Communication

#-Arylation of Carboxamides via Iron-Catalyzed C(sp3)-H Bond Activation

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β-Arylation of Carboxamides via Iron-Catalyzed C(sp^3)–H Bond Activation

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Supporting Information Placeholder

ABSTRACT: A 2,2-disubstituted propionamide bearing an 8-aminoquinolinyl group as the amide moiety can be arylated at the *β*-methyl position with an organozinc reagent in the presence of an organic oxidant, a catalytic amount of an iron salt, and a biphosphine ligand at 50 °C. Various features of selectivity and reactivity suggest the formation of an organometallic intermediate via rate-determining C–H bond cleavage rather than a free-radical-type reaction pathway.

Because of the potential economic and environmental merits[1] compared with precious metals, iron catalysis[2] for C(sp^2)–H bond activation[3] to create a C–C bond has recently seen tremendous development,[4] and iron catalysis for C(sp^3)–H activation[5,6] is expanding as well.[7,8] Except for a few examples, these reactions may be categorized as remote functionalization of the C–H bond, where an organometallic intermediate is stabilized by chelation to the nearby directing group (e.g., chelated metal homoenolate **A** in Figure 1a). Having been interested in homoenolate chemistry for some time,[9] we conjectured that **A** in Figure 1a may serve as a viable intermediate for the conversion of an aliphatic acid derivative such as carboxamide **1** to a *β*-functionalized product (**2** or **3**). We report here an iron-catalyzed arylation of the *β*-methyl position of a 2,2-disubstituted propionamide bearing an 8-aminoquinolinyl group (NH-Q)[6a,10] as the amide moiety in the presence of an organic oxidant[11] under mild thermal conditions. The reaction has less of the radical character previously observed in iron catalysis[7] and a more organometallic character,[12] because the reaction is sensitive to the choice of the ligand and shows complete preference toward C–H bond activation on the methyl group over the benzyl group of **1** (Figure 1a).

A typical procedure optimized after considerable experimentation is described first (Figure 1a). The NH-Q amide **1** (1.22 g, 4 mmol) was added to a THF solution of freshly prepared *p*-anisylmagnesium (Ar) bromide (7 equiv), $ZnBr_2$•TMEDA (3 equiv), then a solution of $Fe(acac)_3$ (10 mol %) and 1,2-bis(diphenylphosphino)benzene (dppbz, 10 mol %) in THF and 1,2-dichloroisobutane[13] (DCIB, 2 equiv) were added, and the mixture was heated at 50 °C for 36 h. Aqueous work-up followed by column chromatography gave 1.40 g of arylated product **2** (85%, Figure 1a) together with the recovery of **1**. Out of the 7 equiv of ArMgBr, 6 equiv form 3 equiv of Ar_2Zn and 1 equiv deprotonates the amide proton. A small amount of the Ar group must have been consumed upon reaction with $Fe(acac)_3$. The use of a smaller amount of organometallic reagent resulted in a lower yield (45% with 2 equiv of organozinc reagent) and slower reaction. Omission of the zinc salt resulted in no formation of the desired product. For reasons yet to be probed, increasing the amount of the zinc reagent, the catalyst, and longer reaction time did not result in higher conversion. Addition of a catalytic amount of water or the use of old Grignard reagent significantly lowered the reaction yield, suggesting that the presence of alkoxide impedes the reaction.

Under similar conditions, the reaction of phenylmagnesium bromide gave **3** in 80% yield together with the recovered **1** (14%) and biaryl (15% based on PhMgBr) because of iron-mediated homocoupling.[14] Interestingly, most of the biaryl formed after the product formation stopped. We found no products either from arylation at the benzylic position[7a] of **1**, from further reaction of the product **2** or **3**, or from arylation of the carboxamide nitrogen.[15]

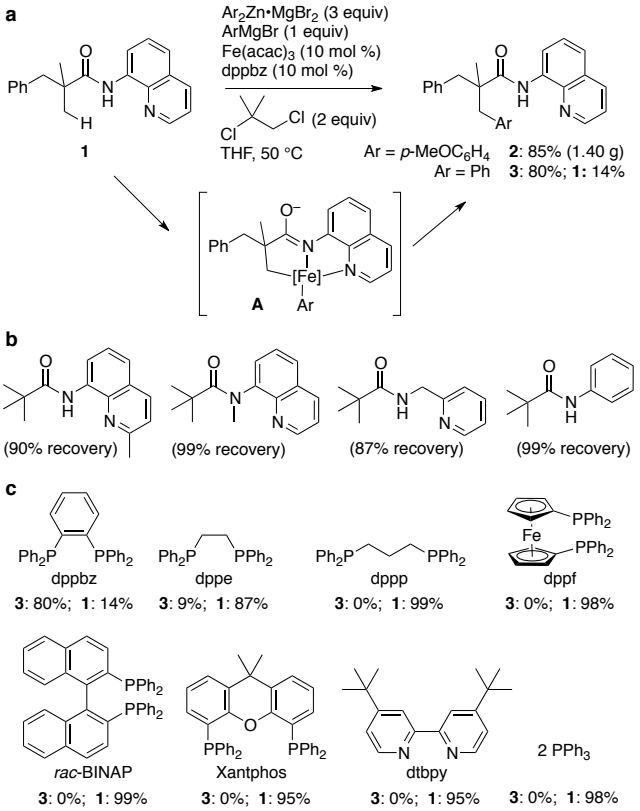


Figure 1. Iron-catalyzed arylation of the *β*-methyl group of 2,2-disubstituted propionamide. (a) Representative example of conversion of **1** to **2** or **3** and a possible intermediate **A**. (b) Representative unreactive substrates under the conditions shown in (a). The recovery of the starting material is shown in parentheses. (c) Representative ligands examined as an illustration

of the unique effectiveness of dppbz. The yield of phenylated product **3** and the recovery of **1** are shown.

The NH-Q directing group and the dppbz ligand were found to be uniquely effective for the reaction (Figure 1). For instance, a 2-methyl group on the quinoline entirely stops the reaction, and a 2-picoline analogue and a simple *N*-phenylcarboxamide did not take part in the reaction at all (Figure 1b). The *N*-methylated derivative of **4** did not react at all (Figure 1b). The importance of the ligand is illustrated in Figure 1c. The reaction did not proceed at all in the absence of a ligand. A bidentate ligand, dppe, which is similar to dppbz except for its slightly larger bite angle and a more flexible backbone gave the product in 9% yield. Other bidentate phosphine ligands with larger bite angles and various degrees of flexibility were entirely inefficient. Bipyridine-type ligands that are the ligand of choice for iron-catalyzed C(sp^2)–H bond activation[13] were ineffective, and monophosphine ligands such as PPh_3 were also ineffective. Such high sensitivity to the ligand structure is less consistent with either a pure radical mechanism or sole inclusion of organozinc species than with a chelated iron intermediate[16,17] such as **A**.

As we found for the structures of the directing group and the ligand, the reaction is sensitive also to the structure of the substrate, as summarized in Table 1, at the bottom of which unreactive substrates are listed. Carboxamides possessing 3-phenyl and 3-naphthyl-2,2-dimethylpropionamide reacted exclusively on one of the two methyl groups (entries 1–6) with retention of fluorine, chlorine, and bromine groups. Pivalamide **4** (entry 7) gave a mixture of monoarylated and diarylated products (**1** and **3**), and no further arylation of **3** occurred. Replacement of one methyl group in the pivalamide with an ethyl group (entry 8) resulted in selective monoarylation, but replacement with a phenyl group shut off the reaction (bottom of Table 1). A cyclohexanecarboxamide (**5**, entry 9) and cyclopentanecarboxamide (**6**, entry 10) reacted well, whereas the corresponding cyclobutane- and cyclopropanecarboxamide (**7** and **8**) did not give the desired product at all. One key feature that one might consider to be crucial for the efficient C–H activation may be the <CH_3–C–C(=O) bond angle (θ) shown below (Figure 2): this angle is much wider for the unreactive substrates **7** and **8** than for **5** and **6**, making the distance between the β-H and amide nitrogen (l) longer, and thus the formation of a chelate intermediate **A** less feasible. However, a smaller θ angle may not be sufficient, because most of the reactive substrates such as **1**, **4**, and unreactive substrates including **2**, **3**, and propionamide (bottom) have a θ angle of ca. 107–109° (data not shown). We note that cyclopropanecarboxamide **8** was completely recovered and a ring-opened product was not produced at all. Cyclohexanecarboxamides not possessing the α-methyl group did not give the desired product, as shown at the bottom of the table.

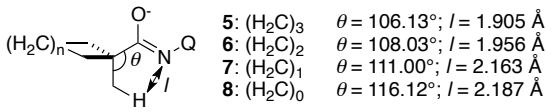
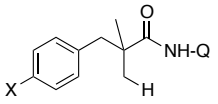
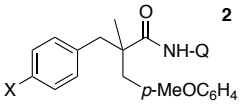
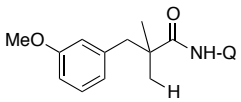
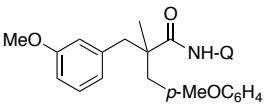
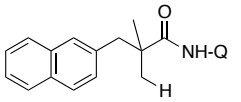
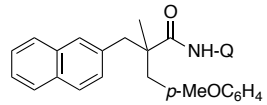
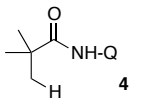
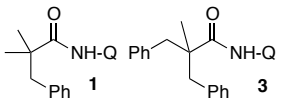
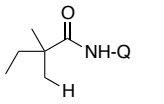
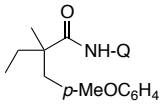
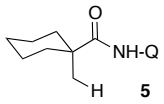
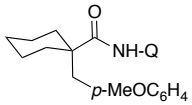
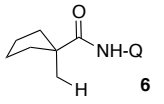
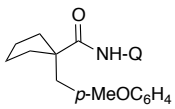
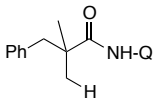
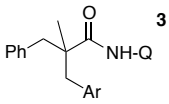
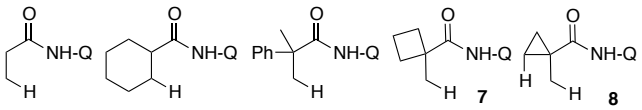


Figure 2. Bond angle and atomic distance for cycloalkylcarboxamides 5–8. MMFF-optimized with H–C–C–C=N fixed in the plane.

Para-substituted arylzinc reagents (entries 12, 13, 16, and 18) reacted well, and meta-substitution (entries 14 and 17) resulted in satisfactory yields, while ortho-substitution totally shut off the reaction (entry 15). Electron-deficient organometallic reagents (entries 16 and 17) tend to give lower yield than electron-rich reagents (entries 12, 13, and 18). A 2-naphthylzinc reagent also gave a satisfactory yield (entry 19). Alkyl- and alkenylzinc reagents did not react under these reaction conditions.

Table 1. Iron-Catalyzed Arylation of 2,2-Disubstituted Propionamide with Organozinc Reagent[a]

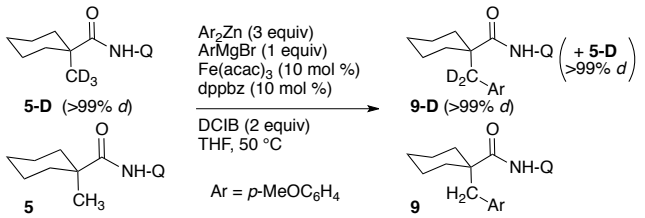
entry	substrate[b]	product[b]		yield (%)[c]
1			**2** X = H	79
2			X = F	74
3			X = Cl	71
4			X = Br	73
5				71
6				83
7			**4** **1** **3**	28+20[d] (33+31)[e]
8				53
9			**5**	75
10			**6**	69
11			**3** Ar = Ph	80
12			Ar = *p*-Tol	78
13			Ar = *p*-*t*-BuC_6H_4	85
14			Ar = *m*-Tol	78
15			Ar = *o*-Tol	0
16			Ar = *p*-FC_6H_4	56
17			Ar = *m*-FC_6H_4	51
18			Ar = *p*-$Me_2NC_6H_4$	80
19			Ar = 2-Naphthyl	69
			**7** **8**	

[a]The reaction was performed under the conditions in Figure 1a using 0.5 mmol of substrate. Unreactive substrates (<5% yield) are shown at the bottom. [b]Q = 8-quinolinyl. [c]Determined by isolation. [d]Determined by GC in the presence of tridecane as an internal standard. [e]20 mol % of catalyst was used.

Kinetic isotope effect (KIE) experiments indicated that the cleavage of the C–H bond is the rate-determining step of the reaction. As depicted in Scheme 1, competition experiments between the deuterated substrate **5-D** and the protio **5** showed a primary KIE of 2.4 when the reactions were performed in parallel, and an intermolecular KIE of 4.0 (at 19% conversion). The

organometallic reagent takes up the β-hydrogen, as demonstrated by partial deuterium incorporation into the recovered organometallic reagent for the reaction of **5-D** (SI). Deuterium scrambling on the product **9-D** or on the recovered **5-D** was not observed.

Scheme 1. KIE Experiments



KIE determined from two parallel reactions: 2.4 ± 0.3 (at 50.0 ± 1.5) °C
KIE determined from an intermolecular competition: 4.0 (19% conversion)

In conclusion, we have found the reaction conditions for replacing a C(sp^3)–H bond with a new C–aryl bond at the β-position of a 2,2-disubstituted carboxamide, where the quinolineamide group acts as a uniquely effective directing group for iron. The overwhelmingly higher reactivity of a methyl group over a benzylic group excludes a radical mechanism, and the high sensitivity of the yield to the structure of the substrate and the ligand suggests involvement of organoiron intermediates in some crucial steps. Further understanding of the reaction parameters in the present reaction will uncover guidelines for designing efficient iron catalysts.

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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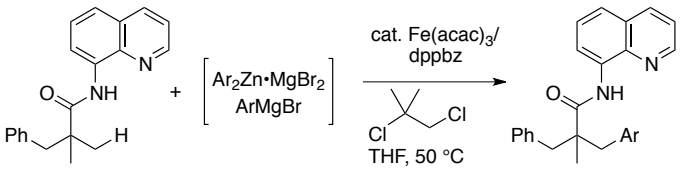

1.22 g

Ar = *p*-$MeOC_6H_4$

1.40 g (85%)