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Ligand-Free Iron-Catalyzed C−F Amination of Diarylamines: A One-Pot Regioselective Synthesis of Diaryl Dihydrophenazines

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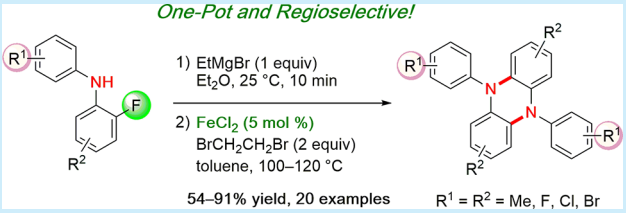
Supporting Information

ABSTRACT: A one-pot synthesis of various 5,10-diaryl-5,10-dihydrophenazines (DADHPs) from diarylamines has been achieved by using an iron-catalyzed C−F amination. Homodimerization of magnesium diarylamides, followed by defluorinative intramolecular cyclization (double *ortho* C−F amination) in the presence of catalytic $FeCl_2$ and stoichiometric 1,2-dibromoethane, affords the corresponding DADHPs with complete regiocontrol. The unique high reactivity of fluorine over other halogens indicates that amination proceeds via an S_NAr mechanism facilitated by iron.

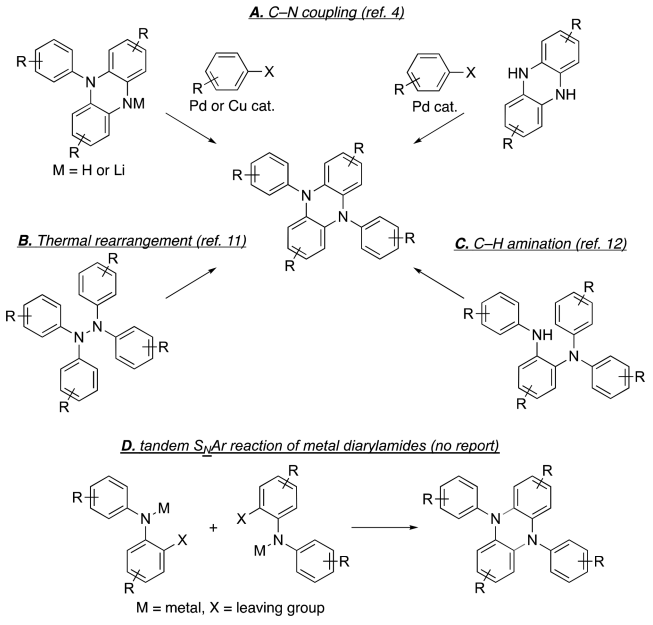


5,10-Diaryl-5,10-dihydrophenazines (DADHPs) have gained considerable research attention due to their promising magnetic properties[1] and their use as organic luminescent materials[2] and photoredox catalysts.[3] However, the synthesis of this class of compounds has been limited by the synthetic drawbacks of existing methods.

The C−N coupling reaction between aryl halides and dihydrophenazine derivatives[4] using copper- or palladium-based catalysts (Schemes 1A) needs prior construction of a dihydrophenazine core via the classical Wohl−Aue reaction[5] or double C−N coupling reaction of two 2-haloanilines.[6] These preparations require harsh conditions[7] and multistep regioselective functionalizations.[8] Moreover, these synthetic methods for DADHPs have drawbacks such as potential contamination of harmful or hazardous residual metals at the late stage and difficulty in the tolerance of chloro and bromo substituents, which can further diversify the DADHPs by consecutive synthetic elaborations.[9,10] Thermal rearrangement of tetraarylhydrazines can produce DADHPs, albeit also giving monomers and oligomers of diarylamines and resulting in low yields of DADHPs (Scheme 1B).[11] We recently reported intramolecular C−H amination of multiply *N*-arylated *o*-phenylenediamines using an iron catalyst (Scheme 1C).[12] While high regioselectivity and functional group tolerance were attained by this method, the low yield of the desired DADHP and difficulty in the synthesis of the precursor, *o*-phenylenediamine, severely limited its synthetic applicability.

Scheme 1D shows a synthesis of DADHPs: double-nucleophilic aromatic substitution (S_NAr) reaction of two metal amides of diarylamines can yield the target DADHPs in a regioselective manner. However, despite the significant progress of S_NAr reactions with amines in recent years,[13,14] no successful examples of this class of reactions have been reported.

Scheme 1. Synthesis of DADHPs



Herein, we report a one-pot synthesis of DADHP from diarylamines by using a novel iron-catalyzed C−F amination reaction (Scheme 2). The homodimerization of magnesium

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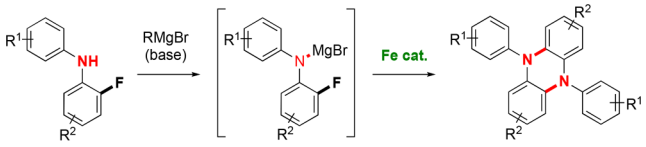
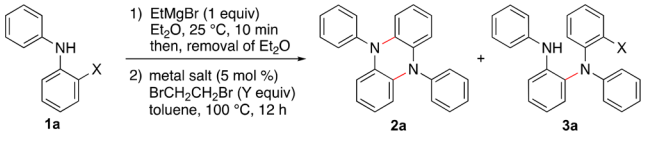
Scheme 2. Iron-Catalyzed Double *Ortho* C−F Amination for Substituted DADHPs



diarylamides by intermolecular amination via C−F bond cleavage, followed by defluorinative cyclization (double *ortho* C−F amination), proceeds in the presence of a catalytic amount of iron salt and a stoichiometric amount of 1,2-dibromoethane to afford the corresponding DADHPs in a highly regioselective manner. The unique high reactivity of fluorine over the other halogens indicates that the present amination proceeds via an S_NAr mechanism promoted by iron.

During our previous study on the iron-catalyzed aromatic aminations of aryl halides with magnesium amides,[15] we observed the formation of DADHP by tandem inter- and intramolecular C−F aminations using 2-fluoro-*N*-phenylaniline as the amine substrate. We further examined the reaction conditions to find that the combination of a catalytic amount of $FeCl_2$ and a stoichiometric amount of 1,2-dibromoethane was effective to obtain the desired DADHP in high yields. As shown in Table 1, diarylamine **1a** was treated with 1 equiv of EtMgBr in

Table 1. Screening of Catalysts[a]



entry	X	metal salt	Y	yield of **2a**[b] (%)	yield of **3a**[b] (%)	recovery of **1a**[b] (%)
1	F	none	0	0	0	>99
2	F	$FeCl_2$	0	11	7	76
3	F	$FeCl_3$	0	11	2	62
4	F	$FeCl_2$	2	78 (76[c])	0	20
5	F	$NiCl_2$	2	34	7	47
6	F	$CoCl_2$	2	15	12	64
7	Cl	$FeCl_2$	2	0	0	>99
8	Br	$FeCl_2$	2	<1	0	99

[a]Reactions were carried out on a 0.3 mmol scale. [b]Yield determined by GC analysis. [c]Isolated yield.

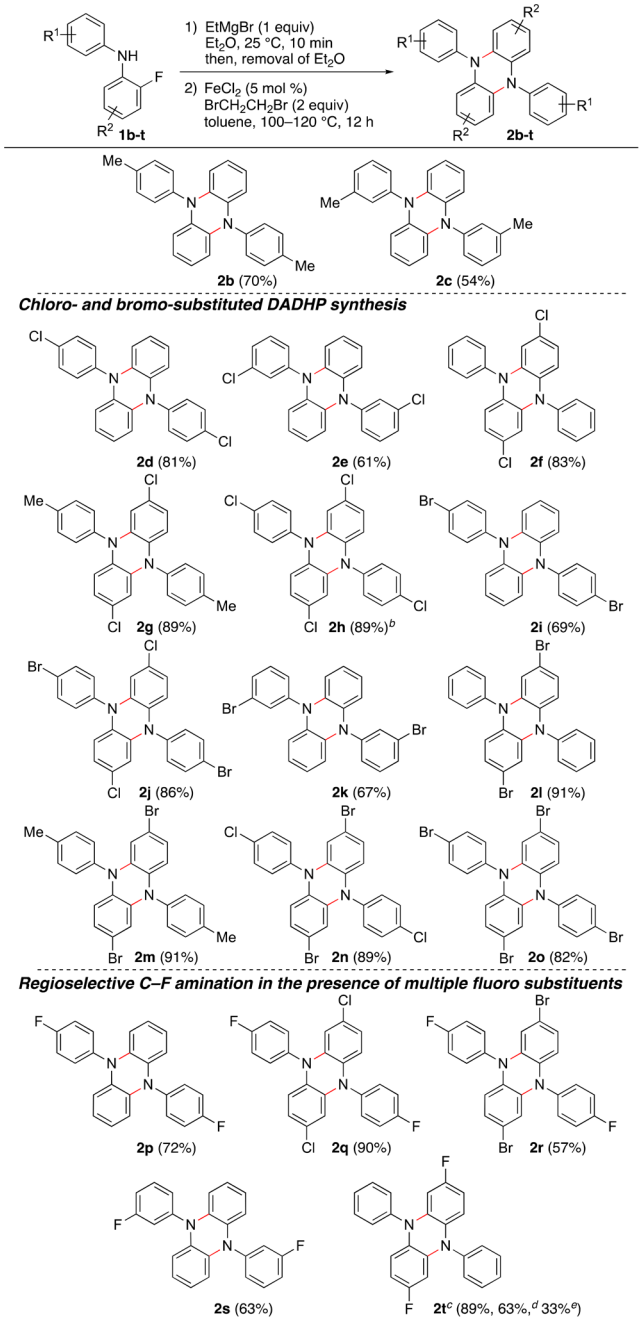
diethyl ether to produce the corresponding magnesium amide. The solvent was then changed to toluene, and after addition of a metal catalyst with or without an additive, the resulting mixture was heated at 100 °C for 12 h.

No reaction occurred in the absence of metal catalyst (entry 1), while the addition of 5 mol % of $FeCl_2$ slightly promoted the reaction to afford a mixture of **2a** and *o*-phenylenediamine **3a** in 11% and 7% yields, respectively (entry 2). An iron(III) salt, $FeCl_3$, also provided **2a**, with reduced formation of **3a**, albeit in low yield (entry 3). The addition of 1,2-dibromoethane promoted the C−F amination dramatically, affording the corresponding DADHP **2a** in 78% yield (entry 4). The reactions of 2-fluoro-*N*-phenylaniline catalyzed by $NiCl_2$ and $CoCl_2$ afforded **2a** in only 34% and 15% yields, respectively, in the presence of 2 equiv of 1,2-dibromoethane, thus demonstrating the advantage of the iron catalyst (entries 5 and 6).

Interestingly, the reactions of diarylamines possessing a chloro or a bromo substituent, instead of the fluoro substituent, did not proceed under the same reaction conditions with entry 4 (entries 7 and 8). The specific reactivity of fluoro substituent indicates that the amination reaction described here likely proceeds via an S_NAr reaction mechanism.[16]

Scheme 3 displays the substrate scope of the one-pot DADHP synthesis based on the optimized procedure, by which a variety of substituted DADHPs were obtained in good to excellent

Scheme 3. Regioselective Synthesis of Substituted DADHPs[a]



[a]Reactions were carried out on a 0.3 mmol scale, and isolated yields are given, unless otherwise noted. [b]Purity of product was 96% by GC analysis. [c]Reaction was carried out at 100 °C for 12 h. [d]Reaction was carried out on a 12 mmol scale. [e]Reaction without $FeCl_2$ and 1,2-dibromoethane, yield determined by GC analysis.

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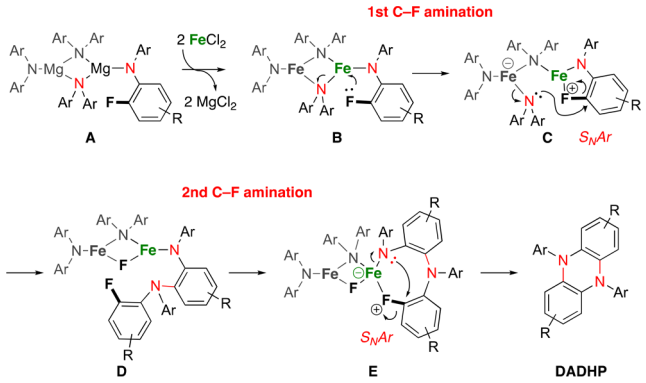
yields with complete regioselectivity. Methyl-substituted DADHPs **2b** and **2c** were obtained in 70% and 54% yields, respectively. The synthetic utility of the amination reaction described here was highlighted by the tolerance of chloro and bromo substituents, which is difficult in the transition-metal-catalyzed C−N coupling reaction of aryl halides. DADHPs **2d**−**o**, which bear chloro and bromo substituents at various positions on the aromatic rings, including the phenazine core, were obtained in 61−91% yields.

It should be noted that this *ortho* C−F amination occurred regioselectively even in the presence of fluoro substituents at the *para* and *meta* positions. The reaction enabled the efficient synthesis of DADHPs **2p**−**t**, bearing fluoro substituents in various positions on the aromatic rings including the phenazine's core. The present reaction was amenable to gram-scale synthesis, affording DADHP **2t** (1.4 g) in 63% yield. The desired DADHP **2t** was obtained in 33% yield in the absence of $FeCl_2$ and 1,2-dibromoethane, although the reaction was sluggish.

Scheme 4 shows a possible reaction mechanism for the iron-catalyzed amination reaction. We assume that the formation of

Scheme 4. Possible Reaction Pathways



dinuclear tetraamide metal complexes (iron[17] and/or magnesium[18]) precedes the C−N bond formation. Heating a toluene solution of magnesium diarylamide leads to significant precipitation of $MgBr_2$, suggesting the formation of magnesium amide dimer **A**.[19] Transmetalation of $FeCl_2$ with magnesium amide affords a four-membered cyclic iron diamide complex **B**.[20] After the formation of the complex in an open form, assisted by coordination of fluoro substituents to the nearby iron center (**C**),[21] the intermolecular C−F amination proceeds most likely via an S_NAr pathway to afford the iron amide complex bearing the corresponding *o*-phenylenediamine **D**. In the second step, the intramolecular C−F amination of the *o*-phenylenediamine via an S_NAr pathway (**E**) affords the corresponding DADHP. When 2,4-difluoro-*N*-phenylaniline was used as the substrate, the two fluoro substituents increased the S_NAr reactivity of the aromatic ring to enable tandem C−F aminations in the absence of the iron catalyst and 1,2-dibromoethane, albeit in low yield under the same conditions of reaction time and temperature. The role of 1,2-dibromoethane remains unclear, although we infer that it could oxidize the iron diamide species to promote the S_NAr reactions. Density functional theory calculations on the reaction pathway are ongoing to examine the proposed mechanism.[22]

In summary, we have developed a one-pot synthesis of DADHPs from diarylamines by using a novel iron-catalyzed *ortho* C−F amination. Homodimerization of magnesium diarylamides by intermolecular amination via C−F bond cleavage, followed by defluorinative cyclization, occurs in the presence of a catalytic amount of iron salt. The *o*-fluoro substituent showed specific reactivity, enabling regioselective synthesis of DADHPs bearing halo substituents (fluoro, chloro, and bromo substituents) at various desired positions on the aromatic ring. These features of the synthetic method described here can increase the structural diversity and availability of DADHPs and will contribute to further development of this class of functional molecules in the fields of material science and synthetic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03702.

Procedures, characterization data, and spectra for all compounds (PDF)

Accession Codes

CCDC 1878774−1878787, 1878875−1878876, 1878961, and 1879251 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(19) Before heating magnesium amide in toluene with or without $FeCl_2$ and 1,2-dibromoethane, no insoluble solid except for $FeCl_2$ was observed in the reaction vessel. Heating the reaction mixture up to 100 °C led to rapid generation of an insoluble white solid, which might be $MgBr_2$, indicating that magnesium amides disproportionate to afford the corresponding magnesium diamides.

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