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Iron-Catalyzed C−C Bond Formation at α-Position of Aliphatic Amines via C−H Bond Activation through 1,5-Hydrogen Transfer

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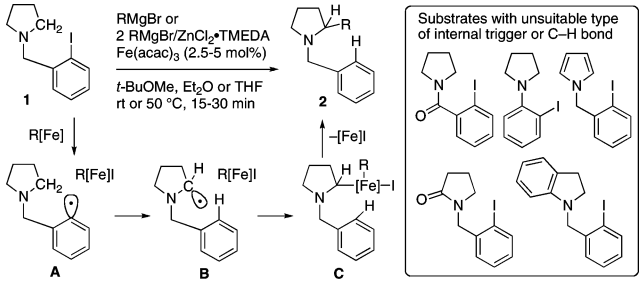
C−C bond-formation reactions that take place through organoiron species are hot topics in catalysis research.[1] During our research in this field,[2] we sometimes observed typical radical-like reactions[2c,d] and examined whether we can strategically exploit this behavior for C−H bond activation on an sp^3 carbon center.[3] We report herein an iron-catalyzed C(sp^3)−H bond activation reaction of an aliphatic amine **1** bearing an *N*-(2-iodophenyl)methyl group (hereinafter *N*-IBn; Scheme 1) with an RM reagent (R = aryl, alkenyl, alkyl; M = MgX, Zn(II)), which produces an α-substituted product **2**. The reaction involves the conversion of an intermediate such as **A** into **B** through 1,5-hydrogen transfer,[4] followed by C(sp^3)−C(sp^2) bond formation through a putative organoiron intermediate **C** to form **2**. α-Branched amines are ubiquitous motifs in biologically active compounds, and the present synthesis is unique among the known syntheses[5] for its ability to couple directly a Grignard or zinc reagent and an unactivated aliphatic amine of considerable variety.[6]

Scheme 1



This work was guided by the unexpected finding that the reaction of Ph_2Zn and 4-iodotoluene in THF in the presence of an iron-bipyridine catalyst[2e−g] principally gives 2-phenyltetrahydrofuran rather than a biaryl coupling product (eq 1).[7] Interestingly, only the phenyl group in Ph_2Zn, but not the 4-tolyl group in the iodide, was introduced to THF. We assume that the reaction involved reductive generation of an aryl radical from the iodoarene,[8] hydrogen abstraction by the aryl radical from the 2-position of THF, and coupling of the 2-tetrahydrofuranyl radical and a phenyl anion. With this conjecture and the radical chemistry literature[4] in mind, we envisioned that the *N*-IBn group in **1** would serve as an internal trigger for the cleavage of the C−H bond next to the amine group; hence, a phenyl anion and **1** can be coupled directly at the sp^3 carbon atom.

To test this idea, we examined a variety of pyrrolidine derivatives (Scheme 1) to find that the reaction of **1** with PhMgBr or Ph_2Zn (1.2−2 equiv) in the presence of 2.5 mol % Fe(acac)$_3$ gives the desired arylated product in ca. 80% yield (Table 1, entries 1, 2), which was accompanied by a small amount (10−15%) of the reduced starting material (i.e., *N*-Bn pyrrolidine). In no case could we find products resulting from arylation of the iodobenzyl group or reaction at the potentially reactive *N*-benzylic methylene position. The reaction performed on a 1-g scale also took place in over 80% isolated yield (entry 1). The bromo analogue of **1** also took part in the reaction but gave a lower yield (entry 5).

Iron sources such as $FeCl_3$ or $FeCl_2$ gave comparable results; however, in the absence of the iron catalyst, **1** was entirely recovered. The choice of the solvent was important: among Et_2O, *t*-BuOMe, and THF, THF was generally less suitable because it tends to undergo competitive arylation (eq 1). The reaction of other compounds shown on the right of Scheme 1 produced none of the desired arylation product but resulted mainly in the reduction of the iodide group.

While both Grignard and diarylzinc reagents reacted in high yield with **1**, the former reacted much faster (<15 min at rt in Et_2O vs 1 h at 50 °C in THF) and exhibited a wider scope (vide infra).[9] We observed acceleration of the Ph_2Zn reaction by a bidentate amine ligand such as bipyridine and bisoxazoline; however, attempts to achieve optical induction by the use of chiral amine ligands uniformly gave an enantiomeric excess of 0%, which suggests that the intermediate responsible for C−C bond formation such as **C** also has a radical character.[2c]

The present reaction is applicable to a variety of aliphatic amines other than pyrrolidine. Six- and seven-membered cyclic amines (entries 3, 4) as well as acyclic aliphatic amines (entries 6, 9) equally served as a good substrate. The phenylation of the asymmetric *N*-methyl-*N*-butylamine took place preferentially at the more substituted chain (entry 6), which corroborates our assumption of the radical character of the intermediates **A** and **B**. The reaction of an aniline substrate was sluggish, and the product was obtained in low yield together with unidentified byproducts (entry 7). 2-Phenylpiperidine underwent phenylation (40%) and reduction (24%), the former taking place predominantly at the 6-position to give 2,6-diphenylpiperidine with modest diastereoselectivity (entry 8).

The yield and the rate of the reaction were found to be rather insensitive to the substituent on the aryl Grignard reagent, as illustrated in entries 9−14. 3-Pyridyl Grignard (entry 15) and alkenyl Grignard (entries 16 and 17) reagents also gave the desired product. The reaction of hexylmagnesium bromide gave the α-alkylation product in a modest yield (entry 18) and also a large amount of dodecane due to oxidative dimerization of the hexyl Grignard reagent and a small amount of a product that can be considered to be the dimerization of a radical species such as **B**.

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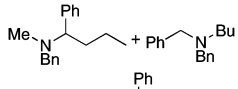
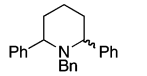
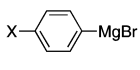
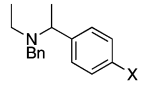
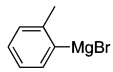
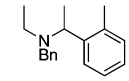
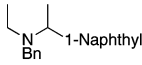
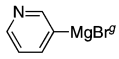
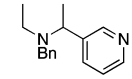
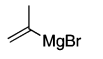
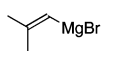
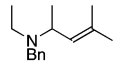
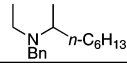
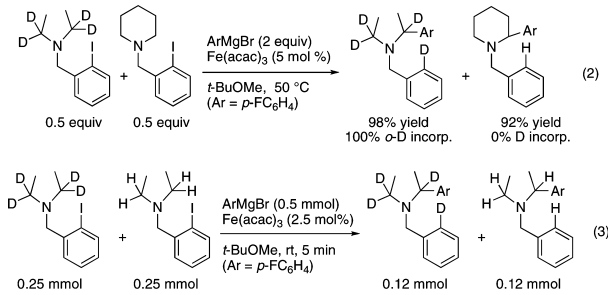
Table 1. Iron-Catalyzed α-Functionalization of Aliphatic Amines with Grignard and Diorganozinc Reagents[a]

entry	substrate[b]	Ar–Metal	product		yield (%)[c]
1		PhMgBr[d]		n = 1	84, 83[f]
2		Ph_2Zn[e]		n = 1	(81)
3		PhMgBr		n = 2	82
4		PhMgBr		n = 3	82
5		PhMgBr			(74)
6		PhMgBr			67 + 8
7		PhMgBr			(17)
8		PhMgBr			40 (*cis*:*trans* = 37:63)
9					91 (X = H)
10					91 (X = F)
11					88 (X = Cl)
12					90 (X = OMe)
13					88
14		1-NaphthylMgBr			79
15		 [g]			54
16					70
17[h]					69
18		n-$C_6H_{13}MgCl$			(47)

[a] Reaction conditions: Amine substrate, Grignard or diorganozinc reagent (1.2−2 equiv), and $Fe(acac)_3$ (2.5−5 mol %) in *t*-BuOMe at 50 °C for 15−30 min. [b] IBn = 2-iodobenzyl; BrBn = 2-bromobenzyl. [c] Isolated yield. The values in parentheses refer to the ^1H NMR yield. [d] Et_2O, rt. [e] THF, 1 h. [f] With 1 g of substrate. [g] Prepared from the corresponding bromide and *i*-PrMgCl and utilized as a benzene solution. [h] In benzene.

Deuterium-labeling experiments indicated that the crucial 1,5-hydrogen transfer takes place intramolecularly. Thus, the reaction of an equimolar mixture of the tetra-deuterated *N*,*N*-diethylamine and the piperidine substrates with *p*-fluorophenylmagnesium bromide resulted in quantitative arylation of both the substrates, where the deuterium atom was quantitatively incorporated at the *o*-position of the *N*-benzyl group of the former without any H/D crossover (eq 2). Competitive arylation of the tetradeuterated and nondeuterated diethylamine substrates gave a 1:1 mixture of the two products (eq 3), thus indicating that there is no intermolecular isotope effect and hence that the 1,5-hydrogen transfer step is not rate determining.

In conclusion, we have developed an iron-catalyzed C−C bond formation at the α-position of aliphatic amines with Grignard or



organozinc reagents. This reaction proceeds under simple and mild conditions in the presence of a catalytic amount of a ubiquitous iron salt. The observed reactivity and selectivity agree well with our conjecture that the iron intermediates shows the characteristics of both a carbon radical and d-block organometallics[10] and that the reaction takes place through intramolecular 1,5-hydrogen transfer followed by reductive elimination. This example suggests that synthetic strategies developed for free radical chemistry, such as radical translocations, will be useful for the development of iron-catalyzed synthetic reactions.[11]

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Supporting Information Available: 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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