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Cobalt-Catalyzed, Imine-Directed Olefin Hydroarylation under Grignard-Free Conditions

Wengang Xu, Jie Hui Pek, and Naohiko 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

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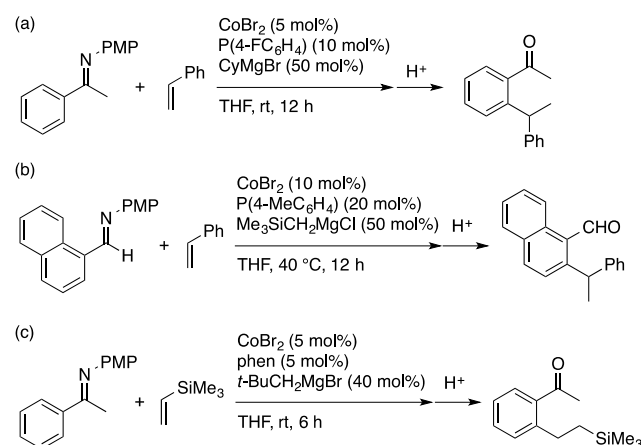
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>.

Abstract. We report here that a cobalt catalyst generated from a cobalt(II) salt and a ligand using magnesium metal is capable of promoting hydroarylation reactions through chelation-assisted C–H activation. With appropriate choice of the ligand and other reaction conditions, ketimine- or aldimine-directed branched selective hydroarylation of styrenes and ketimine-directed hydroarylation of vinylsilane have been achieved. The reported catalytic systems may serve as more convenient alternatives to previously developed catalytic systems employing Grignard reagents as reducing agents.

Keywords: C–H activation; C–C bond formation; Hydroarylation; Alkenes; Cobalt

Regioselective introduction of an alkyl group to an aromatic compound is among the most fundamental tasks in synthetic organic chemistry. The transition metal-catalyzed hydroarylation reaction of olefins through chelation-assisted C–H bond activation offers a step- and atom-economical solution to this task,^[1] which complements conventional alkylation reactions such as Friedel–Crafts reaction and cross-coupling between aryl (or alkyl) halides and alkyl (or aryl) metal reagents. Since the seminal work of Lewis and Smith on ruthenium-catalyzed ortho-ethylation of phenol with ethylene^[2] and the groundbreaking discovery of ruthenium-catalyzed ortho-alkylation of aryl ketones with olefins by Murai and coworkers,^[3] various catalytic systems using late transition metals such as ruthenium,^[4] rhodium,^[5] rhenium,^[6] iridium,^[7] cobalt,^[8] and iron^[9] have been developed for the hydroarylation of olefins assisted by oxygen- and nitrogen-based directing groups. In pursuit of C–H activation with earth-abundant transition metal catalysts,^[10] our group has been committed to the development of cobalt-catalyzed hydroarylation of olefins using sp^2 nitrogen directing groups.^[11,12] For example, we have demonstrated that addition reactions of aryl ketimines or aldimines to styrene or vinylsilane proceed smoothly using cobalt catalysts generated in situ from appropriately selected cobalt(II) salts, phosphine or nitrogen ligands, and

Grignard reagents,^[8c-e] which represents notable examples of C–H activation at mild temperatures (Scheme 1).^[13] The hydroarylation reactions to styrene are also notable for being among limited examples of branched-selective hydroarylation (Scheme 1a, b).^[4b,7b,7d-f,14]



Scheme 1. Imine-directed hydroarylation reactions using ternary catalytic systems comprising cobalt salt, ligand, and Grignard reagent (PMP = *p*-methoxyphenyl)

Despite the notable features, the requirement for a substoichiometric amount of Grignard reagents, including less common ones (e.g., *t*-BuCH₂MgBr and Me₃SiCH₂MgCl), as reductants reduces the practicality and functional group compatibility of these cobalt-catalyzed hydroarylation reactions. To address this problem, we became interested in the search for a more convenient reductant. Although the identity of the active cobalt catalyst in each of the catalytic systems remains unclear, our previous study on the imine-directed hydroarylation of alkynes has implied that the Grignard reagent such as *t*-BuCH₂MgBr is capable of reducing the Co(II) precatalyst to the oxidation state of Co(0).^[15] The ineffectiveness of a mild reductant such as Zn dust, which is known to reduce Co(II) to Co(I),^[16] has also been demonstrated in our early exploration of

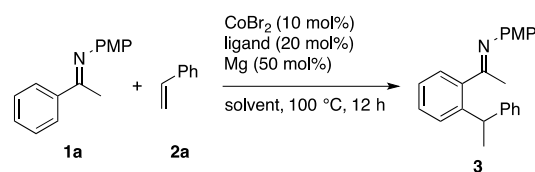
pyridine-directed hydroarylation of alkynes.^[17] On the other hand, Mg metal is used as a reductant in the preparation of a well-defined Co(0) complex Co(PMe₃)₄.^[18] Moreover, Petit and coworkers have recently demonstrated that Co(PMe₃)₄ catalyzes imine-directed hydroarylation of alkynes.^[19] These empirical observations and literature knowledge taken together, we reasoned that magnesium metal would serve as a reductant to generate a catalytically active cobalt species for the olefin hydroarylation. We report here that all the hydroarylation reactions shown in Scheme 1 can indeed be promoted using Mg metal in place of the Grignard reagent, albeit at a higher temperature and with somewhat narrower scopes.

The present study was initially focused on the reaction of acetophenone imine **1a** and styrene **2a**, which was previously achieved in a branched-selective manner using a catalytic system comprising CoBr₂, P(4-FC₆H₄)₃, and CyMgBr in THF at room temperature (Scheme 1a). With CoBr₂ (10 mol%), P(4-FC₆H₄)₃ (20 mol%), and flame-dried Mg turnings (50 mol%) as catalyst precursors, the reaction took place at an elevated temperature of 100 °C to afford the desired hydroarylation product **3** in a modest yield of 56% with exclusive branched selectivity (Table 1, entry 1). We noted that the color of the reaction mixture turned dark brown within 5 min upon heating, during which reduction of the Co(II) precatalyst appeared to take place. Comparable catalytic activities were observed using other unhindered triarylphosphine ligands such as P(4-MeOC₆H₄)₃ and P(3-MeC₆H₄)₃ (entries 2 and 3), while the use of P(2-MeOC₆H₄)₃ drastically slowed the reaction and affected the regioselectivity in slight favor of the linear adduct (entry 4).^[8f] The performance of PCy₃ was inferior to that of P(4-FC₆H₄)₃ (entry 5). The use of a diphosphine ligand such as 1,3-bis(diphenylphosphino)propane (dppp) led to only a trace amount of the product (entry 6), while the reaction was completely shut down under ligand-free conditions (entry 7).

Importantly, we noticed that reduction of the imine **1a** competed with the desired hydroarylation in THF (entries 1–5), affording a substantial amount of the corresponding amine (ca. 20% yield).^[20] The use of Et₂O as the solvent completely suppressed this undesirable byproduct and substantially improved the yield of **3** (entry 6), while cyclopentyl methyl ether (CPME) was only marginally effective (entry 7). Furthermore, a near quantitative yield of **3** was obtained by lowering the reaction temperature to 80 °C (entry 8). The loadings of CoBr₂ and P(4-FC₆H₄)₃ could be reduced to 5 mol% and 10 mol%, respectively, with a slight decrease in the yield of **3** (entry 9). For practicality and safety reasons, one may also perform the reaction in Bu₂O instead of Et₂O without significant decrease in the yield (entry 10). We should also comment on the importance of the cobalt precatalyst. Cobalt salts other than CoBr₂ led to diminished yield (CoCl₂, 20%; CoI₂, 24%) or failed to undergo reduction to generate catalytically

active species (Co(OAc)₂ and Co(acac)₂). Note also that the use of Rieke Mg failed to promote the reaction for unknown reasons.

Table 1. Addition of aryl imine **1a** to styrene **2a** using Mg as a reductant^a

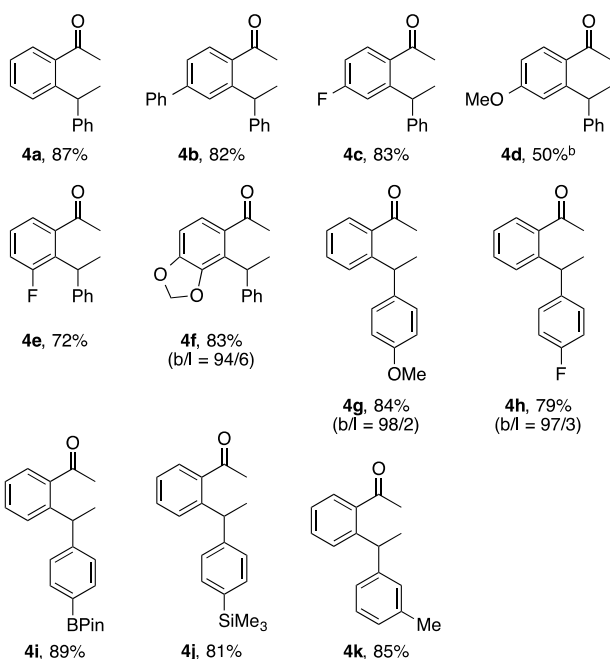
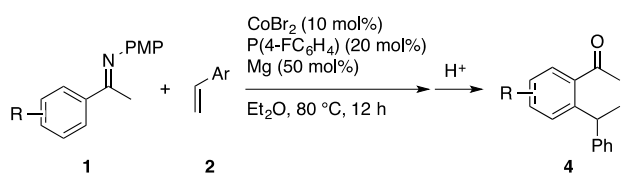


Entry	Ligand	Solvent	Yield (b/l) ^b
1	P(4-FC ₆ H ₄) ₃	THF	56 (> 99/1)
2	P(4-MeOC ₆ H ₄) ₃	THF	55 (> 99/1)
3	P(3-MeC ₆ H ₄) ₃	THF	52 (> 99/1)
4	P(2-MeOC ₆ H ₄) ₃	THF	8 (45/55)
5	PCy ₃	THF	35 (> 99/1)
6	dppp	THF	3 (> 99/1)
7	None	THF	0
8	P(4-FC ₆ H ₄) ₃	Et ₂ O	81 (> 99/1)
9	P(4-FC ₆ H ₄) ₃	CPME	60 (> 99/1)
10 ^c	P(4-FC ₆ H ₄) ₃	Et ₂ O	95 (> 99/1)
11 ^d	P(4-FC ₆ H ₄) ₃	Et ₂ O	90 (> 99/1)
12 ^c	P(4-FC ₆ H ₄) ₃	Bu ₂ O	91 (> 99/1)

^a) The reaction was performed using **1a** (0.2 mmol) and **2a** (0.3 mmol). ^b) Yield and branched/linear (b/l) selectivity were determined by GC. ^c) The reaction temperature was 80 °C. ^d) CoBr₂ (5 mol%) and P(4-FC₆H₄)₃ (10 mol%) were used.

With the optimized catalytic system in hand, we briefly explored the scope of acetophenone imines and styrene derivatives (Table 2). Imines bearing a para-phenyl or fluoro group underwent smooth addition to styrene, affording the branched adduct **4b** and **4c** in good yield, while the one bearing a paramethoxy group reacted sluggishly (see **4d**). As was the case with the original catalytic system, 3-fluoro and 3,4-methylenedioxy groups acted as secondary directing groups to assist regioselective alkylation of the ortho C–H bond of their proximity (see **4e** and **4f**). Styrene derivatives with substituents such as methoxy, fluoro, boryl, and silyl groups smoothly participated in the reaction with **1a** to afford the adducts **4g–4k** in good yields with excellent regioselectivity. However, contrary to our expectation, the catalytic system failed to promote the reaction of styrenes bearing Grignard-sensitive functional groups such as ester and cyano groups, although the functional groups themselves remained intact.

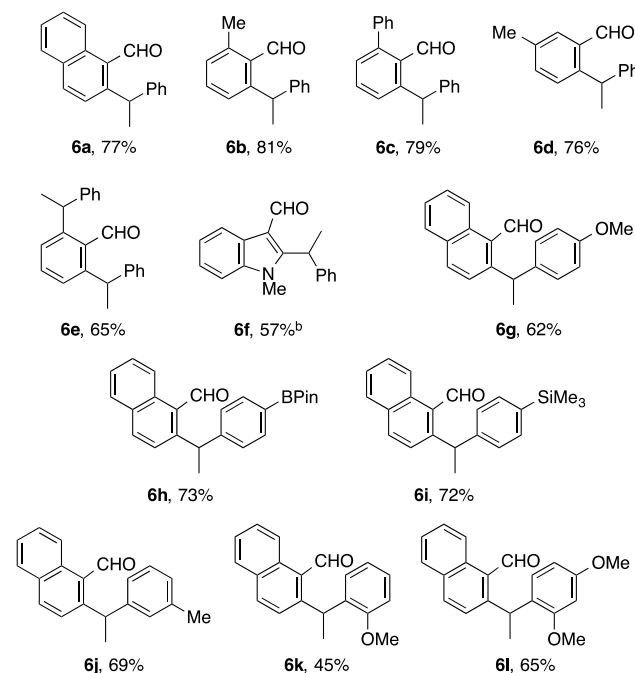
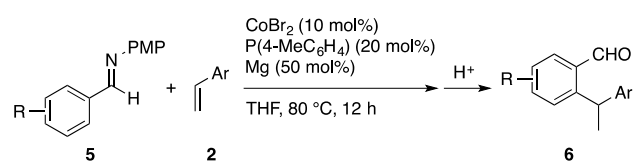
Table 2. Addition of aryl ketimines to styrenes^a



a) The reaction was performed using 0.3 mmol of ketimine and 0.45 mmol of styrene. The b/l ratio was greater than 99/1 unless otherwise indicated in the parentheses. ^b) THF was used as the solvent.

With the demonstration of the feasibility of the ketimine-directed styrene hydroarylation, we next examined aldimine-directed hydroarylation of styrenes using Mg metal as the reductant (Table 3). To our satisfaction, the reaction of an aldimine derived from 1-naphthaldehyde and styrene could be achieved efficiently with minimal modification of the original catalytic system (Scheme 1b), that is, replacement of $\text{Me}_3\text{SiCH}_2\text{MgCl}$ with Mg metal and increase of the reaction temperature to 80 °C, affording the adduct **6a** in 77% yield with exclusive branched selectivity. Unlike the case of the ketimine-directed reaction (vide supra), we did not observe reduction of the aldimine to the corresponding amine, regardless of intrinsically higher reactivity of the latter C=N bond toward reduction. Note also that the use of Et_2O as the solvent was not effective for the case of the aldimine because of its poor solubility. The new catalytic system promoted efficient alkylation of ortho-substituted benzaldehydes (**6b** and **6c**), regioselective alkylation of the less hindered position of meta-methyl benzaldehyde (**6d**), twofold alkylation of parent benzaldehyde with excess styrene (**6e**), and C2-alkylation of indole (**6f**). A range of para-, meta-, and ortho-substituted styrenes were also amenable to the present alkylation (see **6g–6l**).

Table 3. Addition of aryl aldimines to styrenes^a

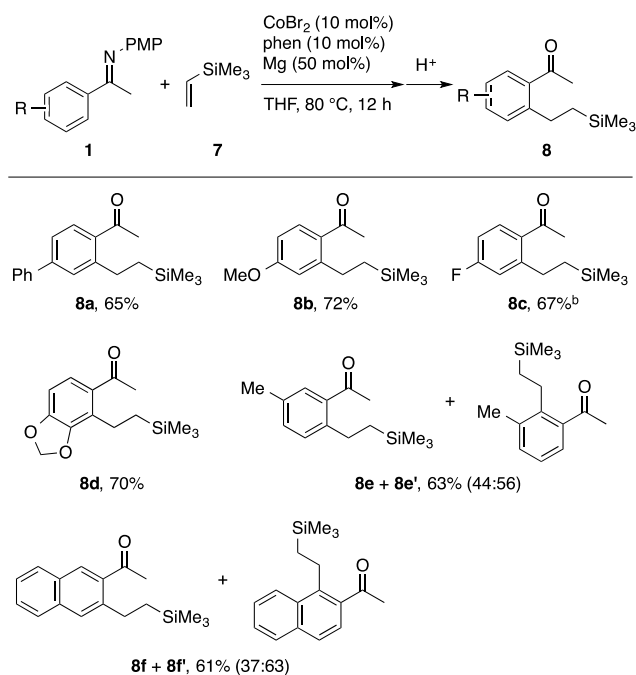


a) The reaction was performed using 0.3 mmol of aldimine and 0.45 mmol of styrene. ^b) $\text{P}(4\text{-FC}_6\text{H}_4)_3$ was used instead of $\text{P}(4\text{-MeC}_6\text{H}_4)_3$.

Finally, we examined ketimine-directed hydroarylation of vinylsilane using Mg metal as the reductant (Table 4). Building on the previous reaction conditions (Scheme 1c), the reaction of 4-phenylacetophenone imine with vinyltrimethylsilane was achieved using increased loadings (10 mol% each) of CoBr_2 and 1,10-phenanthroline (phen) and Mg metal (50 mol%) in THF at 80 °C, affording the expected linear alkylation product **8a** in 65% yield. The reaction did not take place at all using Et_2O instead of THF, presumably due to the poor solubility of cobalt–phenanthroline complexes. Unlike the case of the ketimine-directed addition to styrene (Table 2), 4-methoxy- and 4-fluoroacetophenone imines afforded the desired products **8b** and **8c**, respectively, while the latter product was accompanied by a substantial amount of ortho-alkylation/defluorination product. A 3,4-methylenedioxy group again caused a strong secondary directing effect in C–H activation (see **8d**). Curiously, the reaction of meta-methylacetophenone imine and 2-acetonaphthone imine produced regioisomeric product mixtures (**8e/8e'** and **8f/8f'**) in slight favor of regioisomers produced by activation of the more hindered C–H bonds. This is in sharp contrast to the performance of the original catalytic system, which exclusively afforded **8e** and **8f** through regioselective functionalization of the less hindered C–H bonds.^[8c] The peculiar regioselectivity suggests that the

electronic nature of the catalytically active species generated using Mg metal is different from that of the one generated using the Grignard reagent.

Table 4. Addition of aryl ketimines to vinylsilane^a



^a) The reaction was performed using 0.3 mmol of ketimine and 0.45 mmol of vinylsilane. ^b) The product was obtained as a mixture (2:1) with an ortho-alkylation/defluorination product (overall yield is shown).

In summary, we have demonstrated that Mg metal serves as a convenient reductant for cobalt-catalyzed, imine-directed hydroarylation of alkenes. Replacement of the Grignard reagents in the original ternary catalytic systems with magnesium metal, along with additional slight modification of the reaction conditions (e.g., temperature, solvent, catalyst loading), allowed ketimine- or aldimine-directed branched selective hydroarylation of styrenes as well as ketimine-directed hydroarylation of vinylsilane, albeit with somewhat narrower scopes. The elevated temperature required for the present catalytic systems, as compared with the Grignard-based catalytic systems, may be ascribed to heterogeneous nature of the reduction of the cobalt precatalyst with magnesium, and also to lower reactivity of the present low-valent cobalt species toward C–H activation. The difference between the magnesium- and Grignard-based catalytic systems was manifested in some cases of C=N bond reduction and moderate regioselectivities. Further studies will be directed to the exploration of the scope of Co/Mg catalytic systems in other C–H activation reactions and the investigation of the nature of the low-valent cobalt species.

Experimental Section

Typical Procedure for Ketimine-Directed Hydroarylation of Styrene

In a Schlenk tube were placed Mg turnings (3.6 mg, 0.15 mmol) and CoBr_2 (6.7 mg, 0.030 mmol). The solids were heated using a heat gun at around 300 °C under vacuum for 5 min. After cooling down under nitrogen atmosphere, $\text{P}(4\text{-FC}_6\text{H}_4)_3$ (19.2 mg, 0.060 mmol) and THF (0.20 mL) were added. The resulting mixture was heated at 80 °C for 5 min, during which the color of the mixture turned dark brown. The mixture was cooled to room temperature and THF was removed under reduced pressure. To the residue were added acetophenone imine **1a** (68 mg, 0.30 mmol), styrene (53 μL , 0.45 mmol), and Et_2O (0.75 mL), and then the resulting mixture was stirred at 80 °C for 12 h. The reaction mixture was allowed to cool to room temperature and filtered through a short pad of silica gel. The filtrate was hydrolyzed using 3N HCl (1.0 mL) for 1 h, and then extracted with EtOAc (5 mL x 3). The organic layer was dried over MgSO_4 and concentrated under reduced pressure. The residue was purified on silica gel (eluent: hexane/ EtOAc = 20/1) to afford 1-(2-(1-phenylethyl)phenyl)ethanone (**4a**) (59 mg, 87% yield).

Acknowledgements

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- [20] We do not know the mechanism and the origin of hydride of this reduction at this moment. Control experiments using THF-*d*₈ and pentadeuterated acetophenone imine did not result in any deuterium incorporation into the reduced product.

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