J|A|C|S COMMUNICATIONS

Published on Web 08/16/2010

Cobalt-Catalyzed Hydroarylation of Alkynes through Chelation-Assisted C−H Bond Activation

Ke Gao, Pin-Sheng Lee, Takeshi Fujita, and Naohiko Yoshikai*

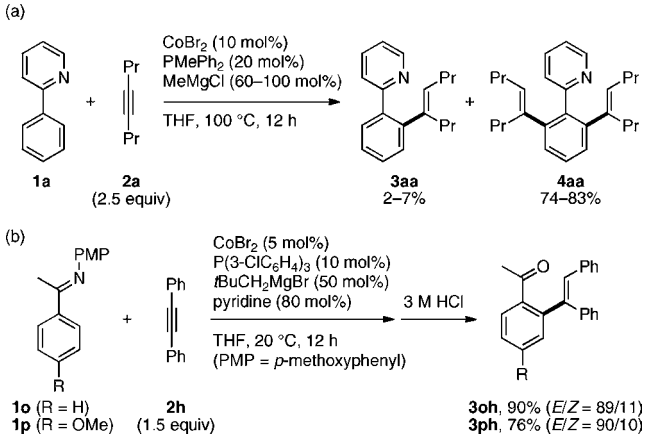
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological Univeristy, 21 Nanyang Link, Singapore 637371

Received July 30, 2010; E-mail: nyoshikai@ntu.edu.sg

Abstract: Ternary catalytic systems consisting of cobalt salts, phosphine ligands, and Grignard reagents promote addition of arylpyridines and imines to unactivated internal alkynes with high regio- and stereoselectivities. Deuterium-labeling experiments suggest that the reaction involves chelation-assisted oxidative addition of the aryl C−H bond to the cobalt center and insertion of the C−C triple bond into the Co−H bond, followed by reductive elimination of the resulting diorganocobalt species.

Chelation-assisted C−H bond cleavage by a transition metal complex is well established as a versatile strategy for regioselective C−H bond functionalization.[1] Among such transformations, alkylation and alkenylation through C−H addition to C−C multiple bonds represent the simplest atom-economical reactions. Since the groundbreaking work of Murai and co-workers,[2] second-row transition metals such as ruthenium and rhodium have been the catalysts of choice.[1a,e,h,3] On the other hand, first-row metals, regardless of their availability,[4] have been rarely exploited for such C−H addition reactions,[5−7] while a number of relevant elementary reactions, e.g., cyclometalation reactions, have been found to date.[8] We report here cobalt-catalyzed addition of arylpyridines and imines to unactivated internal alkynes that stereoselectively afford trisubstituted olefins through *syn*-addition of the *ortho* C−H bond across the C−C triple bond (Scheme 1).[9]

Scheme 1. Cobalt-Catalyzed Hydroarylation of Internal Alkyne



We initially chose 2-phenylpyridine (**1a**) and 4-octyne (**2a**) as model substrates. Extensive screening of cobalt precatalysts, ligands, and reducing agents led us to find that **1a** reacts with **2a** in the presence of a cobalt catalyst generated in situ from $CoBr_2$ (10 mol %), $PMePh_2$ (20 mol %), and MeMgCl (100 mol %) at 100 °C (bath temperature) in THF for 12 h to give an *ortho*-dialkenylated product, **4aa**, in 83% yield, together with a small amount of a monoalkenylated product, **3aa** (Scheme 1a and Table 1, entry 1). The *syn*-addition product was confirmed by nuclear Overhauser effect experiments. A small amount (<3%) of an *ortho*-methylated product was also detected by gas chromatography and gas chromatography/mass spectrometry (vide infra). The amount of MeMgCl could be reduced to 60 mol % without noticeable decrease of the product yield after 12 h, while the reaction rate became slightly lower (entry 2). The reaction became very sluggish with 50 mol % MeMgCl (entry 3) and eventually stopped with less than 40 mol % MeMgCl (see Supporting Information). The use of $CoBr_2(PMePh_2)_2$ as the precatalyst resulted in a similar catalytic performance (entry 4). While low-valent cobalt complexes are well known to catalyze cyclotrimerization of alkynes,[10] only a trace amount of such a product was detected under the above conditions.

Other monodentate phosphines such as PPh_3, PMe_2Ph, and PCy_3 were much less effective (entries 5−7), and bidentate phosphines (dppe, dppp, dppf, etc.) completely stopped the reaction. The use of Grignard reagents other than MeMgCl resulted in much lower yields of the alkenylation products (entries 8−11). Other reducing agents such as BuLi and Et_2Zn did not perform well. $CoBr_2$ worked best among common cobalt precatalysts including $CoCl_2$, $Co(acac)_2$, and $Co(acac)_3$.[11] Other precatalysts (e.g., Mn, Fe, Ni, Cu, Ru, Rh, Pd, and Ir salts) did not catalyze the reaction under otherwise identical conditions (see Supporting Information).

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

			yield (%)[b]	
entry	ligand	RMgX (mol %)	**3aa**	**4aa**
1	$PMePh_2$	MeMgCl (100)	3 [29] (4)	77 [45] (83)
2	$PMePh_2$	MeMgCl (60)	4 [45]	76 [31]
3	$PMePh_2$	MeMgCl (50)	54	19
4[c]		MeMgCl (100)	8	73
5	PPh_3	MeMgCl (100)	36	0
6	PMe_2Ph	MeMgCl (100)	45	34
7	PCy_3	MeMgCl (100)	2	0
8	$PMePh_2$	*n*BuMgBr (100)	41	20
9	$PMePh_2$	*i*PrMgBr (100)	29	36
10	$PMePh_2$	*t*BuMgBr (100)	19	0
11	$PMePh_2$	*t*$BuCH_2MgBr$ (100)	42	9

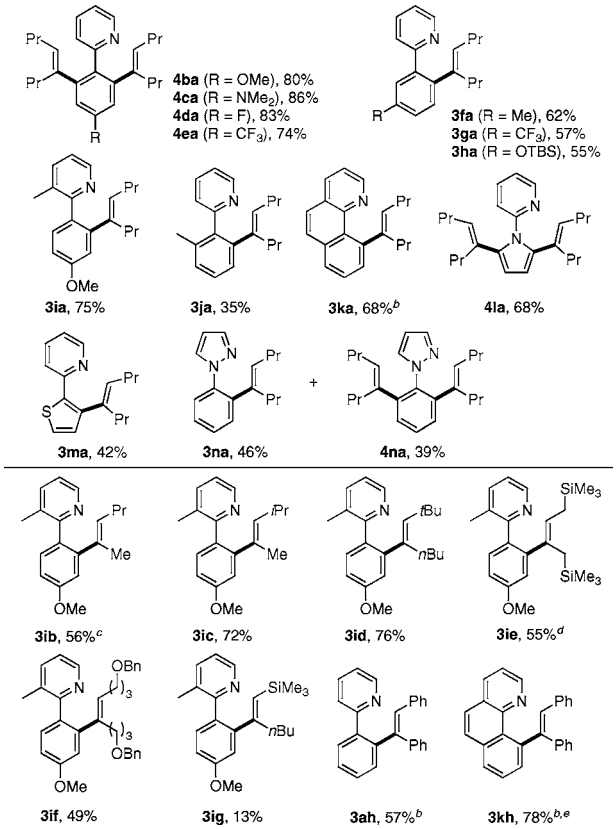
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (2.5 equiv), $CoBr_2$ (10 mol %), ligand (20 mol %), RMgX, THF (0.4 M), 100 °C in sealed vessel, 12 h. [b] Determined by GC using *n*-tridecane as an internal standard. In brackets and parentheses are shown yields at 1 h and isolated yields, respectively. [c] $CoBr_2(PMePh_2)_2$ (10 mol %) was used instead of $CoBr_2$ and $PMePh_2$.

Chart 1 illustrates the scope and limitation of the present reaction. In general, the reaction showed excellent *cis*-stereoselectivity ($E/Z > 99/1$) with a few exceptions (see **3ie** and **3kh**). Arylpyridines bearing methoxy, dimethylamino, fluoro, and trifluoromethyl groups

at the *para* position smoothly reacted with 4-octyne to give the corresponding dialkenylated products **4ba**−**4ea** in good yields of 73−86%. Substrates bearing *meta*-substituents (Me, CF_3, and OTBS) were alkenylated exclusively at the less hindered position to give the products **3fa**−**3ha** in 55−62% yields. A methyl group at the 3-position of the pyridine ring also prevented dialkenylation, and the product **3ia** was obtained in 75% yield. An *ortho*-methyl group significantly slowed the reaction to give **3ja** in 35% yield. The reaction of benzo[*h*]quinoline under the standard conditions was sluggish, while modified conditions employing $P(4\text{-}MeOC_6H_4)_3$ and neopentylmagnesium bromide at 60 °C gave the product **3ka** in 68% yield. Heteroarenes such as pyrrole and thiophene also participated in the reaction (see **4la** and **3ma**). A pyrazolyl group, although not as good as a pyridyl group, also served as a directing group to afford a mixture of mono- (**3na**) and dialkenylation (**4na**) products.

A variety of internal aliphatic alkynes participated in the reaction to give the alkenylated products **3ib**−**3if** in moderate to good yields. Unsymmetrical alkynes underwent C−C bond formation at sterically less hindered positions. While the reaction of 2-hexyne resulted in a modest regioselectivity (71:29), perfect regioselectivity was observed when the bulkier substituent on the alkyne was a secondary or tertiary alkyl group (see **3ib**−**3id**). The presence of silyl and benzyloxy groups could be tolerated (see **3ie**, **3if**). A silylalkyne also participated in the reaction, albeit in a low yield (see **3ig**). The reaction of diphenylacetylene was rather sluggish under the standard conditions, while the modified conditions (vide supra) gave the products **3ah** and **3kh** in 57% and 78% yields, respectively.

Chart 1. Scope of Arylpyridines and Alkynes[a]



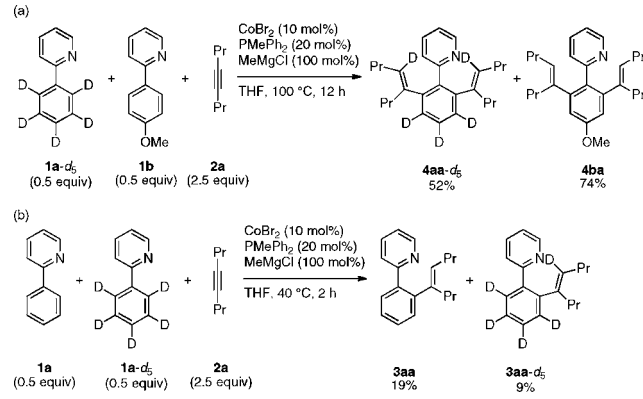
[a] Reaction was performed under the conditions shown in Table 1, entry 1, using either 2.5 equiv (for dialkenylation) or 1.5 equiv (for monoalkenylation) of alkyne for 12−24 h. *E*/*Z* ratio was >99:1 unless otherwise indicated. [b] $P(4\text{-}MeOC_6H_4)_3$ (20 mol %) and tBuCH$_2$MgBr (100 mol %) was used instead of $PMePh_2$ and MeMgCl, and the reaction was performed at 60 °C. [c] Major regioisomer is shown (ratio = 71:29). [d] *E*/*Z* = 16:84. [e] *E*/*Z* = 84:16.

Terminal alkynes such as phenylacetylene and 1-octyne did not participate in the reaction.

Aryl imines **1o** and **1p**, which were derived from the corresponding ketones and *p*-anisidine, were also amenable to hydroarylation reaction by a cobalt/phosphine/Grignard ternary catalytic system (Scheme 1b). While the original system (i.e., $CoBr_2$/$PMePh_2$/MeMgCl, 100 °C) did not tolerate the imine functionality, an alternative system consisting of $CoBr_2$ (5 mol %), $P(3\text{-}ClC_6H_4)_3$ (10 mol %), and tBuCH$_2$MgBr (50 mol %) as essential catalyst precursors and pyridine (80 mol %) as an additive promoted addition of **1o** and **1p** to diphenylacetylene **2h** under remarkably mild conditions (20 °C).[12] After hydrolysis, the alkenylated ketones **3oh** and **3ph** were obtained in good yields and stereoselectivities (*E*/*Z* = ca. 9/1).

To gain insight into the reaction mechanism, several mechanistic experiments were carried out. First, the reaction of a 1:1 mixture of **1a**-d_5 and **1b** with 4-octyne afforded **4aa**-d_5 and **4ba** in 52% and 74% yield, respectively, without any H/D crossover (Scheme 2a). This result clearly shows that the aryl group and the olefinic hydrogen atom in the product molecule come from the same reactant molecule and excludes a deprotonation mechanism for the *ortho* C−H bond cleavage. Second, a competitive reaction of **1a**/**1a**-d_5 with 4-octyne, which was performed at 40 °C and quenched at the early stage, gave a mixture of **3aa** and **3aa**-d_5 in 19% and 9% yields (**3aa**/**3aa**-d_5 = 2.1), respectively (Scheme 2b). The intermolecular kinetic isotope effect value of 2.1 suggests that either C−H bond cleavage or C−H bond formation is a kinetically important first irreversible step of the reaction.[13] Finally, a stoichiometric reaction of **1a**, $CoBr_2(PMePh_2)_2$ (1 equiv), and MeMgCl (10 equiv) at 0 °C for 30 min resulted in *ortho*-methylation of **1a** in 41% yield (see Supporting Information).[14] Although the mechanism of the methylation reaction is not clear at present, this observation suggests that the C−H bond cleavage is a rather facile step in the present catalytic hydroarylation reaction.

Scheme 2. Deuterium-Labeling Experiments



On the basis of the above results, we speculate that the reaction involves chelation-assisted oxidative addition of the aromatic C−H bond (cyclometalation) to the cobalt center,[15,16] insertion of the alkyne into the Co−H bond, and reductive elimination of the resulting alkenylarylcobalt intermediate. While the detailed nature of the catalytically active cobalt species remains elusive at this stage, the necessity of a larger amount (>40 mol %) of the Grignard reagent than required for reduction of cobalt(II) to cobalt(0) (20 mol %) and the considerable effect of the Grignard reagent on the catalytic activity (Table 1) suggest possible involvement of an organocobalt(0)ate species as the reactive species.[17]

In summary, we have reported cobalt-catalyzed addition reactions of arylpyridines and imines to internal alkynes to give trisubstituted

olefins with high regio- and stereoselectivities. Having demonstrated the feasibility of chelation-assisted C−H addition to a C−C multiple bond with a first-row transition metal catalyst, we consider that extension of the present cobalt catalysis will lead to cost-effective alternatives to a variety of existing C−H/olefin and C−H/alkyne coupling reactions under rhodium and ruthenium catalysis.[1a,e,h,9] Expansion of the substrate scope and further mechanistic studies are in progress and will be reported in due course.

Acknowledgment. We thank National Research Foundation, Singapore (NRF-RF2009-05 to N.Y.), and Nanyang Technological University for generous financial support.

Supporting Information Available: Details of experimental procedures and physical properties of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9827. (d) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (e) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013–3039. (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (g) Godula, K.; Sames, D. *Science* **2006**, *312*, 67–72. (h) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101.

(2) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *36*, 529–531.

(3) For iridium-catalyzed reactions, see: (a) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Org. Lett.* **2009**, *11*, 1821–1823. (b) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556–6557. (c) Satoh, T.; Nishinaka, Y.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 615.

(4) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087–4109.

(5) Halbritter, G.; Knoch, F.; Wolski, A.; Kisch, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1603–1605.

(6) For chelation-assisted reactions other than C−H addition to olefins/alkynes, see: (a) Murahashi, S. *J. Am. Chem. Soc.* **1955**, *77*, 6403. (b) Murahashi, S.; Horiie, S. *J. Am. Chem. Soc.* **1956**, *78*, 4816. (c) Kuninobu, Y.; Nishina, Y.; Takeuchi, T.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 6518. (d) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859. (e) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925–2928.

(7) For C−H addition to olefins/alkynes without chelation assistance, see: (a) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 3165. (b) Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 6965. (c) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146–8147. (d) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448–2449. (e) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170–16171. (f) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 5070–5071. (g) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 15996–15997.

(8) Albrecht, M. *Chem. Rev.* **2010**, *110*, 576–623, and references cited therein.

(9) (a) Lim, Y.-G.; Lee, K.-H.; Koo, B. T.; Kang, J.-B. *Tetrahedron Lett.* **2001**, *42*, 7609–7612. (b) Lim, S.-G.; Jun, H. L.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003**, *5*, 2759–2761. (c) Cheng, K.; Yao, B.; Zhao, J.; Zhang, Y. *Org. Lett.* **2008**, *10*, 5309–5312. (d) Katagiri, T.; Mukai, T.; Satoh, T.; Hirano, K.; Miura, M. *Chem. Lett.* **2009**, *38*, 118.

(10) (a) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901–2915. (b) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539–556.

(11) High-purity (99.99%) and normal-grade (99%) $CoBr_2$ gave similar catalytic activities (see Supporting Information).

(12) See Table S3 in Supporting Information for a brief summary of screening of reaction conditions.

(13) Yoshikai, N.; Matsuda, H.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 15258–15259.

(14) Attempts to observe a cyclometalated cobalt species by NMR were unsuccessful.

(15) Klein, H.-F.; Camadanli, S.; Beck, R.; Leudel, D.; Flörke, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 975–977.

(16) Lenges, C. P.; Brookhart, M.; Grant, B. E. *J. Organomet. Chem.* **1997**, *528*, 199–203.

(17) (a) Ohmiya, H.; Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 2207–2213. (b) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374–5375. (c) Kauffmann, T. *Angew. Chem., Int. Ed.* **1996**, *35*, 386–403.

JA106814P