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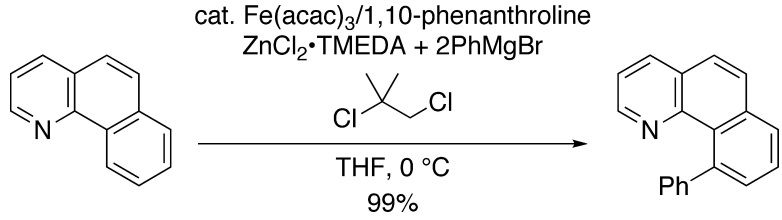


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# Iron-Catalyzed Direct Arylation through Directed C−H Bond Activation

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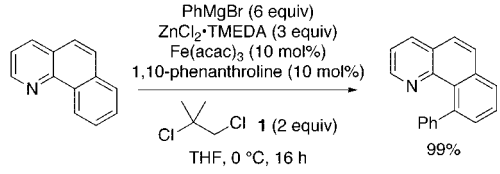
Iron has long been used in organic synthesis as a catalyst for oxidation and Friedel−Crafts reactions, and until recently, its use in homogeneous catalysis has attracted much less attention.[1] We have focused for some time on iron-catalyzed reactions of main-group organometallics and have reported on asymmetric olefin carbozincation[2] and cross-coupling reactions.[3,4] Herein, we report on the cross-coupling of an arylzinc reagent and 2-arylpyridine and its congeners. This reaction represents a rare example of a synthetically viable iron-catalyzed C−C bond formation by way of a C−H bond activation.[5,6]



(1)

The phenylation of α-benzoquinoline with a phenylzinc reagent shown in eq 1 is a representative reaction. A THF mixed solution of phenylmagnesium bromide and $ZnCl_2$•TMEDA (where TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, half-equiv to the Grignard reagent) was allowed to react with α-benzoquinoline (0.4 mmol) at 0 °C in the presence of $Fe(acac)_3$ (10 mol %), 1,10-phenanthroline (phen, 10 mol %), and 1,2-dichloro-2-methylpropane (**1**). After stirring for a period of 16 h, the reaction afforded the phenylated product in a yield of 99% (98% on a 1 g scale).

We carried out extensive investigations to define the best reaction conditions, and Table 1 lists representative data obtained for the phenylation of 2-phenylpyridine **2**. The reaction afforded a monophenylated and a diphenylated product, **3** and **4**, respectively (Table 2, entry 1). The product **4** was derived from **3**, and the rate of this second phenylation was slower than that of the first reaction (vide infra). Although $FeCl_3$ itself (15 mol %) did not catalyze the phenylation reaction at all (entry 1), it showed some catalytic effect (15% yield of **3**, entry 2) in the presence of 2,2′-bipyridine (bpy, 15 mol %). When 1,2-dichloroethane (3 equiv) was present in the reaction, the catalytic turnover dramatically increased, which gave the products **3** and **4** in yields of 53 and 2%, respectively (entry 3).[7] Examination of a variety of dihalide compounds showed that **1** was the most effective additive and effected a near quantitative conversion of **2** to the phenylated product in a period of 24 h (82% for **3** and 9% for **4**, entry 4). There was no sign of the formation of metallic zinc or iron, and the dihalide was converted to the corresponding olefin (see Supporting Information).[8]

Further screening indicated that the reaction took place much faster when 1,10-phenanthroline (phen) was used in place of bpy (entries 5 and 6). The $FeCl_3$/phen/**1** catalytic system achieved a quantitative conversion of **2** with less catalyst (10 mol %) after a period of 9 h. In contrast to bpy and phen, sterically congested neocuproine and tridentate terpyridine were entirely ineffective (entries 7 and 8). The oxidation state and the counteranion of the iron salt had only a minor effect on the catalytic activity. Thus, $FeCl_2$ and $Fe(acac)_3$ showed almost the same catalytic performance as $FeCl_3$ did (entries 9 and 10). Due to the convenience in handling, $Fe(acac)_3$ was the catalyst of choice. Finally, we note that TMEDA was also an indispensable additive, without which the reaction gave the desired product in a much lower yield (entry 11). Neither of the $Ph_2Zn$ reagents prepared from phenyllithium, Mg-free $Ph_2Zn$ and PhZnBr, afforded the phenylated product either in the absence or in the presence of TMEDA. Attempts to speed up the reaction at an elevated temperature resulted in a reduction in the product yield.

***Table 1.*** Screening Conditions for the Iron-Catalyzed Reaction of 2-Phenylpyridine (**2**) with Phenylzinc Reagent[a]

| | | | | yield/%[b] | |
|---|---|---|---|---|---|
| entry | catalyst (mol %) | additive (equiv) | time (h) | **3** | **4** |
| 1 | $FeCl_3$ (15) | none | 36 | 0 | 0 |
| 2 | $FeCl_3$/bpy (15) | none | 36 | 15 | 0 |
| 3 | $FeCl_3$/bpy (15) | $Cl(CH_2)_2Cl$ (3) | 72 | 53 | 2 |
| 4 | $FeCl_3$/bpy (15) | **1** (3) | 24 | 82 | 9 |
| 5 | $FeCl_3$/bpy (10) | **1** (2) | 9 | 53 | 2 |
| 6 | $FeCl_3$/phen (10) | **1** (2) | 9 | 79 | 16 |
| 7 | $FeCl_3$/neocuproine (10) | **1** (2) | 24 | 0 | 0 |
| 8 | $FeCl_3$/terpy (10) | **1** (2) | 24 | 0 | 0 |
| 9 | $FeCl_2$/phen (10) | **1** (2) | 9 | 81 | 16 |
| 10 | $Fe(acac)_3$/phen (10) | **1** (2) | 9 | 83 | 13 |
| 11[c] | $FeCl_3$/bpy (15) | **1** (3) | 24 | 15 | <1 |

[a] Unless otherwise noted, the reaction was carried out on a 0.4 mmol scale at 0 °C. The amount of phenylzinc reagent used was 5 equiv for entries 1−4 and 11 and 4 equiv for entries 5−10. [b] The yield was determined using GC, employing *n*-tridecane as an internal standard. [c] The same reaction as in entry 4, except that TMEDA was absent.

The reaction by default was found to require 2 equiv of $Ph_2Zn$ (PhZnBr was ineffective). Thus, 1 equiv is required for the desired arylation reaction, and 1 equiv is required to remove the hydrogen atom (as revealed by deuterium-labeling experiments; see Supporting Information). The biphenyl forming side reaction also consumes the reagent (up to ca. 50 mol % relative to phenylpyridine). To reduce the amount of the phenyl group attached to the zinc atom, we examined a zinc reagent prepared from equimolar amounts of $ZnCl_2$•TMEDA, PhMgBr, and $Me_3SiCH_2MgBr$ and other related reagents. However, these reagents at best effected only a modest conversion of the starting material (see Supporting Information).

Table 2 summarizes the scope of the iron-catalyzed arylation reaction. The 2-phenylpyridine derivatives bearing either an electron-donating or an electron-withdrawing substituent on the 4-position of the phenyl ring reacted smoothly to give the corresponding phenylated products in excellent yields (entries 1−4), while the reaction took place much faster when the phenyl group bore an electron-donating group (entry 2 versus entries 3 and 4). The 4-dimethylaminopyridine compound in entry 5 showed a reactivity that was comparable to that of the standard reference compound **2**.

The presence of a 3-methyl group on the phenyl ring of **2** (entries 6−11) allowed the phenylation to take place exclusively on the side opposite to the methyl group, probably due to steric hindrance. The rate of the reaction of a variety of arylzinc reagents indicated that the reaction was insensitive to the


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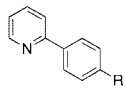
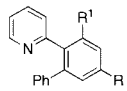
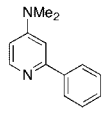
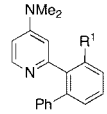
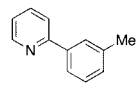
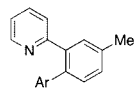
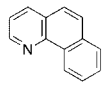
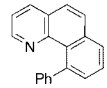
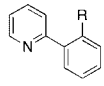
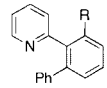
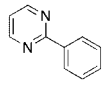
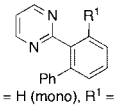
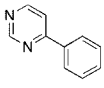
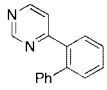
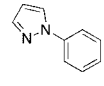
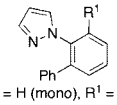
***Table 2.*** Iron-Catalyzed Arylation of 2-Arylpyridine Derivatives with Arylzinc Reagents[a]

| entry | substrate | Ar | product(s) | time (h) | yield (%)[b] mono + di |
|---|---|---|---|---|---|
| 1 |  | Ph |  | 15 | 82 + 12 (R = H) |
| 2 | | | | 6 | 65 + 21 (R = OMe) |
| 3 | | | | 48 | 80 + 20 (R = F) |
| 4 | **2** | | **3** ($R^1$ = H) **4** ($R^1$ = Ph) | 48 | 77 + 13 (R = $CO_2$Et) |
| 5 |  | Ph |  | 24 | 66 + 17 |
| | | | $R^1$ = H (mono), $R^1$ = Ph (di) | | |
| 6 |  | Ph |  | 16 | 89 |
| 7 | | 4-$FC_6H_4$ | | 36 | 78 |
| 8 | | 3-$FC_6H_4$ | | 36 | 82 |
| 9 | | 4-*t*Bu$C_6H_4$ | | 36 | 82 |
| 10 | | 4-MeO$C_6H_4$ | | 36 | 76 |
| 11 | | 2-Me$C_6H_4$ | | 36 | 0 |
| 12 |  | Ph |  | 16 | 99 (98)[c] |
| 13 |  | Ph |  | 48 | 60 (R = Ph) |
| 14 | | | | 48 | 17 (R = Me) |
| 15 |  | Ph |  | 48 | 81 + 9 |
| | | | $R^1$ = H (mono), $R^1$ = Ph (di) | | |
| 16[d] |  | Ph |  | 48 | 18 |
| 17[d] |  | Ph |  | 48 | 59 + 10 |
| | | | $R^1$ = H (mono), $R^1$ = Ph (di) | | |

[a] Unless otherwise noted, the reaction was carried out on a 0.4 mmol scale at 0 °C using 10 mol % of Fe(acac)$_3$/phen, 3 equiv of $ZnCl_2$•TMEDA, 6 equiv of arylmagnesium bromide, and 2 equiv of **1**. [b] Isolated yields of the monoarylated product and (if applicable) the diarylated product. [c] Carried out using 1 g of the substrate. [d] Carried out with 15 mol % of Fe(acac)$_3$/phen, 5 equiv of $ZnCl_2$•TMEDA, 10 equiv of PhMgBr, and 3 equiv of **1**.

electronic effect of the substitutent on the aryl group (entries 6−10), while it was very sensitive to any steric effects, as suggested by the extremely slow reaction of the 2-tolylzinc reagent (entry 11). Neither of zinc reagents prepared from MeMgBr or BuMgBr gave corresponding alkylated products.

Entries 12−14 show the reactions of the substrates having only one *ortho* C−H bond on the phenyl ring. The α-benzoquinoline example shown in entry 12 has already been discussed in eq 1. The 2-(biphenyl-2-yl)pyridine (**3**) in entry 13 is the monophenylated product obtained from **2** (entry 1). We found that the reaction was slower than that of **2** but still took place to give **4** in a yield of 60% after a period of 48 h (entry 13). The reaction of 2-*o*-tolylpyridine was very slow and gave the arylation product in a yield of only 15% (entry 14). We surmise that the restricted conformational possibility of these compounds is responsible for the low reactivity.

Nitrogen-containing heterocycles other than pyridine also undergo the present reaction. 2-Phenylpyrimidine reacted more slowly than the pyridine counterpart **2** did but still gave the corresponding mono- and diphenylated products in comparable yields (entry 15). The reaction was very slow for 4-phenylpyrimidine (entry 16). The reaction of 1-phenyl-1*H*-pyrazole was also slow but gave the desired product in a moderate yield (entry 17). The reaction of 1-phenyl-1*H*-1,2,3-triazole or 1-phenyl-1*H*-1,2,4-triazole gave only a trace amount of the desired product (data not shown). We consider it likely that the extra remote nitrogen groups cause a nonproductive coordination of the metal atom and, hence, interfere with the progress of the desired C−H activation reaction.

In summary, we have developed a new class of homogeneous iron catalysis: an iron-catalyzed C−C bond formation reaction that features C−H bond activation. The overall synthetic transformation formally represents the nucleophilic displacement of the *ortho*-hydrogen atom by an arylzinc nucleophile.[9] We consider it remarkable that the reaction took place at 0 °C since C−H bond activation reactions often require a reaction temperature above 80 °C.[6,9,10] This study shows that the combination of iron, zinc, magnesium, 1,10-phenanthroline, TMEDA, and 1,2-dichloro-2-methylpropane is important for the success of the reaction. We speculate that the phenanthroline coordinates to the iron and TMEDA to the zinc, and that the reaction involves a redox cycle of iron with the dichloride acting as an electron acceptor,[8] but so far, we have obtained no solid evidence that proactively supports such a conjecture. The mechanism and the synthetic scope of the reaction will be the next stage of our investigation.

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**Supporting Information Available:** Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Cross-coupling of 1,2-dichloroethane and the phenylzinc reagent also took place to give phenethyl chloride and 1,2-diphenylethane (ca. 50 and 30%, respectively). On the other hand, the dichloride **1** gave none of such products.
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