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

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Keywords

Michael addition; organocatalysis; cinchona alkaloids; chiral amine; bifunctional catalysis

Chiral amine motifs are ubiquitously presented in numerous biologically active and therapeutically important chiral 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. In parallel to enantioselective additions to achiral imines, catalytic asymmetric conjugate additions with nitrogen nucleophiles, or 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[2,3,4] and organic catalysts[5,6,7], highly enantioselective catalytic aza-Michael reactions to simple α,β -unsaturated ketones remain rare. To our knowledge, only three such reactions have been reported, and all are catalyzed by chiral transition-metal complexes.[3] Inanaga and coworkers reported a chiral Sc-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 Li-Y heterobimetallic complex Shibasaki and coworkers established a highly efficient aza-Michael reaction with a more broad scope, affording high enantioselectivity for a wide range of α,β -unsaturated ketones **1** bearing either an aryl or alkyl β -substituent.[3b,c] However, the ketone substituent (R^2) is limited to aromatic rings for both of the aforementioned reactions. More recently, Jacobsen and coworkers reported the conjugate addition of hydrazoic acid to enones catalyzed by a salen-Al complex.[3d] Notably, this reaction afforded good to excellent enantioselectivity for α,β -unsaturated ketones **1** bearing various alkyl substituents as both the ketone and the β -substituents. Herein, we wish to 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 the β -substituent, thereby providing a synthetically valuable substrate scope that is complementary to those of existing chiral metal-based methods.

MacMillan[6a] first reported the use of chiral secondary amines such as chiral imidazolidinones to activate α,β -unsaturated aldehydes for a highly enantioselective aza-Michael reaction with

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N-siloxycarbamate via iminium catalysis.[8] Presumably, the steric bulk of the chiral secondary amines renders them highly chemoselective for the nucleophilic attack toward the aldehyde group while minimizing catalyst decomposition via 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 an effective chiral secondary amines has not yet been reported.[9] Recently, 9-amino cinchona alkaloid **4**[10] in combination with various acids have been shown to provide an effective catalyst system for the activation of enones **1** for various asymmetric conjugate addition reactions.[11] Presumably, compared to a secondary amine, 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 via iminium catalysis, the quinuclidine motif of cinchona alkaloid **4**, in either the protonated or the free base form, could bind to a nitrogen nucleophiles such as alkoxyamines via hydrogen bonding interactions, thereby activating the nitrogen nucleophile for the nucleophilic attack by bring the nitrogen nucleophile into the approximaty of the activated enone (Scheme 1). 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**. In the presence of 10 mol% of **4** and 40 mol% of TFA (trifluoroacetic acid), 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 (Table 1). Various alkoxyamines bearing either an *N*-carbamate or -sulfonamide group were found to be active toward the **4**-catalyzed aza-Michael reaction. In particular the reaction with the Boc-protected *N*-benzyloxyamine **2g** afforded the highest enantioselectivity, providing the desired adduct in 84% ee (entry 8). Importantly, when the loading of TFA was decreased from 40 mol % to 20 mol %, the reaction was found to proceed in significantly improved enantioselectivity (entry 9 vs 8). A complete reaction could be attained with 20 mol% of **4** and 40 mol % of TFA to afford the desired aza-Michael adduct **3A** in 93% ee (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 out model studies. 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**. Singnificantly, alterations of the steric properties of the aliphatic ketone substituent did not impact negatively on the enantioselectivity of the reaction. Moreover, catalyst **4** was found to also tolerate a significant range of alkyl groups as the β -substituent in **1**. Catalyst **4** was also found to afford excellent enantioselectivity for alkyl vinyl ketones bearing a β -aryl group such as **1I**, albeit in drastically decreased activity (entry 9 vs 8). Reaction optimization studies revealed that the cinchonidine-derived catalyst **5** afforded the optimal enantioselectivity for enone **1I**, and the 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'**(C-NH₂) derived from cinchonine, the corresponding antipode 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 reactions (Table 2). Significantly, among existing highly enantioselective catalytic aza-Michael reactions with enones, the current reactio is unique in its ability to afford high enantioselectivity for alkyl vinyl ketones bearing a β -aryl groups (entries 12-16, Table 2). 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 to the corresponding *N*-Boc β -amino ketones **6** and **7** without deterioration in optical purity.[12]

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 a readily available chiral catalyst, commercially available nitrogen nucleophiles and a convenient operation protocol, this asymmetric aza-Michael reaction of general scope should provide a highly promising method for the asymmetric synthesis of a wide range of optically active chiral amines. Current investigations in these laboratories are focused on the elucidation of the mechanism as well as the expansion of the synthetic utility of this reaction.

Supplementary Material

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Chiral amine motifs are ubiquitously presented in numerous biologically active and therapeutically important chiral 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. In parallel to enantioselective nucleophilic or reductive additions to achiral imines, catalytic asymmetric conjugate additions with nitrogen nucleophiles, or asymmetric aza-Michael reactions, provide another fundamentally important approach toward optically active chiral amines.

Significant progress has been made recently in the development of asymmetric aza-Michael reactions with both chiral metallic and organic catalysts. In particular chiral secondary amines have been shown to be highly effective catalyst for the activation of enals for aza-Michael reactions with various nitrogen nucleophiles. However, highly enantioselective catalytic aza-Michael reactions to simple α,β -unsaturated ketones by organocatalysts has not yet been reported. In fact, only metal-catalyzed efficient aza-Michael reactions of α,β -unsaturated ketones have been reported. These metal-catalyzed reactions demonstrated high enantioselectivity for a broad scope of enones. However, alkyl vinyl ketones bearing an aryl substituent, a class of readily accessible and synthetically versatile enones, have not yet been shown to be good substrates for existing methods. In this communication, we report the first highly enantioselective aza-Michael reaction with α,β -unsaturated ketones catalyzed by a bifunctional organocatalyst. Significantly, this new catalytic asymmetric aza-Michael reaction afforded consistently high enantioselectivity for a wide variety of alkyl vinyl ketones bearing a β -aryl substituent, thereby providing a scope that is complementary to those of existing metal-based catalytic reactions. Additionally, utilizing a readily available chiral catalyst, commercially available and safe reagents and convenient operation protocol, this organocatalytic asymmetric aza-Michael reaction of unique scope should find wide applications in asymmetric synthesis. Thus the current reaction represents a considerable advance in synthetic method development. Apart from its synthetic implication, the current work, as the first organocatalytic asymmetric aza-Michael reaction with α,β -unsaturated ketones, also represents a noteworthy expansion of the scope of asymmetric organocatalysis and further establishes bifunctional organocatalysis as a broadly applicable strategy for

asymmetric reaction development. In view of these practical and conceptual significances, we submit this manuscript for publication as a communication in *Angewandte Chemie*.

References

- [1]. For recent reviews of enantioselective aza-Michael reactions, see: a) Xu L-W, Xia C-G. *Eur. J. Org. Chem* 2005:633–639.; b) Liu M, Sibi MP. *Tetrahedron* 2002;58:7991–8035..
- [2]. For examples of highly enantioselective aza-Michael reactions to carboxylic acid derivatives or surrogates catalyzed by metal-based Lewis acids, see: a) Sibi MP, Shay JJ, Liu M, Jasperse CP. *J. Am. Chem. Soc* 1998;120:6615–6616.; b) Myers JK, Jacobsen EN. *J. Am. Chem. Soc* 1999;121:8959–8960.; c) Zhuang W, Hazell RG, Jørgensen KA. *Chem. Commun* 2001:1240–1241.; d) Sibi MP, Pradagaran N, Ghorpade SG, Jasperse CP. *J. Am. Chem. Soc* 2003;125:11 796–11 797..
- [3]. For examples of highly enantioselective aza-Michael reactions to β -amino ketones catalyzed by metal-based Lewis acids, see: a) Jin XL, Sugihara H, Daikai K, Tateishi H, Jin YZ, Furuno H, Inanaga J. *Tetrahedron* 2002;58:8321–8329.; b) Yamagiwa N, Matsunaga S, Shibasaki M. *J. Am. Chem. Soc* 2003;125:16178–16179. [PubMed: 14692745]; c) Yamagiwa N, Qin H, Matsunaga S, Shibasaki M. *J. Am. Chem. Soc* 2005;127:13419–13427. [PubMed: 16173776]; d) Taylor MS, Zalatan DN, Lerchner AM, Jacobsen EN. *J. Am. Chem. Soc* 2005;127:1313–1317. [PubMed: 15669872].
- [4]. For highly enantioselective aza-Michael reaction of carbamates with α' -hydroxy enones, see: Palomo C, Oiarbide M, Halder R, Kelso M, Gómez-Bengon E, Garcia JM. *J. Am. Chem. Soc* 2004;126:9188–9189. [PubMed: 15281801].
- [5]. For examples of highly enantioselective aza-Michael reactions to carboxylic acid derivatives or surrogates catalyzed by chiral organic catalysts see: a) Horstmann TE, Guerin DJ, Miller SJ. *Angew. Chem Angew. Chem. Int. Ed* 2000;2000:11239:3781–3784. 3635–3638.; b) Guerin DJ, Miller SJ. *J. Am. Chem. Soc* 2002;124:2134–2136. [PubMed: 11878965]; c) Sibi MP, Itoh K. *J. Am. Chem. Soc* 2007;129:8064–8065. [PubMed: 17552527]
- [6]. For examples of enantioselective aza-Michael reactions of enals catalyzed by chiral organic catalysts, see: a) Young K, Chen MY, MacMillan DWC. *J. Am. Chem. Soc* 2006;128:9328–9329. [PubMed: 16848457]; b) Ibrahim I, Rios R, Vesley J, Zhao G-L, Córdova A. *Chem. Commun* 2007:849–851.; c) Vesley J, Ibrahim I, Rios R, Zhao G-L, Xu Y, Córdova A. *Tetrahedron Lett* 2007;48:2193–2198.; d) Vesely J, Ibrahim I, Zhao G-L, Rios R, Córdova A. *Angew. Chem. Int. Ed* 2007;46:778–781.; e) Diner P, Nielsen M, Marigo M, Jørgensen KA. *Angew. Chem. Int. Ed* 2007;46:1983–1987.; f) Uria U, Vicario JL, Bdia D, Carillo L. *Chem. Commun* 2007:2509–2511.; g) Sundén H, Rios R, Ibrahim I, Zhao G-L, Erikson L, Cordova A. *Adv. Synth. Catal* 2007;349:827–832.; h) Li H, Wang J, Xie H, Zu L, Jiang W, Duesler EN, Wang W. *Org. Lett* 2007;9:965–968. [PubMed: 17298072].
- [7]. For examples of moderately enantioselective aza-Michael reactions of enones catalyzed by chiral organic catalysts: see: a) Perdicchia D, Jørgensen KA. *J. Org. Chem* 2007;72:3565–3568. [PubMed: 17391046]; b) Pettersen D, Piana P, Bernardi L, Fini F, Fochi M, Sgarzani V, Ricci A. *Tetrahedron Lett* 2007;48:7805–7808..
- [8]. For recent reviews of iminium catalysis, see: a) Lelais G, MacMillan DWC. *Aldrichimica Acta* 2006;39:79–87.; b) Erkkilä A, Majader I, Pihko PM. *Chem. Rev* 2007;107:5416–5470. [PubMed: 18072802].
- [9]. For examples of enantioselective transfer hydrogenation of enones, see: a) Tuttle JB, Ouellet SG, MacMillan DWC. *J. Am. Chem. Soc* 2006;128:12662–12663. [PubMed: 17002356]; b) Martin NJA, List B. *J. Am. Chem. Soc* 2006;128:13368–13369. [PubMed: 17031944].
- [10]. Cinchona alkaloid **4** was first reported by: Brunner H, Bügler J, Nuber B. *Tetrahedron: Asymmetry* 1995;6:1699–1702..
- [11]. For **4**-catalyzed asymmetric reactions, see: a) Xie J-W, Chen W, Li R, Zeng M, Du W, Yue L, Chen Y-C, Wu Y, Zhu J, Deng J-G. *Angew. Chem., Int. Ed* 2007;46:389–392.; b) Xie J-W, Yue L, Chen W, Du W, Zhu J, Deng J-G, Chen Y-C. *Org. Lett* 2007;9:413–415. [PubMed: 17249775]; c) McCooey SH, Connon SJ. *Org. Lett* 2007;9:599–602. [PubMed: 17243708]; d) Chen W, Du W, Yue L, Li R, Wu Y, Ding L-S, Chen Y-C. *Org. Biomol. Chem* 2007;5:816–821. [PubMed: 17315068]; e) Bartoli G, Bosco M, Carlone A, Pesciaoli F, Sambri L, Melchiorre P. *Org. Lett*

2007;9:1403–1405. [PubMed: 17346059]; f) Liu T-Y, Cui H-L, Zhang Y, Jiang K, Du W, He Z-Q, Chen Y-C. *Org. Lett* 2007;9:3671–3674. [PubMed: 17691800]; g) Carlone A, Bartoli G, Bosco M, Pesciaioli F, Ricci P, Sambri L, Melchiorre P. *Eur. J. Org. Chem* 2007;5492–5495.; h) Ricci P, Carlone A, Bartoli G, Bosco M, Sambri L, Melchiorre P. *Adv. Synth. Catal* 2008;350:49–53.; i) Singh RP, Bartelson K, Wang Y, Su H, Lu X, Deng L. *J. Am. Chem. Soc* 2008;130:2422–2423. [PubMed: 18251543]; j) Wang X, Reisinger CM, List B. *J. Am. Chem. Soc* 2008;130:6070–6071. [PubMed: 18422314]; k) Lu X, Liu Y, Sun B, Cindric B, Deng L. *J. Am. Chem. Soc* 2008;130:8134–8135. [PubMed: 18529055].

[12]. a) Curran DP. *J. Am. Chem. Soc* 1983;105:5826–5833. b) Curran DP, Scanga SA, Fenk CJ. *J. Org. Chem* 1984;49:3474–3478.

5 (CD-NH₂): R=H

Scheme 1.

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

3G: R³=Me, R⁴=*n*-Bu;

3I: R³=Ph, R⁴=Me;

6: 90% ee, 76%

7: 90% ee, 73%

Scheme 2.
Hydrogenation of **3**.

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

entry ^[a]	2	cat.	time (h)	Conv. ^[b] (%)	ee ^[c] (%)	3A
1	2a BnNH ₂	4	12	0	na	
2	2b Bn-NH-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 **1**, 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 TFA (20 mol%). [e] Reaction was run with 0.2 mmol **1**, 0.30 mmol **2**, **4** (20 mol%), and TFA (40 mol%).

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

entry ^[a]	Cat.	Enone	R ³	R ⁴	product	Time(h)	yield(%) 3 ee (%) ^[b] 3
1	4 (5 ^f)	1A	PhCH ₂ CH ₂	Me		72(120)	80(80) 93(84)
2	4	1B	<i>n</i> -pen	Me		72	76 94
3	4	1C	Me	Et		92	83 90
4	4 (5 ^f)	1D	<i>n</i> -pen	Et		162(170)	70(67) 93(90)
5	4 (5 ^f)	1E	<i>n</i> -Hex	Et		120(168)	83(68) 93(91)
6	4	1F	<i>n</i> -Hep	Et		96	70 96
7	4 (5 ^f)	1G	Me	<i>n</i> -Bu		192(196)	74(76) 91(86)
8	4	1H	<i>n</i> -Pr	<i>n</i> -Bu		96	70 95
9 ^[c,d]	4	1I	Ph	Me		24	11 ^[e] 94
10 ^[c,d]	5	1I	Ph	Me		24	13 ^[e] 96
11 ^[c,f]	5	1I	Ph	Me		24	41 ^[e] 93
12 ^[c,g,h]	5	1I	Ph	Me		84	67 90
13 ^[c,g]	5 (5 ^f)	1J	<i>p</i> -F-Ph	Me		96(192)	61(60) 92(87)
14 ^[c,g]	5	1K	<i>p</i> -Cl-Ph	Me		82	71 93
15 ^[c,g]	5	1L	<i>p</i> -Br-Ph	Me		80	70 90
16 ^[c,g]	5	1M	<i>p</i> -Me-Ph	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] Determined by HPLC analysis. [c] Reaction was run with 10 mol% Cat. and 20 mol% TFA. [d] The reaction was checked after 24h. [e] The conversion of the reaction was determined by ¹H NMR analysis. [f] Reaction was run at 40 °C and checked after 24h. [g] Reaction was run with 0.2 mmol **1**, 0.60 mmol **2g** at 40 °C in toluene. [h] Absolute configuration was assigned as S, see Support Information for details.