Asymmetric organocatalytic Michael addition of ketones to vinyl sulfone†

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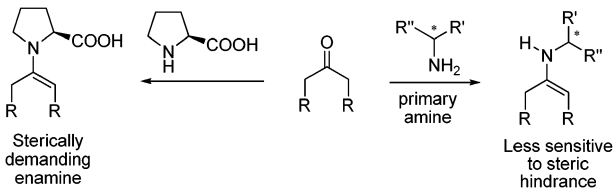
Highly enantioselective organocatalytic Michael addition of ketones to vinyl sulfone catalyzed by a cinchona alkaloid-derived primary amine is reported for the first time; the described synthetic methodology was applied to the synthesis of sodium cyclamate.

Sulfones are useful intermediates in synthetic and medicinal chemistry.[1] Vinyl sulfones[2] are valuable precursors in organic synthesis, and their asymmetric Michael reactions with carbon nucleophiles provide an easy access to optically pure sulfones.[3] Recently, d'Angelo and co-workers employed 1-phenylethylamine-derived chiral imines in Michael additions to vinyl sulfones.[4] With the spectacular advance of organocatalysis in the past few years,[5] a couple of reports employing organocatalytic approaches appeared in the literature. Deng *et al*. described a cinchona alkaloid-mediated enantioselective conjugate addition of α-cyanoacetates to vinyl sulfones for the construction of all carbon quaternary stereocentres.[6] Recently, Alexakis and his co-workers reported asymmetric organocatalytic Michael additions of aldehydes to vinyl sulfones which were promoted by their well-designed *N*-*i*Pr-2,2′-bipyrrolidine catalysts.[7] Very recently, we disclosed an enantioselective organocatalytic Michael addition of aldehydes to vinyl sulfones mediated by silylated biarylprolinol.[8] Despite all these advances, a practical asymmetric organocatalytic Michael addition of ketones to vinyl sulfones is still elusive. Herein we wish to report the first highly enantioselective organocatalytic Michael reaction of cyclic ketones with vinyl sulfone catalyzed by a cinchona alkaloid-derived organocatalyst containing a primary amino function.

Aminocatalysis *via* the enamine intermediate is one of the most important activation methods in asymmetric organocatalysis, and proline and its various structural analogues have found enormous applications in a wide range of reactions.[9] Very recently, chiral primary amines were shown to be effective catalysts in asymmetric organocatalysis.[10] Our group demonstrated for the first time that natural tryptophan is an effective catalyst in intermolecular aldol reactions.[11] Subsequently, we showed that threonine-derived organocatalysts could promote highly enantioselective aldol and Mannich reactions of hydroxyacetone, affording useful chiral 1,2-diol and 1,2-amino alcohol building blocks.[12] To develop an organocatalytic Michael addition of ketones to vinyl sulfone, we reasoned primary amines might be suitable catalysts. The crucial enamine intermediate may be readily formed in the presence of primary amine, whereas steric hindrance may hinder efficient enamine formation when a secondary amine is used as the catalyst (Scheme 1).



Scheme 1 The enamine intermediates in the enamine catalysis.

For the initial studies, we tested a few common secondary and primary amino catalysts in the Michael addition of cyclohexanone **1** to vinyl sulfone **2** (Table 1). Not surprisingly, proline and silylated biarylprolinols **4** only afforded the desired adducts in very low yield (entries 1–3). Threonine-derived catalysts (**5a–c**), previously developed by our group for aldol and Mannich reactions,[12] catalyzed the formation of the desired product in high yield, but the enantioselectivity was disappointing (entries 4–6). Serine-based catalysts (**6a–c**) were much more effective, and the desired Michael adducts were formed in excellent yield and with moderate enantioselectivity (entries 7–9). The cinchonidine-derived primary amine **7** turned out to be an excellent catalyst, giving the desired product in excellent yield and with good enantioselectivity (entry 10). Screening of solvents and acidic additives revealed that chloroform was the best solvent and benzoic acid was the additive of choice (entry 16). When the temperature was lowered to 0 °C, the Michael product **3** was obtained in excellent yield and with excellent enantioselectivity. The absolute configuration of the Michael product **3** was determined to be *R*.[13]

The scope of the reaction was investigated by employing various ketones (Table 2). In the presence of primary amine **7**, the Michael reactions between vinyl sulfone and different cyclic ketones proceeded smoothly, affording the desired adducts in good yield, with moderate diastereoselectivity and excellent enantioselectivity. However, the reactions are not applicable to acyclic ketones.[14]

The Michael adducts of ketones with vinyl sulfone are useful synthetic intermediates. The facile conversion of the ketone

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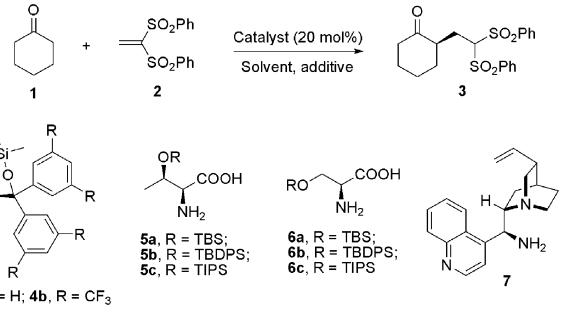
† Electronic supplementary information (ESI) available: Experimental details, analytical data, HPLC chromatogram and NMR spectra of Michael adducts. See DOI: 10.1039/b816307c

Table 1 Screening of organocatalysts for the asymmetric Michael addition of cyclohexanone **1** to vinyl sulfone **2**[a]



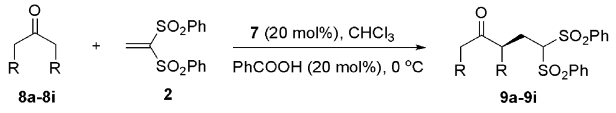
Entry	Catalyst	Solvent	Temp./ °C	Additive	Yield[b] (%)	ee[c] (%)
1	Proline	Toluene	RT	—	< 20	—
2	**4a**	Toluene	RT	—	31	48
3	**4b**	Toluene	RT	—	< 20	—
4	**5a**	Toluene	RT	—	85	21
5	**5b**	Toluene	RT	—	70	−2
6	**5c**	Toluene	RT	—	83	7
7	**6a**	Toluene	RT	—	96	60
8	**6b**	Toluene	RT	—	95	44
9	**6c**	Toluene	RT	—	95	46
10	**7**	Toluene	RT	PhCOOH	86	71
11	**7**	THF	RT	PhCOOH	71	79
12	**7**	MeOH	RT	PhCOOH	95	27
13	**7**	CH_2Cl_2	RT	PhCOOH	94	78
14	**7**	DMSO	RT	PhCOOH	89	38
15	**7**	CH_3CN	RT	PhCOOH	95	49
16	**7**	$CHCl_3$	RT	PhCOOH	86	89
17	**7**	$CHCl_3$	RT	TFA	87	85
18	**7**	$CHCl_3$	RT	CSA	91	85
19	**7**	$CHCl_3$	−20	PhCOOH	45	90
20	**7**	$CHCl_3$	0	PhCOOH	94	92

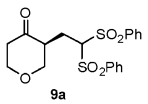
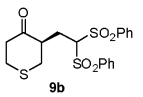
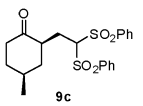
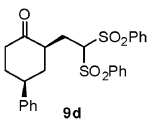
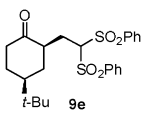
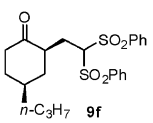
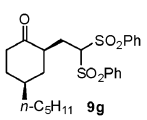
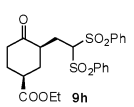
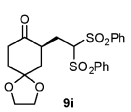
[a] The reactions were performed with cyclohexanone (0.5 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.01 mmol) in anhydrous solvent (0.1 mL) at room temperature for 2 h, unless otherwise specified. [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis.

functionality into an alcohol or amine, in combination with well-established desulfonylation methods,[15] offers a unique asymmetric entry to α-alkylated ketones and their derivatives. To illustrate the value of our asymmetric organocatalytic Michael addition, we applied our methodology as the key step to construct sodium cyclamate, an important compound in the artificial sweeteners industry.[16] As shown in Scheme 2, cinchonidine-derived primary amine **7** mediated efficient Michael addition of cyclohexanone to vinyl sulfone, affording the adduct **3** with 92% ee. Subsequent reduction with $LiAlH_4$ gave *cis*-**10** in good diastereoselectivity. Conversion of the hydroxy group into azide, followed by reduction and protection, then yielded *trans*-**12** as a single diastereomer. Desulfonation with magnesium in methanol and removal of the amino protective group afforded chiral amine salt **13**, the transformation of which into sodium cyclamate is well documented in the literature.[16] It should be noted that the reduction of ketone **3** with L-selectride yielded *trans*-**10**,[17] thus providing an easy access to both *cis*- and *trans*-isomers of sodium cyclamate.

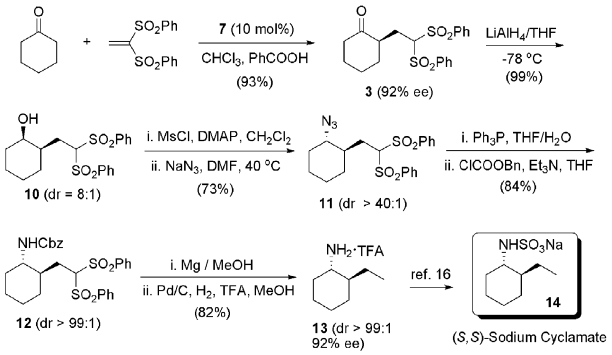
In conclusion, we have disclosed the first highly enantioselective organocatalytic Michael addition of cyclic ketones to vinyl sulfone mediated by a cinchona alkaloid-derived primary amine catalyst. The methodology described in this report provides an easy access to α-alkylated carbonyl compounds and their derivatives, and we anticipate these synthetic methods will find wide applications in organic synthesis.

Table 2 Organocatalytic Michael addition of various cyclic ketones to vinyl sulfone[a]



Entry	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	 **9a**	89	—	91
2	 **9b**	76	—	95
3	 **9c**	84	5 : 1	96
4	 **9d**	92	6 : 1	97
5	 **9e**	93	3 : 1	95
6	 **9f**	90	4 : 1	94
7	 **9g**	78	2.5 : 1	90
8	 **9h**	85	5 : 1	88
9	 **9i**	87	—	90

[a] The reactions were performed with cyclic ketone (0.5 mmol), vinyl sulfone (0.05 mmol) and **7** (0.01 mmol) in anhydrous $CHCl_3$ (0.1 mL) at 0 °C for 2 h. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the crude product. [d] The ee value of the major diastereomer, determined by chiral HPLC analysis.



Scheme 2 A synthesis of (*S*,*S*)-sodium cyclamate.

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