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α-C–H Bond Functionalization of Unprotected Alicyclic Amines: Lewis Acid Promoted Addition of Enolates to Transient Imines

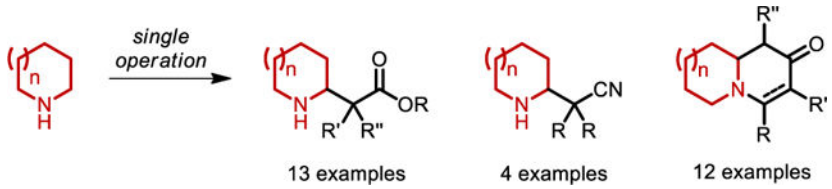
Jae Hyun Kim[†,‡,§], **Anirudra Paul**[†,‡], **Ion Ghiviriga**[‖], **Daniel Seidel**[†,*]

[†]Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611, United States

[‖]Center for NMR Spectroscopy, Department of Chemistry, University of Florida, Gainesville, Florida 32611, United States

Abstract

Enolizable cyclic imines, obtained in situ from their corresponding lithium amides by oxidation with simple ketone oxidants, are readily alkylated with a range of enolates to provide mono- and polycyclic β-aminoketones in a single operation, including the natural product (±)-myrtine. Nitrile anions also serve as competent nucleophiles in these transformations which are promoted by BF_3 etherate. β-Aminoesters derived from ester enolates can be converted to the corresponding β-lactams.



Alicyclic amines are ubiquitous compounds with manifold uses in synthetic and medicinal chemistry.[1] The synthesis of substituted alicyclic amines by means of C–H bond functionalization is an attractive strategy that continues to inspire the development of numerous, mechanistically distinct strategies.[2,3] While the vast majority of studies in this area have focused on 3° or protected 2° amines, few methods have emerged that achieve the synthesis of α-functionalized 2° (i.e. unprotected) alicyclic amines directly from their corresponding parent azacycles.[2,4] This can be attributed largely to the incompatibility of most activation modes with basic amine functionalities and/or N–H bonds. We have recently developed a strategy for the α-C–H bond functionalization of unprotected alicyclic amines that takes advantage of the known propensity of lithium amides to undergo formation of

[*]**Corresponding Author** Daniel Seidel − Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611, United States, seidel@chem.ufl.edu.

[§]Present Addresses

College of Pharmacy, Kangwon National University, Chuncheon 24341 (Republic of Korea)

[‡]These authors contributed equally.

ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and characterization data (PDF).

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transient imines upon reaction with simple ketone oxidants (Scheme 1).[5,6] This method was initially applied to organolithium nucleophiles,[5a] and later extended to Grignard reagents and other organometallics with attenuated nucleophilicities.[5b] Less reactive nucleophiles were found to benefit from or require the use of Lewis acids to activate the imine electrophiles toward addition. More recent advances utilizing this C–H bond functionalization strategy include the functionalization of multiple ring-positions[5c] and the decarboxylative alkylation of transient imines.[5d] Here we report the alkylation of transient imines with a broad range of enolate-type nucleophiles to rapidly convert simple starting materials into a diverse portfolio of functionalized amines, including polycyclic amines.

Mannich reactions are well established as useful tools for the synthesis of valuable β-amino ketones.[7] However, variants utilizing enolates in combination with enolizable imines, in particular enolizable cyclic imines, remain rare,[8] likely due to the limited electrophilicity of imines lacking activating groups and the dearth of methods to generate cyclic imines in their active monomeric forms.[9] The direct synthesis of methylphenidate[10] from piperidine and methyl 2-phenylacetate was selected as the model reaction to study the proposed transformation. Key findings of this survey are summarized in Table 1. Briefly, the presence of a Lewis acid was found to be required to obtain any quantity of methylphenidate, with BF_3 etherate outperforming trimethylsilyl trifluoromethanesulfonate (TMSOTf). Diastereomeric ratios were highly variable depending on conditions. The highest dr favoring the pharmaceutically active *threo* isomer **1a** was 3.2:1 (entry 12) while the *erythro* isomer **1a′** was obtained in up to 10:1 dr (entry 5).[11] The highest overall yield of methylphenidate (**1a** + **1a′**) was obtained in the presence of LiCl additive (entry 20).[12]

To keep the overall procedure as simple as possible while also accommodating potentially less reactive substrates, the conditions of entry 17 (Table 1) were selected for the alkylation of various amines with a number of ester enolates (Scheme 2). Amines with variable ring sizes participated in the reaction and different substitution patterns on the ester were readily accommodated. Product **1d**, derived from a bicyclic amine, as well as products **1f** and **1g**, derived from piperidines containing a substituent in the 4-position, were obtained with excellent levels of diastereoselectivity.[13] The reaction could also be extended to the use of nitrile anions (Scheme 3).

The direct synthesis of bi- and tricyclic enaminones was accomplished by employing dianions derived from 1,3-diketones (Scheme 4). In these reactions, treatment with aqueous base was performed following the addition step to facilitate the intramolecular condensation step. 4-Benzylpiperidine provided the annulation product **3e** with excellent diastereoselectivity.

Bicyclic and tricyclic β-amino ketones were obtained directly from α,β-unsaturated ketone enolates upon reaction with in-situ-generated imines (Scheme 5). Here, the initial nucleophilic addition is followed by an intramolecular heteroconjugate addition step, facilitated by treatment with aqueous base. Product **4a**, obtained with a dr of 5:1, is a direct precursor of the natural product lasubine I. By changing the temperature and reaction time of the last step, the other diastereomer of **4a** (a direct precursor of the natural product lasubine

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II) was obtained as the predominant product with a dr of 1:8.[14] The natural product myrtine (**4d**) was obtained in a single operation, albeit in moderate yield.[15]

β-Aminoesters derived from ester enolates according to Scheme 1 can be converted to the corresponding β-lactams in good yields (Scheme 6).[16] For instance, treatment of **1f** and **1l** with *tert*-butyl magnesium chloride provided bicyclic β-lactams **5** and **6** in 72% and 73% yield, respectively.

In summary, we have achieved the α-alkylation of unprotected alicyclic amines with a range of different enolate-type nucleophiles. This approach provides a convenient platform for the diversification of simple amines via C–H bond functionalization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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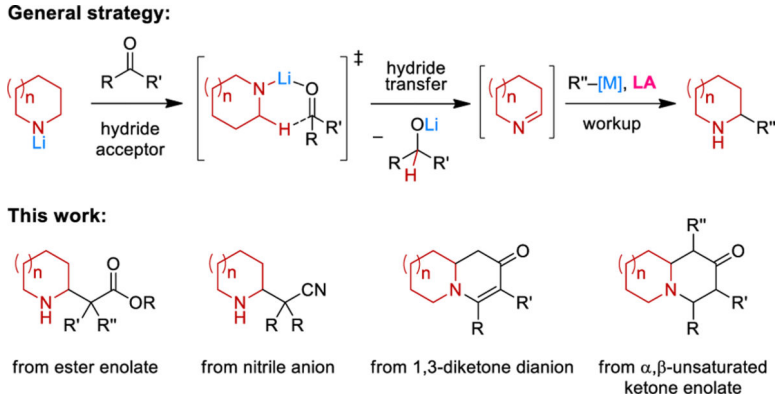

Scheme 1. Li-amide based approach to amine α-C–H bond functionalization

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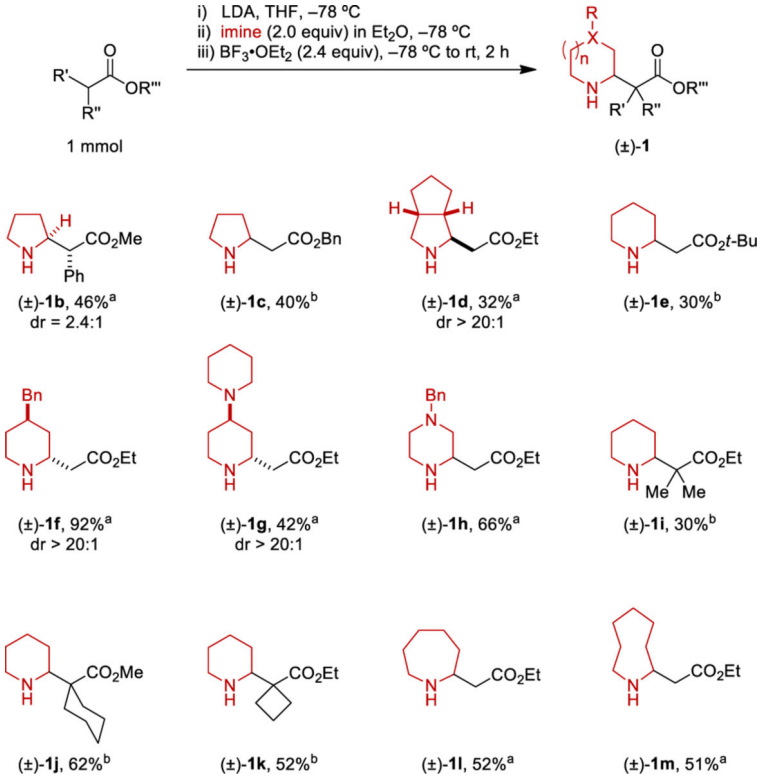
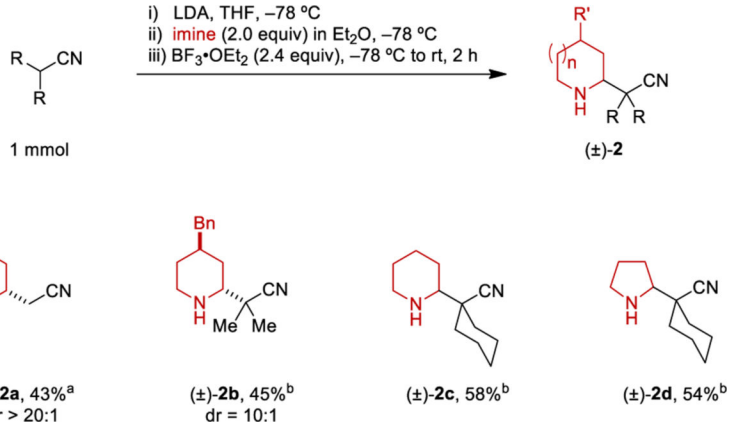


Scheme 2. Scope of the alkylation with ester enolates

[a] Deprotonation performed at –78 °C for 30 min. [b] Deprotonation performed at –78 °C for 15 min and rt for 15 min.



Scheme 3. Alkylation with nitrile anions

[a] Deprotonation performed at –78 °C for 30 min. [b] Deprotonation performed at –78 °C for 15 min and rt for 15 min.

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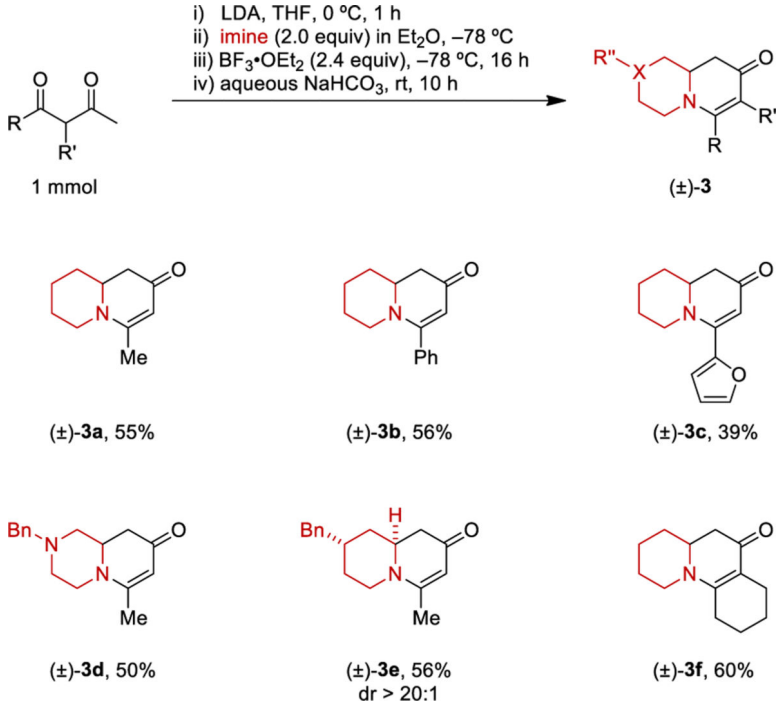

Scheme 4. Alkylation with 1,3-diketone dianions

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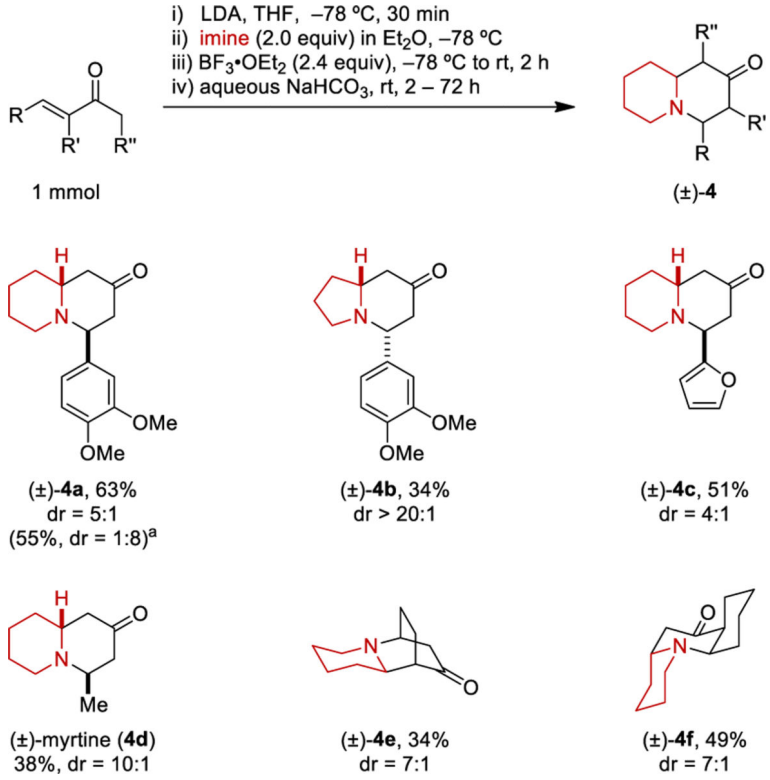

Scheme 5. Alkylation with α,β-unsaturated ketone enolate

[a] Result in parentheses: Step 4 was performed for 48 h at 70 °C.

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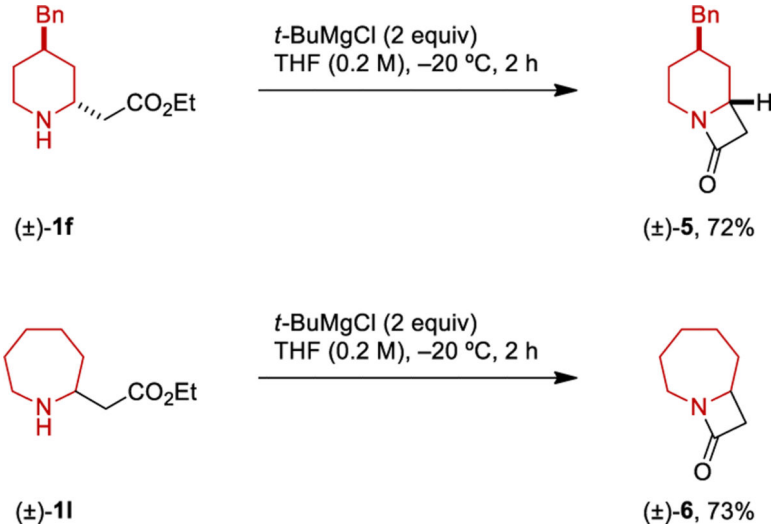

Scheme 6. Formation of β-lactams

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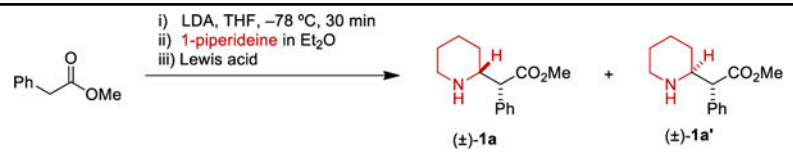
Table 1.

Optimization of methylphenidate synthesis.[a]



entry	method	Lewis acid (equiv)	additive[b] (equiv)	temp [°C]	time [h][c]	dr 1a : 1a′	yield 1a + 1a′ (%)
1	A	–	–	–78 to rt	0 + 2	–	0
2	A[d]	–	LiCl (1.2)	–78 to rt	0 + 2	–	0
3	A	TMSOTf (1.2)	–	–78 to rt	0 + 2	1 : 3.0	38
4	A	$BF_3{\cdot}OEt_2$ (1.2)	–	–78 to rt	0 + 2	1.7 : 1	51
5	A[d]	$BF_3{\cdot}OEt_2$ (1.2)	LiCl (1.5)	–78 to rt	0 + 2	1 : 10	68
6	A[d]	$BF_3{\cdot}OEt_2$ (1.2)	–	–78 to rt	0 + 2	1 : 3.0	58
7	A	$BF_3{\cdot}OEt_2$ (1.2)	HMPA (3.0)	–78 to rt	0 + 2	1 : 1.7	46
8	A	$BF_3{\cdot}OEt_2$ (1.2)	–	–78	16	1 : 4.6	61
9	A	$BF_3{\cdot}OEt_2$ (1.0)	–	–78	16	1 : 5.3	42
10	A	$BF_3{\cdot}OEt_2$ (1.2)	–	–78 to rt	16 + 2	1 : 5.5	65
11	A	$BF_3{\cdot}OEt_2$ (1.2)	–	–78 to 50 °C	2 + 2	2.7 : 1	50
12	A	$BF_3{\cdot}OEt_2$ (2.4)	–	–78 to rt	0 + 2	3.2 : 1	66
13	A	$BF_3{\cdot}OEt_2$ (2.4)	–	–78	16	1 : 6.0	44
14	A	$BF_3{\cdot}OEt_2$ (2.4)	–	–78 to rt	16 + 2	1 : 5.5	62
15	A	$BF_3{\cdot}OEt_2$ (2.4)	–	–78 to 0 °C	0 + 2	2.1 : 1	59
16	A[e]	$BF_3{\cdot}OEt_2$ (2.4)	–	–78 to rt	0 + 2	1 : 4.0	65
17	B	$BF_3{\cdot}OEt_2$ (2.4)	–	–78 to rt	0 + 2	1 : 1.2	84
18	B	$BF_3{\cdot}OEt_2$ (2.4)	–	–78	0.5	1 : 1.5	89
19	B[d]	$BF_3{\cdot}OEt_2$ (2.4)	LiCl (1.2)	–78 to rt	0 + 2	1 : 5.3	63
20	B[d]	$BF_3{\cdot}OEt_2$ (2.4)	LiCl (1.2)	–78	0.5	1 : 3.9	92

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[a] 1-Piperideine (n mmol) was prepared in situ by adding *n*-BuLi (n mmol) to a solution of piperidine (n mmol) in Et_2O at –78 °C, followed by the addition of trifluoroacetophenone (1.05n mmol). Yields are isolated yields of chromatographically purified compounds. Method A: 1-Piperideine (1 mmol), methyl 2-phenylacetate (1.5 equiv) and LDA (1.5 equiv) were used; Method B: methyl 2-phenylacetate (1 mmol), LDA (1 equiv) and 1-piperideine (2 equiv) were used.

[b] Additive was added after LDA, followed by stirring at –78 °C for 30 min.

[c] Reaction time at –78 °C + additional reaction time at noted temperature.

[d] THF/Et_2O (2:1).

[e] 2.5 equiv of methyl 2-phenylacetate and LDA were used.

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