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Letter

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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.6b02576 • Publication Date (Web): 31 Oct 2016

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Direct and Practical Synthesis of Primary Anilines through Iron-Catalyzed C–H Bond Amination

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ABSTRACT: The direct C–H amination of arenes is an important strategy to streamline the discovery and preparation of functional molecules. Herein, we report an operationally simple arene C–H amination reaction that, in contrast to most literature precedent, affords directly the synthetically versatile primary aniline products without relying on protecting group manipulations. Inexpensive Fe(II)-sulfate serves as a convenient catalyst for the transformation. The reaction tolerates a wide scope of arenes, including structurally complex drugs. Importantly, the arene substrates are used as limiting reagents in the transformation. This operationally simple transformation should considerably accelerate the discovery of medicines and functional molecules.

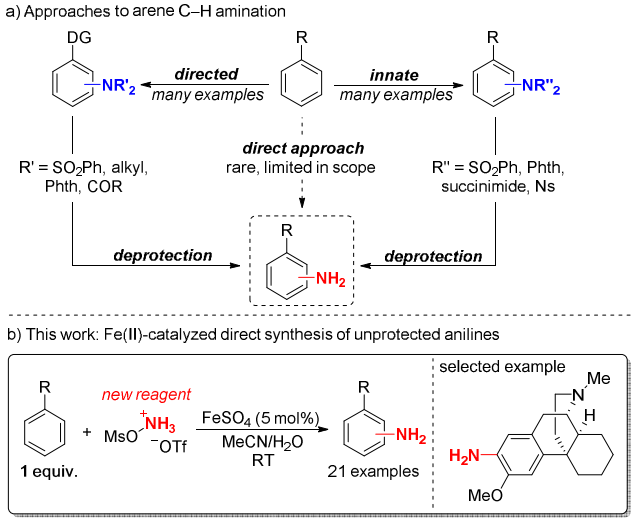
KEYWORDS: iron, aniline, amination, PG free, C–H functionalization, late stage functionalization.

The synthesis of arylamines is important because of their numerous applications in the preparation of pharmaceuticals,[1] agrochemicals,[2] dyes and materials.[3] The traditional approach to aniline synthesis involves the nitration of arenes followed by reduction.[4] Milder cross-coupling strategies using aryl halides as starting materials, most notably the Buchwald-Hartwig[5] and Chan-Lam[6] amination reactions, have been established as convenient alternatives to the nitration protocol to access functionalized aryl amines. Notably, recent reports of cross-coupling reactions have enabled the direct catalytic preparation of primary anilines.[7] Despite its high efficiency and reliability, the cross-coupling approach is limited by the need for prior introduction of suitably placed cross-coupling partners (e.g. halides) onto the aromatic ring.

In contrast, strategies proceeding through direct C–H amination overcome the need for prefunctionalization and offer the promise to considerably streamline the synthesis of valuable aryl amines. Kovacic, Minisci, Skell and Chow were among the first researchers to report on the C–H amination of aromatic rings.[8] Notably, Kovacic and Minisci reported the direct amination of simple benzene derivatives using hydroxylamine *O*-sulfonic acid (HSA) and an aluminium or iron catalyst, respectively. However, while serving as a proof-of-concept, these early protocols were greatly limited in scope and yields, most likely because of the instability of HSA in solution.[9] Considerable research efforts have recently targeted the development of more efficient and broadly applicable catalytic intermolecular C–H amination reactions for the preparation of functional molecules. Directed approaches to C–H amination are very useful when suitably placed functional groups can serve to facilitate the C–H bond functionalization step.[10] An alternative, synthetically complementary approach through the innate C–H amination of simple arenes provides a tool to access anilines without the need for directing groups. Innate C–H amination reactions can thus greatly facilitate the discovery of new materials and medicines through the late-stage C–H amination of densely functionalized molecules. Among the numerous recent reports of innate C–H amination,[11] only a few enable the unreactive arene substrate to be used as the limiting reagent,[12] a critical feature for the application of these reactions to the late-stage amination of valuable substrates. More importantly, as noted by Itami in a very recent review,[13] innate C–H amination protocols have so far relied on the use of nitrogen reagents that bear strongly electron-withdrawing substituents to overcome the otherwise low reactivity of simple arenes through the generation of highly reactive nitrogen species (e.g. nitrene or nitrogen-centered radicals). These reactions thus result in the incorporation of a *protected form* of the amino group (in most cases N–$(SO_2Ph)_2$, phthalimide or succinimide), greatly mitigating the synthetic benefits of the direct C–H amination strategy by adding unnecessary, often complicated deprotection steps to access the primary aniline (Scheme 1a).[14] A rare recent example of the direct installation of the primary amine group has been reported by the group of Nicewicz using a dual catalytic system combining an organophotoredox catalyst and TEMPO in a reaction that proceeds through arene cation radicals resulting from the oxidation of the aromatic ring.[15,16] However, the scope of the reaction was limited to the use of easily oxidized aromatic substrates and afforded only moderate yields of the corresponding products. Thus, a robust and operationally simple catalytic innate C–H amination reaction that leads to the direct preparation of primary anilines from a broad range of arenes used as limiting reagents, including drug molecules, still remains to be developed.

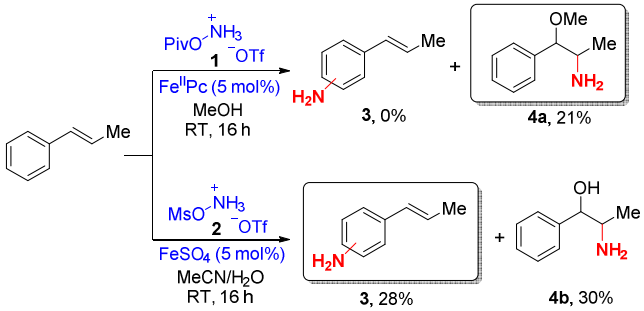
Herein we report a practical, $FeSO_4$-catalyzed C–H amination reaction for the direct synthesis of primary anilines from a broad range of arenes used as limiting reagents, including densely functionalized bioactive compounds. The method uses a new highly reactive, yet shelf-stable, protonated hydroxylamine-derived reagent (Scheme 1b).[17]

Scheme 1. Context of the work



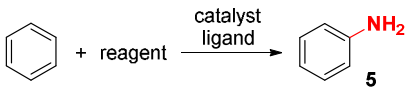
We have recently reported our successful efforts to develop an iron-catalyzed synthesis of unprotected amino alcohols using hydroxylamine-derived reagents and alkenes.[18a] In an attempt to expand the scope of this transformation, we prepared and evaluated several aminating reagents and iron catalysts. Surprisingly, when we used the new aminating reagent $MsONH_3OTf$ **2** and $FeSO_4$ as catalyst, we discovered that the expected aminohydroxylation of β-methyl styrene was competing with the formation of products **3** from direct C–H amination (Scheme 2).

Scheme 2. Serendipitous discovery of a catalytic system exhibiting high intrinsic reactivity towards C–H bonds



The serendipitous discovery of this catalytic system exhibiting unusually high intrinsic reactivity towards aromatic C–H bonds, made us consider the possibility to develop a general and practical C–H amination reaction. The optimum conditions for this transformation highlights its operational simplicity: $FeSO_4$ (5 mol%), $MsONH_3OTf$ (1.5 equiv) in $MeCN/H_2O$ at RT for 16 h. Notably, the arene is used as the limiting reagent, which bodes well for the application of the method to the amination of valuable starting materials. The use of a protonated aminating reagent[8b,12d,19] is important for two reasons: (1) it increases the electrophilicity of the putative aminium radical species and (2) the deactivating ammonium substituent resulting from the amination prevents the overamination of the aromatic ring. A set of control reactions revealed some additional important features of the transformation. The reaction tolerates a relatively broad range of Fe precatalysts (Entries 3-5) but gives lower yields with other metals (Entries 1 and 2). In contrary to our previously developed aminohydroxylation protocol, the addition of nitrogen ligands was, at best, ineffective (Entries 6-10). The newly developed reagent (**2**) is clearly superior to hydroxylamine *O*-sulfonic acid, which is the reagent that was used in the older reports from Kovacic and Minisci (Entry 13). Additionally, our preferred reagent for aminohydroxylation (**1**) performed much worse in the C–H amination reaction than the new reagent (Entry 14). Reagent **2**, which is easily prepared on multigram scale, appears to be a very reactive, yet shelf-stable aminating reagent with broad potential for the development of new amination reactions.

Table 1. Evaluation of reaction conditions[a]



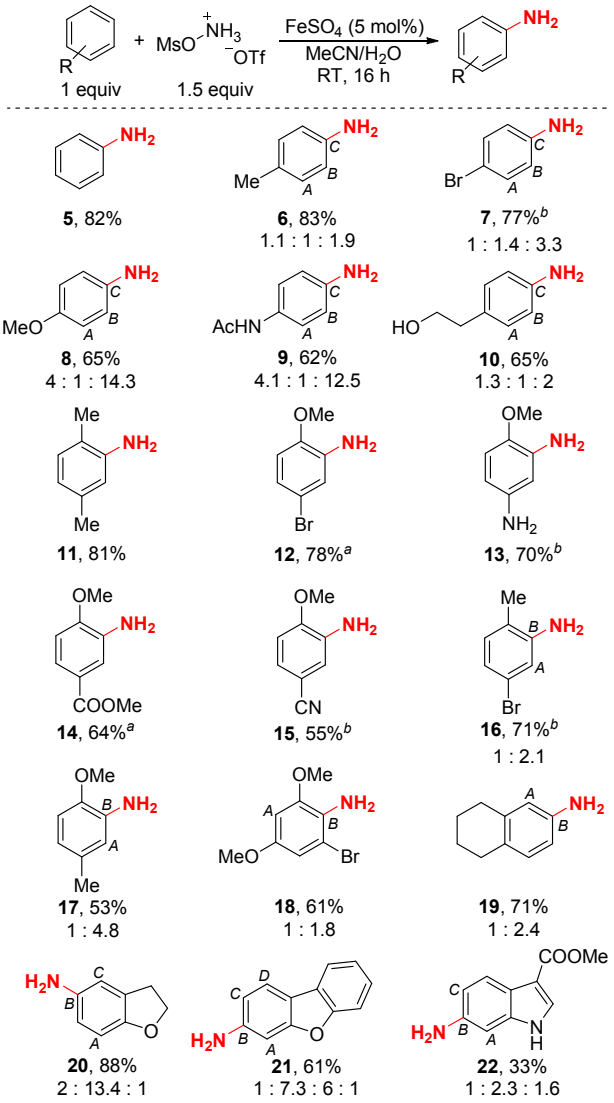
Entry	Catalyst (5 mol%)	Ligand (10 mol%)	Reagent (1.2 eq)	Yield[b]
1	$MnSO_4$	-	**2**	< 5%
2	$Cu(MeCN)_4PF_6$	-	**2**	17%
3	$FeCl_2$	-	**2**	63%
4	$FeBr_2$	-	**2**	67%
5	$Fe(OAc)_2$	-	**2**	73%
6	Fe(II)Pc	-	**2**	23%
7	$FeSO_4$	Bipyridine	**2**	10%
8	$FeSO_4$	Phenanthroline	**2**	27%
9	$FeSO_4$	*tert*-Bu-BOX	**2**	75%
10	$FeSO_4$	Phenyl-Py-BOX	**2**	75%
11	$FeSO_4$	-	**2**	76%
12	$FeSO_4$	-	**2** (1.5 eq)	82%
13	$FeSO_4$	-	HSA	16%
14	$FeSO_4$	-	**1**	42%

[a] 5 mol% catalyst, MeCN/H2O, 16 h, RT. [b] GC-yield.

A wide range of mono-, di- and trisubstituted arenes, always used as limiting reagents, provided the corresponding unprotected anilines in good yields (Scheme 3). This procedure was tolerant of a large range of functional groups, including unprotected amines and hydroxyl groups. Halogen substituents, which can be reactive under transition-metal catalysis, were also tolerated under

our reaction conditions, demonstrating that our protocol efficiently complements traditional amination reactions proceeding through halogen cross-coupling. Resonance donors, such as halogens, methoxy group and acetamide, directed the amination to the para position (**7**, **8**, **9**). Inductive donors, as in **6** and **10**, did not have a strong directing effect. Most of the disubstituted arenes provided the desired products (**11**, **12**, **13**, **14**, **15**) with complete regioselectivity. Interestingly, when 4-methoxyaniline was submitted to the reaction conditions, the amination was exclusively directed to the *ortho* position by the methoxy group (**13**), confirming that amine groups are protonated under the reaction conditions. Finally, we evaluated a few additional heteroarene substrates to expand the scope of the reaction beyond the synthesis of primary anilines. Dihydrobenzofuran and dibenzofuran could undergo amination in good yields and a mildly deactivated indole ring tolerated the desired transformation, albeit in lower yield.

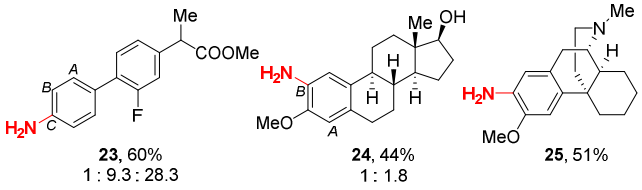
Scheme 3. Substrate scope



[a]Use of 2.5 equiv of reagent. [b]Use of 4.0 equiv of reagent. Isomeric distribution determined by ^{1}H-NMR analysis of the crude reaction mixture.

Due to the high prevalence of carbon-nitrogen bonds in bioactive molecules, we applied the protocol in hand to the late-stage C–H amination of drugs and derivatives (Scheme 4). Surprisingly, to the best of our knowledge, the direct construction of primary anilines through the late-stage C–H amination of drug candidates has not been yet demonstrated, despite the great potential of this approach to lead discovery. A derivative of Flurbiprofen, a common non-steroidal anti-inflammatory drug, was selectively aminated on the more electron-rich aromatic group in good yield. The formation of more than one isomer, rather than being a limitation of our system, may represent an advantage in the generation of compound libraries essential for the drug discovery process.[20] 17ß-Estradiol-3-methyl ether, a bioactive derivative of estrogenic sex hormones, could also undergo the desired transformation, affording two isomers of the desired product (**24**). When dextromethorphan, a blockbuster drug of the morphinan class, was submitted to the reaction conditions, the presence in *meta* position of a quaternary carbon effectively blocked one of the two *ortho* positions, giving only one isomer of the expected free amination product (**25**). Overall, these experiments demonstrate the potential of our methodology for the late-stage amination of densely functionalized drugs.

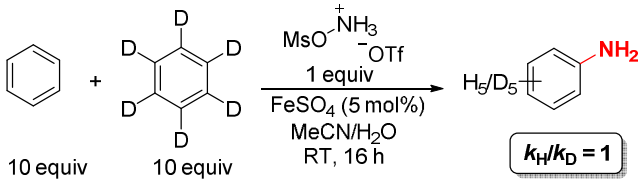
Scheme 4. Late stage functionalization



We have performed several control experiments to obtain mechanistically relevant information. First, intermolecular competition experiments were performed. A *p*-MeO substituted arene reacted much faster than the Me-substituted one, while the Br-substituted substrate led to a much lower rate of amination (Scheme S1 in the Supporting Information). These results reveal a strong dependence of the rate of the reaction on the introduction of substituents affecting the electronics of the aromatic system. In a competition experiment using excess of deuterated benzene and benzene, the ratio of products was determined to be 1 (Scheme 5). It can thus be concluded that no primary kinetic isotope effect is occurring under our reaction conditions, a result that positions the C–H cleavage step after the rate-limiting step of the reaction.[21] Surprisingly, the use of Fe(III)-sulfate as catalyst gave similar results when compared to the standard conditions using Fe(II). To explore the possibility of the iron catalyst acting as a radical chain initiator, we performed a few control experiments using common radical initiators, such as peroxides and AIBN, in place of Fe(II), but no

product was observed even at higher temperature. While, collectively, these experiments suggest that the attack of a highly electrophilic aminating species onto the aromatic ring is likely, the exact nature of this reactive intermediate remains to be determined through detailed mechanistic studies.

Scheme 5. Kinetic Isotope Effect.



In conclusion, we have reported a rare example of direct catalytic synthesis of primary anilines through C–H amination. Our protocol relies on the use of an exceedingly cheap and simple catalyst ($FeSO_4$) and a new hydroxylamine-derived reagent under mild reaction conditions. This transformation tolerates a broad scope of substrates and functionalities, as demonstrated in the late-stage functionalization of several drug derivatives. We believe that this practical approach to C–H amination will be of immediate utility to medicinal chemists and further lays the groundwork for the development of sustainable amination reactions.

ASSOCIATED CONTENT

Supporting Information

The supporting Information is available free of charge via the Internet at http://pubs.acs.org.

General information, materials, instrumentation, procedures and characterization data.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Generous funding from the Max-Planck-Society, the Max-Planck-Institut für Kohlenforschung and the Fonds der chemischen Industrien is acknowledged. We kindly thank Prof. B. List for sharing analytical equipment, and our technical departments for assistance.

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SYNOPSIS TOC: The chemical synthesis of anilines through C–H functionalization is very important for the discovery and synthesis of medicines and other functional molecules. In this research article, we report on an operationally simple reaction that can directly transform arene substrates, including densely functionalized medicines, into primary anilines. The transformation uses a non-toxic, extremely abundant catalyst ($FeSO_4$) and does not rely on any wasteful protecting group manipulation to access the targeted primary anilines.