An efficient enantioselective method for asymmetric Michael addition of nitroalkanes to α , β -unsaturated aldehydes[†]

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The addition of nitroalkanes to α , β -unsaturated aldehydes under the catalysis of (S)-2-(diphenyl(trimethylsilyloxy)methyl)pyrrolidine and lithium acetate as additive afforded γ -nitroaldehydes in good yield and up to 97% ee.

Asymmetric organocatalysis is one of the most rapidly growing and fruitful research areas in synthetic organic chemistry in the past few years.^{1,2} Nowadays, the term asymmetric organocatalysis covers a wide range of organic processes and methodologies, providing efficient and environmentally friendly access to enantiomerically pure compounds including many drugs and bioactive natural products.³

The catalytic asymmetric Michael addition is one of the most thoroughly studied chiral bond-forming processes. Recently, the field of asymmetric organocatalytic Michael addition employing chiral organocatalysts has received widespread attention.⁴ Among these reactions, the conjugate additions of nitroalkanes to α , β -unsaturated carbonyl compounds are especially useful, because their products are precursors to a variety of highly functionalized structures, such as aminocarbonyl compounds, aminoalkanes, and pyrrolidines.⁵ Several organocatalytic methods via an iminium mechanism have been developed for conjugate additions of nitroalkanes to enones,⁶ using L-proline and its derivatives, chiral imidazoline or chiral diamine-dipeptides as catalysts. However, the protocol for achieving the Michael addition of nitroalkanes to α . β -unsaturated aldehydes is still somewhat cumbersome.⁷ The major complication may have been the fact that α,β -unsaturated aldehydes readily undergo 1,2-addition with nitroalkanes under the reaction conditions. Herein, we would like to report a highly efficient and enantioselective method for carrying out this kind of Michael addition based on Lewis base-Brønsted base bifunctional catalysis.

The Michael addition of cinnamaldehyde (1a) and nitromethane (2a) under various conditions was first investigated and representative results are presented in Table 1.

The Michael addition of cinnamaldehyde (1a) and nitromethane (2a) gave poor results under ordinary iminium cata-

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lytic conditions using 5 mol% of 2-(diphenyl(trimethylsilyloxy)methyl)pyrrolidine (4)^{8,9} as the organocatalyst. For example, the reaction in methanol or dichloromethane proceeded to only 14% or 5% conversion after 12 h. A mixed solvent of CH₂Cl₂–MeOH (v/v 9 : 1) improved the conversion slightly to 25% (entries 1–3). A remarkable enhancement was achieved when an additive base, lithium acetate (30 mol%), was introduced to the reaction system,¹⁰ which supposedly enhances the nucleophilicity of deprotonated nitromethane and accelerates the formation of the iminium ion. Under these conditions, the reaction proceeded to full conversion within 12 h in a mixed solvent of CH₂Cl₂–MeOH (9 : 1) with 95% ee. The reactions in methanol or dichloromethane alone also

Table 1Reaction conditions optimization for the enantioselectiveMichael addition of cinnamaldehyde (1a) and nitromethane (2a)

Ph	0 + 1a	—NO ₂	Ph Ph Ph Additive F	0 	2
Entry	4 ^{<i>a</i>} (%)	Additive base	Solvent ^b	Conv. ^{<i>c</i>} (%)	ee^{d} (%)
1	5	None	MeOH	14(12 h)	nd
2	5	None	CH_2Cl_2	5(12 h)	nd
3	5	None	DCM: MeOH 9:1	25(12 h)	94
4	5	LiOAc	MeOH	76(12 h)	94
5	5	LiOAc	CH_2Cl_2	48(12 h)	95
6	5	LiOAc	DCM : MeOH 9 : 1	>99(12 h)	95
7	5	LiOAc	Toluene	17(12 h)	nd
8	5	LiOAc	EtOAc	11(12 h)	nd
9	5	LiOAc	Et ₂ O	17(12 h)	nd
10	5	PhCO ₂ Li	DCM: MeOH 9:1	>99(12 h)	93
11	5	4-FPhCO ₂ Li	DCM: MeOH 9:1	>99(12 h)	95
12	5	4-MeOPhCO ₂ Li	DCM: MeOH 9:1	>99(12 h)	94
13	5	2-NO ₂ PhCO ₂ Li	DCM: MeOH 9:1	>99(12 h)	93
14	5	4-NO2PhCO2Li	DCM: MeOH 9:1	>99(12 h)	93
15	5	LiOH	DCM: MeOH 9:1	91(12 h)	60
16	5	Et ₃ N	DCM: MeOH 9:1	17(12 h)	nd
17	5	DABCO	DCM: MeOH 9:1	47(12 h)	93
18	5	Et ₃ N–AcOH	DCM: MeOH 9:1	95(12 h)	93
19	5	DABCO-AcOH	DCM: MeOH 9:1	96(12 h)	93
20	2	LiOAc	DCM: MeOH 9:1	90(40 h)	94
21	2	LiOAc ^e	DCM: MeOH 1:9	>99(40 h)	95
22	2	LiOAc ^e	MeOH	92(40 h)	94
23	1	LiOAc ^e	DCM: MeOH 1:9	88(72 h)	95

^{*a*} Reaction conditions: cinnamaldehyde (1.0 mmol), nitromethane (3.0 mmol), **4** and additive (0.3 mmol) in solvent (2.0 mL) under room temperature. ^{*b*} The solvent ratio refers to v : v. ^{*c*} The conversion was determined by GC with area percentage. ^{*d*} The enantiomeric excess was determined *via* HPLC using a Chiralpak[®] AD-H column. ^{*e*} Lithium acetate (0.1 mmol) was used.

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afforded conversions of 76% and 48%, and ee's of 94% and 95%, respectively (entries 4–6). These encouraging results indicated that Lewis base–Brønsted base bifunctional catalysis might indeed be operating for this particular type of Michael addition.

A series of other solvents were then investigated, but solvents other than MeOH or CH_2Cl_2 , such as toluene, ethyl acetate or ether, resulted in low conversions (entries 7–9).

The effects of other additives were also investigated. It was found that a series of lithium benzoate derivatives were also suitable for obtaining satisfactory conversion and enantioselectivity, and all of these salts gave results similar to that with lithium acetate (entries 10–14). The addition of a strong base such as lithium hydroxide afforded low enantioselectivity (60% ee) due to the increase in background racemization (entry 15). It is worthy of note that using an organic amine as an additive base did not efficiently improve the reaction outcome. For example, the reaction using triethylamine or DABCO resulted in respectively only 17% or 47% conversion after 12 h (entries 16–17).¹¹ Interestingly, their acetate salts gave satisfying results with >95% conversion. This might be because of the existence of countercations in these salts which favor the formation of the iminium ion (entries 18–19).

More experiments showed that the proportion of the mixed CH_2Cl_2 -MeOH solvent also affected the reaction performance. An increase in the content of methanol led to increased activity. For example, the reaction in 9 : 1 CH_2Cl_2 -MeOH resulted in 90% conversion and 94% ee after 40 h using 2 mol% of 4 and 30 mol% of lithium acetate, while in 1 : 9 CH_2Cl_2 -MeOH, full conversion and 95% ee were obtained within the same time frame even with 2 mol% of 4 and 10 mol% of lithium acetate (entries 20–21). However, the presence of dichloromethane was necessary because the reaction in pure methanol was incomplete (entry 22). Further reduction in catalyst loading to 1 mol% of catalyst 4 and 10 mol% of lithium acetate resulted in 88% conversion after 72 h (entry 23).

To demonstrate the generality of this catalytic Michael addition, the additions of nitromethane to various α , β -unsaturated aldehydes were then evaluated and representative examples are shown in Table 2.‡

The addition of nitromethane to aromatic α , β -unsaturated aldehydes afforded good results. Cinnamaldehyde derivates with electron-withdrawing or donating group on the *ortho-*, *meta-*, or *para-*position of the benzene ring all gave full conversion and good to excellent enantioselectivity ranging from 90% to 97%. (entries 1–10). An aromatic heterocyclic α , β -unsaturated aldehyde such as 3-(furan-2-yl)acrylaldehyde also resulted in 92% ee using 10 mol% of catalyst **4** and 10 mol% of lithium acetate (entry 11).

The addition of nitromethane to aliphatic α , β -unsaturated aldehydes also exhibited promising results. A series of alkenals, such as crotonaldehyde, pentenal, hexenal or decenal, all achieved full conversion and good to excellent enantioselectivity ranging from 81% to 94% ee using 2–10 mol% of catalyst **4** and 10 mol% of lithium acetate (entries 12–16). Aliphatic α , β -unsaturated aldehydes with a functional group such as 2-*trans*-6-*cis*-nonadienal also behaved satisfactorily (entry 17).

R 1	+NO ₂ 2a	4 (2-10 r LiOAc (10 DCM:MeO	nol%) D mol%) H=1:9, r.t.	0 R NO ₂ 3	
Entry	R ^a	4 (%)	Time/h	$\operatorname{Yield}^{b}(\%)$	ee^{c} (%)
1	Ph	2	40	80	95
2	2-MeOC ₆ H ₄	2	48	63	97
3	$2-ClC_6H_4$	2	84	61	95
4	$2-NO_2C_6H_4^d$	5	72	73	92
5	$3-ClC_6H_4$	2	33	72	93
6	$4-FC_6H_4$	2	96	66	96
7	4-MeC ₆ H ₄	5	96	67	93
8	4-BrC ₆ H ₄	5	48	65	92
9	$4-ClC_6H_4$	10	60	61	90
10	4-MeOC ₆ H ₄	10	60	67	92
11	2-Furanyl	10	40	74	92
12	Me	2	96	67	81
13	Et	5	96	74	88
14	<i>n</i> -Pr	5	96	76	90
15	<i>n</i> -Bu	5	72	65	92
16	n-Hept	5	100	60	94
17	Hex-3-en-1-yl	5	72	68	93

^{*a*} Reaction conditions: α,β-unsaturated aldehyde (1.0 mmol), nitromethane (3.0 mmol), **4** and lithium acetate (0.1 mmol) in CH₂Cl₂ : MeOH (1 : 9 v/v, 2.0 mL) at room temperature. ^{*b*} Isolated yield. ^{*c*} The enantiomeric excess was detected using GC or HPLC. For details, see ESI†. ^{*d*} In 9 : 1 CH₂Cl₂ : MeOH (v/v).

This catalytic method was also proven suitable for higher nitroalkanes. For example, Michael addition of nitroethane to cinnamaldehyde progressed to full conversion with 2 mol% of **4** and 10 mol% of lithium acetate within 72 h. The reaction gave two diastereoisomers with a ratio about 48 : 52 and respective ee's of 95% and 96% (Scheme 1).

A very important synthetic application of this kind of Michael addition is the transformation of the addition product to an optically active γ -amino acid. For example, the addition product **3i**', prepared from 4-chlorocinnamaldehyde and nitromethane catalyzed by (*R*)-**4**, could be conveniently converted to the corresponding γ -nitro acid **5i**'.¹² The nitro group of **5i**' was easily reduced to an amino group with the usual hydrogenation process¹³ to afford the optically active (*R*)-baclofen hydrochloride salt, which is an important GABA_B receptor agonist (Scheme 2).¹⁴

In summary, we have developed a new Lewis base–Brønsted base bifunctional catalysis for the asymmetric catalytic Michael addition of nitroalkanes to α , β -unsaturated aldehydes with high efficiency and enantioselectivity, even with a



Scheme 1 Enantioselective Michael addition of cinnamaldehyde and nitroethane.



Scheme 2 Synthetic route for the preparation of the optically active (R)-baclofen hydrochloride salt.

1–2 mol% loading level for the catalyst. The results indicated that this methodology might be of practical and general utility for the synthetic community. Further investigations of the mechanism of this methodology are currently ongoing and results from which will be presented in due course.

Notes and references

‡ General procedure for the Michael addition of nitroalkanes to α,βunsaturated aldehydes: to a mixed solution of 1 : 9 CH₂Cl₂-MeOH (v/v, 2.0 mL) was added α,β-unsaturated aldehyde 1 (1.0 mmol), nitroalkane 2 (3.0 mmol), catalyst 4 (6.5 mg, 0.02 mmol) and lithium acetate (6.6 mg, 0.10 mmol). The reaction mixture was stirred at room temperature for the time indicated in Table 2 and then the solvent was removed under vacuum. Water (5.0 mL) was added to the residue and it was extracted with CH₂Cl₂ three times. The combined organic phases were dried over anhydrous Na₂SO₄, filtered and evaporated under vacuum. The residue was purified by column chromatography on silica gel (350–400 mesh) to yield the desired addition product.

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