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Highly enantioselective conjugate addition of nitroalkanes to enones catalyzed by cinchona alkaloid derived primary amine

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ABSTRACT

A cinchona alkaloid derived primary amine catalyzed conjugate addition of nitroalkanes to enones is described. The process affords the Michael adducts in good yield and with up to 99% ee for both acyclic and cyclic enones.

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The catalytic conjugate addition of nitroalkanes to α,β-unsaturated ketones is one of the important reactions in organic synthesis. The corresponding products are versatile building blocks for transforming into a variety of new functionalities, such as amino alkanes, amino carbonyls, lactones, and pyrrolidines.[1] Recently, the asymmetric version of this reaction has drawn considerable attention, and a number of organocatalysts have been developed in this regard,[2,3] including proline rubidium salts,[4] proline,[5] *trans*-4,5-methano-L-proline,[6] imidazoline,[7] pyrrolidine tetrazole,[8] and cinchona thioureas.[9] Despite these significant advancements, there is still room for improvement in terms of substrate scope and enantioselectivity. It is expected that chiral organocatalysts enabling to achieve a useful level of enantioselectivity (>90%) are highly desirable with a more broad substrate scope.

Chiral primary amine-promoted reactions have emerged as a powerful means in asymmetric synthesis.[10] These catalysts display better catalytic efficiency than secondary amines in many cases.[11] As part of our ongoing research effort toward development of the primary amine catalyzed enantioselective reactions,[12] we are particularly interested in developing new organocatalytic reactions utilizing primary amine-induced iminium activation, which in some cases are difficult to control with chiral secondary amine catalysis. Herein, we reported a chiral cinchona alkaloid derived primary amine **1i** for a conjugate addition of nitroalkanes to acyclic and cyclic enones with high enantioselectivity.

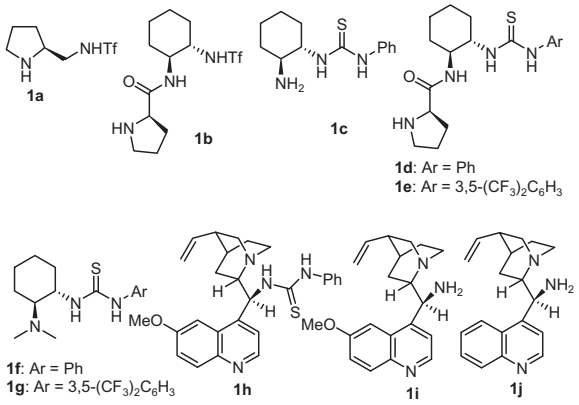

Fig. 1. Structures of the catalysts studied.

Previous studies revealed that both chiral cinchona alkaloid derived catalysts and cyclohexane diamine derived bifunctional catalysts could promote the asymmetric Michael addition reactions.[13] With the precedents in mind, we decided to screen the two series of catalysts (Fig. 1) to probe their capacity in promoting a model asymmetric Michael addition reaction of 4-phenylbut-3-en-2-one (**2a**) with nitromethane (**3a**) (Table 1).

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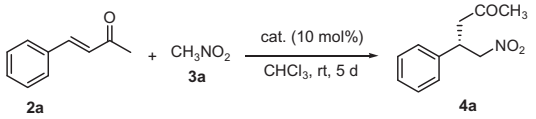
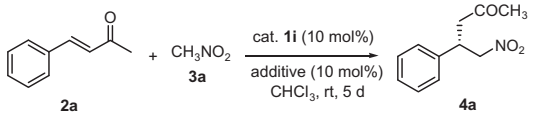
Table 1
Asymmetric Michael addition of (*E*)-4-phenylbut-3-en-2-one (**2a**) to nitromethane (**3a**)[a]



Entry	Cat.	Yield[b] (%)	ee[c] (%)
1	**1a**	32	22
2	**1b**	56	58
3	**1c**	36	93
4	**1d**	72	59
5	**1e**	53	37
6	**1f**	ND[d]	ND[d]
7	**1g**	ND[d]	ND[d]
8	**1h**	ND[d]	ND[d]
9	**1i**	63	97
10	**1j**	36	89

[a] Unless specified, reactions were carried out with **2a** (0.14 mmol) and **3a** (2.1 mmol, 15.0 equiv) in the presence of 10 mol % organocatalyst in 0.2 mL of $CHCl_3$ at rt for 5 d.
[b] Isolated yield.
[c] Determined by HPLC analysis (chirapak AS-H column).
[d] Not determined.

Table 2
Effects of solvents and additives on the asymmetric Michael addition of 4-phenylbut-3-en-2-one (**2a**) to nitromethane (**3a**)[a]

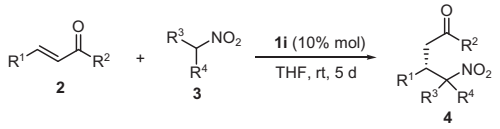


Entry	Solvent	Additive	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	None	35	97
2	$CHCl_3$	None	63	97
3	Toluene	None	35	95
4	Et_2O	None	50	97
5	1,4-Dioxane	None	36	98
6	EtOAc	None	63	97
7	MeOH	None	54	89
8	*i*-PrOH	None	32	92
9	DMSO	None	50	99
10	DMF	None	70	90
11	THF	None	67	99
12	THF	$PhCO_2H$	7	98
13	THF	*p*-TSA	11	92
14	THF	AcOH	7	97
15	THF	CF_3CO_2H	<5	ND[d]
16	THF	Et_3N	35	93
17	THF	AcONa	32	93

[a] Reaction conditions: reactions were carried out with **2a** (0.14 mmol) and **3a** (2.1 mmol, 15.0 equiv) in the presence of 10 mol % cat **1i** and without or with 10 mol % additive at rt for 5 d.
[b] Isolated yield.
[c] Determined by HPLC analysis (chirapak AS-H column).
[d] Not determined.

The initial reactions were performed by using 10 mol % of a catalyst (Fig. 1) at room temperature (rt) in chloroform. Examination of the results from the survey revealed that their catalytic activities varied significantly (Table 1). For example, the process promoted by pyrrolidine trifluoromethane sulfonamide **1a** proceeded with both low yield (32%) and poor enantioselectivity (22%) (entry 1).[14] 1,2-Cyclohexanediamine derivative **1c**[12b] and cinchonine derivative **1j** gave high enantioselectivity (93% and 89%, respectively) but low yields (36% and 36%, respectively) (entries 3 and 10). *N*,*N*-Dimethyl-1,2-cyclohexanediamine thioureas **1f** and **1g**,[13b] and quinine thiourea **1h**[9a] were not effective in this process

Table 3
Asymmetric Michael addition of nitroalkanes **3** to enones **2** catalyzed by **1i**[a]



Entry	R^1	R^2	R^3	R^4	4	Yield[b] (%)	ee[c] (%) (dr)[f]
1	Ph	Me	H	H	**4a**	67	99
2	*p*-$CH_3OC_6H_4$	Me	H	H	**4b**	63	99
3	*o*-$CH_3OC_6H_4$	Me	H	H	**4c**	67	95
4	3,4-$(CH_3)_2OC_6H_3$	Me	H	H	**4d**	63	99
5	*p*-$N(CH_3)_2C_6H_4$	Me	H	H	**4e**	61	99
6	*p*-FC_6H_4	Me	H	H	**4f**	78	95
7	*p*-BrC_6H_4	Me	H	H	**4g**	80	95
8	*p*-$NO_2C_6H_4$	Me	H	H	**4h**	81	95
9	*m*-$NO_2C_6H_4$	Me	H	H	**4i**	62	95
10	*o*-$NO_2C_6H_4$	Me	H	H	**4j**	67	98
11	2-Furanyl	Me	H	H	**4k**	72	92
12[d]	$(CH_2)_4$		H	H	**4l**	53	96
13[d]	*n*-$Me(CH_2)_4$	Me	H	H	**4m**	12	94
14[d]	Ph	Me	Me	Me	**4n**	49	91
15[d]	*p*-BrC_6H_4	Me	Me	Me	**4o**	55	92
16[d]	*o*-$CH_3OC_6H_4$	Me	Me	Me	**4p**	82	94
17[d]	*o*-$NO_2C_6H_4$	Me	Me	Me	**4q**	53	94
18[d]	2-Furanyl	Me	Me	Me	**4r**	51	88
19[d]	$(CH_2)_4$		Me	Me	**4s**	65	93
20	Ph	Me	$(CH_2)_4$		**4t**	45[h]	92
21[d]	Ph	Me	Me	H	**4u**	78[e]	94[g] (1/1)
22[d]	*p*-$CH_3OC_6H_4$	Me	Me	H	**4v**	40[e]	94[g] (1.6/1)
23[d]	$(CH_2)_4$		Me	H	**4w**	77[e]	96[g] (2/1)

[a] Reaction conditions: unless specified, reactions were carried out with **2a** (0.14 mmol) and **3a** (2.1 mmol, 15.0 equiv) in the presence of 10 mol % of cat **1i** at rt for 5 d.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (chiralpak AS-H or AD-H).
[d] Reactions were carried out with **2a** (0.3 mmol) and nitroalkane (15.0 equiv) in the presence of 10 mol % catalyst **1i** in 0.4 mL of THF at rt for 5 d.
[e] Total yield for both diastereomers.
[f] dr determined by ^1H NMR.
[g] ee for both diasteroisomers.
[h] Nitrocyclohexane with 2.5 equiv used.

(entries 6–8). No reactions were observed in these cases. Moreover, the new catalysts **1b**, **1d,** and **1e** we used did not give rise to encouraging outcomes either. The most promising results came from studies with quinine amine **1i**.[15] Notably, good yield (63%) and high level of enantiocontrol (97% ee, entry 10) were achieved. Therefore, **1i** was chosen for further optimization of reaction conditions.

Next, other reaction conditions such as reaction media and additives were investigated. As shown in Table 2, reaction solvents had a significant effect on the Michael addition reaction yield but limited impact on enantioselectivity. However, there is no clear relationship between the reaction efficacy and media property such as polarity (entries 1–11). Among solvents probed, reaction in THF gave a good yield (67%) and the highest enantioselectivity (99% ee) (entry 11). It appeared that additives were not beneficial (entries 12–17). They inhibited the reaction and led to dropping the yields dramatically, though excellent enantioselectivity was maintained.

With the optimized reaction conditions in hand, the scope of the addition of nitroalkanes **3** to enones **2** was explored. The results were summarized in Table 3. Notably, cinchona alkaloid derived primary amine **1i** catalyzed the conjugate addition of nitromethane to enones and afforded the desired products with excellent enantioselectivities (92–99% ee, entries 1–13), but the yields were varied. In general, those enones bearing electron-withdrawing groups (such as F, Br, and NO_2) at *o*-position of the

aromatic ring afforded the desired products with high isolated yields (78–81%) (entries 6–8). Heterocyclic furyl enone also performed well to give the desired product in 72% yield and 92% ee (entry 11). Moreover, the reaction could also be extended to the cyclic substrates with 53% isolated yield and excellent enantioselectivity (96% ee) (entry 12). However, a sharp decrease in isolated yield (12%) was observed for the aliphatic substrate, though a 94% ee was obtained (entry 13). The low yield is due to the slow conversion and a significant amount of starting materials still remained.

Moreover, structural variation of nitroalkanes was found to be tolerated (entries 14–23). Excellent enantioselectivity and moderate to high yield were also obtained when the nucleophilic reagents were expanded to the steric hindrance compounds, such as nitrocyclopentane, 2-nitro-propane, and nitroethane (entries 14–23). It is noteworthy that when nitroethane was used, two diastereomers were produced in high enantioselectivity, but poor dr (entries 21–23).

In summary, a cinchona alkaloid derived primary amine **1i** was reported as an efficient tool for the asymmetric conjugate addition reaction of nitroalkanes to enones. This promoter catalyzed the conjugate addition with a broad substrate scope worked for both acyclic and cyclic enones, and afforded the adducts in good yields and with 91–99% ee. Therefore, the study has expanded the domain of organocatalyzed enantioselective conjugate addition process of nitroalkanes to enones at a useful level.

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Supplementary data

Supplementary data (the syntheses, ^{1}H and ^{13}C NMR copies of new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.019.

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