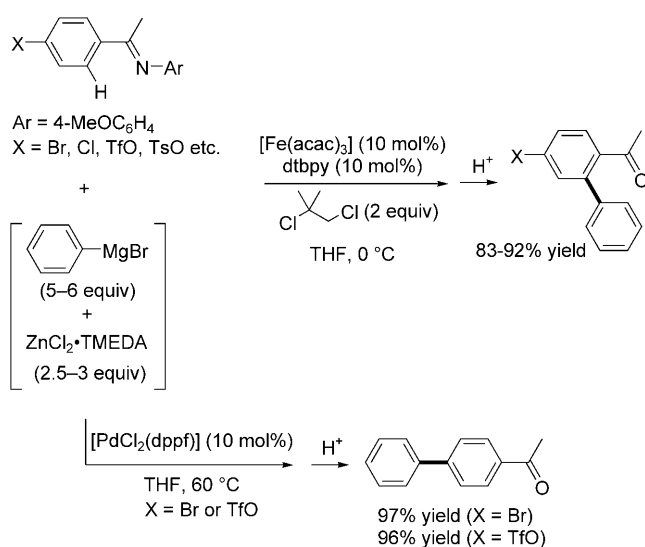


Cross-Coupling

Iron-Catalyzed Chemoselective *ortho* Arylation of Aryl Imines by Directed C–H Bond Activation**

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Iron is cheap, ubiquitous, nontoxic, and ideal for catalysis;^[1] however, the true interest of chemists resides in the unique d-orbital properties of iron that may give rise to unique catalytic activities.^[2] Having an interest in the latter subject as well as in the former,^[3] we reported on asymmetric carbometallation^[4] and on C–H bond activation reactions of pyridine derivatives.^[5] We report herein an iron-catalyzed coupling of an aromatic imine and a diarylzinc reagent which results in the direct displacement of the *ortho*-C–H bond of the imine by the aryl group of the zinc reagent, providing a convenient method for the synthesis of *ortho*-substituted aromatic ketones. A unique feature of this reaction is that the substitution of the *ortho*-hydrogen atom occurs preferentially to that of the electrofugal leaving groups on the same aryl ring. This feature is illustrated in Scheme 1, wherein the reaction of an imine and a Ph₂Zn reagent results in a hydrogen atom substitution under iron catalysis, and in



Scheme 1. Iron- or palladium-catalyzed reaction of a halogen (pseudo-halogen)-bearing aryl imine and a diphenylzinc reagent. Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

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bromine or triflate substitution under palladium catalysis. Control experiments indicated that 1,2-dichloroisobutane (DCIB) is essential to achieve the observed preference for the C–H bond activation in the iron catalysis.

Screening of the substrate and the catalytic system (Table 1) indicated that a combination of 10 mol% of [Fe(acac)₃] (acac = acetylacetonate) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) used together with the mild oxidant, DCIB (2 equiv), and a Ph₂Zn reagent [prepared from 6 equiv of phenylmagnesium bromide and 3 equiv of ZnCl₂·TMEDA (TMEDA = *N,N,N',N'*-tetramethylethylenediamine)] converts effectively an acetophenone-derived imine (e.g., 4-methoxy-*N*-(1-phenylethylidene)aniline) into the corresponding *ortho*-phenylated product. The stoichiometry of the reaction is such that one equivalent of the Ph₂Zn reagent serves to remove the *ortho*-hydrogen atom, another equivalent to introduce the product, and a small amount to generate a low-valent reactive iron catalyst.^[5] A PhZnBr reagent was found to be entirely unreactive. A phenylation reaction did not take place when [Fe(acac)₃] was replaced by [Mn(acac)₃], [Co(acac)₂], or [Ni(acac)₂].^[6] The reaction was complete in about 20 hours at 0 °C; elevated temperatures tend to destroy the catalytic activity.

As shown in Table 1, entry 1, virtually no reaction took place in the absence of any aromatic diamine ligand. 1,10-Phenanthroline (phen, 10 mol%), which served as the best additive in our previous study,^[5] was found to be unsatisfactory, and 2,2'-bipyridine (bpy) was found to not be very

Table 1. Screening the conditions for the iron-catalyzed reaction of aryl imines with a diphenylzinc reagent.^[a]

Entry	R	Ligand	Conversion [%] ^[b]
1	4-MeOC ₆ H ₄	none	2
2	4-MeOC ₆ H ₄	phen	86
3	4-MeOC ₆ H ₄	bpy	54
4	4-MeOC ₆ H ₄	dtbpy	100 (91) ^[c]
5 ^[d]	4-MeOC ₆ H ₄	dtbpy	52
6	Ph	dtbpy	100
7	4-MeC ₆ H ₄	dtbpy	100
8	4-CF ₃ C ₆ H ₄	dtbpy	94
9	2-MeC ₆ H ₄	dtbpy	74

[a] The reaction was carried out on a 0.4 mmol scale. [b] The conversion was determined by GC analysis, employing *n*-tridecane as an internal standard. [c] The yield of the isolated product of the corresponding ketone after hydrolysis is shown in parentheses. [d] Used 1,2-dichloroethane instead of 1,2-dichloroisobutane.

effective (Table 1, entries 2 and 3). After screening a variety of bidentate aromatic amines, we found that using dtbpy leads quantitatively to desired product (Table 1, entry 4). After in situ hydrolysis of the product, the corresponding *ortho*-phenylated ketone was obtained in 91 % yield upon isolation. The use of 1,2-dichloroethane in place of DCIB resulted in much lower conversion (Table 1, entry 5).

We found that an imine group was the best directing group in this C–H bond activation, and chose, for the subsequent studies, the (4-methoxyphenyl)imines **1** because of the ease of their preparation and handling. Acetophenone itself, the corresponding methoxime, and *N,N*-dimethylhydrazone were found to be entirely unreactive. We examined imines derived from aniline, 4-methyl-, 4-methoxy-, 4-trifluoromethyl-, 2-methyl-, and 2-methoxyanilines, all of which gave good to excellent yields after a 20 hour reaction time at 0 °C (Table 1, entries 6–9 and see the Supporting Information). The 4-trifluoromethylphenylimine and the 2-methylphenylimine reacted at a slightly slower rate than the others, which implies that coordination at the imine nitrogen atom is involved in the reaction, but is not the step that greatly affects the reaction rate.

Table 2 summarizes the substrate scope of the iron-catalyzed, imine-directed arylation reaction. Imines derived from acetophenone (**1a**), propiophenone (**1b**), and tetralone (**1c**) gave the desired monophenylated products **2a–2c** in yields ranging from 91% to 99% (Table 2, entries 1–3). A 2-thienyl imine derivative **1d** also smoothly underwent phenylation at the 3-position to give a product **2d** in 96% yield (Table 2, entry 4). The reaction of the aldehyde-derived imine **1e** afforded a mixture of a diphenylated product **3e** (58% yield) and a monophenylated product **2e** (6% yield). We consider that this mixture results from the higher conformational flexibility of the aldehyde-derived imine than that of the ketone-derived imines.

The present reaction shows a good tolerance for halide and pseudohalide groups, which is particularly notable in view of the similarity of the reaction conditions to those of iron-catalyzed cross-coupling of aryl halides and pseudohalides (Table 2, entries 6–12).^[1,7] Chloro- and bromoaryl compounds **1f–1i** reacted more slowly than the parent substrate **1a**, but still gave phenylated products **2f–2i** in yields of 83% to 92% after 48–72 hours (Table 2, entries 6–9). The chlorine atoms of **1f** and **1g** were entirely retained, and the bromine atoms of **1h** and **1i** were reductively removed only to a small extent (3% yield).

Notably, the reaction of the bromide substrate **1h** in the absence of DCIB resulted in a mixture of compounds formed from the C–H bond activation, the reductive removal of the bromide, and the cross-coupling at the C–Br group (see the Supporting Information). The phenylation of *meta*-chloro and *meta*-bromo substrates **1g** and **1i** took place exclusively at the less hindered side of the two *ortho* positions. Reductive removal of the iodine atom in the aryl iodide substrate **1j** was predominant, but the reaction still afforded a reasonable amount of the desired phenylated product **2j** (Table 2, entry 10). The *ortho*-halogenated imines resulted in the complete loss of the halogen atom and gave only an *ortho*-phenylated product, either because of direct halogen sub-

Table 2: Iron-catalyzed direct phenylation of aryl imine derivatives with a diphenylzinc reagent.^[a]

Entry	Substrate	Product	<i>t</i> [h]	Yield [%] ^[b]
1		1a 2a	20	91
2		1b 2b	20	99
3		1c 2c	20	93
4		1d 2d	20	96
5 ^[c]		1e 2e (R = H) 3e (R = Ph)	48 48	6 58
6		1f 2f	72	92
7		1g 2g	72	87
8 ^[d]		1h 2h	48	83
9		1i 2i	72	88
10 ^[d]		1j 2j	3	14
11 ^[e,f]		1k 2k	9 (20)	89 (89)
12 ^[e]		1l 2l	9	89
13		1m 2m	20	94
14 ^[e]		1n 2n	9	90
15		1o 2o	72	57

[a] Unless otherwise noted, the reaction was carried out on a 0.4 mmol scale under the reaction conditions indicated in Scheme 1. [b] Yields of isolated products. [c] Used Fe(acac)₃/dtbpy (15 mol%), PhMgBr (12 equiv), ZnCl₂·TMEDA (6 equiv), and of 1,2-dichloroisobutane (4 equiv). [d] Obtained as a mixture containing a dehalogenated product; yield was determined by ¹H NMR analysis. [e] Used ZnCl₂·TMEDA (2.5 equiv) and PhMgBr (5 equiv). [f] Data for a 1.5 g scale reaction are shown in parentheses (see the Experimental Section).

stitution or of dehalogenation and subsequent phenylation (see the Supporting Information).

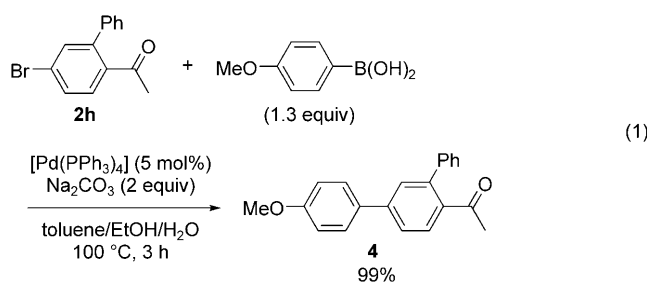
The reaction also tolerates the presence of triflate and tosylate groups (Table 2, entries 11 and 12). The sulfonate

compounds **1k** and **1l** reacted much faster than the parent substrate **1a**, and complete conversion of the starting material was achieved by using a near stoichiometric amount (2.5 equiv) of the diphenylzinc reagent for a shorter reaction time (9 h).^[8]

Overall, the rate of the present reaction was found to show a rather peculiar substituent dependence. Whereas the *para*-methoxy compound **1m** reacted at essentially the same rate as that of the parent compound **1a** (Table 2, entry 13), the *para*-trifluoromethyl compound **1n** was much more reactive (Table 2, entry 14; 90% yield with 2.5 equiv of the diphenylzinc reagent within 9 h). In contrast, the reaction of the *para*-cyano compound **1o** was much more sluggish, and gave the product **2o** in 57% yield after 72 hours (Table 2, entry 15). The order of reactivity of the substituted acetophenone-derived imines can be qualitatively summarized as 4-CF₃, OTf, OTs > H (parent), 4-OMe > 4-X, 2-X (X = Br, Cl) > 4-CN, suggesting that the C–H bond activation reaction is influenced by both the inductive and resonance effects of the substituent.^[9]

The scope of the diaryl reagents was studied for the reaction of the triflate substrate **1k** (Table 3). 4-Methoxyphenylzinc and 4-*tert*-butylphenylzinc reagents smoothly participated in the reaction, and afforded the corresponding arylation products **2p** and **2q** in 88% and 86% yields, respectively (Table 3, entries 2 and 3). In contrast, the reaction of the 4-chlorophenylzinc reagent was much more sluggish (Table 3, entry 4). A 2-tolylzinc reagent did not give the arylation products at all, perhaps because of the steric effect (Table 3, entry 5). A Me₂Zn reagent prepared from MeMgBr gave the expected methylation product **2t**, albeit in a low yield (Table 3, entry 6).^[10,11]

The compatibility of the present catalysis with aryl–X (halogen or pseudohalogen) bonds allows us to carry out regioselective, sequential functionalization of aromatic C–H and C–X bonds. For example, the bromo biaryl **2h**, obtained by the iron catalysis, was quantitatively converted into a terphenyl derivative by palladium-catalyzed Suzuki–Miyaura coupling with 4-methoxyphenylboronic acid [Eq. (1)].



In summary, we have developed an iron-catalyzed imine-directed conversion of an *ortho* C–H bond into a C–C bond. The reaction takes place under mild conditions (0 °C in THF) and tolerates the presence of reactive functional groups such as aryl bromides, chlorides, and sulfonates. The reaction provides not only an interesting new example of C–H bond activation,^[12,13] but also a new synthesis for biaryl com-

Table 3: Iron-catalyzed direct arylation of aryl imine **1k** with a diarylzinc reagent.^[a]

Entry	R	Product	t [h]	Yield [%] ^[b]	
1	Ph		9	89	2k
2	4-MeOC ₆ H ₄		20	88	2p
3	4- <i>t</i> BuC ₆ H ₄		20	86	2q
4	4-ClC ₆ H ₄		72	52	2r
5	2-MeC ₆ H ₄		72	0	2s
6	Me		72	18	2t

[a] Unless otherwise noted, the reaction was carried out on a 0.4 mmol scale under the reaction conditions indicated in the equation. [b] Yields of isolated products.

pounds.^[14] The reaction exhibits some unusual characteristics which are difficult to understand at this time, and will be an interesting subject of mechanistic studies in the future.

Experimental Section

Iron-catalyzed phenylation of the imine **1k:** ZnCl₂·TMEDA (2.53 g, 10.0 mmol) was placed in a Schlenk tube, cooled to 0 °C, and then a THF solution of phenylmagnesium bromide (17.2 mL, 1.16 M, 20.0 mmol) was added dropwise to the reaction mixture. After stirring the mixture for 1 h, the imine **1k** (1.49 g, 4.0 mmol), THF (20 mL), 1,2-dichloroisobutane (0.92 mL, 8.0 mmol), and a 0.1 M solution of Fe(acac)₃ and 4,4'-di-*tert*-butyl-2,2'-bipyridine in THF (4.0 mL, 0.4 mmol) were sequentially introduced. The reaction mixture was stirred at 0 °C for 20 h and then quenched by the addition of 3 N HCl (40 mL). The resulting mixture was stirred for 3 h at room temperature and extracted with ethyl acetate (20 mL × 3). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: n-hexane/EtOAc 19:1) to give the ketone **2k** as a colorless oil (1.23 g, 89% yield).

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