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Rapid functionalization of multiple C–H bonds in unprotected alicyclic amines

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The synthesis of valuable bioactive alicyclic amines containing variable substituents in multiple ring positions typically relies on multistep synthetic sequences that frequently require the introduction and subsequent removal of undesirable protecting groups. Although a vast number of studies have aimed to simplify access to such materials through the C–H bond functionalization of feedstock alicyclic amines, the simultaneous introduction of more than one substituent to unprotected amines has never been accomplished. Here we report an advance in C–H bond functionalization methodology that enables the introduction of up to three substituents in a single operation. Lithiated amines are first exposed to a ketone oxidant, generating transient imines that are subsequently converted to endocyclic 1-azaallyl anions, which can be processed further to furnish β-substituted, α,β-disubstituted, or α,β,α′-trisubstituted amines. This study highlights the unique utility of in situ-generated endocyclic 1-azaallyl anions, elusive intermediates in synthetic chemistry.

The transformation of typically unreactive C–H bonds in feedstock alicyclic amines to C–C or C–X bonds provides a highly desirable entry to functionalized heterocycles[1], which are ubiquitous components of bioactive natural products and pharmaceutical drugs[2,3]. Considerable progress has been made in the α-C–H bond functionalization of cyclic amines[4–10], although, with few exceptions[11–14], most methods are incompatible with the presence of amine N–H bonds, thus requiring the introduction of a protecting group on the amine nitrogen atom, which often hampers further transformations. The functionalization of more remote C–H bonds in cyclic amines is severely underdeveloped and the few known methods are limited to the synthesis of tertiary, *N*-aryl or *N*-acyl amines[15–30]. The simultaneous functionalization of more than one ring position is rare and has yet to be achieved for the direct formation of secondary amine products. Functionalization of three ring positions in a single operation is all but unknown. Here we report a strategy that achieves the regioselective β-C–H bond functionalization of secondary alicyclic amines. This approach further enables the introduction of up to three substituents in a single operation, all without requiring protecting groups or transition metals.

The substantial pharmaceutical relevance of alicyclic amines that contain β-substituents—often in combination with other ring substituents—makes new methods for β-C–H bond and multi-C–H bond functionalization highly desirable[2,3,31–34], given that traditional approaches to such heterocycles typically require multistep sequences[35]. Existing methods for the β-C–H bond functionalization of alicyclic amines and their derivatives typically involve the formation of enamine or enamide intermediates, which can be generated through different reaction pathways. Endocyclic enamines accessed by oxidative transformation of tertiary amines can undergo β-functionalization with appropriate acceptors such as β-nitrostyrenes, a method that also introduces a degree of ring unsaturation (Fig. 1a)[15,16]. Oxidatively generated *N*-aryl enamines have also been used in formal [2 + 2][17] and [4 + 2][36] cycloadditions, *cis*-diacetoxylations[37] and β-silylations[18] (not shown). β-Alkylation of amines such as piperidine can be achieved with primary alcohols in the presence of a ruthenium catalyst, a process that is coupled to the concurrent *N*-alkylation of the amine (Fig. 1b)[19,20]. In the presence of a finely tuned palladium catalyst, α-metallated *N*-Boc amines can undergo β-arylation in a sequence that involves β-hydride elimination, also providing a certain percentage of α-arylated product (Fig. 1c)[21]. Palladium-catalysed β-C–H bond activation followed by cross-coupling with aryl halides can be achieved using protected alicyclic amines with preinstalled carboxamide directing groups in certain ring positions (Fig. 1d)[22–26]. Although this type of reaction does not involve an enamide intermediate, it cannot be performed on unsubstituted alicyclic amines. Transition metal-free direct condensation-based methods for the β-C–H functionalization of alicyclic amines are also known. These reactions invariably lead to amine *N*-alkylation and can involve the concurrent functionalization of the α-position (for example, Fig. 1e)[27,28]. A unique transformation that motivated the present study is the reaction of *N*-lithiated pyrrolidine with a non-enolizable imine, leading to β-C–H functionalization and aromatization (Fig. 1f)[38].

Inspired by seminal work of Wittig and Hesse on the hydricity of *N*-lithiated amines (Fig. 1f)[38,39], we recently developed a method for direct α-C–H bond functionalization of unprotected alicyclic amines (Fig. 1g)[12,14]. This transformation involves the addition of organometallic nucleophiles to cyclic imines such as 1-piperideine (**2**), which is generated in situ from *N*-lithiated amines such as **1** and simple ketone oxidants. We recognized that imines such as **2** may also provide a starting point for β-C–H functionalization (Fig. 1h). Specifically, deprotonation of **2** was envisioned to provide endocyclic 1-azaallyl anion **4**. The 1-azaallyl anion (a type of species also classified as a metalloenamine or an aza-enolate) could then engage an alkylating reagent, resulting in the formation of new imine **5**. Reductive work-up of **5** would provide β-functionalized amine **6**; furthermore, reaction of imine **5** with a nucleophile could provide α,β-difunctionalized amine **8** via the intermediacy of lithiate **7** (Fig. 1i). Finally, one could envision the preparation of α,β,α′-trifunctionalized amines in a single operation (Fig. 1j). This would involve exposing lithiate intermediate **7** to additional ketone oxidant to regioselectively generate

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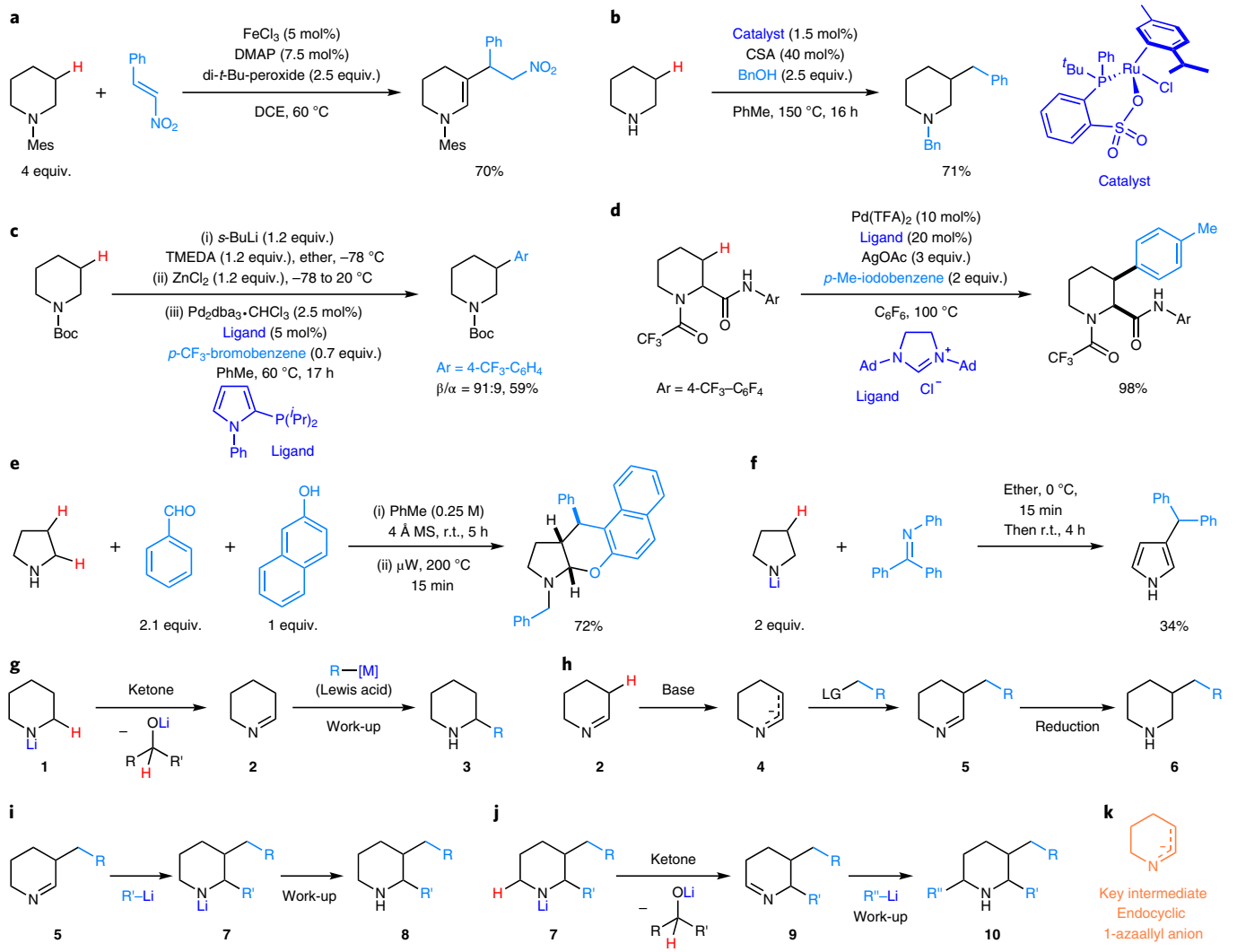
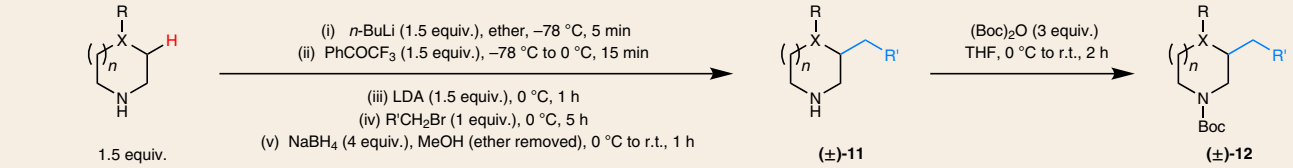
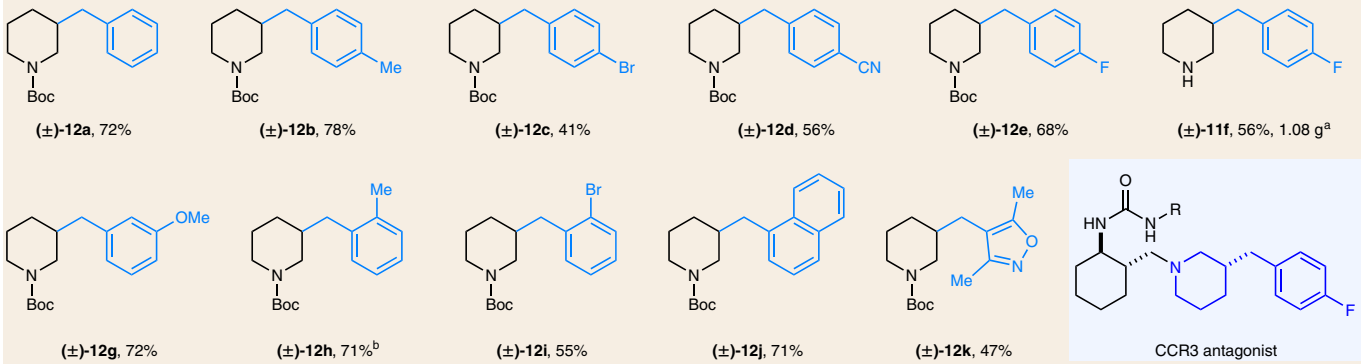


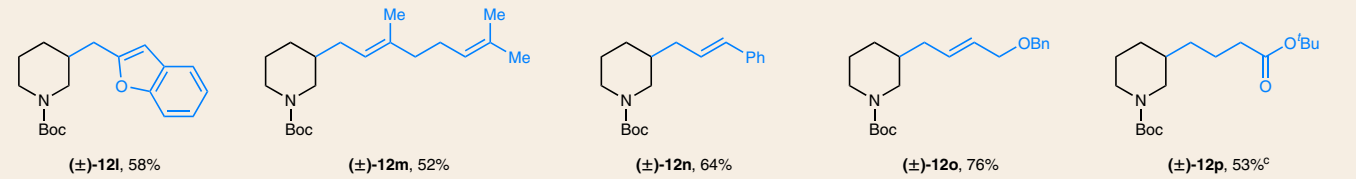
Fig. 1 | Selected methods for the β-C–H bond functionalization of alicyclic amines and a new strategy for the multifunctionalization of secondary alicyclic amines. a, Oxidative β-alkylation of *N*-aryl amines with β-nitrostyrenes. **b**, Redox-neutral β-alkylation/*N*-alkylation of piperidine with alcohols. **c**, β-Arylation of *N*-Boc amines via a deprotonative/cross-coupling approach. **d**, Palladium-catalysed β-arylation of *N*-acyl amines containing an α-directing group. **e**, Redox-neutral condensation-based approach for amine α,β-difunctionalization with concurrent *N*-alkylation. **f**, β-Alkylation/aromatization of *N*-lithiated pyrrolidine. **g**, Amine α-C–H bond functionalization via transient imines. **h**, The proposed strategy for amine β-functionalization. **i**, The proposed strategy for amine α,β-difunctionalization. **j**, The proposed strategy for amine α,β,α′-trifunctionalization. **k**, The endocyclic 1-azaallyl anion as the key intermediate. Challenges include an elusive intermediate, substantial angle strain, and an ambident nucleophile (*C*- versus *N*-alkylation). DMAP, 4-dimethylaminopyridine; DCE, 1,2-dichloroethane; CSA, camphorsulfonic acid; TMEDA, tetramethylethylenediamine; Ad, adamantyl; MS, molecular sieve; LG, leaving group.

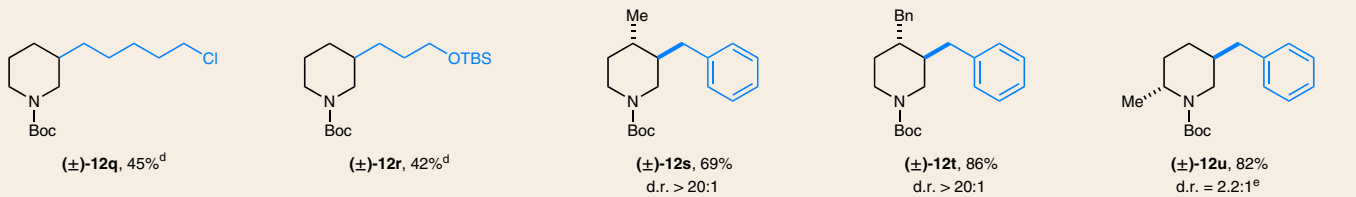
imine **9**, followed by addition of a second nucleophile to provide trisubstituted amine **10** following work-up. Access to any of these substitution patterns hinges on the ability to first generate endocyclic 1-azaallyl anion **4**. Indeed, an endocyclic 1-azaallyl anion intermediate was invoked in the reaction leading to β-substituted pyrrole, in which a second equivalent of the imine oxidant acts as the electrophile that is engaged by the endocyclic 1-azaallyl anion (Fig. 1f)[38]. However, beyond the isolated example by Wittig, simple endocyclic 1-azaallyl anions have remained exceptionally rare intermediates in organic synthesis[40,41]. This is in stark contrast to acyclic and exocyclic 1-azaallyl anions, widely used nucleophiles that are well known to undergo selective alkylation at the C-terminus[42,43]. In a rare example that involves trifluoroacetylation, endocyclic 1-azaallyl anions have shown ambident behaviour, meaning they can react on the carbon or nitrogen terminus, in addition to undergoing side reactions such as addition to the imine product corresponding to **5** (ref. [41]). The dearth of reactions that involve endocyclic 1-azaallyl anions is perhaps not surprising, as these species are expected to exhibit substantial angle strains. Another important factor that potentially hampers access to unsubstituted endocyclic 1-azaallyl anions is the fact that endocyclic imines such as 1-pyrroline and 1-piperideine are difficult to prepare as their corresponding monomers due to their strong propensity to trimerize[44]. Imine trimers are stable under basic conditions, preventing their deprotonation. These challenges notwithstanding, we hypothesized that the conditions that enable the in situ-generation of monomeric endocyclic imines from lithiated alicyclic amines and ketones could be compatible with subsequent deprotonation by an appropriate base to access endocyclic 1-azaallyl anions in a single operation from their parent amines.

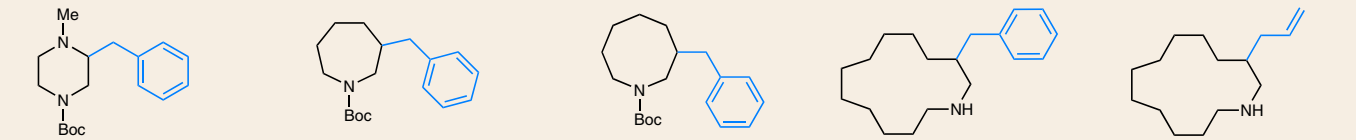
Table 1 | C–H bond functionalization of secondary alicyclic amines









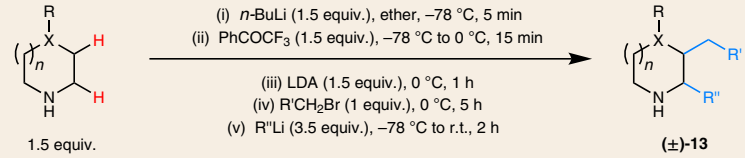


Reactions were performed on a 1 mmol scale. Yields correspond to isolated yields of chromatographically purified β-functionalized amines or *N*-Boc amines. [a]The reaction was performed on a 10 mmol scale. The yield corresponds to the isolated yield of the free secondary amine after column purification and subsequent bulb-to-bulb distillation. [b]The reaction time for the alkylation step was 8 h. [c]4-Bromo-*t*-butyl crotonate was used as the electrophile and the conjugate C=C bond was reduced by $NaBH_4$. The allylation step was performed at −20 °C. [d]Alkyl iodides were used as electrophiles and the reaction time for the alkylation step was 24 h. [e]Phenyl *t*-butyl ketone was used as the hydride acceptor. [f]1.1 Equivs. of 1-azaallyl anion were used. The reaction time for the benzylation step was 16 h, using benzyl chloride as the electrophile. [g]2 Equivs. of 1-azaallyl anion were used. CCR3, C–C chemokine receptor type 3; TBS, *tert*-butyldimethylsilyl; d.r., diastereomeric ratio.

Results and discussion

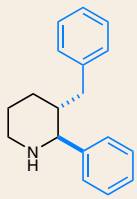
Following considerable experimentation and optimization aimed at avoiding competitive and undesirable *N*-alkylation (Supplementary Table 1), conditions were identified that allowed for simple yet efficient syntheses of β-functionalized secondary alicyclic amines from their corresponding parent heterocycles (Table 1). The requisite monomeric cyclic imines were prepared in situ from *N*-lithiated amines and trifluoroacetophenone. Subsequent deprotonation with lithium diisopropylamide (LDA) resulted in the formation of endocyclic 1-azaallyl anions, which engaged a variety of benzylic, allylic, and alkyl halides. Following the reduction of the intermediate imines (see structure **5**, Fig. 1) with sodium borohydride, β-substituted amines were obtained in typically good yields. Although not strictly necessary, *N*-Boc protection was performed on most crude amine products to facilitate product isolation. Higher-molecular-weight products such as (±)-**11y** and (±)-**11z** were found to be relatively non-polar and were easily isolated as free amines. For reactions conducted on a larger scale, more polar amine products could be readily isolated in their free base form by purification involving bulb-to-bulb distillation, as demonstrated in the synthesis of amine (±)-**11f**. This product represents the core structure of potent CCR3 antagonists and previously required at least five steps to be synthesized in its racemic form[45]. The amine β-alkylation is compatible with a range of functional groups, including halides, nitriles, esters, ethers, alkenes, and different heterocycles. Various ring sizes of the amine starting materials were also readily accommodated. Piperidines

Table 2 | α,β-Difunctionalization of secondary alicyclic amines

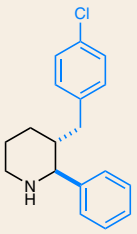


1.5 equiv.

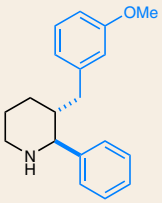
(±)-13



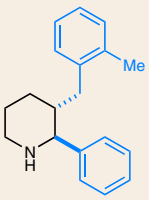
(±)-13a, 61%, d.r. = 6:1 (X-ray)



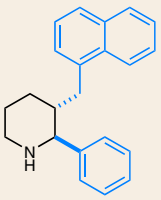
(±)-13b, 47%, d.r. = 5:1



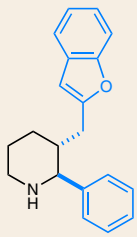
(±)-13c, 56%, d.r. = 6:1



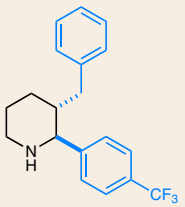
(±)-13d, 59%, d.r. = 7.5:1[a]



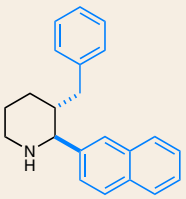
(±)-13e, 67%, d.r. = 9:1



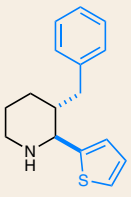
(±)-13f, 47%, d.r. = 1.8:1



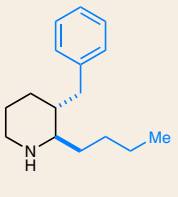
(±)-13g, 63%, d.r. = 6:1



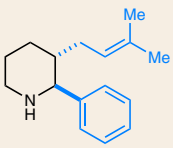
(±)-13h, 65%, d.r. = 7.5:1



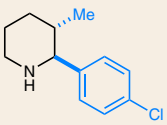
(±)-13i, 50%, d.r. = 1.3:1



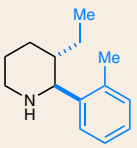
(±)-13j, 68%, d.r. > 20:1



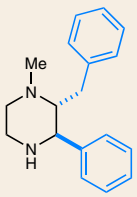
(±)-13k, 70%, d.r. = 6:1



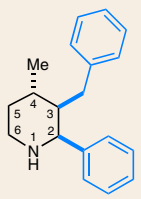
(±)-13l, 63%, d.r. = 5:1[b]



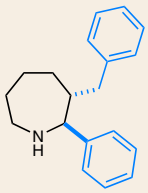
(±)-13m, 52%, d.r. = 8:1[c]



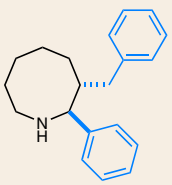
(±)-13n, 69%, d.r. = 10:1



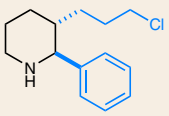
(±)-13o, 68%, d.r. = 2.2:1 (2,3-*cis*, 2,4-*trans* : 2,3-*trans*, 2,4-*cis*)



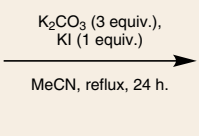
(±)-13p, 22%, d.r. > 20:1



(±)-13q, 72%, d.r. > 20:1 (X-ray)



(±)-13r, 59%, d.r. = 5:1[c]



(±)-14, 60%

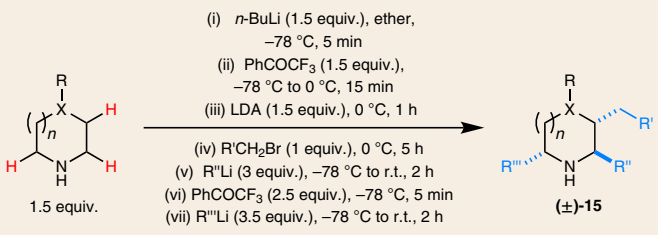
Reactions were performed on a 1 mmol scale. Yields correspond to isolated yields of chromatographically purified α,β-difunctionalized secondary alicyclic amines. [a]The reaction time for the alkylation step was 8 h. [b]MeI was used as the electrophile. [c]Alkyl iodides were used as electrophiles and the reaction time for the alkylation step was 24 h.

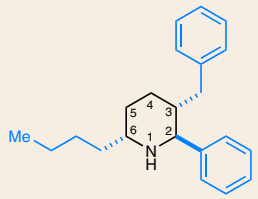
with existing substituents at the C4 position underwent product formation with excellent levels of diastereoselectivity. 2-Methylpiperidine underwent regioselective β′-benzylation in good yield, providing product (±)-**12u** as a 2.2:1 mixture of diastereomers.

A simple modification of the procedure described above (namely, the replacement of the $NaBH_4$ reduction step with the addition of an organolithium nucleophile) enabled the preparation of a broad range of α,β-difunctionalized secondary alicyclic amines (Table 2). Difunctionalized amines were obtained in moderate to good yields from their readily available parent heterocycles. Good to excellent diastereoselectivities were observed in many cases, and with the exception of (±)-**13n**, all product diastereomers were readily separable. α,β-Difunctionalized secondary amine products are valuable building blocks that facilitate access to other structurally diverse compounds; product (±)-**13r**, for instance, could be readily transformed to bicyclic tertiary amine (±)-**14**.

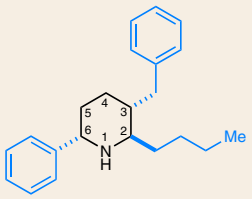
We sought to explore the unprecedented functionalization of three ring positions in a single operation (Table 3) to further demonstrate the strengths and capabilities of our method for C–H bond functionalization of secondary alicyclic amines. Following the introduction of two substituents as outlined in Table 2, an *N*-lithiated (±)-**13a** intermediate was exposed to trifluoroacetophenone, followed by addition of *n*-butyl lithium. This resulted in the efficient synthesis of α,β,α′-trifunctionalized amine (±)-**15a**, bearing three different substituents. The position of the substituents can be changed at will, simply by changing the order of addition. This

Table 3 | α,β,α′-Trifunctionalization of secondary alicyclic amines

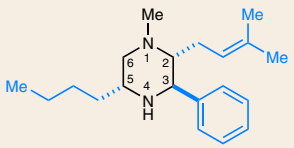




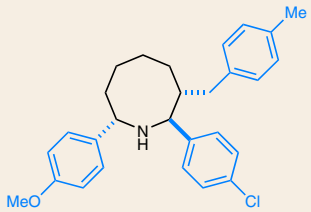
(±)-15a, 55%, d.r. = 8:1
(2,3-*trans*, 2,6-*trans* : 2,3-*cis*, 2,6-*trans*)



(±)-15b, 23%, d.r. = 2.4:1
(2,3-*trans*, 2,6-*trans* : 2,3-*trans*, 2,6-*cis*)



(±)-15c, 28%, d.r. = 12:1
(2,3-*trans*, 2,5-*cis* : 2,3-*cis*, 2,5-*trans*)



(±)-15d, 40%, d.r. > 20:1

Reactions were performed on a 1 mmol scale. Yields correspond to isolated yields of chromatographically purified α,β,α′-trifunctionalized secondary alicyclic amines.

is exemplified by the synthesis of (±)-**15b**, a constitutional isomer of (±)-**15a**. Similar transformations were successfully conducted with *N*-methyl piperazine and azocane to provide the corresponding trifunctionalized products (±)-**15c** and (±)-**15d**. Although the yields for the triple C–H functionalization of amines were lower, as expected, the ability to rapidly introduce three different substituents in well-defined ring positions should be of considerable utility to drug discovery programmes.

In conclusion, we have developed procedures for the facile β- and multi-C–H functionalization of secondary alicyclic amines utilizing in situ-generated endocyclic 1-azaallyl anions as key intermediates. In contrast to the majority of approaches that enable the functionalization of a single C–H bond, this method does not require protecting groups or transition metals.

Online content

Any Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41557-020-0438-z.

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Data availability

The data that support the findings of this study are available within the paper and its Supplementary Information. Crystallographic data for structures (±)-**13a** and (±)-**13q** have been deposited at the Cambridge Crystallographic Data Centre, under deposition nos. 1935815 ((±)-**13a**) and 1935816 ((±)-**13q**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/

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Author contributions

W.C. developed the amine β- and multifunctionalization and explored the scope. A.P. performed initial studies on the amine β-functionalization and α,β-difunctionalization. K.A.A. performed crystallographic analyses for compounds (±)-**13a** and (±)-**13q**. D.S. conceived and supervised the project. D.S. and W.C. wrote the manuscript. All authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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