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C–H Amination of Arenes with Hydroxylamine

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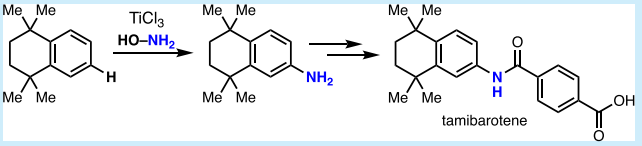
ABSTRACT: This Letter describes the development of a Ti^{III}-mediated reaction for the C–H amination of arenes with hydroxylamine. This reaction is applied to a variety of electron-rich (hetero)arene substrates, including a series of natural products and pharmaceuticals. It offers the advantages of mild conditions (room temperature), fast reaction rates (<30 min), compatibility with ambient moisture and air, scalability, and the use of inexpensive commercial reagents.



Aniline derivatives ($ArNH_2$) appear in a wide variety of specialty chemicals, materials, natural products, and pharmaceuticals.[1] As such, synthetic methods for the formation of $ArNH_2$ are highly sought-after in organic synthesis. In general, the most common approaches involve transition-metal catalyzed cross-coupling,[2] arene nitration/reduction,[3] and arene C–H amination protocols.[4−6] However, due to high reagent/catalyst costs as well as reactivity concerns, process-scale preparations of $ArNH_2$ still largely rely on nitration of the corresponding aromatic precursor followed by hydrogenation to yield the aniline products (Figure 1A).[7]

We sought to develop a practical alternative to nitration/reduction that enables the direct conversion of arenes (Ar–H) to $ArNH_2$. Recent reports have shown that *O*-protected hydroxylamine derivatives (e.g., **A**–**D** in Figure 1B) are effective reagents for Fe-catalyzed arene C–H amination.[4−6] A key step of these reactions involves Fe-mediated N–O bond cleavage to release an aminyl radical ($H_2N^{\bullet}$). This radical (and/or its conjugate acid $H_3N^{\bullet+}$) then reacts with the arene substrate, ultimately affording an aniline product.[8] While this is a conceptually attractive approach, in practice current methods are limited by the requirement for an electron-withdrawing substituent on oxygen to facilitate N–O bond scission.[9] These functionalized hydroxylamine derivatives can be expensive and/or require multistep synthesis, thus rendering them less practical for larger scale applications. Herein, we develop a method that accesses an analogous reaction manifold using the commodity chemical hydroxylamine as the aminating reagent (Figure 1C). This transformation is high yielding, inexpensive, and scalable and thus offers a complement to existing C–H amination methods as well as more traditional nitration/reduction sequences.

Pioneering early work by Keller, Kovacic, and Minisci demonstrated the feasibility of the Ti^{III}-mediated amination of electron-rich arenes using hydroxylamine.[10−13] However, these early examples were very limited due to their narrow substrate scope, low yields, formation of side products, and the requirement for large excesses of arene substrate.[14] For

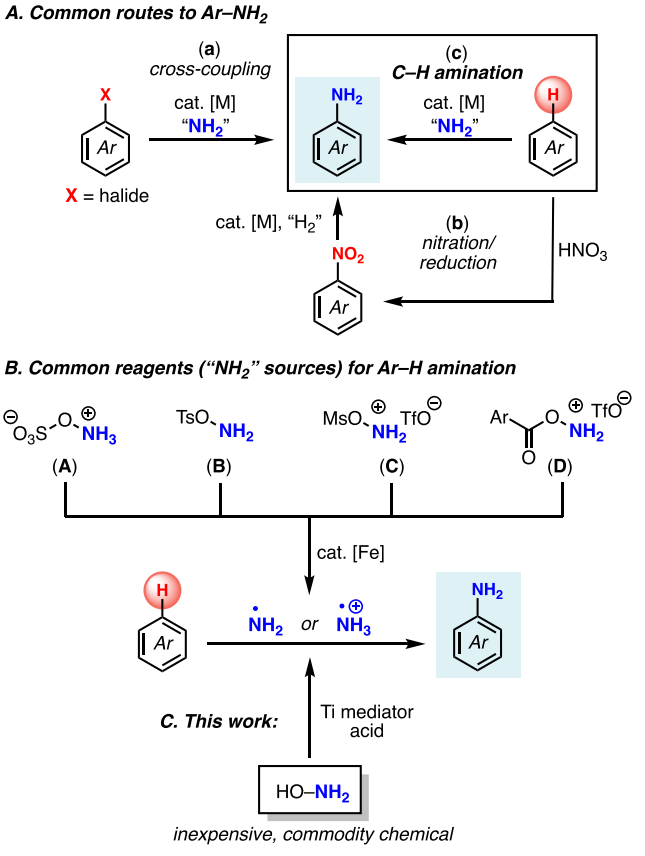


Figure 1. (A) Synthetic approaches to Ar–NH_2. (B) Reagents for Ar–H amination. (C) This work: H_2NOH as a reagent for C–H amination.

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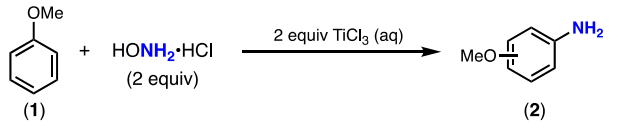
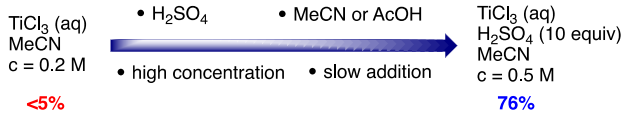
example, under Minisci's original reaction conditions (using excess arene in methanol), the $TiCl_3$-mediated amination of anisole (**1**, 4 equiv) with hydroxylamine (1 equiv) afforded <18% yield of aniline **2** (based on hydroxylamine as the limiting reagent; Figure 2, entry 1). To address these limitations, we initially evaluated a series of first row transition metal salts (e.g., Ti, V, Cr, Mn, Fe, Co, Ni, Cu) as redox mediators for this transformation. Among these, only titanium(III) salts proved effective. Extensive optimization revealed that several factors have a favorable impact on the rate and yield of the reaction (Figure 2). These include the use of (1) sulfuric acid as an additive,[15] (2) high concentration of the arene, (3) acetonitrile or acetic acid as solvent, and (4) slow addition of Ti^{III} (as a solution in HCl). Overall, the optimal conditions were found to involve the slow addition of $TiCl_3$ to a mixture of arene substrate (1 equiv), hydroxylamine hydrochloride (2 equiv), and sulfuric acid (10 equiv) in acetonitrile at room temperature. This afforded a combined 76% yield of **2** (76% isolated, 1:2.2 ortho-/para-isomer, 5:2 mono-/diamination).[16] Importantly, these conditions employ the arene substrate as the limiting reagent and afford <5% side products (the mass balance is predominantly starting material). The reaction does not require the exclusion of air/moisture, and it affords comparable yield upon scaling from 1 to 10 mmol (*vide infra*). Furthermore, reaction progress can be conveniently monitored by the decolorization of the unreacted Ti^{III}.



Key Optimization Parameters:

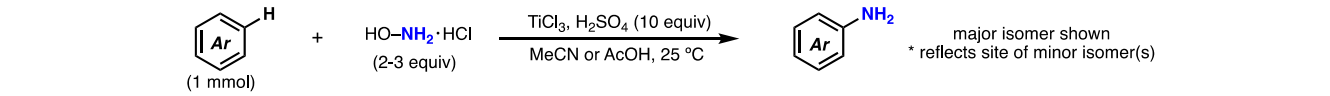


Conditions (deviation from standard)[a]	Yield **2**[b]
literature (Minisci): MeOH solvent, c = 0.5 M	18%
slow addn of [Ti]	7%
slow addn of [Ti], H_2SO_4 (10 equiv)	39%
slow addn of [Ti], H_2SO_4 (10 equiv), 0.25 M	51%
slow addn of [Ti], H_2SO_4 (10 equiv), 0.5 M	76%
slow addn of [Ti], H_2SO_4 (10 equiv), 0.5 M, AcOH solvent	72%

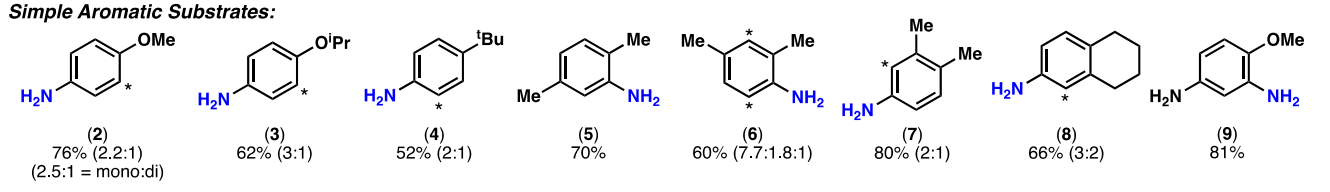
Figure 2. Reaction optimization. [a]Conditions: substrate (0.2 mmol), $NH_2OH{\cdot}HCl$ (0.4 mmol), $TiCl_3$ (0.4 mmol, added over 20 min), MeCN (2.0 mL) unless stated otherwise. [b]GC yield, mono-/diamination, ortho/para isomer observed; see Supporting Information for complete details.

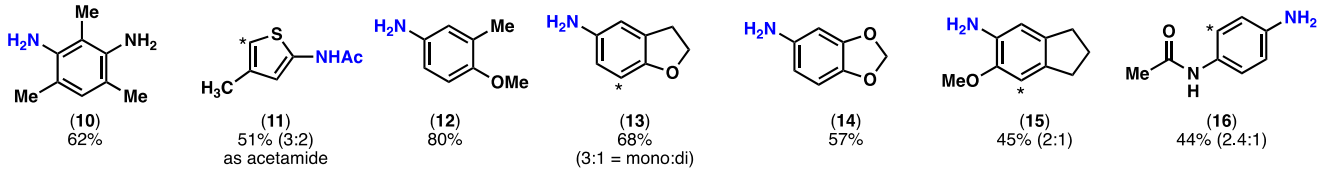
We next examined the reactivity of a panel of arene substrates under the optimized reaction conditions (Scheme 1). Good to excellent yields were obtained with various mono-, di-, and trisubstituted arenes bearing electron-donating substituents. In contrast, less electron-rich arenes (e.g., benzene) afforded low yields (see p S10 for substrates that afforded yields of ≤10%). As with anisole, small amounts

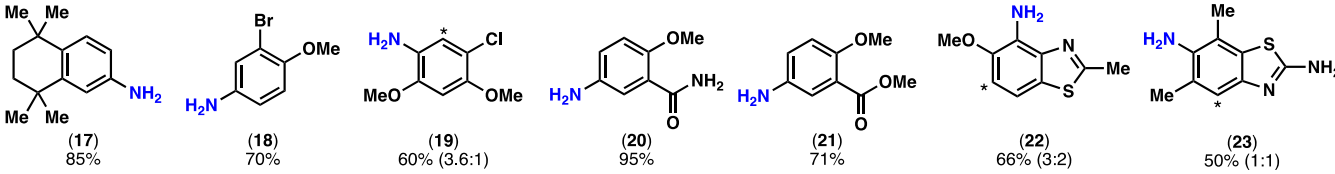
Scheme 1. Substrate Scope of C−H Amination



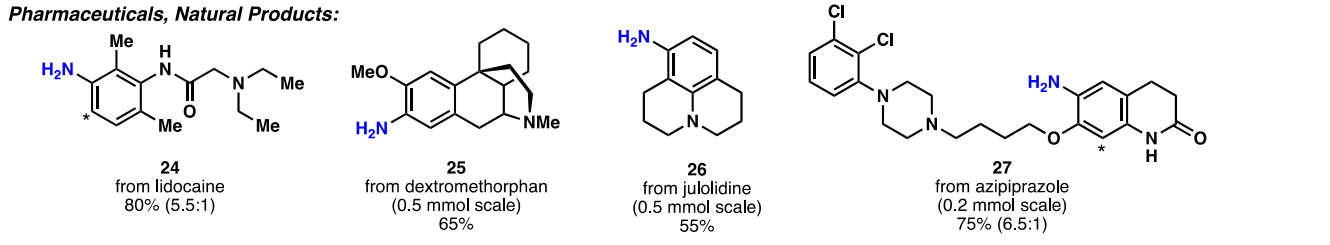
Simple Aromatic Substrates:







Pharmaceuticals, Natural Products:



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(typically ≤20% yield) of diamination products were also observed for some substrates (see Supporting Information for details). Generally, 2−3 equiv of hydroxylamine hydrochloride were required to achieve maximum yield. Functional groups such as ethers, esters, amides, free amines, chlorides, and bromides were tolerated. Several heterocyclic arenes underwent ring amination to afford thiophene **11** and benzathiazoles **22** and **23**. The observed selectivities are in line with those reported for other C(sp^2)−H amination reactions with aminyl radicals.[4−6] The reaction is sensitive to sterics, with C−H amination occurring preferentially at sterically less encumbered sites (for example, see **4** and compare **8** with **17**). In cases where low solubility of the substrate resulted in precipitation (e.g., **23**), additional volumes of acetonitrile, hydroxylamine hydrochloride, and sulfuric acid were added to maximize conversions. Acetonitrile was found to be the most general solvent, but the use of acetic acid significantly improved the conversion with several substrates (e.g., **14**, **18**, **26**).

Several pharmaceuticals and natural products with denser and more complex substitution patterns were also effective substrates. Notably, arene amination was selective for the more electron-rich ring in azipiprazole (**27**). While some of the more complex substrates afforded mixtures of isomeric products (**24** and **27**), these examples demonstrate the potential for applying this method in the late stage C−H amination of relatively complex intermediates.[17]

As shown in Figure 3A, this procedure is readily scalable. For instance, the C−H amination to form **17**, an intermediate in

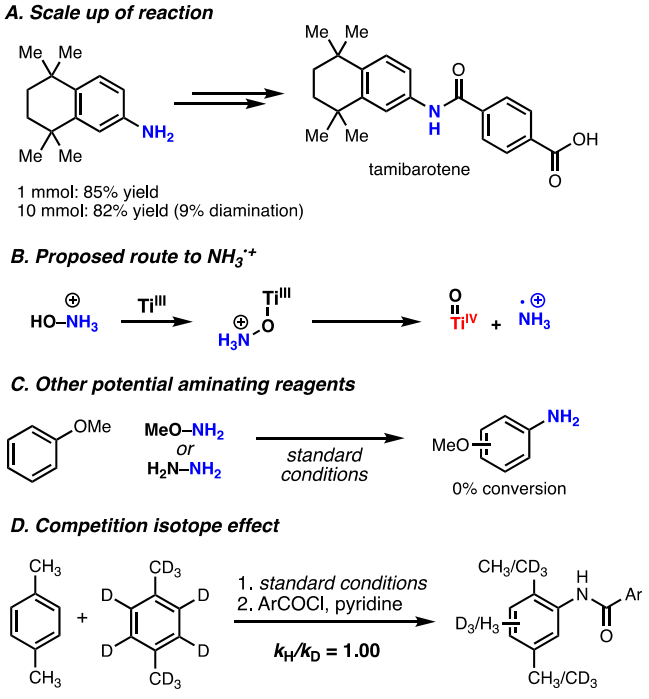

Figure 3. (A) Scale up of reaction. (B−D) Mechanism studies.

the synthesis of tamibarotene, was scaled from 1 to 10 mmol without additional optimization. A slight exotherm of the scale-up reaction was noted, but this was easily controlled by adjusting the rate of Ti^{III} addition and/or by external cooling.

Mechanistically, we propose that hydroxylamine interacts with the oxophilic Ti^{III} via the free hydroxyl group (Figure 3B).[10−15] This proposal is supported by control studies with *O*-substituted hydroxylamines and/or hydrazine, which show no consumption of the starting material nor formation of any aminated products (Figure 3C). Inner-sphere electron transfer then likely occurs, resulting in N−O bond homolysis. This would release a Ti(IV) oxo species along with the aminyl radical. This electrophilic radical can then engage electron-rich arene substrates by analogy to literature reports.[4−6,12] Competition experiments between *p*-xylene-H_{10} and *p*-xylene-D_{10} show a competition isotope effect (k_H/k_D) of 1.00 (Figure 3D), which is consistent with an aromatic substitution pathway wherein C−H cleavage occurs after the rate- and product-determining step.[18,19] Notably, the electron-rich product of these transformations is expected to be deactivated toward further amination due to protonation of the aniline under the reaction conditions. This likely explains why monoamination predominates in all of these systems, despite the presence of an excess of hydroxylamine and Ti(III) under our standard conditions.[16]

Overall, this report describes the development/optimization of a method for the direct C−H amination of electron-rich arenes using hydroxylamine. This protocol uses an inexpensive and commercially available mediator ($Ti^{III}Cl_3$) and is insensitive to adventitious moisture and air. Furthermore, the reaction is readily scaled without significant adjustment to the reaction conditions. Given the operational simplicity and wide availability of the reagents, this transformation offers a potentially attractive complement to nitration/reduction sequences.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00598.

Procedure details and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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