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Diversification of unprotected alicyclic amines via C–H bond functionalization: Decarboxylative alkylation of transient imines

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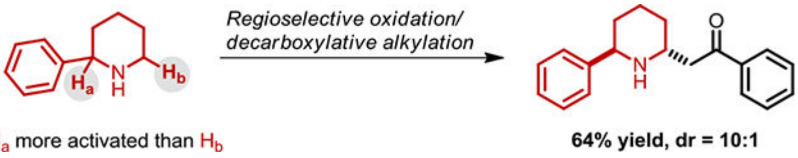
Abstract

Despite extensive efforts by many practitioners in the field, methods for the direct α-C–H bond functionalization of unprotected alicyclic amines remain rare. A new advance in this area utilizes N-lithiated alicyclic amines. These readily accessible intermediates are converted to transient imines through the action of a simple ketone oxidant, followed by alkylation with a β-ketoacid under mild conditions to provide valuable β-amino ketones with unprecedented ease. Regioselective α′-alkylation is achieved for substrates with existing α-substituents. The method is further applicable to the convenient one-pot synthesis of polycyclic dihydroquinolones through the incorporation of a S_NAr step.

Graphical Abstract



N-lithiated alicyclic amines are converted to transient imines through the action of a simple ketone oxidant, followed by alkylation with a β-ketoacid under mild conditions to provide valuable β-amino ketones with unprecedented ease. Regioselective α′-alkylation is achieved for substrates with existing α-substituents. The method is further applicable to the convenient one-pot synthesis of polycyclic dihydroquinolones through the incorporation of a S_NAr step.

Keywords

C–H bond functionalization; alicyclic amines; decarboxylative C–C bond formation; Mannich reaction; annulation

Driven largely by the importance of this class of compounds in synthetic and medicinal chemistry,[1] the synthesis of substituted alicyclic amines by means of C–H bond functionalization remains a highly active area of research.[2,3] In stark contrast to the

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numerous advances that have been achieved with 3° or protected 2° amines, highly desirable methods for the direct synthesis of α-functionalized 2° (i.e. unprotected) alicyclic amines from their corresponding parent amines remain limited (Scheme 1).[3j,4] Moreover, α′-C–H bond functionalization of 2° alicyclic amines with an existing α-substituent is exceptionally challenging,[3j,5,6] especially with electronically activating substituents that favor functionalization at the substituted site. Leveraging the known ability of lithium amides to generate imines upon reaction with simple ketone oxidants (e.g., **1** → **2**, Scheme 1),[7] we recently developed a new method for the C–H bond functionalization of unprotected alicyclic amines.[8] Specifically, transient cyclic imines **2** generated from the oxidation of lithium amides **1** engage organolithium nucleophiles to provide α-functionalized products. Regioselective α'-C–H bond functionalization of α-substituted alicyclic amines was also achieved.[8a] The scope of the nucleophile could be expanded to other organometallics such as Grignard reagents by using Lewis acids to activate the imine intermediates.[8b] However, α′-C–H bond functionalization of α-substituted amines proved to be incompatible with Lewis acid activation, hampering our efforts to further expand the scope of nucleophiles. Particularly attractive would be new methods in which α'-C–H bond functionalization is achieved with non-organometallic nucleophiles. Here we report an approach for the rapid diversification of transient imines **2** via decarboxylative alkylation with β-ketoacids **3** to provide β-aminoketones **4**. In addition, utilizing *o*-fluoroaryl-β-ketoacids **5**, polycyclic amines **6** can be obtained in a single operation via a process that involves a subsequent S_NAr reaction.

Mannich reactions and their decarboxylative variants employing β-keto acids represent valuable tools for the synthesis of β-amino ketones from imines.[9–11] Despite the utility of the corresponding products, the use of enolizable cyclic imines in these reactions has largely remained limited to easily accessible alicyclic imines such as 1-pyrroline and 1-piperideine.[12–15] This is likely the result of the limited availability/stability of enolizable cyclic imines, in particular chiral variants possessing a substituent in the α-position. In order to determine whether the in-situ-generation of alicyclic imines via lithium amide oxidation is compatible with the decarboxylative Mannich process, we evaluated a range of reaction conditions. Key findings with the model substrates piperidine and β-keto acid **3a** are summarized in Scheme 2. Following amine deprotonation and treatment with trifluoroacetophenone to rapidly access 1-piperideine, β-keto acid **3a** (1.5 equiv) was added, followed by stirring at room temperature. Desired β-amino ketone **4a** was obtained in 39% yield. The yield of **4a** could be increased to 50% by employing 2.5 equivalents of **3a**. Considering that the Li-alkoxide resulting from the reduction of trifluoroacetophenone may interfere with the subsequent decarboxylative alkylation,[16] the addition of acidic additives was explored. Indeed, small to appreciable improvements in yield were observed in all cases. Trifluoroacetic acid (TFA) outperformed acetic acid as an additive, presumably because lithium acetate is still sufficiently basic to partially impede the addition process. Under the optimized conditions, product **4a** was obtained in 76% yield.

The scope of the reaction was explored with a broad range of alicyclic amines and β-keto acids (Scheme 3). Different ring sizes and substitution patterns on both reaction partners were readily accommodated. Both aryl and alkyl ketones could be introduced. Synthetically useful yields of β-amino ketones **4** were obtained in most cases. Particularly useful are reactions with amines that contain α-substituents. Regioselective substitution of the α′-position was observed in all cases. Diastereoselectivities ranged from poor to excellent (vide infra). Using *o*-fluoroaryl-β-keto acids **5** and adding an S_NAr step without the need for isolating intermediates enabled the efficient preparation of various polycyclic dihydroquinolones **6**. These species, which are now available directly from their unfunctionalized amines, are rather challenging to prepare by other means.[17,18]

As shown in Scheme 3, products **4p**–**4y** were obtained predominantly as *trans*-diastereomers. The *trans*-diastereomers are in fact the kinetic products of these reactions, as it has been established that the corresponding *cis*-isomers are thermodynamically more stable.[19] Interconversion of the diastereomers is possible, presumably via a retro-Mannich or retro-conjugate addition pathway. Indeed, simply changing the reaction conditions in the synthesis of product **4p** allowed for a complete reversal of diastereoselectivity in favor of the *cis*-isomer (Scheme 4).

In summary, we have achieved the α-alkylation of unprotected alicyclic amines via a decarboxylative Mannich process involving regioselective C–H bond functionalization. Adding an S_NAr step to the overall reaction sequence, this process was further extended to the synthesis of polycyclic dihydroquinolones in a single operation.

Supplementary Material

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Acknowledgements

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[18]. While full consumption of the amine starting materials was typically observed, a quantitative assessment of the mass balance is not yet possible. Competing imine-trimer formation cannot be ruled out at present and intractable polar byproducts are often formed. In case of α-substituted amine starting materials, small amounts of the regioisomeric imines were also observed. These species did not engage in the alkylation reaction and were readily separable from the target compounds.

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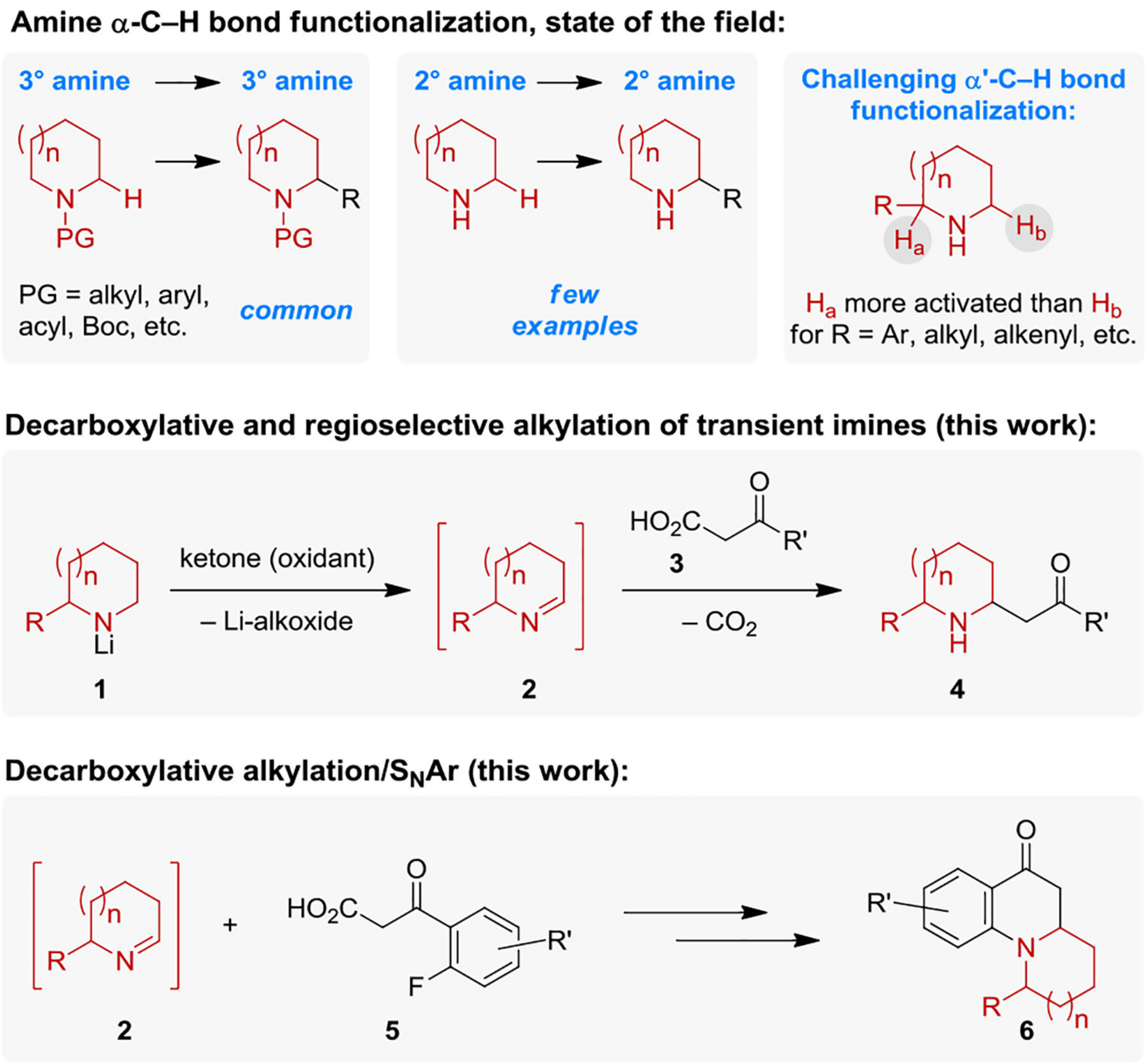
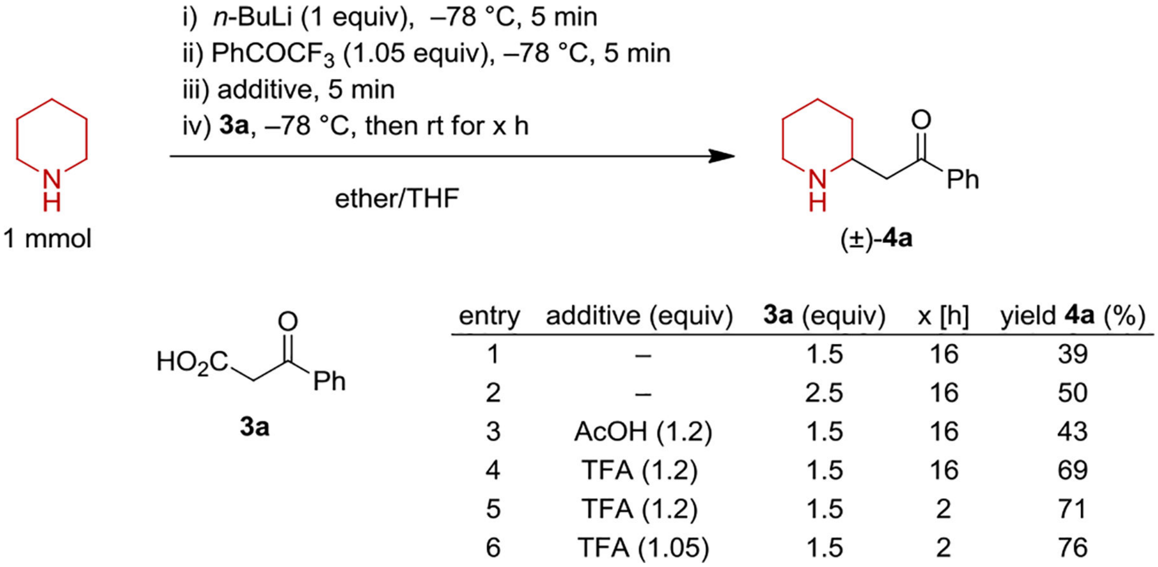


Scheme 1.

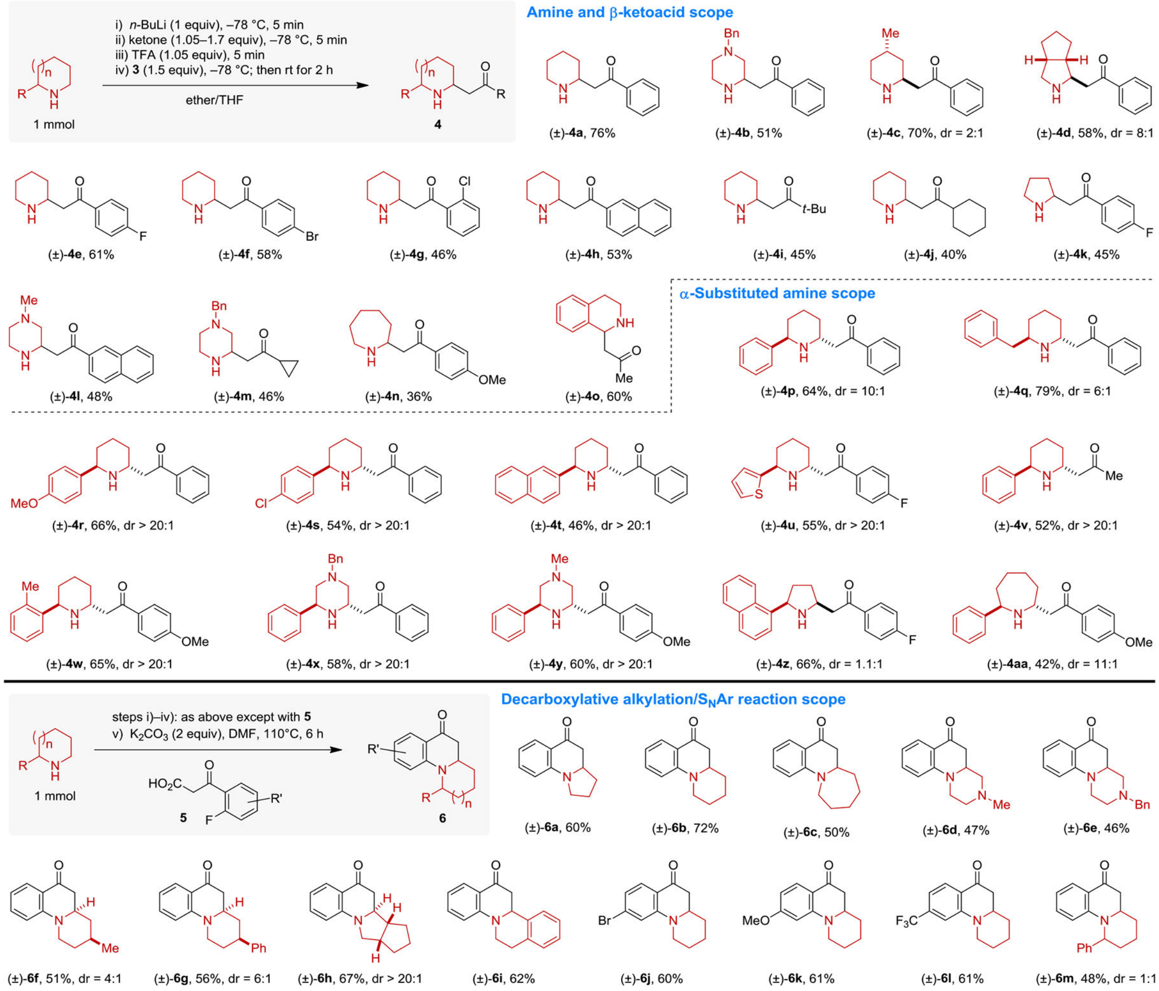
Ovefrview of methods for the C–H bond functionalization of amines and present strategy.



entry	additive (equiv)	**3a** (equiv)	x [h]	yield **4a** (%)
1	–	1.5	16	39
2	–	2.5	16	50
3	AcOH (1.2)	1.5	16	43
4	TFA (1.2)	1.5	16	69
5	TFA (1.2)	1.5	2	71
6	TFA (1.05)	1.5	2	76

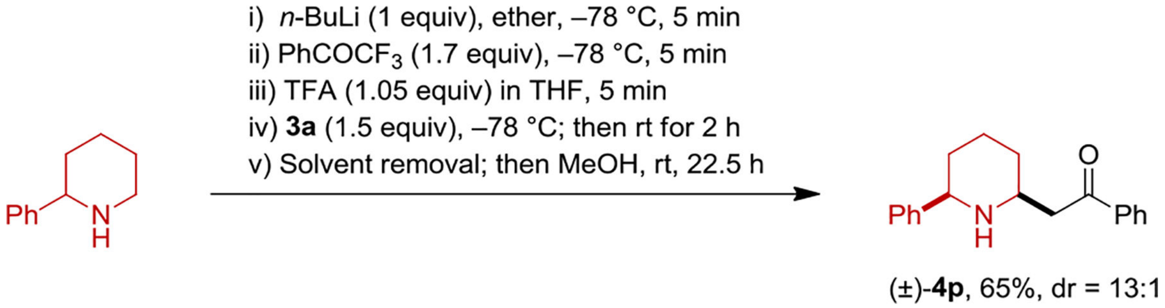
Scheme 2.

Selected optimization reactions.



Scheme 3.

Reaction scope.



Scheme 4.

Formation of *cis*-product.