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

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Cite This: *Org. Lett.* 2021, 23, 797−801 Read Online

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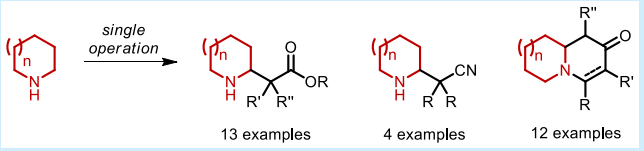
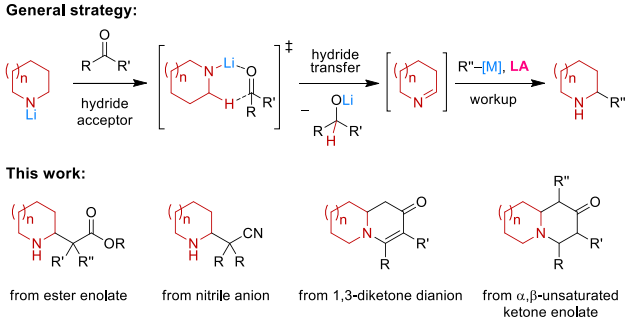
ABSTRACT: Enolizable cyclic imines, obtained in situ from their corresponding lithium amides by oxidation with simple ketone oxidants, are readily alkylated with a range of enolates to provide mono- and polycyclic β-aminoketones in a single operation, including the natural product (±)-myrtine. Nitrile 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] Whereas 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 largely attributed to the incompatibility of most activation modes with basic amine functionalities 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 the formation of 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.

Scheme 1. Li-Amide-based Approach to Amine α-C−H Bond Functionalization



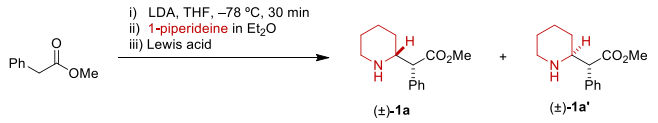
Mannich reactions are well established as useful tools for the synthesis of valuable β-amino ketones.[7] However, variants utilizing enolates in combination with enolizable imines, in particular, enolizable cyclic imines, remain rare,[8] likely due to the limited electrophilicity of imines lacking activating 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. The key findings of this survey are summarized in Table 1. In brief, 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 the conditions. The highest dr favoring the pharmaceutically active threo isomer **1a** was 3.2:1 (entry 12), whereas 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

Received: December 4, 2020
Published: January 19, 2021

https://dx.doi.org/10.1021/acs.orglett.0c04024
Org. Lett. 2021, 23, 797−801

Table 1. Optimization of Methylphenidate Synthesis[a]

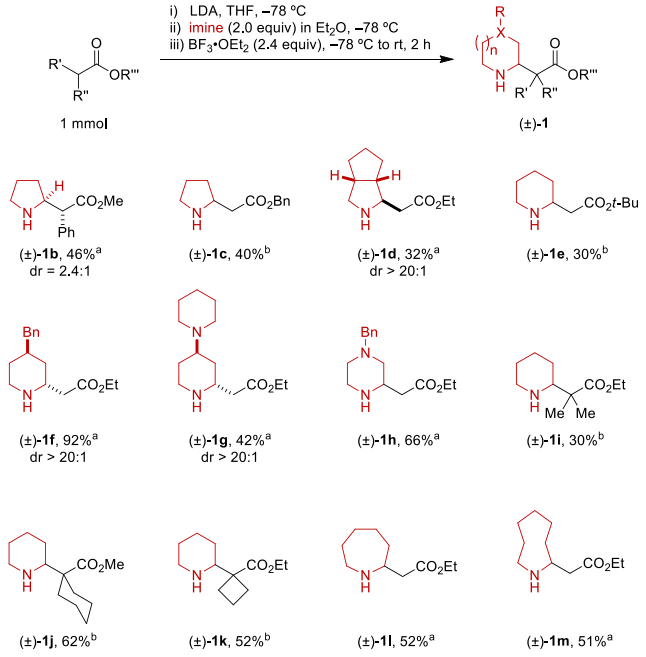


entry	method	Lewis acid (equiv)	additive (equiv)[b]	temp (°C)	time (h)[c]	dr 1a/1a′	yield 1a + 1a′ (%)
1	A			−78 to rt	0 + 2		0
2	A[d]		LiCl (1.2)	−78 to rt	0 + 2		0
3	A	TMSOTf (1.2)		−78 to rt	0 + 2	1:3.0	38
4	A	$BF_3{\cdot}OEt_2$ (1.2)		−78 to rt	0 + 2	1.7:1	51
5	A[d]	$BF_3{\cdot}OEt_2$ (1.2)	LiCl (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

[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 (1.05*n* 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 was used.

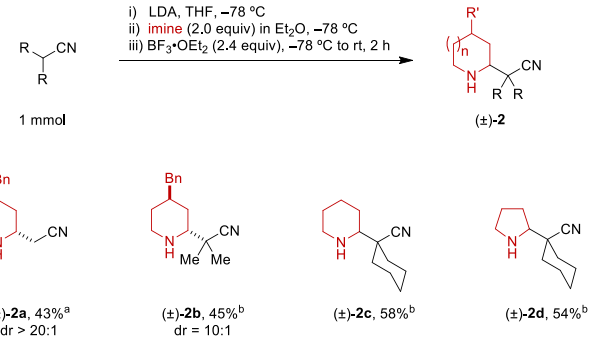
alkylation of various amines with a number of ester enolates (Scheme 2). Amines with variable ring sizes participated in the reaction, and different substitution patterns on the ester were readily accommodated. Product **1d**, derived from a bicyclic amine, as well as products **1f** and **1g**, derived 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).

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 at rt for 15 min.

Scheme 3. Alkylation with Nitrile Anions

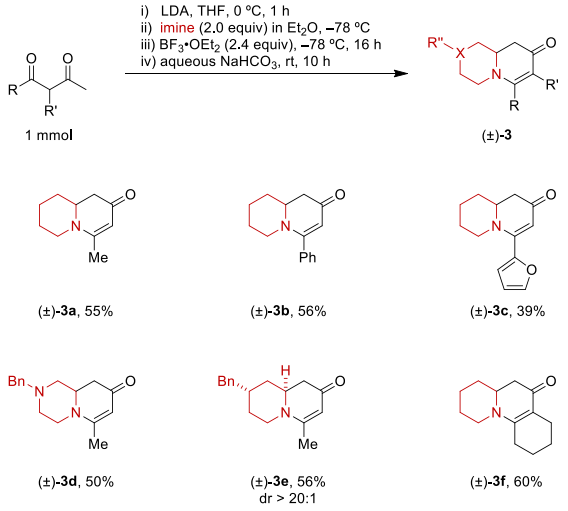


[a]Deprotonation performed at −78 °C for 30 min. [b]Deprotonation performed at −78 °C for 15 min and at rt for 15 min.

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 an aqueous base was performed following the addition step to facilitate the intramolecular condensation step. 4-Benzylpiper-

https://dx.doi.org/10.1021/acs.orglett.0c04024
Org. Lett. 2021, 23, 797−801

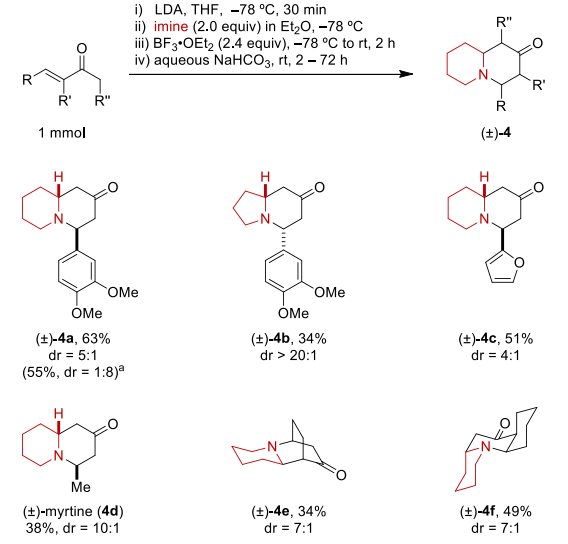
Scheme 4. Alkylation with 1,3-Diketone Dianions



idine provided the annulation product **3e** with excellent diastereoselectivity.

Bicyclic and tricyclic β-amino ketones were directly obtained from α,β-unsaturated ketone enolates upon reaction with in-situ-generated imines (Scheme 5). Here the initial nucleophilic

Scheme 5. Alkylation with α,β-Unsaturated Ketone Enolate

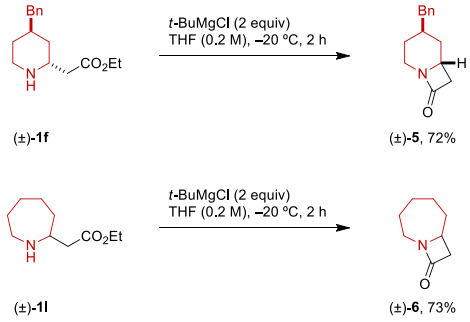


[a]Result in parentheses: Step 4 was performed for 48 h at 70 °C.

addition is followed by an intramolecular heteroconjugate addition step, facilitated by treatment with an 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 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, the treatment of **1f** and **1l** with *tert*-butyl magnesium chloride provided bicyclic β-lactams **5** and **6** in 72 and 73% yield, respectively.

Scheme 6. Formation of β-Lactams



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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04024.

Experimental procedures and characterization data (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the NIH–NIGMS (grant no. R01GM101389) is gratefully acknowledged. Mass spectrometry instrumentation was supported by a grant from the NIH (S10 OD021758-01A1).

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https://dx.doi.org/10.1021/acs.orglett.0c04024
Org. Lett. 2021, 23, 797−801