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Iron-Catalyzed Oxidative Monoarylation of Primary Amines with Organozinc Reagents

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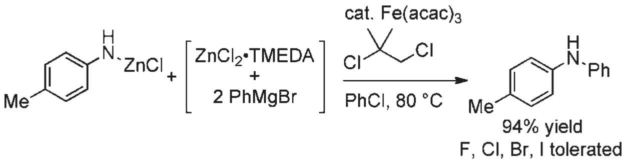
ABSTRACT



The reaction of a primary zinc amide with a diorganozinc reagent gives a secondary amine in the presence of Fe(acac)$_3$ as a catalyst and 1,2-dichloroisobutane (DCIB) as an oxidant. Halogen groups such as F, Cl, Br, and I are tolerated well. The dichloride oxidant and heat are essential to achieve the C–N bond formation presumably from a catalytic iron intermediate species bearing aryl and amido groups.

Intensive research continues to explore new properties of iron, motivated by the interest in pure science as well as in finding solutions to the issues related to the environment[1] and the scarcity of chemical elements.[2–4] Research on catalysis is no exception. Various new types of iron catalysis have received recent interest,[5] including an attempted cross-coupling-type synthesis of aromatic amine derivatives.[6,7] We report here a new reactivity of an iron amide intermediate that enables the oxidative coupling of a primary aryl amine with an arylzinc reagent to selectively obtain a secondary amine (Scheme 1, right). Our design of the catalytic system was inspired by the pioneering work of Yamamoto on the copper-mediated oxidative coupling of an organolithium compound and an amine (Scheme 1, top left),[8] which has not received proper attention until Knochel's recent revisit to this stoichiometric chemistry.[9] The reaction is retrosynthetically complementary to the much explored cross-coupling synthesis under palladium,[10] nickel,[11] or copper[12] catalysis and possesses some attractive features: the use of nontoxic and ubiquitous metal salt [Fe(acac)$_3$] and a simple ligand (TMEDA), and the tolerance of aryl chloride, bromide, and iodide groups. This last feature makes the present amine synthesis complementary to the cross-coupling approaches using

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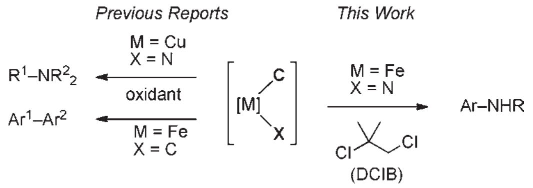
aryl halides as the coupling partner. Aryl amines[13] have been key players in pharmaceutical research and have become increasingly popular also in organic electronics research, which is our current concern.[14]

Scheme 1. Oxidant-Promoted Reductive Elimination from an Organoiron Amide To Form a C–N or C–C Bond



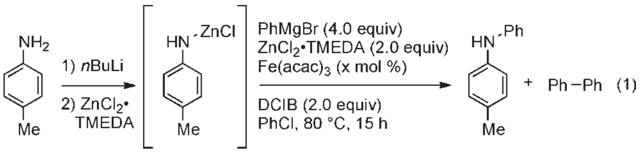
To probe the stoichiometry necessary for the iron-mediated C–N coupling, we first studied the stoichiometric coupling reaction using $Fe(acac)_3$ (Table 1). The reaction between 1.0 equiv of in situ generated primary zinc amide from *p*-toluidine **1** and 1.0 equiv of diphenylzinc reagent (prepared from PhMgBr and $ZnCl_2 \cdot TMEDA$) in chlorobenzene at 80 °C after 15 h afforded none of the desired product **3** with recovery of starting material **1** in 86% yield (based on iron) and gave only the biphenyl **4**[15] in 8% yield (entry 1). The same reaction in the presence of 2.0 equiv of 1,2-dichloroisobutane (DCIB)[15] as an oxidant produced **3** and **4** in 33 and 47% yields, respectively (entry 2). Further investigation on the amount of **1** and "Ph_2Zn" (entries 3–5) showed that the use of 2.0 equiv each of **1** and diphenylzinc in the presence of 2.0 equiv of DCIB yielded **3** and **4** in 93 and 61% yields, respectively (entry 5). When the reaction temperature was lowered to 25 °C, the reaction gave the products **3** and **4** in 22 and 69% yields, respectively (entry 6), indicating that the C–N bond formation requires high temperature.[16] We obtained essentially the same result when using $Fe(acac)_2$. From these stoichiometric experiments, we can speculate the following. (1) Two amide molecules act as a ligand for iron, in which more than one aryl moiety coordinates to iron, and (2) the oxidant is crucial for C–N bond formation.

Table 1. Oxidative Phenylation of *p*-Toluidine (**1**) with Diphenylzinc Using 1.0 Equiv of $Fe(acac)_3$[a]

entry	**1** (equiv)	"Ph_2Zn"[b] (equiv)	DCIB (equiv)	temp (°C)	**3** (%)	**4** (%)	**1** (%)
1	1.0	1.0	0	80	0	8	86
2	1.0	1.0	2.0	80	33	47	62
3	1.0	2.0	2.0	80	42	114	53
4	2.0	1.0	2.0	80	33	19	158
5	2.0	2.0	2.0	80	93	61	98
6	2.0	2.0	2.0	rt	22	69	176

[a] Reaction conditions: zinc amide **2** was generated from the corresponding amine (1.0 or 2.0 equiv), *n*-BuLi in hexane (1.0 or 2.0 equiv), and $ZnCl_2 \cdot TMEDA$ (1.0 or 2.0 equiv), and then it was allowed to react with an organozinc reagent generated from PhMgBr in Et_2O (2.0 or 4.0 equiv) and $ZnCl_2 \cdot TMEDA$ (1.0 or 2.0 equiv) in the presence of $Fe(acac)_3$ (0.30 mmol) and DCIB (2.0 equiv) in chlorobenzene at 80 °C for 15 h. Yields were determined by gas chromatography (GC) using *n*-tridecane as an internal standard. [b] "Ph_2Zn" was prepared from PhMgBr and $ZnCl_2 \cdot TMEDA$ in chlorobenzene.

Having learned the essential role of DCIB and heat, we next explored the catalytic conditions and achieved the desired C–N coupling in isolated yield as high as 94% (eq 1). A typical example for the iron-catalyzed oxidative monoarylation is as follows: the reaction of zinc amide **2** generated from *p*-toluidine (32.1 mg, 0.30 mmol), *n*-BuLi, and $ZnCl_2 \cdot TMEDA$ with diphenylzinc (2.0 equiv) generated from PhMgBr and $ZnCl_2 \cdot TMEDA$ in the presence of 20 mol % of $Fe(acac)_3$ as a catalyst and 2.0 equiv of DCIB as an oxidant in chlorobenzene at 80 °C for 15 h gave the desired *N*-phenyl-*p*-toluidine **3** in 94% isolated yield after chromatographic purification on silica gel. The catalyst loading could be reduced to 5 mol % at the expense of reduced reaction rate. The use of pure diphenylzinc resulted in complete recovery of the starting amine. This observation suggests the necessary presence of the magnesium(II) ion, whereas aryl Grignard reagents only took part in the C–N bond formation in low yield and gave largely biphenyl. The same reaction performed on a 1 g scale (9.3 mmol) afforded **3** in 85% yield. The side product **4** (109%; 0.33 mmol) formed by the iron-catalyzed homocoupling[17] of the zinc reagent could be removed readily by column chromatography. The reaction selectively afforded the secondary amine and did not produce the diarylated product (*N*,*N*-diphenyl-*p*-toluidine).



1 (yields based on 1)

2

x = 5 mol % **3**: 90% **4**: 81%
20 mol % 94% 109%

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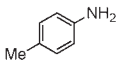
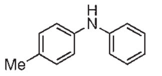
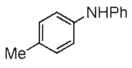
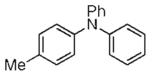
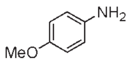
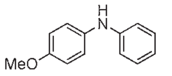
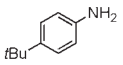
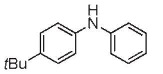
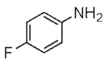
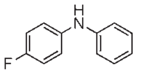
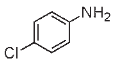
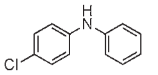
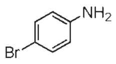
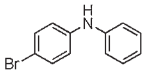
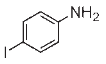
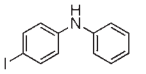
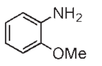
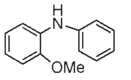
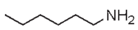
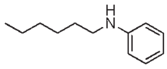
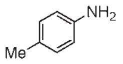
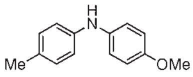
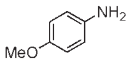
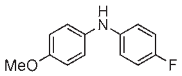
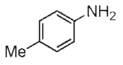
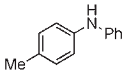
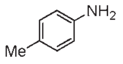
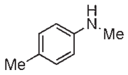
[16] While monitoring of the reation system by NMR was difficult, cyclic voltammetric measurements indicated that the heat is necessary to drive the reaction probably through promotion of the ligand exchange on iron. The reversible reduction wave of Fe(II) at −1.44 V (vs ferrocene) observed for a solution of $Fe(acac)_2$ in chlorobenzene at ambient temperature became irreversible upon addition of the zinc amide, which shifted the oxidation peak to around −0.70 V. This indicates that no reaction takes place by the addition of zinc amide, and the ligand exchange only takes place by the reaction with reduced iron species.[7] Upon addition of diphenylzinc, no change was observed by CV. After heating this mixture at 60 °C, two new reversible reduction waves at −0.58 and −0.99 V were observed, which suggests the formation of iron species that can be reduced more easily than $Fe(acac)_2$.

Table 2. Reaction Conditions for Iron-Catalyzed Oxidative Phenylation of *p*-Toluidine (**1**)[a]

entry	catalyst	oxidant	**3** (%)[b]	**4** (%)[b]	**1** (%)[b]
1	none	DCIB	0	0	92
2	$Fe(acac)_3$	DCIB	95	116	4
3[c]	$Fe(acac)_3$	DCIB	32	28	57
4	$Fe(acac)_3$ (≥94.2%)	DCIB	84	93	10
5	$FeCl_3$	DCIB	86	82	13
6	$Fe(acac)_2$	DCIB	88	96	12
7	CuI (Cu_2O)	DCIB	0(0)	64(66)	92(92)
8	$Fe(acac)_3$ + dppp (phen)	DCIB	82(75)	93(92)	8(10)
9	$Fe(acac)_3$	none	0	17	88
10	$Fe(acac)_3$	*t*-BuCl	26	44	58
11	$Fe(acac)_3$	1,2-dibromoethane	44	51	5
12	$Fe(acac)_3$	dibenzoyl peroxide	29	13	0
13	$Fe(acac)_3$	dioxygen	55	46	0
14	$Fe(acac)_3$	air	39	50	0

[a] Reaction conditions: the zinc amide **2** was generated from *p*-toluidine (**1**, 0.30 mmol), *n*-BuLi in hexane (1.0 equiv), and $ZnCl_2 \cdot TMEDA$ (1.0 equiv), and then it was allowed to react with a diphenylzinc reagent generated from PhMgBr in Et_2O (4.0 equiv) and $ZnCl_2 \cdot TMEDA$ (2.0 equiv) in the presence of 20 mol % of $Fe(acac)_3$ (≥99.9% purity unless otherwise noted) and DCIB (2.0 equiv) in chlorobenzene at 80 °C for 15 h; dppp = 1,3-bis(diphenylphosphino)propane; phen = 1,10-phenanthroline. [b] Yields were determined GC using *n*-tridecane as an internal standard. [c] 1.0 equiv of DCIB was used.

Table 3. Iron-Catalyzed Oxidative Arylation of Various Primary Amines with Diorganozinc Reagents[a]

entry	amine	RMgBr	product	yield (%)[b]
1		PhMgBr		94
2		PhMgBr		0
3		PhMgBr		92
4		PhMgBr		87
5		PhMgBr		77
6		PhMgBr		76
7		PhMgBr		78
8		PhMgBr		54
9		PhMgBr		16[c]
10		PhMgBr		13[c]
11		4-$MeOC_6H_4MgBr$		96
12		4-FC_6H_4MgBr		85
13		PhMgBr[d]		44[c]
14		MeMgBr		12[c]

[a] Reaction conditions: the zinc amide **2** was generated from the corresponding amine (0.30–1.0 mmol), *n*-BuLi in hexane (1.0 equiv), and $ZnCl_2 \cdot TMEDA$ (1.0 equiv), and then it was allowed to react with an organozinc reagent generated from RMgBr in Et_2O (4.0 equiv) and $ZnCl_2 \cdot TMEDA$ (2.0 equiv) in the presence of $Fe(acac)_3$ (20 mol %) and DCIB (2.0 equiv) in chlorobenzene at 80 °C for 15 h. See the Supporting Information for details. [b] Isolated yield after purification on silica gel. In low-yielding reactions, the starting amine was recovered. [c] GC yield obtained using *n*-tridecane as an internal standard. [d] The monophenylzinc reagent was prepared from an equimolar amount of PhMgBr and $ZnCl_2 \cdot TMEDA$.

Various conditions were examined to optimize the catalytic reaction (Table 2). No product formed in the absence of the iron catalyst (entry 1). Several iron sources of different purities catalyzed the reaction with equal ease (entries 2 and 4–6), and copper salts did not catalyze the reaction (entry 7). These results suggest that contaminants in the iron source do not play any significant role.[6b] Phosphine- and pyridine-type ligands did not affect the catalytic activity, which implies that the anionic amine binds more strongly to the iron center than these neutral ligands (entry 8).[18]

Both the choice and the amount of the oxidant were crucial for the reaction. As can be seen by the comparison among the entries 2 and 10–14, DCIB was found to serve as the best oxidant for the C–N coupling to give **3** (entry 2), which was the same with our previously reported C–C bond formation reaction.[15a,d–f] Reducing the amount of DCIB to 1.0 equiv led to a significant decrease in the yields of both C–N and C–C bond formation (entry 3). Without DCIB, the C–N bond formation did not take place at all (entry 9). Other oxidants such as organic halides (entries 10 and 11), dibenzoyl peroxide (entry 12), dioxygen (entry 13), or air (entry 14) performed less satisfactorily. When dioxygen or air was employed as an oxidant, homocoupling of the amine partner proceeded to form a small amount (4–7%) of 4,4′-dimethylazobenzene[19] in addition to biphenyl (**4**). Addition of TEMPO did not significantly affect the reaction. The reaction proceeded the best in electron-deficient aromatic solvents such as chlorobenzene or trifluoromethylbenzene (see Supporting Information)

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as was found in an iron-catalyzed C–C bond formation,[15e,f] suggesting a certain role in the catalysis, for example, by stabilizing a low-valent iron species.[20] The reaction temperature of 80 °C was necessary to promote the C–N bond formation, and the reaction at room temperature gave only biphenyl due to C–C homocoupling. Notably, in all cases, the formation of diarylated tertiary amine was not observed.

With the optimized conditions in hand, we investigated the scope of this reaction (Table 3). While *p*-toluidine (**1**) gave *N*-phenyl-*p*-toluidine (**3**) in 94% yield (entry 1), the reaction of a secondary amine (entry 2) gave none of the desired product. Aniline derivatives possessing an electron-donating or an electron-withdrawing group (entries 1 and 3–7) were smoothly monoarylated in good to excellent yields. The reaction tolerated the presence of aromatic halides such as F, Cl, Br, and I (entries 5–8), which marks the difference between this reaction and the popular cross-coupling routes to aryl amines. An ortho-substituted aniline reacted poorly (16% yield; entry 9), suggesting steric effects. A primary alkylamine also took part in the reaction, albeit with low yield (13%) and no recovery of starting material (entry 10). Entries 11–14 illustrate the scope of the organozinc reagent. Both electron-rich or electron-deficient diarylzinc reagents (entries 11 and 12) underwent the coupling reaction in good yields. The reaction with a monophenylzinc reagent resulted in low yield (entry 13). The reaction with dimethylzinc gave the desired monomethylated product in 12% yield (entry 14) together with a small amount of a dimethylated product. Heteroaryl or alkenyl reagents did not react under these conditions, as previously observed for iron-catalyzed C–H functionalization reactions.[15a,b,e,f]

In conclusion, we have developed an iron-catalyzed oxidative reaction of a primary amine with an organozinc reagent that selectively produces the corresponding secondary aryl amine. This new type of reaction is a new entry to the rapidly expanding repertoire of iron catalysis. The results of the stoichiometric reactions suggest that the crucial iron intermediate species contains more than 1 equiv of aryl and amide ligands and, upon heating and oxidation by DCIB, gives a mixture of aryl amine and diaryl products. Driving the reaction selectively into the desired C–N bond forming manifold apparently needs further mechanistic information, which serves as an interesting subject for future studies.

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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.