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Ni(II)-Catalyzed Oxidative Coupling between C(sp^2)–H in Benzamides and C(sp^3)–H in Toluene Derivatives

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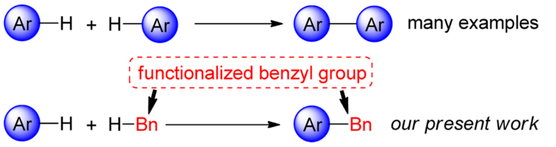
Supporting Information

ABSTRACT: Oxidative coupling between C(sp^2)–H bonds and C(sp^3)–H bonds is achieved by the Ni(II)-catalyzed reaction of benzamides containing an 8-aminoquinoline moiety as the directing group with toluene derivatives in the presence of heptafluoroisopropyl iodide as the oxidant. The method has a broad scope and shows high functional group compatibility. Toluene derivatives can be used as the coupling partner in an unreactive solvent.

Progress in the catalytic functionalization of C–H bonds for the construction of C–C bonds has advanced significantly, and efficient and straightforward methods for preparing complex molecules starting from easily available compounds are now available.[1] Various functionalized compounds such as halides and organometallic reagents can be used as coupling partners for C–C bond formation with the cleavage of C–H bonds. In contrast, oxidative C–H/C–H coupling is an ideal and environmentally attractive strategy because the reaction does not require functionalized compounds for coupling and stoichiometric amounts of halogenated or organometallic byproducts are not generated. In a pioneering study, Fagnou reported on such a reaction: the Pd-catalyzed reaction of indole derivatives with benzene derivatives (solvent) resulting in the formation of arylation products.[2] The reaction involves the sequential activation of C–H bonds on two aromatic compounds (an indole C–H bond and a benzene C–H bond) followed by C–C bond formation. Following this pioneering example, a number of reactions involving oxidative C–H/C–H coupling have been reported.[3,4] However, most of these examples involve the coupling of C(sp^2)–H/C(sp^2)–H bonds with activation of one, the other, or both of C(sp^2)–H bonds, as in C–H bonds in electron-rich aromatic compounds or acidic C–H bonds. Oxidative C(sp^2)–H/C(sp^3)–H coupling represents the next targeted reaction.[5] In fact, Li reported on an oxidative coupling involving C(sp^3)–H bonds in the Ru(II)-catalyzed reaction of 2-arylpyridines with cycloalkanes, in which only simple cycloalkanes were used as the coupling partner as well as the solvent and a strong oxidant, such as di-*tert*-butyl peroxide was used to generate radical species from the cycloalkanes.[5a] Oxidative C(sp^2)–H/C(sp^3)–H coupling without the use of such strong oxidants and the introduction of functionalized alkyl groups continues to be a challenging issue (Scheme 1). Here we report on the Ni(II)-catalyzed benzylation of ortho C–H bonds in aromatic amides with toluene derivatives. It is noteworthy that the toluene derivative need not also be the solvent. Various functionalized benzyl groups can be introduced with the cleavage of C(sp^2)–H bonds.

Scheme 1. Oxidative Cross-Coupling of C–H/C–H Bonds



A key to the success of achieving oxidative C(sp^2)–H/C(sp^3)–H coupling would be how to activate C(sp^3)–H bonds without using a strong oxidant such as di-*tert*-butyl peroxide to generate a radical species. Thus, a new methodology to promote the cleavage of C(sp^3)–H bonds and to introduce functionalized alkyl groups needs to be developed. We recently reported on the Ni(II)-catalyzed functionalization of C–H bonds by taking advantage of an 8-aminoquinolinyl directing group.[6,7] On the basis of various mechanistic studies, it appears that nickel species with radical character are involved as a key intermediate in the Ni-catalyzed functionalization of C–H bonds.[7] In addition, inspired by recent observations that Ni(I) species can catalyze cross-coupling reactions with alkyl halides,[8] we focused our efforts on the use of our recently developed Ni(II)-catalyzed chelation system for oxidative C–H/C–H coupling. Our initial investigation centered on a strategy for generating radical species without the use of strong oxidizing reagents. Various alkyl halides were examined as radical sources. The benzylation of ortho C–H bonds proceeded when heptafluoroisopropyl iodide ($^iC_3F_7I$) was used as the halide. The reaction of amide **1a** (0.3 mmol) with $^iC_3F_7I$ (0.6 mmol) in the presence of $Ni(OTf)_2$ (0.03 mmol) as the catalyst, Na_2CO_3 (0.6 mmol) as the base, and PPh_3 (0.03 mmol) as the ligand in toluene (1 mL) at 140 °C for 24 h gave the benzylation product **2a** in 54% isolated yield and **3** in 33% yield (Table 1, entry 1). To avoid the formation of **3**, the 5-position in the quinoline ring was blocked by a methoxy group, as in **1b**. As expected, the isolated yield of **2b** was dramatically improved to 91% (entry 2). The reaction also produced **2b** in 75% NMR yield in the absence of PPh_3 (entry 3). While the presence of PPh_3 as a ligand was not crucial for the reaction to proceed, PPh_3 was added because the product yields were consistently higher than the yields in the absence of PPh_3. Other perfluoroalkyl or -aryl iodides were not effective (entries 4–7). The reaction was also dependent on the base used in the reaction. The results indicated that Na_2CO_3 was base of choice (entry 2). A decrease in the

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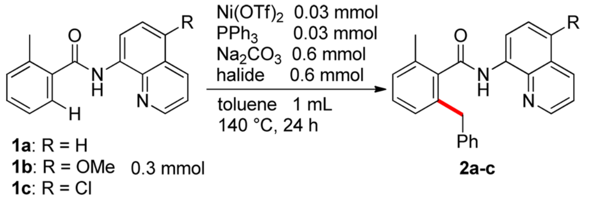
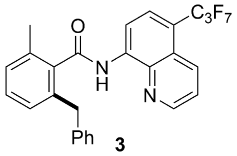
Table 1. Optimization of the Reaction Conditions[a]



entry	amide	halide	base	yields (%)[b] 2	1
1	**1a**	$^{i}C_3F_7I$	Na_2CO_3	56 (54)	3 (2)
2	**1b**	$^{i}C_3F_7I$	Na_2CO_3	94 (91)	trace
3[c]	**1b**	$^{i}C_3F_7I$	Na_2CO_3	75	13
4	**1b**	n-$C_6F_{13}I$	Na_2CO_3	30	40
5	**1b**	C_6F_5I	Na_2CO_3	0	60
6	**1b**	CF_3CH_2I	Na_2CO_3	39[d]	0
7	**1b**	C_6Br_6	Na_2CO_3	0	90
8	**1b**	$^{i}C_3F_7I$	Cs_2CO_3	73	13
9	**1b**	$^{i}C_3F_7I$	K_2CO_3	10	73
10	**1b**	$^{i}C_3F_7I$	$NaHCO_3$	59	37
11	**1b**	$^{i}C_3F_7I$	Li_2CO_3	0	63
12	**1b**	$^{i}C_3F_7I$	NaOAc	21	63
13[e]	**1b**	$^{i}C_3F_7I$	Na_2CO_3	94 (91)	trace
14[e]	**1c**	**$^{i}C_3F_7I$**	**Na_2CO_3**	**96 (94)**	**0**

[a] Reaction conditions: **1** (0.3 mmol), $Ni(OTf)_2$ (0.03 mmol), PPh_3 (0.03 mmol), Na_2CO_3 (0.6 mmol), and halide (0.6 mmol) in toluene (1 mL) at 140 °C for 24 h. [b] NMR yields. Values in parentheses are isolated yields. [c] No PPh_3. [d] **2d** was obtained in 58% yield. [e] $^{i}C_3F_7I$ (0.36 mmol) was used.

amount of $^{i}C_3F_7I$ (0.36 mmol, 1.2 equiv with respect to **1b**) did not affect the product yield (entry 2 vs 13). Finally, the use of a chloro group as in **1c** gave the benzylation product **2c** in 94% isolated yield (entry 14).



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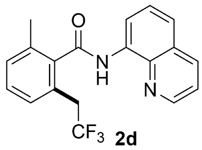
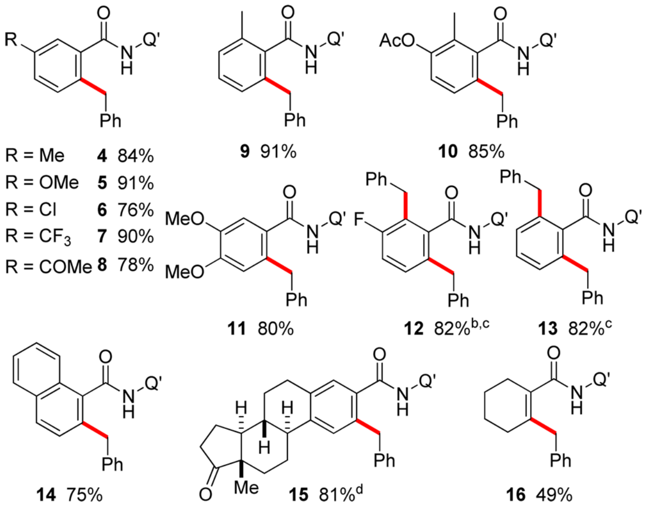


2d

With the optimized reaction conditions in hand, the reaction of various benzamides in toluene as the solvent was examined (Table 2). A wide variety of functional groups on the benzamide are tolerated in the reaction. The less hindered C−H bonds were exclusively activated to give benzylation products **4**−**8**, **11**, and **15** in the reaction of meta-substituted aromatic amides. In the case of an m-fluoro substrate and a simple benzamide, dibenzylation products **12** and **13**, respectively, were obtained in high yields. In all cases, no coupling between the ortho C−H bonds in the benzamide and $C(sp^2)$−H bonds in toluene was observed.

In the benzylation (Table 2), toluene was used as the coupling partner as well as the solvent. In order to develop a more useful reaction for organic synthesis, we examined the reaction with functionalized toluene derivatives in a common unreactive solvent. The use of 3 equiv of toluene in 0.7 mL of methycyclohexane, octane, ethylbenzene, n-butylbenzene, cumene, and 4-methyltetrahydropyran gave no reaction. To our delight, when 3 equiv of toluene in 0.7 mL of benzene as the solvent was used under otherwise standard reaction conditions, **2c** was obtained in 49% NMR yield. Because of its low boiling point, benzene was replaced with $tert$-butylbenzene, which was also found to be a good solvent. The use of 10 equiv of toluene in $tert$-butylbenzene gave **2c** in 84% yield. The results for the reaction of **1c** with various toluene derivatives under the newly optimized conditions are summarized in Table 3. Various functional groups, even bromides and iodides, are tolerated under the current catalytic system. The presence of substituents at the ortho position had no effect on the efficiency of the reaction, as in **24**, **25**, **26**, and **28**.

Table 2. Ni(II)-Catalyzed Ortho-Benzylation of Benzamides in Toluene[a]

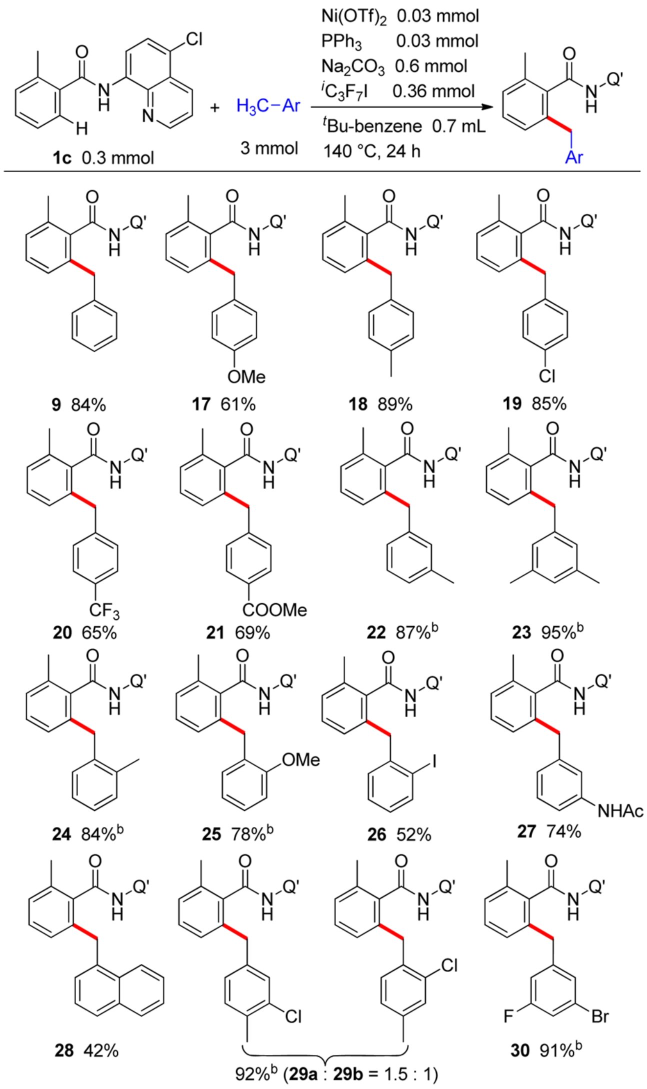


[a] Reactions were conducted on a 0.3 mmol scale. Isolated yields are reported. Q′ = 5-chloro-8-aminoquinolinyl group. [b] Run at 160 °C. [c] $^{i}C_3F_7I$ (0.9 mmol) was used. [d] The reaction was conducted on a 0.15 mmol scale, and 15 mol % catalyst was used.

To gain insights into the reaction mechanism, deuterium-labeling experiments were performed. When the deuterated benzamide **1c**-d_7 was reacted under the standard reaction conditions, but for 4 h, **2c** was produced in 52% isolated yield along with recovery of 41% of **1c**-d_7 in which H/D exchange was observed between only the ortho C−H bond and the NH bond. The D content at the ortho C−H bond was decreased to 0.48D (Scheme 2a). This result clearly indicates that C−H bond activation in benzamides is reversible under the reaction conditions. When toluene-d_8 was used as the solvent in the reaction of **1c**, the reaction was slower than the reaction in toluene (Scheme 2b). Furthermore, no H atom was detected in the benzylic position in the product, and no deuterium atom was incorporated into the recovered **1c**. In the ^{1}H NMR spectrum of the product, 1.52H was observed in the benzylic position, indicating that the reaction in toluene is 3.2 times faster when toluene-d_8 is used (1.52/0.48) when the reaction of **1c** in a 1:1 mixture of toluene and toluene-d_8 was carried out (Scheme 2c)

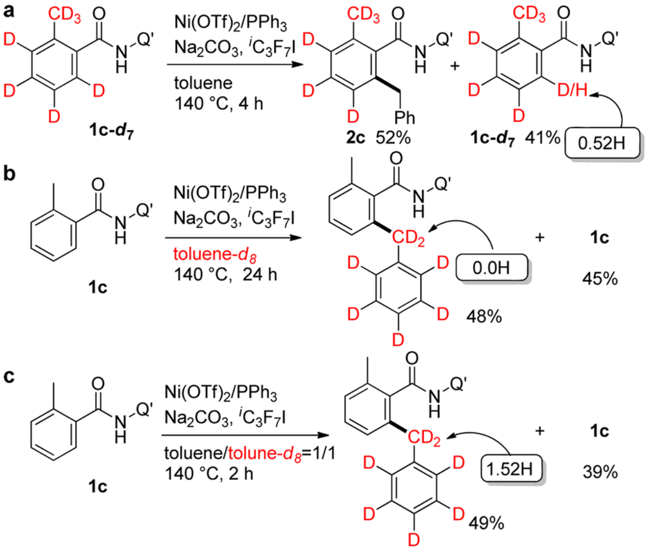
The most important issue to be addressed is what the actual benzylation species is and how it is generated. It was found that a reaction of $^{i}C_3F_7I$ in the presence of $Ni(OTf)_2/Na_2CO_3$ in toluene at 140 °C for 24 h generated benzyl iodide in 40% NMR yield. Curiously, a nickel complex was not required to generate the benzyl iodide, as benzyl iodide was formed in 21% NMR yield even in the absence of $Ni(OTf)_2$. Although benzyl iodide was formed only in 40% yield, catalytic C−H benzylation proceeded smoothly as shown in Table 2. These results suggest that benzyl iodide is formed to some extent under the reaction conditions but that it does not contribute to the benzylation as the major

Table 3. Ni(II)-Catalyzed Ortho-Benzylation of Benzamides with Toluene Derivatives[a]

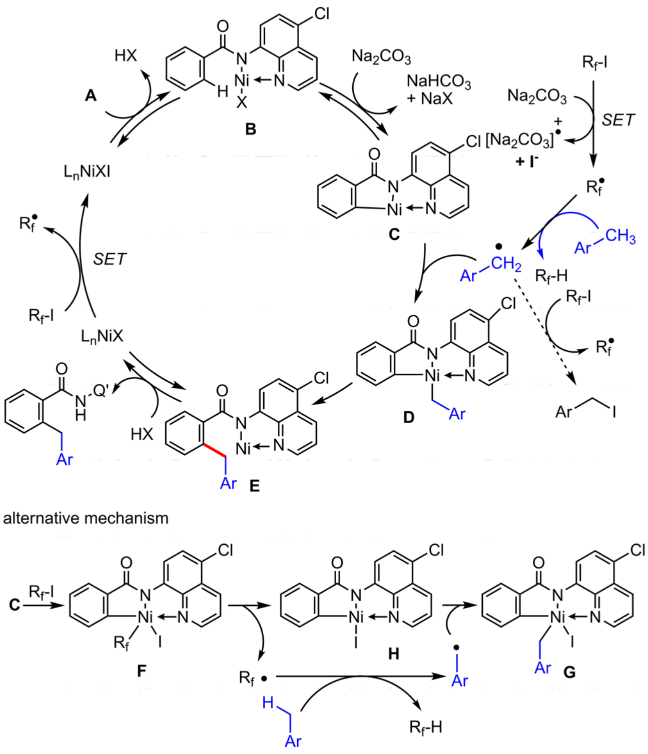


[a]Reactions were conducted on a 0.3 mmol scale. Isolated yields are reported. [b]Toluene derivative (1.0 mL) was used as the solvent.

Scheme 2. Deuterium-Labeling Experiments



Scheme 3. Reaction Mechanism



path because the benzylation of C−H bonds proceeded smoothly even when the generation of benzyl iodides was not efficient.

On the basis of the above results and data taken from previous reports, a plausible reaction mechanism is proposed in Scheme 3. Coordination of amide **A** to the Ni(II) center gives Ni(II) complex **B** with the generation of HX, which is trapped by Na_2CO_3. The C−H bonds in complex **B** then undergo reversible cleavage to give nickelacycle **C**. Base-promoted single-electron transfer (SET) of R_f−I[9] followed by abstraction of a hydrogen from toluene generates a benzyl radical and R_f−H.[10] The reaction of complex **C** with the benzyl radical affords Ni(III) species **D**, from which reductive elimination and protonation occurs to give the final product with generation of the Ni(I) complex. The reaction of Ni(I)X with R_f−I regenerates the Ni(II) complex with the generation of an R_f radical.[11] The addition of TEMPO completely quenched the reaction. These results suggest that the reaction involves the formation of a free radical.

Another alternative mechanism involves the oxidative addition of R_f−I to complex **C** to give Ni(IV) complex **F**, which reacts with toluene to afford complex **G** via the complex **H**. The step from **F** to **G** would be expected to proceed via a radical mechanism because the oxidative addition of $^iC_3F_7I$ to transition-metal complexes[12] and the abstraction of a H atom radical by a heptafluoroisopropyl radical are known.[13] As shown in Table 1, n-$C_6F_{13}I$ was not effective, although $^iC_3F_7I$ showed high activity. It is known that secondary perfluoroalkyl radicals undergo H atom abstraction faster than primary perfluoroalkyl radicals.[13] If perfluoroalkyl anion were involved in the reaction, perfluoroalkene would be generated by β-fluoro elimination.[14] However, no perfluoroalkene was detected.

In summary, we have reported on a unique strategy that enables oxidative C(sp^2)−H/C(sp^3)−H coupling via a Ni(II)-catalyzed reaction of benzamides with toluene derivatives. The presence of heptafluoroisopropyl iodide is essential for the reaction to proceed. Its role is to generate a benzyl radical via H atom abstraction from the toluene derivative. The reaction does not require a toluene derivative as the solvent. The scope of the reaction is broad with regard to both benzamides and coupling partners. Although the reaction mechanism is not clear, we anticipate that the strategy developed here may provide inspirations for the design of new functionalizations of C−H bonds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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