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Nickel-catalyzed chelation-assisted direct arylation of unactivated C(sp^3)–H bonds with aryl halides†

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In this work, we have disclosed the nickel-catalyzed unactivated β-C(sp^3)–H bond arylation of aliphatic acid derivatives with aryl iodides/bromides *via* bidentate chelation-assistance of an 8-aminoquinoline moiety. These preliminary results indicate the intrinsic catalytic potential of nickel metal for unactivated C(sp^3)–H bond arylation.

The C(sp^2)–C(sp^3) bonds extensively exist in synthetic products, naturally occurring molecules, pharmaceuticals, and bioactive compounds. The construction of C(sp^2)–C(sp^3) bonds has attracted great interest from organic chemists for a long time. Transition metal-catalyzed direct C–H bond functionalization has been one of the most promising methods for the C–C bond formation.[1] The C(sp^2)–C(sp^3) bond formation *via* catalytic direct C(sp^3)–H bond arylation relies heavily on palladium(II) catalysis.[2–4] In recent years, the nickel-catalyzed direct C–H bond functionalization has received more and more attentions due to the abundance, low cost and particular electronic properties of nickel metal.[5] In spite of significant efforts, the Ni-catalyzed direct C(sp^3)–H arylation remains rare. In 2011, Hartwig and co-workers disclosed the nickel-catalyzed α-arylation and heteroarylation of ketones with aryl halides.[6] Very recently, Lei and co-workers reported the nickel-catalyzed oxidative C(sp^3)–H bond arylation of tetrahydrofuran and 1,4-dioxane with arylboronic acids.[7] However, these direct arylation reactions occurred at the activated α-C(sp^3)–H bonds adjacent to oxygen atoms (ether derivatives) and carbonyl groups (ketones), and the nickel-catalyzed arylation of unactivated C(sp^3)–H bonds is still a highly challenging topic.

The chelation-assistance strategy has become an efficient means for the functionalization of unactivated C–H bonds.[8] In particular, the 8-aminoquinoline group has recently attracted wider and wider attention since the seminal work by Daugulis in 2005.[3a,d,j] Various metal catalysts (*e.g.*, Pd, Rh, and Ru) have been applied extensively, whereas the chelation-assisted examples involving nickel catalysts are rare. In 2011, Chatani and co-workers uncovered the first nickel-catalyzed *ortho*-C(sp^2)–H bond activation to achieve regioselective oxidative cycloaddition of aromatic amides to alkynes using the bidentate auxiliary strategy.[5c] Lately, the same group developed the nickel-catalyzed chelation-assisted *ortho*-C(sp^2)–H alkylation of aromatic amides.[5d] Inspired by these pioneering studies, it is reasonable to assume that the activation of unactivated C(sp^3)–H bonds would be achieved through nickel catalysis with the assistance of a bidentate directing group.[9] Herein, we wish to report the nickel-catalyzed unactivated primary β-C(sp^3)–H bond arylation of aliphatic acid derivatives with aryl iodides/bromides (eqn (1)). During the submission of this manuscript, Chatani *et al.* reported the direct arylation of C(sp^3)–H bonds of aliphatic amides by using the same directing group.[10] However, only aryl iodides were employed as the coupling partner in their work.

(1)

Considering that 8-aminoquinoline has been proven to be a powerful bidentate auxiliary in transition metal-catalyzed direct C–H bond activation, a variety of α,α-disubstituted propionic acids were first decorated with 8-aminoquinoline to *N*-(quinolin-8-yl)propanamide derivatives. In our initial exploration, it was found that the reaction of 2-benzyl-3-(4-methoxyphenyl)-2-methyl-*N*-(quinolin-8-yl)propanamide **1a** with 1-iodo-4-methoxybenzene **2a** gave the desired product **3a** in 24% yield in the presence of $Ni(OTf)_2$, PPh_3 and K_2CO_3 in 1,4-dioxane at 140 °C for 24 h (ESI,† Table S1, entry 1). After screening various bases (*e.g.*, K_2CO_3, Na_2CO_3, K_3PO_4 and Li_2CO_3), Na_2CO_3 gave the best yield of 35% (ESI,† Table S1, entries 1–4). Upon addition of DMSO and PivOH, the product yield was improved greatly to 83% at 160 °C (ESI,† Table S1, entry 9). Other nickel(II) catalysts

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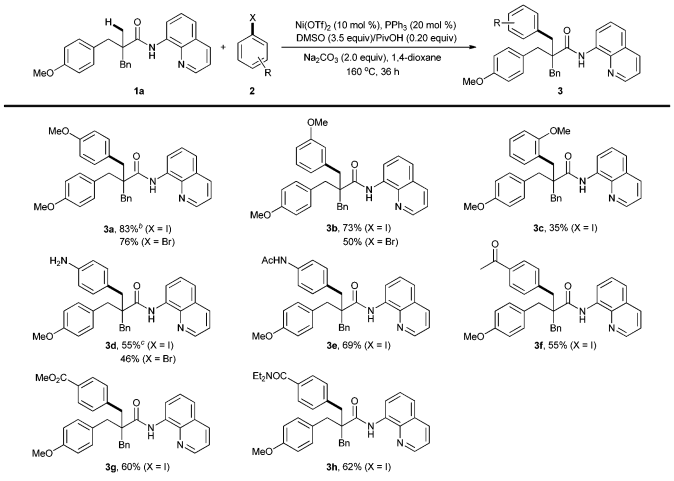
such as $Ni(OAc)_2$ and $NiCl_2$ provided **3a** in moderate yields under otherwise identical conditions (ESI,† Table S1, entries 13 and 14). Interestingly, a nickel(0) catalyst such as $Ni(cod)_2$ could also deliver **3a** in 62% yield (ESI,† Table S1, entry 15). The yield decreased to 54% when the reaction was performed in the absence of PPh_3 (ESI,† Table S1, entry 10). In addition, other frequently used directing groups such as pyridin-2-ylmethanamine and 2-(methylthio)aniline could not promote arylation. Thus, the best result was obtained by using $Ni(OTf)_2$ (10 mol%) as the catalyst, PPh_3 (20 mol%) as the ligand, Na_2CO_3 (2.0 equiv.) as the base, PivOH (0.2 equiv.) and DMSO (3.5 equiv.) as the additives in dry 1,4-dioxane at 160 °C.

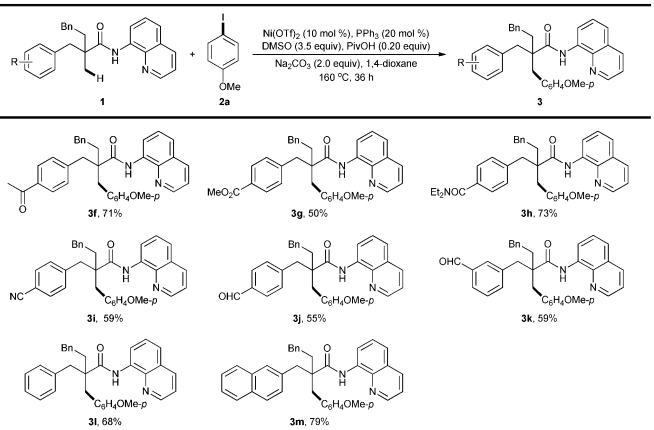
With the optimized reaction conditions in hand, we investigated the generality of the reaction of **1a** with aryl iodides as shown in Table 1. We found that the reactions of aryl iodides with electron-donating groups (except the *ortho*-substituted methoxy group) could deliver the cross-coupled products in satisfactory yields (Table 1, **3a–3e**). Aryl iodides bearing electron-withdrawing groups such as *p*-CH_3CO–, *p*-CO_2Me, and *p*-$CONEt_2$ also proceeded smoothly to afford the desired products **3f**, **3g** and **3h** in 55%, 60% and 62% yields, respectively. Notably, a variety of functional groups such as alkyloxy, ketone, ester, amide, acetamido, and even free amino groups were tolerated under the optimized reaction conditions, which is useful in further synthetic transformations. We were pleased to find that aryl bromides could also undergo the β-C(sp^3)–H bond arylation in synthetically useful yields (Table 1). It is worth noting that transition metal-catalyzed direct C(sp^3)–H bond arylation with aryl bromides is still a difficult task in the synthetic organic community and is underrepresented to date. To the best of our knowledge, this is the first attempt to achieve transition metal-catalyzed chelation-assisted direct arylation of unactivated C(sp^3)–H bonds with aryl bromides. These preliminary results indicated the intrinsic potential of nickel catalysis in the C(sp^3)–H bond arylation with aryl bromides.

Table 1 Nickel-catalyzed β-C(sp^3)–H bond arylation of aliphatic amide **1a** with aryl halides[a]



[a] Conditions: $Ni(OTf)_2$ (10 mol%), PPh_3 (20 mol%), Na_2CO_3 (2.0 equiv.), PivOH (0.2 equiv.), DMSO (3.5 equiv.), amide **1a** (0.2 mmol), and aryl iodide (3.0 equiv.) or aryl bromide (4.0 equiv.) in dry 1,4-dioxane (1 mL) at 160 °C for 36 h. Isolated yields. [b] **2a** (2.0 equiv.) for 24 h. [c] 22% of **1a** was recovered.

Table 2 Nickel-catalyzed β-C(sp^3)–H bond arylation of various aliphatic amides with 1-iodo-4-methoxybenzene **2a**[a]



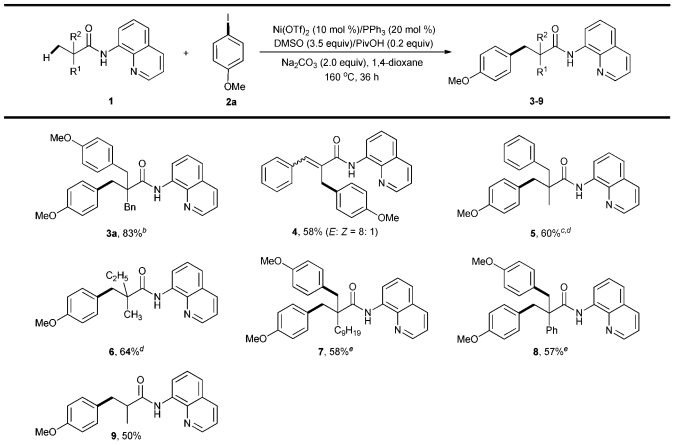
[a] Conditions: $Ni(OTf)_2$ (10 mol%), PPh_3 (20 mol%), Na_2CO_3 (2.0 equiv.), PivOH (0.2 equiv.), DMSO (3.5 equiv.), amide **1** (0.2 mmol) and **2a** (3.0 equiv.) in dry 1,4-dioxane (1 mL) at 160 °C for 36 h. Isolated yields.

To explore the effect of the R substituent of the phenyl ring of aliphatic acid derivatives **1** on the primary β-C(sp^3)–H bond arylation, an array of amides **1** were investigated accordingly. To our delight, α,α-dibenzyl substituted propionic acid derivatives bearing either electron-donating or electron-withdrawing substituents on the phenyl ring afforded the desired products in synthetically useful yields (Table 1, **3a**; Table 2, **3f–3l**). Notably, the current methodology was compatible with some important functional groups such as Ac, CO_2Me, $CONEt_2$, CN and CHO. The coupling reaction of 2-methyl-2-(naphthalen-2-ylmethyl)-3-phenyl-*N*-(quinolin-8-yl)propanamide with **2a** could also generate the β-arylated product **3m** in 79% yield.

To examine the synthetic usefulness of our protocol, we turned our attention to other aliphatic acid derivatives, while 2,2-dibenzyl-substituted propanamides could smoothly afford the arylated products **3**. As shown in Table 3, the nickel-catalyzed C(sp^3)–H bond arylation exhibited a relatively broad substrate scope for aliphatic acid derivatives. 2-Methyl-3-phenyl-acrylamide reacted with 1-iodo-4-methoxybenzene **2a** to afford the coupled product **4** in 58% yield. Isobutyramides could couple with **2a** to afford the single arylated products. For example, the reaction of 2,2-dimethyl-3-phenylpropanamide with **2a** delivered the desired product **5** in 60% yield. Isobutyramide with an α-ethyl substituent proceeded well to yield the arylated product **6** in 64% yield. Interestingly, the diarylated products could be obtained by increasing the amount of 1-iodo-4-methoxybenzene **2a** (Table 3, **7** and **8**). It should be noted that 2-methyl-2-phenylpropanamide selectively underwent C(sp^3)–H bond activation of the methyl group instead of the C(sp^2)–H bond of the phenyl ring to generate the arylated product **8**. In addition to the methyl group of quaternary carbon centers, the methyl group of tertiary carbon centers could also undergo direct C(sp^3)–H bond arylation with aryl iodides. The reaction of *N*-(quinolin-8-yl)isobutyramide with **2a** provided the desired product **9** in 50% yield.

In summary, we have developed the nickel-catalyzed unactivated β-C(sp^3)–H bond arylation of aliphatic acid derivatives

Table 3 Scope of aliphatic amides in Ni-catalyzed β-C(sp^3)–H bond arylation[a]



[a] Conditions: $Ni(OTf)_2$ (10 mol%), PPh_3 (20 mol%), Na_2CO_3 (2.0 equiv.), PivOH (0.2 equiv.), DMSO (3.5 equiv.), amide **1** (0.2 mmol), and 1-iodo-4-methoxybenzene **2a** (3.0 equiv.) in dry 1,4-dioxane (1 mL) at 160 °C for 36 h. Isolated yields. [b] **2a** (2.0 equiv.) for 24 h. [c] 2-Nitrobenzoic acid instead of PivOH was used. [d] At 150 °C. [e] **2a** (4.0 equiv.).

with aryl iodides *via* bidentate chelation-assistance of an 8-aminoquinoline moiety. Besides aryl iodides, aryl bromides are also capable of undergoing the cross-coupling reactions to a certain extent. Further studies to extend the scope and clarify the detailed mechanism[11] are ongoing in our laboratory.

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