

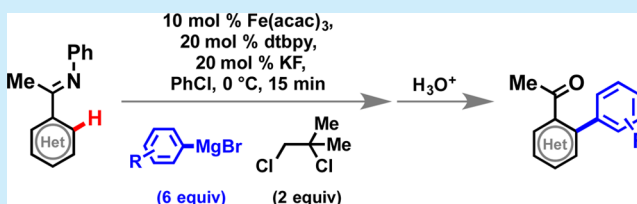
Iron-Catalyzed Arylation of Heterocycles via Directed C–H Bond Activation

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S Supporting Information

ABSTRACT: The iron-catalyzed arylation of aromatic heterocycles, such as pyridines, thiophenes, and furans, has been achieved. The use of an imine directing group allowed for the ortho functionalization of these heterocycles with complete conversion in 15 min at 0 °C. Yields up to 88% were observed in the synthesis of 15 heterocyclic biaryls.

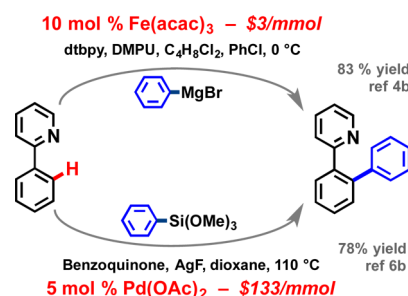


There is an increasing need in both the fine chemical and pharmaceutical industries for the development of new methods that easily provide substituted heterocycles. One of the methods that have been extensively explored for this function is the direct conversion of carbon–hydrogen (C–H) bonds into carbon–carbon (C–C) bonds.¹ This process is considered a “green” synthetic pathway because it eliminates the prefunctionalization steps required in modern coupling reactions and, therefore, directly reduces time, expenses, and hazardous waste. In fact, the ACS Green Chemistry Roundtable described C–H functionalizations of heterocycles as the most desirable new reactions that could benefit the pharmaceutical industry.^{2,3}

For decades, precious metals, namely palladium, have been the primary catalysts used for both traditional coupling and C–H arylation reactions.⁴ Iron catalysts, which are readily available, cheap, and nontoxic, have been relatively unexplored for coupling reactions. However, new methods are emerging that suggest an important role for this transition metal in modern organic synthesis.⁵ Notably, Nakamura has recently developed an iron-catalyzed C–H arylation reaction.⁶ Comparison of the metallic catalyst used in two similar methods for the direct C–H arylation of 2-phenylpyridine shows that the iron-catalyzed reaction proceeds at lower temperatures and is higher yielding and the catalyst is 22 times cheaper (Scheme 1).^{4b,6b,7} Though the utility of iron-catalyzed C–H arylation reactions is apparent, the scope of these potentially transformative reactions has yet to be expanded to include the arylation of highly desired heterocycles, and the mechanism is still not fully understood. Herein, we describe the ability to perform directed C–H arylations of heterocyclic substrates using cheap and nontoxic iron catalysts.

Our initial studies commenced with the pyridine substrate shown in Table 1. Nakamura's conditions that were previously shown in Scheme 1 were not optimal, producing only a 67% yield (entry 3). Also in contrast to Nakamura's work, the monoarylated product was exclusively obtained; the diarylated product was never observed for any of the reactions presented herein. Extended reaction times led to deterioration of the

Scheme 1. Comparison of C–H Arylation Methods



reaction's yield, possibly as a consequence of reduction of the imine; on a few occasions, the corresponding amine was isolated as a minor product.

Careful control of reaction conditions allowed for complete conversion in 15 min. Notable difficulty arose with regards to the drop rate of the Grignard reagent and the stir rate of the reaction.^{6b} It appears that the size of the reaction vessel can also dramatically alter yield. Dropwise Grignard addition into small, narrow vials provided almost no reaction, with exclusive homocoupling of the Grignard reagent resulting in biphenyl formation. This is likely caused by a combination of small surface area for substrate reactivity and inadequate stir rates. Larger flasks (e.g., 35–50 mL round-bottom flasks for a 0.55 mmol reaction), providing more surface area, and high stir rates proved to be the best choice (see Supporting Information for details.)

The reactions were very clean; the only compounds that could be observed by GCMS were the starting materials, the biaryl product and biphenyl, arising from homocoupling of the Grignard reagent. To minimize the aerobic iron-catalyzed homocoupling, an inert atmosphere and excess Grignard reagent were required.⁸ Additionally, we employed additives

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Table 1. Optimization of Pyridine Arylation

entry	catalyst (loading)	ligand ^a (loading)	additive	% conversion ^b
1	Fe(acac) ₃ (20 mol %)	dtbpy (20 mol %)	DMPU	73
2	Fe(acac) ₃ (10 mol %)	dtbpy (20 mol %)	DMPU	90
3	Fe(acac) ₃ (10 mol %)	dtbpy (10 mol %)	DMPU	67
4	Fe(acac) ₃ (5 mol %)	dtbpy (20 mol %)	DMPU	58
5	Fe(acac) ₃ (10 mol %)	bpy (20 mol %)	DMPU	15
6	Fe(acac) ₃ (10 mol %)	bphen (20 mol %)	DMPU	37
7	Fe(acac) ₃ (10 mol %)	dtbpy (20 mol %)	KF	100
8	Fe(acac) ₃ (10 mol %)	dtbpy (20 mol %)	none	100
9	FeF ₃ ·3H ₂ O (10 mol %)	dtbpy (20 mol %)	KF	18
10	FeCl ₃ (10 mol %)	dtbpy (20 mol %)	KF	76
11	Fe(acac) ₂ (10 mol %)	dtbpy (20 mol %)	KF	7

^adtbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl, bpy = 2,2'-bipyridine, bathophenanthroline. ^bAll reactions were performed on a 0.55 mmol substrate scale. Conversion was calculated by subtracting $A_{\text{starting material}}/A_{\text{product}}$ from 100%, where $A_{\text{starting material}}$ and A_{product} were calculated using the areas of the corresponding peaks in the gas chromatogram.

such as DMPU⁹ or KF¹⁰ which have been previously shown to minimize Grignard homocoupling.

The best conversion was achieved with a catalyst/ligand ratio of 1:2 (Table 1, entry 2). As shown by Nakamura, 4,4'-di-*tert*-butyl bipyridine (dtbpy) appeared to be the optimal ligand (entries 2, 5, and 6). Interestingly, the use of FeF₃·3H₂O showed 18% product formation, with no biphenyl present (entry 9); but the optimal catalyst was Fe(acac)₃ (entries 7 and 8), so this was used for subsequent experiments. We ultimately chose to perform the reactions in the presence of the KF additive (entry 7) due to a slight suppression of the biphenyl byproduct. Interestingly, an iron(II) catalyst was ineffective (entry 11). Future research efforts in our laboratory will be directed toward identifying the catalytic intermediates in this reaction, including the oxidation state of the iron in this process. Further screening of solvents and oxidants showed that our original choices, chlorobenzene and 1,2-dichloro-2-methylpropane, were optimal. When our optimized conditions were applied to the nonheterocyclic substrate derived from acetophenone, diarylated products were observed, as previously shown by Nakamura (not shown).⁶

A screen of directing groups was performed (Table 2). Use of the *para*-methoxyphenyl (PMP) directing group showed promising conversion (entry 3), but complete conversion was achieved using aniline derivatives (entry 1). Comparison of the imines derived from heterocyclic aldehydes and ketones (entries 1 and 4) showed drastic steric requirements for reaction conversion. Oxime ethers and alkyl imines completely inhibited the reaction (entries 2 and 5), possibly by strong coordination to the iron catalyst.

Our optimized reaction conditions were then applied to a variety of heterocyclic substrates (Table 3). In most cases, the imine group could be easily hydrolyzed to the ketone.¹¹ Several nitrogen-containing heterocyclic biaryls could only be isolated as imines (entries 1 and 3) because the hydrolysis of these compounds proved more difficult than expected, presumably due to protonation of the heterocycle's basic nitrogen. For reactions that did not reach complete conversion, the isolated yields were reduced considerably due to difficult chromatographic separations.

Table 2. Directing Group Optimization

entry	substrate	% conversion ^a	% yield ^b
1		>99 ^c	88
2		0	—
3		39	38
4		0	—
5		0	—

^aAll reactions were performed on a 0.55 mmol substrate scale. Conversion was calculated by subtracting $A_{\text{starting material}}/A_{\text{product}}$ from 100%, where $A_{\text{starting material}}$ and A_{product} were calculated using the areas of the corresponding peaks in the gas chromatogram. ^bIsolated yields obtained after flash chromatography. ^cTrace starting material detected by ¹H NMR but not by GC.

Table 3. Substrate Scope

entry	product	% conversion ^a	% yield ^b
1		>99	88 ^c
2		>99	34
3		>99	67 ^c
4		100	25
5		0	–
6		90	52
7		100	60
8		100	15
9		100	82
10		50	45 (91 ^d)
11		0	–

^aAll reactions performed on a 0.55 mmol scale. Conversion was calculated by subtracting $A_{\text{starting material}}/A_{\text{product}}$ from 100%, where $A_{\text{starting material}}$ and A_{product} were calculated using the areas of the corresponding peaks in the gas chromatogram. ^bYields obtained after hydrolysis of imine and purification by flash chromatography, unless otherwise noted. ^cIsolated as imine with trace starting material detected by ¹H NMR. ^dBased on recovered starting material.

The yields of the arylations were sterically dependent, and opposing trends were observed for pyridines, thiophenes, and furans. Comparison of sulfur-containing compounds shows that benzothiophene was less reactive than thiophene (entries 10 and 9), and 3-methyl thiophene (entry 11) was completely

Table 4. Grignard Reagent Scope

entry	product	% conversion ^a	% yield ^b
1		100	70
2		50	32
3		95	71
4		75	63

^aAll reactions performed on a 0.55 mmol scale. Conversion was calculated by subtracting $A_{\text{starting material}}/A_{\text{product}}$ from 100%, where $A_{\text{starting material}}$ and A_{product} were calculated using the areas of the corresponding peaks in the gas chromatogram. ^bYields obtained after hydrolysis of imine and purification by flash chromatography.

nonreactive, indicating a decrease in reactivity with increasing steric hindrance.

Analysis of the oxygen-containing heterocycles shows that conversions and yields increased with steric constraints (entries 6–8). Azole substrates appear to be more robust (entries 1–4). Notably, chlorinated pyridines can be readily substituted, allowing for subsequent functionalization (entry 3). A quinoline substrate was nonreactive (entry 5); however, this could be attributed to the aldehyde-derived directing group described in Table 2, entry 3.

As the thiophene substrate provided the highest yields, it was used to generate a brief Grignard scope (Table 4). Halogen-substituted aromatic Grignard reagents reduced the conversion and decreased the overall yield (entries 2 and 3). Electron-donating groups also appeared to slightly decrease the yield (entries 1 and 4). Methyl and cyclohexyl Grignard reagents afforded no reaction. The elucidation of the seemingly contradictory electronic and steric trends for this reaction will be the subject of future studies.

In summary, we have shown that iron-catalyzed arylation via C–H bond activation can be successfully carried out on a variety of N-, S-, and O-containing heterocycles at 0 °C, over 15 min. Future work will involve insight into the reaction mechanism to provide further understanding and reaction control.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures as well as characterization of previously unknown 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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