ORGANIC
LETTERS

2011
Vol. 13, No. 12
3232–3234

Cobalt-Catalyzed Coupling of Alkyl Grignard Reagent with Benzamide and 2-Phenylpyridine Derivatives through Directed C–H Bond Activation under Air

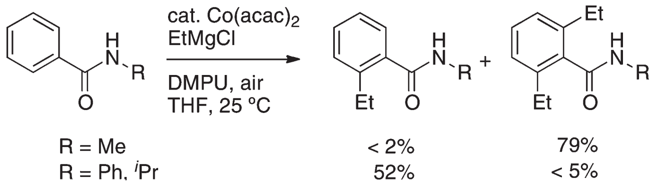
Quan Chen, Laurean Ilies, Naohiko Yoshikai,[†] and Eiichi Nakamura*

Department of Chemistry, School of Science, The University of Tokyo, Hongo, Bunkyo-ku,
Tokyo 113-0033, Japan

nakamura@chem.s.u-tokyo.ac.jp

Received April 27, 2011

ABSTRACT



Aromatic carboxamides and 2-phenylpyridine derivatives can be ortho-alkylated with Grignard reagents in the presence of a cobalt catalyst and DMPU as a ligand. The reaction proceeds smoothly at room temperature, using air as the sole oxidant. The dialkylated product is selectively obtained when *N*-methylcarboxamide is employed as a substrate, whereas *N*-phenyl- or *N*-isopropylcarboxamide preferentially gives the monoalkylated product.

Introduction of an alkyl group to an aromatic molecule through transition-metal-catalyzed directed C–H bond activation has recently emerged[1] as an attractive method for C–C bond formation. This approach allows the regioselective introduction of a primary alkyl group, which is prone to isomerization in Friedel–Crafts chemistry.[2] However, this class of reactions still remains a challenge for organic chemists[3] because of the propensity of alkyl organometallic reagents to undergo β-hydride elimination. Successful examples[4] include the directed alkylation of an aromatic C–H bond with an alkylboron reagent or tetraalkyltin catalyzed by palladium at high temperature (>100 °C) using Cu(II)/benzoquinone as an oxidant.[5,6] We report herein that an inexpensive and benign cobalt salt[7–9] catalyzes an oxidative alkylation reaction of an aromatic carboxamide or 2-phenylpyridine derivative with an alkyl Grignard reagent in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU).[10] The

---

[†] Present address: Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371.

(1) (a) Ackermann, L. *Chem. Commun.* **2010**, 4866–4877. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (d) *Handbook of C–H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005. (e) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101. (f) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972. (g) Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875–1877.

(2) Roberts, R. M.; Khalaf, A. A. *Friedel–Crafts Alkylation Chemistry. A Century of Discovery*; Marcel Dekker: New York, 1984.

(3) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677–685.

(4) (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78–79. (b) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634–12635.

(5) Oxidative methylation: (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511. (b) Zhang, Y.; Feng, J.; Li, C.-J. *J. Am. Chem. Soc.* **2008**, *130*, 2900–2901.

(6) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278–6282.

(7) (a) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087–4109. (b) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061–6067. (c) Nakamura, E.; Sato, K. *Nat. Mater.* **2011**, *10*, 158–161. (d) Yoshikai, N. *Synlett* **2011**, 1047–1051.

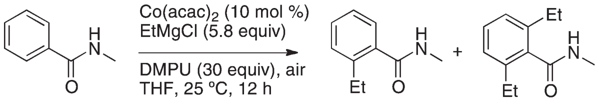
(8) (a) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435–1462. (b) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537–3562. (c) Gosmini, C.; Bégouin, J.-M.; Moncomble, A. *Chem. Commun.* **2008**, 3221–3233. (d) Yorimitsu, H.; Oshima, K. *Pure Appl. Chem.* **2006**, *78*, 441–449.

(9) (a) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249–12251. (b) Ding, Z.; Yoshikai, N. *Org. Lett.* **2010**, *12*, 4180–4183. (c) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 400–402.

10.1021/ol2011264

reaction proceeds at room temperature in the presence of air as the sole oxidant (eq 1). We also show that selectivity toward mono- or dialkylation can be controlled by tuning the directing group.

While cobalt/diamine-catalyzed directed oxidative arylation of an arylpyridine with a zinc or Grignard reagent has been recently reported,[11] the use of alkyl Grignard reagents possessing a β-hydrogen gave poor results. In light of our recent finding that DMPU may serve to stabilize alkylcobalt intermediates,[12] we investigated the cobalt-catalyzed reaction of *N*-methylbenzamide (**1**) with EtMgCl in the presence of a cobalt catalyst and dry air as an oxidant (Table 1). After considerable experimentation, we found that the reaction of **1** with a THF solution of EtMgCl (ca. 6 equiv) in the presence of $Co(acac)_2$ (10 mol %) and DMPU (30 equiv) in a Schlenck rection tube under an atmosphere of dry air gives a dialkylated product **3** in 79% isolated yield and a trace amount (<2%) of the monoalkylated product **2** (eq 1).



(1)

1 **2**: < 2% **3**: 79%

DMPU was crucial for achieving high yield and selectivity (Table 1, entry 2). In its absence (entry 1), **2** and **3** were obtained unselectively in poor yield, together with the recovery of the starting amide **1**. Other Lewis basic ligands such as tetramethylurea (TMU, entry 3), 1,3-dimethyl-2-imidazolidinone (DMI, entry 4), and hexamethylphosphoramide (HMPA, entry 5) performed less satisfactorily. The diamines used previously[11] as ligands for the cobalt-catalyzed arylation of arylpyridine were inefficient in this reaction (entries 6 and 7). High-purity (99.99%) $Co(acac)_3$ (entry 8) performed similarly to $Co(acac)_2$ of >98% purity, while the reaction did not proceed at all in the absence of a catalyst (entry 9). Only a trace amount of the products formed under nitrogen (entry 10).

Table 1. Reaction Conditions for the Cobalt-Catalyzed Alkylation of *N*-Methylbenzamide (**1**) with EtMgCl^a

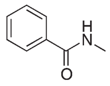
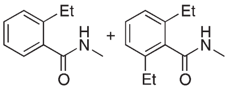
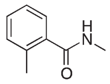
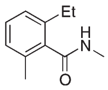
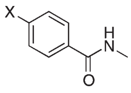
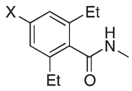
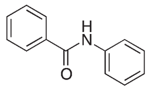
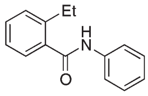
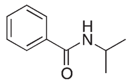
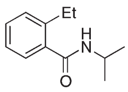
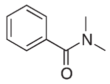
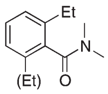
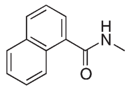
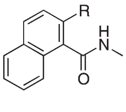
entry	catalyst	ligand	**2**^{b} (%)	**3**^{b} (%)
1	$Co(acac)_2$	none	9	11
2	$Co(acac)_2$	DMPU	<2	80 (79)
3	$Co(acac)_2$	TMU	5	50
4	$Co(acac)_2$	DMI	30	22
5	$Co(acac)_2$	HMPA	2	59
6	$Co(acac)_2$	TMEDA^c	<2	<2
7	$Co(acac)_2$	dtbpy^d	<2	<2
8	$Co(acac)_3{}^e$	DMPU	5	75
9	none	DMPU	0	0
10^f	$Co(acac)_2$	DMPU	3	11

[a] Reaction conditions: **1** (0.50 mmol), cobalt catalyst (0.05 mmol), EtMgCl, ligand (30 equiv) in THF under dry air at 25 °C for 12 h. [b] The yield was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yield in parentheses. [c] 1 equiv; TMEDA = *N,N,N′,N′*-tetramethylethylenediamine. [d] 10 mol %; dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridyl. [e] 99.99% purity. [f] Performed under a nitrogen atmosphere.

Table 2 summarizes the scope of the reaction with benzamide derivatives. At least 2 equiv of the Grignard reagent are necessary for deprotonation of the secondary benzamide and for accepting the ortho-hydrogen atom. The material balance for the benzamide was generally good, and the starting material was recovered when the yield was low. The byproducts were typically those produced by the homocoupling and β-hydride elimination of the organometallic reagent. As already discussed, the dialkyl product **3** was selectively obtained in entry 1, and this selectivity was observed even when a smaller amount of the ethyl Grignard reagent was used (entry **2**). The preferred formation of the dialkylation product of the *N*-methylamide substrate **1** suggests that the second alkylation takes place before the cobalt species dissociates from the monoalkylated amide. Note that the ortho-monoalkylated substrate **2** (entry 4) reacted more slowly than the unsubstituted benzamide **1**. Dialkylzinc reagents could also be utilized (entry 3), but the reaction was slower and the monoalkylated product was favored over the dialkylated product.

Substrates possessing an electron-donating or an electron-withdrawing substituent reacted smoothly to give the corresponding diethylated products in good yield (entries 5

Table 2. Cobalt-Catalyzed Oxidative Alkylation of Aromatic Carboxamides with Grignard Reagents^a

entry	substrate	R–M	product	yield (%)^b
1		EtMgCl		< 2 + 79
2		EtMgCl^c		(7 + 68)
3		Et_2Zn^d		(38 + 20)
4		EtMgCl		57
5		EtMgCl		61 (X = OMe)
6		EtMgCl		69^e (X = F)
7^f		EtMgCl		52
8^f		EtMgCl		52
9		EtMgCl		0
10		MeMgCl		68
11		EtMgCl		86
12		$(CH_3)_2CHCH_2MgCl$		20
13		$CH_3(CH_2)_6CH_2MgCl$		49
14		CyMgCl		trace

[a] For the reaction conditions, see eq 1 and the Supporting Information. [b] Isolated yield. ^{1}H NMR yield in parentheses. [c] 4.2 equiv. [d] Prepared in situ from $ZnCl_2 \cdot TMEDA$ and 2EtMgBr. [e] A product from the defluorination of **3** was also observed in 12% yield. [f] 20 mol % of $Co(acac)_2$ was used.

and 6). As with the unsubstituted benzamide **1**, the monoalkylated product was observed in a trace amount (< 2%) for the electron-deficient substrate (entry 6), whereas 7% of the monoalkylated product was observed for the electron-rich substrate (entry 5).

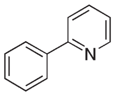
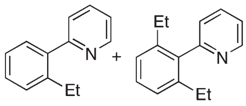
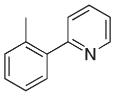
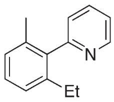
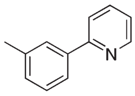
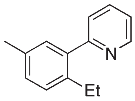
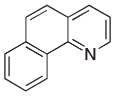
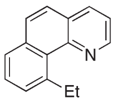
Interestingly, we could suppress the formation of the dialkylated product by the choice of a suitable organic substituent on the amide nitrogen atom. Thus, *N*-phenyl- or *N*-isopropylamides (entries 7 and 8) yielded the desired monoalkylated product together with a trace amount (< 5%) of a dialkylated product. Notably, a tertiary amide (entry 9) did not react at all, suggesting the importance of the anionic nitrogen atom.

A variety of alkyl Grignard reagents could be utilized under the standard conditions as illustrated for the reaction with *N*-methyl-1-naphthalenecarboxamide (entries 10–14). Methyl and ethyl Grignard reagents took part in the reaction in good yield (entries 10 and 11), whereas the isobutyl Grignard reagent gave a lower yield (entry 12). Octyl Grignard reagent introduced the octyl group in 49% yield (entry 13). Secondary alkyl Grignard reagents such as cyclohexylmagnesium chloride (entry 14) did not afford the desired product. Note that in all of these cases, no products arising from the activation of the potentially reactive C(8)–H bond were observed.

To our satisfaction, arylpyridines reacted with EtMgCl in excellent yield under similar conditions (Table 3), indicating that the anionic nitrogen ligand is not mandatory for the reaction to take place smoothly. 2-Phenylpyridine largely gave the monoalkylated product (entry 1), and this propensity to monoalkylation stands in contrast to the *N*-methylbenzamide reaction described above. The second ortho-alkylation is slow but takes place in high yield, as shown in entry 2. 2-(3-Tolyl)pyridine (entry 3) reacted at the less hindered side in 87% yield. Benzo[*h*]quinoline (entry 4) could also be alkylated in high yield.

In summary, we have shown that a cobalt catalyst can introduce a β-hydrogen-possessing alkyl anion into the ortho-position of a secondary benzamide or 2-phenylpyridine derivative through directed C–H bond activation. The key in controlling the reactivity of the alkylcobalt species was the utilization of DMPU as a crucial ligand. The present reaction is a rare example of oxidative C–H bond functionalization using an inexpensive and nontoxic catalyst under mild conditions (25 °C),[13] under atmospheric air as the sole oxidant. The mono- vs dialkylation selectivity and the high reactivity of arylpyridine derivatives suggest that this reaction may be mechanistically different from the previously reported coupling with alkyl chlorides,[12a] where arylpyridines were largely unreactive. The reaction adds to the rapidly increasing repertoire of catalytic C–H activation of benzamide derivatives,[14] which are a common structural motif in natural products and bioactive compounds, and have also recently emerged as a scaffold of interest for materials science.

Table 3. Cobalt-Catalyzed Oxidative Alkylation of Arylpyridine Congeners with EtMgCl[a]

entry	substrate	product	yield (%)[b]
1			80 + 17
2			93
3			87
4			83

[a] Reaction conditions: pyridine substrate (0.50 mmol), Co(acac)$_2$ (13 mg, 0.05 mmol), DMPU (1.21 mL, 10.0 mmol), and EtMgCl (1.6 mmol) in THF under dry air at 25 °C for 12 h. See the Supporting Information for details. [b] Isolated yield. ^{1}H NMR yield in parentheses.

Acknowledgment. We thank MEXT (KAKENHI Specially Promoted Research for E.N., No. 22000008) and the Global COE Program for Chemistry Innovation. Q.C. thanks the University of Tokyo for the Special Scholarship for International Students.

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

---

(10) (a) Korn, T. J.; Schade, M. A.; Cheemala, M. N.; Guevara, S. W. S. A.; Cahiez, G.; Knochel, P. *Org. Lett.* **2006**, *8*, 725–728. (b) Rohbogner, C. J.; Diene, C. R.; Korn, T. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 1874–1877.

(11) (a) Chen, Q.; Yamakawa, T.; Yoshikai, N.; Nakamura, E. The 89th Annual Meeting of the Chemical Society of Japan, 2F2–29, 2009. (b) Li, B.; Wu, Z.-H.; Gu, Y.-F.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1109–1113.

(12) (a) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428–429. (b) Ilies, L.; Chen, Q.; Zeng, S.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 5221–5223.

(13) (a) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859. (b) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925–2928. (c) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Synlett* **2010**, 313–316. (d) Yoshikai, N.; Mieczkowski, A.; Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 5568–5569. (e) Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 6557–6559. (f) Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 7672–7675.

(14) (a) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655–2658. (b) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155. (c) Shabashov, D.; Daugulis, O. *Org. Lett.* **2006**, *8*, 4947–4949. (d) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886–9887. (e) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275–1277. (f) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908–6909. (g) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565–10569. (h) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1064–1067.