LIBERATED α,β-FUNCTIONALIZATION OF SATURATED CYCLIC AMINES

Reported by Brett Nelson Cain 2 March 2021

INTRODUCTION:

It is difficult to overstate the abundance of N-heterocycles in organic chemistry. Apart from being well-represented among common organic reagents (PyBOP, DBU, etc.), they are ubiquitous among the thousands of small molecules produced by the pharmaceutical industry. For example, among FDA-approved drugs, the saturated rings piperidine, piperazine, and pyrrolidine were all included among the top five most frequently encountered nitrogen heterocycles and ultimately 59% of FDA-approved small molecules contained at least one saturated N-heterocycle.[1] Accordingly, methods to functionalize these motifs have been well-researched over the past half-century with transformations involving the α-functionalization of a secondary amine being the most common (Figure 1). Although useful, these methods often require the amine to be protected and the liberation of these motifs can be difficult and/or problematic in late-stage syntheses limiting their widespread practical usage. Other strategies of cyclic amine α-functionalization entail the concurrent alkylation of the free amine (or start with a tertiary amine) and often use transition-metal catalysts which can be difficult to obtain and operationally non-trivial to use. Considering the wealth of reactions available to unprotected secondary amines, being able to decorate the periphery of these rings while leaving the nitrogen untouched would be of great value to synthetic chemists. To this end, research to develop general, one-pot methods for transition metal and protecting group-free cyclic amine α,β-functionalization has been expanding.

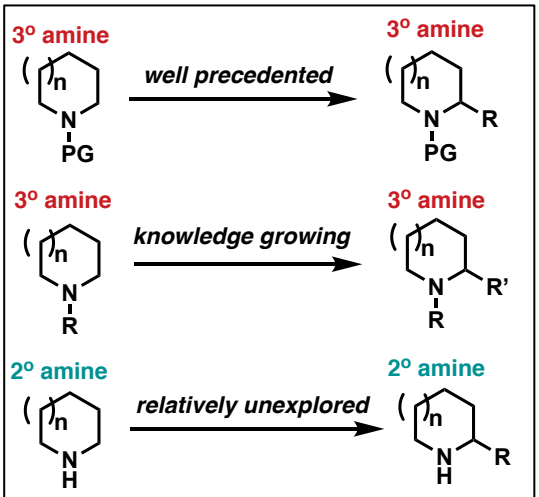


Figure 1. The current state of aliphatic α-cyclic amine functionalization

HYDRIDE DONATION AND RESULTING IMINES — A STRATEGY:

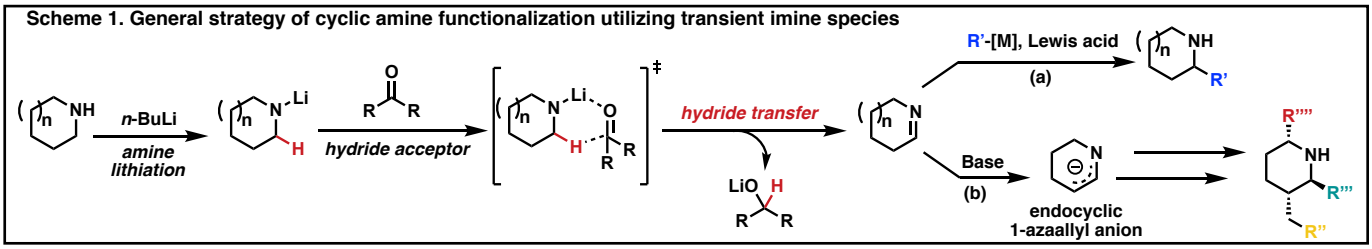
In 1971,Wittig demonstrated that lithium alkylamides could serve as effective hydride donors with the ability to reduce a variety of carbonyl species.[2] Although originally noted as an unproductive, troublesome side-reaction in the attempted enolization of ketones, the α-hydride donor ability of amines has recently been exploited in the synthesis of substituted azapines, tetrahydroquinolones, and spiro-oxindoles, among others.[3] Following hydride transfer, the nitrogen species is converted to an imine, or enamine upon tautomerization, which can be used to create a variety of structurally diverse motifs. Oxidatively-generated N-aryl enamines have been used as crucial intermediates in the formation of

bicyclic amino acid derivatives via formal [2+2] cycloadditions with substituted alkynes. Additionally, the nucleophilicity of these enamines has been harnessed to achieve β-alkylation with suitable β-nitrostyrene electrophiles. While useful, such procedures typically either start with a tertiary amine or introduce a degree of unsaturation into the N-heterocycle.

TRANSITION METAL- AND PROTECTING GROUP-FREE CYCLIC AMINE FUNCTIONALIZATION:

The ability to functionalize a given cyclic amine and retain the free amine as a functional handle after the desired transformation could lend the simple N-heterocycle to be thought of as a springboard to complexity. Combining the hydride-donating ability of lithiated amines with conditions to optimize the reactive nature of the resulting imine has led to methods that are able to achieve this goal (Scheme 1). Although seemingly straightforward, this strategy had to overcome several challenges such as transient imine trimerization and imine deprotonation by other lithiated amines *in-situ*. Early efforts involved trapping the reactive imine with strong organolithium nucleophiles which enabled the successful *α*-functionalization of various pyrrolidine and piperidine-based substrates (Scheme 1a).[4] The scope of nucleophiles could be expanded by Lewis-acid activation of the transient imine using boron trifluoride etherate. This simple addition expanded the scope of this protocol in allowing the use of weaker nucleophiles such as lithium acetylides and heteroaryllithium species.[5]

Scheme 1. General strategy of cyclic amine functionalization utilizing transient imine species



Useful in its own right, this transient imine can be transformed further in cyclic amine β-functionalization by reaction of the base-generated, endocyclic 1-azaallyl anion with a suitable electrophile, typically benzylic or allylic halides (Scheme 1b).[7] Demonstrating the power of this strategy, a general, one-pot protocol has been developed which enables the synthesis of *α*,β- and *α*,β,*α*'-substituted cyclic amines. Although the examples of one-pot, di- and tri-substitution are currently limited, the practical utility of such chemistry assures that this technology will be of interest for years to come.

REFERENCES

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