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Iron-Catalyzed C(sp^2)–H Bond Functionalization with Organoboron Compounds

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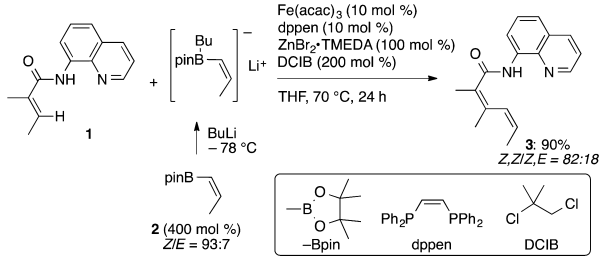
Supporting Information

ABSTRACT: We report here that an iron-catalyzed directed C–H functionalization reaction allows the coupling of a variety of aromatic, heteroaromatic, and olefinic substrates with alkenyl and aryl boron compounds under mild oxidative conditions. We rationalize these results by the involvement of an organoiron(III) reactive intermediate that is responsible for the C–H bond-activation process. A zinc salt is crucial to promote the transfer of the organic group from the boron atom to the iron(III) atom.

Functionalization of an intrinsically unreactive C–H bond has received wide attention for its synthetic efficiency and the production of potentially less waste than the classical substitution reactions.[1] C–H functionalization catalyzed by palladium[2] and other precious metals[3] has found widespread use for the coupling of a hydrocarbon bearing a directing group and a shelf-stable organoboron compound that is readily available and tolerant of a variety of functional groups. However, the use of precious metals to catalyze reactions is not without limitations; for instance, they are expensive, rather toxic, and unsuitable for alkenyl–alkenyl and alkenyl–arene couplings (cf. Scheme 1) where the diene and styrene products

Scheme 1. Iron(III)-Catalyzed Stereospecific Alkenyl–Alkenyl Coupling

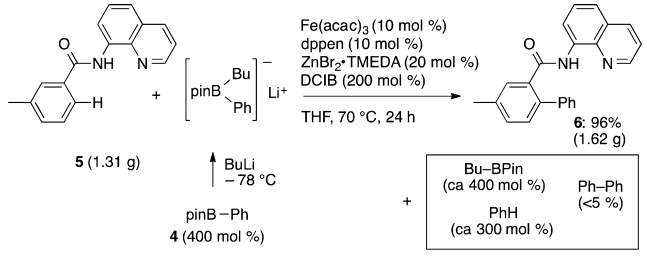


are prone to isomerize[3a] or to undergo further transformations.[2c] One probable reason for this limitation is the preferred interaction of the 4d and 5d orbitals in these metals with the π-bonds in the product. Hence, we conjectured that a transition metal with a minimum π-back-donation ability promotes C–H bond activation[4,5] over interaction with the π-bonds in the product. We report here that iron(III) catalysis[6,7] complements or surpasses precious metal catalysis for substrate scope and for advantages such as abundance in nature, low cost, and lack of toxicity.[8]

As illustrated for the synthesis of a (*Z*,*Z*)-diene **3** by coupling of the (*E*)-*N*-(quinolin-8-yl)tiglamide **1** and *Z*-alkenylboronic acid pinacol ester **2** (Scheme 1), the reaction utilizes BuLi for the conversion of **2** to the corresponding borate at low temperature, a catalytic amount of Fe(acac)$_3$ and a zinc halide, a bidentate diphosphine ligand ((*Z*)-1,2-bis(diphenylphosphino)ethene: dppen), and 1,2-dichloroisobutane (DCIB), which keeps the reaction conditions mildly oxidative.[9] Compound **2** is first activated with BuLi,[10] followed by in situ boron-to-iron transmetalation catalyzed by the zinc halide.[11,12] The reaction of BuLi with the Lewis acidic boron atom is rapid enough to allow the use of a variety of functionalized boronates for this coupling reaction (e.g., halides and silyl ether, see below). This procedure allows selective formation of organoiron(III) intermediates without formation of a reduced iron species[13] that has been an inevitable side reaction when more electron-rich organomagnesium or zinc reagents were used as the source of the R group.[9]

We studied the reaction conditions for the reaction of benzamide **5** and Ph–Bpin (**4**) (Scheme 2): the borate was

Scheme 2. Iron(III)-Catalyzed Aryl–Aryl Coupling



prepared from **4** (20 mmol) and BuLi (slightly less than 20 mmol) at −78 °C, and then at room temperature a solution of Fe(acac)$_3$ (0.5 mmol), dppen (0.5 mmol), ZnBr$_2$·TMEDA (1.0 mmol), and **5** (1.31 g, 5.0 mmol) in THF was added. DCIB (10 mmol) was added and the reaction mixture was stirred at 70 °C for 24 h to obtain an *ortho*-phenylated amide **6** in 96% yield (1.62 g) after purification by column chromatography on silica gel. Careful exclusion of moisture was needed to ensure reproducibility. We note that 2 equiv of R are consumed for removal of two hydrogen atoms from the substrate, and 1 equiv was consumed for delivery of a phenyl group. This procedure is applicable with little modification to the coupling of alkenyl, aryl, and heteroaryl compounds bearing the quinolylamide or

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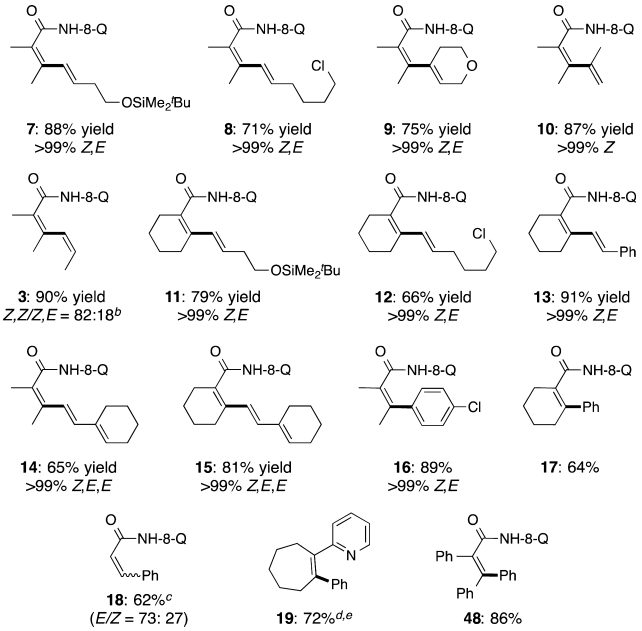
pyridine group, with alkenyl and aryl boron compounds (Tables 1 and 2).

Table 1. Products of the Iron-Catalyzed Reaction of Alkene Carboxamides and Alkenylpyridine with Alkenyl and Aryl Boronates[a]



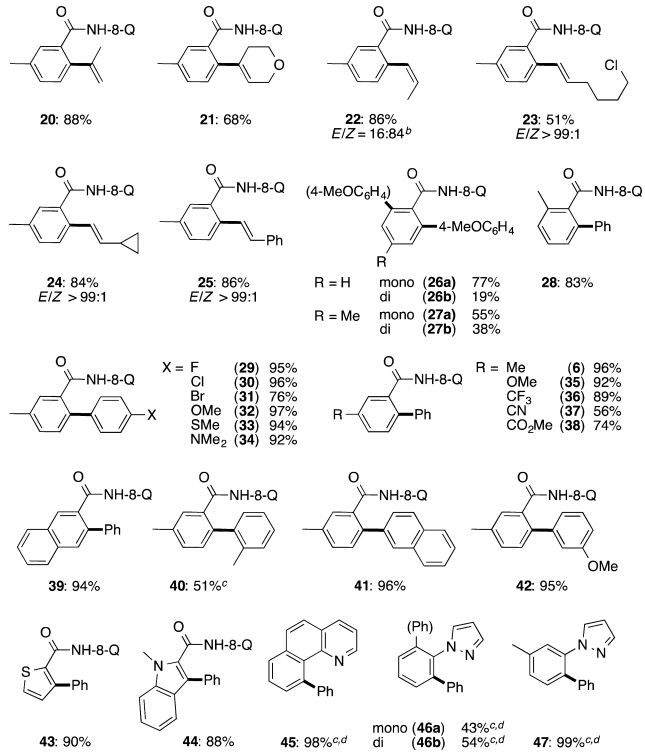
[a]The reaction was performed on a 0.4 mmol scale, following the procedure described in the text. The yield is based on a pure isolated product. 8-Q = 8-quinolyl. See the Supporting Information for details. [b]The stereochemical purity of the starting organoboron was E/Z = 7:93. [c]At 50 °C. [d]Using *sec*-BuLi as a base. [e]At 30 °C.

As illustrated in Table 1, the use of organoborate reagents allowed the *syn*-selective C−H functionalization of olefins bearing an 8-quinolylamide (NH-8-Q) or pyridine group, which can be carried out with tolerance of diene, triene, ether, silylether, and chloride groups. The stereochemistry of *E*-boronates was entirely retained, while that of (*Z*)-1-propenylboronate **2** (*E*/*Z* = 7:93) was retained to an extent of 80−90%, as illustrated by the synthesis of (*Z*,*Z*)-2,3-dimethylhexa-2,4-dienoic acid amide **3** with 100% selectivity for the 2*Z* bond and 82% selectivity for the 3*Z* bond (88% retention). (*Z*,*E*,*E*)-Trienes **14** and **15** were similarly prepared in good yield with 100% retention of the *E*-geometry in the dienylboronate. Alkenylamides were also arylated with arylboronates (e.g., **16**, **17**, and **48**). While tiglamide **1** gave the product **16** with 100% *Z* selectivity, an acrylic acid amide gave cinnamic acid amide **18** with only 27% *Z*-selectivity because of the in situ isomerization of the initial *Z*-product.[9c] Methacrylic acid amide gave only a trace amount of the corresponding alkenylated or arylated product.

Table 2 summarizes the reactions of aryl and heteroaryl substrates with aryl and alkenyl boronate esters. The top of the table shows the stereoselective synthesis of styrene derivatives, including the synthesis of (*Z*)-1-propenyl product **22** from **2** (84% *Z* from 93% *Z*-boronate) as well as a *trans*-stilbene product **25** (starting from 100% (*E*)-styrene boronate) and a 2-propenylated product **20**. We did not observe any ring-opening side reactions in the synthesis of vinylcyclopropane product **24**.

When unsubstituted or *para*-substituted benzamides were used as a substrate, mono- and diarylation occurred to give

Table 2. Products of the Iron-Catalyzed Reaction of Arene and Heteroarene Carboxamides, Arylpyridine, and Arylpyrazoles with Alkenyl and Aryl Boronates[a]



[a]The reactions were performed under the same reaction conditions as those used in Table 1. The yield is based on a pure isolated product. See the Supporting Information for details. [b]The stereochemical purity of the starting organoboron was E/Z = 7:93. [c]Using *sec*-BuLi as a base. [d]At 30 °C.

26a,b and **27a,b**, respectively. A *meta*-substituent in the benzamide shut off the arylation in the nearby *ortho*-position, which resulted in the exclusive formation of monoarylated products **6**, **29**−**42**. *Ortho*-steric hindrance in the aryl boronate partner was tolerated as illustrated for *ortho*-tolyl boronate, which gave **40** in 51% yield.

Functional group tolerance is an asset of the boron reagents. For instance, aryl fluoride (**29**), chloride (**30**), bromide (**31**), sulfide (**33**), amine (**34**), nitrile (**37**), and ester (**38**) are well tolerated, demonstrating the synthetic advantage over less selective organozinc or -magnesium reagents.[9] Ester- and nitro-groups on the boron reagent were not tolerated. Heteroatom-containing thiophene and indole also served as good substrates to give amides **43** and **44** in ca. 90% yield.

We can couple Ph−Bpin with arene and alkene substrates bearing a pyridine- or a pyrazole-directing group in good to excellent yield (Table 1, compound **19**; Table 2, compounds **45**−**47**). However, these substrates are prone to give a larger amount of the biphenyl side product, which suggests that anionic chelation by the quinolylamide anion[14] provides a uniquely effective coordination environment for the iron(III) catalysis. The biphenyl formation was suppressed to a synthetically viable level by carrying out the reaction at 30 °C instead of the standard temperature of 70 °C.

We obtained several pieces of information on the mechanism of the iron catalysis, including the key finding that a stoichiometric organoiron(III) without added DCIB is effective for C−H functionalization (eq 1 and Table 3). Thus, the

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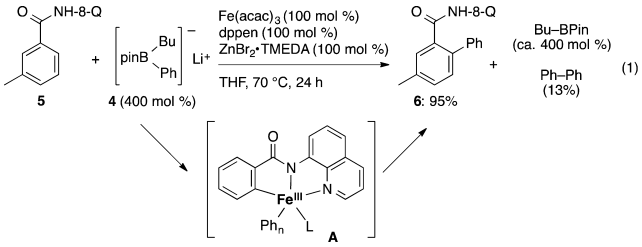
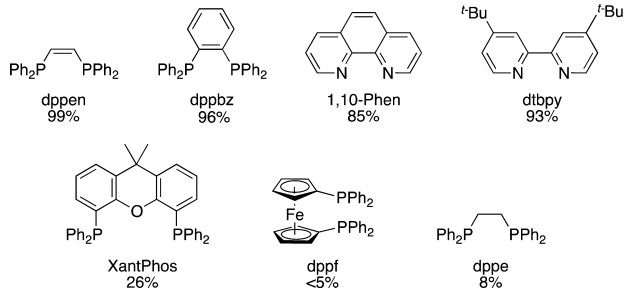


reaction of **5** with 4 equiv of Ph−Bpin **4**/BuLi using a stoichiometric or catalytic amount of iron(III) (entries 1, 5, and 6) produces the phenylated product **6** in nearly quantitative yield and only a small amount of biphenyl (13%). These results indicate that a phenyliron(III) intermediate effectively participates in the C−H cleavage and C−C bond formation through a metallacycle such as **A** (eq 1), rather than being consumed by oxidation of the phenyl ligand. The use of 3 equiv of R−Bpin/BuLi resulted in a much lower yield, which suggests that the presence of two R groups on the iron(III) atom is necessary (entry 2). The dppen ligand is necessary for the reaction (entries 3 and 10). An iron(II) catalyst is much inferior to iron(III) under both stoichiometric (38% yield, entry 4) and catalytic conditions (0% yield, entry 9). The added zinc(II) salt is absolutely necessary,[11,12] but a catalytic amount suffices (entries 5−7), and so is the iron(III) catalyst (entry 8).

The list of effective ligands (Table 4 top) as opposed to those that are ineffective (Table 4 bottom) seems rather unusual in comparison with the ligand preference in a related precious metal catalyzed C−H functionalization.[2,3] Because the product was obtained in 27% yield in the absence of dppen (entry 10, Table 3), we see that electron-donating ligands such as dppe and dppf inhibit the reaction, while electron-accepting ligands for metal-to-ligand electron transfer (MLCT), of which 1,10-Phen is a typical example, promote the reaction. This trend apparently contradicts the role of an iron(III) intermediate in the C−H bond-activation step and, hence, suggests that the ligand facilitates the process involving an iron(I) intermediate that is formed by the C−C bond-forming reductive elimination of the initial iron(III) intermediate. There is a recent report on the involvement of an iron(I) intermediate in a related reaction that undergoes oxidative addition to R−X to form an iron(III) species.[15] Given the intrinsic instability of iron(I) species, we consider that the ligand stabilizes the iron(I) species through MLCT, for which there are ample examples in iron chemistry.[16] In the catalytic reaction, this iron(I) species is reoxidized by DCIB[9] to the iron(III) species.

Table 4. Effect of the Ligand on the Catalytic *Ortho*-phenylation of 5 with Ph−Bpin/BuLi



In summary, the C−H functionalization of a quinolinyl amide with an R−BPin organoborate reagent in the presence of iron and zinc catalysts allows us to synthesize a wide variety of C−H functionalization products. The key discovery is a zinc-mediated transmetalation from boron to iron to form an organoiron(III) intermediate that undergoes C−H cleavage and C−C bond formation in preference to the oxidation of the R group. Overall, the reaction illustrates the synthetic significance of iron catalysis, which has been attracting growing attention in recent years.

■ 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.

Table 3. Effect of Several Key Parameters on the Stoichiometric and Catalytic *Ortho*-phenylation of 5 with Ph−Bpin/BuLi[a]

entry	Fe source (mol %)	Zn(II) (mol %)	DCIB (mol %)	dppen (mol %)	6[b] (%)	5[b] (%)	Ph_2[c] (%)
1	Fe(III), 100	$ZnBr_2$·L, 100	0	100	95	0	13
2[d]	Fe(III), 100	$ZnBr_2$·L, 100	0	100	58[c]	36[c]	14
3	Fe(III), 100	$ZnBr_2$, 100	0	0	0	91[e]	44
4[d]	Fe(II), 100	$ZnBr_2$·L, 100	0	100	38[c]	56[c]	7
5	Fe(III), 10	$ZnBr_2$·L, 20	200	10	96	0	<5
6	Fe(III), 10	$ZnBr_2$·L, 100	200	10	99	0	0
7	Fe(III), 10	none	200	10	0	96	0
8	none	$ZnBr_2$·L, 100	200	10	0	98	0
9	Fe(II), 10	$ZnBr_2$·L, 50	200	10	0	64[c]	<5
10	Fe(III), 10	$ZnBr_2$·L, 100	200	0	27	72	6
11	Fe(III), 10	$ZnBr_2$·L, 100	0	10	13	84	0

[a]Fe(II) = $Fe(acac)_2$; Fe(III) = $Fe(acac)_3$; L = TMEDA. [b]Yield determined by NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c]Yield determined by GC using tridecane as an internal standard. [d]With 300 mol % Ph−Bpin/BuLi; the reaction produced ca. 300 mol % Bu−Bpin (GC). [e]Upon quenching with D_2O, no D was incorporated into the *ortho* site of **5** (GC−MS).

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