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

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Supporting Information

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] as the reaction is sensitive to the choice of the ligand and shows a complete preference for 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 tetrahydrofuran (THF) solution of freshly prepared ArMgBr (Ar = *p*-anisyl) (7 equiv) and $ZnBr_2$·TMEDA (3 equiv). 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 workup followed by column chromatography gave 1.40 g (85% yield) of arylated product **2** (Figure 1a) together with the recovery of **1**. Out of the 7 equiv of ArMgBr, 6 equiv forms 3 equiv of Ar_2Zn and 1 equiv deprotonates the amide proton. A small amount of the Ar group must have been consumed upon

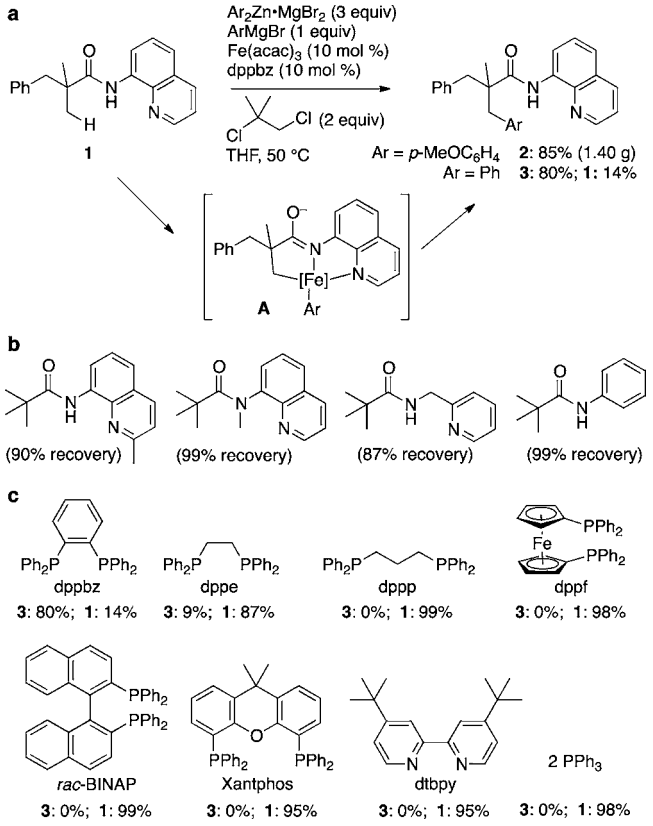

Figure 1. Iron-catalyzed arylation of the β-methyl group of 2,2-disubstituted propionamides. (a) Representative example of the conversion of **1** to **2** or **3** and a possible intermediate **A**. (b) Representative unreactive substrates under the conditions shown in (a). The recovery of the starting 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.

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 amounts of the zinc reagent and the catalyst and using a longer reaction time did not result in higher conversion. Addition of a catalytic amount of water or the use of old Grignard reagent significantly

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lowered the reaction yield, suggesting that the presence of alkoxide impedes the reaction.

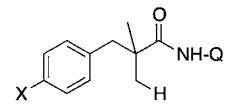
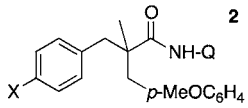
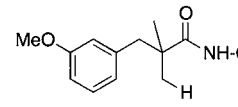
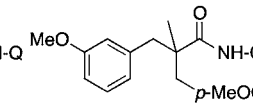
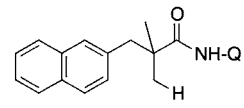
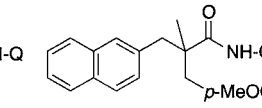
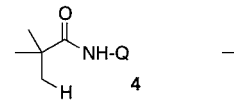
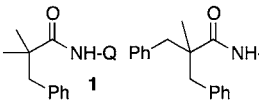
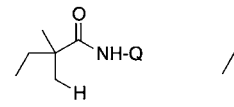
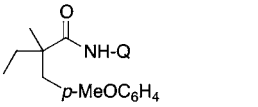
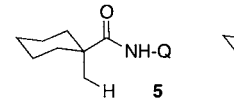
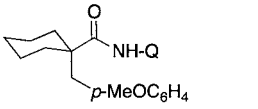
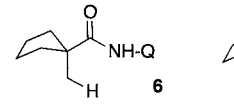
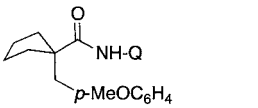
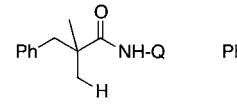
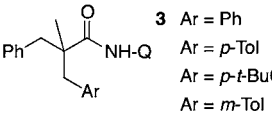
Under similar conditions, the reaction of phenylmagnesium bromide gave **3** in 80% yield together with recovered **1** (14%) and biaryl (15% based on PhMgBr) resulting from iron-mediated homocoupling.[14] Interestingly, most of the biaryl was formed after the product formation stopped. We found no products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

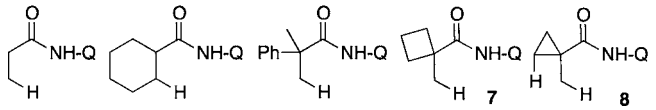
The NH-Q directing group and the dppbz ligand were found to be uniquely effective for the reaction (Figure 1). For instance, a 2-methyl group on the quinoline entirely stopped the reaction, and a 2-picoline analogue and a simple *N*-phenylcarboxamide did not take part in the reaction at all (Figure 1b). 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. The bidentate ligand 1,2-bis(diphenylphosphino)-ethane (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 was also sensitive to the structure of the substrate, as summarized in Table 1, at the bottom of which unreactive substrates are listed. Carboxamides possessing 3-aryl- 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). Cyclohexanecarboxamide **5** (entry 9) and cyclopentanecarboxamide **6** (entry 10) reacted well, whereas the corresponding cyclobutane- and cyclopropanecarboxamides **7** and **8** did not give the desired product at all. One key feature that might be considered crucial for efficient C−H activation may be the CH_3−C−C(=O) bond angle (θ in 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 may not be sufficient, as most of the reactive substrates such as **1** and **4** as well as unreactive substrates including **2**, **3**, and propionamide (Table 1 bottom) have $\theta \approx 107-109°$ (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 Table 1.

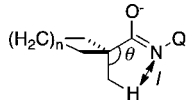
Para-substituted arylzinc reagents (Table 1, entries 12, 13, 16, and 18) reacted well, and meta substitution (entries 14 and 17) resulted in satisfactory yields, while ortho substitution totally

Table 1. Iron-Catalyzed Arylation of 2,2-Disubstituted Propionamides 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				28+20[d] (33+31)[e]
8				53
9				75
10				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



[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 % catalyst was used.



5: $(H_2C)_3$ θ = 106.13°; l = 1.905 Å
6: $(H_2C)_2$ θ = 108.03°; l = 1.956 Å
7: $(H_2C)_1$ θ = 111.00°; l = 2.163 Å
8: $(H_2C)_0$ θ = 116.12°; l = 2.187 Å

Figure 2. Bond angles θ and β-H−N distances (l) for cycloalkylcarboxamides **5**−**8** (MMFF-optimized with H−C−C−C=N fixed in the plane).

shut off the reaction (entry 15). Electron-deficient organometallic reagents (entries 16 and 17) tended to give lower yields than electron-rich reagents (entries 12, 13, and 18). A 2-

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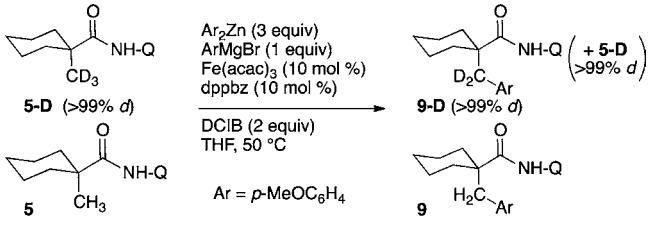
naphthylzinc reagent also gave a satisfactory yield (entry 19). Alkyl- and alkenylzinc reagents did not react under these reaction conditions.

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

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)

between **5** and the deuterated substrate **5-D** 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** (see the Supporting Information). Deuterium scrambling in the product **9-D** or the recovered **5-D** was not observed.

In conclusion, we have found 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 quinolinamide 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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Notes

The authors declare no competing financial interest.

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