

5-Pyrrolidin-2-yltetrazole as an asymmetric organocatalyst for the addition of ketones to nitro-olefins

Alexander J. A. Cobb, Deborah A. Longbottom, David M. Shaw and Steven V. Ley*

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW.

E-mail: svl1000@cam.ac.uk; Tel: +44 (0)1223 336398

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The organocatalytic Michael addition of enamines derived from ketones to a range of nitro-olefins has been effected using the L-proline derived 5-pyrrolidin-2-yltetrazole 1.

Asymmetric organocatalysis is becoming an increasingly well-investigated area of organic chemistry. This is primarily because of the obvious advantages it holds over its metal-mediated counterpart; there is no need for expensive and often toxic metals, and organocatalysts are generally easier to make and more easily recoverable than standard catalytic reagents.¹

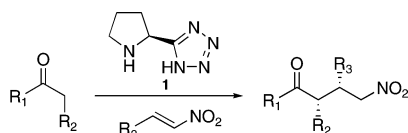
We recently reported the first use of proline-derived organocatalyst **1**² in an asymmetric Mannich-type reaction.³ Prior to this, no use of a tetrazole in catalytic asymmetric organocatalysis had been reported and subsequently the importance of this catalyst over proline itself has been recognised in other reaction processes.⁴

Herein, we report a further use of this organocatalyst in the Michael-type reaction of a range of ketones with nitro-olefins (Scheme 1). This reaction has been the subject of two recent independent studies using L-proline as the organocatalytic component and DMSO or methanol as the solvent and it was noted that there was a need to improve the enantioselectivities of the reactions or lower the reaction times.⁵

It was hoped that the more soluble organocatalyst **1** would facilitate these aims and allow this reaction to be performed in conventional solvents with improved enantioselectivity and no loss of yield. In order to determine this, the solvent scope for this catalyst was screened using the reaction of cyclohexanone as the ketone and β-nitrostyrene as the Michael acceptor. This gave Michael adduct **2** whose relative stereochemistry was proven by X-ray diffraction. DMSO, methanol, dichloromethane and THF were all screened as solvents for this reaction (Table 1).

Interestingly, the reaction in DMSO was comparable to proline, but the new organocatalyst **1** appeared to give more rapid reaction as seen by thin layer chromatography (Table 1, Entries 1 and 2). As has been observed previously, the reaction in methanol gave improved enantioselectivity over DMSO.^{5b} More significantly however, organocatalyst **1** gave an improved yield and equivalent enantioselectivity to L-proline under the same conditions (Table 1, Entries 3 and 4), although these figures could not be improved with heating. In dichloromethane, the organocatalyst gave a modest yield at room temperature (Table 1, Entry 7) although this is highly significant, as L-proline again failed to give any product under the same conditions (Table 1, Entry 6). Furthermore, in refluxing dichloromethane, the yield is improved considerably with no substantial loss of enantioselectivity (Table 1, Entry 9) and indeed, slightly better than the literature example of L-proline in DMSO (23%).^{5a}

The promising results in methanol prompted us to investigate the scope of other alcoholic solvents in the same reaction. Varying ratios of methanol, ethanol and isopropanol were explored (Table 2).



Scheme 1 General pyrrolidine-mediated nitro-Michael addition

In general, it appeared that increasing the amount of IPA gave highly improved yields. Conversely, methanol and ethanol improved the enantioselectivity, but deteriorated the yield. These investigations showed that the compromise of ethanol–IPA (1 : 1) gave the best overall result. Furthermore, all these reactions were carried out for just 24 hours, in keeping with our requirement for shorter reaction times than those performed in the literature.

Final optimisation of the reaction conditions was then carried out using reduced amounts of ketone and/or organocatalyst **1** which were screened in both isopropanol–ethanol (1 : 1) as well as in refluxing dichloromethane. The studies showed that the yield of the reaction for the conjugate addition of cyclohexanone to β-

Table 1 Solvent screen for the conjugate addition of cyclohexanone (20 vol%) into β-nitrostyrene. Reactions performed for 24 h.

Entry	Catalyst	Solvent	T/°C	Yield (%) ^{a,b}	Ee (%) ^c
1	L-Proline	DMSO	20	93	35
2	1	DMSO	20	97	35
3	L-Proline	MeOH	20	37	57
4	1	MeOH	20	61	53
5	1	MeOH	50	42	53
6	L-Proline	DCM	20	0	—
7	1	DCM	20	20	40
8	L-Proline	DCM	Reflux	0	—
9	1	DCM	Reflux	98	37
10	1	THF	20	33	25

^a Based on isolated product. ^b All drs were >15 : 1 by ¹H NMR spectroscopy. ^c Determined by chiral HPLC (Daicel Chiralpak AD-H column).

Table 2 Further optimisation studies for the conjugate addition of cyclohexanone into β-nitrostyrene using 15 mol% of organocatalyst **1**. All reactions conducted for 24 h.

Entry	Catalyst	Solvent	Cyclohexanone (eq.)	Yield (%) ^{a,b}	Ee (%) ^c
1	1	MeOH	20	61	53
2	1	MeOH–IPA (2 : 1)	20	56	53
3	1	MeOH–IPA (1 : 1)	20	65	61
4	1	MeOH–IPA (1 : 2)	20	76	58
5	1	EtOH	20	65	65
6	1	EtOH–IPA (2 : 1)	20	80	59
7	L-Proline	EtOH–IPA (1 : 1)	20	78	47
8	1	EtOH–IPA (1 : 1)	20	96	62
9	1	EtOH–IPA (1 : 2)	20	100	56
10	1	IPA	20	80	40
11	L-Proline	EtOH–IPA (1 : 1)	1.5	52	51
12	1	EtOH–IPA (1 : 1)	1.5	80	62

^a Based on isolated product. ^b All drs were >15 : 1 by ¹H NMR spectroscopy. ^c Determined by chiral HPLC (Daicel Chiralpak AD-H column).

nitrostyrene was significantly better in dichloromethane than in alcoholic solvents. However, the substantially better enantioselectivities obtained in alcoholic solvents encouraged us to pursue further optimisation under these conditions. It was found that reducing the amount of catalyst lowered the yield significantly. Nevertheless, this decrease in catalyst amount had little effect on the enantioselectivities. Ultimately, the optimal amount of catalyst was found to be 15 mol%.

Decreasing the amount of ketone in the reaction did not lower the yield of product significantly or have any effect on enantioselectivity and it was found that the amount of ketone could be reduced to 1.5 equivalents with no reduction in enantioselectivity (Table 2, Entry 12). This is a significant improvement on literature reports, which generally use a large excess of ketone.⁵

More significantly the tetrazole catalyst **1** shows clear advantages over L-proline in both alcoholic solvent systems and dichloromethane. In alcoholic solvents, the organocatalyst outperformed proline both in terms of product yield and enantioselectivity (Table 2, Entries 7, 8 and 11, 12). In dichloromethane, L-proline did not provide any product under the same conditions for the same period of time.

Following this thorough optimisation study, a range of ketones and nitro-olefins were tested under the best conditions (ethanol–isopropanol (1 : 1) and 1.5 equivalents of ketone [Table 2, Entry 12]). Several nitro-olefins were screened using cyclohexanone and the results are shown below (Table 3).

Under these conditions it was found that the yields were generally good and that the type of substituent appears to not influence the enantioselectivity of the reaction, with ees ranging from 55% to 65%. β -3-Dinitrostyrene was found to be the best Michael acceptor (Table 3, Entry 3) in terms of yield and enantioselectivity, and was tested against a range of ketones (Table 4). Furthermore, the ‘unnatural’ enantiomer **15** of the tetrazole catalyst was made by the same synthetic route^{2a,3} and used for the first time in an asymmetric organocatalytic reaction, providing the opposite stereoselectivity in comparable yield.

Though these results are more modest than the corresponding aldol and Mannich reactions, they show that tetrazole **1** outperforms proline under the conditions used. One reason for this could be the larger hydrogen-bonded transition state proposed for this reaction (8-membered ring).^{5b} In contrast, Houk and Bahmanyar suggest a hydrogen-bonded 6-membered transition state for the aldol and Mannich reactions where a more rigid chiral environment exists.⁶

The improvement over proline is interesting if the tetrazole participates in the transition state in the same way as proline does.

Table 3 Use of various nitro-olefins under optimised conditions.

Entry	R	Yield (%) ^{a,b}	Ee (%) ^c
1	<i>p</i> -MeO-C ₆ H ₄ 3	83	58
2	2-Furanyl 4	59	65
3	<i>m</i> -NO ₂ -C ₆ H ₄ 5	92	65
4	2-Thiophene 6	74	57
5	<i>p</i> -CF ₃ -C ₆ H ₄ 7	58	55
6	2-Pyridinyl 8	47	60

^a Based on isolated product. ^b All drs were > 15 : 1 by ¹H NMR spectroscopy. ^c Determined by chiral HPLC (Daicel Chiralpak AD-H column).

Table 4 Further investigation of the scope of the reaction.

Product	Ketone	Catalyst	t/h	Yield (%) ^a	Dr (syn : anti) ^b	Ee (%) ^c
9		L-Proline	24	47	10 : 1	40
9		1	24	62	10 : 1	70
14		15	24	67	10 : 1	73 ^d
10		1	24	100	6 : 1	54
11^e		1	24	71	9 : 1	32
12		1	48	72	—	33
13		1	72	68	> 19 : 1	65

^a Based on isolated product. ^b Determined by ¹H NMR spectroscopy. ^c Determined by chiral HPLC (Daicel Chiralpak AD-H column). ^d Chiral HPLC showed that opposite enantiomer **14** was formed. ^e * Indicates position of enamine formation.

However, this could be ascribed either to the difference in hydrogen-bonding strengths between the tetrazole and the carboxylic acid functionality or to the increased size of the tetrazole moiety.

In conclusion, several advances in the asymmetric addition of a ketone to a nitro-olefin have been discovered, using the more effective and active organocatalyst **1**. The results are a definite improvement on those previously reported in literature for this reaction with L-proline. Whenever compared to L-proline, this organocatalyst far outperforms it, in terms of yield, enantioselectivity, reaction times and stoichiometry.

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Notes and references

- P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2001, **40**, 3726.
- (a) R. G. Almquist, W.-R. Chao and C. Jennings-White, *J. Med. Chem.*, 1985, **28**, 1067; (b) available from Synnovation Ltd, Epsom, UK.
- A. J. A. Cobb, D. M. Shaw and S. V. Ley, *Synlett*, 2004, **3**, 558.
- (a) H. Torii, M. Nakadai, K. Ishihara, S. Saito and H. Yamamoto, *Angew. Chem., Int. Ed.*, 2004, **43**, 1983; (b) N. Momiyama, H. Torii, S. Saito and H. Yamamoto, *Proc. Natl. Acad. Sci. USA*, 2004, **15**, 5374; (c) A. Hartikka and P. I. Arvidsson, *Tetrahedron: Asymmetry*, 2004, **15**, 1831.
- (a) B. List, P. Pojarliev and H. J. Martin, *Org. Lett.*, 2001, **3**, 2423; (b) D. Enders and A. Seki, *Synlett*, 2002, **26**; (c) for a recent study see J. M. Betancort, K. Sakthivel, R. Thayumanavan, F. Tanaka and C. F. Barbas III, *Synthesis*, 2004, **9**, 1509.
- (a) S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **123**, 12911; (b) S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **123**, 11273; (c) S. Bahmanyar, K. N. Houk, H. J. Martin and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 2475; (d) L. Hoang, S. Bahmanyar, K. N. Houk and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 16.