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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Cobalt-Catalyzed Chemoselective Insertion of Alkene into the Ortho C−H Bond of Benzamide

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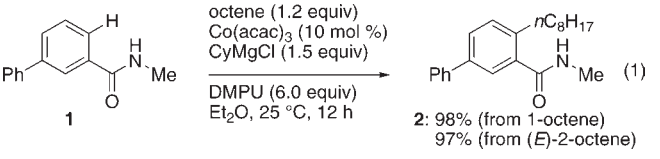
Supporting Information

ABSTRACT: Insertion of 1-alkene, 2-alkene, and styrene into the ortho C−H bond of benzamide in the presence of an inexpensive cobalt catalyst, DMPU as a crucial ligand, and cyclohexylmagnesium chloride proceeds smoothly at 25 °C to selectively give the ortho-alkylated product. Notable features of this reaction include the structural variety of the alkene and the amide substrate and the tolerance of functional groups such as halide, olefin, ester, and amide groups.

Since the seminal work of Murai,[1] ruthenium- and rhodium-catalyzed C−H bond activation of an aromatic compound followed by insertion of an olefin has become a powerful synthetic tool.[2,3] The reaction generally requires the use of a rare transition metal catalyst[4] at high reaction temperature and tolerates a rather limited range of olefins. We report here the ortho alkylation of a secondary benzamide[5] with a nearly stoichiometric amount of 1-alkene, 2-alkene, or styrene via cobalt-catalyzed C−H bond activation in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) and an essentially catalytic amount of a Grignard reagent. The reaction reported in this communication features the use of an inexpensive cobalt catalyst,[6,7] room-temperature conditions, and the tolerance of aryl halide, olefin, ester, and amide groups. The reaction allows the use of various simple and functionalized alkene substrates, including 1-alkene, 2-alkene, and styrene.[8] The reaction adds to the rapidly expanding repertoire of cobalt-catalyzed C−H bond activation reactions.[9−11]

6-Octylation of *N*-methyl-3-phenylbenzamide (**1**) with 1-octene is illustrative (eq 1). A diethyl ether solution of cyclohexylmagnesium chloride (CyMgCl, 2.9 mL, 2.44 M, 7.1 mmol) and then 1-octene (0.89 mL, 5.7 mmol) were added dropwise to a mixture of $Co(acac)_3$ (169 mg, 0.47 mmol), **1** (1.00 g, 4.7 mmol), and DMPU (3.4 mL, 28 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 12 h, and after workup, *N*-methyl-2-octyl-5-phenylbenzamide (**2**) was obtained in 98% yield (1.50 g).



When (*E*)-2-octene was employed under similar conditions (eq 1), the reaction took place at the terminal position, presumably after olefin isomerization,[12] to give the same 2-alkylated benzamide **2** in quantitative yield. On the other hand, (*E*)-3-octene did not give the alkylation product at all under otherwise identical conditions.

Under these conditions, a tertiary amide such as *N*,*N*-dimethylbenzamide was entirely unreactive, and 2-phenylpyridine and an acetophenone imine that previously served as excellent substrates[8] gave the expected octylation products in only <10% yield, suggesting that the deprotonated amide functions as a crucial directing group. *N*-Phenylacetamide did not react under the present conditions.

The key reaction parameters were optimized for a less reactive substrate, *N*-methyl-1-naphthalenecarboxamide (**3**), using 1.2 equiv of 1-octene and 10 mol % $Co(acac)_3$ in the presence of a variety of alkyl Grignard reagents and ligands in diethyl ether at 25 °C for 12 h. The alkylation took place exclusively at the 2-position. Representative data are summarized in Table 1. Comparison of entries 1 and 2 indicates the necessary presence of DMPU,[11,13] as no desired product was obtained in its absence. The conditions in eq 1 utilizing 1.5 equiv of CyMgCl gave *N*-methyl-2-octyl-1-naphthalenecarboxamide (**4**) in 80% yield (73% isolated yield) together with 19% recovery of the starting amide **3** (entry 2). The use of only 1.2 equiv of Grignard reagent still furnished the product in 69% yield (entry 3), indicating that the reaction is essentially catalytic for the Grignard reagent (1 equiv of CyMgCl is consumed to deprotonate the NH of the amide). Thus, 1-octene is formally inserted between the ortho carbon and hydrogen atoms of the carboxamide. This is contrary to the related alkylation reaction with alkyl chloride that needed more than 2 equiv of the Grignard reagent, which formally accepts the NH proton and the ortho hydrogen atom.[11] Cyclopentylmagnesium chloride (CyptMgCl) (entry 4) and MeMgCl (entry 5) performed similarly, but the latter also gave a small amount of 2-methylated product. Me_3SiCH_2MgCl (entry 6) was far less efficient.

Notably, ligands commonly used for cobalt-catalyzed C−H bond activation, such as PCy_3 (entry 7) and IMes·HCl (entry 8) previously used by Yoshikai,[8] as well as $PMePh_2$[10a] (entry 9) and TMEDA[10c] (entry 10) did not afford the desired product but instead gave back the starting amide. $Co(acac)_2$, $CoCl_2$, or $CoBr_2$ complexes used under otherwise the same conditions as in entry 2 gave **4** in lower yield (59, 31, or 15%, respectively), and the absence of a cobalt catalyst resulted in complete recovery of the starting material (see the Supporting Information for details).

Table 2 illustrates the scope of the aromatic amide in the reaction with 1-octene. For all carboxamides, the reaction took

Received: January 22, 2011
Published: March 23, 2011

dx.doi.org/10.1021/ja200645w | *J. Am. Chem. Soc.* 2011, 133, 5221–5223

Table 1. Key Reaction Parameters for the Cobalt-Catalyzed Reaction of *N*-Methyl-1-naphthalenecarboxamide (3) with 1-Octene To Give *N*-Methyl-2-octyl-1-naphthalenecarboxamide (4)[a]

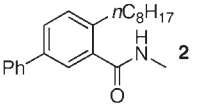
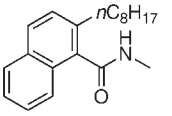
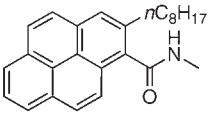
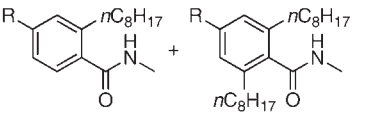
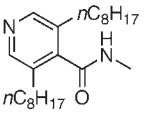
entry	RMgCl	ligand	4 (%)[b]	3 (%)[b]
1	CyMgCl	none	0	96
2	CyMgCl	DMPU	80	19
3	CyMgCl[c]	DMPU	69	11
4	CyptMgCl	DMPU	61	21
5	MeMgCl	DMPU	84	10[d]
6	Me_3SiCH_2MgCl	DMPU	3	89
7	CyMgCl	PCy_3	0	95
8	CyMgCl	IMes·HCl	0	96
9	CyMgCl	$PMePh_2$	0	90
10	CyMgCl	TMEDA	0	98

[a] The reaction conditions are described in eq 1 and the Supporting Information. [b] ^{1}H NMR yield in the presence of 1,1,2,2-tetrachloroethane as an internal standard. [c] 1.2 equiv of CyMgCl was used instead of the standard 1.5 equiv. [d] A 2-methylated product was also obtained in <10% yield.

place exclusively at the ortho position, as illustrated already for the formation of **2** and **4** (entries 1 and 2). *N*-Methyl-1-pyrenecarboxamide also reacted smoothly at the ortho position (entry 3), suggesting that the method may be useful in organic semiconductor chemistry, where the introduction of long alkyl chains increases the solubility of the compounds. When the benzamide has two equally reactive ortho positions, double alkylation tends to predominate (entries 4−9). The reactions in entries 5−9, in particular, gave the double alkylation product exclusively when 2.2 equiv of 1-octene was used. When 1.2 equiv of 1-octene was used in the reaction in entry 4, we still obtained the dialkylation product (40%) together with the monoalkylation product (39%) and recovery of the starting amide (15%). Thus, we speculate that the second alkylation takes place quickly after the first alkylation and that the cobalt catalyst is released from the amide substrate only after the second alkylation is complete.[3] In contrast to previous studies,[3,8] both electron-rich (entry 5) and electron-deficient amides (entry 6) reacted equally well. The chloride group in 4-chlorobenzamide was retained to give the 2,6-dioctyl product in 74% yield when MeMgCl was used (entry 7), while it was largely reduced when CyMgCl was used. This contrast between the Me and Cy groups suggests that the Cy group acts as a hydrogen donor. When we used MeMgCl, even 4-bromobenzamide (entry 8) gave a modest yield (22%) of the desired octylated product with retention of the bromide group, together with debrominated products (18%). *N*-Methylisonicotinamide[14] reacted smoothly to give the dialkylated product exclusively (entry 9).

As illustrated in Table 3, we can employ a considerable variety of olefinic substrates, including a wide variety of terminal and internal alkenes as well as styrene and 1-phenyl-1-propene. Trimethylvinylsilane, which has been a standard substrate since Murai's study, served as an excellent substrate (entry 1). 2-Substituted-1-alkenes reacted very smoothly in this reaction (entries 2 and 4), although they are generally poor substrates in Murai-type reactions.[3] The reaction tolerates the presence of functional groups such as ester and olefin (entries 3 and 4). The internal olefin in DL-limonene did not take part in the reaction, and the product was expectedly a 57:43 diastereomeric mixture (entry 4).

Table 2. Cobalt-Catalyzed Ortho Octylation of Benzamide Derivatives with 1-Octene [a]

entry	product	yield (%)[b]
1	 **2**	98
2	 **4**	73
3		64
4[c]		28 + 66 (R = H)
5[c]		< 1 + 83 (R = OMe)
6[c]		< 1 + 86 (R = F)
7[c,d]		< 1 + 74[e] (R = Cl)
8[c,d]		< 1 + 22[f] (R = Br)
9[c]		83

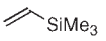
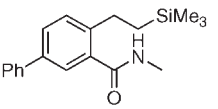
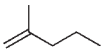
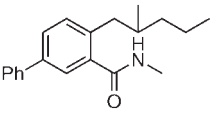
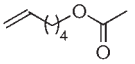
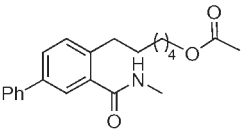
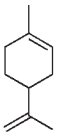
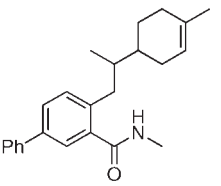
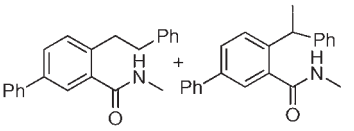
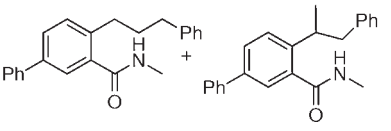
[a] The reaction was performed with 1.2 equiv of 1-octene under the conditions described in eq 1 (see the Supporting Information for details). [b] Isolated yield. Most of the amide starting material was recovered when the yield was low. [c] 2.2 equiv of 1-octene was used. [d] MeMgCl (1.5 equiv) was used instead of CyMgCl. [e] A dechlorinated product was observed in trace amount (<5%). [f] ^{1}H NMR yield; debrominated products were observed in 18% yield.

Styrene gave a mixture of two regioisomers in a 2:1 ratio favoring C−C bond formation at the terminal position (entry 5). Like 2-octene, 1-phenyl-1-propene reacted predominantly at the terminal position after isomerization of the olefin (entry 6).

In summary, we have developed a new cobalt-catalyzed C−H bond activation method for insertion of a nearly stoichiometric amount of a simple or functionalized alkene into the ortho C−H bond of a secondary benzamide derivative in the presence of 1.5 equiv of CyMgCl. The unique features of the present conditions include the structural variety of the alkene and the aromatic carboxamide substrates that can be employed as well as the tolerance of functional groups including bromide, chloride, olefin, amide, and ester groups. The crucial role of DMPU for the success of the reaction is notable and will be the subject of further studies. The present olefin insertion reaction is synthetically complementary to the iron-catalyzed C−H bond functionalization with organometallic coupling partners that we have

dx.doi.org/10.1021/ja200645w | *J. Am. Chem. Soc.* 2011, 133, 5221–5223

Table 3. Cobalt-Catalyzed Alkylation of *N*-Methyl-3-phenylbenzamide (1) with Various Olefins [a]

entry	alkene	product	yield (%)[b]
1			98
2			97
3			67[c]
4			94[d]
5			56 (69:31)[e]
6			92 (94:6)[e]

[a] The reaction was performed with 1.2 equiv of alkene under the conditions described in eq 1 (see the Supporting Information for details). [b] Isolated yield. Most of the amide starting material was recovered when the yield was low. [c] ^{1}H NMR yield, because of difficulty in separating the product from unreacted starting materials. [d] Obtained as a 57:43 mixture of diastereoisomers. [e] Ratio of linear and branched isomers, as determined by ^{1}H NMR analysis.

been investigating for some time[15,16] with the ultimate goal of achieving sustainable and selective reactions for complex organic synthesis.[17]

■ ASSOCIATED CONTENT

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

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■ ACKNOWLEDGMENT

We thank MEXT (KAKENHI Specially Promoted Research, 22000008 to E.N.) and the Global COE Program for Chemistry Innovation. X.Z. thanks the Japan Society for the Promotion of Science for a Research Fellowship for Young Scientists (P10033). Q.C. thanks the University of Tokyo for the Special Scholarship for International Students.

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