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Michael reaction of ketones and β-nitrostyrenes catalyzed by camphor-10-sulfonamide-based prolinamide

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ABSTRACT

Novel camphor sulfonamide based organocatalysts were evaluated for their catalytic activity in the Michael reaction of ketones with nitroolefins. Reaction of ketones with β-nitrostyrenes in the presence of 20 mol % organocatalyst **1a** and benzoic acid under solvent-free conditions at 0 °C provided the desired Michael adducts with high chemical yields (up to 97%) and excellent stereoselectivities (>99:1).

1. Introduction

Catalytic asymmetric Michael addition plays an important role among the numerous asymmetric carbon–carbon bond-forming reactions, since it represents one of the most elegant and attractive ways to introduce chirality into a Michael acceptor.[1,2] Due to the simplicity of the asymmetric organocatalytic approach, the Michael addition of various donors and acceptors has been studied in the presence of organcatalysts.[3] The proline-catalyzed Michael addition between ketones and *trans*-β-nitrostyrene was first demonstrated by Barbas,[4a] List,[4b] and Enders,[4c] the adducts were obtained with good yields but with very low enantioselectivities. Since then, numerous pyrrolidine-based[5–9] and thiourea-based[10] organocatalysts have been used in asymmetric Michael additions. Michael additions of carbonyl compounds onto nitroalkenes using chiral amines as organocatalysts, which promote the reaction via an enamine pathway, have been studied in several laboratories.[7,9,11] Among these, good levels of asymmetric induction could be obtained by proline derivatives[7,9] where the amide moiety is a part of a chiral cavity in which the reaction takes place.

In continuation of our work on asymmetric synthesis,[12] we recently synthesized camphor-based novel organocatalysts **1a–c** (Fig. 1) with the appended prolinamide group and found that these catalysts exert good stereochemical control in the aldol reactions of ketones with aromatic aldehydes.[13] The bifunctional organocatalyst **1a** plays a significant role in determining the stereochemical outcome of the reaction presumably by stabilizing the transition state via hydrogen bonding between the aldehyde and amide moiety of the enamine formed from the catalyst and ketone and effective shielding of one of the faces of the enamine by the benzyl moiety of the catalyst. Since the amine catalyzed Michael addition of ketones to nitroolefins proceeds via an enamine intermediate, similar to the proline-promoted aldol reaction, we reasoned that this class of organocatalysts could also be successfully used in this reaction. To verify this hypothesis, the camphor sulfonamide-based prolinamides were initially tested as organocatalysts in the asymmetric Michael addition of cyclohexanone to aromatic nitroolefins. Herein, we report our preliminary results on camphorsulfonamide-based prolinamide mediated organocatalytic intermolecular Michael reactions.

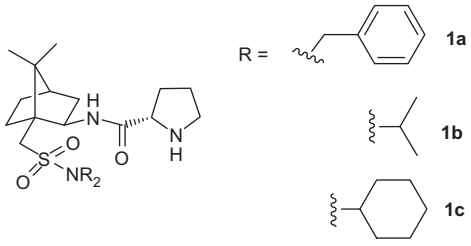

Figure 1. Structures of organocatalysts **1a–c**.

2. Results and discussion

We chose the Michael addition of cyclohexanone to β-nitrostyrene **2a** as the model reaction by using organocatalyst **1a**. A survey of polar and non-polar solvents revealed that all of the reactions proceeded smoothly and were complete within 16–30 h at room temperature without using any co-catalyst. However, high chemical yields with poor selectivity were observed between *syn* and *anti* Michael adducts in all cases. When the reaction was performed in 15 equiv of cyclohexanone without using an additional solvent, the reaction was complete within 14 h to afford adduct **3a** with high chemical yield and acceptable enantioselectivity (Table 1, entry 6).

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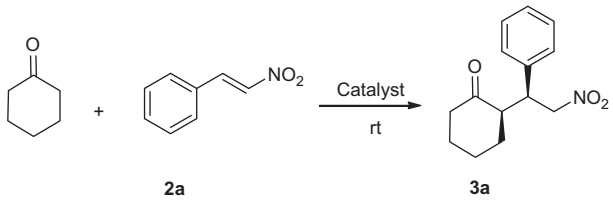
Table 1
Screening of reaction conditions and organocatalysts[a]



2a 3a

Entry	Catalyst (mol %)	Solvent	Time (h)	Yield (%)	dr[b] (*anti*:*syn*)	ee [c] (%)
1	**1a** (20)	$CHCl_2$	16	77	80:20	36
2	**1a** (20)	$CHCl_3$	20	80	85:15	53
3	**1a** (20)	MeOH	20	85	80:20	30
4	**1a** (20)	H_2O	28	60	65:35	32
5	**1a** (20)	H_2O:MeOH	30	80	70:30	45
6	**1a** (15)	Neat	14	88	88:12	53
7	**1a** (20)	Neat	10	92	90:10	61
8	**1a** (30)	Neat	10	90	90:10	59
9	**1b** (20)	Neat	14	80	92:8	44
10	**1c** (20)	Neat	8	93	85:15	53

[a] All reactions were carried out with cyclohexanone (3 mM) and β-nitrostyrene **2a** (0.2 mM).
[b] Determined by ^{1}H NMR (500 MHz) analysis of the crude sample.
[c] Determined by HPLC analysis using Chiralpak AS-H column.

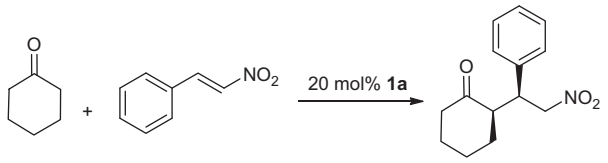
Optimum results were obtained with 20 mol % catalyst. The use of 15 mol % and 30 mol % of the organocatalyst led to a minor loss of stereocontrol (Table 1, entries 6–8). The prolinamides **1b** and **1c** derived from *N*,*N*-diisopropyl camphor-10-sulfonamide and *N*,*N*-dicyclohexyl camphor-10-sulfonamide, respectively, were used as catalysts; the catalytic activity was found to be less in comparison with the prolinamide **1a** derived from *N*,*N*-dibenzyl camphor-10-sulfonamide.

The asymmetric induction was further improved upon by carrying out the reaction at different temperatures, under solvent-free conditions using a catalyst and a co-catalyst[8,9,14] (Table 2). The addition of 15 mol % carboxylic acid as co-catalyst significantly accelerated the reaction rate relative to that carried out in the absence of a co-catalyst. From the carboxylic acids employed, benzoic acid afforded the best result in terms of reaction time and selectivity (Table 2, entry 1, 95:5 dr, 65% ee). Thus the acidic co-catalyst plays an important role on the reaction. Moreover, the reaction temperature was found to be an essential factor with regard to the enantioselectivity of the reaction. The stereoselectivity was gradually increased by decreasing the reaction temperature from 20 to 0 °C (Table 2, entries 1 and 5). However, further lowering of the temperature to −30 °C resulted in a slight decrease in the enantiomeric purity of adduct **3a** as well as the reaction rate (Table 2, entry 6). Under the optimal reaction conditions (20 mol % catalyst, 15 mol % PhCOOH as the co-catalyst at 0 °C, entry 5, Table 2) organocatalyst **1a** demonstrated the best catalytic activity. All of the reactions proceeded with a diastereoselectivity in favor of *syn*-diastereoisomer.

Encouraged by these initial results, we next investigated the reactions of other nitroolefins **2b–k** to expand upon the scope of the Michael addition with cyclohexanone under the optimal reaction conditions in the presence of organocatalyst **1a**. The results are summarized in Table 3. In all of the cases studied, the adducts were obtained in very high to excellent chemical yields regardless of the electronic nature of the substitutions on the aromatic nucleus. The diastereomeric discrimination of the products was high to excellent with the exception of adduct **3i** derived from 4-methoxynitrostyrene **2i** (Table 3, entry 9) where the *syn* and *anti* adducts were obtained in moderate 84:16 ratio. The reaction of nitrostyrene **2b** (R = *o*-NO_2) provided better asymmetric induction in comparison to that of nitrostyrene **2c** (R = *m*-NO_2) (Table 3, entries 2 and 3). However, the halogen-substituted nitrostyrenes **2d–g** afforded the corresponding Michael adducts **3d–g** in comparable enantiomeric excess. Among the 4-methyl and 4-methoxy-nitoolefins **2h**,**i** as Michael acceptors, the former furnished the Michael adduct in better dr and ee values (Table 3, entries 8 and 9). The reaction of cyclohexanone with α-naphthylnitrostyrene **2j** resulted in the formation of adduct **3j** almost exclusively with *syn* stereochemistry and a very high enantiomeric excess of 89% (Table 3, entry 10). Moreover, 2-(2-nitrovinyl)furan **2k** yielded adduct **3k** in very high diastereoselectivity and very good enantioselectivity.

The use of other symmetrical cycloalkanones, such as 4-methyl, 4-ethyl-cyclohexanones, and γ-pyrone as Michael donors was

Table 2
Effect of additives on the Michael reaction of cyclohexanone with β-nitrostyrene **2a** in the presence of **1a**[a]

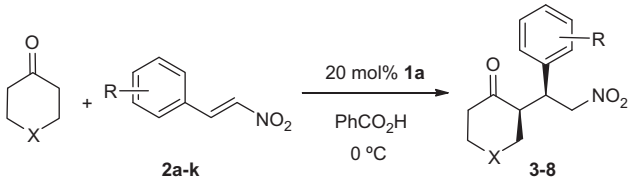


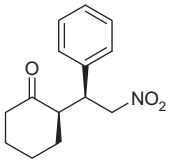
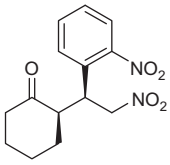
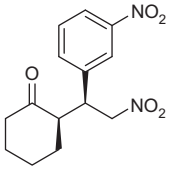
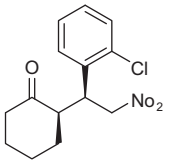
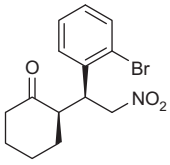
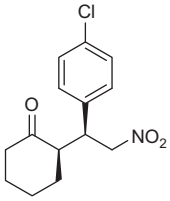
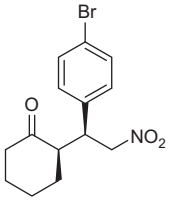
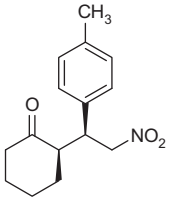
2a 3a

Entry	Solvent	Additive	Temp (°C)	Time (h)	Yield (%)	dr[b] (*anti*:*syn*)	ee[c] (%)
1	Neat	PhCOOH	rt	7	94	95:5	65
2	$CHCl_3$	PhCOOH	rt	18	88	80:20	57
3	Neat	4-$NO_2C_6H_4$COOH	rt	18	85	80:20	53
4	Neat	—	0	18	90	92:8	71
5	**Neat**	**PhCOOH**	**0**	**12**	**95**	**95:5**	**79**
6	Neat	PhCOOH	−30	24	92	92:8	75
7	Neat	4-$NO_2C_6H_4$COOH	0	30	80	85:15	59
8	Neat	Et_3N	0	36	75	93:7	62
9	Neat	Isobutyric acid	0	30	70	77:23	60
10	Neat	3-$CF_3C_6H_4$COOH	0	32	89	90:10	61

[a] The reactions were carried out with cyclohexanone (3 mM) and β-nitrostyrene (0.2 mM) and 15 mol % of additive.
[b] Determined by ^{1}H NMR (500 MHz) analysis of the crude sample.
[c] Determined by HPLC analysis using Chiralpak AS-H column.

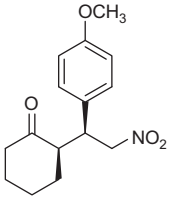
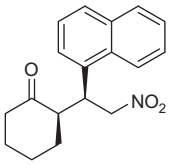
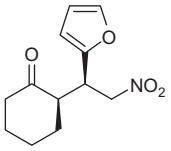
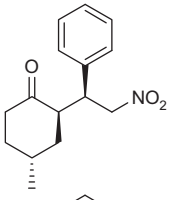
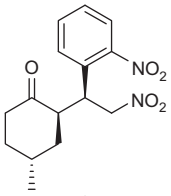
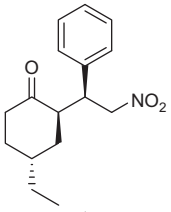
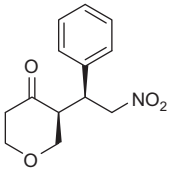
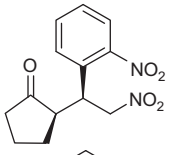
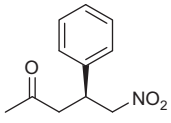
Table 3
Michael reaction of ketones with substituted β-nitrostyrenes in presence of **1a**[a]



Entry	Product		Time (h)	Yield (%)	dr[b] (*anti*:*syn*)	ee (%)[c]
1		**3a**	12	95	95:5	79
2		**3b**	14	96	97:3	77[d]
3		**3c**	14	92	93:7	67[d]
4		**3d**	18	94	92:8	69
5		**3e**	18	92	97:3	68
6		**3f**	18	95	95:5	71
7		**3g**	18	92	92:8	70[d]
8		**3h**	24	90	95:5	72

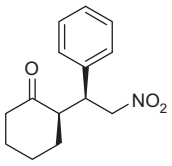
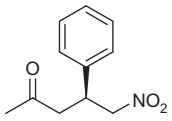
(*continued on next page*)

Table 3 (*continued*)

Entry	Product		Time (h)	Yield (%)	dr[b] (*anti*:*syn*)	ee (%)[c]
9		**3i**	24	89	84:16	60
10		**3j**	16	94	>99:1	89
11		**3k**	18	90	95:5	78[d]
12		**4a**	14	92	—	76[e]
13		**4b**	14	96	—	65[d]
14		**5a**	15	94	—	71
15		**6a**	16	97	93:7	75[d]
16		**7a**	12	90	85:15	75[d]
17		**8a**	18	89	—	50

[a] All the reactions were carried out with cycloalkanone (3 mM) and β-nitrostyrene (0.2 mM) at 0 °C.
[b] Determined by ^{1}H NMR (500 MHz) analysis of the crude sample.
[c] Determined by HPLC analysis using Chiralpak AS-H column unless otherwise mentioned.
[d] Determined with Chiralpak AD-H column.
[e] Determined with Chiralcel OD-H column.

Table 4
Comparison of results from **1a** and proline-catalyzed reactions[a]

Entry	Catalyst (mol %)	Product	Yield (%)	dr (*anti*:*syn*)	ee (%)
1	Proline (15)		94	95:5	−23
2	**1a** (20)		95	95:5	79
		3a			
3	Proline (15)		97	—	−7
4	**1a** (20)		89	—	50
		8a			

[a] Organocatalyst **1a**-catalyzed reactions were performed at 0 °C under neat conditions and proline-catalyzed reactions were performed at room temperature in DMSO.

evaluated as well and products **4a**,**b**, **5a** and **6a** were obtained in excellent yields and with good to very good enantioselectivities. The results are shown in Table 3. The reaction of nitrostyrene **2b** (R = *o*-NO_2) with cyclopentanone as a Michael donor was also performed to afford the adduct **7a** with very good enantiomeric excess. The reaction between acetone and nitrostyrene **2a** under the present catalytic system was then examined. Product **8a** was obtained in very high chemical yield albeit in moderate enantiomeric purity.

The asymmetric induction achieved by the catalytic system presented herein was good to very good. The results obtained from a couple of Michael reactions mediated by L-proline[4b] are compared in Table 4.

3. Conclusion

In conclusion, new prolinamide derived organocatalysts that contain a structural rigid bicyclic camphor scaffold and amide moiety were used for the first time in Michael additions. We have demonstrated a practical application of camphor-10-sulfonamide based prolinamide for the Michael additions of ketones with β-nitrostyrenes. In these transformations, the catalyst exhibited good catalytic activity and the reaction proceeded in excellent diastereoselectivity with good to high enantioselectivity, which may be potentially useful for preparing enantiomerically enriched γ-nitroketones.

4. Experimental

4.1. General

The structures of Michael adducts were confirmed from their IR, ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral studies. The absolute configuration of the major *syn* adducts is as shown in structures and is based on the retention times reported in the literature.[7a,11b,15]

4.2. Typical procedure for the enantioselective Michael reaction catalyzed by organocatalyst 1a

A mixture of a nitrostyrene (0.2 mmol), organocatalyst **1a** (20 mol %), benzoic acid (15 mol %), and cycloalkanone/acetone (05–1.0 mL) was stirred for 12–24 h at 0 °C. The reaction was monitored by TLC at regular intervals. Upon completion of reaction, the crude product was submitted to ^{1}H NMR (500 MHz) to determine the diastereomeric excess. The residue was subjected to column chromatography on silica gel to afford pure product. The HPLC of the Michael adduct was performed on a chiral stationary phase using hexane-isopropanol as the eluting solvent.

Acknowledgments

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