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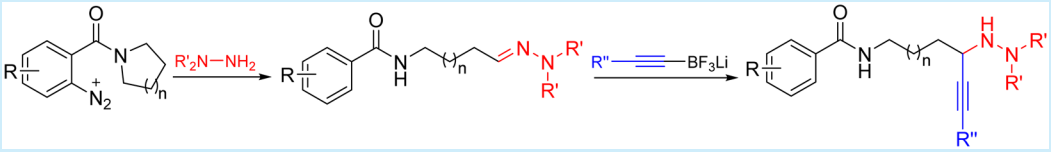
Redox-Neutral α-Amino C−H Functionalization: When the Catalyst Is Also the Nucleophile

Saad Shaaban, Joongsuk Oh,[†] and Nuno Maulide*

University of Vienna, Faculty of Chemistry, Institute of Organic Chemistry, Währinger Strasse 38, 1090 Vienna, Austria

Supporting Information



ABSTRACT: A redox-neutral functionalization of cyclic amines that leads to acyclic products is presented. The reaction hinges on generation of transient aryl radical intermediates by catalytic activation with a simple hydrazine. Those aryl radicals subsequently undergo translocation and further oxidation prior to trapping with the same hydrazine, thus resulting in an overall process where the catalyst unusually also acts as the nucleophile.

The reduction of aryldiazonium salts (accompanied by the release of nitrogen gas) is a well-established route to access aryl radicals,[1] which are useful intermediates in synthesis.[2] An array of inorganic and organic catalysts can be employed in this reduction process.[3] These include organic dyes,[4] tetrathiafulvalene,[5] and ascorbic acid.[6]

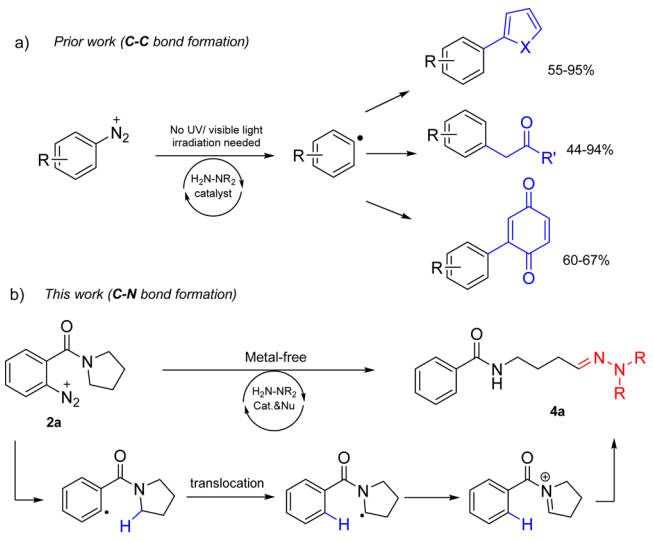
On the other hand, the construction of C−N bonds is of significant importance in organic chemistry,[7] given the almost ubiquitous presence of nitrogen in biologically relevant synthetic constructs. This is illustrated by the wide range of amination methods available in the literature.[8] In particular, hydrazines constitute a well-known family of aminating reagents[9] ranging from classical condensation reactions with carbonyl derivatives[10] to transition-metal-catalyzed transformations.[11]

We have recently shown that hydrazines are excellent catalysts for the reduction of aryldiazonium salts with rapid liberation of nitrogen gas, notably without the requirement for any UV or visible light.[12] The resulting aryl radicals could be engaged in several C−C bond forming processes (Scheme 1a).[12]

Given the high synthetic relevance of amination processes, we speculated that a suitable hydrazine promoter might, if employed in stoichiometric amounts, additionally serve as a nucleophile for C−N bond formation thus fulfilling an unusual dual role. Herein we report a metal-free, mild procedure for redox-neutral α-amino functionalization[13] with concomitant C−N bond formation, where the catalyst and nucleophile are the same entity (Scheme 1b).

At the outset, we focused on a system typified by diazonium salt **2a**. Herein (Scheme 1b), reduction of the diazonium salt moiety should trigger a 1,5-hydrogen migration,[14] generating an α-amino radical that might, upon additional oxidation and nucleophilic capture, generate the product **4a**. We thus hypothesized that the use of 1 equiv of 4-aminomorpholine **3a** with diazonium salt **2a** in DMSO should lead to product **4a**

Scheme 1. (a) Previous Work on Hydrazine As a Catalyst for C−C Bond Formation; (b) Our Hypothesis for Metal-Free C−N Bond Formation



or its ring-chain isomer. As shown in Table 1, under these conditions we observed formation of linear product **4a** in moderate yield (entry 1). Screening different solvents (entries 2−5) revealed that acetonitrile is the best medium for this transformation. Increasing the amount of hydrazine to 1.3 equiv led to higher yields in a shorter reaction time (entry 6). A further increase of either parameter (entries 7 and 8) did not lead to better results.

With suitable reaction conditions in hand, we delineated the scope of this transformation. As seen in Scheme 2, different

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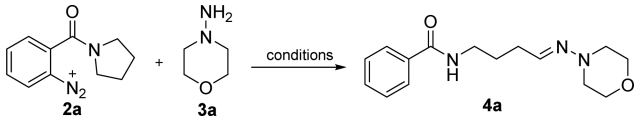
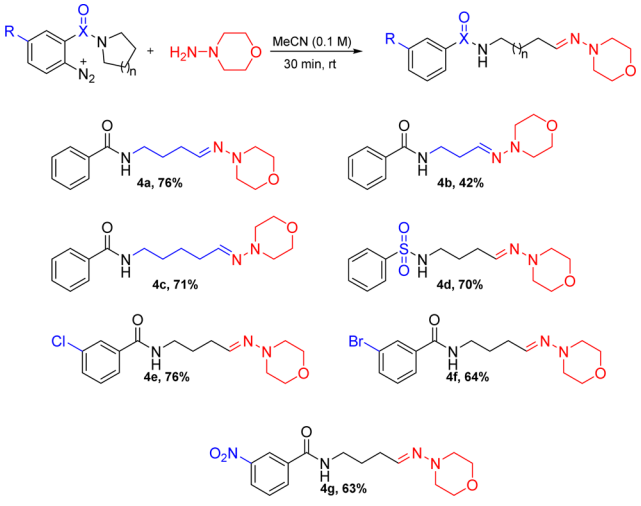
Table 1. Optimization of Reaction Conditions[a]



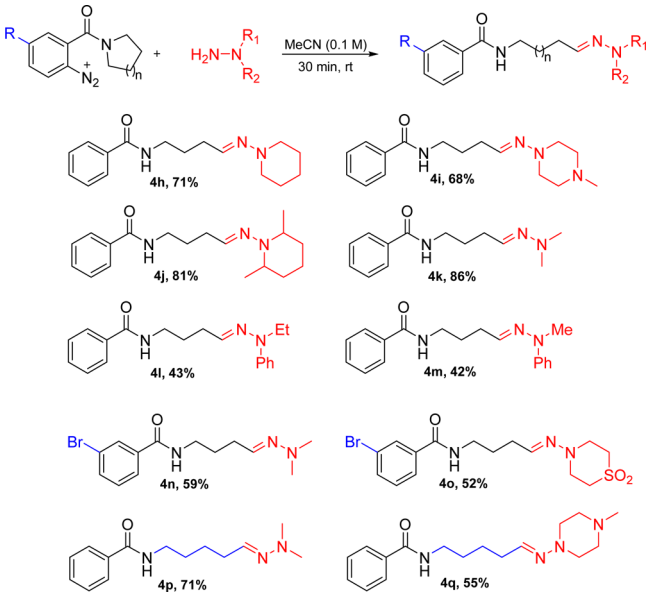
entry	3a (equiv)	solvent	time (h)	yield (%)[b,c]
1	1	DMSO	2	30[b]
2	1	DMF	2	22[b]
3	1	MeCN	2	61[b]
4	1	dioxane	2	–
5	1	hexane	2	–
6	**1.3**	**MeCN**	**0.5**	**76**[c]
7	1.3	MeCN	1	76[b]
8	2	MeCN	0.5	76[b]

[a]Reactions were performed at rt at 0.1 M concentration. [b]NMR yield. [c]Isolated yield.

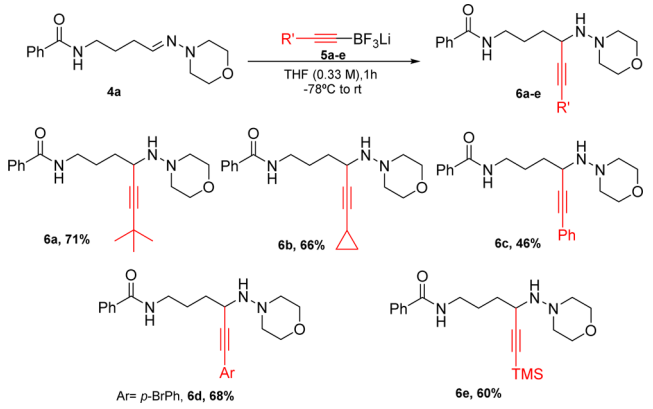
Scheme 2. Scope of Substrate on Cyclic Amines



Scheme 3. Scope of Hydrazines



Scheme 4. Scope of Alkynes for C–C Bond Formation



cyclic amines underwent this transformation in moderate to good yields (**4a–4c**). Sulfonamides were also suitable coupling partners, as exemplified by the formation of ω-aminohydrazone **4d** in good yield. The presence of functional groups on the aromatic ring, affording opportunities for further synthetic elaboration,[15] was not detrimental to the overall process (**4f–4g**).

Different substituted hydrazines also worked well in this transformation. As seen in Scheme 3, a range of hydrazines furnished the C–N coupling products in good to excellent yield, including sterically demanding cases (**4h–4j**). Dimethyl hydrazine and arylated derivatives led to the expected products in moderate to good yield (**4k–4m**), and this regardless of the nature of the aryl diazonium salt partner (**4n–4o**). Piperidine moieties in the starting diazonium salt similarly led to the functionalized hydrazones with comparable efficiency to their pyrrolidine counterparts (**4p–4q**).

The presence of a hydrazone moiety in the products of these reactions[16] suggests opportunities for further functionalization.[17] For instance, alkynylation with lithium (alkynyl)-trifluoroborate nucleophiles **5a–e** led to the nucleophilic addition products **6a–e**. As seen in Scheme 4, different aliphatic **6a**, cyclic **6b**, arylated **6c,d**, and silylated **6e** alkynes were smoothly introduced. This will furnish masked 1,4 diamines that are interesting compounds with multiple biological activities.[18]

Based on literature precedent,[4a,12,14,19] a plausible mechanism for this transformation can be proposed (Scheme 5). Reaction between hydrazine **3** and diazonium salt **2a** presumably leads to the tetrazene intermediate,[12,19a] which spontaneously fragments to generate aryl radical **8** with extrusion of N_2. Aryl radical **8** undergoes 1,5 hydrogen migration to give α-amino radical intermediate **10**. This undergoes a subsequent oxidation, either by amine radical carbocation **9** furnishing intermediate **11** and regenerating hydrazine **3** or by oxidation with diazonium salt **2a** releasing again aryl radical **8**. Intermediate **11** will then be trapped by nucleophilic hydrazine **3** to give **12**. Finally, under the slightly acidic conditions of the reaction medium, intermediate **12** will rearrange with ring opening to give products **4a**.

In conclusion, we developed a metal-free, redox neutral methodology for C–N bond formation that hinges on the use of a hydrazine promoter that fulfills a dual role. The resulting ω-aminohydrazones can be further functionalized by nucleophilic addition. The concept of a promoter which is also a stoichiometric reagent, thus obviating the need for additional catalysts, is an intriguing approach to synthesis.

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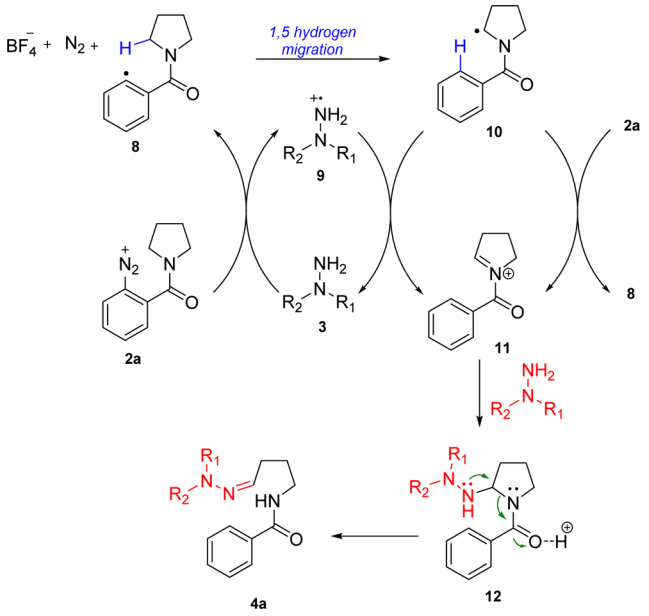
Scheme 5. Plausible Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03431.

Experimental procedures and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nuno.maulide@univie.ac.at.

Present Address

†Department of Chemistry, University of Texas at San Antonio, One UTSA Circle, San Antonio, TX 78249. E-mail: oh.joongsuk@gmail.com.

Notes

The authors declare no competing financial interest.

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