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Enantioselective Organocatalytic Intramolecular Aza-Michael Reaction: a Concise Synthesis of (+)-Sedamine, (+)-Allosedamine, and (+)-Coniine

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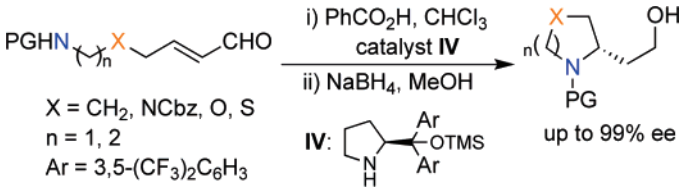
ABSTRACT



The intramolecular aza-Michael reaction of carbamates bearing remote α,β-unsaturated aldehydes under organocatalytic conditions took place with good yields and excellent ee's when Jørgensen catalyst IV was used in the process, giving rise to the enantioselective formation of several five- and six-membered heterocycles. The developed methodology was applied to the synthesis of three piperidine alkaloids.

In the past decade, organocatalysis has emerged as a powerful synthetic tool,[1] one that is complementary to transition metal-based catalysis in asymmetric synthesis. The success of this methodology is based on several factors: (1) organocatalysts are available (or easily synthesized) in both enantiomerically pure forms, (2) they are moisture stable so that reactions can be conducted under air atmosphere and, in some cases, in water, (3) generally, reactions are operationally simple (practically mix and stir), (4) and most importantly, excellent or moderate to excellent results are obtained in terms of both enantioselectivity and yield.

Conjugate addition of amines or their synthetic equivalents to α,β-unsaturated compounds constitutes one of the most interesting methods in C−N bond formation because the resulting β-amino carbonyl adducts are privileged structures that are present in natural products and used in pharmaceutical agents.[2] Despite the importance of this methodology, catalyzed enantioselective aza-Michael reactions remain elusive and can thus be considered as a challenging task.[3] In fact, only very recently have several organocatalyzed nucleophilic nitrogen addition reactions to α,β-unsaturated carbons been presented in their intermolecular version.[4] Most of these reactions take advantage of the enhancement of nucleophilicity produced by the presence of a heteroatom in the α-position relative to the nitrogen-centered nucleophile (α-effect).[5]

Encouraged by our recent results in aza-Michael reactions,[6] we decided to explore the organocatalytic version of this

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(1) See, for example: (a) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (b) Gillena, G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693. (c) Marcia de Figueiredo, R.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575. (d) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2007. (e) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.

(2) *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E. C., Soloshonok, V. A., Eds.; Wiley-VCH Ltd.: New York, 2005.

(3) For recent reviews see: (a) Vicario, J. L.; Badia, D.; Carrillo, L. *Synthesis* **2007**, 2065. (b) Vicario, J. L.; Carrillo, L.; Etxebarria, J.; Reyes, E.; Ruiz, N. *Org. Prep. Proced. Int.* **2005**, *37*, 513. (c) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633.

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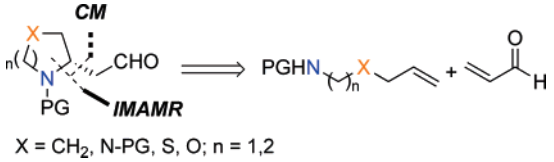
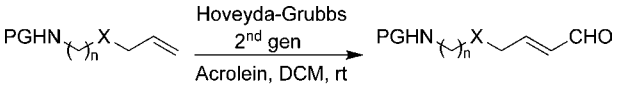
reaction.[7] Herein, we describe a very high enantioselective organocatalytic intramolecular aza-Michael reaction (IMAMR) of carbamates bearing remote α,β-unsaturated aldehydes as Michael acceptors (Scheme 1). The application of this strategy for the synthesis of three piperidine alkaloids is also presented.

Scheme 1. Synthetic Strategy



Starting amines **2** were assembled through a cross-metathesis reaction of the corresponding unsaturated amines **1**[8] with acrolein catalyzed by second-generation Hoveyda−Grubbs catalyst [Cl_2(IMes)Ru=CH(*o*-*i*-PrOC_6H_4)]. The reaction proceeded in DCM at room temperature, affording the desired products in general good yields (Table 1).

Table 1. Preparation of the Starting Amines **2**

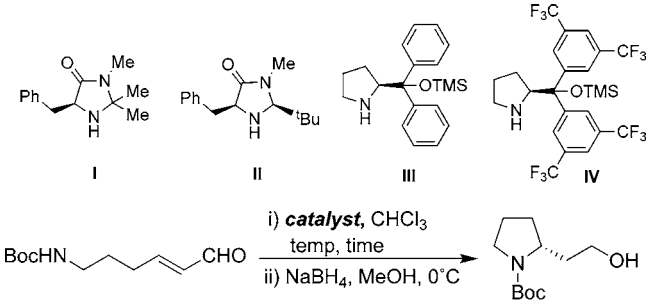


1 **2**

entry	**1**	PG	X	*n*	**2**	yield (%)
1	**1a**	Boc	CH_2	1	**2a**	81
2	**1b**	Cbz	CH_2	1	**2b**	83
3	**1c**	Boc	CH_2	2	**2c**	60
4	**1d**	Cbz	CH_2	2	**2d**	70
5	**1e**	Boc	O	1	**2e**	56
6	**1f**	Boc	O	2	**2f**	84
7	**1g**	Boc	N-Cbz	1	**2g**	43
8	**1h**	Boc	N-Cbz	2	**2h**	44
9	**1i**	Boc	S	1	**2i**	87
10	**1j**	Boc	S	2	**2j**	60

In order to find optimum conditions and catalysts, substrate **2a** was subjected to the intramolecular protocol under different reaction conditions. The initial attempt was carried out with catalyst **I** and lasted 120 h with temperatures ranging from −20° to 15 °C. After reduction of the corresponding aldehyde, amino alcohol **3a** was isolated in 60% yield, although with less than 5% ee (Table 2, entry 1). Catalyst **II** proved to be a great deal more reactive, and when it was used at −20 °C for 7 h, **3a** was isolated in 73% yield and with 27% ee (Table 2, entry 2). Under the same conditions, catalyst **III** (20 mol %) afforded the desired product in 78% yield and with 40% ee (Table 2, entry 3).

Table 2. Catalyst Screening and Optimization Reaction Conditions[a]



2a **3a**

entry	cat.	additive	temp (°C)	time (h)	yield (%)	ee (%)[b]
1	**I**	HCl	−20	120	60	<5
2	**II**	TFA	−20	7	73	27
3	**III**	$PhCO_2H$	−20	7	78	40
4	**III**	$PhCO_2H$	−30	22	71	75
5	**IV**	$PhCO_2H$	−40	22	74	79
6	**IV**	$PhCO_2H$	−50	22	71	93
7	**IV**	$PhCO_2H$	−60	45	67	93

[a] In all cases 0.2 equiv of catalyst and additive was used in 0.1 M solution. [b] Determined by means of chiral-phase HPLC analysis.

An important improvement in ee (75%) was achieved when the reaction was performed at −40 °C (Table 2, entry 4), but at lower temperatures, the addition did not take place. We then decided to use Jørgensen catalyst **IV** (20 mol %) since good results for organocatalyzed conjugated additions to α,β-unsaturated aldehydes with this catalyst had previously been described.[9] To our delight, when the reaction was carried out at −50 °C for 22 h, the desired amino alcohol **3a** was isolated in 71% yield and with 93% ee (Table 2, entry 6). When lower temperatures were used, however, no

(4) With carbamates as nitrogen nucleophiles: (a) Ibrahem, I.; Ríos, R.; Vesely, J.; Zhao, G.-L.; Córdova, A. *Chem. Commun.* **2007**, 849. (b) Vesely, H.; Ibrahem, I.; Zhao, G.-L.; Ríos, R.; Córdova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 778. (c) Sundén, H.; Ríos, R.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Adv. Synth. Catal.* **2007**, *349*, 827. (d) Vesely, J.; Ibrahem, I.; Ríos, R.; Zhao, G.-L.; Xu, Y.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 2193. (e) Li, H.; Wang, J.; Xie, H.; Zu, L.; Jiang, W.; Duesler, E. N.; Wang, W. *Org. Lett.* **2007**, *9*, 965. (f) Chen, Y. K.; Yoshida, M.; McMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328. With azides as nitrogen nucleophiles: (g) Horstmann, T. E.; Guerin, D. J.; Miller, S. C. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635. (h) Guerin, D. J.; Miller, S. C. *J. Am. Chem. Soc.* **2002**, *124*, 2134. With hydrazones as nitrogen nucleophiles: (i) Perdicchia, D.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 3565. With triazols as nitrogen nucleophiles: (j) Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1983. (k) Wang, J.; Li, H.; Zu, L.; Wang, W. *Org. Lett.* **2006**, *8*, 1391.

(5) Heaton, M. M. *J. Am. Chem. Soc.* **1978**, *100*, 2004.

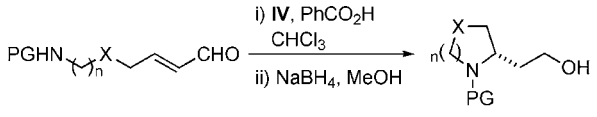
(6) (a) Fustero, S.; Chiva, G.; Piera, J.; Volonterio, A.; Zanda, M.; González, J.; Ramallal, A. M. *Chem. Eur. J.* **2007**, *13*, 8530. (b) Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129*, 6700. (c) Sani, M.; Bruché, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060.

(7) Only one example of organocatalytic intramolecular aza-Michael reaction has been described before, using amides as nitrogen nucleophiles, although with poor levels of enantioselectivity: Takasu, K.; Maiti, S.; Ihara, M. *Heterocycles* **2003**, *59*, 51.

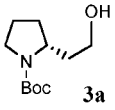
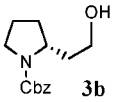
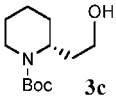
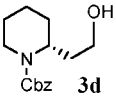
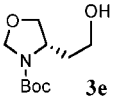
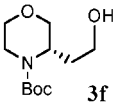
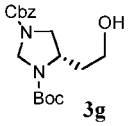
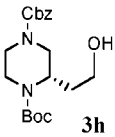
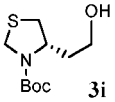
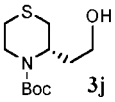
(8) For the preparation of amines **1**, see Supporting Information.

(9) (a) Brandau, S.; Landa, A.; Franzen, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4305. (b) Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475. (c) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354. (d) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710.

Table 3. Scope of the Organocatalytic Intramolecular Aza-Michael Reaction



2 **3**

entry	**2**	temp (°C)	time (h)	product **3**	yield (%)	*ee* (%)[a]
1	**2a**	-50	22	 **3a**	71	93
2	**2b**	-50 → -30	40	 **3b**	61	99
3	**2c**	-50	20	 **3c**	63	94
4	**2d**	-50 → -30	48	 **3d**	60	94
5	**2e**	-50 → -40	44	 **3e**	80	90
6	**2f**	-50 → -30	70	 **3f**	50	85
7	**2g**	-50 → -10	72	 **3g**	31	96
8	**2h**	-50 → -40	62	 **3h**	74	93
9	**2i**	-50 → 10	96	 **3i**	43	91
10	**2j**	-50 → -20	80	 **3j**	30	96

[a] Determined by means of chiral-phase HPLC analysis.

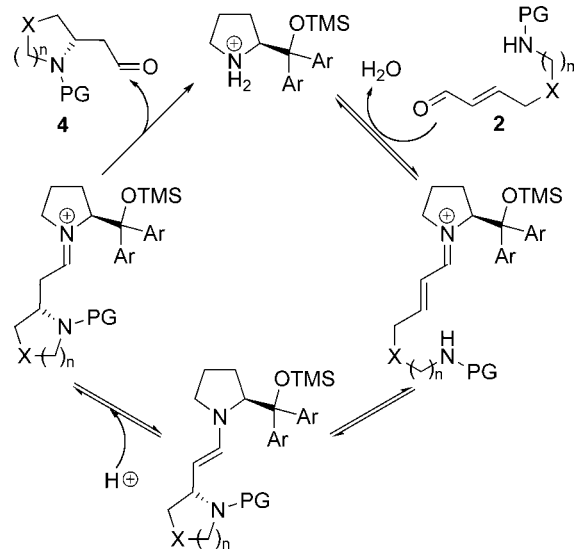
improvement in the final ee was observed (Table 2, entry 7).[10]

Having determined the optimal reaction conditions (Table 2, entry 6), we turned our attention to the scope of the process. We first evaluated the influence of the nitrogen-protecting group on the selectivity of the final product and found that the reaction was highly efficient when either Boc or Cbz were used as protecting groups (Table 3, entries 1, 2). The formation of the derivatives **3c** and **3d**, both containing a six-membered ring, also took place with excellent ee (Table 3, entries 3, 4). We then decided to extend this methodology to the preparation of other substrates containing different heteroatoms within the alkyl chain since the resulting reaction products could be potentially valuable heterocycles to use in medicinal chemistry. The organocatalytic intramolecular aza-Michael reaction led to the formation of the corresponding five- and six-membered ring heterocycles containing oxygen, nitrogen, and sulfur in yields ranging from 30 to 80% and with excellent ee (up to 96%) (Table 3, entries 5−10).

The absolute configuration of the newly created stereocenter was determined to be *R* by comparing the $[\alpha]^D$ values and NMR data of compound **3a** with those described in the literature[11] (see experimental section in Supporting Information). Identical stereochemical development was assumed for all the substrates.

The mechanism commonly invoked to rationalize the organocatalytic conjugate additions of nitrogen nucleophiles to α,*β*-unsaturated carbonyl compounds involves activation of the substrate by the catalyst through the iminium ion mechanism, thereby facilitating the intramolecular addition of the nucleophile to the *β*-carbon atom. The *si* face of the *E*-diene intermediate is shielded by the chiral group of the catalyst, approaching the nitrogen atom on the *re* face. When X = O, S, or N-PG, the priority of the substituents is reversed, and the approach in these cases is on the *si* face (Scheme 2).

Scheme 2. Plausible Reaction Pathway for the Organocatalytic Reaction

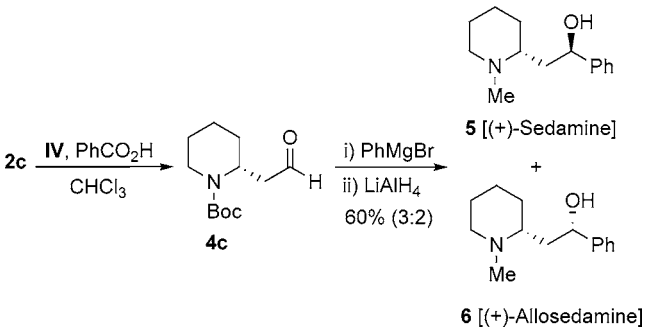


As mentioned above, the previously described examples of the organocatalytic intermolecular aza-Michael reaction take advantage of the presence of one heteroatom in the α-position relative to the nitrogen-centered nucleophile, thus

allowing the reaction to occur at room temperature. It is noteworthy that in the intramolecular version described herein, no α-effect is necessary to enhance the nucleophilicity of the nitrogen, carrying out the addition at a much lower temperature.

Finally, we decided to apply our newly developed methodology to the total synthesis of three piperidine alkaloids.[12] When piperidine **4c** (obtained from **2c**) was treated with phenyl magnesium bromide, a 3:2 mixture of diastereoisomers was obtained in the secondary alcohol. After chromatographic separation and reduction of the Boc nitrogen-protecting group with lithium aluminum hydride, (+)-sedamine **5** and (+)-allosedamine **6** were obtained (Scheme 3).[13] Wittig reaction and hydrogenation of the double bond

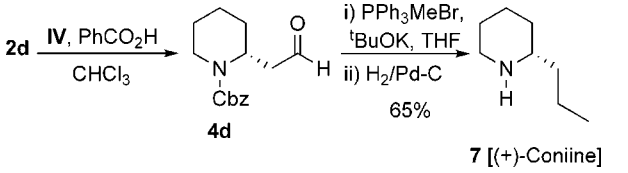
Scheme 3. Synthesis of (+)-Sedamine **5** and (+)-Allosedamine **6**



generated from **4d** gave rise to (+)-coniine **7**[14] in a very simple manner (Scheme 4).[15]

In conclusion, we have developed a very high enantioselective organocatalytic intramolecular aza-Michael addition reaction of carbamates containing pendant conjugated aldehydes which proceeds in good yields and high enantioselectivities. The process, efficiently catalyzed by prolinol derivative **IV**, is useful for the enantioselective preparation of several five- and six-membered ring heterocycles. Finally, the synthetic utility of the novel organocatalytic reaction was confirmed by the concise synthesis of three piperidine alkaloids. The application of this methodology to the total synthesis of several other alkaloids is currently underway.

Scheme 4. Synthesis of (+)-Coniine **7**



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Supporting Information Available: Experimental procedures and NMR spectra for **1**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The use of other solvents did not improve the final ee; thus, when substrate **2a** was subjected to the reaction conditions described in Table 2 (entry 6) but using toluene as solvent, compound **3a** was obtained in 72% yield and 68% ee.

(11) Deng, X.; Many, N. S. *Tetrahedron: Asymmetry* **2005**, *16*, 661.

(12) Reynolds, T. *Phytochemistry* **2005**, *66*, 1399.

(13) For recent synthesis of sedamine and allosedamine see: (a) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734. (b) Zheng, G.; Dwoskin, L. P.; Crooks, P. A. *J. Org. Chem.* **2004**, *69*, 8514. (c) Angoli, M.; Barilli, A.; Lesma, L.; Passarella, D.; Riva, S.; Silvani, A.; Danielli, B. *J. Org. Chem.* **2003**, *68*, 9525.

(14) For recent synthesis of coniine see: (a) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org. Lett.* **2007**, *9*, 2473. (b) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646.

(15) The preparation of these piperidine alkaloids is an additional confirmation of the absolute stereochemistry of the newly created stereocenter.