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Hydroxamic acids as chemoselective (*ortho*-amino)arylating reagents *via* sigmatropic rearrangement

Saad Shaaban,[a] Veronica Tona,[a][+] Bo Peng[b][+] and Nuno Maulide*[a]

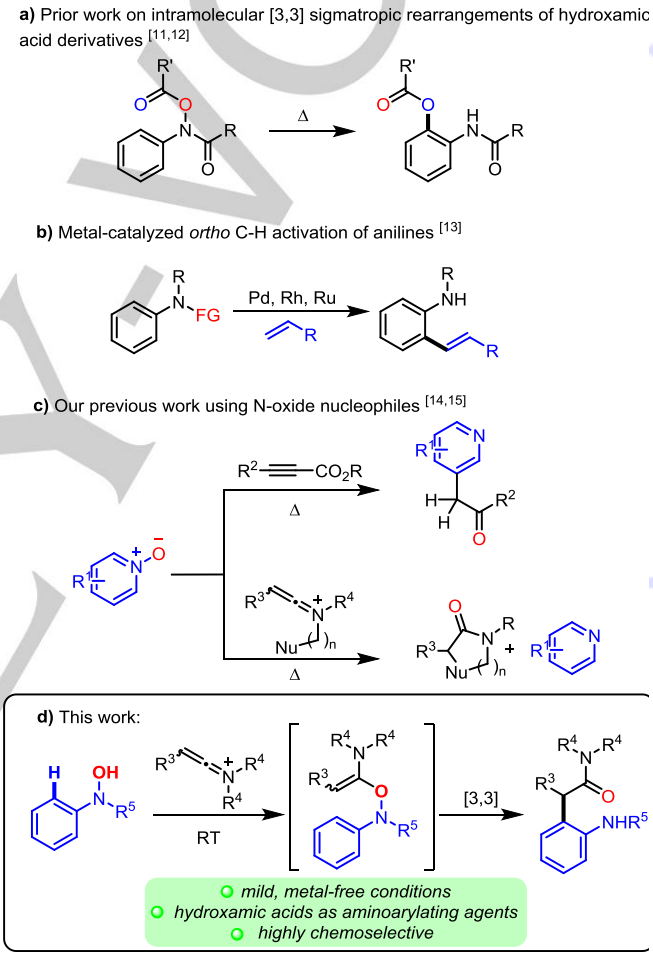
Abstract: The use of readily available hydroxamic acids as reagents for chemoselective (*ortho*-amino)arylation of amides is presented in this manuscript. The reaction proceeds under metal-free mild conditions, displays a very broad scope and constitutes a direct entry for the metal-free attachment of aniline residues to carbonyl derivatives.

Nitrogen-containing arenes are of importance in Chemistry, Biology and Materials. Many pharmaceuticals and natural products contain aniline cores.[1] Over the past years, many methodologies have been developed to introduce nitrogen into aromatic moieties.[2]

The amide linkage belongs to a restricted group of key chemical bonds of life.[3] Although research on amide bond formation is well established, the activation of this bond has only become more intensive in recent decades.[4] Among the most successful methods is the treatment of a carboxamide with triflic anhydride, which generates an activated intermediate with a myriad of possible reaction pathways available.[5] The generation of this reactive intermediate was well studied by Ghosez,[6] Charette,[7] Movassaghi[8] and others.[9] Our group has also recently contributed to this chemistry.[10]

N-aryl hydroxyamic acid derivatives were previously used to achieve a formal *ortho* C-H activation with C-O bond formation.[11] This elegant intramolecular rearrangement, which usually requires high temperature (Scheme 1a), has been employed recently by Tomkinson under mild conditions for C-O and C-N bond formation.[12] Primary and secondary aniline derivatives are also well-known as *ortho*-directing groups for metal-catalyzed C-H functionalization (Scheme 1b).[13]

We have recently shown that pyridine-*N*-oxides can serve as *meta*-arylating reagents in the presence of activated alkynes via thermal [3,3] sigmatropic rearrangement (Scheme 1c, top reaction).[14] Additionally, we and others[15] have observed that addition of pyridine-*N*-oxides to keteniminium intermediates allows formation of an electrophilic enolonium-like species, prone to interception by appropriate nucleophiles (Scheme 1c, bottom reaction).



Scheme 1. a) Intramolecular rearrangement of hydroxamic acids. b) Metal-catalyzed *ortho* C-H activation of aniline derivatives. c) Pyridine-*N*-oxides as arylating or Umpolung reagents. d) Proposed metal-free *ortho*-amino-arylation with hydroxamic acids via [3,3] rearrangment.

We thus hypothesized that readily available *N*-aryl hydroxamic acid derivatives could be suitable reagents for an *ortho*-amino-arylation process, as depicted in Scheme 1d. Herein, we report a chemoselective and mild aminoarylation of amides, under metal-free conditions, that delivers synthetically useful aniline cores to carboxamide moieties.

At the outset, we hypothesized that several N,O-nucleophiles might be able to promote an arylation reaction manifold. We thus investigated structurally diverse species for this reaction, as

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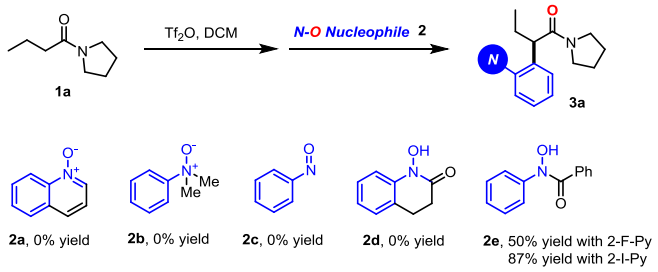
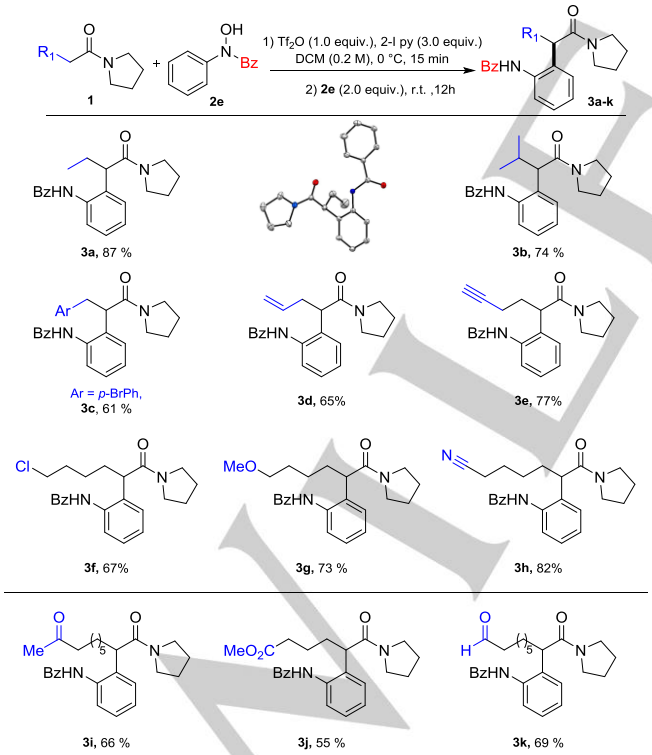
depicted in Scheme 2. Much to our surprise, *N,N*-dimethylaniline-*N*-oxide (**2b**), an apparently prime candidate for this transformation, led to no detectable product. A similar fate awaited nitrosobenzene **2c**, probably due to low nucleophilicity. Although the cyclic hydroxamic acid **2d** was equally unsuccessful, its acyclic variant **2e** was uniquely able to mediate aminoarylation of activated amide **1a** in good yield. Following optimization (see Supporting information for details), a very good 87% yield of aminoarylated product **3a** was obtained. [16]

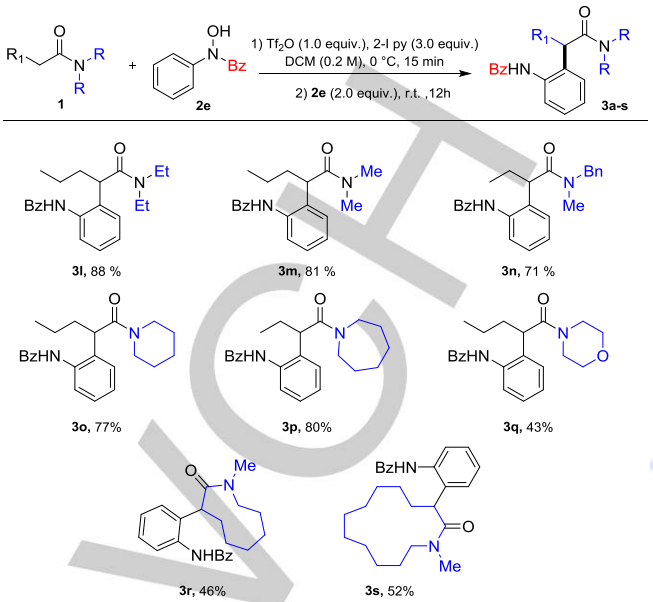


Scheme 2. Identification of hydroxamic acids as suitable (aminoarylating) reagents.

We thus set to explore the scope of this transformation. As seen in Scheme 3, a large range of different functional groups were tolerated in this reaction.



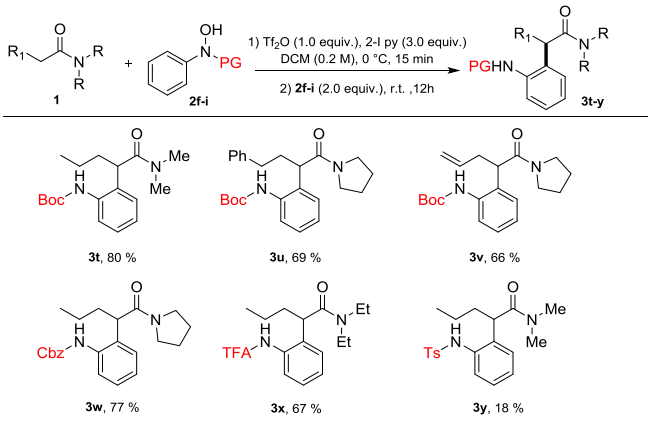
Scheme 3. Substrate scope for the chemoselective amide arylation.



Scheme 4. Substrate scope for different amide backbones

Alkyl, branched alkyl and aryl chains afforded the desired products in good yield (**3a-c**). Other functional groups such as an alkene (**3d**), alkyne (**3e**), ether (**3g**), nitrile (**3h**), or alkyl chloride (**3f**) were also found not to interfere with this highly chemoselective aminoarylation reaction.

More important, an ester, a free methyl ketone and even a terminal carbaldehyde were tolerated. In all these cases, activation took place selectively at the amide carbonyl furnishing the α-aminoarylated products in chemoselective fashion and good yield (**3i-k**). As shown in Scheme 4, it was also important that the nature of the amide appears to play only a negligible role, with several *N*-alicyclic and *N*-aliphatic amides successfully undergoing aminoarylation (**3l-3p**). Morpholine **3q**, presumably a less electron-donating moiety provided only a modest yield of product. Importantly, 8- and 12-membered-ring lactams were smoothly α-arylated (**3r** and **3s** respectively).



Scheme 5. Substrate scope for differently protected hydroxamic acids.

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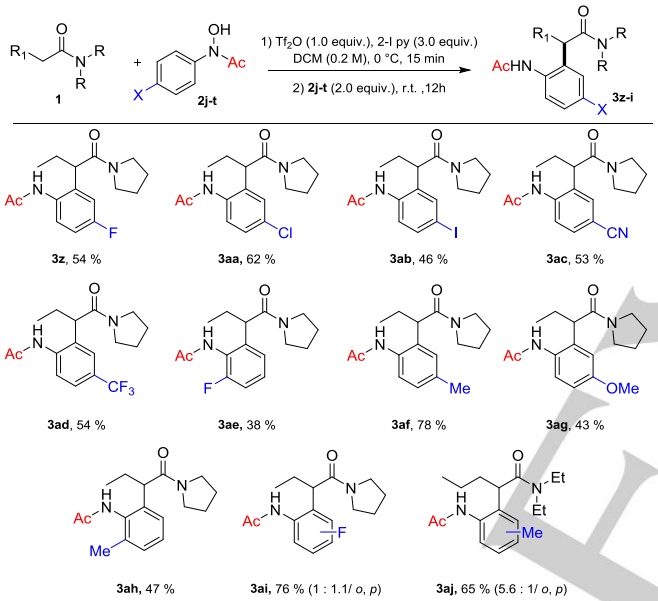
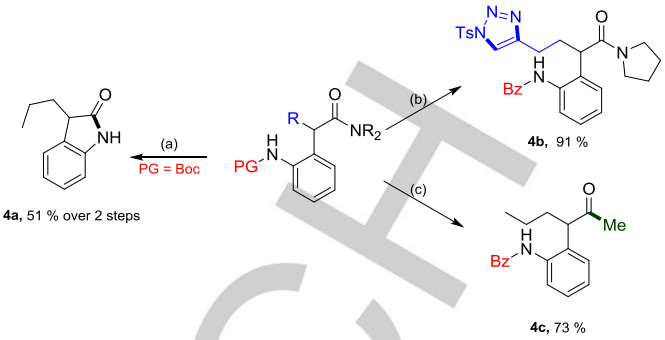
We then investigated different protecting groups on the hydroxamic acid partner. As seen in Scheme 5, Boc-protected hydroxamic acid **2f** furnished the desired products - with a more convenient functionality for post-reaction deprotection - in very good yields (**3t-3v**). The Cbz- **2g** and TFA-protected **2h** also gave the desired products (**3w** and **3x** respectively) in good yield. A Ts-protected hydroxamic acid **2i** delivered the desired product **3y** in low yield, presumably due to its poor nucleophilicity.

Finally, we examined different aryl moieties. As seen in Scheme 6, a variety of substituted-hydroxamic acids **2j-t** smoothly underwent the desired aminoarylation in moderate to good yield (**3z-3ai**). This furnishes a possibility for further elaboration on the final products.[17] Interestingly, whilst the *m*-Fluoro derivative led to 1.1:1 mixtures of regioisomers, use of a *m*-methyl-substituted hydroxamic acid favored the *ortho* product in 5.6:1 ratio.



Scheme 6. Scope of substrate with different *N*-Aryl-hydroxamic acid.

The presence of an aniline moiety in the final products offers a considerable synthetic advantage, and we set out to showcase this. As seen in Scheme 7, deprotection of the Boc group enables formation of the 3-substituted oxindole **4a** in good yield. This amounts to a 2-step synthesis of oxindoles from amides and hydroxamic acids. Other transformations possible include 3+2-cycloaddition to **4b** or – in the case of a morpholine amide – direct conversion to a ketone **4c** upon treatment with a Grignard. The latter reaction effectively connects the chemistry herein with an access to α-aminoarylated ketones.[18]



Scheme 7. Derivatization of the product. a) amide **3t**, TFA (10 equiv.) 1.5 h then (0.1 M) KOH (10 equiv.) and reflux for 1h. b) amide **3e**, Cu(thiophenecarboxylate) (2 mol%), TsN_3 (1.1 equiv.), 4 h. c) amide **3q**, MeMgBr (3.0 equiv.), THF, 2 h.

In conclusion, we herein report the first example of the use of hydroxamic acids for aminoarylation of carboxamide derivatives.[19] This transformation proceeds under mild conditions and is highly chemoselective, always arylating the amide component even in presence of ester, ketone or aldehyde functionality. Aminoarylation offers a range of interesting opportunities in synthesis resulting from the presence of an aniline in the final products, and our preliminary results highlight this.

Acknowledgements

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Keywords: aminoarylation • chemoselective • hydroxamic acid • amide • sigmatropic rearrangement

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[16] The use of *N*-oxides **2a** and **2b** led to the formation of the α-ketoamide product in low yield. The use of **2c** and **2d** led to no observable products and only starting material was recovered. For the α-oxidation of amides with pyridine N-oxides, see: A. de la Torre, D. Kaiser, N. Maulide, *J. Am. Chem. Soc.* **2017**, *139*, 6578-6581.

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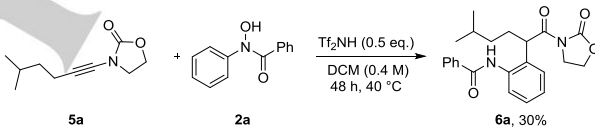
[19] The analogous arylation of an ynamide is possible in low yield, as shown below. Treatment of ynamide **5a** with triflimide and *N*-phenyl hydroxamic acid **2a** leads to **6a** in 30% yield.



5a **2a** **6a**, 30%

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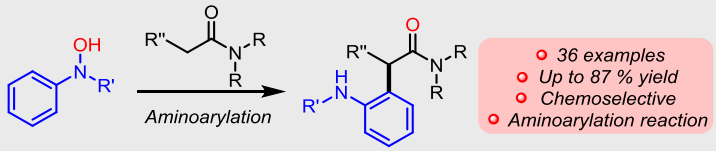

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