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Synthesis of Diarylamines Catalyzed by Iron Salts

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Diarylamines constitute a valuable family of organic compounds that are of utmost importance in biological, pharmaceutical, and material sciences.[1] Therefore, the search and development of simple and improved procedures towards the assembly of such a desirable framework represents an elusive goal of particular interest for industrial and academic chemists. The transition-metal-catalyzed cross-coupling of anilines and aryl halides or their equivalents is one of the most powerful and straightforward methods for the preparation of diarylamines. Palladium,[2] copper,[3] and nickel[4] are among the most widely used metals to perform such carbon–nitrogen bond-forming processes, and highly efficient methods are currently available. Nevertheless, aside from the reliability of the existing protocols, the development of a novel catalyst based on cheaper and environmentally benign metals would clearly represent a major advance of significant synthetic practical value.

Owing to its low price, sustainability, and exceptional versatility, iron has attracted a great deal of attention in the field of catalysis, and it is lately evolving into an increasingly powerful and convenient alternative to accomplish a vast array of organic transformations.[5] In this respect, we have recently demonstrated that the adequate combination of $FeCl_3$ and certain supporting ligands results in the formation of catalysts suitable to effect important arylation reactions, rendering novel protocols that display complementary advantages to the previously well-established palladium- and copper-catalyzed arylations. In particular, the use of *N*,*N*′-dimethylethylendiamine (DMEDA) was found to be crucial for *N*-[6a–c] and *S*-arylations[7] as well as Sonogashira coupling.[8a] The success of the cross-coupling of aryl halides with oxygen nucleophiles relied on the use of $FeCl_3$ in combination with 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD).[9] Although several nitrogen nucleophiles (*N*-heterocycles,[6a] primary amides,[6c] and sulfoximines[6b]) smoothly underwent the target cross-couplings, all early attempts conducted with anilines failed, and the corresponding diarylamines were never observed. The poor nucleophilicity of the aniline moiety has also been manifested in the selective arylation of other nucleophiles in the presence of competing free-amino groups.[8a] Very recently, Fu and co-workers developed an alternative iron/copper co-catalyzed *N*-arylation process of both aliphatic and aromatic amines featuring the use of 10 mol% of $FeCl_3$, 10 mol% of CuO, and 20 mol% of *rac*-BINOL as the catalyst system.[6f] Likewise, after the present work was complete, Liu and co-workers disclosed a novel arylation protocol involving the use of Fe_2O_3 and L-proline in DMSO at 135 °C and NaO*t*Bu as base.[10] Despite the potential of the latter method for the *N*-arylation of aliphatic amines, only three examples of aniline substitutions were reported with the highest yield obtained for the corresponding diarylamine being 54%. Apparently, an effective iron-catalyzed *N*-arylation of anilines is still to be found. In this context, we hypothesized that the use of activated substrates could lead to a solution. Thus, the iron-catalyzed arylation of *N*-protected anilines, followed by NH-liberation of the resulting arylated products was proposed to provide diarylamines in a new and practical tandem process.

We first evaluated the influence of acetyl as an *N*-protecting group, and thus the coupling of acetanilide (**1a**) and iodobenzene (**2**) was selected as a model reaction to optimize the reaction conditions. The results of this preliminary screening are summarized in Table 1. When applying the previously reported conditions for the iron-catalyzed *N*-arylation (Table 1, entries 1 and 2), diarylamine **3a** was obtained in low yield along with unreacted starting material **1a**. The choice of the base was found to be critical for the reaction outcome, and the use of Cs_2CO_3 led to the desired arylated product in a better yield (Table 1, entry 3), albeit full conversion was again not achieved. Other bases (Na_2CO_3, Ag_2CO_3, $BaCO_3$, Li_2CO_3, NaOAc) provided only trace amounts of product **3a**. With toluene as the solvent better yields were achieved than with chlorobenzene (Table 1, entries 3 and 16). Other solvents such as butanol

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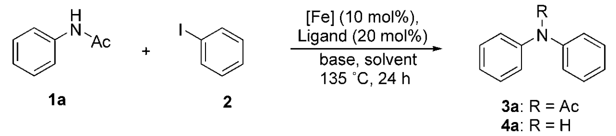
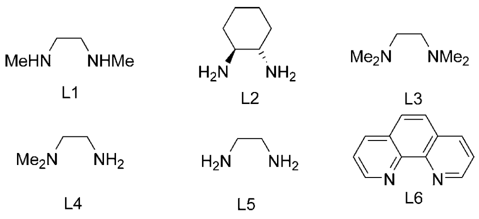
Table 1. Reagent screening for the iron-catalyzed coupling of acetanilide (**1a**) with phenyl iodide (**2**).[a]



Entry	Fe source	Ligand	Base	Solvent	**3a** [%][b]
1	$FeCl_3$	L1	K_3PO_4	PhMe	10
2	$FeCl_3$	L1	K_2CO_3	PhMe	21
3	$FeCl_3$	L1	Cs_2CO_3	PhMe	75
4	$FeCl_3$	L1	NaOMe	PhMe	traces[c]
5	$FeCl_3$	L2	Cs_2CO_3	PhMe	65
6	$FeCl_3$	L2	K_2CO_3	PhMe	23
7	$FeCl_3$	L3	Cs_2CO_3	PhMe	0
8	$FeCl_3$	L4	Cs_2CO_3	PhMe	traces
9	$FeCl_3$	L5	Cs_2CO_3	PhMe	traces
10	$FeCl_3$	L6	Cs_2CO_3	PhMe	traces
11	$FeCl_3$	L6	Cs_2CO_3	PhMe	traces
12	$Fe(acac)_3$	L1	Cs_2CO_3	PhMe	traces
13	$FeCl_3{\cdot}6H_2O$	L1	Cs_2CO_3	PhMe	traces
14	Fe_2O_3	L1	Cs_2CO_3	PhMe	traces
15	$Fe(OAc)_2$	L1	Cs_2CO_3	PhMe	traces
16	$FeCl_3$	L1	Cs_2CO_3	PhCl	41
17	$FeCl_3$	L1	Cs_2CO_3	PhMe	**4a** (91)[c]

[a] Reaction conditions: **1a** (1.0 equiv), **2** (1.5 equiv), Fe source (0.1 equiv), ligand (0.2 equiv), base (2.0 equiv), solvent (1 mL mmol^{-1}), 135 °C, under argon. [b] Yield of isolated product after flash chromatography. [c] $FeCl_3$ (0.15 equiv) and DMEDA (0.30 equiv) were employed. Yield of isolated diphenylamine (**4a**) after arylation and subsequent deprotection with NaOMe; acac = acetylacetonate.



and acetonitrile proved entirely inadequate, leading to deprotection of **1a** and unreacted starting material, respectively. In reference to the nature of the catalyst, the most effective system resulted from combining $FeCl_3$ with DMEDA, while other iron sources and diamine-type ligands exhibited lower catalytic activity (Table 1, entries 5–15).[11] Interestingly, increasing the catalyst loading (to 15 mol % of $FeCl_3$ and 30 mol % of DMEDA) had a perceptibly beneficial effect on the reaction outcome, and full conversion was achieved. Now, however, a considerable amount of the *N*-deprotected **4a** was obtained along with the desired *N*-acetyl diarylamine **3a**. By performing a basic hydrolysis with NaOMe[12] after the the iron-catalyzed arylation, diphenylamine (**4a**) was isolated in a remarkable 91 % yield (Table 1, entry 17). A one-pot synthesis of diphenylamine (**4a**) was performed by adding NaOMe to the *N*-arylation reaction mixture once the acetanilide (**1a**) was completely consumed. Notably, other *N*-protecting groups (benzoyl, trifluoroacetyl, *tert*-butyloxycarbonyl (Boc), tosyl, and benzyl) were not suitable under the optimized conditions of the *N*-arylation. Either no reaction occurred or deprotection was observed to yield the corresponding aniline. As expected, in the absence of catalyst the formation of the target product was not detected.

Next the scope of the process was investigated by exploring the cross-coupling of numerous acetanilides with differently substituted aryl iodides[13] under the optimized conditions for the synthesis of **4a** (Table 2). A variety of acetanilides bearing both electron-donating and electron-withdrawing substituents smoothly underwent the arylation/deprotection sequence to deliver the corresponding diarylamines in good to excellent yields (Table 2, entries 1–15). Likewise, variously substituted aryl iodides could be employed but several electronic restrictions were observed. Whereas the coupling of 4-iodoanisole and 4-fluoroacetanilide (Table 2, entry 9) took place to lead to diarylamine **4d** in excellent yield, other experiments performed with such an electron-rich aryl iodide and related acetanilides were unsuccessful. Moreover, the steric effect was highly significant, and when using *ortho*-substituted aryl iodides only trace amounts of the desired diarylamines **4** were obtained regardless of the electronic nature of the substituent. Interestingly, *ortho* substituents in the acetanilide were better tolerated, and the corresponding diarylamines **4** could be accessed, albeit in moderate yields (Table 2, entries 16–18).

In summary, we have developed a practical and convenient synthesis of diarylamines based on a tandem iron-catalyzed *N*-arylation of acetanilides followed by cleavage of the acetyl group. This strategy overcomes the synthetic limitations associated with the poor reactivity of aromatic amines under iron catalysis and serves as a complementary alternative approach for the preparation of diarylamines.

Experimental Section

General procedure for the synthesis of diarylamines: A sealable tube equipped with a magnetic stir bar was charged with acetanilide **1** (1.0 equiv), aryl iodide **2** (1.5 equiv, if solid), Cs_2CO_3 (2.0 equiv), and $FeCl_3$ (0.15 equiv). The aperture of the tube was then covered with a rubber septum, and an argon atmosphere was established. Aryl halide **2** (1.5 equiv, if liquid), *N,N'*-dimethylethylendiamine (0.30 equiv), and toluene (1 mL mmol^{-1} of acetanilide) were added by using a syringe. The septum was then replaced by a teflon-coated screw cap, and the reaction vessel was placed in an oil bath kept at 135 °C. After the mixture had been stirred at this temperature for 24 h, it was cooled to room temperature, and NaOMe (9.0 equiv) and toluene (0.5 mL) were added. After the reaction mixture had been stirred under reflux for 1.5 h, it was cooled to room temperature and then diluted with dichloromethane. The resulting solution was directly filtered through a pad of silica and concentrated to yield the diarylamine **4**, which was purified by silica gel chromatography. The identity and purity of the known products was confirmed by ^1H and ^{13}C NMR spectroscopic analysis, and the new products were fully characterized.

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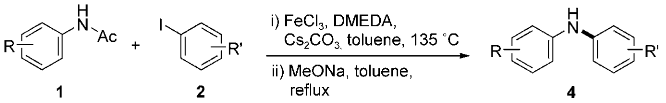
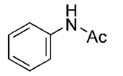
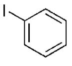
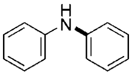
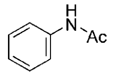
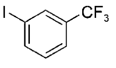
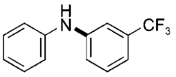
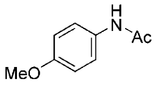
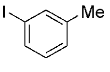
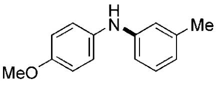
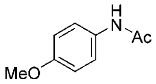
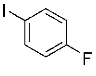
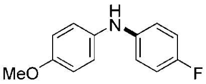
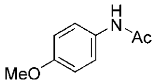
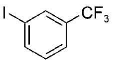
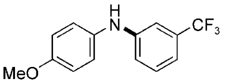
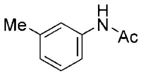
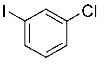
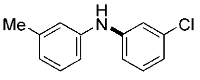
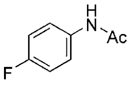
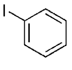
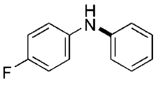
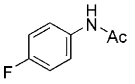
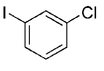
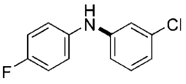
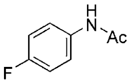
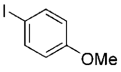
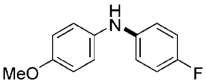
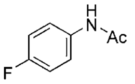
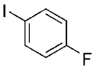
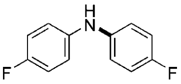
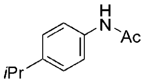
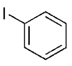
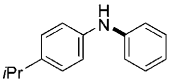
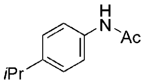
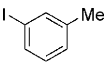
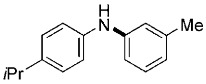
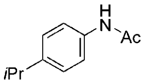
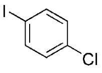
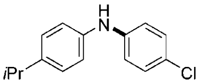
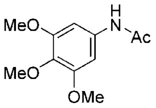
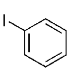
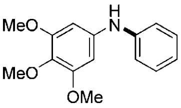
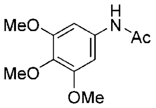
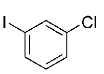
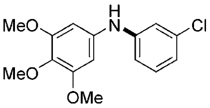
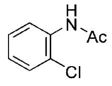
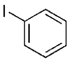
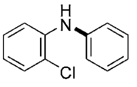
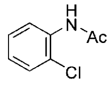
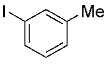
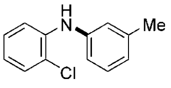
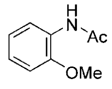
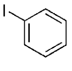
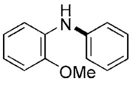
Keywords: anilines · arylation · catalysis · cross-coupling · iron

Table 2. Synthesis of various diarylamines **4**.[a]



Entry	**1**	**2**	**4**[b]		Yield [%]
1				**4a**	91
2				**4b**	66
3				**4c**	88
4				**4d**	80
5				**4e**	47
6				**4f**	82
7				**4g**	94
8				**4h**	91
9				**4d**	92
10				**4i**	50
11				**4j**	80
12				**4k**	63
13				**4l**	83
14				**4m**	68
15				**4n**	57
16				**4o**	43
17				**4p**	38
18				**4q**	55

[a] Reaction conditions: i) **1** (1.0 equiv), **2** (1.5 equiv), $FeCl_3$ (0.15 equiv), DMEDA (0.3 equiv), Cs_2CO_3 (2.0 equiv), toluene (1 mL mmol^{-1}), 135 °C, under argon, 24 h; ii) MeONa (9.0 equiv), toluene (0.5 mL), reflux, 1.5 h. [b] Yield of isolated product after flash chromatography.

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