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Direct α-C–H bond functionalization of unprotected cyclic amines

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Cyclic amines are ubiquitous core structures of bioactive natural products and pharmaceutical drugs. Although the site-selective abstraction of C–H bonds is an attractive strategy for preparing valuable functionalized amines from their readily available parent heterocycles, this approach has largely been limited to substrates that require protection of the amine nitrogen atom. In addition, most methods rely on transition metals and are incompatible with the presence of amine N–H bonds. Here we introduce a protecting-group-free approach for the α-functionalization of cyclic secondary amines. An operationally simple one-pot procedure generates products via a process that involves intermolecular hydride transfer to generate an imine intermediate that is subsequently captured by a nucleophile, such as an alkyl or aryl lithium compound. Reactions are regioselective and stereospecific and enable the rapid preparation of bioactive amines, as exemplified by the facile synthesis of anabasine and (–)-solenopsin A.

Fully or partially saturated nitrogen heterocycles are key constituents of numerous pharmaceutical drugs[1]. However, of the many diverse methods that enable the synthesis of functionalized derivatives of such heterocycles, the vast majority require multistep sequences[2]. A particularly attractive entry to substituted saturated nitrogen heterocycles is the modification of readily available amines via the transformation of poorly reactive but ubiquitous C–H bonds[3,4]. Significant challenges notwithstanding, major efforts by the synthetic community continue to focus on the development of methods for the direct functionalization of C–H bonds, which include C–H bonds in the α-position of the amine nitrogen atom[3,4]. Although highly desirable for further processing, current protocols are largely incompatible with the presence of a free amine N–H bond, which interferes with C–H bond functionalization. Thus, progress in amine C–H functionalization has largely been limited to methods that rely on protected or tertiary amines. Furthermore, the use of directing groups is a strict requirement of many approaches. These directing groups typically double as amine-protecting groups and not infrequently are hard to remove, which significantly limits the applicability of the underlying methods. Here we report a conceptually new strategy that addresses several important limitations.

Outlined in Fig. 1 are the most common approaches for amine α-C–H bond functionalization. A widely applied method utilizes *N*-Boc (Boc, *t*-butyloxycarbonyl)-protected pyrrolidine and related heterocycles as starting materials[5–11]. As an example, α-deprotonation of *N*-Boc-protected pyrrolidine with a strong base in the presence of a chiral ligand, followed by transmetallation and, finally, by palladium/phosphine ligand-catalysed coupling with an aryl halide, results in the formation of α-arylated *N*-Boc pyrrolidine in highly enantioenriched form (Fig. 1a)[12]. Other approaches based on a directing group utilize a transition-metal catalyst in the absence of an exogenous base (Fig. 1b)[13–15]. The undoubtedly most-widely explored method involves the oxidative C–H functionalization and capture of intermediate iminium ions with various nucleophiles, such as alkynes (Fig. 1c)[16–18]. Although highly useful for certain substrates, the scope of most reactions in this category is often limited to moderately activated *N*-aryl amines. Somewhat related, although mechanistically distinct, are photoredox-based approaches (Fig. 1d)[19–21]. Other strategies for the α-C–H bond functionalization of tertiary amines that are not depicted in Fig. 1 include hydrogen-atom[22] or hydride transfer[23] and metal–carbenoid insertion[24]. Isolated examples of other amine C–H bond functionalizations have been reported, including the functionalization of more remote sites[8,25,26]. None of the methods described above are applicable to the C–H bond functionalization of secondary amines.

Methods for the direct α-C–H bond functionalization of secondary amines are rare and essentially limited to hydroaminoalkylation[27] (Fig. 1e). Although impressive results have been achieved with this approach, mechanistic constraints mean the method cannot be used to introduce aryl, alkenyl or alkynyl groups or non-α-branched alkyl groups. Our group has developed a mechanistically unique method for the α-C–H bond functionalization of secondary amines that features azomethine ylides as intermediates (Fig. 1f)[28,29]. However, reactions invariably involve *N*-alkylation; thus, the products of these reaction are themselves tertiary amines.

A new concept for the α-C–H bond functionalization of secondary amines is depicted in Fig. 1g, using pyrrolidine as a prototypical example. Lithiated pyrrolidine (**1**), readily obtained by *in situ* deprotonation of pyrrolidine, engages a sacrificial hydride acceptor (a simple carbonyl compound) to provide cyclic imine **4** (via the proposed transition state **2**) in addition to lithium alkoxide **3**. Capture of imine **4** by an organolithium reagent furnishes the functionalized amine **5**. The ability of lithium amides such as **1** to serve as hydride donors is well documented[30]. Similarly, there is precedent for the nucleophilic addition of organolithium species to imines[31]. However, these steps apparently have not been applied in sequence. In addition, there seem to have been no concerted efforts to utilize this unique reactivity for amine α-functionalization. This is perhaps not surprising, as there are significant challenges associated with this proposal. Early work by Wittig and Hesse, who reported on the ability of lithiated amines to serve as hydride donors in reactions with carbonyl compounds such as benzophenone, established that imines such as **4** are deprotonated rapidly by the corresponding lithium amide starting material (for example, **1**) to form a 1-azaallyl anion (for example, **6**) and free amine, in this case pyrrolidine[32]. The

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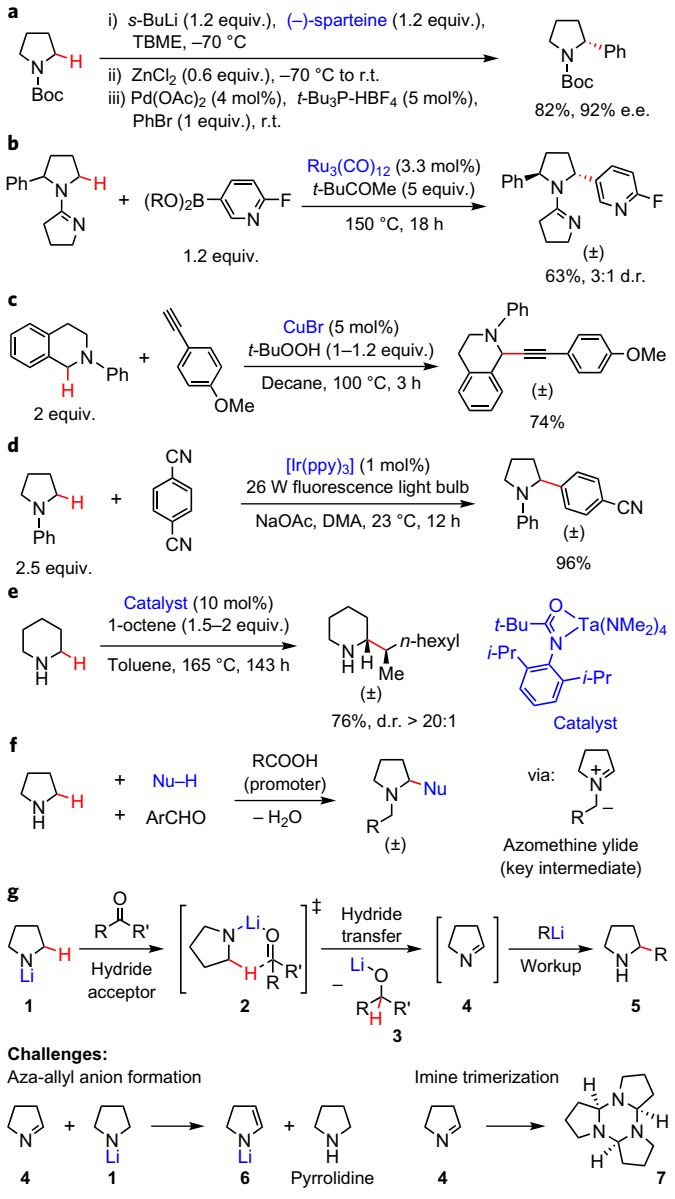


Figure 1 | Methods for amine α-C–H bond functionalization and the new concept for secondary amines. A summary of some of the most widely used methods for amine α-C–H bond functionalization **a**, Deprotonative/cross-coupling approach. **b**, Directing-group-based approach that involves oxidative C–H insertion by a metal catalyst. **c**, Oxidative approach (cross-dehydrogenative coupling). **d**, Photoredox-based method. **e**, Hydroaminoalkylation. **f**, Redox-neutral condensation. **g**, This work, an intermolecular hydride-transfer-based approach. TBME, *t*-butyl methyl ether; r.t., room temperature.

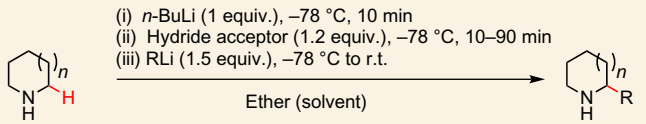
results by Wittig and Hesse appear to suggest that deprotonation is a more-rapid process than hydride transfer and the outcome of their experiments was dominated by 1-azaallyl anion reactivity[32]. Another well-appreciated challenge is the known propensity of imines, such as **4**, to undergo trimerization[33]. Several conditions must be met to execute the proposed amine α-functionalization successfully. First, reaction conditions must be identified under which the rate of hydride transfer significantly exceeds the rates of both imine deprotonation (by lithium amide **1**) or trimerization. In addition, the rate of nucleophilic addition must be greater than both the rates of imine deprotonation (by the nucleophile) or trimerization.

After significant experimentation (Supplementary Table 1), we developed a simple procedure for the α-C–H bond functionalization of a broad range of cyclic N–H amines (Table 1). Deprotonation of the amine, followed by the addition of a hydride acceptor and, finally, an organolithium nucleophile facilitated the formation of a range of products. This method is applicable to amines of various ring sizes. Aryl lithiums that bear different functional groups and heteroaryl lithium reagents were found to be competent nucleophiles. Although simple *n*-alkyl lithium reagents, such as *n*-BuLi (commercial solution in hexanes), were viable nucleophiles, *s*-BuLi (commercial solution in cyclohexane) and MeLi (commercial solution in ether) did not participate in the title reaction. Organolithium compounds outperformed other organometallic nucleophiles in all cases. For instance, the replacement of PhLi for PhMgBr or Ph_2CuLi resulted in the formation of **8** in 21 and 41% yields, respectively. Benzophenone was identified as the hydride acceptor of choice in the case of pyrrolidine. Remarkably, hydride transfer was found to occur rapidly at –78 °C. In some cases, *t*-butyl phenyl ketone outperformed benzophenone as the hydride acceptor. For substrates with attenuated reactivities, trifluoroacetophenone was identified as an efficient hydride acceptor. A high level of *trans*-diastereoselectivity was observed for products **23**, **24** and **29**. The relative stereochemistry of **29** is complementary to that observed in the α-functionalization of *N*-Boc-4-substituted piperidine through deprotonative α-lithiation, in which the corresponding *cis* diastereomers are formed with excellent selectivity[8].

A highly attractive feature of the new α-C–H bond functionalization strategy is its applicability to the regioselective functionalization of amines with an existing α-substituent (Table 2). Reactions are highly regioselective and lead to the replacement of the electronically less activated and sterically more accessible C–H bond, which allows for the synthesis of α,α′-disubstituted amines. The majority of the reactions are highly diastereoselective and lead to the preferential formation of the *trans*-configured products, consistent with the nucleophile attacking the less-hindered face of the intermediate imine. An exception is product **36**, which is formed with a slight preference for the *cis* isomer, possibly because of the silyl ether acting as a weak directing group. Importantly, reactions are highly stereospecific. For instance, amine (*R*)-**8** was converted into product (*R*,*R*)-**39** without a loss of enantiomeric excess. This finding was exploited in a one-step synthesis of the natural product (–)-solenopsin A (ref. 34) from the readily available amine (*R*)-**48**. The natural product anabasine (**26**)[35], itself obtained in one step (Table 1), was readily converted into derivative **49**. Further demonstrating the utility of this method for drug discovery, late-stage intermediates to the commercial drugs, varenicline[36] and risperidone[37] readily underwent α-C–H bond functionalization with high levels of diastereoselectivity.

Control experiments were performed to test for the potential involvement of the above-mentioned 1-pyrroline trimer **7** (Fig. 2). Apparently, this compound is not an intermediate in this process, as judged by the fact that **7** does not undergo the formation of 2-phenyl pyrrolidine (**8**) when exposed to the standard reaction conditions (Fig. 2a). The same is true when the reaction is performed in the presence of lithium alkoxide generated *in situ* (which corresponds to compound **3** in Fig. 1). To shed light on the relative rates of the different reaction steps and potentially to simplify the set-up conditions, a number of experiments were performed (Fig. 2b). The addition of *n*-BuLi to a preformed mixture of pyrrolidine and benzophenone, followed by the addition of phenyl lithium, resulted in the formation of **8** with a similar efficiency to that with the conditions in Table 1, in which the addition of *n*-BuLi preceded the addition of benzophenone. This indicates that the deprotonation of pyrrolidine by *n*-BuLi is significantly faster than any reaction of *n*-BuLi with benzophenone. The procedure for the formation of **8** could be simplified further by

Table 1 | α-C–H bond functionalization of cyclic amines.



(±)-**8**, 60%* (±)-**9**, 48%* (±)-**10**, 62%* (±)-**11**, 48%* (±)-**12**, 56%* (±)-**13**, 57%* (±)-**14**, 61%*

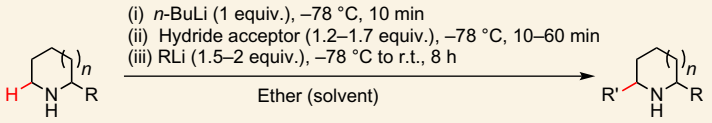
(±)-**15**, 58%* (±)-**16**, 51%* (±)-**17**, 53%* (±)-**18**, 62%* (±)-**19**, 50%* (±)-**20**, 59%* (±)-**21**, 56%*

(±)-**22**, 50%* (±)-**23**, 58%* d.r. > 25:1 (±)-**24**, 73%* d.r. > 25:1 (±)-**25**, 61%† (±)-**26**, 58%† (anabasine) (±)-**27**, 63%† (±)-**28**, 62%‡

(±)-**29**, 72%‡ d.r. > 25:1 (±)-**30**, 72%† (±)-**31**, 52%† (±)-**32**, 55%† (±)-**33**, 80%* (±)-**34**, 70%* (±)-**35**, 64%*

*Benzophenone was used as the hydride acceptor (10 min reaction time). †*t*-Butyl phenyl ketone was used as the hydride acceptor (30–90 min reaction time). ‡Trifluoroacetophenone was used as the hydride acceptor (60 min reaction time).

Table 2 | Regioselective and stereospecific α-C–H bond functionalization of cyclic amines.



36, 79%* d.r. = 1.8:1 (±)-**37**, 60%† d.r. = 2.3:1 (±)-**38**, 52%† d.r. > 25:1 (±)-**39**, 51%† d.r. > 25:1 (±)-**40**, 56%† d.r. > 25:1 (±)-**41**, 64%† d.r. > 25:1

(±)-**42**, 78%‡ d.r. > 25:1 (±)-**43**, 61%‡ d.r. > 25:1 (±)-**44**, 68%‡ d.r. > 25:1 (±)-**45**, 73%† d.r. > 25:1 (±)-**46**, 58%† d.r. > 25:1 (±)-**47**, 65%† d.r. > 25:1

(*R*)-**8** 90% e.e. (*R*,*R*)-**39**, 53% d.r. > 25:1, 90% e.e. (*R*)-**48** > 99% e.e. (–)-**solenopsin A**, 66% d.r. = 4:1, > 99% e.e. (±)-**26**, (anabasine) (±)-**49**, 70% d.r. > 25:1

Varenicline **50** (±)-**51**, 68% d.r. > 25:1 (±)-**52**, 62% d.r. > 25:1 **Risperidone** (±)-**53**, 56%‡ d.r. > 25:1

*Benzophenone was used as the hydride acceptor (10 min reaction time). †*t*-Butyl phenyl ketone was used as the hydride acceptor (60 min reaction time). ‡Trifluoroacetophenone was used as the hydride acceptor (60 min reaction time).

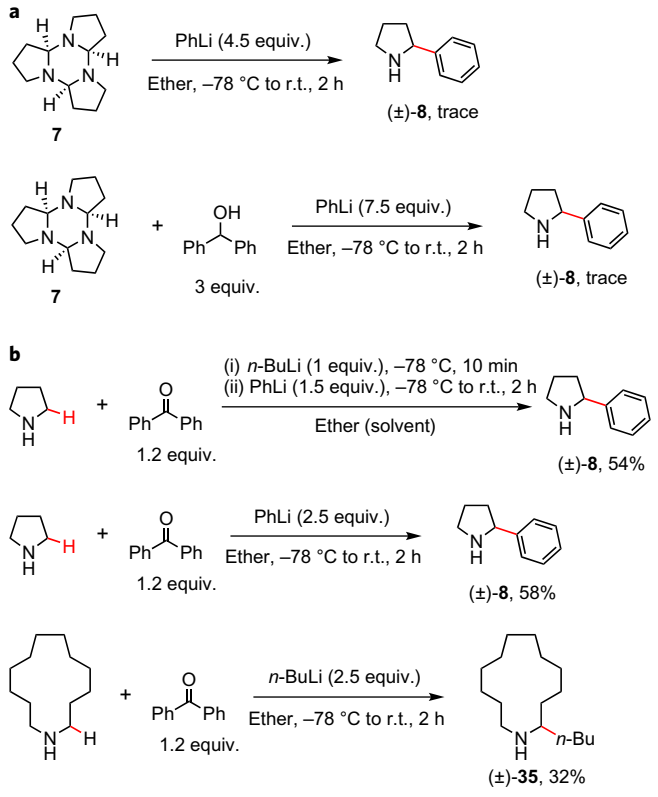


Figure 2 | Control studies and simplification of the set-up conditions. **a**, The 1-pyrroline trimer **7** is not involved as an intermediate in the functionalization of the pyrrolidine α-C–H bond. **b**, Experiments that involve pre-mixing of the amine and hydride acceptor.

employing phenyl lithium as the base in the first step. Simply adding an excess of phenyl lithium to a mixture of pyrrolidine and benzophenone led to the formation of **8** in a nearly identical yield to that observed before. This experiment establishes, rather unexpectedly, that the rates of both pyrrolidine deprotonation and hydride transfer vastly exceed the rate of the potentially competing addition of phenyl lithium to benzophenone, a known process[38]. We also evaluated this simplified reaction set-up in the α-*n*-butylation of azacyclotridecane. Although the yield of **35** was substantially lower than that in the stepwise process (32 versus 64%), this result is quite remarkable as it indicates that the reduction of benzophenone by the intermediate lithium amide can compete with the known reduction of benzophenone by *n*-BuLi (ref. 39).

In conclusion, we have developed an operationally convenient method for the α-C–H bond functionalization of cyclic N–H amines. This approach complements existing methodology, is protecting-group free and is uniquely effective in the stereospecific functionalization of cyclic amines with pre-existing substituents. In contrast to the vast majority of current approaches for amine C–H functionalization, no transition metals are required in this process.

Data availability. Crystallographic data for the structure reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition number CCDC 1535260 ((±)-**45**). Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. All other data supporting the findings of this study, including experimental procedures and compound characterization, are available within the Article and its Supplementary Information, or from the corresponding author upon reasonable request.

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Author contributions

W.C. and L.M. developed the amine α-functionalization and contributed equally to this work. A.P. further developed the reaction and expanded the scope. D.S. conceived and supervised the project and wrote the manuscript. All the authors discussed the results and commented on the manuscript.

Additional information

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Competing financial interests

The authors declare no competing financial interests.