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Original article

Asymmetric catalyzed intramolecular aza-Michael reaction mediated by quinine-derived primary amines

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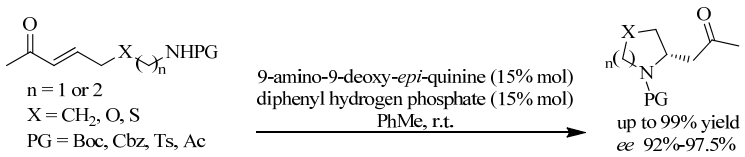
Graphical Abstract



An intramolecular organocatalytic enantioselective aza-Michael reaction of carbamates, sulfonamides and acetamides to *α,β*-unsaturated ketones has been developed with excellent enantioselectivity and very good yield.

ABSTRACT

An intramolecular organocatalytic enantioselective aza-Michael reaction of carbamates, sulfonamides and acetamides to *α,β*-unsaturated ketones was developed. This process is promoted by 9-amino-9-deoxy-epi-quinine and diphenyl hydrogen phosphate to afford a straightforward and expeditious synthesis of several synthetically useful five- and six-membered heterocycles with excellent enantioselectivity (92%-97.5% *ee*) and very good yields (up to 99%).

Keywords:
Asymmetric catalysis
Intramolecular aza-Michael reaction
Primary amine
Five- and six-membered heterocycles
Pyrrolidine and piperidine

Enantioselective organocatalytic

1. Introduction

The field of organocatalysis [1] has expanded in recent years, since the discovery of the proline-catalyzed aldol reaction [2]. During this period, an overwhelming number of novel, highly efficient organocatalysts have been reported in the literature. In particular, chiral secondary amines are extremely powerful reagents that have dominated the field of amino catalysis [3]. However, in spite of the tremendous success of the use of secondary amines in the asymmetric functionalization of aldehydes, only minor progress has been achieved in the corresponding transformations of ketones, because of the inherent difficulties in generating congested covalent intermediates between chiral secondary amines and ketones. Primary amine catalysis offers the unique possibility of participating in processes between sterically demanding partners [4] and chiral primary amines have also been demonstrated to be effective catalysts in a wide range of enantioselective organic reactions [5], especially for the activation of challenging substrates, such as *α,α*-disubstituted aldehydes [6] and ketones [7].

β-Amino carbonyl derivatives bearing heterocyclic nitrogen atoms have become attractive targets in organic and medicinal chemistry, as they are versatile synthetic intermediates that can be used in the preparation of a wide variety of heterocycles [8]. Among the *β*-amino carbonyl molecules, pyrrolidine and piperidine moieties are extremely valuable scaffolds due to their widespread occurrence in diverse biologically active natural products and pharmaceutical agents [9], as well as their utility as chiral auxiliaries and chiral ligands in asymmetric catalysis [10]. The aza-Michael reaction is the most direct method for selectively creating a

carbon–nitrogen bond at the *β*-position of an activated olefin. Despite the importance of this methodology, organocatalytic enantioselective aza-Michael reactions remained undeveloped until very recently [11] and can thus be considered to be challenging Moreover, most of the present work has focused on intermolecular aza-Michael reactions and only a few reports involving enantioselective organocatalytic intramolecular reactions have been published, especially for *α*,*β*-unsaturated ketones.

As part of our continuing interest in the development of a general and highly selective methodology for an intramolecular aza-Michael reaction (IMAMR), herein we described an operationally simple, very high enantioselective organocatalytic IMAMR for carbamates bearing an *α*,*β*-unsaturated ketone using chiral primary amines and a weak organic acid as co-catalyst. The application of this methodology for the synthesis of several enantiomeric five- and six-membered heterocycles was also conducted. Starting carbamates, sulfonamides and acetamides bearing conjugated ketones **1** were easily obtained in moderate to high yields through a cross-metathesis reaction of the corresponding unsaturated N-protected amines with vinyl ketones in the presence of second-generation Hoveyda-Grubbs catalyst.

2. Results and discussion

In order to find the optimum conditions and catalysts for the enantioselective IMAMR, the model reaction was performed with catalyst **I** (Fig. 1) and various organic acids as co-catalyst in $CHCl_3$ for 40 h at room temperature (Table 1, entries 1-5). The results indicated that low yields were achieved when weak acids, such as CH_3COOH, 2-F-C_6H_4COOH and 2-NO_2-C_6H_4COOH, were used (Table 1, entries 1-3). A significant improvement in yield (90%) and *ee* (75%) was achieved when the reaction was performed in the presence of trifluoroacetic acid, and a higher yield (95%) and *ee* value (89%) of **2a** was observed when the slightly weaker acid, DPP (diphenyl hydrogen phosphate), was used (Table 1, entries 4-5). Further screening showed that toluene was a suitable solvent (Table 1, entry 7). Interestingly, in contrast to a previous report [12], the use of a chiral co-catalyst, such as (*S*)-**IV**, (*R*)-**V** and (*R*)-**VI** (Fig. 1), had a negative effect on both the enantioselectivity and yield of the reactions (Table 1, entries 10-12). Furthermore, increasing the co-catalyst loading from 15 mol% to 30 mol% resulted in a slight decrease in yield (96%) and *ee* (94%) (Table 1, entry 14). When a lower temperature was used, however, there was no improvement in the final *ee* (81%) and yield (65%) (Table 1, entry 13). Under the same condition, no improvement in the *ee* and yield was observed when catalysts **II** and **III** were used (Table 1, entries 15 and 16). Meanwhile, the yield of **2a** was decreased when the loading of catalyst **I** was reduced (Table 1, entries 17 and 18).

With the optimized conditions in hand, to further explore the influence of protecting groups on the enantioselectivity and yield of the IMAMR (Table 2), substrates **1b-1e**, bearing carbamates, sulfonamides, or acetamides as nitrogen-protecting groups, were investigated. Excellent asymmetric induction and yield were observed when Cbz, Boc and Ts were used as protecting groups (Table 2, entries 1-3). Even when substrate **1e**, which has very weak nucleophilicity of the acetyl amide [12d], was tested, the IMAMR still provided the desired product **2e** with excellent yield (95%) and *ee* (93%). Unlike previous reports [13], our current methodology suggested that placing a heteroatom in the *α*-position relative to the nitrogen-centered nucleophile (*α*-effect) to enhance nucleophilicity was unnecessary. More importantly, this method allowed a highly enantioselective assembly of a stereogenic nitrogen-containing carbon center in the functionalized 2-substituted piperidines, providing an efficient synthetic method for many biologically active 2-substituted piperidine alkaloids [14].

Our attention was then turned to other substrates containing different heteroatoms within the alkyl chain, since the corresponding products could be potentially valuable in medicinal chemistry. Table 3 shows that under the same conditions, reaction of substrates **1f-1i**, which contain oxygen, and sulfur in the alkyl chain, led to the corresponding five- or six-membered heterocycles in yields ranging from 55% to 97% and with excellent *ee* (92%-97%) (Table 3).

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Finally, the absolute configuration of the newly created stereocenter was determined to be *R* by comparing the $[\alpha]_D^{25}$ values and NMR data of compound **2a-2c** with those described in the literatures [15-17] and identical stereochemical development was assumed for **2d-2i**.

3. Conclusion

In conclusion, we have developed a highly efficient and enantioselective organocatalytic IMAMR of carbamates bearing an *α*,*β*-unsaturated ketone using 9-amino-9-deoxy-*epi*-quinine and DPP as co-catalysts. Importantly, a series of synthetically useful 2-substituted five- and six-membered heterocycles could be directly produced in a highly enantioselective fashion (92%-97.5% *ee*). It is worth noting that in the IMARMR described herein, no *α*-effect was necessary to enhance the nucleophilicity of the nitrogen and the process took place with very high yield and excellent *ee* values even if acetamide was used as a nitrogen-protecting group.

4. Experimental

All solvents and reagents were used as purchased and received from Aldrich without any further purification. Mass spectra and high-resolution mass spectra were measured on a Finnigan MAT-95 mass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were determined on Bruker AM-400 instrument using tetramethylsilane as an internal reference. Data are presented as follows: chemical shift, multiplicity, coupling constant in hertz (Hz). The signals of the ^{13}C NMR were assigned using DEPT experiments and on the basis of previously published data. The enantiomeric excess (*ee*) was measured by HPLC (chiralcel OD-H, *n*-hexane/i-PrOH= 97/3, flow rate 1.5 mL/min). Silica gel 60H (200-300 mesh) manufactured by Qingdao Haiyang Chemical Group Co., China) was used for general chromatography.

General procedure for the organocatalytic IMAMR reaction at room temperature: The chiral primary amine **I** (0.015 mmol) was added to a solution of DPP (0.015 mmol) in toluene (0.6 mL) and the mixture was stirred for 15 min at room temperature. Then substrate **1** (0.1 mol) was added. When TLC indicated there was no remaining starting substrate **1,** the solvent was removed and the residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt= 7:1), affording the aza-Michael adducts **2a-i**.

^{1}H NMR and ^{13}C NMR spectra for all compounds are available in Supporting information and typical spectral data of some compounds are listed below.

Benzyl 2-(2-oxopropyl)pyrrolidine-1-carboxylate (**2a**): Yield: 98%. $[\alpha]_D^{25}$ +35.5 (*c* 0.15, $CHCl_3$). *ee* 95%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 (m, 5H), 5.12 (s, 2H), 4.22 (m, 1H), 3.42 (m, 2H), 3.24-2.84 (m, 1H), 2.42 (dd, 1H, *J* = 16.4, 9.6 Hz), 2.22-2.00 (m, 4H), 1.90-1.78 (m, 2H), 1.70-1.60 (m, 1H); Major: ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.2, 154.6, 136.8, 128.4, 128.4, 127.9, 127.9, 127.8, 66.5, 53.9, 47.5, 46.3, 30.8, 30.3, 23.6; Minor: ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.2, 154.6, 137.6, 128.4, 128.4, 127.9, 127.9, 127.8, 66.8, 53.2, 48.5, 46.6, 31.6, 30.3, 22.8; HRMS (EI) calcd. for $C_{15}H_{19}NO_3$ (M^+): 261.1365, found 261.1369.

Benzyl 2-(2-oxopropyl)piperidine-1-carboxylate (**2b**): Yield: 99%. $[\alpha]_D^{25}$ +14.0 (*c* 0.13, $CHCl_3$). *ee* 97.5%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 (m, 5H), 5.11 (d, 2H, *J* = 3.2 Hz), 4.80 (m, 1H), 4.03 (m, 1H), 2.85 (t, 1H, *J* = 12.2 Hz), 2.68 (m, 2H), 2.13 (s, 3H), 1.52 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.7, 155.2, 136.7, 128.4, 128.4, 127.9, 127.8, 127.8, 67.0, 47.4, 44.2, 39.7, 30.0, 28.2, 25.1, 18.7; HRMS (EI) calcd. for $C_{16}H_{21}NO_3$ (M^+): 275.1521, found 275.1526.

tert-Butyl 2-(2-oxopropyl)piperidine-1-carboxylate (**2c**): Yield: 97%. $[\alpha]_D^{25}$ +7.3 (*c* 0.1, $CHCl_3$). *ee* 92%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.72 (brs, 1H), 3.97 (m, 1H), 2.77 (t, *J* = 12.4 Hz, 1H), 2.64 (dd, *J* = 7.1, 2.8 Hz, 2H), 2.18 (s, 3 H), 1.70-1.45 (m, 5H), 1.43 (s, 9H), 1.43-1.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.1, 154.7, 79.6, 47.2, 44.3, 39.3, 30.0, 28.3, 28.3, 28.3, 25.2, 18.8; HRMS (EI) calcd. for $C_{13}H_{23}NO_3$ (M^+): 241.1678, found 241.1672.

1-(1-Tosylpiperidin-2-yl)propan-2-one (**2d**): Yield: 97%. $[\alpha]_D^{25}$ +23.0 (*c* 0.18, $CHCl_3$). *ee* 95%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, 2H, *J* = 8.2 Hz), 7.27 (d, 2H, *J* = 8.2 Hz), 4.51 (m, 1H), 3.78 (m, 1H), 2.92 (td, 1H, *J* = 13.6, 2.4 Hz), 2.78 (dd, 1H, *J* = 16.0, 9.6 Hz), 2.59 (dd, 1H, *J* = 16.0, 4.4 Hz), 2.41 (s, 3H), 2.12 (s, 3H), 1.55-1.25 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.0, 143.1, 138.0, 129.6, 129.6, 127.0, 127.0, 48.6, 43.8, 41.1, 30.2, 27.6, 24.5, 21.4, 18.3; HRMS (EI) calcd. for $C_{15}H_{21}NO_3S$ (M^+): 295.1242, found 295.1251.

1-(1-Acetylpiperidin-2-yl)propan-2-one (**2e**): Yield: 95%. $[\alpha]_D^{25}$ +44.0 (*c* 0.2, $CHCl_3$). *ee* 93%. Major: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.26 (m, 1H), 3.59 (d, 1H, *J* = 18.0 Hz), 3.12 (dt, 1H, *J* = 18.0, 3.2 Hz), 2.79 (d, 1H, *J* = 9.2 Hz), 2.63 (t, 1H, *J* =9.2 Hz), 2.20 (s, 3H), 2.04 (s, 3H), 1.75-1.30 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.3, 169.4, 44.7, 44.2, 42.1, 29.8, 28.1, 25.8, 21.9, 18.8; Minor: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.62-4.48 (m, 2H), 2.79 (d, *J* = 9.2 Hz, 1H), 2.63 (t, 1H, *J* =9.2 Hz), 2.57-2.47 (m, 1H), 2.17 (s, 3H), 2.14 (s, 3H), 1.75-1.30 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.9, 169.4, 49.2, 44.1, 36.9, 30.9, 29.3, 25.3, 21.5, 19.2; HRMS (EI) calcd. for $C_{10}H_{17}NO_2$ (M^+): 183.1259, found 183.1266.

tert-Butyl 3-(2-oxopropyl)morpholine-4-carboxylate (**2f**): Yield: 97%. $[\alpha]_D^{25}$ +38.5 (*c* 0.15, $CHCl_3$). *ee* 97%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.38 (brs, 1H), 3.85-3.67 (m, 3H), 3.56 (dd, 1H, *J* = 12.0, 2.0 Hz), 3.43 (td, 1H, *J* = 11.7, 2.4 Hz), 3.06 (brs, 2H), 2.56 (d, 1H, *J* = 15.3 Hz), 2.18 (s, 3H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.5, 154.3, 80.2, 68.9, 66.7, 47.2, 42.4, 39.1, 30.4, 28.2, 28.2, 28.2; HRMS (EI) calcd. for $C_{12}H_{21}NO_4$ (M^+): 243.1471, found 243.1472.

tert-Butyl 4-(2-oxopropyl)oxazolidine-3-carboxylate (**2g**): Yield: 96%. $[\alpha]_D^{25}$ +67.0 (*c* 0.11, $CHCl_3$). *ee* 94%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.90-4.65 (m, 2H), 4.20-4.10 (m, 2H), 3.72-3.66 (m, 1H), 3.25-2.85 (m, 1H), 2.65-2.45 (m, 1H), 2.13 (s, 3H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.8, 152.5, 80.4, 78.6, 72.5, 51.4, 46.0, 30.2, 28.3, 28.2, 28.3; HRMS (EI) calcd. for $C_{11}H_{19}NO_4$ (M^+): 229.1314, found 229.1323.

Benzyl 3-(2-oxopropyl)thiomorpholine-4-carboxylate (**2h**): Yield: 55%. $[\alpha]_D^{25}$ +18.5 (*c* 0.1, $CHCl_3$). *ee* 95%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (m, 5H), 5.13 (s, 2H), 4.99 (brs, 1H), 4.34 (m, 1H), 3.45-2.90 (m, 3H), 2.80-2.30 (m, 4H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.1, 155.1, 136.4, 128.5, 128.5, 128.1, 127.9, 127.9, 67.5, 46.4, 43.0, 40.7, 31.1, 30.4, 27.4; HRMS (EI) calcd. for $C_{15}H_{19}NO_3S$ (M^+): 293.1086, found 293.1089.

(*S*)-Benzyl 4-(2-oxopropyl)thiazolidine-3-carboxylate (**2i**): Yield: 91%. $[\alpha]_D^{25}$ +14.2 (*c* 0.18, $CHCl_3$). *ee* 92%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45-7.28 (m, 5H), 5.13 (s, 2H), 4.70-4.45 (m, 2H), 4.33 (d, 1H, *J* = 9.2 Hz), 3.24 (dd, 1H, *J* = 12.0, 6.4 Hz), 3.03-2.70 (m, 3H), 2.18-2.02 (m, 3H); Major: ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.5, 153.4, 136.1, 128.5, 128.5, 128.1, 127.9, 127.9, 67.3, 56.3, 47.8, 45.9, 35.3, 30.2; Minor: ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.5, 153.4, 136.1, 128.5, 128.5, 128.1, 127.9, 127.9, 67.3, 55.3, 48.5, 46.7, 36.3, 30.2; HRMS (EI) calcd. for $C_{14}H_{17}NO_3S$ (M^+): 279.0929, found 279.0936.

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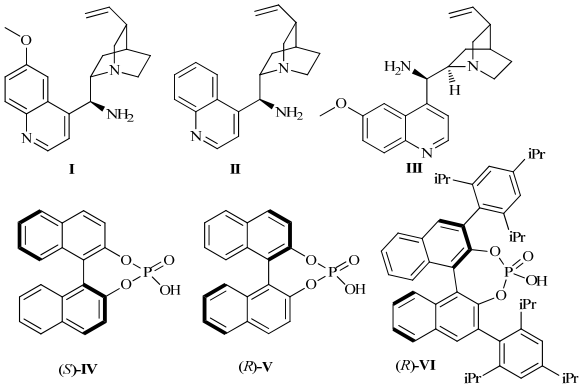
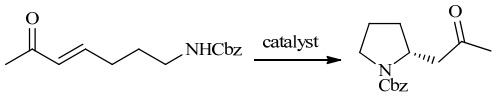


Fig. 1. Structures of catalysts and organic acids used in this report.

Table 1

Catalyst screening and optimization of reaction conditions.



1a **2a**

Entry	cat.(mol %)	Acid (mol%)	Solvent	Temp (°C)	Yield (%)	*ee* (%)[b]
1	**I** (15)	CH_3COOH (15)	$CHCl_3$	25	5	n.d.
2	**I** (15)	2-F-C_6H_4COOH (15)	$CHCl_3$	25	10	n.d.
3	**I** (15)	2-NO_2-C_6H_4COOH (15)	$CHCl_3$	25	10	n.d.
4	**I** (15)	TFA (15)	$CHCl_3$	25	90	75
5	**I** (15)	DPP (15)	$CHCl_3$	25	95	89
6	**I** (15)	TFA (15)	Toluene	25	91	86
7	**I** (15)	DPP (15)	Toluene	25	98	95
8	**I** (15)	DPP (15)	THF	25	83	89
9	**I** (15)	DPP (15)	Acetone	25	50	82
10	**I** (15)	(*S*)-**IV** (15)	Toluene	25	65	87
11	**I** (15)	(*R*)-**V** (15)	Toluene	25	91	81
12	**I** (15)	(*R*)-**VI** (15)	Toluene	25	65	71
13	**I** (15)	DPP (15)	Toluene	-10	65	81
14	**I** (15)	DPP (30)	Toluene	25	96	94
15	**II** (15)	DPP (15)	Toluene	25	90	79
16	**III** (15)	DPP (15)	Toluene	25	85	-72
17	**I** (10)	DPP (15)	Toluene	25	16	95
18	**I** (5)	DPP (15)	Toluene	25	6	95

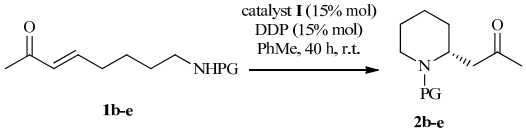
TFA = trifluoroacetic acid; DPP = diphenyl hydrogen phosphate. n.d. = no detected.

[a] In all cases, reactions were carried out in the specified solvent and time (40 h).

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

Table 2

Influence of the nitrogen-protecting group on the IMAMR.

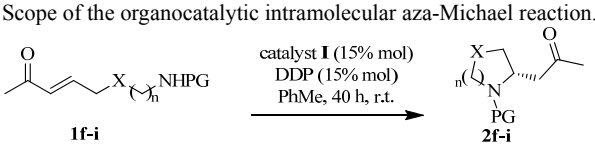


1b-e **2b-e**

Entry	Substrate	PG	Product	Yield (%)	*ee* (%)[a]
1	**1b**	Cbz	**2b**	99	97.5
2	**1c**	Boc	**2c**	97	92
3	**1d**	Ts	**2d**	97	95
4	**1e**	Ac	**2e**	95	93

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

Table 3
Scope of the organocatalytic intramolecular aza-Michael reaction.



1f-i **2f-i**

Entry	X	n	PG	Product	Yield (%)	*ee* (%)[a]
1	O	2	Boc	**2f**	97	97
2	O	1	Boc	**2g**	96	94
3[b]	S	2	Cbz	**2h**	55	95
4	S	1	Cbz	**2i**	91	92

[a] Determined by means of chiral-phase HPLC analysis.
[b] Reaction time = 4 days