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Nickel-Catalyzed Direct Alkylation of C−H Bonds in Benzamides and Acrylamides with Functionalized Alkyl Halides via Bidentate-Chelation Assistance

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Supporting Information

ABSTRACT: The alkylation of the ortho C−H bonds in benzamides and acrylamides containing an 8-aminoquinoline moiety as a bidentate directing group with unactivated alkyl halides using nickel complexes as catalysts is described. The reaction shows high functional group compatibility. In reactions of meta-substituted aromatic amides, the reaction proceeds in a highly selective manner at the less hindered C−H bond.

The catalytic transformation of C−H bonds has recently emerged as one of the most promising and powerful methods for the construction of C−C bond frameworks.[1] A wide variety of transformations of C−H bonds have been developed, many of which involve the use of various transition-metal complexes as catalysts. The use of complexes of low-cost and more abundant metals, especially nickel, in the transformation of C−H bonds has attracted recent attention.[2] However, most of the Ni-catalyzed transformations of C−H bonds reported to date involve C(sp^2)−H bonds in pyridine derivatives[3] or activated C(sp^2)−H bonds in specific aromatic systems, such as perfluorobenzene[4] or azole derivatives,[5] which have acidic C−H bonds. Transformations of C(sp^2)−H bonds in benzene rings using Ni complexes are still rare,[6] although a pioneering example of chelation-assisted cyclometalation leading to the activation of C(sp^2)−H bonds in a benzene ring was achieved using a Ni complex.[7]

Chelation-assisted transformation has become a common and powerful method for the regioselective functionalization of ortho C−H bonds. A wide variety of functional groups have been evaluated for use as directing groups in the transformation of C−H bonds to date. However, although tremendous progress has been made,[1] the development of new types of directing groups continues to be important in terms of exploring novel types of transformations of C−H bonds that cannot be achieved when conventional directing groups are used. Bidentate directing groups have recently attracted the attention of researchers because they offer the possibility of developing new types of transformations of C−H bonds. Sames utilized an *N,O*-bidentate directing system in the vinylation and carbonylation of C(sp^3)−H bonds, but the reaction required a stoichiometric amount of a Pd catalyst.[8] In 2005, Daugulis reported the arylation of unactivated C(sp^3)−H bonds using 8-aminoquinoline and picolinamide as *N,N*-bidentate directing groups in conjunction with $Pd(OAc)_2$ as a catalyst.[9] Daugulis's promising results encouraged the development of a number of transformations of C−H bonds using a similar chelation system in conjunction with $Pd(OAc)_2$ as the catalyst.[10] No other bidentate directing systems for transition-metal-catalyzed transformations of C−H bonds had been reported when this project was initiated.[11] It is known that Pd complexes can be used to catalyze many different types of transformations of C−H bonds. However, the ability to use other transition metals would open possibilities to explore new catalytic reactions of C−H bonds.[6c,12,13] In a previous study, we reported that the Ru(0)-catalyzed C−H bond carbonylation of aromatic amides with a 2-pyridinylmethylamine moiety as the *N,N*-bidentate directing group results in the formation of phthalimide derivatives.[12a] This new directing group is also applicable to Ru-catalyzed carbonylation of aliphatic amides, which involves the activation of unactivated C(sp^3)−H bonds.[12c,d] The system was also found to be applicable to Ni(0)-catalyzed oxidative annulation of aromatic amides with alkynes, leading to the formation of isoquinolones.[6c] Quite recently, we reported on the Ru(II)-catalyzed ortho arylation of aromatic amides with 2-pyridinylmethylamine or 8-quinolinylamine as bidentate directing groups.[13] Herein we report that the use of Ni(II) complexes in conjunction with the *N,N*-bidentate system can be applied to C−H bond alkylation with *unactivated* alkyl halides. The direct alkylation of C−H bonds in a benzene ring with unactivated alkyl halides is limited to a few examples[1f,14] compared with the extensively studied C−H bond arylation, as the oxidative addition of alkyl halides is unfavorable and the resulting alkylmetal complexes tend to favor *β*-hydride elimination.

The reaction of amide **1a** (0.3 mmol) with butyl bromide (0.45 mmol) in the presence of $Ni(OTf)_2/PPh_3$ as a catalyst and Na_2CO_3 as a base in toluene at 140 °C for 24 h gave ortho-butylation product **2a** in 79% NMR yield along with the recovery of 15% of the unreacted **1a**. The product yield was significantly affected by the nature of the base used: Li_2CO_3, 3%; K_2CO_3, 0%; NaOAc, 5%; $NaHCO_3$, 41%; 2,6-lutidine, 0%. The use of 2 equiv of butyl bromide improved the yield of the isolated product to 88% (91% NMR yield) (eq 1). The addition of phosphine

(1)

ligands was also important. No reaction occurred when the reaction was carried out in the absence of PPh_3. A variety of Ni

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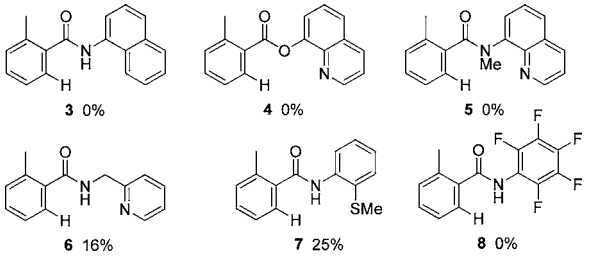
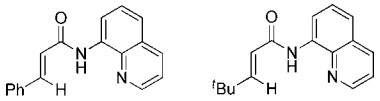
complexes could be used as the catalyst [NMR yields: $Ni(OAc)_2$, 70%; $NiBr_2(dme)$, 76%; $NiCl_2$, 66%; $Ni(cod)_2$, 51%]. Curiously, Ni(0) also showed catalytic activity.[15] In all cases, the starting amide **1a** was recovered when the yield of product **2a** was low.

We next examined the effect of directing groups. No reaction occurred when the corresponding *N*-2-naphthylbenzamide **3** or ester **4** was used as the substrate in place of **1a**, indicating that coordination in an *N*,*N*′ fashion by the 8-aminoquinoline moiety is essential for the reaction to proceed. Furthermore, the use of *N*-methylamide **5** failed to give the phenylation product, indicating that the presence of a proton on the amide nitrogen is required for the reaction to proceed, although NH is not included in the product at first sight. The use of a 2-pyridinylmethylamine (as in **6**) or 2-(methylthio)aniline (as in **7**) moiety as the bidentate directing group resulted in low yields of the alkylation products. The reaction appears to be more efficient with the 8-aminoquinoline motif.



With the optimized reaction conditions in hand, we examined the scope of the reaction. Table 1 shows the results for reactions of various aromatic amides with butyl bromide under the standard reaction conditions. A variety of functional groups were tolerated in the reaction. The reaction of meta-substituted substrates resulted in selective alkylation exclusively at the less hindered C−H bond, irrespective of the electronic nature of the substituent, indicating that the regioselectivity of the reaction is controlled by the steric nature of the substituent groups. In general, electron-withdrawing groups tended to give the butylation products in higher yields. The addition of NaI (as in **1b** and **1c**) was found improve the yield; this is discussed below.

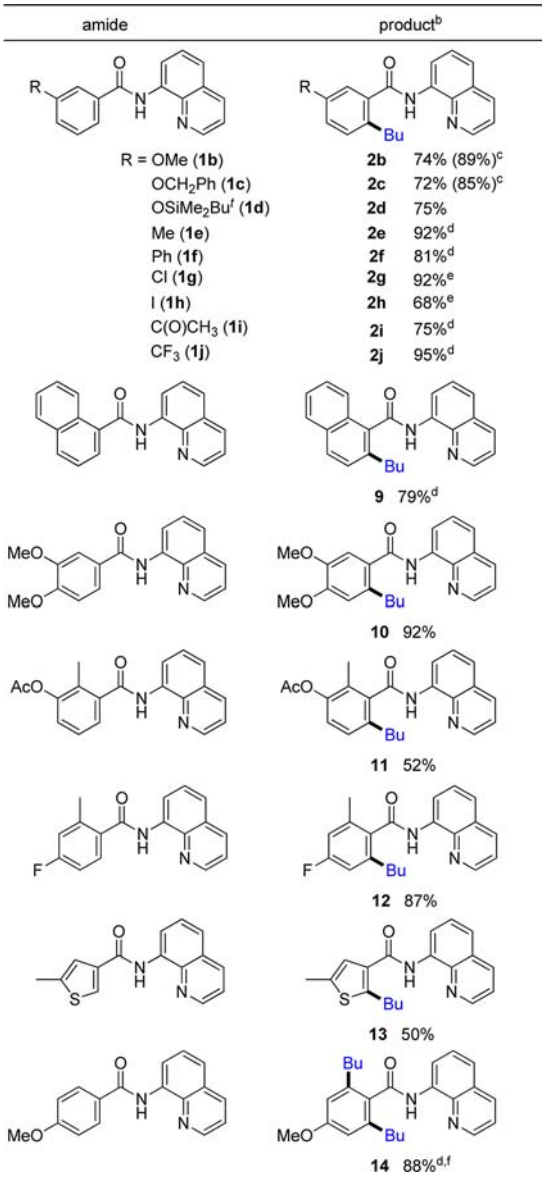
This alkylation reaction was also applicable to α,β-unsaturated amides, as shown in Table 2. However, the reaction was limited to trisubstituted α,β-unsaturated amides, suggesting that the presence of a substituent at the α-carbon is an important factor in terms of the reactivity of the substrate. Thus, **19** and **20** did not give the corresponding butylation products.



A variety of alkyl bromides were applicable to the alkylation reaction, as shown in Table 3. Octyl iodide as well as octyl bromide gave alkyation products in high yields. When octyl chloride was used, **21** was not produced. However, the addition of NaI (2 equiv) dramatically improved the yield of the isolated product to 88%. This salt effect was also observed in the case of other sterically demanding or functionalized alkyl halides. Various functional groups were tolerated in the reaction.

Several studies were carried out in an attempt to determine the reaction mechanism. We anticipated that under the reaction conditions employed, the alkylation takes place via the addition of the C−H bond with the alkene, which may involve the generation of an alkyl halide via dehydrobromination. However, when **1a** was reacted with octene, no alkylation products were produced, indicating that the alkyl halide itself functions as a coupling partner.

Table 1. Butylation of C−H Bonds in Aromatic Amides[a]



[a]Reaction conditions: amide (0.3 mmol), BuBr (0.6 mmol), $Ni(OTf)_2$ (0.03 mmol), PPh_3 (0.06 mmol), and Na_2CO_3 (0.6 mmol) in toluene (1 mL) at 140 °C for 24 h. [b]Isolated yields are shown. [c]NaI (0.6 mmol) was added. [d]Run at 160 °C. [e]BuI (0.6 mmol) was used instead of BuBr. [f]BuBr (1.2 mmol) was used.

The deuterated amide **1a**-d_7 was reacted with BuBr for 8 h under otherwise standard reaction conditions (eq 2). We observed a significant amount of H/D exchange at the ortho position (the D content decreased from >98% to 51%) and on the nitrogen in the recovered amide. *Even in the absence of BuBr*, a significant amount of H/D exchange again occurred at the ortho position (the D content decreased from >98% to 43%) and on the nitrogen, indicating that cleavage of the C−H bond is reversible and rapid. These results indicate that cleavage of the C−H bond likely is not the rate-determining step in the reaction.

Finally, we performed competition experiments using a 1:1 mixture of **1b** and **1j** with octyl bromide (eq 3). However, **1j** reacted

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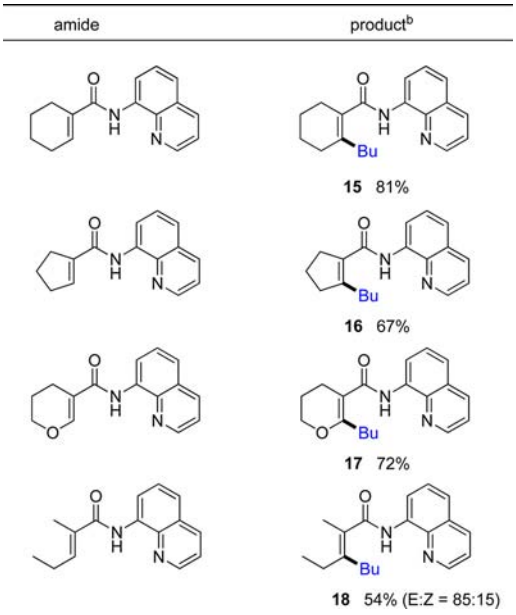
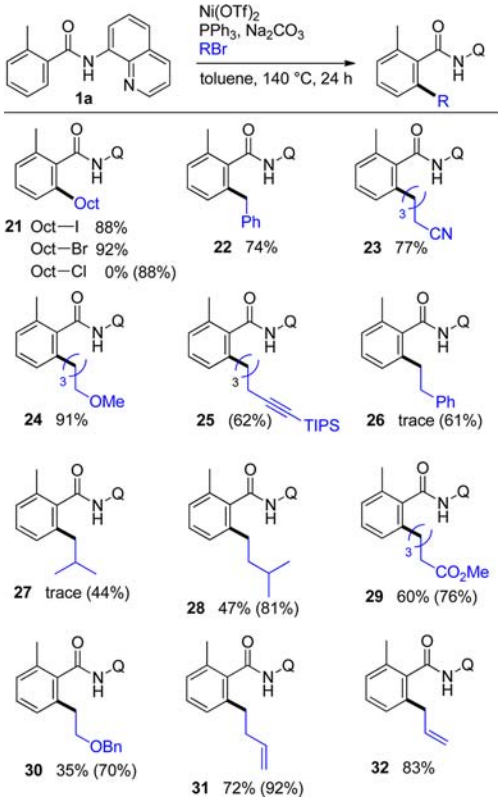
Table 2. Butylation of C−H Bonds in α,β-Unsaturated Amides[a]



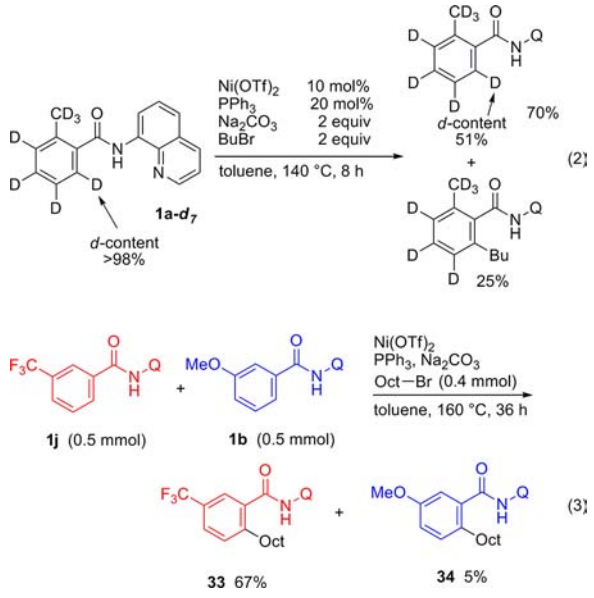
[a]Reaction conditions: amide (0.3 mmol), BuBr (0.6 mmol), $Ni(OTf)_2$ (0.03 mmol), PPh_3 (0.06 mmol), and Na_2CO_3 (0.6 mmol) in toluene (1 mL) at 140 °C for 24 h. [b]Isolated yields are shown.

Table 3. Alkylation of C−H Bonds in Aromatic Amides with Functionalized Alkyl Halides[a,b]



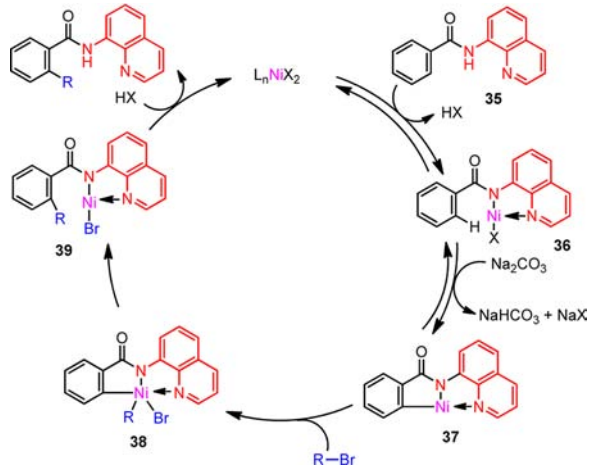
[a]Reaction conditions: **1a** (0.3 mmol), RBr (0.6 mmol), $Ni(OTf)_2$ (0.03 mmol), PPh_3 (0.06 mmol), and Na_2CO_3 (0.6 mmol) in toluene (1 mL) at 140 °C for 24 h. [b]Isolated yields are shown. Values in parentheses are yields obtained with added NaI (0.6 mmol).

to give mainly **33** in the competition experiments. This result suggests that the electron-withdrawing group facilitates the reaction.



A proposed mechanism for the reaction is shown in Scheme 1. Coordination of amide **35** to the Ni center followed by ligand

Scheme 1. Proposed Mechanism



exchange with concomitant generation of HX gives Ni complex **36**, which undergoes reversible cyclometalation to give **37**, probably via a concerted metalation−deprotonation mechanism. Oxidative addition of RBr followed by reductive elimination gives **39**, which undergoes protonation to afford the desired alkylation product with the regeneration of Ni(II).[16,17] As shown in eq 2, cleavage of the C−H bond appears to be a reversible and rapid step and is not the rate-determining step.

In summary, we have reported the development of a new catalytic system that takes advantage of chelation assistance by an 8-aminoquinoline moiety. This represents the first example of Ni-catalyzed ortho alkylation of benzamides and acrylamide derivatives with unactivated alkyl halides in which C−H bonds are cleaved. The reaction proceeds in a highly selective manner at the less hindered C−H bond in the reaction of meta-substituted aromatic amides.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic data. 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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