C-H FUNCTIONALIZATION

Functionalization of cyclic amines

Many synthetic chemists build their molecules of choice from simple organic substrates by applying methodologies for C–H bond functionalization. A challenge arises when elaborate products are desired, in which case these reactions must also proceed in a selective manner. Several unreactive C–H bonds can be found in the aliphatic N-heterocycles of biologically active compounds, and many alkaloid motifs (including nornicotine and anabasine) characteristically feature an alkyl and/or aryl substituent in the α -position relative to a secondary amine. The pharmaceutical importance of this motif has inspired the development of efficient methodologies for selective α -functionalization of cyclic amines, with present approaches including N-protection and subsequent manipulation of the α -C–H bond in the tertiary amine, or the use of transition metal catalysts to exploit the amine as a directing group. In a recent *Nature Chemistry* paper, a team led by Daniel Seidel took up the gauntlet and uncovered a new approach to selectively α -functionalize cyclic unprotected aliphatic amines. Their operationally simple and convenient method, which complements existing methodology, gives new access to a range of 2-alkylated and 2-arylated pyrrolidines, piperidines and higher NH-containing macrocycles. “The new methodology is free of protecting groups and is uniquely effective for the stereospecific functionalization of cyclic amines with pre-existing substituents”, says Seidel.

More than half a century ago, the pioneering studies of Wittig described the reactivity of lithium amides with carbonyl compounds. Such work, along with reports into the nucleophilic addition of organolithium compounds to imines,

inspired Seidel’s team to devise an elegant one-pot three-step reaction sequence. It begins by deprotonating a cyclic secondary amine *in situ* to generate a lithium amide. This intermediate converts into the corresponding cyclic imine upon donation of a H^- to a sacrificial ketone, such as $PhC(O)Ph$ or $PhC(O)Bu$. Finally, the resulting imine is captured by an organolithium nucleophile to provide an α -functionalized amine. Although the individual steps in the overall process are well precededented, this work marked their first application in sequence. The murky prospect of typical side-reactions — prominent among which are aza-allyl anion formation and cyclic imine trimerization — has undoubtedly discouraged other researchers from attempting this challenging transformation. Yet, they did not deter the team from carrying out a “low-risk, high-reward project involving reactions that are easy to try, have a perhaps marginal chance of success, but could potentially reveal interesting new reactivity”, said Seidel.

The utility of the protocol goes far beyond the introduction of organic groups in commercial reagents such as $nBuLi$ or $PhLi$, and one can install a variety of alkyl and aryl groups by use of the appropriate organolithium precursor. There are further aspects that point to the practicality of this appealing new methodology. Indeed, the substrate scope is not limited to unsubstituted cyclic amines but also includes pre-functionalized amines, which can be converted into products with excellent *trans* diastereoselectivities. The reactions also preserve the configuration of chiral amine precursors, as exemplified by the one-pot diastereoselective preparation of enantiopure solenopsin A, an alkaloid present in fire ant venom.

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After some preliminary mechanistic and kinetic studies, Seidel’s team further simplified the procedure and, despite moderate yields, α -*n*-butylation of azacyclotridecane proceeded after adding 2.5 equivalents of $nBuLi$ to a mixture of the starting amine and $PhC(O)Ph$ under cryogenic conditions. A remarkable mechanistic implication is that the α -functionalized product can form only if the rates of amine deprotonation and H^- transfer to the ketone are much faster than the reaction of the organolithium with $PhC(O)Ph$. Although a mechanistic understanding of the overall process and an even broader substrate scope in both the amine and the nucleophile would be desirable, this disarmingly simple methodology — free of transition metals and protecting groups — is expected to inspire many future studies on selective C–H functionalization.

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