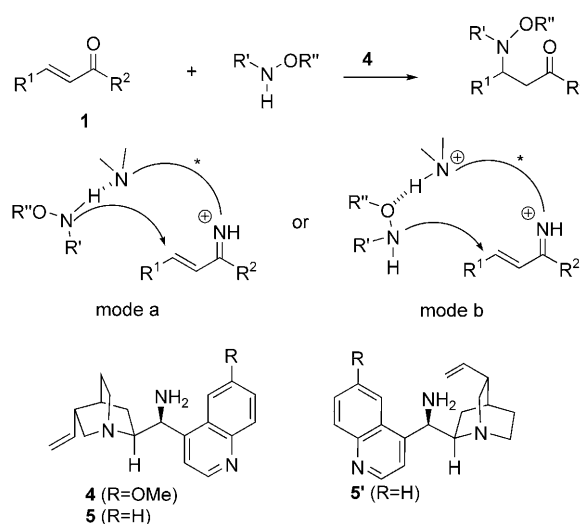


Asymmetric Aza-Michael Reactions of α,β -Unsaturated Ketones with Bifunctional Organic Catalysts**

Xiaojie Lu and Li Deng*

Chiral amine motifs are present in numerous biologically active and therapeutically important molecules. Consequently chiral amines constitute one of the most important classes of chiral building blocks in organic synthesis. Accordingly, significant efforts have been devoted to the development of catalytic enantioselective transformations of inexpensive achiral precursors into optically active chiral amines. Alongside enantioselective additions to achiral imines, catalytic asymmetric conjugate additions with nitrogen nucleophiles (aza-Michael reactions) provide another fundamentally important approach toward optically active chiral amines.^[1]

Although much progress has been made recently in the development of asymmetric aza-Michael reactions with both chiral metallic^[2–4] and organic catalysts,^[5–7] highly enantioselective catalytic aza-Michael additions to simple α,β -unsaturated ketones remain rare. To our knowledge, only three such reactions have been reported, and all are catalyzed by chiral metal complexes.^[3] Inanaga and co-workers reported a chiral scandium complex as a highly effective Lewis acid catalyst for an asymmetric aza-Michael reactions of *o*-alkoxyhydroxylamines to acyclic enones.^[3a] Applying bifunctional catalysis with a chiral lithium–yttrium heterobimetallic complex, Shibasaki and co-workers established a highly efficient aza-Michael reaction with a broader scope, affording high enantioselectivity for a wide range of α,β -unsaturated ketones **1**, (see Scheme 1) bearing either an aryl or alkyl β -substituent (R^1).^[3b,c] However, the ketone substituent (R^2) is limited to aromatic rings for both of the aforementioned reactions. More recently, Jacobsen and co-workers reported the conjugate addition of hydrazoic acid to enones catalyzed by a salen–aluminum complex.^[3d] Notably, this reaction afforded good to excellent enantioselectivity for α,β -unsaturated ketone **1**, bearing various alkyl substituents as R^1 and R^2 . Herein, we report the first highly enantioselective aza-Michael reaction with α,β -unsaturated ketones catalyzed by a chiral organic catalyst. Significantly, this new catalytic asymmetric aza-Michael reaction afforded consistently excellent enantioselectivity for a wide variety of alkyl vinyl ketones bearing either an alkyl or aryl group as R^1 , thereby providing



Scheme 1. Proposed activation modes of aza-Michael addition of α,β -unsaturated ketones **1** with **4**.

a synthetically valuable substrate scope that is complementary to those of existing chiral metal-based methods.

MacMillan and co-workers^[6a] first reported the use of chiral secondary amines, in this case chiral imidazolidinones, to activate α,β -unsaturated aldehydes for highly enantioselective aza-Michael reactions with *N*-silyloxycarbamate using iminium catalysis.^[8] Presumably, the steric bulk of the chiral secondary amines renders them highly chemoselective for nucleophilic attack at the aldehyde group, while minimizing catalyst decomposition through conjugate additions to enals. On the other hand, α,β -unsaturated ketones **1** are sterically more demanding and electronically less active toward iminium formation with chiral amines. The activation of enones for asymmetric aza-Michael reactions by chiral secondary amines has not yet been reported.^[9] Recently, 9-amino cinchona alkaloid **4**,^[10] in combination with various acids, has been shown to provide an effective catalyst system for the activation of enones **1** for various asymmetric conjugate addition reactions.^[11] Presumably, compared to secondary amines, the sterically less-hindered primary amine in **4** reacts more readily with the ketone functionality in **1** to initiate the iminium catalysis. Thus, we reasoned that, while the primary amine activated the enone in the presence of acid by iminium catalysis, the quinuclidine motif of cinchona alkaloid **4**, in either the free base (Scheme 1, mode a) or the protonated form (mode b), could bind to nitrogen nucleophiles, such as alkoxyamines, through hydrogen-bonding interactions, thereby activating the nitrogen nucleophile for nucleophilic

[*] X. Lu, Prof. L. Deng
Department of Chemistry, Brandeis University
Waltham, MA, 02454-9110(USA)
Fax: (+1) 781-736-2516
E-mail: deng@brandeis.edu

[**] We are grateful for financial support from the National Institute of Health (GM-61591).

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200802785>.

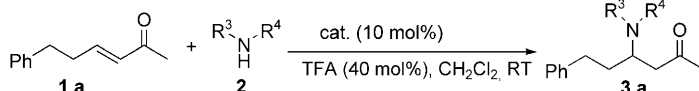
attack by bringing it into the proximity of the activated enone. We anticipated that this bifunctional catalysis by cinchona alkaloid **4** could be applied to the development of an efficient asymmetric aza-Michael reaction with α,β -unsaturated ketones **1**.

Accordingly, we investigated the aza-Michael reaction of various nucleophiles to enone **1a** catalyzed by the 9-amino cinchona alkaloid **4** (Table 1). In the presence of 10 mol % of

over, catalyst **4** was found to also tolerate a significant range of alkyl groups as the β -substituent (R^1) in **1**. Catalyst **4** was also found to afford excellent enantioselectivity for alkyl vinyl ketones bearing a β -aryl group, such as **1i**, albeit with drastically decreased activity (Table 2, entry 9 cf. entry 8). Reaction optimization studies revealed that the cinchonidine-derived catalyst **5** (see Scheme 1) afforded the optimal enantioselectivity for enone **1i**. Enantioselectivity remained

high when the reaction was carried out in toluene at 40 °C, to provide the corresponding adduct in synthetically useful yield. Utilizing catalyst **5'** (see Scheme 1) derived from cinchonine (in place of **4**), the corresponding antipodes of **3** were generated in good to excellent optical purity (Table 2). Thus alkyl vinyl ketones **1** bearing both β -aryl and alkyl groups could be employed for this cinchona alkaloid-catalyzed aza-Michael reaction (Table 2). Significantly, among existing highly enantioselective catalytic aza-Michael reactions with enones, the current reaction is unique in its ability to afford high enantioselectivity for alkyl vinyl ketones bearing β -aryl groups (Table 2, entries 12–16). As illustrated in Scheme 2, the enantiomerically enriched Michael adducts **3g** and **3i**, which bear substituents of various steric and electronic properties, could be readily converted into the corresponding *N*-Boc-protected β -amino

Table 1: Asymmetric aza-Michael reaction of α,β -unsaturated ketones **1** with **4**.

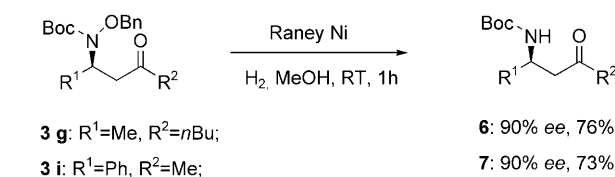
					
Entry ^[a]	2	Cat.	<i>t</i> [h]	Conv. [%] ^[b]	<i>ee</i> 3a [%] ^[c]
1	2a BnNH ₂	4	12	0	na
2	2b BnNH-Boc	4	12	0	na
3	2c MeO-NH-Ts	4	12	64	75
4	2d BnO-NH-Ts	4	48	52	67
5	2e TBSO-NH-Boc	4	12	38	83
6	2f MeO-NH-Boc	4	12	88	77
7	2g BnO-NH-Boc	4	12	87	84
8	2g BnO-NH-Boc	5	12	79	82
9 ^[d]	2g BnO-NH-Boc	4	12	48	93
10 ^[e]	2g BnO-NH-Boc	4	72	99	93

[a] Unless noted, reactions were run with 0.1 mmol **1a**, 0.15 mmol **2**, see Supporting Information for details. [b] Determined by ¹H NMR analysis. [c] Determined by HPLC analysis. [d] Reaction was run with 20 mol % TFA. [e] Reaction was run with 0.2 mmol **1a**, 0.30 mmol **2**, 20 mol % **4**, and 40 mol % TFA. TFA = trifluoroacetic acid.

4 and 40 mol % of trifluoroacetic acid (TFA), the conversion and the enantioselectivity of the aza-Michael reaction was found to be greatly influenced by the electronic as well as the steric properties of the nitrogen nucleophiles. Various alkoxyamines bearing either an *N*-carbamate or *N*-sulfonamide group were found to be active toward the **4**-catalyzed aza-Michael reaction. The reaction with Boc-protected *N*-benzyloxyamine **2g** afforded the highest enantioselectivity, providing the desired adduct in 84 % *ee* (Boc = *tert*-butoxycarbonyl, Table 1, entry 7). Importantly, when the loading of TFA was decreased from 40 mol % to 20 mol %, the reaction was found to proceed in significantly improved enantioselectivity (Table 1, entry 9). 99 % conversion could be attained with 20 mol % of **4** and 40 mol % of TFA to afford the desired aza-Michael adduct **3a** in 93 % *ee* (Table 1, entry 10).

Encouraged by this promising result, we investigated the scope of the 9-amino cinchona alkaloid-catalyzed aza-Michael reaction under the optimal conditions defined through our model studies (as for Table 1, entry 10). As illustrated in Table 2, the high enantioselectivity afforded by catalyst **4** could be extended to a wide range of alkyl vinyl ketones **1a–h**. Significantly, alterations of the steric properties of the aliphatic ketone substituent (R^2) did not impact negatively on the enantioselectivity of the reaction. More-

over, catalyst **4** was found to also tolerate a significant range of alkyl groups as the β -substituent (R^1) in **1**. Catalyst **4** was also found to afford excellent enantioselectivity for alkyl vinyl ketones bearing a β -aryl group, such as **1i**, albeit with drastically decreased activity (Table 2, entry 9 cf. entry 8).



Scheme 2. Hydrogenation of **3**.

In summary, we have developed the first highly enantioselective aza-Michael reaction of simple α,β -unsaturated ketones with an organic catalyst. It is particularly noteworthy that this new catalytic asymmetric aza-Michael reaction is effective for a broad range of alkyl vinyl ketones bearing both aryl and alkyl β -substituents. Utilizing commercially available nitrogen nucleophiles and readily available chiral catalysts, this asymmetric aza-Michael reaction provides a highly promising method for the asymmetric synthesis of a wide range of optically active chiral amines. Our current investigations are focused on the elucidation of the mechanism, as

Table 2: Asymmetric aza-Michael addition of α,β -unsaturated ketones **1** with **4**.

$ \begin{array}{c} \text{R}^1-\text{CH}=\text{CH}-\text{C}(=\text{O})-\text{R}^2 \\ \text{1} \end{array} + \begin{array}{c} \text{Boc}-\text{N}(\text{OBn})-\text{H} \\ \text{2g} \end{array} \xrightarrow[\text{TFA (40 mol\%), CH}_2\text{Cl}_2]{\text{cat. (20 mol\%)}} \begin{array}{c} \text{Boc}-\text{N}(\text{OBn})-\text{CH}(\text{R}^1)-\text{CH}_2-\text{C}(=\text{O})-\text{R}^2 \\ \text{3} \end{array} $								
Entry ^[a]	Cat.	Enone	R ¹	R ²	Product	t [h] ^[b]	yield 3 [%] ^[b]	ee 3 [%] ^[b,c]
1	4(5')	1a	PhCH ₂ CH ₂	Me		72 (120)	80 (80)	93 (84)
2	4	1b	nPen	Me		72	76	94
3	4	1c	Me	Et		92	83	90
4	4(5')	1d	nPen	Et		162 (170)	70 (67)	93 (90)
5	4(5')	1e	nHex	Et		120 (168)	83 (68)	93 (91)
6	4	1f	nHep	Et		96	70	96
7	4(5')	1g	Me	nBu		192 (196)	74 (76)	91 (86)
8	4	1h	nPr	nBu		96	70	95
9 ^[d,e]	4	1i	Ph	Me		24	11 ^[f]	94
10 ^[d,e]	5	1i	Ph	Me		24	13 ^[f]	96
11 ^[d,g]	5	1i	Ph	Me		24	41 ^[f]	93
12 ^[d,h,i]	5	1i	Ph	Me		84	67	90
13 ^[d,h]	5(5')	1j	p-FC ₆ H ₄	Me		96 (192)	61 (60)	92 (87)
14 ^[d,h]	5	1k	p-ClC ₆ H ₄	Me		82	71	93
15 ^[d,h]	5	1l	p-BrC ₆ H ₄	Me		80	70	90
16 ^[d,h]	5	1m	p-MeC ₆ H ₄	Me		96	57	86

[a] Unless noted, reactions were run with 0.2 mmol **1**, 0.30 mmol **2g**, see Supporting Information for details. [b] Values in parentheses refer to 5'-catalyzed reactions, affording the opposite enantiomer of **3**. [c] Determined by HPLC analysis. [d] Reaction was run with 10 mol % catalyst and 20 mol % TFA. [e] The reaction was checked after 24 h. [f] The conversion of the reaction was determined by ¹H NMR analysis. [g] Reaction was run at 40 °C and checked after 24 h. [h] Reaction was run with 0.2 mmol **1** and 0.60 mmol **2g** at 40 °C in toluene. [i] Absolute configuration was assigned as *S*, see Supporting Information for details.

well as the expansion of the general scope and synthetic utility of this reaction.

Received: June 12, 2008
Published online: August 29, 2008

Keywords: alkaloids · amines · asymmetric catalysis · enones · Michael addition

- [1] For recent reviews of enantioselective aza-Michael reactions, see: a) L.-W. Xu, C.-G. Xia, *Eur. J. Org. Chem.* **2005**, 633–639; b) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991–8035.
- [2] For examples of highly enantioselective aza-Michael additions to carboxylic acid derivatives or surrogates, catalyzed by metal-based Lewis acids, see: a) M. P. Sibi, J. J. Shay, M. Liu, C. P. Jasperse, *J. Am. Chem. Soc.* **1998**, *120*, 6615–6616; b) J. K. Myers, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, *121*, 8959–8960; c) W. Zhuang, R. G. Hazell, K. A. Jørgensen, *Chem. Commun.* **2001**, 1240–1241; d) M. P. Sibi, N. Pradagaran, S. G. Ghorpade, C. P. Jasperse, *J. Am. Chem. Soc.* **2003**, *125*, 11796–11797.
- [3] For examples of highly enantioselective aza-Michael reactions to β -amino ketones, catalyzed by metal-based Lewis acids, see: a) X. L. Jin, H. Sugihara, K. Daikai, H. Tateishi, Y. Z. Jin, H. Furuno, J. Inanaga, *Tetrahedron* **2002**, *58*, 8321–8329; b) N. Yamagiwa, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 16178–16179; c) N. Yamagiwa, H. Qin, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13419–13427; d) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 1313–1317.
- [4] For an example of highly enantioselective aza-Michael reactions of carbamates with α' -hydroxyenones, see: C. Palomo, M. Oiarbide, R. Halder, M. Kelso, E. Gómez-Bengón, J. M. García, *J. Am. Chem. Soc.* **2004**, *126*, 9188–9189.
- [5] For examples of highly enantioselective aza-Michael reactions to carboxylic acid derivatives or surrogates catalyzed by chiral organic catalysts see: a) T. E. Horstmann, D. J. Guerin, S. J. Miller, *Angew. Chem.* **2000**, *112*, 3781–3784; *Angew. Chem. Int. Ed.* **2000**, *39*, 3635–3638; b) D. J. Guerin, S. J. Miller, *J. Am. Chem. Soc.* **2002**, *124*, 2134–2136; c) M. P. Sibi, K. Itoh, *J. Am. Chem. Soc.* **2007**, *129*, 8064–8065.
- [6] For examples of enantioselective aza-Michael reactions of enals catalyzed by chiral organic catalysts, see: a) K. Young, M. Y. Chen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328–9329; b) I. Ibrahim, R. Rios, J. Vesely, G.-L. Zhao, A. Córdova, *Chem. Commun.* **2007**, 849–851; c) J. Vesely, I. Ibrahim, R.

- Rios, G.-L. Zhao, Y. Xu, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 2193–2198; d) J. Vesely, I. Ibrahim, G.-L. Zhao, R. Rios, A. Córdova, *Angew. Chem.* **2007**, *119*, 792–795; *Angew. Chem. Int. Ed.* **2007**, *46*, 778–781; e) P. Dinér, M. Nielsen, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 2029–2033; *Angew. Chem. Int. Ed.* **2007**, *46*, 1983–1987; f) U. Uriá, J. L. Vicario, D. Bdia, L. Carillo, *Chem. Commun.* **2007**, 2509–2511; g) H. Sundén, R. Rios, I. Ibrahim, G.-L. Zhao, L. Erikson, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 827–832; h) H. Li, J. Wang, H. Xie, L. Zu, W. Jiang, E. N. Duesler, W. Wang, *Org. Lett.* **2007**, *9*, 965–968.
- [7] For examples of moderately enantioselective aza-Michael reactions of enones catalyzed by chiral organic catalysts: see: a) D. Perdicchia, K. A. Jørgensen, *J. Org. Chem.* **2007**, *72*, 3565–3568; b) D. Pettersen, P. Piana, L. Bernardi, F. Fini, M. Fochi, V. Sgarzani, A. Ricci, *Tetrahedron Lett.* **2007**, *48*, 7805–7808.
- [8] For recent reviews of iminium catalysis, see: a) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79–87; b) A. Erkkilä, I. Majader, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470.
- [9] For examples of enantioselective transfer hydrogenation of enones, see: a) J. B. Tuttle, S. G. Ouellet, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 12662–12663; b) N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13368–13369.
- [10] Cinchona alkaloid **4** was first reported by: H. Brunner, J. Bügler, B. Nuber, *Tetrahedron: Asymmetry* **1995**, *6*, 1699–1702.
- [11] For **4**-catalyzed asymmetric reactions, see: a) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Angew. Chem.* **2007**, *119*, 393–396; *Angew. Chem. Int. Ed.* **2007**, *46*, 389–392; b) J.-W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J.-G. Deng, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 413–415; c) S. H. McCooley, S. J. Connon, *Org. Lett.* **2007**, *9*, 599–602; d) W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2007**, *5*, 816–821; e) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403–1405; f) T.-Y. Liu, H.-L. Cui, Y. Zhang, K. Jiang, W. Du, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 3671–3674; g) A. Carlone, G. Bartoli, M. Bosco, F. Pesciaioli, P. Ricci, L. Sambri, P. Melchiorre, *Eur. J. Org. Chem.* **2007**, 5492–5495; h) P. Ricci, A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Adv. Synth. Catal.* **2008**, *350*, 49–53; i) R. P. Singh, K. Bartelson, Y. Wang, H. Su, X. Lu, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 2422–2423; j) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070–6071; k) X. Lu, Y. Liu, B. Sun, B. Cindric, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 8134–8135.
- [12] a) D. P. Curran, *J. Am. Chem. Soc.* **1983**, *105*, 5826–5833; b) D. P. Curran, S. A. Scanga, C. J. Fenk, *J. Org. Chem.* **1984**, *49*, 3474–3478.