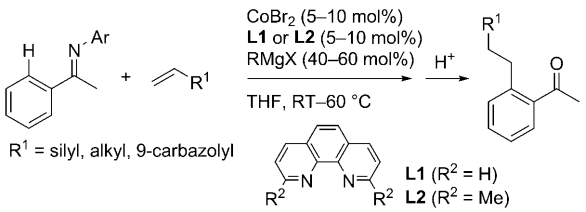
C–H Bond Functionalization

DOI: 10.1002/ange.201101823

Cobalt–Phenanthroline Catalysts for the *ortho* Alkylation of Aromatic Imines under Mild Reaction Conditions**

*Ke Gao and Naohiko Yoshikai**

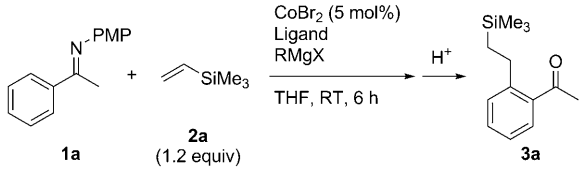
Chelation-assisted C–H activation followed by insertion of an unsaturated molecule offers a straightforward, regioselective, and atom-economical method for C–C bond formation.[1] While rare-transition-metal catalysts (e.g. Ru, Rh, Pd) have played major roles in this and related types of C–H bond functionalization, the development of cost-effective alternatives has attracted increasing interest.[2] We recently developed cobalt–phosphine and cobalt–carbene catalysts that promote *ortho* alkenylation and *ortho* alkylation reactions of aryl pyridine and imine derivatives by insertion of alkynes and styrenes, respectively.[3] These reactions represent the recent emergence of cobalt catalysis for C–H bond functionalization;[4–6] cobalt catalysis is attractive because of the low cost of the catalysts as well as the unique reactivities or selectivities often achieved.[7] We report herein a significant expansion of the scope of this chemistry, achieved with cobalt–phenanthroline (**L1** or **L2**) catalysts, which allow the *ortho* alkylation of aromatic imines with a variety of olefins under mild reaction conditions (Scheme 1).[8–10]



Scheme 1. *ortho* Alkylation of aromatic imines with a cobalt-phenanthroline catalyst.

From the screen of the cobalt catalysts for the addition of the acetophenone imine **1a** (PMP = *p*-methoxyphenyl) to vinyltrimethylsilane (**2a**, 1.2 equiv), we identified 1,10-phenanthroline (**L1**) as an inexpensive and effective ligand (Table 1). Thus, the reaction took place smoothly at room temperature (20 °C) in the presence of a cobalt catalyst generated from $CoBr_2$ (5 mol%), **L1** (5 mol%), and tBuCH$_2$MgBr (40 mol%) to afford the alkylation product **3a** within 6 hours, in 85% yield upon isolation (Table 1, entry 1). No dialkylation product was observed. The room-temperature conditions are in stark contrast to those used for the related reactions of imines under rhodium or ruthenium catalysis, which typically require heating at 130–150 °C.[8,9] Among other phenanthroline-type ligands, bathophenanthroline performed as efficiently as **L1** (Table 1, entries 2–4). The use of other Grignard reagents such as MeMgCl and Me_3SiCH_2MgCl led to lower yields (Table 1, entries 5 and 6). Little conversion was observed when the amount of tBuCH$_2$MgBr was reduced to 20 mol% (Table 1, entry 7). The cobalt–phosphine and cobalt–carbene catalysts developed previously by our group[3] were much less effective (Table 1, entries 8–10).

Table 1: Optimization of *ortho* alkylation of acetophenone imine **1a** with vinyltrimethylsilane **2a**[a]



Entry	Ligand (mol%)	RMgX (mol%)	Yield [%][b]
1	**L1** (5)	tBuCH$_2$MgBr (40)	87 (85)
2	bpy (5)	tBuCH$_2$MgBr (40)	19
3	bathophen (5)	tBuCH$_2$MgBr (40)	88
4	**L2** (5)	tBuCH$_2$MgBr (40)	50
5	**L1** (5)	MeMgCl (40)	20
6	**L1** (5)	Me_3SiCH_2MgCl (40)	67
7	**L1** (5)	tBuCH$_2$MgBr (20)	7
8	PMe_2Ph (10)	MeMgCl (40)	3
9	PCy_3 (5)	Me_3SiCH_2MgCl (40)	21
10	IMes·HCl (5)	tBuCH$_2$MgBr (40)	20

[a] Reaction was performed on a 0.3 mmol scale at 0.3 M concentration. [b] Determined by GC using *n*-tridecane as an internal standard. The yield of the isolated product is shown in parentheses. bathophen = bathophenanthroline, bpy = 2,2′-bipyridine, Cy = cyclohexyl, IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene.

The optimized catalytic system was applicable to a wide variety of aromatic imines (Table 2). Tolerated substituents on the aromatic ring included methoxy (**3b**, **3j**), chloro (**3d**, **3f**), fluoro (**3i**), trifluoromethyl (**3g**), and cyano (**3h**) groups (Table 2, entries 1, 3, and 5–9), although the product yields in the latter two cases were modest. An imine derived from 4-bromoacetophenone did not participate in the reaction but afforded a product resulting from the cross-coupling at the C–Br bond with the Grignard reagent (< 5%). Imines derived

[*] K. Gao, Prof. N. Yoshikai
Division of Chemistry and Biological Chemistry
School of Physical and Mathematical Sciences
Nanyang Technological University
Singapore 637371 (Singapore)
Fax: (+65) 6791-1961
E-mail: nyoshikai@ntu.edu.sg
Homepage: http://www3.ntu.edu.sg/home/nyoshikai/yoshikai_group/Home.html

[**] We thank the Singapore National Research Foundation (NRF-RF2009-05) and Nanyang Technological University for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201101823.

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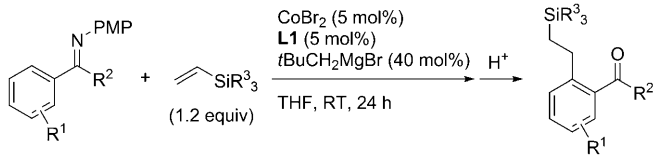
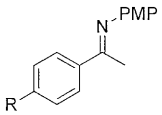
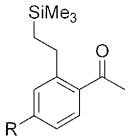
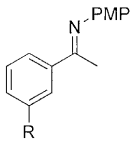
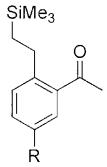
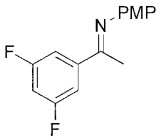
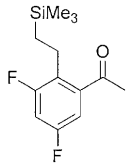
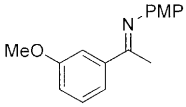
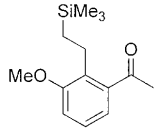
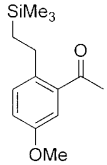
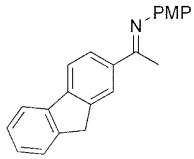
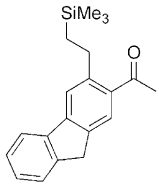
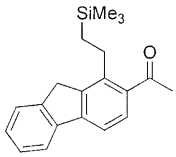
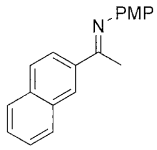
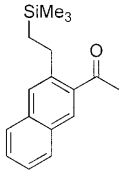
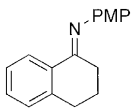
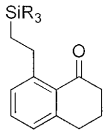
Table 2: Scope of aromatic imines for *ortho* alkylation with vinylsilanes.



Entry	Imine		Product		Yield [%][a]
1		**1b**		**3b** (R = OMe)	81
2		**1c**		**3c** (R = Ph)	79
3[b]		**1d**		**3d** (R = Cl)	70
4		**1e**		**3e** (R = Me)	74
5[b,c]		**1f**		**3f** (R = Cl)	58
6[b,c]		**1g**		**3g** ($R = CF_3$)	41
7		**1h**		**3h** (R = CN)	24
8		**1i**		**3i**	60
9		**1j**		**3j**	61
				**3j′**	30
10		**1k**		**3k**	39
				**3k′**	37
11		**1l**		**3l**	80
12		**1m**		**3m** ($R_3 = Me_3$)	92
13				**3n** ($R_3 = Me_2Ph$)	93
14[b,d]				**3o** ($R_3 = Ph_3$)	84

from *meta*-substituted acetophenones reacted exclusively at the less-hindered position (**3e**–**3h**; Table 2, entries 4–7) except for the one bearing a methoxy group, which preferentially reacted at the proximal position (**3j** and **3j′**, regioselectivity = 2:1; Table 2, entry 9). This may be due to the secondary directing effect of the methoxy group that has been previously observed for related reactions with ruthenium and iridium catalysts.[9c,d,10c,d,f,11,12] The imine derived from 2-fluorenyl methyl ketone afforded an approximately 1:1 mixture of two regioisomers (**3k** and **3k′**; Table 2, entry 10) without interference from the acidic proton of the fluorenyl group ($pK_a \approx 22$).[13] In contrast to this lack of regioselectivity, the imine derived from 2-acetonaphthone was alkylated exclusively at the less-hindered position in good yield (**3l**; Table 2, entry 11). Interestingly, this regioselectivity is complementary to the regioselectivity achieved with the ruthenium-catalyzed *ortho* alkylation of 2-acetonaphthone.[10b,14]

Imines derived from carbonyl groups other than an acetyl group also served as excellent directing groups for the reaction, as exemplified by the products **3m**–**3q**. In addition to the trimethylsilyl group, dimethylphenylsilyl and triphenylsilyl groups could be employed as the silyl groups of the vinylsilanes (**3n** and **3o**; Table 2, entries 13 and 14), while no alkylation took place with vinyltriethoxysilane. Note that 2-phenylpyridine also participated in the reaction with **2a** at 60 °C, affording the corresponding alkylation product **3r** in 72 % yield (Table 2, entry 17).[15]

Prompted by the successful *ortho* alkylation with vinylsilanes, we next explored the scope of olefinic reaction partners. Although the reaction of the tetralone-derived imine and 3,3-dimethyl-1-butene under cobalt–phenanthroline catalysis met with limited success (< 30 % yield), a relatively simple modification of the catalytic system allowed us to achieve

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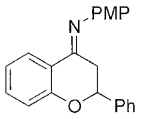
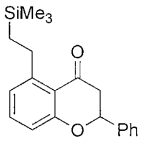
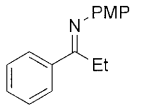
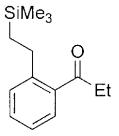
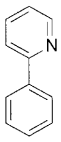
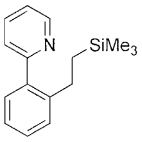
Table 2: (Continued)

Entry	Imine		Product		Yield [%][a]
15[b]		**1n**		**3p**	89
16		**1o**		**3q**	93
17[b,e]		**1p**		**3r**	72

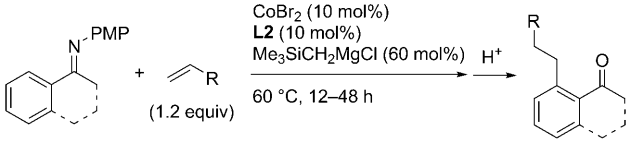
[a] Yields of the isolated products. [b] Catalyst loading was doubled. [c] Reaction time was 36 h. [d] Reaction time was 48 h. [e] Performed at 60 °C.

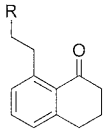
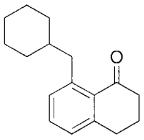
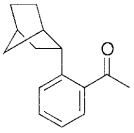
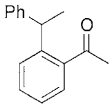
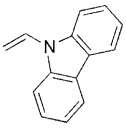
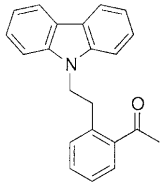
ortho alkylation with a variety of olefins (Table 3). Thus, a modified catalytic system consisting of $CoBr_2$ (10 mol %), neocuproine (**L2**; 10 mol %), and Me_3SiCH_2MgCl (60 mol %) promoted the reaction to afford the product **3s** in 73 % yield and a small amount of an *ortho*-trimethylsilylmethylation product (10 %; Table 3, entry 1).[5d] The use of an aryl Grignard reagent 4-$MeOC_6H_4MgBr$ instead of Me_3SiCH_2MgCl afforded **3s** in 78 % yield with only a small amount (1 %) of an *ortho*-arylation product.

Terminal olefins bearing allylic hydrogen atoms also participated in the reaction to afford the alkylation products **3t**–**3w** in moderate to good yield (Table 3, entries 2–5), even though such olefins have been reported to undergo isomerization to the corresponding internal olefins in the presence of a cobalt catalyst and a Grignard reagent.[16] The addition reaction to the exocyclic double bond of methylenecyclohexane also took place, albeit in low yield (**3x**; Table 3, entry 6). An internal olefin such as *trans*-oct-2-ene afforded only a small amount (5 %) of the *n*-octylation product, while its *cis* isomer was entirely unreactive. Not unexpectedly, norbornene participated in the reaction to afford the adduct **3y** in 76 % yield (Table 3, entry 7). The catalytic system also allowed hydroarylation of styrene,[3b] thus affording the branched product **3z** as the major product (Table 3, entry 8). To the best of our knowledge, 9-vinylcarbazole is a new substrate for *ortho* alkylation through C–H bond functionalization (**3aa**; Table 3, entry 9).

To probe the reaction mechanism, we examined the degree of H/D scrambling that occurred during the reaction of [D_5]-**1a** and vinyldimethylphenylsilane **2b** under cobalt–**L1** catalysis (Scheme 2). The deuterium content at the *ortho* position of the acetophenone that was recovered after a 1 hour reaction had decreased to 85 %. The

Table 3: Addition of aromatic imine to various olefins.



Entry	Imine	Olefin	Product		Yield [%][a]
1	**1m**			**3s** (R = *t*Bu)	73 (78)[b]
2	**1m**			**3t** (R = *n*-C_6H_{13})	62
3	**1m**			**3u** (R = *c*-C_6H_{13})	68
4[c]	**1m**			**3v** (R = $PhCH_2$)	54
5[d]	**1m**			**3w** (R = Me_3SiCH_2)	57
6	**1m**			**3x**	18
7	**1a**			**3y**	76
8	**1a**			**3z**	76 (86:14)[e]
9	**1a**			**3aa**	52

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

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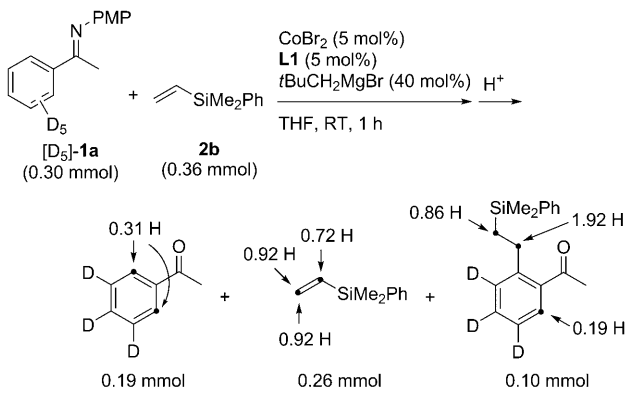

Scheme 2. Deuterium-labeling experiment.

recovered vinylsilane contained 28% deuterium at the α position, while the degree of deuteration at the β position was much lower (8%). The deuterium distribution in the alkylation product was consistent with these observations. The present result is in stark contrast to the H/D scrambling in the cobalt-catalyzed styrene hydroarylation, where significant deuterium incorporation was observed at both the α and β positions of styrene.[3b]

It is worthwhile to compare the above result with the previous studies on H/D scrambling in the Murai reaction, i.e. ruthenium-catalyzed *ortho* alkylation of aromatic ketones with vinylsilanes.[10b,g,17] While the Murai reaction at high temperature (135 °C) led to nearly complete (i.e. statistical) scrambling of the *ortho* D atoms of [D_5]acetophenone and the vinylic protons of vinylsilane,[10b] only partial H/D scrambling took place under mild reaction conditions (25 °C) when using a highly active catalyst, as reported recently.[10g] Our result is closer to the latter case, and suggests that the present reaction involves reversible C–H oxidative-addition[18] and olefin-insertion[19] steps, while such an equilibrium process may not be significantly faster than the product-forming step (i.e. reductive elimination). The small amount of deuterium incorporation into the β position of vinylsilane suggests that the olefin-insertion step predominantly leads to a linear aryl(alkyl)cobalt intermediate.

In summary, we have developed cobalt–phenanthroline catalysts for the *ortho* alkylation of aromatic imines with a variety of olefins under mild reaction conditions. The present cobalt catalysis may serve as an inexpensive and mild alternative to rhodium and ruthenium catalysis, which traditionally require high reaction temperatures.[8–10,15] Because monoalkylation products are formed exclusively, the present reaction may be complementary to the ruthenium-catalyzed *ortho* alkylation of aromatic ketones,[9c,d,10] a reaction which often affords dialkylation products in the absence of any steric bias on the aromatic substrates. The regioselectivity observed for the product **3l** also highlights the complementary nature of the cobalt and ruthenium catalysis. Further synthetic and mechanistic exploration of the cobalt-catalyzed C–H bond functionalization is currently under way.

Received: March 15, 2011
Published online: June 10, 2011

Keywords: alkenes · alkylation · C–H activation · cobalt · imines

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