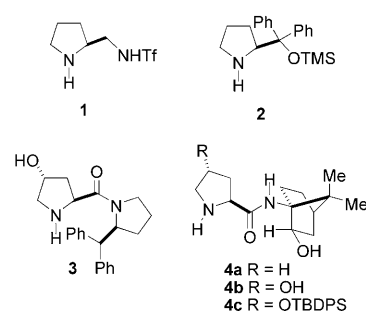


Novel Prolinamide–Camphor-Containing Organocatalysts for Direct Asymmetric Michael Addition of Unmodified Aldehydes to Nitroalkenes

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The Michael reaction is generally regarded as one of the most efficient, atom-economical and powerful carbon–carbon bond-forming reactions in organic chemistry.^[1] The development of organocatalytic asymmetric Michael reactions has been a significant research focus for several years.^[2] The direct asymmetric Michael addition of carbonyl compounds with nitroalkenes to produce enantiomerically enriched nitroalkanes has been described.^[3,4] Among these reactions, the Michael addition of unmodified aldehydes to nitroalkenes is of particular interest because of the valuable synthetic intermediates that are generated.^[4] Betancort and Barbas originally reported the organocatalytic asymmetric Michael addition of unmodified aldehydes to nitroalkenes with moderate to good enantioselectivities.^[4a] Recently 3,3'-bimorpholine derivatives,^[4b] a chiral primary amine/thiourea catalyst^[4c] and L-prolinol^[4d] organocatalysts have been developed for the Michael addition of aldehydes to nitroolefins. Highly diastereo- and enantioselective conjugate additions that involve aldehydes were independently reported by the research groups of Wang,^[4e] Hayashi,^[4f] and Palomo^[4g] using pyrrolidine sulfonamide (**1**), diphenylprolinol silyl ether (**2**) and *trans*-4-hydroxyprolylamide (**3**) respectively. However, some of these reactions required a large excess of donor source (up to 10 equiv of aldehyde) and high catalyst loadings (between 10 and 20 mol%). Despite the excellent results achieved from previous studies, the development of an efficient organocatalyst for direct asymmetric Michael addition of aldehydes to various aryl- and alkyl nitroalkenes with low catalyst loading remains challenging in asymmetric synthesis.

The metal-free, small, privileged organic molecules that catalyze enantioselective reactions have attracted much at-

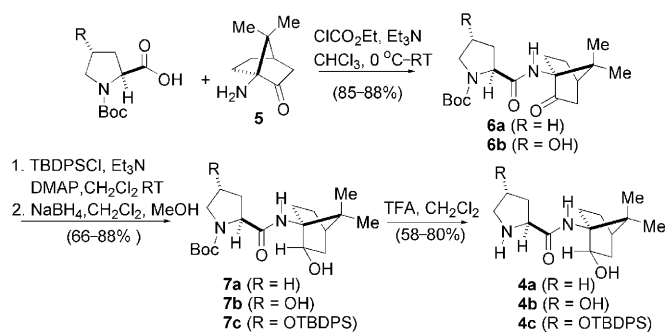


tention in recent years. Organocatalysts are usually highly efficient and selective, stable under aerobic and aqueous reaction conditions, nontoxic, environmentally friendly, and thus highly desirable as catalysts/catalytic systems.^[5,6] In light of this, we have recently developed a series of camphor-based pyrrolidinyl organocatalysts that have proven their efficacy as catalysts in asymmetric synthesis.^[7] In continuation of our research interest in organocatalysis, we designed and synthesized a new prolinamide–camphor organocatalysts and have shown it to be efficient catalysts for direct asymmetric Michael reaction. Herein, we wish to report an excellent diastereo- and enantioselective direct Michael addition of aldehydes with nitroalkenes catalyzed by bifunctional organocatalysts **4a–c**. The desired Michael products were obtained with high chemical yields (up to 94%) and excellent stereoselectivities (up to 99:1 d.r. and >99% *ee*) with 5 mol% of organocatalyst **4b**.

In asymmetric organocatalysis there is a strong demand for the design and synthesis of highly stereoselective, readily accessible, and tunable catalysts. The synthesis of novel prolinamide–camphor organocatalysts **4a–c** begins with the Boc-protected L-proline and *trans*-4-hydroxy L-proline. Treatment of Boc L-proline and *trans*-4-hydroxy L-proline with 1-amino-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**5**)^[8] under standard coupling conditions (ethyl chloroformate and Et₃N in CHCl₃) to give the corresponding amides (**6a** and **6b**) in 85 and 88% isolated yields, respectively (Scheme 1). Sodium borohydride reduction of **6a** and **6b** to

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Scheme 1. Synthesis of prolinamide–camphor organocatalysts **4a–c**.

provide the corresponding *exo*-alcohols **7a** and **7b** as a single diastereomer, which was treated with trifluoroacetic acid (TFA) in CH₂Cl₂ to generate the desired organocatalysts **4a** and **4b** without incident.

On the other hand, the *trans*-4-hydroxy group in **6b** (R = OH) was protected as its TBDPS ether derivative, and subsequent NaBH₄ reduction to give the corresponding *exo*-alcohol **7c**. The *exo*-alcohol (**7c**) was treated with TFA in CH₂Cl₂ to yield organocatalyst **4c**. The synthetic route is quite straightforward and can be easily scaled up to gram quantities (2.0 g). The structures of organocatalysts **4a–c** were fully characterized by IR, ¹H, and ¹³C NMR spectroscopy and HRMS, and the absolute stereochemistry of organocatalysts **4a** and **4b** were further confirmed by single-crystal X-ray analyses (see the Supporting Information).^[9]

The Michael reaction of propionaldehyde and *trans*-β-nitrostyrene was selected as model substrates in the presence of catalytic quantities of organocatalysts **4a–c**. We initially focused on solvent effects in the Michael reactions at ambient temperature. Organocatalyst **4a** was first examined and led to high reactivities and good stereoselectivities in CHCl₃ (Table 1, entry 1). High chemical yield (94%) and diastereoselectivity (93:7), but poor enantioselectivity (36% *ee*) was observed in MeOH catalyzed by **4a** (Table 1, entry 2). A modest result was achieved when the reaction was performed in hexanes (Table 1, entry 3). Substantial improvement in stereoselectivity (91% *ee*) was observed when the reaction was carried out in CHCl₃ and catalyzed by **4b** at ambient temperature (Table 1, entry 4). Although the reactivity was improved, unsatisfactory stereoselectivity was observed when the reaction was carried out with very polar protic solvents (Table 1, entry 5). The desired Michael product **8a** was obtained with high chemical yields and moderate enantioselectivities in hexanes and toluene (Table 1, entries 6 and 7). The progress of the reaction was fast under solvent-free conditions and good diastereo- and enantioselectivities were observed (Table 1, entry 8). When we performed the reaction in brine using organocatalyst **4b** to generate **8a**, high chemical yield (92%) was achieved with high *syn*-diastereoselectivity, but only 70% *ee* (Table 1, entry 9). Reasonably, good results were achieved when H₂O was used as the reaction medium (Table 1, entry 10). Reactivity was dramatically improved and high levels of stereoselectivity evolved

Table 1. Optimization of enantioselective Michael addition of propionaldehyde to *trans*-β-nitrostyrene catalyzed by **4a–c**.^[a]

4a–c (mol %)	solvent or solvent system	<i>T</i> [°C]	<i>t</i> [h]	Yield ^[b] [%]	d.r. ^[c]	<i>ee</i> ^[d] [%]
1 4a (20)	CHCl ₃	RT	48	85	78:22	80
2 4a (20)	MeOH	RT	36	94	93:7	36
3 4a (20)	hexanes	RT	48	76	61:39	76
4 4b (20)	CHCl ₃	RT	24	89	90:10	91
5 4b (20)	MeOH	RT	12	97	92:8	66
6 4b (20)	hexanes	RT	24	92	77:23	69
7 4b (20)	toluene	RT	24	94	87:13	89
8 4b (20)	neat	RT	12	94	88:12	71
9 4b (20)	brine	RT	12	92	92:8	70
10 4b (20)	water	RT	24	89	73:27	74
11 4a (20)	CHCl ₃ /MeOH (9:1)	RT	36	87	76:24	76
12 4b (20)	CHCl ₃ /MeOH (9:1)	RT	12	92	91:9	90
13 4b (10)	CHCl ₃ /MeOH (9:1)	RT	15	92	93:7	92
14 4b (5)	CHCl ₃ /MeOH (9:1)	RT	24	90	94:6	92
15 4b (2)	CHCl ₃ /MeOH (9:1)	RT	48	78	95:5	90
16 4c (20)	CHCl ₃ /MeOH (9:1)	RT	72	80	85:15	77
17 4b (10)	CHCl ₃ /MeOH (9:1)	0	48	92	95:5	94
18 4b (5)	CHCl ₃ /MeOH (9:1)	0	96	85	95:5	93
19 4b (10)	CHCl ₃ /MeOH (9:1)	–20	72	30	96:4	90

[a] Unless otherwise specified, all reactions were carried out using propionaldehyde (0.6 mmol), *trans*-β-nitrostyrene (0.2 mmol) and 5–20 mol % catalysts **4a–c** in the solvent (0.2 mL) indicated. [b] Isolated yield. [c] Determined by ¹H NMR and HPLC analysis. [d] *ee* of the *syn* product was determined by chiral HPLC analysis (see Supporting Information).

when 20 mol % of catalysts **4b** was used in solvent system CHCl₃/MeOH (9:1) (Table 1, entry 12). Lowering the concentration of **4b** to 10 mol % resulted in slightly improved selectivity (Table 1, entry 13). To our surprise, the 5 mol % catalyst loading also efficiently catalysed the Michael reaction in a variety of solvent systems, such as CHCl₃/MeOH, CHCl₃/IPA, CHCl₃/EtOH, and CH₂Cl₂/MeOH.^[10] However, the best results were achieved in CHCl₃/MeOH (9:1) to afford the desired product with excellent stereoselectivity (*syn/anti* ratio 94:6 and 92% *ee*; Table 1, entry 14). Although the stereoselectivity retained, the reactivity dropped significantly when 2 mol % catalyst was used (Table 1, entry 15). Interestingly, the reactivity and stereoselectivity significantly decreased when we performed the reaction with 20 mol % of organocatalyst **4c** (Table 1, entry 16). The diastereo- and enantioselectivities were improved when the reaction was carried out at 0 °C with 10 mol % of organocatalyst **4b** (Table 1, entry 17). The rate of the reaction decreased in the presence of 5 mol % catalyst **4b** at 0 °C with the same level of stereoselectivity (Table 1, entry 18). The reactivity dropped significantly when the reaction was carried out at –20 °C with retention of stereoselectivity (Table 1, entry 19). As indicated from Table 1, both catalysts **4a** and **4c** performed poorly in the reaction between propionaldehyde and *trans*-β-nitrostyrene (Table 1, entries 11 and 16 vs. entry 14), indicating that the hydroxyl group in **4b** must play some role in determining the stereochemical

outcomes of the reaction. Similar phenomena have been previously observed.^[4g]

Encouraged by these results, we further optimized catalysis conditions in the presence of 5 mol% of various acid additives. No significant improvement was achieved in either reactivity or selectivity in the presence of various organic acids (benzoic acid, acetic acid, 3,5-dinitrobenzoic acid, and TFA). The protonation of the amine catalyst may subsequently hinder the enamine formation. To verify this, organocatalyst **4b** was treated with TFA in CHCl₃. Upon slow evaporation of CHCl₃, it was clearly demonstrated that organocatalyst **4b** had crystallized as a TFA salt. The chemical structure of this salt was established by single-crystal data analysis (see Supporting Information).^[9] The absolute configuration of the resulted adduct was determined by comparison of the value of the optical rotation with that of previously described^[4a,c-g,m] and was found to be (*R,S*). It is worth mentioning that three equivalents of propionaldehyde was used as a donor for β-nitrostyrene in this catalytical process.

With the optimal reaction conditions realized, we further proceeded to examine a variety of nitroalkenes reacting with propionaldehyde to establish the general utility of this asymmetric transformation (Table 2). All reactions were performed in a CHCl₃/MeOH (9:1) solvent system in the presence of 5 to 10 mol% of catalyst **4b** either at ambient temperature or at 0°C. Various aromatic substituted nitroalkenes reacted well with propionaldehyde donor to give the desired Michael products (**8a–i**) with 75–92% yields and high to excellent diastereo- and enantioselectivities (Table 2, entries 1–9). In the case of heteroaromatic nitroalkenes, the corresponding Michael adducts (**8j** and **8k**) were obtained with high to excellent diastereo- and enantioselectivities (Table 2, entries 10 and 11). The aliphatic nitroalkene was also an excellent Michael acceptor for this catalytic system. Treatment of (4-nitro-but-3-enyl)benzene and 4-methyl-1-nitro-pent-1-ene with propanal under the optimum reaction conditions to give the desired products (**8l** and **8m**) with excellent stereoselectivities (Table 2, entries 12 and 13). In addition to propionaldehyde, other linear aldehydes, such as butyraldehyde and valeraldehyde, or branched aldehydes, such as isovaleraldehyde, can be employed successfully as the Michael donors with *trans*-β-nitrostyrene to give the Michael adducts (**8n–p**; Table 3, entries 1–3). These donors were then used to react with both electron-rich and electron-deficient nitroalkenes. To our satisfaction, these reactions proceeded smoothly and the desired Michael products (**8q–v**) were obtained with high levels of chemical yields (80–90%) and stereoselectivities (Table 3, entries 4–9). The heteroaromatic Michael acceptor reacted smoothly with isovaleraldehyde to provide the **8w** with reasonable good chemical yield and stereoselectivity (Table 3, entry 10). Interestingly, the alkyl-substituted nitroalkenes, such as, (4-nitro-but-3-enyl)benzene and 4-methyl-1-nitro-pent-1-ene, are also excellent Michael acceptors to give the desired Michael products (**8x** and **8y**) in moderate yields with high stereoselectivities (Table 3, entries 11 and 12). Unfortunately, the acetaldehyde reacts sluggishly with *trans*-β-nitrostyrene

Table 2. Enantioselective Michael addition of propionaldehyde to *trans*-β-nitroalkene catalyzed by **4b**.^[a]

Product	Cat. 4b [mol %]	<i>T</i> [°C]	<i>t</i> [d]	Yield ^[b] [%]	d.r. ^[c]	<i>ee</i> ^[d] [%]
1	5	RT	1.0	90	94:6	92
	10	0	2.0	92	95:5	94
2	5	RT	2.0	84	96:4	94
	10	0	3.0	88	98:2	96
3	5	RT	1.0	92	93:7	90
	10	0	1.5	89	95:5	89
4	5	RT	2.0	89	95:5	94
	10	0	2.5	88	95:5	96
5	5	RT	1.5	83	83:17	90
	10	0	2.5	88	91:9	97
6	5	RT	2.5	89	93:7	90
	10	0	5.0	83	95:5	96
7	5	RT	1.5	80	93:7	91
	10	0	2.5	75	97:3	94
8	5	RT	2.0	89	92:8	94
	10	0	4.0	84	98:2	96
9	5	RT	2.0	82	93:7	94
	10	0	3.0	76	97:3	96
10	5	RT	2.0	80	97:3	98
	10	0	4.0	74	98:2	>99
11	5	RT	2.0	89	90:10	94
	10	0	3.0	94	91:9	97
12	10	0	4.0	64	99:1	95
13	10	0	4.0	46	89:11	99

[a] Unless otherwise specified, all reactions were carried out using propionaldehyde (0.6 mmol), nitroalkenes (0.2 mmol) and 5 or 10 mol% catalyst **4b** in CHCl₃/MeOH. [b] Isolated yield. [c] *syn/anti* ratio was determined by ¹H NMR and HPLC analysis. [d] *ee* of the *syn* product was determined by chiral HPLC analysis (see: Supporting Information).

in the presence of organocatalyst **4b** under the optimum reaction condition. Only trace amount of desired Michael product formation was observed by the crude ¹H NMR analysis.

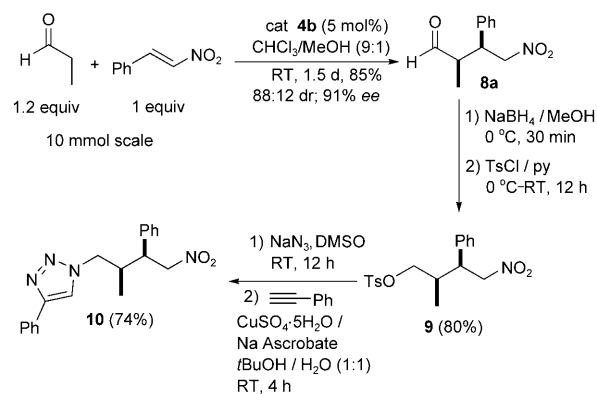
The utility of this approach is illustrated in the reaction of propionaldehyde with β-nitrostyrene on a 10 mmol scale, which produced **8a** with an 85% isolated yield and high level of diastereo- and enantioselectivity (*syn/anti* 88:12;

Table 3. Enantioselective Michael addition of unmodified aldehydes to nitroalkenes catalyzed by **4b**.^[a]

Product	Cat. 4b [mol %]	<i>T</i> [°C]	<i>t</i> [d]	Yield ^[b] [%]	d.r. ^[c]	<i>ee</i> ^[d] [%]
	10	0	4.0	86	98:2	96
	10	0	5.0	78	99:1	91
	10	RT	3.5	85	91:9	84
	10	0	4.0	84	97:3	93
	10	0	3.5	82	93:7	93
	10	0	5.0	88	98:2	92
	10	RT	3.0	90	95:5	90
	10	0	5.0	80	99:1	89
	10	0	5.0	84	95:5	87
	10	RT	5.0	76	93:7	79
	10	0	5.0	60	95:5	96
	10	0	5.0	42	99:1	89

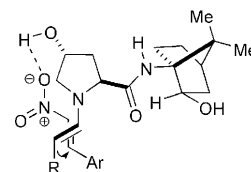
[a] Unless otherwise specified, all reactions were carried out using various aldehydes (0.6 mmol), nitroalkenes (0.2 mmol) and 10 mol% catalyst **4b** in CHCl₃/MeOH. [b] Isolated yield. [c] *syn/anti* ratio was determined by ¹H NMR and HPLC analysis. [d] *ee* of the *syn* product was determined by chiral HPLC analysis (see: Supporting Information).

91% *ee*; Scheme 2). As shown in Scheme 2, the Michael product **8a** was converted into corresponding δ -nitro alcohol followed by tosylation with TsCl in the presence of pyridine. The tosylated product **9** was treated with sodium azide and subsequent “click” chemistry^[11] in the presence copper-catalyzed cycloaddition to afford enantiomerically enriched triazole derivative (**10**). The stereochemistry of the 1,4-triazole derivative was retained during the reaction process. The triazole derivatives are important building blocks in medicinal

Scheme 2. Synthesis of triazole derivative (**10**) from Michael adduct **8a**.

chemistry and find various applications in both material science and pharmaceutical research.^[12]

Though further studies are needed to elucidate the mechanism of the Michael addition, the reaction is believed to proceed through an enamine process and the stereochemical induction can be explained as follows. The bifunctional organocatalyst (**4b**) pyrrolidine moiety reacts with the unmodified aldehyde to form nucleophilic enamine and the 4-hydroxy functionality activated the nitro group through hydrogen bonding to organize a favourable transition model (Figure 1).^[4f,g] The neighboring rigid bicyclic camphor structural scaffold can serve as an efficient stereocontrolling element. Approach of the nitro olefin from the less-hindered *si* face of the enamine would produce the observed stereochemistry.

Figure 1. Proposed transition-state model for the Michael reaction catalyzed by **4b**.

In summary, new prolinamide-derived organocatalysts **4a–c** that contain a structural rigid bicyclic camphor scaffold were used for the first time in organocatalysis. We have demonstrated a practical application of organocatalysts **4a–c** in the Michael addition of aldehydes with nitroalkenes to generate corresponding products with high chemical yields and high to excellent levels of diastereo- and enantioselectivities. This represents an attractive alternative method of organocatalytic asymmetric Michael addition. Further studies of the catalysts used in organocatalysis are currently underway.

Experimental Section

General procedure for the asymmetric Michael reaction: The aldehyde (0.6 mmol) was added to a mixture of catalyst **4b** (2.7 mg, 0.01 mmol) and the corresponding nitroalkene (0.2 mmol) in CHCl₃/MeOH (9:1, 0.2 mL). The reaction mixture was stirred at either ambient temperature or 0°C for the requisite times as indicated in Tables 1–3. After the nitroalkene was consumed, as seen by TLC analysis, the reaction mixture was subject to flash column chromatography on silica gel (ethyl acetate/hex-

anes=1:5) to give a pure Michael product. The enantiomeric excess of Michael products was determined by chiral HPLC analysis. (2*R*, 3*S*)-2-Methyl-4-nitro-3-phenyl-butanal (**8a**): The enantiomeric purity was determined by using Chiralcel OD-H (*i*PrOH/hexanes, 10:90, flow rate 1.0 mL min⁻¹, λ=254 nm); *t*_R=31.7 min (minor); *t*_R=46.7 min (major).

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Keywords: asymmetric catalysis • camphor • Michael addition • nitroalkenes • organocatalysis • triazoles

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