4-methoxyaniline (**11j**, 69.6 mg, 0.20 mmol) and diphenylacetylene (**2a**, 42.8 mg, 0.24 mmol). Silica gel chromatography (eluent: hexane/EtOAc/ NEt_3 = 100/3/2) of the crude product afforded a mixture of the title compound and its double bond isomer **12k'** (5:1 by 1H NMR analysis) as a yellow fluffy solid (101.5 mg, 96% yield); Mp = 90–92 °C; R_f 0.39 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, $CDCl_3$): δ 3.70 (s, 3H), 5.75 (s, 1H), 6.15 (s, 1H), 6.71 (app. d, J = 9.2 Hz, 2H), 6.88–6.90 (m, 1H), 6.95–6.98 (m, 2H), 7.03–7.32 (m, 12H), 7.36 (t, J = 7.3 Hz, 2H), 7.48 (dd, J = 8.2 Hz, 1.4 Hz, 2H), 7.75 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 69.8, 113.8, 114.3 (2C), 122.7, 124.5 (2C), 126.6, 127.4 (2C), 127.8, 128.0 (2C), 128.2, 128.3 (2C), 128.4 (2C), 128.5 (2C), 128.6 (2C), 129.5 (2C), 131.1 (2C), 132.8, 133.1, 137.0, 139.3, 140.2, 140.6, 140.7, 142.8, 155.8; HRMS (ESI) Calcd for $C_{36}H_{29}ClNO$ $[M + H]^+$ 526.1938, found 526.1938.

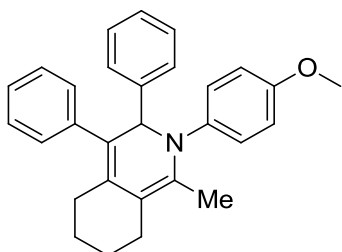


1-(4-Methoxyphenyl)-5,6-dimethyl-2,3,4-triphenyl-1,2-dihydropyridine (12l): The general procedure was applied to (*E*)-4-methoxy-*N*-((*E*)-3-methyl-4-phenylbut-3-en-2-ylidene)aniline (**11k**, 53.1 mg, 0.20 mmol) and diphenylacetylene (**2a**, 42.8 mg, 0.24 mmol). Silica gel chromatography (eluent: hexane/EtOAc/ $\text{NEt}_3 = 100/1/2$) of the crude product afforded the title compound as a yellow fluffy solid (68.6 mg, 77% yield); Mp = 61–63 °C; R_f 0.48 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 1.52 (s, 3H), 1.82 (s, 3H), 3.79 (s, 3H), 5.46 (s, 1H), 6.83–6.86 (m, 3H), 6.92–6.95 (m, 3H), 7.11 (d, $J = 8.7$ Hz, 2H), 7.16–7.26 (m, 6H), 7.32 (d, $J = 7.3$ Hz, 1H), 7.35–7.37 (m, 2H), 7.65 (d, $J = 6.9$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.1, 17.2, 55.8, 68.3, 114.5 (2C), 117.2, 121.3, 124.2 (2C), 125.6, 126.6, 127.3 (4C), 127.7 (2C), 128.1 (2C), 128.2 (2C), 129.3 (2C), 130.8, 133.0, 137.3, 140.4, 140.5, 141.1, 144.0, 155.8; HRMS (ESI) Calcd for $\text{C}_{32}\text{H}_{30}\text{NO}$ $[\text{M} + \text{H}]^+$ 444.2327, found 444.2330.



1-(4-Methoxyphenyl)-4,5,6-trimethyl-2,3-diphenyl-1,2-dihydropyridine (12m): The general procedure was applied to (*E*)-4-methoxy-*N*-((*E*)-3-methylpent-3-en-2-ylidene)aniline (**11l**, 40.7 mg, 0.20 mmol) and diphenylacetylene (**2a**, 42.8 mg, 0.24 mmol) with 10 mol% of the catalytic system.

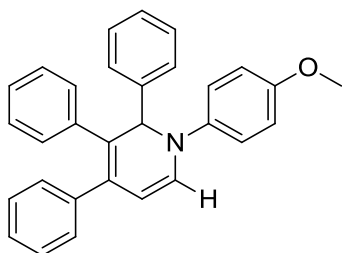
Silica gel chromatography (eluent: hexane/EtOAc/NEt₃ = 100/1/2) of the crude product afforded the title compound as a yellow sticky solid (53.9 mg, 71% yield); Mp = 118–119 °C; *R_f* 0.39 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 1.82 (s, 3H), 1.86 (s, 3H), 1.89 (s, 3H), 3.78 (s, 3H), 5.43 (s, 1H), 6.83 (app. d, *J* = 9.2 Hz, 2H), 6.98 (app. d, *J* = 8.7 Hz, 2H), 7.07–7.16 (m, 3H), 7.20–7.25 (m, 5H), 7.31–7.33 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 14.1, 16.1, 17.2, 55.7, 68.5, 114.4 (2C), 117.1, 123.8 (2C), 124.1, 125.9, 126.6 (2C), 126.9, 128.0 (2C), 128.2 (2C), 129.0, 129.4 (2C), 132.0, 140.1, 142.3, 144.0, 155.5; HRMS (ESI) Calcd for C₂₇H₂₈NO [M + H]⁺ 382.2171, found 382.2173.



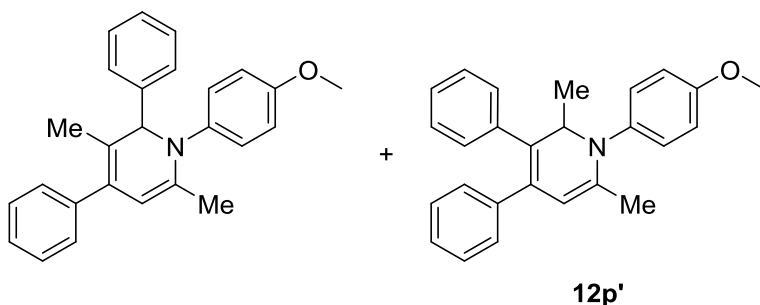
2-(4-Methoxyphenyl)-1-methyl-3,4-diphenyl-2,3,5,6,7,8-hexahydroisoquinoline

(12n): The general procedure was applied to (*E*)-*N*-(1-(cyclohex-1-en-1-yl)ethylidene)-4-methoxyaniline (**11m**, 45.9 mg, 0.20 mmol) and diphenylacetylene (**2a**, 42.8 mg, 0.24 mmol) with 10 mol% of the catalytic system. Silica gel chromatography (eluent: hexane/EtOAc/NEt₃ = 100/1/2) of the crude product afforded the title compound as a yellow fluffy solid (64.6 mg, 79% yield); Mp = 90–92 °C; *R_f* 0.39 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 1.46–1.51 (m, 1H), 1.54–1.62 (m, 1H), 1.66–1.82 (m, 5H), 2.03–2.09 (m, 1H), 2.19–2.27 (m, 1H), 2.52–2.59 (m, 1H), 2.66–2.72 (m, 1H), 3.77 (s, 3H), 5.32 (s, 1H), 6.82 (app. d, *J* = 9.2 Hz, 2H), 7.00 (app. d, *J* = 9.2 Hz, 2H), 7.07–7.13 (m, 3H), 7.20–7.35 (m, 5H), 7.40 (d, *J* = 7.3 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 16.7, 24.5, 24.7, 25.9, 28.1, 55.7, 68.4, 114.3 (2C), 118.7, 121.6, 123.7 (2C), 125.9, 127.0 (3C), 128.1 (2C), 128.2 (2C), 129.2 (2C), 130.6, 131.0, 140.5, 141.6, 144.2, 155.5; HRMS (ESI) Calcd for C₂₉H₃₀NO [M + H]⁺ 408.2327, found

408.2326.

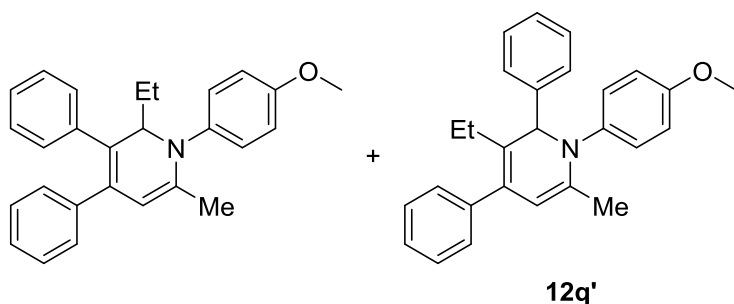


1-(4-Methoxyphenyl)-2,3,4-triphenyl-1,2-dihydropyridine (12o): The general procedure was applied to (*E*)-4-methoxy-*N*-((*E*)-3-phenylallylidene)aniline (**11n**, 47.5 mg, 0.20 mmol) and diphenylacetylene (**2a**, 42.8 mg, 0.24 mmol) with 10 mol% of the catalytic system. Silica gel chromatography (eluent: hexane/EtOAc/NEt₃ = 100/1/2) of the crude product afforded the title compound as a yellow fluffy solid (65.3 mg, 79% yield); Mp = 57–59 °C; *R_f* 0.40 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 3.76 (s, 3H), 5.48 (d, *J* = 7.3 Hz, 1H), 5.87 (s, 1H), 6.72 (dd, *J* = 7.3 Hz, 1.4 Hz, 1H), 6.85 (app. d, *J* = 8.7 Hz, 2H), 6.99–7.16 (m, 12H), 7.23–7.25 (m, 3H), 7.37–7.39 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 55.8, 65.6, 106.8, 114.8 (2C), 119.2 (2C), 121.8, 126.2, 126.69, 126.74 (2C), 127.6, 128.1 (4C), 128.4 (2C), 129.4 (2C), 129.7, 130.0 (2C), 133.1, 139.9, 140.9, 141.0, 142.2, 155.3; HRMS (ESI) Calcd for C₃₀H₂₆NO [M + H]⁺ 416.2014, found 416.2019.



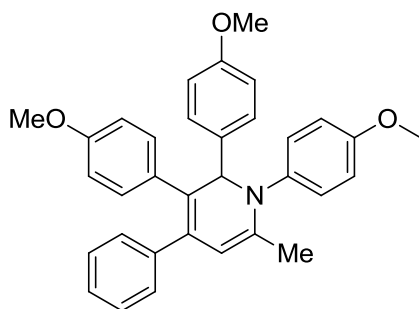
1-(4-Methoxyphenyl)-3,6-dimethyl-2,4-diphenyl-1,2-dihydropyridine (12p) and 1-(4-methoxyphenyl)-2,6-dimethyl-3,4-diphenyl-1,2-dihydropyridine (12p'): The

general procedure was applied to (*E*)-4-methoxy-*N*-((*E*)-4-phenylbut-3-en-2-ylidene)aniline (**11a**, 50.3 mg, 0.20 mmol) and 1-phenyl-1-propyne (**2e**, 30.1 μ L, 0.24 mmol). Silica gel chromatography (eluent: hexane/ NEt_3 = 100/2) of the crude product afforded a mixture of the title compound and its minor regioisomer **12p'** (85:15 by ^1H NMR analysis) as a yellow oil (52.9 mg, 72% yield); R_f 0.50 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3 , major isomer): δ 1.70 (s, 3H), 1.78 (s, 3H), 3.78 (s, 3H), 4.99 (s, 1H), 5.11 (s, 1H), 6.79 (app. d, J = 9.2 Hz, 2H), 6.95 (app. d, J = 8.7 Hz, 2H), 7.09–7.18 (m, 2H), 7.22–7.35 (m, 6H), 7.46–7.48 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3 , major isomer): δ 18.9, 20.4, 55.6, 71.5, 104.5, 114.1 (2C), 114.2, 126.6, 127.1(2C), 127.5 (2C), 127.6 (2C), 128.1 (2C), 128.5 (2C), 129.0 (2C), 131.4, 137.7, 139.7, 141.4, 144.3, 156.8; HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{26}\text{NO}$ [$\text{M} + \text{H}$] $^+$ 368.2014, found 368.2014.



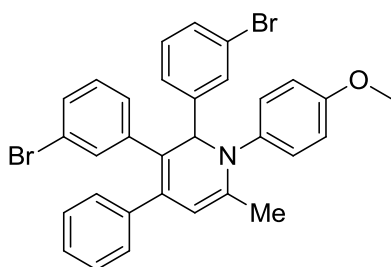
2-Ethyl-1-(4-methoxyphenyl)-6-methyl-3,4-diphenyl-1,2-dihydropyridine (12q) and 3-ethyl-1-(4-methoxyphenyl)-6-methyl-2,4-diphenyl-1,2-dihydropyridine (12q'): The general procedure was applied to (*E*)-4-methoxy-*N*-((*E*)-4-phenylbut-3-en-2-ylidene)aniline (**11a**, 50.3 mg, 0.20 mmol) and 1-phenyl-1-butyne (**2f**, 34.1 μ L, 0.24 mmol). Silica gel chromatography (eluent: hexane/ NEt_3 = 100/2) of the crude product afforded a mixture of the title compound and its regioisomer **12q'** (53:47 by ^1H NMR analysis) as a yellow oil (71.0 mg, 93% yield); R_f 0.41 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 0.82 (t, J = 7.8 Hz, 3H,

12q'), 1.06 (t, $J = 7.3$ Hz, 3H, **12q**), 1.61–1.67 (m, 1H, **12q**), 1.74 (s, 3H, **12q'**), 1.87–1.97 (m, 3H, **12q**, 2H, **12q'**), 2.20–2.25 (m, 1H, **12q**), 3.78 (s, 3H, **12q'**), 3.79 (s, 3H, **12q**), 4.34 (dd $J = 9.2$ Hz, 4.1 Hz, 1H, **12q**), 5.08 (s, 1H, **12q'**), 5.14 (s, 1H, **12q'**), 5.62 (s, 1H, **12q**), 6.81 (app. d, $J = 9.2$ Hz, 2H, **12q'**), 6.84 (app. d, $J = 8.7$ Hz, 2H, **12q**), 6.90 (app. d, $J = 8.2$ Hz, 2H), 6.98–7.36 (m, 10H, **12q**, 10H, **12q'**), 7.50 (d, $J = 7.80$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 10.9, 13.6, 19.9, 20.3, 24.5, 55.6, 55.7, 67.8, 69.3, 105.9, 110.9, 114.1 (2C), 114.3 (2C), 122.8, 123.6, 125.6, 126.1 (2C), 126.3, 126.6, 127.3 (2C), 127.47 (2C), 127.54, 127.9 (2C), 128.1 (2C), 128.2 (2C), 128.4 (2C), 128.9 (2C), 129.38 (2C), 129.41 (2C), 131.9, 132.1, 137.5, 137.6, 139.6, 140.4, 141.2, 141.3, 141.6, 144.2, 156.3, 156.9. Signals of **12q** and **12q'** could not be distinguished; HRMS (ESI) Calcd for $\text{C}_{27}\text{H}_{28}\text{NO}$ $[\text{M} + \text{H}]^+$ 382.2171, found 382.2166.



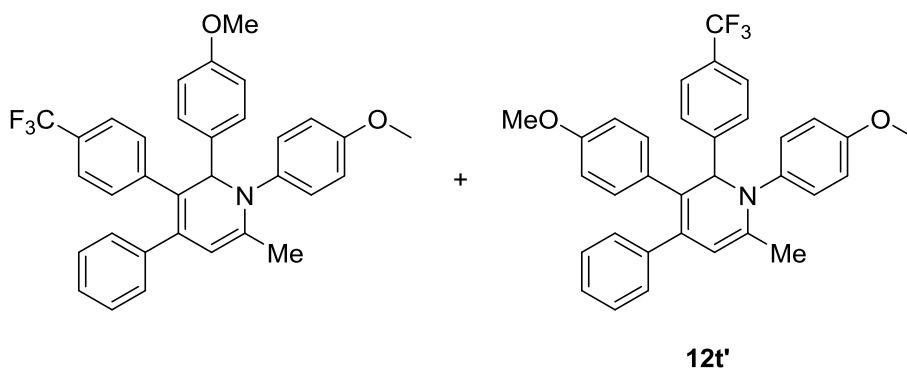
1,2,3-Tris(4-methoxyphenyl)-6-methyl-4-phenyl-1,2-dihydropyridine (12r): The general procedure was applied to (*E*)-4-methoxy-*N*-((*E*)-4-phenylbut-3-en-2-ylidene)aniline (**11a**, 50.3 mg, 0.20 mmol) and 1,2-bis(4-methoxyphenyl)ethyne (**2g**, 60.7 mg, 0.24 mmol). Silica gel chromatography (eluent: hexane/EtOAc/ CH_2Cl_2 / $\text{NEt}_3 = 100/4/5/2$) of the crude product afforded the title compound as a yellow fluffy solid (80.8 mg, 83% yield); Mp = 69–71 °C; R_f 0.29 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 1.85 (s, 3H), 3.66 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 5.39 (s, 2H), 6.56 (d, $J = 8.2$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 2H), 6.85–6.88 (m, 4H), 7.07 (d, $J = 8.7$ Hz, 2H), 7.15–7.22 (m, 3H), 7.26 (d, $J = 6.9$ Hz, 2H), 7.44

(d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.2, 55.2, 55.4, 55.6, 69.5, 108.0, 113.3 (2C), 113.7 (2C), 114.2 (2C), 118.5, 126.5, 127.2 (2C), 128.2 (2C), 128.6 (2C), 129.7 (2C), 130.7 (2C), 133.0, 133.5, 135.7, 138.4, 139.3, 141.8, 156.9, 157.6, 159.1; HRMS (ESI) Calcd for $\text{C}_{33}\text{H}_{32}\text{NO}_3$ [$\text{M} + \text{H}$] $^+$ 490.2382, found 490.2381.



2,3-Bis(3-bromophenyl)-1-(4-methoxyphenyl)-6-methyl-4-phenyl-1,2-dihydropyridine

(12s): The general procedure was applied to (*E*)-4-methoxy-*N*-((*E*)-4-phenylbut-3-en-2-ylidene)aniline (**11a**, 50.3 mg, 0.20 mmol) and 1,2-bis(3-bromophenyl)ethyne (**2h**, 84.3 mg, 0.24 mmol). Silica gel chromatography (eluent: hexane/ CH_2Cl_2 / $\text{NEt}_3 = 100/6/2$) of the crude product afforded the title compound as a yellow fluffy solid (70.5 mg, 60% yield); Mp = 70–72 °C; R_f 0.47 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 1.89 (s, 3H), 3.80 (s, 3H), 5.41 (s, 1H), 5.44 (s, 1H), 6.79–6.81 (m, 1H), 6.85–6.89 (m, 3H), 7.07–7.09 (m, 3H), 7.11–7.13 (m, 1H), 7.17–7.24 (m, 6H), 7.37 (d, $J = 7.8$ Hz, 1H), 7.42 (d, $J = 8.2$ Hz, 1H), 7.64 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.3, 55.7, 69.3, 108.0, 114.5 (2C), 116.3, 122.2, 122.7, 125.8, 127.2 (3C), 128.4 (2C), 128.5, 128.9, 129.4 (2C), 129.5, 130.1, 130.2, 130.9, 132.1, 135.8, 138.7, 140.0, 140.6, 142.3, 145.4, 157.4; HRMS (ESI) Calcd for $\text{C}_{31}\text{H}_{26}\text{Br}_2\text{NO}$ [$\text{M} + \text{H}$] $^+$ 586.0381, found 586.0378.



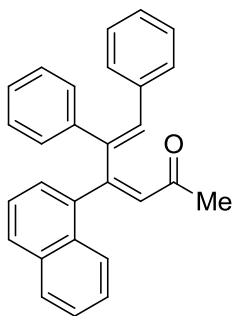
1,2-Bis(4-methoxyphenyl)-6-methyl-4-phenyl-3-(4-(trifluoromethyl)phenyl)-1,2-dihydropyridine (12t) and

1,3-bis(4-methoxyphenyl)-6-methyl-4-phenyl-2-(4-(trifluoromethyl)phenyl)-1,2-dihydropyridine (12t'): The general procedure was applied to

(*E*)-4-methoxy-*N*-((*E*)-4-phenylbut-3-en-2-ylidene)aniline (**11a**, 50.3 mg, 0.20 mmol) and 1-methoxy-4-((4-(trifluoromethyl)phenyl)ethynyl)benzene (**2i**, 66.3 mg, 0.24 mmol).

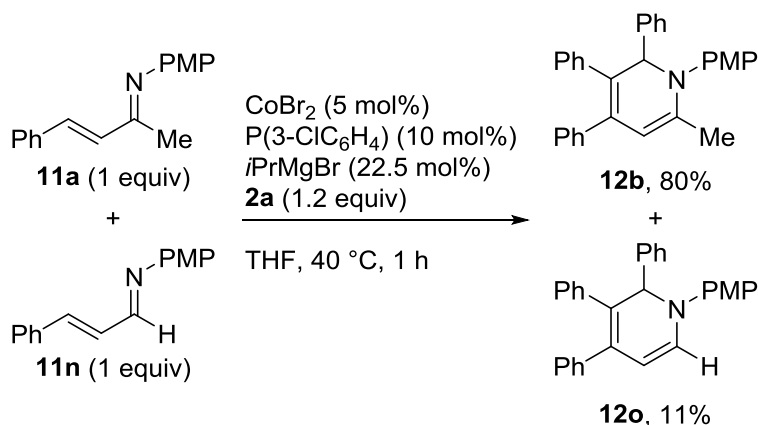
Silica gel chromatography (eluent: hexane/EtOAc/NEt₃ = 100/2/2) of the crude product afforded a mixture of the title compound and its minor regioisomer (89:11 by ¹H NMR analysis) as a yellow fluffy solid (90.5 mg, 86% yield). The regiochemistry of the major isomer **12t** was confirmed by HMQC and HMBC analyses; Mp = 65–67 °C; *R_f* 0.36

hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 1.85 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 5.36 (s, 1H), 5.41 (s, 1H), 6.83–6.88 (m, 4H), 6.93 (d, *J* = 4.8 Hz, 2H), 7.07 (app. d, *J* = 9.2 Hz, 2H), 7.21–7.25 (m, 7H), 7.40 (d, *J* = 9.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 20.4, 55.4, 55.7, 69.3, 106.9, 113.9 (2C), 114.3 (2C), 116.6, 124.8 (q, ³*J*_{C-F} = 3.1 Hz, 2C), 127.1, 127.2 (q, ²*J*_{C-F} = 33.9 Hz, 2C), 127.7 (2C), 128.4 (2C), 128.5 (2C), 129.6 (2C), 129.7 (2C), 135.1, 136.0, 138.8, 140.4, 141.0, 144.7, 157.4, 159.4. The signal of the CF₃ carbon could not be identified because of signal overlapping with the minor isomer; HRMS (ESI) Calcd for C₃₃H₂₉F₃NO₂ [M + H]⁺ 528.2150, found 528.2151.

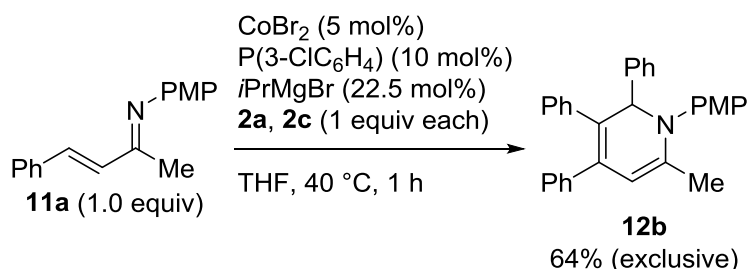


(3Z,5E)-4-(Naphthalen-1-yl)-5,6-diphenylhexa-3,5-dien-2-one (14): The general procedure was applied to (*E*)-4-methoxy-*N*-((*E*)-4-(naphthalen-1-yl)but-3-en-2-ylidene)aniline (**11o**, 60.3 mg, 0.20 mmol) and diphenylacetylene (**2a**, 42.8 mg, 0.24 mmol). Silica gel chromatography (eluent: hexane/EtOAc/ NEt_3 = 100/1/2) of the crude material afforded an inseparable mixture of **11o** and its β -alkenylated product. Hydrolysis of this mixture in THF/1 N HCl solution was followed by separation with preparative HPLC (eluent = CHCl_3 , flow rate = 3.5 mL/min, R.T. = 52.1–56.6 min) afforded a title compound as a red solid (16.0 mg, 21% yield); Mp = 70–71 °C; R_f 0.23 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 1.46 (s, 3H), 6.11 (s, 1H), 6.32 (s, 1H), 6.61 (d, J = 7.3 Hz, 2H), 6.95–7.02 (m, 3H), 7.35 (d, J = 6.9 Hz, 2H) 7.43 (d, J = 7.3 Hz, 2H) 7.47–7.52 (m, 4H), 7.58 (t, J = 7.6 Hz, 1H), 7.91–7.95 (m, 2H), 7.65 (d, J = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 30.1, 125.5, 125.6, 126.4, 127.1, 127.6, 128.0, 128.1 (2C), 128.2, 128.7, 128.9, 129.5 (2C), 130.16 (2C), 130.23 (2C), 132.3, 132.6, 133.8, 135.9, 136.2, 138.1, 138.5, 143.5, 154.6, 200.4; **HRMS** (ESI) Calcd for $\text{C}_{28}\text{H}_{22}\text{O}$ [$\text{M} + \text{H}$] $^+$ 375.1749, found 375.1745.

Competition Experiments



Competition of Ketimine and Aldimine (Scheme 3.6a): According to the general procedure, an equimolar mixture of imines **11a** and **11n** (0.2 mmol each) was subjected to the reaction with diphenylacetylene **2a** (0.24 mmol) for 1 h. Crude products were analyzed by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard, which indicated formation of the adducts **12b** and **12o** in 80% and 11% yields, respectively.



Competition of Dialkyl- and Diarylalkynes (Scheme 3.6b): According to the general procedure, imine **11a** (0.2 mmol) was subjected to the reaction with an equimolar mixture of diphenylacetylene **2a** and 4-octyne **2c** (0.2 mmol each) for 1 h. Crude products were analyzed by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard, which indicated exclusive formation of the adduct of diphenylacetylene **12b** in 64% yield.

3.5 Reference

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Cobalt-Catalyzed C2-Alkylation of Indoles with Aryl-Substituted Alkenes through Tandem Alkene Isomerization–Hydroarylation

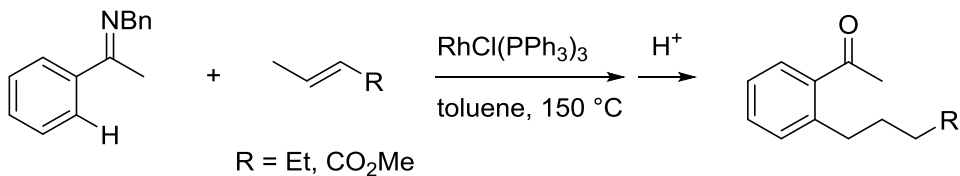
4.1 Introduction

Hydroarylation of alkene allows an atom-economical approach to alkylation of aromatic compounds. Particularly, hydroarylation involving chelation-assisted C–H activation by a low-valent transition metal catalyst is attractive because of a predictable regioselectivity with respect to the arenes.^{1,2,3,4,5} However, the desired hydroarylation is sometimes hampered by the propensity of low-valent transition metal complexes for catalyzing isomerization of alkenes.⁶ Indeed, isomerization to a thermodynamically more stable, but unreactive internal alkene is often the cause of less efficient or unsuccessful hydroarylation of internal alkenes bearing allylic hydrogens.^{2b,3a,c,7}

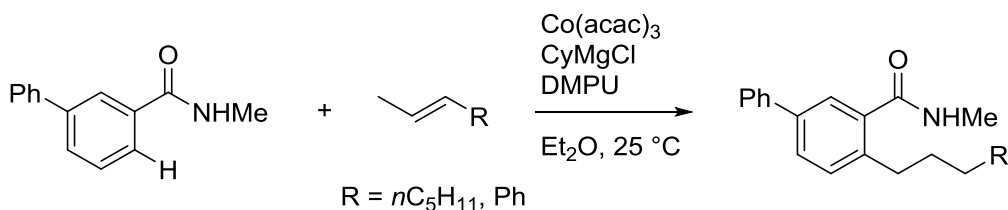
In a few cases, isomerization of an internal alkene to a terminal one is followed by hydroarylation to afford a primary alkylation product. For example, Jun and co-workers reported rhodium-catalyzed addition reactions of an aromatic imine to internal alkenes including a substituted acrylate, affording the corresponding primary alkylation products (Scheme 4.1a).^{3e,f} Nakamura and co-workers reported that cobalt-catalyzed reactions of a benzamide derivative with (*E*)-2-octene and (*E*)- β -methylstyrene gave the corresponding primary alkylation products (Scheme 4.1b).^{4b} In these cases, anti-Markovnikov selectivity of the catalysts would be the driving force for the observed regioselectivity.

Scheme 4.1. Transition Metal-Catalyzed Tandem Alkene Isomerization Linear-Selective Hydroarylation

(a) Jun et al.



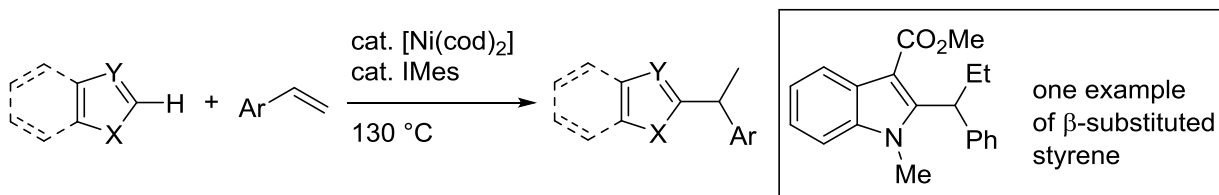
(b) Nakamura et al.



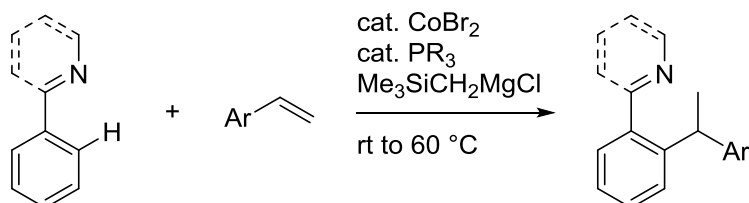
Like the above cases, linear adducts are typically major products in transition metal-catalyzed hydroarylation of terminal olefins. As notable exceptions to this selectivity, several examples of branched-selective hydroarylation of styrene derivatives have been reported.⁸ Representative among these examples is the nickel(0)-catalyzed reaction of a heteroarene with a styrene to afford a 1,1-diarylalkane, which was developed by Nakao, Hiyama, and co-workers (Scheme 4.2a).⁹ In addition to various vinylarenes, β -methylstyrene was also reported to participate in the reaction to afford a 1,1-diarylpropane derivative. Our group reported cobalt-catalyzed branched-selective hydroarylation of styrenes using 2-phenylpyridines and aromatic imines as the aromatic substrates (Scheme 4.2b).^{4a,e} Recently, Shibata and co-workers reported iridium-catalyzed hydroarylation of styrenes with *N*-acylindoles, which also affords the corresponding branched adducts with high regioselectivity (Scheme 4.2c).^{5c} We reported a single example of the addition of an aryl aldimine to a β -substituted styrene (i.e., *cis*- β -trimethylsilylstyrene), no such internal alkene was examined in Shibata's work. Thus, generally speaking, β -substituted styrenes have been scarcely employed as substrates for hydroarylation.

Scheme 4.2. Transition Metal-Catalyzed Branched-Selective Hydroarylation of Styrenes

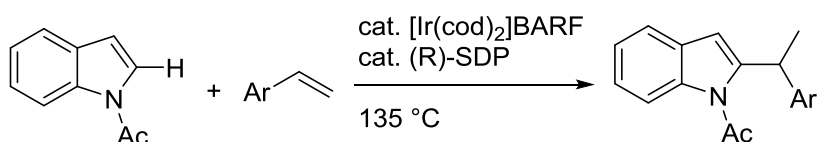
(a) Nakao and Hiyama et al



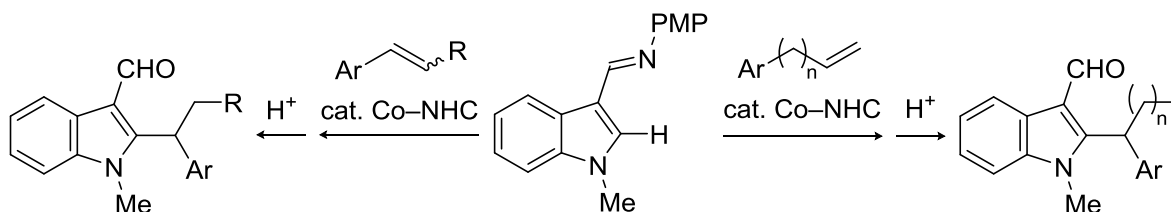
(b) Yoshikai et al



(c) Shibata et al



(d) This work

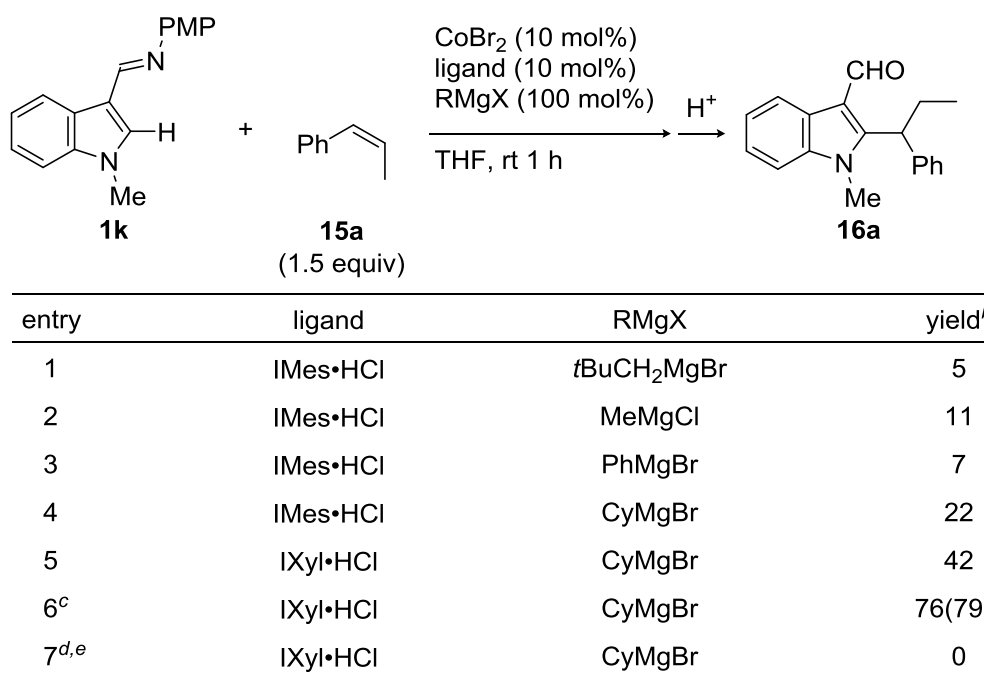


I describe in this chapter that a cobalt-*N*-heterocyclic carbene catalyst promotes branched-selective addition of a 3-iminoindole derivative to a β -substituted styrene to afford a 1,1-diarylalkane product in moderate to good yield (Scheme 4.2d). Interestingly, the same catalytic system also promotes the reaction of the indole substrate with non-conjugated aryl alkenes such as allyl-, homoallyl-, and bishomoallylbenzenes to afford the corresponding 1,1-diarylalkanes through a tandem alkene isomerization-hydroarylation process.^{10,11,12,13} Mechanistic experiments using a deuterium-labeled substrate and secondary alkyl Grignard reagents suggested that the substrate and the

Grignard undergo exchange of the hydrogen atoms.

4.2 Results and Discussion

I chose aldimine **1k**, derived from *N*-methylindole-3-carboxyaldehyde and *p*-anisidine, and *cis*- β -methylstyrene **15a** as model substrates for the initial stage of the present study. The reaction of **1k** and **15a** in the presence of CoBr₂ (10 mol%), IMes•HCl (1,3-dimesitylimidazolium chloride, 10 mol%) and *t*BuCH₂MgBr (100 mol%) afforded, upon acidic hydrolysis, the C2-alkylated indole **16a** in 5% yield with exclusive branched-selectivity (Table 1, entry 1). While the use of MeMgCl or PhMgBr instead of *t*BuCH₂MgBr did not significantly improved the catalytic activity (entries 2 and 3), an apparent increase in the product yield (22%) was observed using CyMgBr (entry 4). In all the cases, the branched adduct **16a** was obtained exclusively. With CyMgBr as the Grignard reagent, the use of IXyl•HCl (1,3-bis(2,6-xylyl)-imidazolium chloride) instead of IMes•HCl further improved the product yield to 42% (entry 5). Moreover, addition of 2 equivalents of TMEDA as an additive significantly improved the catalytic activity to afford the product **16a** in 79% yield (entry 6). Note that no reaction took place in the absence of CoBr₂ (entry 7).

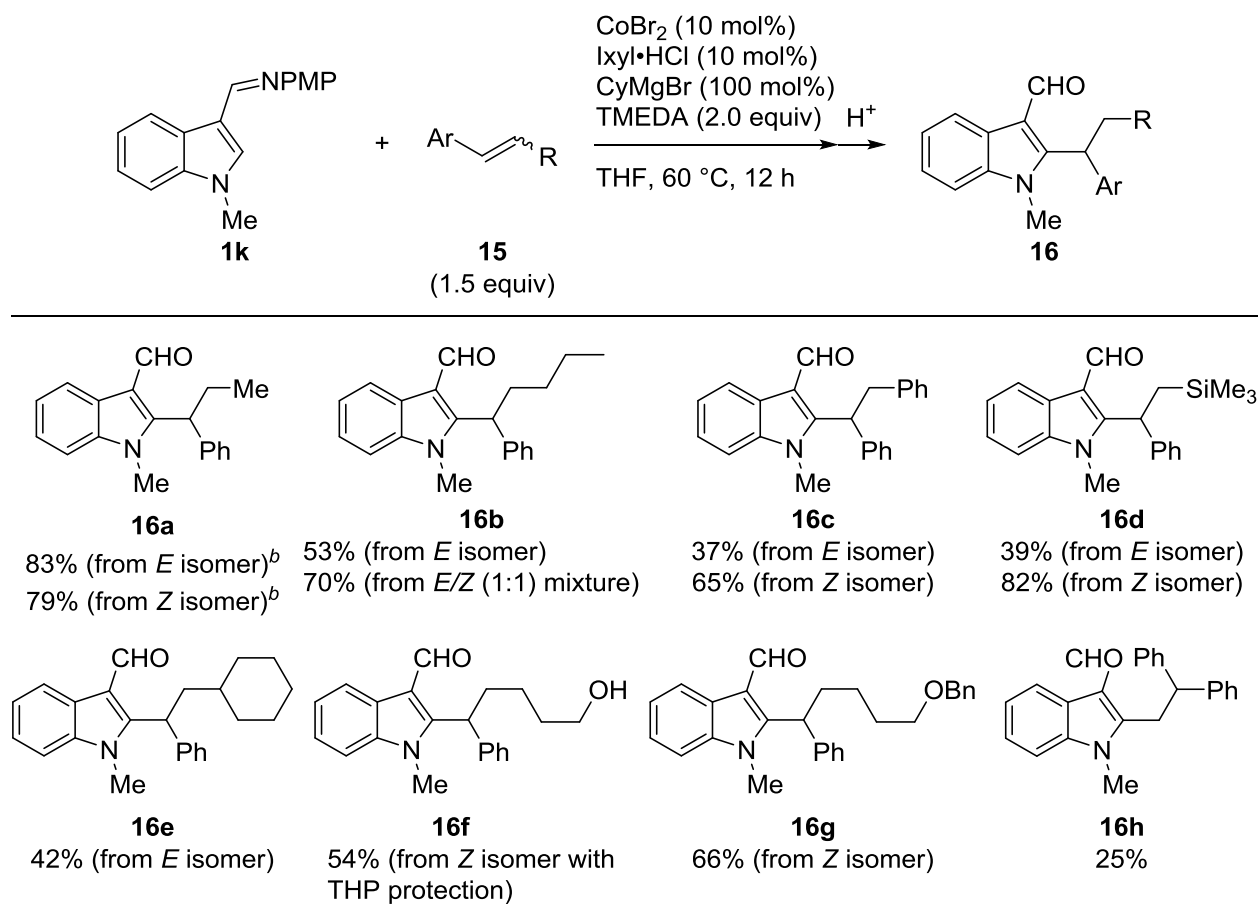
Table 4.1. Cobalt-Catalyzed Branched-Selective Hydroarylation of *cis*- β -Methylstyrene^a

^a The reaction was performed on a 0.2 mmol scale. ^b Determined by GC using *n*-tridecane as an internal standard. ^c 2.0 equiv. of TMEDA was added as an additive. ^d Isolated yield ^e CoBr₂ was omitted.

With the optimized reaction conditions in hand, the scope of β -substituted styrenes was examined using **1k** as the reaction partner (Scheme 4.3). *Trans*- β -methylstyrene afforded 1,1-diarylpentane **16a** in 83% yield. The use of *trans*- β -propylstyrene afforded **16b** in 53% yield with exclusive regioselectivity, while 1:1 mixture of *cis*- and *trans*- β -propylstyrene afforded the same product in a better yield of 70%. These results indicate that the *cis*-isomer is more reactive than the *trans*-isomer. The same trend was also observed for β -trimethylsilylstyrene and stilbene. While *trans*- β -trimethylsilylstyrene and *trans*-stilbene afforded 1,1-diarylpentanes **16c** and **16d** in 37% and 39% yields, respectively, the corresponding *cis*-isomers afforded the same products in much higher yields of 65% and 82%, respectively. Sterically hindered *trans*- β -cyclohexylstyrene was amenable to the reaction. β -Substituted styrenes bearing

THP ether and benzyloxy groups afforded the corresponding 1,1-diarylalkanes in moderate yields. While 1,1-diphenylethylene afforded a linear adduct **16h** in a low yield, β,β -dimethylstyrene failed to take part in the present reaction.

Scheme 4.3. Cobalt-Catalyzed Branched-Selective Hydroarylation of β -Substituted Styrenes^a

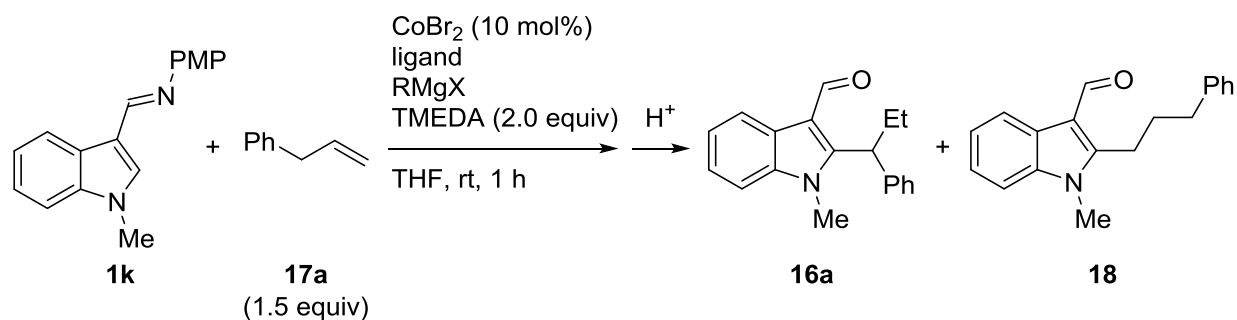


^a The reaction was performed on a 0.2 mmol scale. ^b The reaction was performed at rt for 1 h.

Notably, the use of allylbenzene **17a** instead of β -methylstyrene in the reaction with **11a** resulted in the formation of the same 1,1-diarylpropane product **16a** in 81% yield with exclusive regioselectivity (Table 4.2, entry 1). The catalytic system likely promoted facile isomerization of allylbenzene **17a** to β -methylstyrene prior to C–C bond

Chapter 4

formation. We screened the reaction conditions to improve the reaction efficiency, which eventually revealed that the original reaction conditions were optimum. When the amount of TMEDA was reduced to 1 equivalent, the yield of **16a** decreased to 78% (entry 2). In the absence of TMEDA, the yield of **16a** further decreased to 70% (entry 3). The catalyst loading could be reduced to 5 mol% without significant decrease in the catalytic activity (entry 4). The use of 1.2 equivalents of allylbenzene **17a** led to a slightly lower yield of **16a** (entry 5). Replacement of IXyl•HCl with IMes•HCl, PPh₃, or PCy₃ did not improve the catalytic activity (entries 6, 8 and 9). The use of IPr•HCl (1,3-bis(2,6-diisopropylphenyl)imidazolium chloride) completely shut down the reaction (entry 7). Using *i*PrMgBr or *t*BuCH₂MgBr, the yields of **16a** were decreased to 29% and 13%, respectively (entries 10 and 11). Me₃SiCH₂MgCl was entirely ineffective (entry 12).

Table 4.2. Branched-Selective Addition of 3-Iminoindole **1a** to Allylbenzene **5a**^a

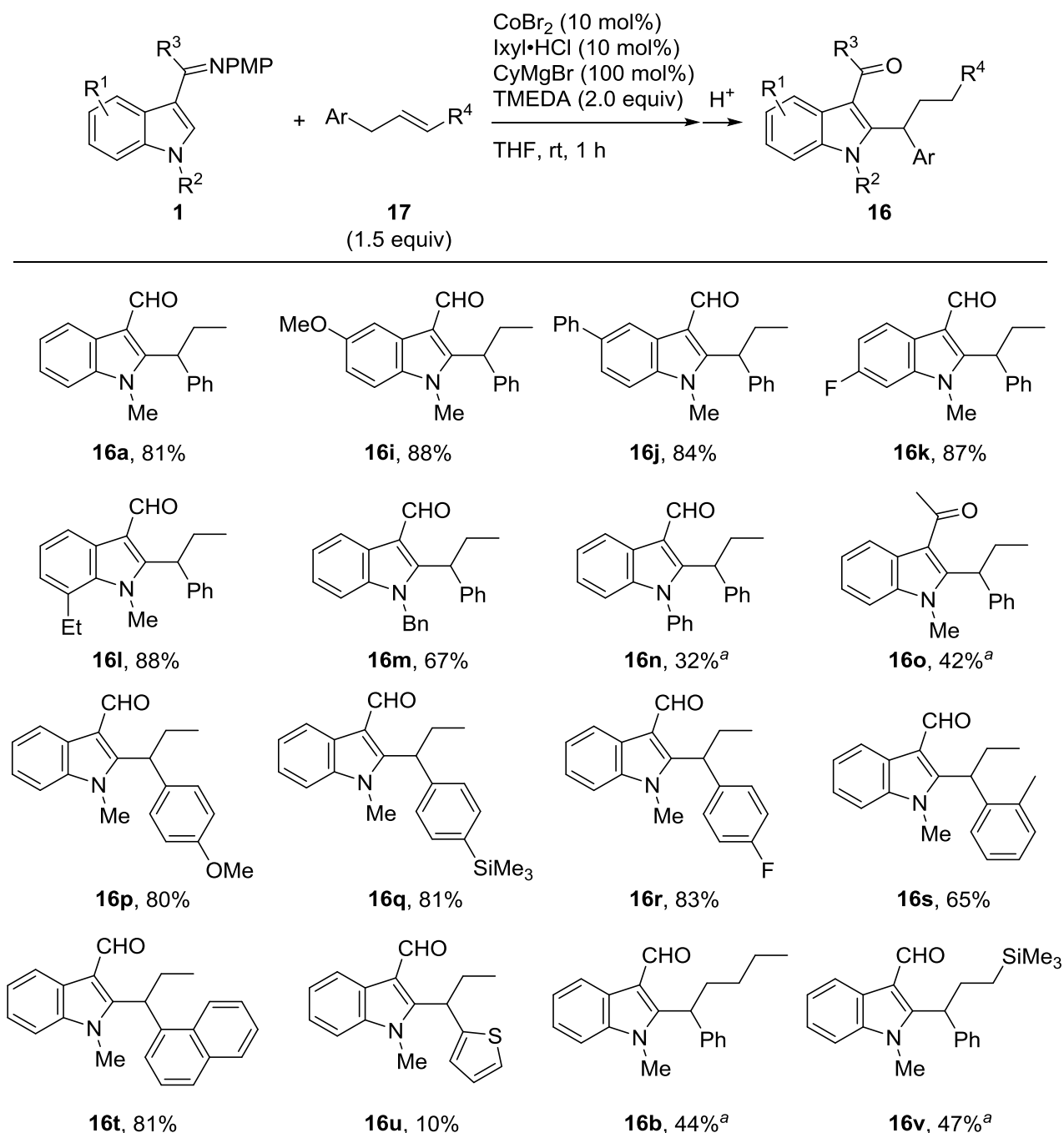
entry	ligand (mol%)	RMgX (mol%)	yield (%) (16a : 18) ^b
1	IXyl•HCl (10)	CyMgBr (100)	87 (>99:1) ^c
2 ^d	IXyl•HCl (10)	CyMgBr (100)	78 (>99:1)
3 ^e	IXyl•HCl (10)	CyMgBr (100)	70 (>99:1)
4 ^f	IXyl•HCl (5)	CyMgBr (50)	74 (>99:1)
5 ^g	IXyl•HCl (10)	CyMgBr (100)	71 (>99:1)
6	IMes•HCl (10)	CyMgBr (100)	40 (>99:1)
7	IPr•HCl (10)	CyMgBr (100)	<1
8	PPh_3 (20)	CyMgBr (100)	43 (>99:1)
9	PCy_3 (20)	CyMgBr (100)	27 (99:1)
10	IXyl•HCl (10)	<i>i</i> PrMgBr (100)	29 (>99:1)
11	IXyl•HCl (10)	<i>t</i> BuCH ₂ MgBr (100)	13 (>99:1)
12	IXyl•HCl (10)	$\text{Me}_3\text{SiCH}_2\text{MgCl}$ (100)	<1

^a The reaction was performed on a 0.2 mmol scale. ^b Determined by GC or ¹H NMR. ^c The isolated yield was 81%. ^d 1.0 equiv. of TMEDA was used. ^e TMEDA was omitted from the reaction. ^f 5 mol% of CoBr_2 and 1 equiv. of TMEDA were used. ^g 1.2 equiv. of **15a** was used.

I explored the addition reaction of 3-iminoindoles to allylbenzenes (Scheme 4.4). Imines bearing methoxy, phenyl, fluoro or ethyl groups on indole moiety participated in the present reaction to afford 1,1-diarylpropanes **16i-16l** in high yields with exclusive branched-selectivity. Indole substrates bearing *N*-phenyl and *N*-benzyl groups were also amenable to the reaction. A substrate derived from 3-acetylindole afforded the corresponding 1,1-diarylpropane **16o** albeit in a moderate yield.

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I next explored the scope of allylbenzenes using imine **1k** as the reaction partner. The reaction tolerated allylbenzenes bearing methoxy, trimethylsilyl, and fluoro groups at the *para*-position of the benzene ring to afford the corresponding 1,1-diarylpropanes **16p-16r** in high yields with exclusive branched-selectivity. Sterically hindered 1-allyl-2-methylbenzene and 1-allylnaphthalene were also amenable to the present reaction conditions to afford the corresponding 1,1-diarylalkanes **16s** and **16t** in 65% and 81% yields, respectively. 1-Allylthiophene furnished the desired 1,1-diarylpropane **16u** albeit in a low yield. The use of allylbenzene derivatives bearing ethyl and trimethylsilyl groups at the terminal positions afforded the corresponding 1,1-diarylalkanes **16b** and **16v** at elevated temperature.

Scheme 4.4. Cobalt-Catalyzed Addition of 3-Iminoindoles to Allylbenzenes

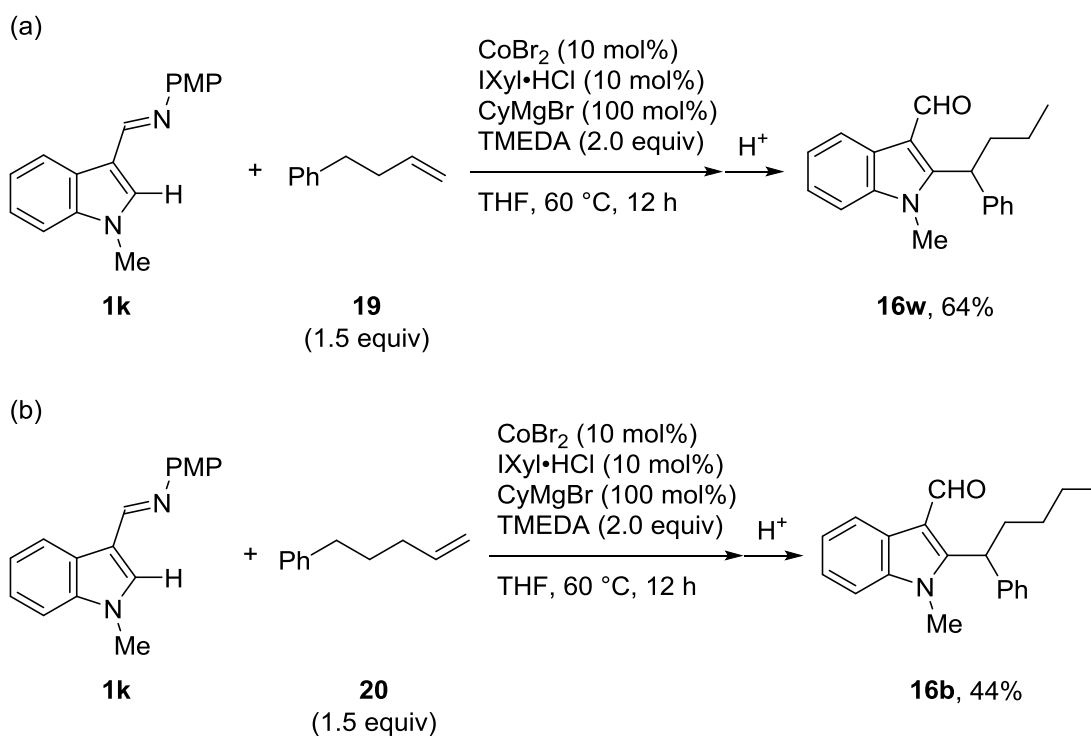
^aThe reaction was performed at 60 °C for 12 h.

As was the case with allylbenzene, the reaction of homoallylbenzene **19** and **1k** resulted in C–C bond formation at the α -position of the phenyl group, thus affording 1,1-diarylbutane **16w** in 64% yield without formation of other regioisomers (Scheme 4.5a). Note that, in the absence of TMEDA, the reaction of **19** and **1k** became sluggish

(46%). Furthermore, 1,4-diarylbutane **21**, which arose from linear-selective hydroarylation of **19** before isomerization, was obtained in 5% yield. The use of bishomoallylbenzene also afforded the corresponding 1,1-diarylpentane in 44% yield exclusively (Scheme 4.5b).

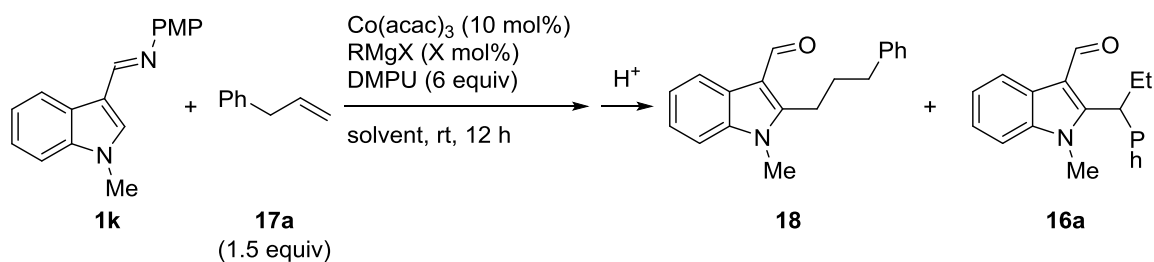
During the above investigation, I found that the isomerization of allylbenzene to β -methylstyrene ($E/Z >95:5$) completed before substantial conversion of the indole substrate **1k**. This observation indicates that olefin isomerization and hydroarylation take place through independent catalytic cycles. Indeed, in the absence of **1k**, the Co–IXy–CyMgBr system caused isomerization of allylbenzene to β -methylstyrene within a few minutes. On the other hand, the isomerization of homoallylbenzene to β -ethylstyrene was much slower; even after substantial conversion of **1k**, we observed a mixture of but-2-en-1-ylbenzene and β -ethylstyrene.

Scheme 4.5. Branched-Selective Addition of 3-Iminoindole to Homoallylbenzene and Bishomoallylbenzene



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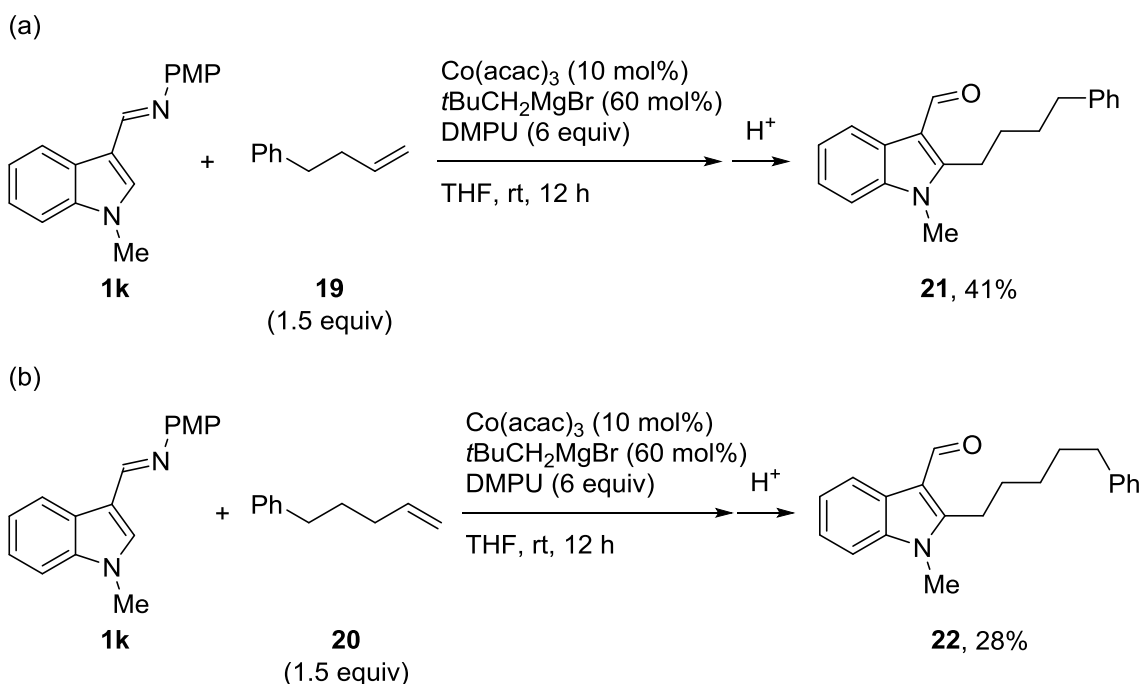
Next, we reexamined the reaction of **1k** and **17a** in order to achieve a linear-selective addition (Table 4.3). The Co(acac)₃-DMPU-CyMgCl catalytic system in Et₂O, which was reported by Nakamura (see Scheme 4.1b), afforded the adduct in 37% overall yield with a poor linear/branched ratio of 38:62 (entry 1). Using 80 mol% or 60 mol% of Grignard reagent, the ratio of linear/branched selectivity increased to 54:46 and 73:27, respectively without significant decrease of the catalytic activity (entries 2 and 3). Using 40 mol% of Grignard reagent, the linear/branched selectivity was further improved to 88:12, although the yield of the adduct decreased drastically to 11% (entry 4). The addition of PPh₃ or IMes•HCl to the Co-DMPU-CyMgCl system significantly changed the regioselectivity in favor of the branched adduct (entries 5 and 6). The use of THF instead of Et₂O did not cause significant improvement either in the product yield or in the regioselectivity (entry 7). The use of *i*PrMgBr instead of CyMgBr in THF afforded the product in 23% yield with a slightly better regioselectivity. Using *t*BuCH₂MgBr in THF, the yield of product improved to 57% in a high regioselectivity (95:5) in THF (entry 9). With this modified catalytic system, homoallylbenzene **19** and bishomoallylbenzene **20** reacted with imine **1k** to afford the linear adducts **21** and **22** in 41% and 28% yields, respectively with high regioselectivity (>10:1) (Scheme 4.6).

Table 4.3. Cobalt-Catalyzed Linear-Selective Hydroarylation of Allylbenzene^a

entry	RMgX	X	solvent	yield (%) (18:16a) ^b
1	CyMgBr	100	Et ₂ O	37 (38:62)
2	CyMgBr	80	Et ₂ O	40 (54:46)
3	CyMgBr	60	Et ₂ O	31 (73:27)
4	CyMgBr	40	Et ₂ O	11 (88:12)
5 ^c	CyMgBr	60	Et ₂ O	54 (4:96)
6 ^d	CyMgBr	60	Et ₂ O	34 (9:91)
7	CyMgBr	60	THF	23 (65:35)
8	<i>i</i> PrMgBr	60	THF	23 (74:62)
9	<i>t</i> BuCH ₂ MgBr	60	THF	57 (95:5) ^e

^a The reaction was performed on a 0.2 mmol scale. ^b Determined by GC or NMR. ^c 10 mol% of IMes·HCl was added as a ligand. ^d 20 mol% of PPh₃ was added as a ligand. ^e Isolated yield was 50%.

Scheme 4.6. Linear Selective Addition of 3-Imionindole to Homoallylbenzene and Bishomoallylbenzene

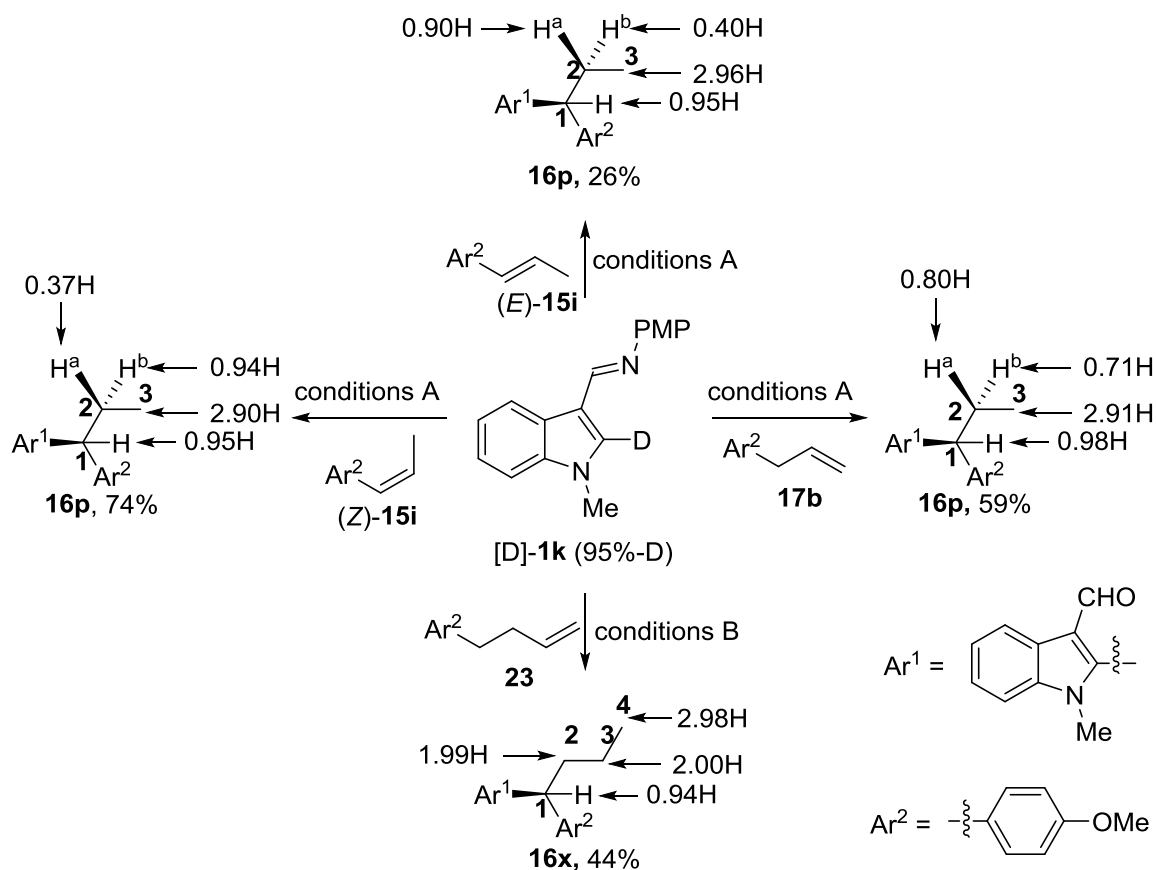


A series of experiments using deuterium-labeled substrate [D]-**1k** were performed to gain mechanistic insights into the present reaction (Scheme 4.7). The reactions of [D]-**1k** with *Z*- and *E*-isomers of 1-methoxy-4-(prop-1-en-1-yl)benzene **15i** afforded the product **16p** in 74% and 26% yields, respectively. These results also show higher reactivity of the *Z*-isomer than the *E*-isomer. The ^1H NMR analysis of both of the products revealed that the deuterium atom was mainly incorporated into the 2-position of **16p** in a diastereoselective manner and that the *E*- and the *Z*-isomer afforded opposite diastereomers. The assignment of the relative stereoselectivity of **16p** is tentative and is based on the assumption of a *syn*-hydroarylation mechanism. The unreacted olefin was recovered as a 1:1 mixture of the *E*- and the *Z*-isomers in the reaction of the *Z*-isomer. When the *E*-isomer was used, the unreacted olefin was recovered as the *E*-isomer in a pure form.

The reaction of [D]-**1k** and 4-methoxyallylbenzene **17b** afforded **16p** in 59%

yield. ^1H NMR analysis of this product indicated low diastereoselectivity and moderate deuterium incorporation (0.49D in total) into the 2-position (Scheme 4.7c). Note that, the deuterium content at the C2-position of the recovered indole was 77%. The unreacted olefin was recovered as *E*-**15i** with less than 10% of deuterium incorporation. Furthermore, the reaction of [D]-**1k** and 1-homoallyl-4-methoxybenzene **23** afforded the corresponding 1,1-diarylbutane **16x** in 44% yield with almost no deuterium incorporation (Scheme 4.7d). The deuterium content at the C2-position of the recovered indole was 54%. The ^1H NMR analysis of the unreacted olefins was practically difficult because they were recovered as a mixture of (*E*)- and (*Z*)-isomers of 1-(but-1-en-1-yl)-4-methoxybenzene and 1-(but-2-en-1-yl)-4-methoxybenzene.

Scheme 4.7. Reaction of C2-Deuterated Substrate [D]-**1k**

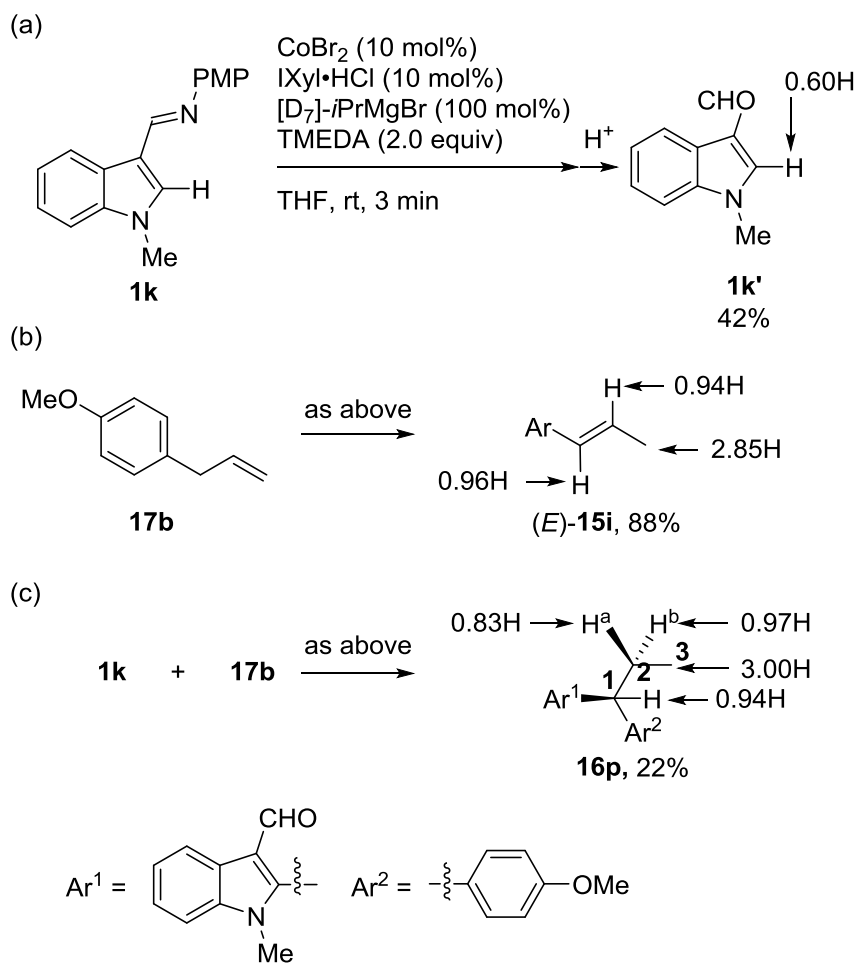


Conditions A: CoBr_2 (10 mol%), IXyl $\cdot\text{HCl}$ (10 mol%), CyMgBr (100 mol%), TMEDA

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(2.0 equiv), THF, rt, 3 min. Conditions B: CoBr₂ (10 mol%), IXyl•HCl (10 mol%), CyMgBr (100 mol%), TMEDA (2.0 equiv), THF, 60 °C, 1 min. The number of protons on each carbon atom was determined by ¹H NMR spectroscopy using the integration of the indole C4-H as the reference. The assignment of the diastereotopic protons H^a and H^b in **16p** is based on the assumption of a *syn*-hydroarylation mechanism.

A series of control experiments were performed to prove the origin of the above anomalous observations (Scheme 4.8). We used [D₇]-*i*PrMgBr instead of CyMgBr in the following experiments. Non-deuterated **1k** was subjected to the reaction without allylbenzene. After hydrolysis, aldehyde **1k'** was recovered in 42% yield with 40% deuterium incorporation into the C2-position (Scheme 4.8a). The source of the deuterium atom would be from the β-position of the Grignard reagent. The rest of imine **1k** was largely reduced by the Grignard reagent. The reaction of 4-methoxyallylbenzene **17b** alone afforded (*E*)-**15i** in 88% yield without significant deuterium incorporation at the olefinic and allylic positions (Scheme 4.8b). The reaction of **1k** and **17b** afforded **16p** in 22% yield with partial deuterium incorporation at the 2-position in a diastereoselective manner (Scheme 4.8c).

Scheme 4.8. Control Experiments Using Deuterated Grignard Reagent^a

^aThe number of protons on each carbon atom was determined by ¹H NMR spectroscopy using the integration of the indole C4-H as the reference (a,c) or the methoxy CH₃ (b) as the reference.

The relevance of the present catalytic species and reaction pathway to the well-defined cobalt-NHC complex remains unclear.¹⁴ Furthermore, it appears premature to interpret the above observations unambiguously. Nevertheless, some speculation about mechanisms can be made. Hydrometalation-β-hydride elimination and allylic C–H activation-reductive elimination are typical mechanisms of isomerization of alkene.¹⁵ While the control experiment in Scheme 4.8b does not give us a concrete evidence for the discrimination of these mechanisms, we speculate that the latter is more likely in light of

a proposed mechanism for alkene isomerization using a related Co-NHC-Grignard catalytic system.¹³ Hydroarylation of alkene with a low-valent transition metal catalyst is generally considered to involve three major steps, that is, oxidative addition of C–H bond to the metal center, insertion of alkene into the M–H bond, and C–C bond-forming reductive elimination.¹ We also prefer this mechanistic framework.⁴ However, the H/D exchange of **1k** caused by [D₇]-*i*PrMgBr (Scheme 4.8a) and poor deuterium incorporation into **16x** (Scheme 4.7d) apparently indicate that the actual reaction mechanism is more complicated than such a three-step mechanism. We speculate that a low valent cobalt hydride species is generated from the cobalt precatalyst and the secondary alkyl Grignard reagent. This putative species undergoes exchange of hydrogen atoms with the indole substrate, which causes the poor incorporation of the original C2-H atom into the hydroarylation product. The regio- and diastereoselective deuterium incorporation observed for (*Z*) and (*E*)-**15i** (Scheme 4.7a,b) may point to regio- and stereoselective (most likely *syn*-selective) insertion of these alkenes into the Co–H bond. Upon the alkene insertion, the resulting alkylcobalt intermediate would prefer to undergo reductive elimination rather than β -hydride elimination because the latter pathway would deteriorate the diastereoselectivity of the deuterium incorporation.

4.3 Conclusion

In summary, I have developed a Co–NHC–CyMgBr catalytic system for C2-alkylation of indole with β -substituted styrenes. Allyl-, homoallyl- and bishomoallylbenzene derivatives also afforded corresponding 1,1-diarylalkanes through a tandem alkene isomerization-hydroarylation sequence. The Co–DMPU–*t*BuCH₂MgBr catalytic system allows complementary, linear selective alkylation. Deuterium-labeling experiments shed light on the involvement of the secondary alkyl Grignard reagents in the C–H activation step. We speculated that the secondary alkyl Grignard reagents also play

important roles in other relevant cobalt-catalyzed C–H functionalization reactions.¹⁶

4.4 Experimental Section

Material and Methods

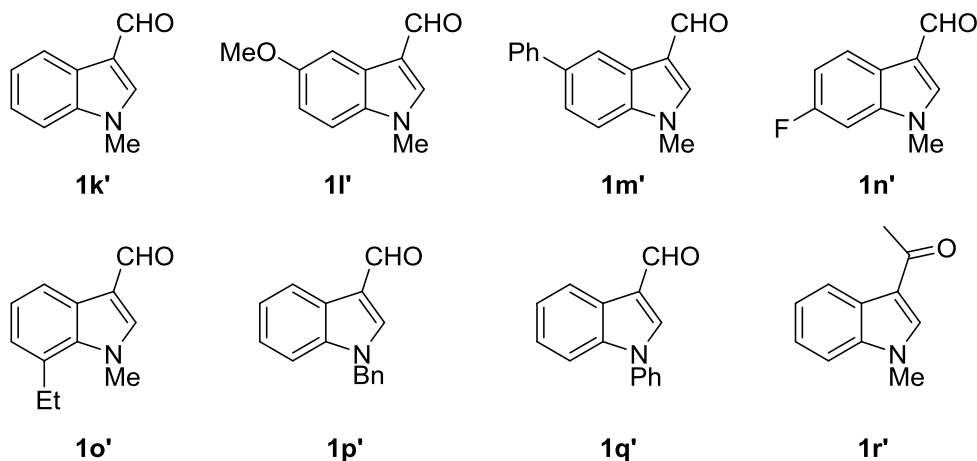
General. All reactions dealing with air- or moisture-sensitive compound were performed by standard Schlenk techniques in oven-dried reaction vessels under nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. Flash chromatography was performed as described by Still et al.,¹⁷ using 40–63 mm (Si 60, Merck) or 40–50 mm (Silica Gel 60N, Kanto Chemical) silica gel. ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were recorded on JEOL ECX-400 (400 MHz) NMR spectrometers. ¹H and ¹³C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and CHCl₃ (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 mm film thickness). High-resolution mass spectra (HRMS) were obtained with a Q-ToF Premier LC HR mass spectrometer.

Materials. Unless otherwise noted, reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. Anhydrous cobalt(II) bromide (99%) was purchased from Aldrich and used as received. THF was distilled over Na/benzophenone. TMEDA and DMPU were distilled over CaH₂. 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 indole substrates

(1) 1-Alkyl(aryl)-3-formyl(acetyl)indole derivatives

Precursors to the 3-iminoindole substrates, i.e., 1-alkyl(aryl)-3-formyl(acetyl)indoles (**1k'**–**1r'**), were prepared as follows:



1k', **1p'** and **1r'**: Prepared from 1*H*-indole-3-carbaldehyde or 1-(1*H*-indol-3-yl)ethanone through N-alkylation with methyl iodide or benzyl bromide using NaH as a base. The ^1H NMR spectra showed good agreement with the literature data.¹⁸

1q': Prepared from 1*H*-indole-3-carbaldehyde through Cu-catalyzed N-arylation with iodobenzene.¹⁹ The ^1H NMR spectrum showed good agreement with the literature data.²⁰

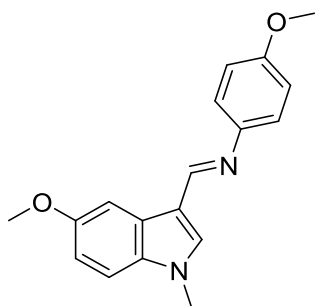
1l', **1n'**, and **1o'**: Prepared from the corresponding 1*H*-indoles through Vilsmeier–Haack formylation followed by N-methylation according to typical literature procedures. The ^1H NMR spectra of **1l'** and **1n'** showed good agreement with the literature data.^{18b}

7-Ethyl-1-methyl-1*H*-indole-3-carbaldehyde (1o'): Brown solid; Mp = 79–80 °C; R_f 0.36 (hexane/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3): δ 1.34 (t, $J = 7.8$ Hz, 3H), 3.08 (q, $J = 7.8$ Hz, 2H), 4.06 (s, 3H), 7.09 (d, $J = 7.3$ Hz, 1H), 7.21 (t, $J = 7.8$ Hz, 1H), 7.52 (s, 1H), 8.18 (dd, $J = 7.8$ Hz, 0.9 Hz, 1H), 9.94 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.8, 25.3, 38.0, 117.8, 120.1, 123.4, 125.2, 126.9, 128.6, 136.0, 141.3, 184.5; HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_{14}\text{NO}$ $[\text{M} + \text{H}]^+$ 188.1075, found 188.1071.

1-Methyl-5-phenyl-1*H*-indole-3-carbaldehyde (1m'): To a solution of 5-bromo-1-methyl-1*H*-indole-3-carbaldehyde (714 mg, 3.0 mmol), phenylboronic acid (439 mg, 4.5 mmol) and Na₂CO₃ (2.5 g, 24 mmol) in a mixture of DME (12 mL), EtOH (4.5 mL) and H₂O (12 mL) was added Pd(PPh₃)₄ (173 mg, 0.15 mmol) at room temperature. The resulting mixture was heated to reflux and stirred for 11 h. After cooling to room temperature, the reaction mixture was extracted with EtOAc (15 mL x 3). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (eluent = hexane/EtOAc/MeOH = 1/1/0 to 50/50/3) to afford the title compound as a white solid (476 mg, 67% yield). Mp = 163–165°C; R_f 0.26 (hexane/EtOAc = 1/1); ¹H NMR (400 MHz, CDCl₃): δ 3.89 (s, 3H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.59 (dd, *J* = 8.7 Hz, 1.8 Hz, 1H), 7.65–7.70 (m, 3H), 8.54 (d, *J* = 1.4 Hz, 1H), 9.99 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 34.0, 110.3, 118.5, 120.7, 123.9, 126.0, 127.1, 127.7 (2C), 128.9 (2C), 136.7, 137.5, 139.9, 141.7, 184.5; HRMS (ESI) Calcd for C₁₆H₁₄NO [M + H]⁺ 236.1075, found 236.1074.

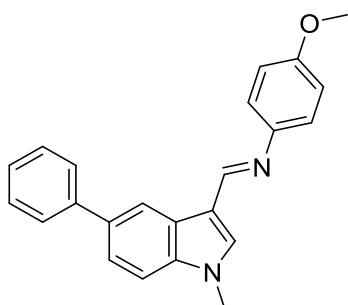
(2) 1-Alkyl(aryl)-3-iminoindole derivatives

General procedure: To a suspension of indole-3-carbaldehyde derivative and Na₂SO₄ (1 g per 1 mmol of aldehyde) in CH₂Cl₂ (0.25 M) was added *p*-anisidine (1.1 equiv) at room temperature. The resulting mixture was stirred for 12 h, filtered, and concentrated under reduced pressure. The crude product was purified by recrystallization using EtOH/CH₂Cl₂/hexane. The ¹H NMR spectrum of **1k** showed good agreement with the literature data.²¹



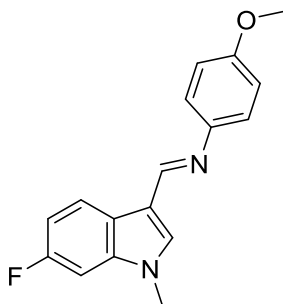
(E)-1-(5-Methoxy-1-methyl-1H-indol-3-yl)-N-(4-methoxyphenyl)methanimine (1l):

Gray solid (16%); Mp = 104–105 °C; ^1H NMR (400 MHz, CDCl_3): δ 3.78 (s, 3H), 3.82 (s, 3H), 3.91 (s, 3H), 6.92 (app. d, $J = 8.7$ Hz, 2H), 6.96 (dd, $J = 8.7$ Hz, 2.2 Hz, 1H), 7.21–7.24 (m, 3H), 7.42 (s, 1H), 8.00 (d, $J = 2.8$ Hz, 1H), 8.59 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 33.5, 55.6, 56.0, 103.9, 110.4, 113.6 (2C), 114.4, 114.8, 122.0 (2C), 126.6, 133.1, 134.3, 146.9, 153.0, 155.8, 157.4; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 295.1447, found 195.1443.



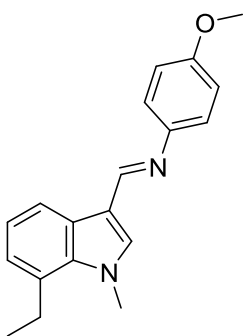
(E)-N-(4-Methoxyphenyl)-1-(1-methyl-5-phenyl-1H-indol-3-yl)methanimine (1m):

Yellow solid (39%); Mp = 128–130 °C; ^1H NMR (400 MHz, CDCl_3): δ 3.83 (s, 3H), 3.86 (s, 3H), 6.93 (app. d, $J = 8.7$ Hz, 2H), 7.23 (app. d, 9.2 Hz, 2H), 7.32 (t, $J = 6.9$ Hz, 1H), 7.40 (d, $J = 8.7$ Hz, 1H), 7.45 (t, $J = 7.3$ Hz, 2H), 7.52 (s, 1H), 7.57 (dd, $J = 8.7$ Hz, 1.8 Hz, 1H), 7.71 (d, $J = 7.8$ Hz, 2H), 8.66 (s, 1H), 8.70 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 33.6, 55.8, 109.9, 114.5 (2C), 115.7, 120.9, 122.1 (2C), 123.2, 126.7, 126.8, 127.8 (2C), 128.8 (2C), 134.4, 135.3, 137.6, 142.5, 146.9, 152.7, 157.6; HRMS (ESI) Calcd for $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 341.1654, found 341.1657.



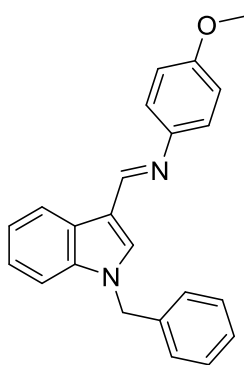
(E)-1-(6-Fluoro-1-methyl-1H-indol-3-yl)-N-(4-methoxyphenyl)methanimine (1n):

White solid (52%); Mp = 144–146 °C; ^1H NMR (400 MHz, CDCl_3): δ 3.75 (s, 3H), 3.82 (s, 3H), 6.92 (app. d, $J = 9.2$ Hz, 2H), 6.98–7.03 (m, 2H), 7.21 (app. d, $J = 8.7$ Hz, 2H), 7.40 (s, 1H), 8.45 (dd, $J = 8.7$ Hz, 5.5 Hz, 1H), 8.56 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 33.5, 55.7, 96.3 (d, $^2J_{\text{C-F}} = 25.9$ Hz), 110.2 (d, $^2J_{\text{C-F}} = 24.0$ Hz), 114.5 (2C), 115.6, 122.1 (2C), 122.5, 123.8 (d, $^3J_{\text{C-F}} = 9.6$ Hz), 134.5, 138.3 (d, $^3J_{\text{C-F}} = 12.5$ Hz), 146.6, 152.5, 157.6, 160.7 (d, $^1J_{\text{C-F}} = 241.4$ Hz); HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{16}\text{FN}_2\text{O}$ [$\text{M} + \text{H}$] $^+$ 283.1247, found 283.1248.

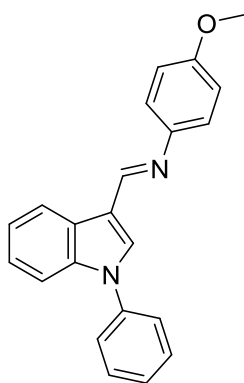


(E)-1-(7-Ethyl-1-methyl-1H-indol-3-yl)-N-(4-methoxyphenyl)methanimine (1o):

White solid (50%); Mp = 144–146 °C; ^1H NMR (400 MHz, CDCl_3): δ 1.34 (t, $J = 7.8$ Hz, 3H), 3.10 (t, $J = 7.8$ Hz, 2H), 3.81 (s, 3H), 4.03 (s, 3H), 6.91 (d, $J = 8.7$ Hz, 2H), 7.06 (d, $J = 7.3$ Hz, 1H), 7.16–7.23 (m, 3H), 7.38 (s, 1H), 8.34 (d, $J = 7.8$ Hz, 1H), 8.59 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.9, 25.5, 37.5, 55.7, 114.5 (2C), 114.8, 120.1, 121.96, 122.05 (2C), 124.3, 127.7, 128.2, 136.0, 135.9, 147.0, 152.8, 157.5; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}$ [$\text{M} + \text{H}$] $^+$ 293.1654, found 293.1652.

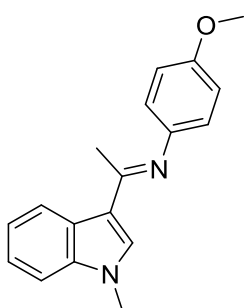


(E)-1-(1-Benzyl-1H-indol-3-yl)-N-(4-methoxyphenyl)methanimine (1p): The condensation of aldehyde **1p'** and *p*-anisidine was performed in EtOH without any dehydrating agent. Recrystallization from CH₂Cl₂/hexane afforded the title compound as a yellow fluffy solid (86%); Mp = 130–131 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.81 (s, 3H), 5.31 (s, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.12–7.15 (m, 2H), 7.20–7.23 (m, 2H), 7.25–7.30 (m, 6H), 7.53 (s, 1H), 8.45–8.50 (m, 1H), 8.62 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 50.7, 55.7, 110.2, 114.5 (2C), 115.9, 121.9, 122.1 (2C), 122.5, 123.6, 126.5, 127.2 (2C), 128.2, 129.1 (2C), 133.3, 136.6, 137.6, 146.8, 152.9, 157.6; HRMS (ESI) Calcd for C₂₃H₂₁NO₂ [M + H]⁺ 341.1654, found 341.1657.

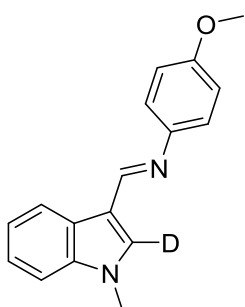


(E)-N-(4-Methoxyphenyl)-1-(1-phenyl-1H-indol-3-yl)methanimine (1q): The condensation of aldehyde **1q'** and *p*-anisidine was performed in EtOH without any dehydrating agent, affording the title compound as white precipitates in an analytically pure form (46%); Mp = 124–125 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.83 (s, 3H), 6.94 (d,

$J = 8.7$ Hz, 2H), 7.25 (d, $J = 9.2$ Hz, 2H), 7.30–7.35 (m, 2H), 7.40–7.44 (m, 1H), 7.51–7.57 (m, 5H), 7.75 (s, 1H), 8.56–8.58 (m, 1H), 8.72 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 55.7, 110.9, 114.5 (2C), 117.3, 122.1 (2C), 122.4, 122.7, 124.1, 124.8 (2C), 126.8, 127.6, 130.0 (2C), 132.9, 137.4, 139.1, 146.7, 152.7, 157.7; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 327.1497, found 327.1497.



(*E*)-*N*-(4-Methoxyphenyl)-1-(1-methyl-1*H*-indol-3-yl)ethan-1-imine (1r): To a mixture of 1-(1-methyl-1*H*-indol-3-yl)ethan-1-one (1.47 g, 8.49 mmol) and MS 4A (8.0 g) in toluene (17 mL) was added *p*-anisidine (1.15 g, 9.33 mmol) at room temperature. The resulting mixture was stirred for 5 d, filtered, and concentrated under reduced pressure. Recrystallization from CH_2Cl_2 afforded the title compound as a white solid (770 mg, 2.77 mmol, 33%); Mp = 217–218 °C; ^1H NMR (400 MHz, CDCl_3): δ 2.24 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 6.81 (app. d, $J = 8.7$ Hz, 2H), 6.90 (app. d, $J = 8.7$ Hz, 2H), 7.23–7.32 (m, 3H), 7.48 (s, 1H), 8.57 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 18.2, 33.4, 55.8, 109.4, 114.3 (2C), 117.4, 121.5 (2C), 121.6, 123.0, 123.6, 126.4, 132.0, 138.0, 145.7, 155.6, 161.9; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 279.1497, found 279.1497.

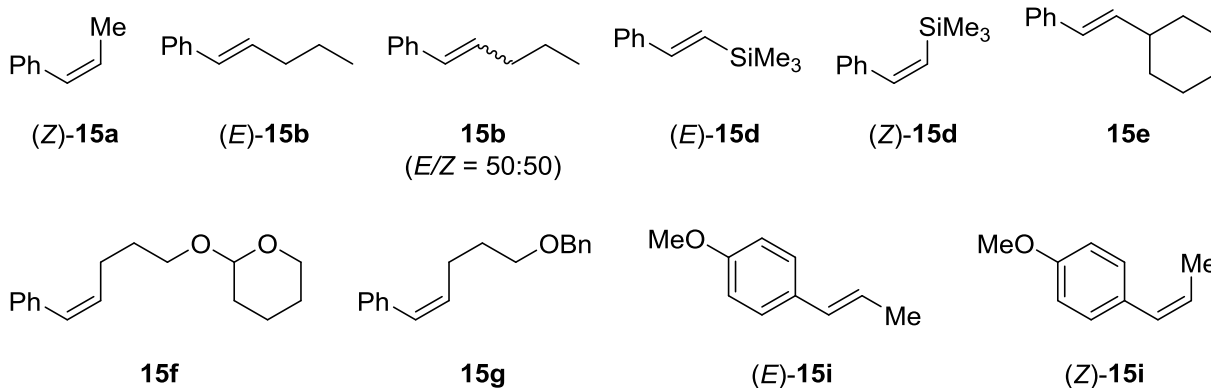


(E)-1-(2-Deuterio-1-methyl-1H-indol-3-yl)-N-(4-methoxyphenyl)methanimine

([D]-1k): The title compound was prepared from 1-methyl-2-deuterio-1H-indole (96% D; prepared according to the literature procedure) through Vilsmeier–Haack formylation and condensation with *p*-anisidine. The deuterium content at the 2-position was determined to be 95% by ¹H NMR analysis.

Preparation of alkenes**(1) β-Substituted styrene derivatives**

β-Substituted styrene derivatives **15a**, **15b**, **15d**, **15e**, **15f**, **15g** and **15i** were prepared as follows:



(Z)-15a: Prepared as described in the literature.²²

(E)- and (Z)-15d: Prepared as described in the literature.^{23,24}

15e: Prepared as described in the literature.²⁵

(E)-15i: Prepared as described in the literature.²⁶

(Z)-15i: Prepared from 1-methoxy-4-(prop-1-yn-1-yl)benzene through palladium-catalyzed

cis-hydrogenation.²² The ¹H NMR spectrum showed good agreement with the literature data.²⁷

15b (*E/Z* = 50:50): Prepared by Wittig reaction of benzaldehyde and butyltriphenylphosphonium bromide according to a typical procedure employing *n*-BuLi as a base. The ¹H NMR spectrum showed good agreement with the literature data.

(E)-15b: Prepared by isomerization of an *E/Z* mixture of **15b**. To a mixture of pent-1-en-1-ylbenzene (*E/Z* = 50:50, 292 mg, 0.2 mmol), CoBr₂ (43.7 mg, 0.20 mmol), 1,3-bis(2,6-dimethylphenyl)-1*H*-imidazol-3-ium chloride (63.0 mg, 0.20 mmol) was added MeMgCl (3.0 M in THF, 0.67 mL, 0.2 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 12 h, quenched with water at room temperature, and extracted with Et₂O (5 mL x 3). The combined organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (eluent = hexane) to afford the title compound as a colorless oil (85% yield, *E/Z* = 95:5). The ¹H NMR spectrum showed good agreement with the literature data.²⁸

(Z)-2-((5-Phenylpent-4-en-1-yl)oxy)tetrahydro-2*H*-pyran (15f): To a solution of (*Z*)-5-phenylpent-4-en-1-ol (*E/Z* = 3:97, 324 mg, 2.0 mmol; prepared according to the literature procedure²⁹) and pyridinium *p*-toluenesulfonate (50.3 mg, 0.2 mmol) in CH₂Cl₂ (4 mL) was added 3,4-dihydro-2*H*-pyran (252 mg, 3.0 mmol) at room temperature. The reaction mixture was stirred for 11 h and concentrated under reduced pressure. The crude material was purified by short pass silica gel chromatography (eluent = hexane/EtOAc = 25/1) to afford the title compound a colorless oil (480 mg, *E/Z* = 3:97, 97% yield); R_f 0.61 (hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃): δ 1.45–1.60 (m, 4H), 1.63–1.70 (m, 1H), 1.74–1.82 (m, 3H), 2.40–2.49 (m, 2H), 3.37–3.49 (m, 2H), 3.73–3.83 (m, 2H), 4.53–4.54 (m, 1H), 5.67 (dt, *J* = 11.9 Hz, 7.3 Hz, 1H), 6.43 (d, *J* = 11.9 Hz, 1H), 7.18–7.35 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 19.7, 25.5, 25.7, 30.2, 30.9, 62.4, 67.0, 99.0, 126.7, 128.3 (2C), 128.9 (2C), 129.5, 132.5, 137.8; HRMS (ESI) Calcd for C₁₆H₂₃O₂ [M + H]⁺

247.1698, found 247.1701.

(Z)-(5-(Benzyloxy)pent-1-en-1-yl)benzene (2g): To a solution of (Z)-5-phenylpent-4-en-1-ol (*E/Z* = 3:97, 908 mg, 5.6 mmol) in THF (25 mL) was added NaH (60% mineral oil, 246 mg, 6.2 mmol) at 0 °C. The resulting mixture was warmed to 75 °C and stirred for 30 min, followed by the addition of benzyl bromide (376 mg, 2.2 mmol) at 50 °C. After additional stirring for 3 h, the reaction mixture was quenched with water and extracted with Et₂O (10 mL x 3). The combined organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (eluent = hexane/EtOAc = 100/0 to 100/3) to afford the title compound a colorless oil (1.08 g, *E/Z* = 3:97, 76% yield); *R_f* 0.61 (hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃): δ 1.77 (quint, *J* = 6.9 Hz, 2H), 2.44 (qd, *J* = 7.3 Hz, 1.6 Hz, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 4.47 (s, 2H), 5.66 (dt, *J* = 11.9 Hz, 7.3 Hz, 1H), 6.43 (d, *J* = 11.9 Hz, 1H), 7.20–7.33 (m, 10 H); ¹³C NMR (100 MHz, CDCl₃): δ 24.5, 30.2, 69.9, 73.1, 126.7, 127.7, 127.8 (2C), 128.3 (2C), 128.5 (2C), 129.0 (2C), 129.5, 132.5, 137.8, 138.8; HRMS (ESI) Calcd for C₁₈H₂₁O [M + H]⁺ 253.1592, found 253.1587.

(2) Allylbenzene derivatives

Allylbenzene derivatives **17h**, **17c**, **17d**, **17e**, **17f**, **17g** and **17i** were prepared as follows:

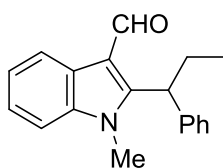
20: Prepared as described in the literature.³⁸

23: Prepared as described in the literature.³⁹

Cobalt-Catalyzed C2-Alkylation of Indoles with Aryl-Substituted Alkenes

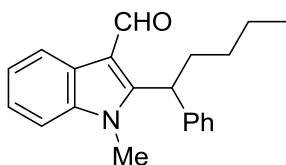
General Procedure: 1-Methyl-2-(1-phenylpropyl)-1H-indole-3-carbaldehyde (16a).

To a solution of (*E*)-*N*-(4-methoxyphenyl)-1-(1-methyl-1*H*-indol-3-yl)methanimine (**1k**, 52.9 mg, 0.20 mmol), (*E*)-prop-1-en-1-ylbenzene (*E*-**15a**, 35.5 mg, 0.30 mmol), CoBr₂ (0.1 M solution in THF, 0.2 mL, 0.02 mmol), 1,3-bis(2,6-dimethylphenyl)-1*H*-imidazol-3-ium chloride (6.3 mg, 0.02 mmol) and TMEDA (60 μ L, 0.4 mmol) in THF (0.03 mL) was added CyMgBr (0.46 M in THF, 0.44 mL, 0.2 mmol) at room temperature. The resulting mixture was stirred for 1 h, followed by quenching with water (0.5 mL). After addition of THF (1.0 mL) and 3M HCl (0.4 mL), the mixture was stirred for another 1 h and then extracted with EtOAc (2 mL x 3). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (eluent = hexane/EtOAc = 100/15) to afford the title compound as an orange solid (45.8 mg, 83% yield).

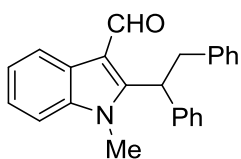


Mp = 116–117 °C; R_f 0.46 (hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃): δ 1.00 (t, *J* = 7.3 Hz, 3H), 2.18–2.23 (m, 1H), 2.49–2.56 (m, 1H), 3.48 (s, 3H), 4.92 (dd, *J* = 9.6 Hz, 5.9 Hz, 1H), 7.27–7.31 (m, 8H), 8.38–8.40 (m, 1H), 10.30 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 12.9, 25.6, 31.4, 42.4, 109.5, 116.2, 121.6, 123.2, 123.6, 126.0, 127.1, 127.6 (2C), 129.0 (2C), 137.6, 140.6, 152.0, 185.2; HRMS (ESI) Calcd for C₁₉H₂₀NO [M + H]⁺

278.1545, found 278.1544. The same product was obtained using allylbenzene **17a** or (*Z*)-prop-1-en-1-ylbenzene ((*Z*)-**15a**) instead of (*E*-**15a**) in 81% or 79% yield, respectively.

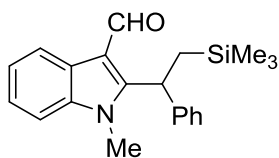


1-Methyl-2-(1-phenylpentyl)-1H-indole-3-carbaldehyde (16b): **1k** (52.9 mg, 0.20 mmol) and pent-2-en-1-ylbenzene (**15b**, *E/Z* = 50:50, 43.9 mg, 0.30 mmol) were reacted according to the general procedure with modification of temperature, reaction time (60 °C, 12 h), and purification/hydrolysis steps. The crude imine product was subjected to silica gel chromatography (eluent = hexane/EtOAc/NEt₃ = 100/9/2) prior to acidic hydrolysis. Silica gel chromatography (eluent = hexane/EtOAc = 100/10) of the crude aldehyde afforded the title compound as a red solid (42.7 mg, 70% yield); Mp = 65–66 °C R_f 0.47 (hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃): δ 0.88 (t, *J* = 7.3 Hz, 3H), 1.20–1.29 (m, 1H), 1.33–1.45 (m, 3H), 2.14–2.24 (m, 1H), 2.41–2.50 (m, 1H), 3.49 (s, 3H), 5.01 (dd, *J* = 10.1 Hz, 6.0 Hz, 1H), 7.21–7.33 (m, 8H), 8.38–8.41 (m, 1H), 10.32 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 14.0, 22.8, 30.4, 31.3, 32.3, 40.6, 109.4, 115.9, 121.5, 123.1, 123.5, 125.9, 127.0, 127.5 (2C), 128.9 (2C), 137.5, 140.6, 152.3, 185.1; HRMS (ESI) Calcd for C₂₁H₂₄NO [M + H]⁺ 306.1858, found 306.1857. The same product was also obtained using (*E*)-pent-1-en-1-ylbenzene ((*E*)-**15b**), pent-2-en-1-ylbenzene (**17h**, *E/Z* = 17:83), or pent-4-en-1-ylbenzene (**20**) instead of **15b** in 53%, 44%, or 44% yield, respectively.



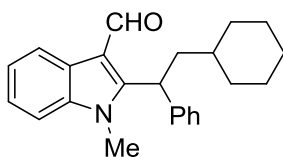
2-(1,2-Diphenylethyl)-1-methyl-1H-indole-3-carbaldehyde (16c): **1k** (52.9 mg, 0.20

mmol) and *cis*-stilbene ((*Z*)-**15c**, 54.1 mg, 0.30 mmol) were reacted according to the general procedure with modified temperature and reaction time (60 °C, 12 h). Silica gel chromatography (eluent = hexane/EtOAc = 10/100) of the crude product afforded the title compound as an orange oil (43.8 mg, 65% yield); R_f 0.46 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 3.38 (s, 3H), 3.46 (dd, $J = 13.3$ Hz, 10.5 Hz, 1H), 3.83 (dd, $J = 13.3$ Hz, 5.5 Hz, 1H), 5.19 (dd, $J = 10.5$ Hz, 5.5 Hz, 1H), 6.96–6.99 (m, 2H), 7.11–7.15 (m, 3H), 7.20–7.28 (m, 4H), 7.30–7.35 (m, 4H), 8.27–8.30 (m, 1H), 10.02 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 31.0, 39.7, 43.3, 109.5, 115.4, 121.7, 123.1, 123.5, 125.9, 127.0, 127.3, 127.6 (2C), 128.76 (2C), 128.82 (2C), 129.1 (2C), 137.2, 138.6, 140.6, 151.5, 185.2; HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{22}\text{NO}$ $[\text{M} + \text{H}]^+$ 340.1701, found 340.1701. Same compound was also observed using *trans*-stilbene ((*E*)-**15c**) in 37% yield as determined by ^1H NMR analysis of the crude material using 1,1,2,2-tetrachloroethane as an internal standard.

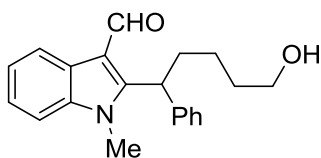


1-Methyl-2-(1-phenyl-2-(trimethylsilyl)ethyl)-1H-indole-3-carbaldehyde (16d): **1k** (52.9 mg, 0.20 mmol) and (*Z*)-trimethyl(styryl)silane ((*Z*)-**15d**, 52.9 mg, 0.30 mmol) were reacted according to the general procedure with modification of temperature, reaction time (60 °C, 12 h), and purification/hydrolysis steps. The crude imine product was subjected to silica gel chromatography (eluent = hexane/EtOAc/ NEt_3 = 100/8/2) prior to acidic hydrolysis. Silica gel chromatography (eluent = hexane/EtOAc = 100/10) of the crude aldehyde afforded the title compound as a white solid (55.1 mg, 83% yield); Mp = 105–107 °C; R_f 0.50 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ -0.13 (s, 9H), 1.54 (dd, $J = 14.6$ Hz, 10.5 Hz, 1H), 1.72 (dd, $J = 14.6$ Hz, 6.0 Hz, 1H), 3.47 (s, 3H), 5.26

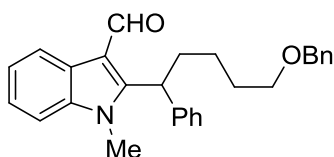
(dd, $J = 10.5$ Hz, 6.0 Hz, 1H), 7.20–7.33 (m, 8H), 8.37–8.39 (m, 1H), 10.40 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ -1.2 (3C), 20.3, 31.6, 35.7, 109.4, 114.9, 121.5, 123.2, 123.7, 126.0, 127.0, 127.4 (2C), 128.9 (2C), 137.6, 142.0, 153.3, 184.9; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{26}\text{NOSi}$ $[\text{M} + \text{H}]^+$ 336.1784, found 336.1783. The same product was also obtained using (*E*)-trimethyl(styryl)silane ((*E*)-**15d**) instead of (*Z*)-**15d** in 39% yield.



2-(2-Cyclohexyl-1-phenylethyl)-1-methyl-1H-indole-3-carbaldehyde (16e): **1k** (52.9 mg, 0.20 mmol) and (*E*)-(2-cyclohexylvinyl)benzene (**15e**, 55.9 mg, 0.30 mmol) were reacted according to the general procedure with modification of temperature, reaction time (60 °C, 12 h), and purification/hydrolysis steps. The crude imine product was subjected to silica gel chromatography (eluent = hexane/EtOAc/ NEt_3 = 100/8/2) prior to acidic hydrolysis. Silica gel chromatography (eluent = hexane/EtOAc = 100/10) of the crude aldehyde afforded the title compound as an orange oil (29.2 mg, 42% yield); R_f 0.50 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 0.98–1.04 (m, 2H), 1.14–1.17 (m, 3H), 1.25–1.29 (m, 1H), 1.62–1.68 (m, 5H), 1.91 (d, $J = 13$ Hz, 1H), 2.10–2.13 (m, 1H), 2.27–2.31 (m, 1H), 3.50 (s, 3H), 5.15 (t, $J = 7.8$ Hz, 1H), 7.21–7.33 (m, 8H), 8.39–8.40 (m, 1H), 10.34 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 26.1, 26.2, 26.6, 31.5, 33.4, 34.3, 35.7, 37.9, 40.6, 109.5, 115.7, 121.7, 123.2, 123.6, 126.0, 127.1, 127.7 (2C), 129.0 (2C), 137.6, 140.8, 152.3, 185.1; HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{28}\text{NO}$ $[\text{M} + \text{H}]^+$ 346.2171, found 346.2171.

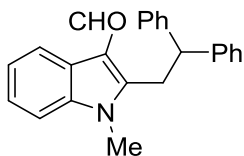


2-(5-Hydroxy-1-phenylpentyl)-1-methyl-1*H*-indole-3-carbaldehyde (16f): **1k** (52.9 mg, 0.20 mmol) and (*Z*)-2-((5-phenylpent-4-en-1-yl)oxy)tetrahydro-2*H*-pyran (**15f**, 73.9 mg, 0.30 mmol) were reacted according to the general procedure with modified temperature and reaction time (60 °C, 12 h). Hydrolysis was performed at 40 °C for 1 h. Silica gel chromatography (eluent = hexane/EtOAc = 1/1) of the crude product afforded the title compound as a yellow oil (35.0 mg, 54% yield); R_f 0.21 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.30–1.38 (m, 1H), 1.45–1.52 (m, 1H), 1.54–1.70 (m, 2H), 1.82 (brs, 1H), 2.19–2.78 (m, 1H), 2.43–2.52 (m, 1H), 3.45 (s, 3H), 3.60 (t, $J = 6.4$ Hz, 2H), 5.04 (dd, $J = 9.6$ Hz, 6.0 Hz, 1H), 7.21–7.33 (m, 8H), 8.35–8.38 (m, 1H), 10.30 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 24.6, 31.4, 32.4, 32.7, 40.8, 62.6, 109.6, 115.9, 121.4, 123.2, 123.6, 126.0, 127.1, 127.6 (2C), 129.0 (2C), 137.6, 140.5, 152.1, 185.2; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_2$ [$\text{M} + \text{H}$] $^+$ 322.1807, found 322.1810.

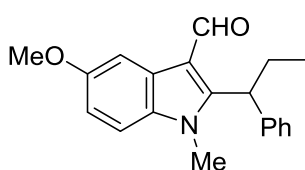


2-(5-(Benzyloxy)-1-phenylpentyl)-1-methyl-1*H*-indole-3-carbaldehyde (16g): **1k** (52.9 mg, 0.20 mmol) and (*Z*)-(5-(benzyloxy)pent-1-en-1-yl)benzene (**15g**, 76.2 mg, 0.30 mmol) were reacted according to the general procedure with modified temperature and reaction time (60 °C, 12 h). Silica gel chromatography (eluent = hexane/EtOAc = 100/10 to 100/15) of the crude product afforded the title compound as a yellow oil (54.1 mg, 66% yield); R_f 0.32 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.29–1.40 (m, 1H), 1.46–1.59 (m, 1H), 1.46–1.71 (m, 2H), 2.16–2.26 (m, 1H), 2.41–2.52 (m, 1H), 3.43 (t, $J = 6.4$ Hz, 2H), 3.46 (s, 3H), 4.43 (s, 2H), 5.01 (dd, $J = 9.6$ Hz, 6.0 Hz, 1H), 7.21–7.36 (m, 13H), 8.38–8.40 (m, 1H), 10.31 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 25.2, 29.8, 31.4, 32.5, 40.8, 70.0, 73.1, 109.5, 115.9, 121.6, 123.2, 123.6, 126.0, 127.1, 127.6 (2C), 127.7,

127.9 (2C), 128.5 (2C), 129.0 (2C), 137.6, 138.6, 140.5, 152.1, 185.1; HRMS (ESI) Calcd for $C_{28}H_{30}NO_2$ $[M + H]^+$ 412.2277, found 412.2281.

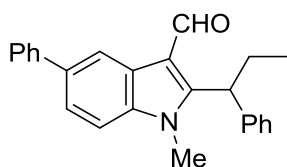


2-(2,2-Diphenylethyl)-1-methyl-1H-indole-3-carbaldehyde (16h): **1k** (52.9 mg, 0.20 mmol) and ethene-1,1-diyldibenzene (**15h**, 54.1 mg, 0.30 mmol) were reacted according to the general procedure with modified temperature and reaction time (60 °C, 12 h). Silica gel chromatography (eluent = hexane/EtOAc = 100/12) of the crude product afforded the title compound as an orange solid (17.1 mg, 25% yield); Mp = 56–58 °C; R_f 0.42 (hexane/EtOAc = 3/1); 1H NMR (400 MHz, $CDCl_3$): δ 3.20 (s, 3H), 3.77 (d, J = 7.8 Hz, 2H), 4.35 (t, J = 7.8 Hz, 1H), 7.14 (d, J = 6.4 Hz, 4H), 7.19–7.32 (m, 9H), 8.22–8.24 (m, 1H), 9.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 31.8, 52.5, 109.7, 114.6, 121.0, 123.0, 123.3, 126.1, 127.2 (2C), 128.1 (4C), 128.8 (4C), 137.1, 143.1 (2C), 149.3, 184.3; HRMS (ESI) Calcd for $C_{19}H_{20}NO$ $[M + H]^+$ 340.1701, found 340.1701.



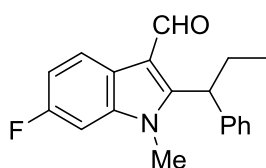
5-Methoxy-1-methyl-2-(1-phenylpropyl)-1H-indole-3-carbaldehyde (16i): (*E*)-1-(5-Methoxy-1-methyl-1H-indol-3-yl)-*N*-(4-methoxyphenyl)methanimine (**11**, 58.9 mg, 0.20 mmol) and **17a** (35.5 mg, 0.30 mmol) were reacted according to the general procedure. Silica gel chromatography (eluent = hexane/EtOAc = 100/12 to 100/15) of the crude product afforded the title compound as a black solid (54.0 mg, 88% yield); Mp = 101–102 °C; R_f 0.31 (hexane/EtOAc = 3/1); 1H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, J = 7.3 Hz, 3H), 2.15–2.21 (m, 1H), 2.47–2.52 (m, 1H), 3.46 (s, 3H), 3.90 (s, 3H), 4.82 (dd, J

= 10.1 Hz, 6.4 Hz, 1H), 6.92 (dd, $J = 9.2$ Hz, 2.8 Hz, 1H), 7.15 (d, $J = 9.2$ Hz, 1H), 7.20–7.32 (m, 5H), 7.93 (d, $J = 2.3$ Hz, 1H) 10.24 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.9, 25.8, 31.4, 42.5, 56.0, 103.3, 110.3, 113.7, 116.0, 126.5, 127.0, 127.5 (2C), 129.0 (2C), 132.4, 140.1, 152.1, 157.0, 185.1; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_2$ [$\text{M} + \text{H}$] $^+$ 308.1651, found 308.1655.



1-Methyl-5-phenyl-2-(1-phenylpropyl)-1H-indole-3-carbaldehyde (16j):

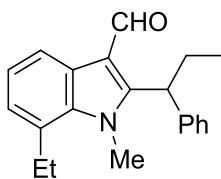
(*E*)-*N*-(4-Methoxyphenyl)-1-(1-methyl-5-phenyl-1*H*-indol-3-yl)methanimine (**1m**, 68.1 mg, 0.20 mmol) and **17a** (35.5 mg, 0.30 mmol) were reacted according to the general procedure. Silica gel chromatography (eluent = hexane/EtOAc = 100/12) of the crude product afforded the title compound as a brown solid (59.6 mg, 84% yield); Mp = 146–147 °C; R_f 0.34 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.01 (t, $J = 7.8$ Hz, 3H), 2.15–2.29 (m, 1H), 2.45–2.57 (m, 1H), 3.48 (s, 3H), 4.91 (dd, $J = 10.1$ Hz, 6.0 Hz, 1H), 7.21–7.34 (m, 7H), 7.43 (t, $J = 7.8$ Hz, 2H), 7.52 (dd, $J = 7.8$ Hz, 1.8 Hz, 1H), 7.68 (d, $J = 7.3$ Hz, 2H), 8.65 (d, $J = 1.8$ Hz, 1H), 10.32 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.9, 25.6, 31.5, 42.5, 109.8, 116.4, 120.1, 123.2, 126.4, 127.0, 127.1, 127.6 (2C), 127.7 (2C), 128.8 (2C), 129.0 (2C), 136.8, 137.0, 140.5, 141.9, 152.6, 185.2; HRMS (ESI) Calcd for $\text{C}_{25}\text{H}_{24}\text{NO}$ [$\text{M} + \text{H}$] $^+$ 354.1858, found 354.1859.



6-Fluoro-1-methyl-2-(1-phenylpropyl)-1H-indole-3-carbaldehyde (16k):

(*E*)-1-(6-Fluoro-1-methyl-1*H*-indol-3-yl)-*N*-(4-methoxyphenyl)methanimine (**1n**, 56.5 mg,

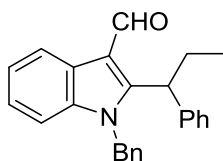
0.20 mmol) and **17a** (35.5 mg, 0.30 mmol) were reacted according to the general procedure. Silica gel chromatography (eluent = hexane/EtOAc = 100/10) of the crude product afforded the title compound as a yellow oil (51.2 mg, 87% yield); R_f 0.40 (hexane/EtOAc = 3/1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 1.00 (t, $J = 7.3$ Hz, 3H), 2.15–2.22 (m, 1H), 2.48–2.55 (m, 1H), 3.43 (s, 3H), 4.86 (dd, $J = 10.1$ Hz, 6.4 Hz, 1H), 6.94 (dd, $J = 9.6$ Hz, 2.3 Hz, 1H), 7.01–7.07 (m, 1H), 7.22–7.34 (m, 5H), 8.33 (dd, $J = 8.7$ Hz, 5.5 Hz, 1H), 10.28 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 12.9, 25.7, 31.5, 42.5, 96.4 (d, $^2J_{\text{C-F}} = 26.8$ Hz), 111.4 (d, $^2J_{\text{C-F}} = 24.0$ Hz), 116.3, 122.1, 122.8 (d, $^3J_{\text{C-F}} = 9.6$ Hz), 127.2, 127.6 (2C), 129.1 (2C), 138.0 (d, $^3J_{\text{C-F}} = 11.5$ Hz), 140.4, 152.6 (d, $^4J_{\text{C-F}} = 1.9$ Hz), 160.7 (d, $^1J_{\text{C-F}} = 241.4$ Hz), 185.1; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{19}\text{FNO}$ $[\text{M} + \text{H}]^+$ 296.1451, found 296.1451.



7-Ethyl-1-methyl-2-(1-phenylpropyl)-1H-indole-3-carbaldehyde (16l):

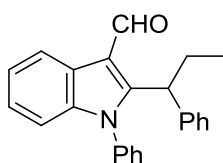
(*E*)-1-(7-Ethyl-1-methyl-1H-indol-3-yl)-*N*-(4-methoxyphenyl)methanimine (**10**, 58.5 mg, 0.20 mmol) and **17a** (35.5 mg, 0.30 mmol) were reacted according to the general procedure. Silica gel chromatography (eluent = hexane/EtOAc = 100/10) of the crude product afforded the title compound as a yellow solid (53.7 mg, 88% yield); Mp = 91–93 °C; R_f 0.46 (hexane/EtOAc = 3/1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 1.00 (t, $J = 7.8$ Hz, 3H), 1.29 (t, $J = 7.3$ Hz, 3H), 2.15–2.23 (m, 1H), 2.50–2.57 (m, 1H), 3.05 (t, $J = 7.3$ Hz, 2H), 3.70 (s, 3H), 5.03 (dd, $J = 10.1$ Hz, 6.0 Hz, 1H), 7.07 (d, $J = 7.3$ Hz, 1H), 7.19–7.27 (m, 4H), 7.30–7.33 (m, 2H), 8.32 (d, $J = 7.8$ Hz, 1H), 10.30 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 12.9, 16.9, 25.3, 26.1, 34.5, 41.9, 116.3, 119.3, 123.2, 125.4, 127.0, 127.2, 127.4 (2C), 128.0, 129.0 (2C), 135.6, 140.8, 152.2, 185.2; HRMS (ESI) Calcd for

$C_{21}H_{24}NO$ $[M + H]^+$ 306.1858, found 306.1858.



1-Benzyl-2-(1-phenylpropyl)-1H-indole-3-carbaldehyde (16m):

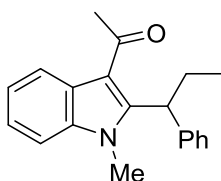
(*E*)-1-(1-Benzyl-1*H*-indol-3-yl)-*N*-(4-methoxyphenyl)methanimine (**1p**, 68.1 mg, 0.20 mmol) and **17a** (35.5 mg, 0.30 mmol) were reacted according to the general procedure. Silica gel chromatography (eluent = hexane/EtOAc = 100/10) of the crude product afforded the title compound as a white solid (47.2 mg, 66% yield); Mp = 154–156 °C; R_f 0.43 (hexane/EtOAc = 3/1); 1H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, J = 7.3 Hz, 3H), 2.03–2.09 (m, 1H), 2.31–2.38 (m, 1H), 4.78 (dd, J = 9.6 Hz, 6.4 Hz, 1H), 5.21 (d, J = 3.7 Hz, 2H), 6.88–6.90 (m, 2H), 7.12 (d, J = 8.7 Hz, 1H), 7.19–7.33 (m, 10H), 8.45 (d, J = 7.8 Hz, 1H), 10.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.0, 26.8, 43.2, 47.8, 110.4, 116.5, 121.9, 123.3, 123.9, 125.9 (2C), 126.2, 127.2, 127.7 (2C), 127.8, 129.0 (4C), 136.1, 137.4, 140.7, 152.2, 185.7; HRMS (ESI) Calcd for $C_{25}H_{24}NO$ $[M + H]^+$ 354.1858 found 354.1858.



1-Phenyl-2-(1-phenylpropyl)-1H-indole-3-carbaldehyde (16n):

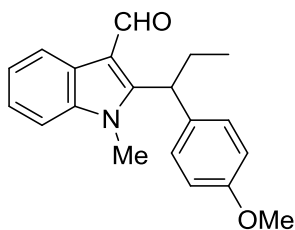
(*E*)-1-(1-Phenyl-1*H*-indol-3-yl)-*N*-(4-methoxyphenyl)methanimine (**1q**, 65.2 mg, 0.20 mmol) and **17a** (35.5 mg, 0.30 mmol) were reacted according to the general procedure with modified temperature and reaction time (60 °C, 12 h). Silica gel chromatography (eluent = hexane/EtOAc = 100/10) of the crude product afforded the title compound as an orange solid (21.5 mg, 32% yield); Mp 121–122 °C; R_f 0.32 (hexane/EtOAc = 3/1); 1H

NMR (400 MHz, CDCl₃): δ 0.95 (t, $J = 7.4$ Hz, 3H), 2.10–2.20 (m, 1H), 2.26–2.32 (m, 1H), 4.42 (dd, $J = 9.2$ Hz, 6.9 Hz, 1H), 6.85 (d, $J = 8.2$ Hz, 1H), 7.00 (d, $J = 7.8$ Hz, 1H), 7.11 (d, $J = 6.8$ Hz, 2H), 7.17–7.25 (m, 5H), 7.31 (t, $J = 7.3$ Hz, 1H), 7.41–7.45 (m, 1H), 7.48–7.52 (m, 2H), 8.43 (d, $J = 8.2$ Hz, 1H), 10.33 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 12.9, 28.3, 44.0, 111.0, 115.7, 121.9, 123.5, 123.9, 126.9, 127.8 (2C), 128.7 (2C), 128.9, 129.3, 129.6, 129.8 (2C), 136.5, 138.9, 141.5, 153.2, 186.2; HRMS (ESI) Calcd for C₂₄H₂₂NO [M + H]⁺ 340.1701, found 340.1701.

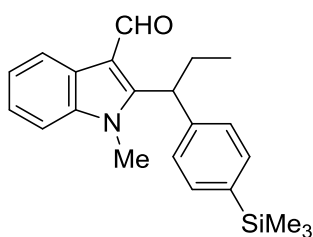


1-(1-Methyl-2-(1-phenylpropyl)-1H-indol-3-yl)ethan-1-one (16o):

(*E*)-*N*-(4-Methoxyphenyl)-1-(1-methyl-1*H*-indol-3-yl)ethan-1-imine (**1r**, 55.7 mg, 0.20 mmol) and **17a** (35.5 mg, 0.30 mmol) were reacted according to the general procedure with modified temperature and reaction time (60 °C, 12 h). Silica gel chromatography (eluent = hexane/EtOAc = 10/1 to 100/15) of the crude product afforded the title compound as a yellow solid (24.2 mg, 42% yield); Mp = 97–99 °C; R_f 0.55 (hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃): δ 0.96 (t, $J = 7.8$ Hz, 3H), 2.07–2.14 (m, 1H), 2.43–2.50 (m, 1H), 2.78 (s, 3H), 3.37 (s, 3H), 6.01 (dd, $J = 10.0$ Hz, 5.9 Hz, 1H), 7.16–7.20 (m, 1H), 7.22–7.31 (m, 7H), 7.95–7.97 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 12.3, 24.1, 31.5, 32.6, 40.7, 109.8, 116.1, 121.1, 122.1, 122.3, 126.4 (2C), 127.5 (2C), 128.7 (2C), 137.4, 141.6, 149.5, 195.5; HRMS (ESI) Calcd for C₂₀H₂₂NO [M + H]⁺ 292.1701, found 292.1702

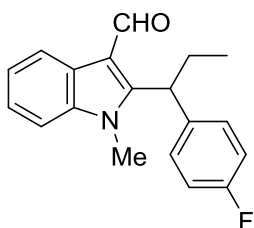


2-(1-(4-Methoxyphenyl)propyl)-1-methyl-1H-indole-3-carbaldehyde (16p): 1k (52.9 mg, 0.20 mmol) and 1-allyl-4-methoxybenzene (**17b**, 44.5 mg, 0.30 mmol) were reacted according to the general procedure. Silica gel chromatography (eluent = hexane/EtOAc = 100/13) of the crude product afforded the title compound as a red oil (48.9 mg, 80% yield); R_f 0.28 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.00 (t, $J = 7.3$ Hz, 3H), 2.13–2.23 (m, 1H), 2.47–2.51 (m, 1H), 3.50 (s, 3H), 3.78 (s, 3H), 4.87 (dd, $J = 9.9$ Hz, 6.4 Hz, 1H), 6.85 (app. d, $J = 8.7$ Hz, 2H), 7.18 (app. d, $J = 8.7$ Hz, 2H), 7.26–7.33 (m, 3H), 8.38–8.41 (m, 1H), 10.30 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.9, 25.8, 31.3, 41.7, 55.4, 109.4, 114.3 (2C), 116.1, 121.6, 123.1, 123.5, 125.9, 128.6 (2C), 132.5, 137.6, 152.4, 158.6, 185.2; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 308.1651, found 308.1655.

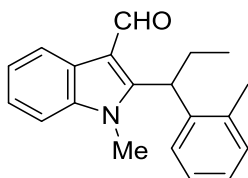


1-Methyl-2-(1-(4-(trimethylsilyl)phenyl)propyl)-1H-indole-3-carbaldehyde (16q): 1k (52.9 mg, 0.20 mmol) and (4-allylphenyl)trimethylsilane (**17c**, 57.1 mg, 0.30 mmol) were reacted according to the general procedure. Silica gel chromatography (eluent = hexane/EtOAc = 100/10) of the crude product afforded the title compound as a red oil (56.4 mg, 81% yield); R_f 0.45 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 0.24 (s, 9H), 1.00 (t, $J = 7.3$ Hz, 3H), 2.17–2.25 (m, 1H), 2.48–2.55 (m, 1H), 3.52 (s, 3H), 4.89 (dd, $J = 9.6$ Hz, 5.9 Hz, 1H), 7.24–7.31 (m, 5H), 7.46 (app. d, $J = 8.2$ Hz, 2H), 8.38–8.41

(m, 1H), 10.30 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ -1.0 (3C), 12.8, 25.6, 31.3, 42.4, 109.4, 116.1, 121.6, 123.1, 123.5, 125.9, 126.9 (2C), 133.9 (2C), 137.5, 139.2, 141.1, 152.0, 185.2; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{28}\text{NOSi}$ $[\text{M} + \text{H}]^+$ 350.1940, found 350.1938.

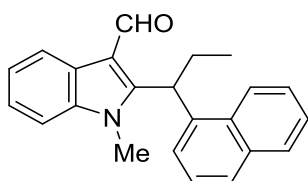


2-(1-(4-Fluorophenyl)propyl)-1-methyl-1H-indole-3-carbaldehyde (16r): **1k** (52.9 mg, 0.20 mmol) and 1-allyl-4-fluorobenzene (**17d**, 40.9 mg, 0.30 mmol) were reacted according to the general procedure. Silica gel chromatography (eluent = hexane/EtOAc = 100/12) of the crude product afforded the title compound as a yellow solid (49.0 mg, 83% yield); Mp = 108–110 °C; R_f 0.31 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 0.99 (t, J = 7.3 Hz, 3H), 2.16–2.24 (m, 1H), 2.45–2.52 (m, 1H), 3.49 (s, 3H), 4.92 (dd, J = 10.1 Hz, 6.0 Hz, 1H), 7.00 (t, J = 8.7 Hz, 2H), 7.21–7.25 (m, 2H), 7.26–7.33 (m, 3H), 8.36–8.39 (m, 1H), 10.30 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.8, 25.8, 31.3, 41.7, 109.5, 115.9 (d, $^2J_{\text{C-F}}$ = 21.1 Hz, 2C), 116.1, 121.5, 123.2, 123.7, 126.0, 129.1 (d, $^3J_{\text{C-F}}$ = 8.6 Hz, 2C), 136.4, 137.5, 151.4, 163.2 (d, $^1J_{\text{C-F}}$ = 247.2 Hz, 2C), 185.1; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{19}\text{FNO}$ $[\text{M} + \text{H}]^+$ 296.1451, found 296.1447.

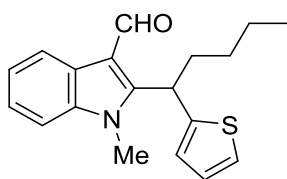


1-Methyl-2-(1-(o-tolyl)propyl)-1H-indole-3-carbaldehyde (16s): **1k** (52.9 mg, 0.20 mmol) and 1-allyl-2-methylbenzene (**17e**, 44.5 mg, 0.30 mmol) were reacted according to the general procedure. Silica gel chromatography (eluent = hexane/EtOAc = 100/10) of the crude product afforded the title compound as a light brown solid (37.9 mg, 65%

yield); Mp = 113–115 °C; R_f 0.35 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.08 (t, $J = 7.3$ Hz, 3H), 2.10 (s, 3H), 2.20–2.28 (m, 1H), 2.38–2.45 (m, 1H), 3.57 (s, 3H), 4.83 (dd, $J = 8.8$ Hz, 7.7 Hz, 1H), 7.12 (d, $J = 7.3$ Hz, 1H), 7.19 (t, $J = 7.3$ Hz, 1H), 7.24–7.31 (m, 4H), 7.51 (d, $J = 7.7$ Hz, 1H), 8.33–8.36 (m, 1H), 10.31 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.8, 20.2, 27.4, 31.1, 41.4, 109.5, 115.2, 121.5, 123.2, 123.4, 126.1, 126.4, 127.2, 127.4, 131.5, 137.2, 137.4, 138.5, 151.5, 185.7; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{22}\text{NO}$ [$\text{M} + \text{H}$] $^+$ 292.1701, found 292.1701.

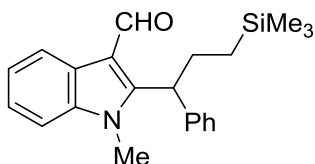


Methyl-2-(1-(naphthalen-1-yl)propyl)-1H-indole-3-carbaldehyde (16t): **1k** (52.9 mg, 0.20 mmol) and 1-allylnaphthalene (**17f**, 50.5 mg, 0.30 mmol) were reacted according to the general procedure. Silica gel chromatography (eluent = hexane/EtOAc = 100/12) of the crude product afforded the title compound as a grey solid (53.3 mg, 81% yield); Mp = 137–139 °C; R_f 0.31 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.14 (t, $J = 7.3$ Hz, 3H), 2.32–2.40 (m, 1H), 2.51–2.58 (m, 1H), 3.49 (s, 3H), 5.49–5.53 (m, 1H), 7.18–7.30 (m, 3H), 7.37–7.48 (m, 3H), 7.63 (d, $J = 7.4$ Hz, 1H) 7.79 (d, $J = 8.2$ Hz, 1H), 7.82–7.84 (m, 1H), 8.00–8.02 (m, 1H), 8.35 (d, $J = 5.5$ Hz, 1H), 10.46 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.0, 27.8, 31.2, 40.9, 109.6, 115.3, 121.2, 123.1, 123.3, 123.4, 125.4, 125.5, 126.0, 126.4, 126.9, 128.4, 129.2, 132.1, 134.3, 136.2, 137.4, 151.6, 185.6; HRMS (ESI) Calcd for $\text{C}_{23}\text{H}_{22}\text{NO}$ [$\text{M} + \text{H}$] $^+$ 328.1701, found 328.1698.



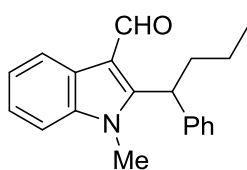
1-Methyl-2-(1-(thiophen-2-yl)propyl)-1H-indole-3-carbaldehyde (16u): **1k** (52.9 mg,

0.20 mmol) and 2-allylthiophene (**17g**, 37.3 mg, 0.30 mmol). Silica gel chromatography (eluent = hexane/EtOAc = 100/10) of the crude product afforded the title compound as a yellow solid (5.7 mg, 10% yield); Mp = 85–87 °C; R_f 0.35 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 0.98 (t, J = 7.3 Hz, 3H), 2.23–2.31 (m, 1H), 2.51–2.58 (m, 1H), 3.59 (s, 3H), 5.10 (dd, J = 10.2 Hz, 5.5 Hz, 1H), 6.82–6.84 (m, 1H), 6.96 (dd, J = 5.1 Hz, 3.6 Hz, 1H), 7.22 (d, J = 5.1 Hz, 1H), 7.29–7.34 (m, 3H), 8.37–8.39 (m, 1H), 10.28 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.7, 27.8, 31.5, 38.9, 109.6, 115.7, 121.7, 123.3, 123.8, 124.68, 124.74, 125.9, 127.2, 137.7, 145.3, 150.5, 184.9; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{18}\text{NOS}$ $[\text{M} + \text{H}]^+$ 284.1109, found 284.1108.



1-Methyl-2-(1-phenyl-3-(trimethylsilyl)propyl)-1H-indole-3-carbaldehyde (16v): **1k**

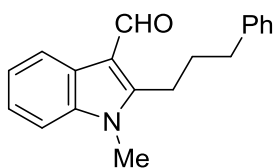
(52.9 mg, 0.20 mmol) and (*E*)-trimethyl(3-phenylprop-1-en-1-yl)silane (**17i**, 57.1 mg, 0.30 mmol) were subjected to the general procedure with modification of temperature, reaction time (60 °C, 12 h), and purification/hydrolysis steps. The crude imine product was subjected to silica gel chromatography (eluent = hexane/EtOAc/ NEt_3 = 100/8/2) prior to acidic hydrolysis. Silica gel chromatography (eluent = hexane/EtOAc = 10/1) of the crude aldehyde afforded the title compound as an orange oil (27.6 mg, 39% yield); R_f 0.50 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 0.00 (s, 9H), 0.41 (td, J = 13.7 Hz, 4.1 Hz, 1H), 0.63 (dd, J = 13.7 Hz, 4.1 Hz, 1H), 2.14–2.23 (m, 1H), 2.42–2.49 (m, 1H), 3.51 (s, 3H), 4.94 (dd, J = 9.6 Hz, 4.1 Hz, 1H), 7.22–7.36 (m, 8H), 8.40–8.42 (m, 1H), 10.31 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ -1.6 (3C), 15.5, 27.3, 31.4, 44.2, 109.5, 116.3, 121.7, 123.2, 123.6, 126.0, 127.1, 127.7 (2C), 129.0 (2C), 137.6, 140.7, 152.2, 185.3; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{28}\text{NOSi}$ $[\text{M} + \text{H}]^+$ 350.1940, found 350.1938.



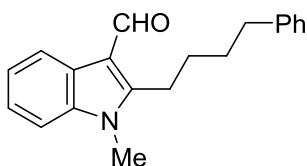
1-Methyl-2-(1-phenylbutyl)-1H-indole-3-carbaldehyde (16w): **1k** (52.9 mg, 0.20 mmol) and but-3-en-1-ylbenzene (**19**, 39.7 mg, 0.30 mmol) were reacted according to the general procedure with modified temperature and reaction time (60 °C, 12 h). Silica gel chromatography (eluent = hexane/EtOAc = 100/13) of the crude product afforded the title compound as a yellow oil (37.4 mg, 64% yield); R_f 0.52 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 0.98 (t, $J = 7.3$ Hz, 3H), 1.29–1.33 (m, 1H), 1.40–1.45 (m, 1H), 2.15–2.21 (m, 1H), 2.39–2.45 (m, 1H), 3.49 (s, 3H), 5.03 (dd, $J = 9.6$ Hz, 6.0 Hz, 1H), 7.22–7.34 (m, 8H), 8.38–8.40 (m, 1H), 10.31 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 21.6, 31.4, 34.8, 40.6, 109.5, 116.0, 121.6, 123.2, 123.6, 126.0, 127.1, 127.6 (2C), 129.0 (2C), 137.6, 140.7, 152.3, 185.2; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{22}\text{NO}$ [$\text{M} + \text{H}$] $^+$ 292.1701, found 292.1702.

A Procedure for Linear-Selective C2-Alkylation of Indole Substrate 1k:
1-Methyl-2-(3-phenylpropyl)-1H-indole-3-carbaldehyde (18). To a solution of **1k** (52.9 mg, 0.2 mmol), **17a** (35.5 mg, 0.30 mmol), CoBr_2 (0.1 M solution in THF, 0.2 mL, 0.02 mmol), DMPU (0.15 mL, 1.2 mmol) in THF (0.23 mL) was added $t\text{BuCH}_2\text{MgBr}$ (1.85 M in THF, 0.07 mL, 0.12 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 12 h, followed by quenching with water (0.5 mL). After addition of THF (1.0 mL) and 3M HCl (0.4 mL), the mixture was stirred for another 1 h, and then extracted with EtOAc (2 mL x 3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (eluent = hexane/EtOAc = 100/20) to afford the title compound as a

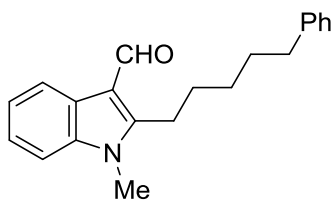
yellow solid (27.7 mg, 50% yield).



Mp = 106–108 °C; R_f 0.28 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 2.02 (quint, $J = 7.8$ Hz, 2H), 2.78 (t, $J = 8.2$ Hz, 2H), 3.10 (t, $J = 7.8$ Hz, 2H), 3.63 (s, 3H), 7.19–7.23 (m, 3H), 7.27–7.33 (m, 5H), 8.26–8.28 (m, 1H), 10.11 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 24.1, 29.9, 31.7, 35.5, 109.5, 114.2, 121.2, 123.1, 123.4, 126.0, 126.5, 128.6 (2C), 128.8 (2C), 137.3, 141.0, 151.5, 184.3; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{20}\text{NO}$ [$\text{M} + \text{H}$] $^+$ 278.1545, found 278.1549.



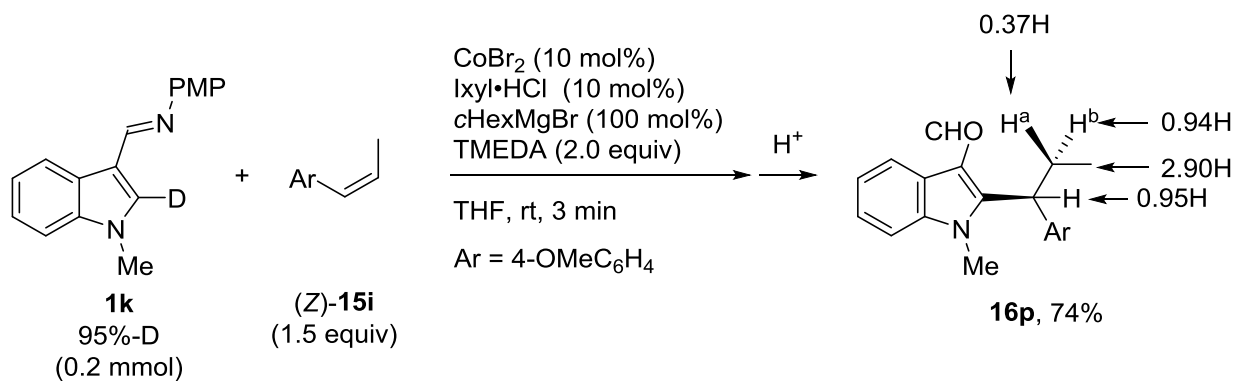
1-Methyl-2-(4-phenylpropyl)-1H-indole-3-carbaldehyde (21): **1k** (52.9 mg, 0.20 mmol) and but-3-en-1-ylbenzene (**19**, 39.7 mg, 0.30 mmol) were reacted according to the above procedure. Silica gel chromatography (eluent = hexane/EtOAc = 100/18) of the crude product afforded a mixture of title compound and C2-neopentylated product. Further purification on PTLC (eluent = hexane/EtOAc = 100/10, five times developments) afforded the title compound as a yellow oil (24.0 mg, 41% yield); R_f 0.31 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.68–1.79 (m, 4H), 2.69 (t, $J = 6.9$ Hz, 2H), 3.09 (t, $J = 7.8$ Hz, 2H), 3.65 (s, 3H), 7.15 (d, $J = 7.3$ Hz, 2H), 7.19 (d, $J = 7.3$ Hz, 1H), 7.27–7.29 (m, 5H), 8.26–8.28 (m, 1H), 10.15 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 24.5, 29.6, 29.9, 31.0, 35.6, 109.5, 114.1, 121.1, 123.1, 123.3, 125.9, 126.1, 128.55 (2C), 128.59 (2C), 137.3, 141.8, 151.7, 184.3; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{22}\text{NO}$ [$\text{M} + \text{H}$] $^+$ 292.1701, found 292.1702.



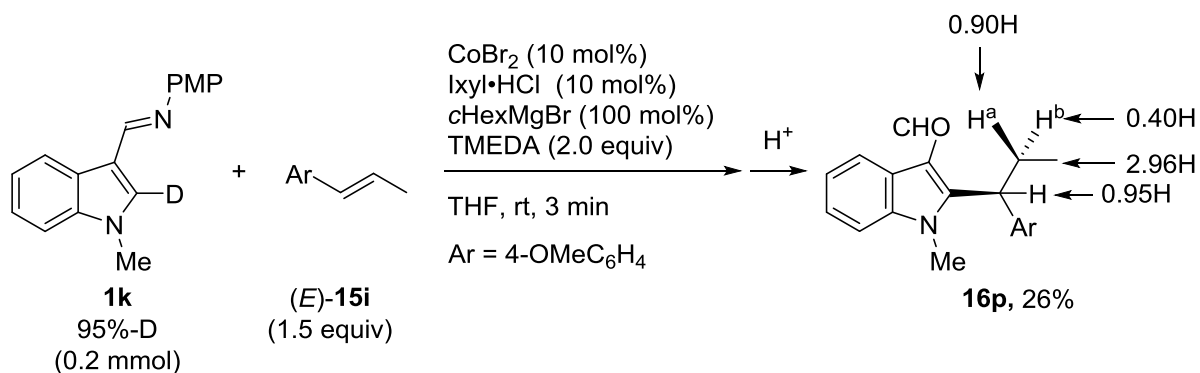
1-Methyl-2-(5-phenylpropyl)-1H-indole-3-carbaldehyde (22): **1k** (52.9 mg, 0.20 mmol) and pent-4-en-1-ylbenzene (**20**, 43.9 mg, 0.30 mmol) were reacted according to the above procedure. Silica gel chromatography (eluent = hexane/EtOAc = 100/18) of the crude product afforded a mixture of the title compound and C2-neopentylated product. Further purification on PTLC (eluent = hexane/EtOAc = 100/10, five times developments) afforded the title compound as a red solid (17.3 mg, 28% yield); Mp = 61–62 °C; R_f 0.32 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.46–1.52 (m, 2H), 1.63–1.74 (m, 4H), 2.61 (t, $J = 7.3$ Hz, 2H), 3.07 (t, $J = 7.8$ Hz, 2H), 3.69 (s, 3H), 7.15 (d, $J = 6.9$ Hz, 2H), 7.18 (d, $J = 7.3$ Hz, 1H), 7.27–7.31 (m, 5H), 8.26–8.29 (m, 1H), 10.15 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 24.6, 29.2, 29.9, 30.2, 31.3, 36.0, 109.5, 114.1, 121.2, 123.1, 123.3, 125.9, 126.0, 128.5 (2C), 128.6 (2C), 137.3, 142.4, 151.2, 184.3; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{24}\text{NO}$ $[\text{M} + \text{H}]^+$ 306.1858, found 306.1859.

Deuterium-Labeling Experiments

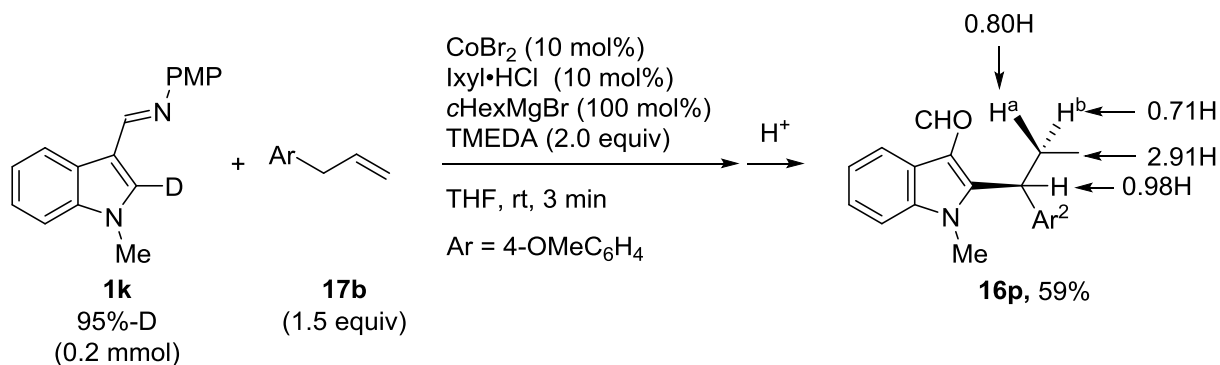
1. Reactions of C2-Deuterated Indole Substrate



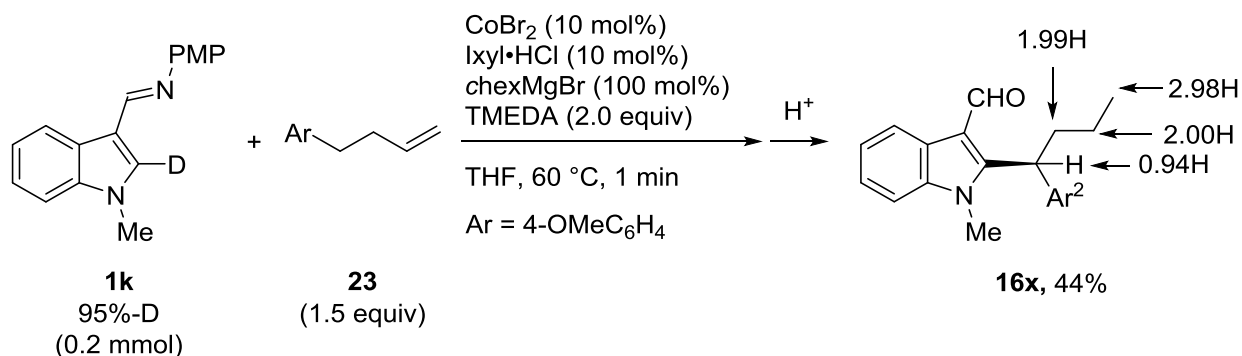
Reaction of [D]-1k and (Z)-15i: To a solution of [D]-**1k** (53.1 mg, 0.2 mmol, 95% D), (Z)-1-methoxy-4-(prop-1-en-1-yl)benzene ((Z)-**15i**, 44.5 mg, 0.3 mmol), CoBr_2 (0.1 M solution in THF, 0.2 mL, 0.02 mmol), 1,3-bis(2,6-dimethylphenyl)-1*H*-imidazol-3-ium chloride (6.3 mg, 0.02 mmol) and TMEDA (60 μL , 0.4 mmol) in THF (0.03 mL) was added CyMgBr (0.46 M in THF, 0.44 mL, 0.2 mmol) at room temperature. After stirring for 3 min, the reaction was immediately quenched with water (0.5 mL). Hydrolysis, workup, and purification were performed as described in the general procedure to afford the hydroarylation product **16p** in 74% yield. The ^1H NMR integrations of the protons on C1, C2, and C3 (relative to 3H of the methoxy group) were 0.95, 0.37/0.94, and 2.90, respectively (see scheme/attached spectrum). Protons H^a and H^b on the C2 position were assigned with assumption of a *syn*-hydroarylation mechanism.



Reaction of [D]-1k and (E)-15i: [D]-1k and (E)-15i were reacted according to the above procedure to afford the hydroarylation product **16p** in 26% yield. The ¹H NMR integrations of the protons on C1, C2, and C3 (relative to 3H of the methoxy group) were 0.95, 0.90/0.40, and 2.96, respectively (see scheme/attached spectrum). Protons H^a and H^b on the C2 position were assigned with assumption of a *syn*-hydroarylation mechanism.



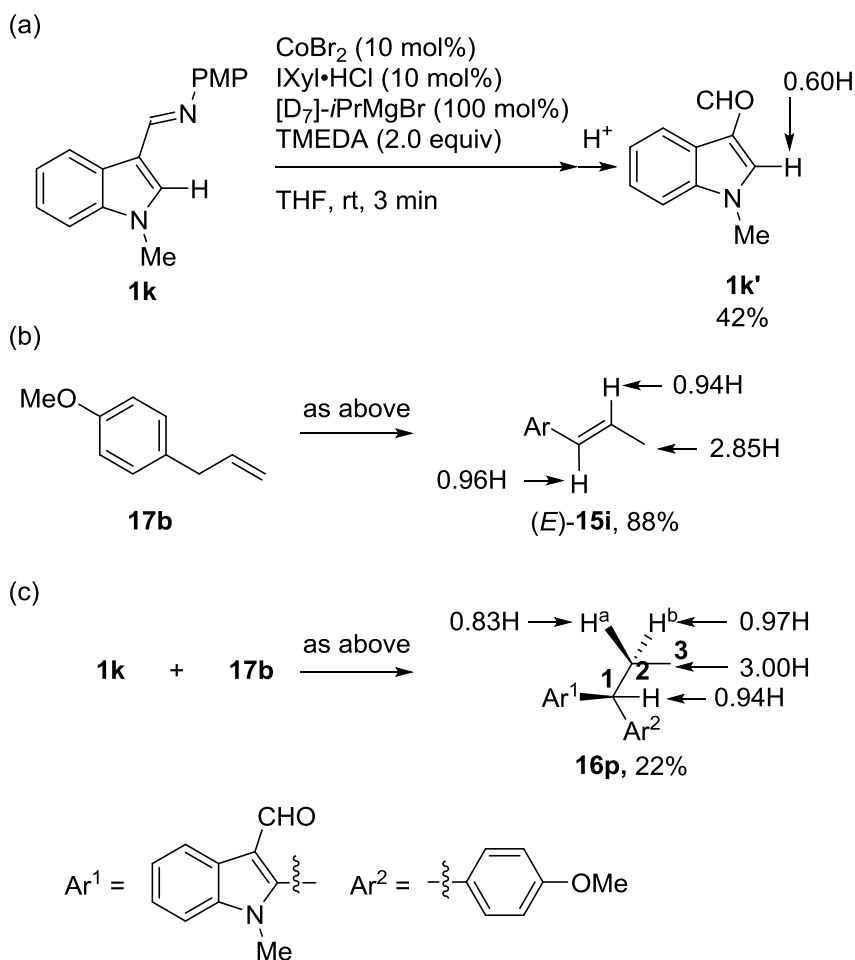
Reaction of [D]-1k and 17b: [D]-1k and 17b were reacted according to the above procedure to afford the hydroarylation product **16p** in 59% yield. The ¹H NMR integrations of the protons on C1, C2, C3, and C4 (relative to 3H of the methoxy group) were 0.98, 0.80/0.71, and 2.91, respectively (see scheme/attached spectrum)



Reaction of [D]-1k and 2: [D]-**1k** and 1-(but-3-en-1-yl)-4-methoxybenzene **23** were reacted according to the above procedure with modified temperature and reaction time (60 °C, 1 min) to afford the hydroarylation product **16x** in 44% yield. The ^1H NMR integrations of the protons on C1, C2, C3 and C4 (relative to 3H of the methoxy group) were 0.94, 1.99, 2.00, and 2.98, respectively (see scheme/attached spectrum). The authentic sample of **16x** was obtained by the reaction of **1k** and **23** according to the general procedure with modified temperature and reaction time (60 °C, 12 h).

2-(1-(4-Methoxyphenyl)butyl)-1-methyl-1H-indole-3-carbaldehyde (16x): Yellow oil (37.2 mg, 58% yield); R_f 0.32 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 0.96 (t, $J = 7.8$ Hz, 3H), 1.25–1.30 (m, 1H), 1.40–1.44 (m, 1H), 2.12–2.17 (m, 1H), 2.35–2.41 (m, 1H), 3.49 (s, 3H), 3.77 (s, 3H), 4.96 (dd, $J = 10.1$ Hz, 6.0 Hz, 1H), 6.84 (app. d, $J = 8.7$ Hz, 2H), 7.17 (d, $J = 8.7$ Hz, 2H), 7.25–7.32 (m, 3H), 8.37–8.40 (m, 1H), 10.30 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 21.5, 31.4, 35.0, 39.8, 55.5, 109.4, 114.3 (2C), 115.9, 121.6, 123.2, 123.5, 125.9, 128.6 (2C), 132.6, 137.6, 152.7, 158.6, 185.2; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 322.1807, found 322.1808.

2. Reactions Using Deuterated Grignard Reagent



Reaction of 1k: To a solution of **1k** (52.9 mg, 0.20 mmol), CoBr_2 (0.1 M solution in THF, 0.2 mL, 0.02 mmol), 1,3-bis(2,6-dimethylphenyl)-1*H*-imidazol-3-ium chloride (6.3 mg, 0.02 mmol) and TMEDA (60 μL , 0.40 mmol) in THF (0.23 mL) was added $[\text{D}_7]\text{-}i\text{PrMgBr}$ (0.82 M in THF, 0.24 mL, 0.2 mmol) at room temperature. The resulting mixture was stirred for 3 min and then immediately quenched with water (0.5 mL). Hydrolysis, workup, and purification were performed as described in the general procedure to afford the aldehyde **1k'** in 42% yield. ^1H NMR integration (relative to 3H of N-methyl group) of the proton on C2 was 0.60.

Reaction of 17b: In the above procedure, **1k** was replaced by **17b** (0.30 mmol). After quenching with water, the resulting mixture was worked up and purified to afford the alkene (*E*)-**15i** in 88% yield. ^1H NMR integrations (relative to 3H of methoxy group) of

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the protons on C1, C2, and C3 were 0.96, 0.94, and 2.85, respectively.

Reaction of 1k and 17b: **1k** (0.20 mmol) and **17b** (0.30 mmol) were reacted according to the above procedure to afford the hydroarylation product **16p** in 22% yield. ¹H NMR integrations (relative to 3H of methoxy group) of the protons on C1, C2, and C3 were 0.93, 0.82/0.95, and 3.00, respectively

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This thesis has disclosed chelation-assisted cobalt-catalyzed insertion of C–C multiple bond into C(sp²)–H bond. Chapter 2 describes aldimine-directed hydroarylation of alkyne. The obtained *ortho*-alkenylated benzaldehyde was transformed into naphthalene and indene derivatives by utilizing the alkenyl group and the formyl group as synthetic handles. Chapter 3 describes cobalt-catalyzed annulation of α,β -unsaturated imine and alkyne to afford 1,2-dihydropyridine. The reaction likely proceeds via cobalt-catalyzed β -C–H bond alkenylation followed by electrocyclization of the resulting azatriene intermediate. This reaction features mild reaction conditions, inexpensive catalytic system, and tolerance of a variety of functional groups. Chapter 4 describes cobalt-catalyzed C2-alkylation of indole with β -substituted styrene. Allyl, homoallyl, and bishomoallylbenzenes also afforded the corresponding 1,1-diarylalkanes through tandem isomerization-hydroarylation sequence.

Through this research program, new cobalt catalysts was developed, which exhibited its efficiency in insertion of C–C multiple bonds into C(sp²)–H bonds. These catalytic systems served as alternative catalysts for reactions catalyzed by second-row transition metals. Furthermore, isomerization/hydroarylation tandem process to afford 1,1-diarylalkane was achieved with the cobalt catalyst, which was not observed with second-low transition metals.