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α,α′-C−H Bond Difunctionalization of Unprotected Alicyclic Amines

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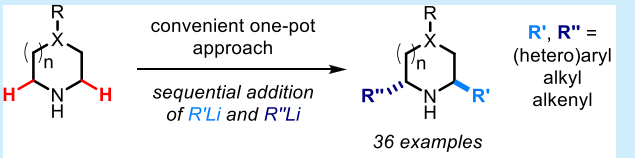
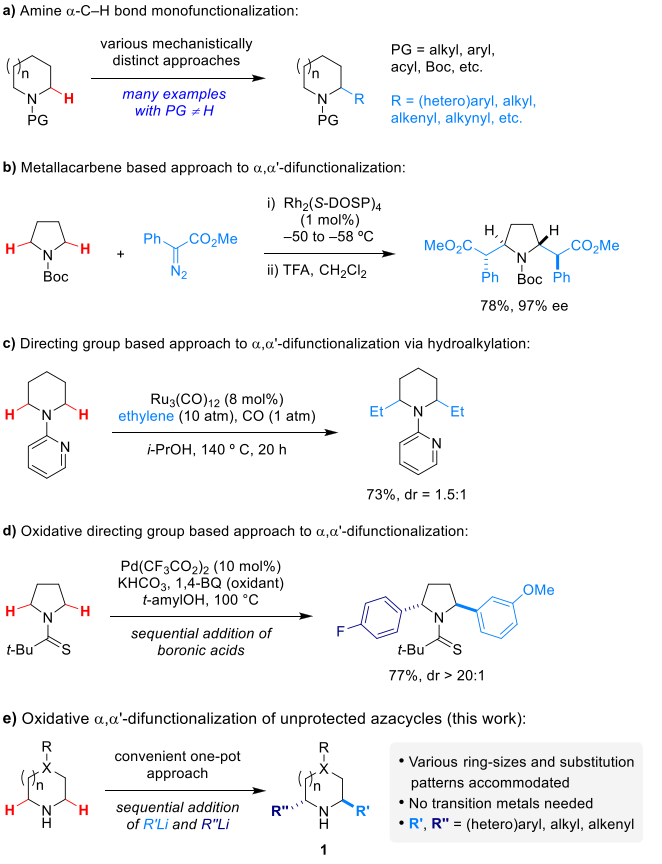
ABSTRACT: A simple one-pot procedure enables the sequential, regioselective, and diastereoselective introduction of the same or two different substituents to the α- and α′-positions of unprotected azacycles. Aryl, alkyl, and alkenyl substituents are introduced via their corresponding organolithium compounds. The scope of this transformation includes pyrrolidines, piperidines, azepanes, and piperazines.



Fully or partially saturated azacycles are ubiquitous core structures of bioactive materials.[1] The introduction of ring substituents via the C−H bond functionalization of the parent heterocycles is a particularly attractive strategy for accessing complex amines, and is continuing to inspire the development of diverse synthetic strategies.[2,3] While numerous methods for the α-C−H bond functionalization of amines have emerged, procedures that achieve an α,α′-C−H bond difunctionalization in a single operation remain rare (Scheme 1).[4−6] Selected examples include the rhodium-catalyzed metal carbenoid insertion involving carbamates (Scheme 1b)[4a,c] and the ruthenium-catalyzed hydroalkylation of *N*-2-pyridylamines (Scheme 1c).[4b] A rare method enabling the introduction of two different substituents is the palladium-catalyzed diarylation of thioamides with boronic acids (Scheme 1d).[4d] Here we report a practical one-pot approach for the α,α′-C−H bond difunctionalization of unprotected alicyclic amines (Scheme 1e). This method utilizes simple ketone oxidants and organolithium nucleophiles, without requiring the use of transition-metal catalysts.

We recently reported a method for the α-C−H bond functionalization of unprotected cyclic amines.[7,8] These substrates are first converted to their corresponding lithium amides **2** (deprotonation with *n*-BuLi) before being exposed to a ketone oxidant (e.g., benzophenone) to form imines **3** in their monomeric forms (see Scheme 2).[9] The addition of an organolithium nucleophile to **3** results in lithium amide **4**, which, upon workup, provides an α-substituted amine product. Instead of quenching the reaction upon the formation of **4**, we rationalized that the addition of an appropriate ketone oxidant should lead to the formation of imine **5**. The subsequent addition of a second organolithium nucleophile, followed by workup, should provide the α,α′-difunctionalized amine **1** in a single operation. Indeed, we previously showed that α-substituted lithium amides **4** can be converted to α,α′-disubstituted products **5**.[7] Conducting the α,α′-difunctionalization in a single operation would save 1 equiv of base and

Scheme 1. Overview of Methods for Amine α,α′-C−H Bond Difunctionalization



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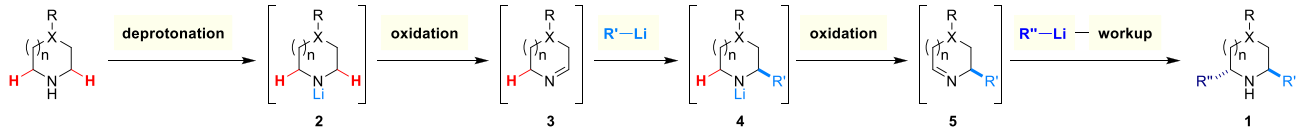
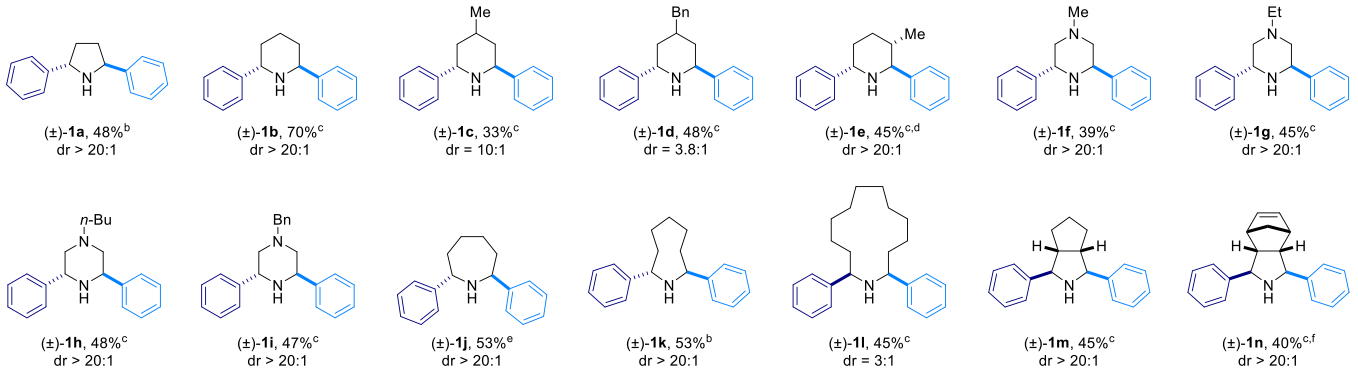
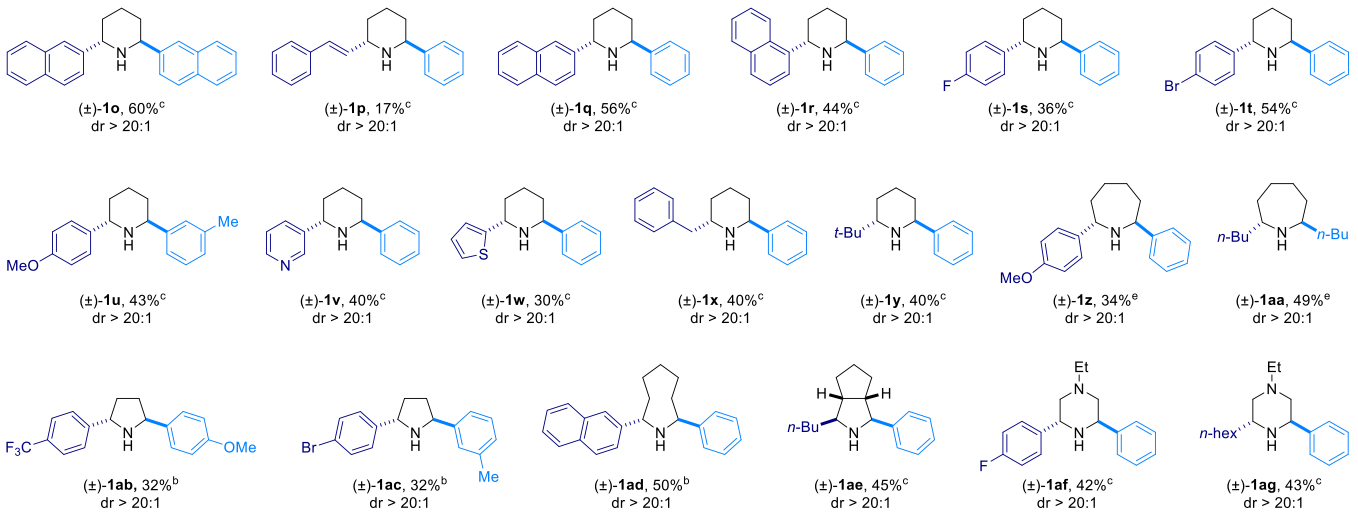
Scheme 2. Scope of the Reaction[a]



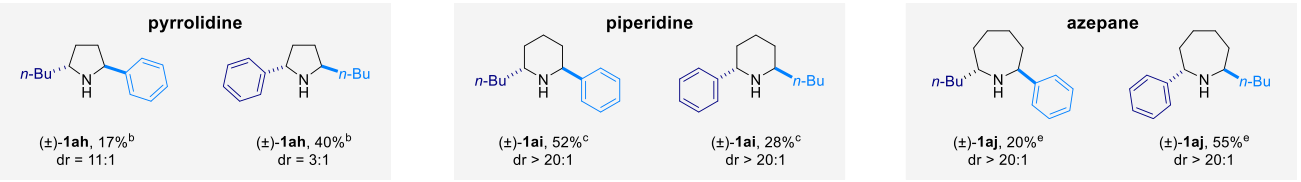
Amines



Substituents



Order of addition



[a]Reactions were performed in ether solution at −78 °C with 1 mmol of amine, *n*-BuLi (1 equiv), first ketone oxidant (1.05 equiv), R′−Li (1.07−1.5 equiv), second ketone oxidant (1.2−1.7 equiv), and R″−Li (1.5−2.0 equiv). See the Supporting Information for further details. [b]Benzophenone (first oxidation) and *t*-butyl phenyl ketone (second oxidation) were used. [c]Trifluoroacetophenone (first and second oxidation) was used. [d]While four diastereomers could potentially be formed for product **1e**, we only observed trace amounts of a second diastereomer. [e]Trifluoroacetophenone (first oxidation) and *t*-butyl phenyl ketone (second oxidation) were used. [f]Reaction was performed on a 0.5 mmol scale starting with the corresponding hydrochloride salt of the amine.

streamline the entire sequence while also having the potential to provide higher overall yields. Following significant optimization (see the Supporting Information for details), the scope of the transformation was established as summarized in Scheme 2. The α,α′-diphenylation was accomplished with a range of amines. Likewise, the introduction of two different substituents (aryl, heteroaryl, alkyl, and alkenyl) could be demonstrated on a range of amines. While the yields are mostly moderate and, in some cases, low, the simplicity of the approach largely compensates for this shortcoming. In all cases studied previously with a two-step approach, the present one-pot strategy provides significantly higher yields.[10] For the introduction of two different substituents, we investigated possible effects based on the order of addition. Selected

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examples are included in Scheme 2. For the product **1ah** derived from pyrrolidine, the introduction of phenyl followed by *n*-Bu resulted in a low yield but good diastereoselectivity, while the introduction of *n*-Bu followed by phenyl provided an improved yield but at the expense of diastereoselectivity. In contrast, for **1ai** derived from piperidine, the introduction of the phenyl group first was found to be beneficial. For the azepane-derived product **1aj**, the introduction of the *n*-Bu group first provided favorable results. For both **1ai** and **1aj**, the order of addition did not impact the excellent level of diastereoselectivity.

In summary, we have achieved the one-pot α,α'-difunctionalization of various unprotected cyclic amines. The method is operationally simple and exhibits a significant synthetic utility.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02187.

Experimental details, characterization data, X-ray data, and copies of NMR spectra (PDF)

Accession Codes

CCDC 2039636−2039637 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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