Nickel-Catalyzed Direct Arylation of C(sp^3)−H Bonds in Aliphatic Amides via Bidentate-Chelation Assistance

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ABSTRACT: The Ni-catalyzed, direct arylation of C-(sp^3)−H (methyl and methylene) bonds in aliphatic amides containing an 8-aminoquinoline moiety as a bidentate directing group with aryl halides is described. Deuterium-labeling experiments indicate that the C−H bond cleavage step is fast and reversible. Various nickel complexes including both Ni(II) and Ni(0) show a high catalytic activity. The results of a series of mechanistic experiments indicate that the catalytic reaction does not proceed through a Ni(0)/Ni(II) catalytic cycle, but probably through a Ni(II)/Ni(IV) catalytic cycle.

The transition metal-catalyzed functionalization of C−H bonds has emerged as a powerful tool for the formation of C−C and C−heteroatom bonds in recent years.[1] A wide variety of catalytic functionalizations of C(sp^2)−H has already been developed to date and have had a significant impact in the field of organic chemistry. It can now be said that it is no longer difficult to develop the functionalization of C(sp^2)−H bonds. In this sense, the catalytic functionalization of C(sp^2)−H bonds is now recognized as one of general organic synthetic reactions available to organic chemists. Because of this, much attention is currently focused on the functionalization of C(sp^3)−H bonds, which continues to be a challenging issue.[2] However, most of the functionalization reactions of C(sp^3)−H bonds reported involve the use of palladium complexes as catalysts. Transition metal complexes other than palladium complexes also show catalytic activity, but only in limited types of functionalizations of C(sp^3)−H bonds, such as dehydrogenation, borylation, carbonylation, and similar reactions.[3]

Recently, the utilization of a bidentate directing group in the transformation of C−H bonds has significantly grown in popularity since the seminal discovery by Daugulis,[4] and this area appears to show a high potential for exploring new types of transformations of C−H bonds which cannot be achieved using conventional directing groups.[5,6] Various types of functionalizations of C(sp^3)−H bonds have been achieved using the bidentate-chelation system in conjunction with Pd(II) catalysts.[7] We also reported on the Ru$_3$(CO)$_{12}$-catalyzed carbonylation of C(sp^3)−H bonds in aliphatic amides with a pyridinylmethylamino moiety as the bidentate directing group.[6b,c] Nakamura reported on the Fe-catalyzed arylation of C(sp^3)−H bonds in aliphatic amides having an 8-aminoquinolinyl moiety with Grignard reagents.[8] We report here on the Ni-catalyzed β-arylation of aliphatic amides 1 containing a bidentate directing group with aryl iodides via the cleavage of unactivated C(sp^3)−H

bonds (Scheme 1). To the best of our knowledge, Ni-catalyzed transformation of C(sp^3)−H bonds have been restricted to only

Scheme 1. Nickel-Catalyzed Direct Arylation of C(sp^3)−H Bonds in Aliphatic Amides
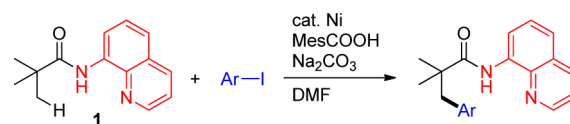
one example, i.e., the Ni(0)-catalyzed cycloaddition of formamide with alkynes.[9]

The reaction of amide **1a** (0.3 mmol) with 4-iodoanisole (0.6 mmol) in the presence of Ni(OTf)$_2$ (0.03 mmol) as a catalyst and Na$_2$CO$_3$ (0.6 mmol) as a base in DMA (0.6 mL) at 140 °C for 24 h gave the β-arylation product **1b** in 40% NMR yield along with the recovery of 44% of the unreacted **1a**, and no evidence of any biarylated product or any other products produced by reaction at the methylene or benzene C−H bonds was found (entry 1, Table 1). The addition of benzoic acid as an additive improved the yield of **1a** to 70% (entry 2). Further investigation revealed that the addition of a sterically bulky carboxylic acid, such as 2,4,6-trimethylbenzoic acid (MesCOOH) or [1,1′:3′,1″-terphenyl]-2′-carboxylic acid (2,6-Ph$_2$C$_6$H$_3$COOH), also improved the product yield (entries 3−7). The efficiency of the reaction was also significantly affected by the choice of the base used. Na$_2$CO$_3$ was determined to be the best base for this reaction (entries 8−11). Among the solvents examined, DMF was the solvent of choice. Curiously, not only Ni(II) complexes but also a Ni(0) complex showed a high catalytic activity, resulting in high yields of the β-arylation product (entry 18).

We next examined the effect of directing groups (Figure 1). The reaction did not proceed at all when N-2-naphthylbenzamaide **2** or the ester **3** was used. The use of other directing groups, such as **4** or **5**, also resulted in no reaction.

Table 2 shows the scope of the substrates under the standard reaction conditions. The reaction was sensitive to the structure of the amides. Some examples of unreactive amides are listed at the bottom of Table 2. Aliphatic amides possessing no hydrogen at the α-position reacted efficiently. The reactions proceeded exclusively at the methyl group in a highly regioselective manner, as in the cases of **6a**, **7a**, **8a**, and **9a**, and methylene and benzene C−H bonds were not arylated. Although the reaction of cyclohexanecarboxamide **10a** resulted in selective mono-

Table 1. Optimaization of the Nickel-Catalyzed Direct Arylation of Aliphatic Amide 1a with 4-iodoanisole[a]
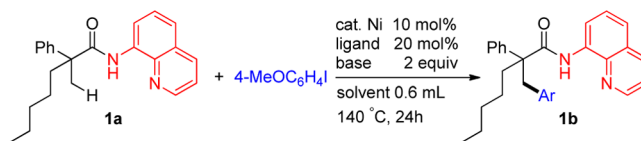
entry	catalyst	ligand	base	solvent	yield (1b/1a)[b] (%)/(%)
1	Ni(OTf)$_2$	none	Na$_2$CO$_3$	DMA	40/44
2	Ni(OTf)$_2$	PhCOOH	Na$_2$CO$_3$	DMA	70/22
3	Ni(OTf)$_2$	2-PhC$_6$H$_4$COOH	Na$_2$CO$_3$	DMA	72/24
4	Ni(OTf)$_2$	MesCOOH	Na$_2$CO$_3$	DMA	82 (78) /17
5	Ni(OTf)$_2$	2,6-^{i}Pr$_2$C$_6$H$_3$COOH	Na$_2$CO$_3$	DMA	74/23
6	Ni(OTf)$_2$	2,6-Ph$_2$C$_6$H$_3$COOH	Na$_2$CO$_3$	DMA	81/21
7	Ni(OTf)$_2$	1-AdCOOH	Na$_2$CO$_3$	DMA	72/27
8	Ni(OTf)$_2$	MesCOOH	Li$_2$CO$_3$	DMA	49/35
9	Ni(OTf)$_2$	MesCOOH	NaHCO$_3$	DMA	14/72
10	Ni(OTf)$_2$	MesCOOH	K$_2$CO$_3$	DMA	0/103
11	Ni(OTf)$_2$	MesCOOH	Cs$_2$CO$_3$	DMA	57/42
12	Ni(OTf)$_2$	MesCOOH	Na$_2$CO$_3$	DMF	88 (83)/12
13	Ni(OTf)$_2$	MesCOOH	Na$_2$CO$_3$	toluene	59/38
15	Ni(OTf)$_2$	MesCOOH	Na$_2$CO$_3$	AcOH	0/99
16	NiCI$_2$	MesCOOH	Na$_2$CO$_3$	DMF	81/10
17	Ni(OAc)$_2$	MesCOOH	Na$_2$CO$_3$	DMF	81/10
18	Ni(cod)$_2$	MesCOOH	Na$_2$CO$_3$	DMF	79/ 10

[a]Reaction conditions: amide 1a (0.3 mmol), 4-iodoanisole (0.6 mmol), catalyst (0.03 mmol), ligand (0.06 mmol), base (0.6 mmol) in solvent (0.6 mL) at 140 °C for 24 h. [b]NMR yields. The number in parentheses is the isolated yield.
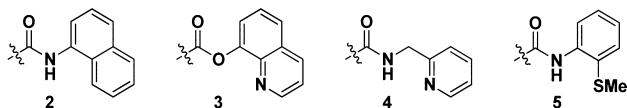

Figure 1. Ineffective directing groups.

arylation only at the methyl group, cycloheptanecarboxamide 11a gave a mixture of monoarylated 11b and biarylated products 11c, the latter involving the arylation at the cyclic methylene C−H bonds. When cyclobutanecarboxamide 12a and cyclo-pentanecarboxamide 13a were used, the arylation of β-methlyene C−H bonds was the predominant reaction. The structure of 12c was confirmed from X-ray crystallography data, which show that the introduced aryl groups are located cis to the directing group.[10] This also indicates the importance of the directing group.

A 5 mmol scale reaction of 6a was successfully performed in a 30-mL two-necked flask (Scheme 2).

The scope of aryl iodides with various substituents at the para position was examined using 1a as the substrate. The results showed that common functional groups, including esters, iodides, chlorides, and amines, were compatible in the present reaction. Electron-rich aryl iodides tended to give the products in slightly higher yields than electron-poor aryl iodides. Ortho-substituted aryl iodides were unreactive. Phenyl bromides and triflates did not give arylation products.

To gain insights into the mechanism for the reaction, deuterium-labeling experiments were carried out. The deuter-ated amides 1a-d_3 were reacted with 4-iodoanisole for 3 h under standard conditions (Scheme 3). H/D exchange between the methyl C−D bond and N−H bond was detected. Thus, the D content in the recovered amide decreased from >99% to 76%, and the D content of the amide nitrogen increased from 0% to 23%. H/D exchange was also observed, even in the absence of 4-iodoanisole. These results suggest that the cleavage of C−H

bonds is rapid and reversible, and it occurs before the reaction with the aryl iodide. In sharp contrast, Ni(0)-catalyzed deuterium-labeling experiments gave different results. In the presence of 4-iodoanisole, H/D exchange in both the product and the recovered amide was observed, similar to the Ni(II)-catalyzed reaction. However, *in the absence of 4-iodoanisole, no H/D exchange occurred.* These results suggest that the presence of an aryl iodide is required for the cleavage of C−H bonds to take place in the case of the Ni(0)-catalyzed reaction.

Product distribution was examined in detail, in order to develop a better understanding of the difference between the Ni(0)- and Ni(II)-catalyzed reactions (Scheme 4). In the reaction of 1a with 4-butyl-1-iodobenzene in the presence of 30 mol % Ni(cod)$_2$, the arylation product 1o was obtained in 67% NMR yield with 32% of the starting amide 1a being recovered, and butylbenzene was produced in 86% yield/Ni(0) and no biaryl derivative was formed. In sharp contrast, when Ni(OTf)$_2$ was used as the catalyst, 1o was obtained in 65% NMR yield with 36% of the starting amide being recovered, but neither butylbenzene nor biaryl were detected. It is known that Ni(0) complexes react with Ar−X to give homocoupling products Ar−Ar with the generation of a Ni(II) complex;[11] however, the results in Scheme 4 indicate that such a reaction did not take place under the present reaction. Instead, the results suggest that the Ni(0) complex was oxidized by 4-butyl-1-iodobenzene with the generation of butylbenzene. The results of the above analyses indicate that the catalytic active species in this reaction is not the Ni(0) complex but rather, the Ni(II) complex.
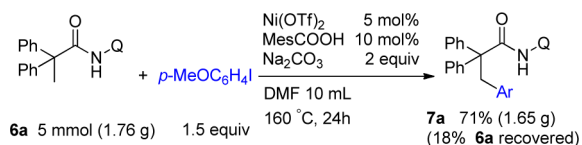
A proposed mechanism for the reaction is shown in Scheme 5. Coordination of the amide to the Ni center followed by ligand exchange with the concomitant generation of HX gives the Ni complex 15, which undergoes reversible cyclometalation to give 16, probably via a concerted-metalation−deprotonation mech-anism. The oxidative addition of iodobenzene gives the high-valent Ni(IV) complex 17. The Ni(IV) complex 17 undergoes

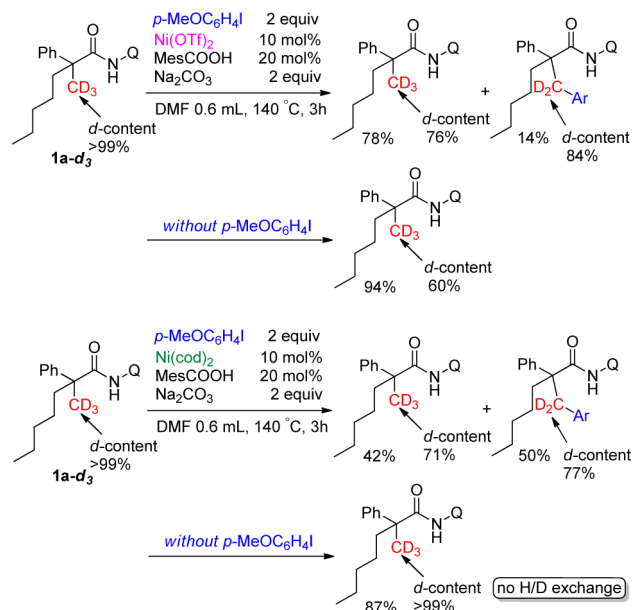**Table 2. Nickel-Catalyzed Direct Arylation of Aliphatic Amides with Aryliodides[a]**

Scheme 2. Large-Scale Reaction of 6a

Scheme 3. Deuterium-Labeling Experiments

Scheme 4. Product Distribution

The number in parentheses is the yield of the recovered **1a**.

[a]Reaction conditions: amide (0.3 mmol), aryl iodides (0.6 mmol), Ni(OTf)₂ (0.03 mmol), MesCOOH (0.06 mmol), Na₂CO₃ (0.6 mmol) in DMF (0.6 mL) at 140 °C for 24 h in 5-mL screw-capped vial. [b]Isolated yields by column chromatography. The number in parentheses is the yield of the recovered starting amide. [c]The stereochemistry is not determined, but only the single isomer exists. [d]2,6-Ph₂C₆H₃COOH was used instead of MesCOOH, and 4-iodoanisole (0.9 mol) was used. [e]Purified by GPC.
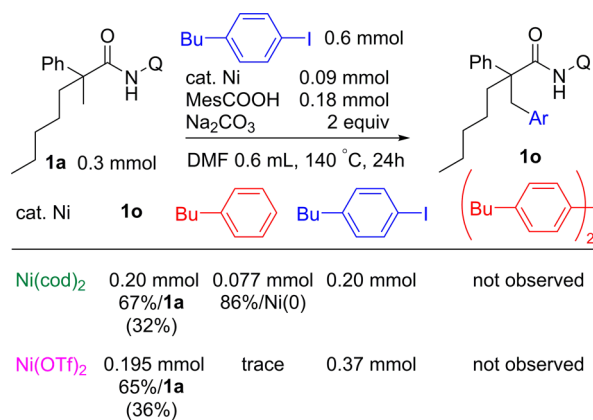
reductive elimination to give **18** which, on protonation, affords the desired arylation product with the regeneration of Ni(II).[12] In the case of the Ni(0)-catalyst, the reaction of the Ni(0) complex with iodobenzene to form Ph−Ni−I species which reacts with the amide **1** generates the Ni(II) complex **15** with the

generation of benzene. Alternatively, Ph−Ni−I species would react with HX to generate Ni(II) with the generation of benzene.[13] In order to gain additional insight into the mechanism, we performed a radical trapping experiment. The addition of 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO) did not inhibit the reaction, and the arylation product **1o** was obtained in moderate yield (53%). This suggests that a single electron transfer (SET) was not involved in this reaction; however, additional experiments will be needed to exclude a Ni(I)/Ni(III) catalytic cycle.

In summary, we report on the first example of the nickel-catalyzed direct arylation of unactivated C(sp³)−H bonds in aliphatic amides, in which the presence of a bidentate directing group, such as an 8-aminoquinoline moiety is required for the

Scheme 5. Proposed Mechanism

H–X = HI, NaHCO$_3$, H$_2$O, **1**
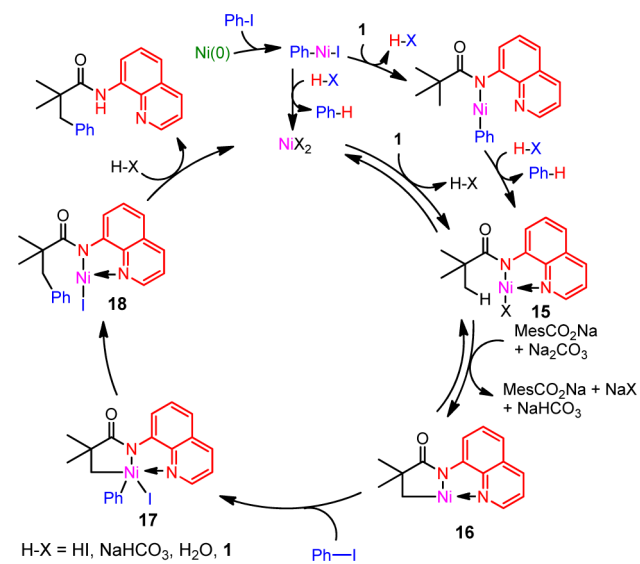
reaction to proceed. Unlike the Fe-catalyzed arylation of aliphatic amides with ArMgBr/Ar$_2$Zn using a similar chelation-assisted system,[8] the present reaction shows high functional group compatibility. Experiments involving stoichiometric reactions are currently underway, in attempts to isolate or detect the active catalytic species.

■ 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.

■ ACKNOWLEDGMENTS

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(12) Alternatively, the ligand exchange with **1** would directly provide the complex **15** from **18** without regeneration of NiX$_2$.

(13) See Supporting Information of the paper by Weix et al. Shrestha, R.; Dorn, S. C. M.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 751.