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Iron-Catalyzed Aromatic Amination for Nonsymmetrical Triarylamine Synthesis

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Ⓢ *Supporting Information*

ABSTRACT: Novel iron-catalyzed amination reactions of various aryl bromides have been developed for the synthesis of diaryl- and triarylamines. The key to the success of this protocol is the use of *in situ* generated magnesium amides in the presence of a lithium halide, which dramatically increases the product yield. The present method is simple and free of precious and expensive metals and ligands, thus providing a facile route to triarylamines, a recurrent core unit in organic electronic materials as well as pharmaceuticals.

Transition-metal-catalyzed aromatic amination is widely used for the synthesis of arylamines, which are of particular interest in the fields of organic electronics and bioactive compounds.[1,2] Despite recent improvements to Pd- and Cu-catalyzed amination methodologies, such as the Buchwald–Hartwig and catalytic Ullmann reactions,[3] new methods that do not require hazardous and expensive transition metals and ligands are highly desired for the efficient production of functional arylamines. Although considerable effort has been devoted to the development of iron-catalyzed amination reactions in the past decade,[4] they have limited substrate scope and are unsuited for the synthesis of triarylamines,[5,6] which are among the most prevailing hole-transport materials.[1] In addition, Buchwald and Bolm reported that the product yields of the reported iron-catalyzed amination reactions are sensitive even to trace quantities of copper contaminants, especially in the presence of *N*,*N*′-dimethylethylenediamine (DMEDA).[7] Hence, further investigation of suitable routes to triarylamines is needed from synthetic and mechanistic perspectives. Herein, we report a facile and environmentally benign method based on iron-catalyzed aromatic amination for synthesizing diaryl- and triarylamines and provide mechanistic insights obtained through experimental and computational studies on the iron amide species.

Since the standard conditions for Pd- or Cu-catalyzed aromatic amination[3] were not effective for iron catalysis, our study began with an extensive screening of bases and additives. We eventually found that the combination of a Grignard reagent (base) and a lithium bromide (additive) dramatically promoted the amination of aryl bromides with arylamines.[8] The reaction between *p*-bromoanisole **1** and magnesium diphenylamide **2**, prepared *in situ* from diphenylamine and an ethyl Grignard reagent, was carried out in xylene at 140 °C for 12–48 h, using a variety of catalysts and additives (Scheme 1).

Scheme 1. Iron-Catalyzed Amination Reaction Between 1 and 2

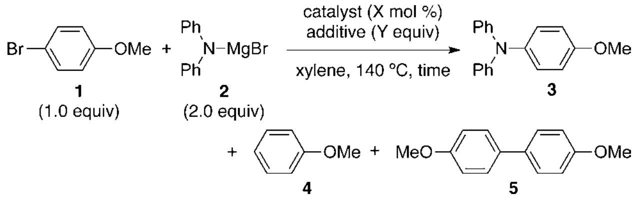


Table 1 summarizes the results of this initial screening of catalyst systems based on iron and other transition metals. The reaction between **1** and **2** in the presence of 5 mol % $FeCl_2$ gave the desired product **3** in 10% yield (entry 1), while the reaction between **1** and diphenylamine in the presence of conventional inorganic bases (K_3PO_4, Cs_2CO_3, $NaHCO_3$, *t*-BuOK) did not give any coupling product. The addition of LiBr

Table 1. Screening of Catalysts and Additives[a]

				yield (%)[b]			
entry	catalyst (X mol %)	additive (Y equiv)	time (h)	3	4	5	recovery of 1 (%)[b]
1	$FeCl_2$ (5.0)	none	24	10	0	0	89
2	$FeCl_2$ (5.0)	LiBr (0.2)	24	26	0	0	67
3	$FeCl_2$ (5.0)	LiBr (2.0)	12	51	0	0	41
			24	95	0	0	0
4	$FeCl_2$ (5.0)	LiBr (4.0)	12	>99	0	0	0
5	$FeCl_2$ (0.5)	LiBr (4.0)	48	99	0	0	0
6	$PdCl_2$ (0.5)	LiBr (4.0)	48	6	4	0	80
7	$CuCl_2$ (0.5)	LiBr (4.0)	48	2	0	0	92
8	$CoCl_2$ (0.5)	LiBr (4.0)	48	27	4	0	47
9	$NiCl_2$ (0.5)	LiBr (4.0)	48	88	4	6	0
10	$Ni(acac)_2$ (0.5)	LiBr (4.0)	48	80	3	8	0
11	$Ni(acac)_2$ (0.0005)	LiBr (4.0)	48	8	0	0	90

[a]Reactions were carried out on a 1.0 mmol scale. [b]Yield was determined by GC analysis using undecane as an internal standard.

Received: October 5, 2012
Published: November 26, 2012

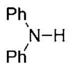
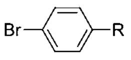
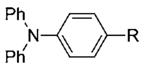
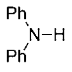
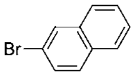
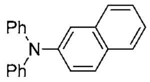
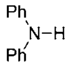
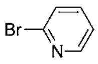
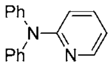
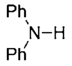
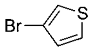
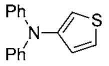
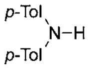
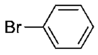
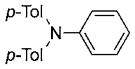
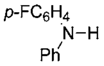
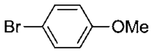
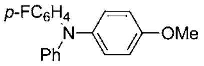
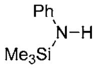
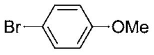
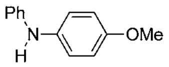
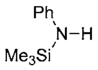
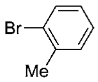
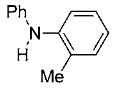
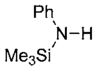
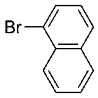
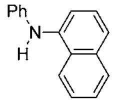
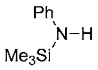
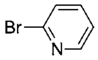
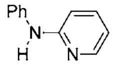
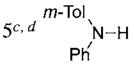
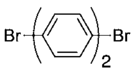
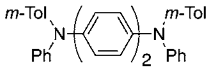
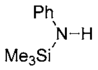
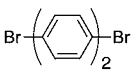
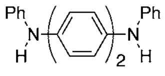
dx.doi.org/10.1021/ja309845k | *J. Am. Chem. Soc.* 2012, 134, 20262–20265

accelerated the reaction and the optimum yield (99%) was achieved when using 4.0 equiv of LiBr (entries 2−4).[9] The increased yield is probably due to the deaggregation of magnesium amide by the lithium salt to facilitate transmetalation of the amide ligand from magnesium to iron.[10] Notably, magnesium diphenylamide, prepared from lithium diphenylamide and $MgBr_2$, gave good yield (95%), while lithium diphenylamide gave a very poor yield (2%) under the same conditions.[11] Complete conversion could be achieved even with 0.5 mol % $FeCl_2$ when the reaction was done in 48 h (entry 5).[12]

To clarify the effects of the metal contaminants, the iron salts were analyzed by inductively coupled plasma mass spectrometry and atomic emission spectroscopy (ICP-MS and ICP-AES). Since ppm-order amounts of Pd, Cu, Co, and Ni were found in some iron salts, we performed the amination reaction in the presence of these transition-metal catalysts. As in entries 6−8, $PdCl_2$, $CuCl_2$, and $CoCl_2$ showed poor catalytic activities under the same reaction conditions. As reported by Yang,[13] $NiCl_2$ and $Ni(acac)_2$ showed catalytic activity comparable to that of the iron catalysts but gave lower product yields owing to the competing homocoupling of *p*-bromoanisole (entries 9 and 10). Since the amount of nickel contaminant in $FeCl_2$ was determined to be 12.9 ppm by the above-mentioned analysis,[14] we examined the use of 5×10^{-4} mol % $Ni(acac)_2$ (1000 ppm of 0.5 mol %) as the catalyst to confirm the low reactivity and, hence, concluded that nickel contamination does not play an important role in the present iron-catalyzed amination reaction (entry 11).

Table 2 summarizes the substrate scope of the aromatic amination. As shown in entries 1−10, a variety of aryl- and heteroaryl bromides could be coupled with diarylamines to give the corresponding triarylamines in good yields. Although anilines did not participate in the reaction, a protected aniline, *N*-(trimethylsilyl) aniline, coupled with the aryl bromides to give, upon hydrolysis, the corresponding diarylamines in excellent yields (entries 11−14).[15] The reactions with *N*-(trimethylsilyl)aniline proceeded more smoothly in dibutyl ether than in xylene. As shown in entries 15 and 16, the hole-transport material, *N,N*′-diphenyl-*N,N*′-di(*m*-tolyl)benzidine (TPD), and its precursor could be prepared from 4,4′-dibromo-1,1′-biphenyl in 82% and 87% yields, respectively. Aryl bromides possessing an ester or nitrile group underwent the addition of magnesium amides to the electrophilic functional groups, and desired amination products were not obtained. Ketone and nitro groups were not tolerated under the reaction conditions and gave complex mixtures (data not shown). The limited functional group compatibility compared to the Pd-catalyzed aminations[5,6] is due to the high reactivity of the magnesium amides, and further study to find suitable combinations of a base and a neutral amine is needed to overcome this limitation.

Table 2. Substrate Scope[a]

entry	amine	aryl halide	product	yield (%)[b]
1 2 3 4 5				92 (R = Me) 90 (R = OMe) 88 (R = NMe_2) 59 (R = Cl) 77 (R = F)
6				90
7				82
8				61
9				96
10				82
11[c]				96
12[c]				76
13[c]				97
14[c]				98
15[c,d]				82
16[c,d]				87

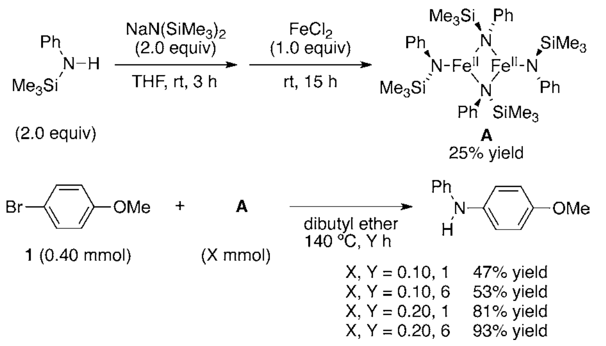
[a] Reactions were carried out on a 1.00 mmol scale according to the procedure described in Table 1 (entry 4), unless otherwise noted. [b] Isolated yield. [c] Reaction was carried out in dibutyl ether. [d] Reaction was carried out on a 0.50 mmol scale using 4.0 equiv of amine.

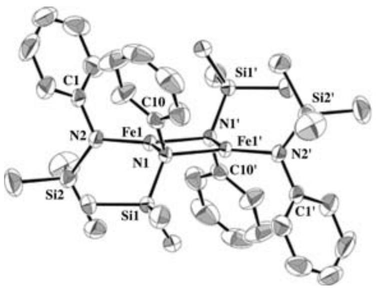
Despite the relatively narrow substrate scopes in terms of functional group, one advantage of the present method is the efficient reaction with aryl bromides, particularly those possessing electron-donating groups, which have been limitedly utilized in Cu-catalyzed aminations.[6b,g−i]

To gain further insights into the mechanism, we prepared an iron(II) diamide complex **A** according to Power's method[16] and conducted a stoichiometric reaction (Scheme 2). Deprotonation of *N*-(trimethylsilyl)aniline with sodium bis(trimethylsilyl)amide (NaHMDS), followed by treatment with $FeCl_2$, gave a dimer complex of iron(II) diamide **A** in 25% yield. X-ray crystallography analysis showed that **A** was dimeric, with each trigonal-planar iron bound to one terminal and two bridging amide groups (Figure 1).[16] Aromatic amination of **1** in Bu_2O at 140 °C for 6 h gave the desired product in 53% and 93% yields in the presence of 0.25 and 0.50 equiv of **A**, respectively. This result clearly shows that the iron(II) diamide can be a reactive intermediate in which one of two amide groups (per iron) takes part in the amination.

Figure 2 shows a plausible mechanism on the basis of the stoichiometric studies. The precatalyst, $FeCl_2$, reacts with 2.0 equiv of magnesium amide to form monomeric and dimeric iron(II) diamide complexes, which are in monomer−dimer equilibrium.[17,18] The coordinatively unsaturated monomer may undergo oxidative addition with an aryl bromide to form a

Scheme 2. Preparation of Iron(II) Diamide Complex A and the Stoichiometric Reaction





Selected bond lengths

Fe1–N2	1.9147(18) Å
Fe1–N1	2.0702(18) Å
Fe1–N1'	2.0348(16) Å
Fe1–Fe1'	2.7408(7) Å

Selected angles

N2–Fe1–N1	130.88(7)°
N2–Fe1–N1'	132.89(8)°
N1–Fe1–N1'	96.23(6)°
Fe1–N1–Fe1'	83.77(6)°
Fe1–N2–C1	114.04(13)°
Fe1–N2–Si2	128.45(10)°
C1–N2–Si2	117.46(14)°
C10–N1–Si1	115.22(13)°

Figure 1. ORTEP drawing of **A**. Thermal ellipsoids are shown at 50% probability; hydrogen atoms are omitted for clarity.

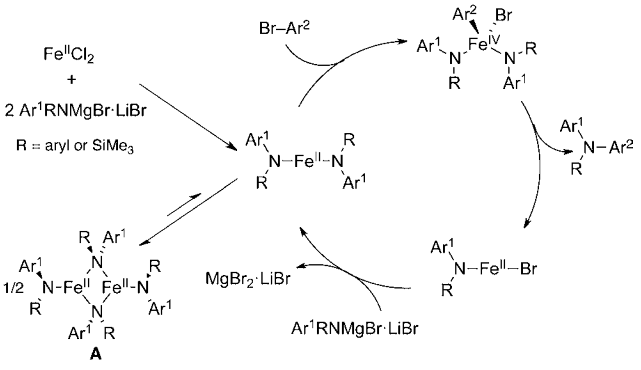


Figure 2. Possible catalytic cycle of iron-catalyzed aromatic amination.

formal iron(IV) intermediate. Successive reductive elimination of the coupling product affords iron(II) monoamide complex. Regeneration of the active species completes the catalytic cycle via the LiBr-assisted transmetalation with magnesium amide.

To evaluate the nonconventional Fe(II)−Fe(IV) mechanism,[19,20] we performed a set of DFT calculations and have located an energetically reasonable reaction coordinates, starting from monomer **B** (Figure 3).[21] Monomer **B**, which is 5.4 kcal/mol higher in energy than dimer **A**, undergoes oxidative addition with bromobenzene (Ph−Br) through the formation of σ-complex (**C**) to give the iron(IV) intermediate **D**. The overall activation energy from **A** to **D** via **TS$_{CD}$** is 26.7 kcal/mol, which is in fair agreement with the experimental finding that the reaction proceeds smoothly at 140 °C. Although oxidative addition is an endothermic process, rapid reductive elimination of the coupling product from **D** gives the stable σ-complex **E**, which can drive the C−N coupling reaction forward. Dissociation of the coupling product (**E** to **F**) and subsequent transmetalation with magnesium amide regenerates the iron diamide **B** to complete the catalytic cycle, or alternatively, the dimer formation from **F** to **G**[22] and the transmetalation regenerates the starting dimer **A**, the experimentally determined reactive intermediate.

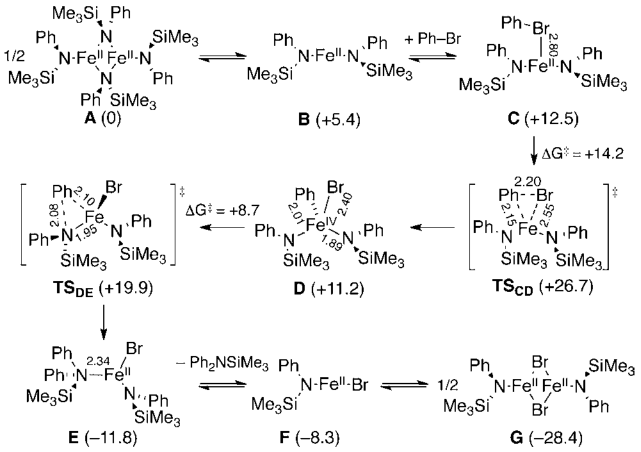


Figure 3. Reaction pathways for oxidative addition and reductive elimination. Gibbs free energies (ΔG, calculated at the B3LYP/6-31G(d) level) relative to **A** are given in kcal/mol in parentheses.

In summary, we have developed an efficient iron-catalyzed aromatic amination between diaryl- or arylsilyl amines and aryl bromides, which affords high product yields and selectivity, in the presence of a simple catalyst system. The key to the success of the reaction is the combined use of magnesium amide and lithium salt additives, which promotes the catalyst turnover. A stoichiometric reaction involving a newly synthesized iron(II) diamide complex and DFT studies on the reaction pathway reveals that the present reaction proceeds via a nonconventional Fe(II)−Fe(IV) mechanism. These mechanistic insights will aid the design of new carbon−nitrogen and other carbon−heteroatom bond formations in the future.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data. 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.

■ ACKNOWLEDGMENTS

Research was supported by the Japan Society for the Promotion of Science (JSPS) through the “Funding Program for Next Generation World-Leading Researchers (NEXT Program),” initiated by the Council for Science and Technology Policy (CSTP) and the Japan Science and Technology Agency (JST), the Core Research for Evolutional Science and Technology (CREST) Program. We are grateful to Professor Kazuyuki Tatsumi, Associate Professor Yasuhiro Ohki, Mr. Takayoshi

Hashimoto, and Mr. Genki Kawase at Nagoya University for their guidance on the synthesis of iron amides. We also thank Mr. Sigma Hashimoto and Mr. Yoshihiro Okada at Kyoto University for experimental supports. Synchrotron X-ray absorption measurements were performed at BL14B2 (2011B1945, 2012A1595) and BL27SU (2011B1418, 2012A1636) in SPring-8 with the approval of JASRI.

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(10) LiCl deaggregates TMPMgCl resulting in formation of a highly active deprotonation reagent (Knochel–Hauser base): (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958. X-ray crystallographic and NMR spectroscopic studies: (b) García-Álvarez, P.; Graham, D. V.; Hevia, E.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; O'Hara, C. T.; Weatherstone, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 8079. (c) Armstrong, D. R.; García-Álvarez, P.; Kennedy, A. R.; Mulvey, R. E.; Parkinson, J. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 3185.

(11) LiHMDS is as effective as BuLi and gave 92% yield of **3** in the presence of $MgBr_2$; See the SI for details.

(12) The other iron salts, $FeCl_3$, $Fe(acac)_2$, and $Fe(acac)_3$, showed comparable catalytic activities, although a small amount (2–3%) of anisole was formed as a side product; details in SI.

(13) Nickel phosphine complexes are reported to be suitable for aromatic amination of aryl halides, including inert chlorides: (a) Yang, L.-M.; Chen, C. *Org. Lett.* **2005**, *7*, 2209. (b) Yang, L.-M.; Chen, C. *J. Org. Chem.* **2007**, *72*, 6324.

(14) ICP-MS analysis of $FeCl_2$ showed the presence of <0.1, 35.8, 26.9, and 12.9 ppm Pd, Cu, Co, and Ni, respectively; see SI for additional ICP-MS analysis.

(15) Reaction with magnesium bis(trimethylsilylamide) prepared from LiHMDS and $MgBr_2$ gave <5% yield of corresponding amination product under same conditions.

(16) Bond lengths and angles are similar to those reported for related iron(II) diamide complexes, $[Fe\{N(SiMe_3)_2\}_2]_2$ and $[Fe(NPh_2)_2]_2$: Olmstead, M. M.; Power, P. P.; Shoner, S. C. *Inorg. Chem.* **1991**, *30*, 2547.

(17) Dimer form is stable in solid and solution states; see SI and ref 16.

(18) Preliminary synchrotron X-ray absorption measurements have shown that iron diamides oxidation state was not lower than +II state. Details will be reported in a separate paper.

(19) Fe(II)–Fe(III) mechanism was proposed for iron-catalyzed cross coupling of alkyl halides: (a) Noda, D.; Sunada, Y.; Hatakeyama, T.; Nakamura, M.; Nagashima, H. *J. Am. Chem. Soc.* **2009**, *131*, 6078. (b) Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 10674. (c) Kawamura, S.; Ishizuka, K.; Takaya., H.; Nakamura, M. *Chem. Commun.* **2010**, *46*, 6054. (d) Hatakeyama, T.; Okada, Y.; Yoshimoto, Y.; Nakamura, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 10973. (e) Hatakeyama, T.; Fujiwara, Y.; Okada, Y.; Itoh, T.; Hashimoto, T.; Kawamura, S.; Ogata, K.; Takaya, H.; Nakamura, M. *Chem. Lett.* **2011**, *40*, 1030. (f) Ghorai, S. K.; Jin, M.; Hatakeyama, T.; Nakamura, M. *Org. Lett.* **2012**, *14*, 1066. (g) Hatakeyama, T.; Hashimoto, T.; Kathriarachchi, K. K. A. D. S.; Zenmyo, T.; Seike, H.; Nakamura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 8834.

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(21) Reaction coordinate was investigated for high-spin state (**A**: $S = 4$, others: $S = 2$) because **A** and **B** in high-spin state are stable by >20 kcal/mol as compared to those in low- and intermediate-spin states; details in SI.

(22) Nitrogen-bridged dimer was less stable by 1.9 kcal/mol (Gibbs free energy) than **G**; details in SI.