A versatile organocatalyst for the asymmetric conjugate addition of nitroalkanes to enones

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5-Pyrrolidin-2-yltetrazole performs as an improved catalyst for the asymmetric addition of a range of nitroalkanes to cyclic and acyclic enones, with good to excellent enantioselectivity.

The asymmetric conjugate addition of carbon nucleophiles to electron-poor alkenes is an important synthetic process for the formation of carbon–carbon bonds. The utility of this reaction is due, in part, to the broad spectrum of nucleophilic "donors" and electrophilic "acceptors" that can be employed in the transformation.[1] Nitroalkanes are a particularly valuable source of stabilised carbanions, as the strongly electron-withdrawing nature of the nitro group (pK_a $MeNO_2$ = 10) facilitates generation of the nitronate anion under mild conditions. Additionally, the nitro group is a versatile functional group[2] that can be converted to a ketone (Nef reaction), reduced to an amine, or modified by radical substitution with hydrogen.

A variety of catalyst systems have been developed for the asymmetric conjugate addition of nitroalkanes to chalcones.[1] These include chiral crown ethers,[3] chiral Lewis acids,[4] and phase-transfer catalysts derived from cinchona alkaloids.[5] Recently, use of an aluminium–salen catalyst with substrates other than chalcones was reported.[6] Proline rubidium salts have been used to catalyse the addition of nitroalkanes to both acyclic and cyclic α,β-unsaturated enones with moderate to good enantioselectivities (41–84%).[7,8] It has since been shown that the use of proline (**1**, Fig. 1) with an amine additive led to improved enantioselectivities for cyclic enones (61–93%),[9] but the use of proline for acyclic systems has yet to be reported. Imidazoline catalyst **2** (20 mol%) was reported to give good enantioselectivities for the conjugate addition of nitroalkanes to acyclic α,β-unsaturated enones (34–86%). However, only moderate enantioselectivity (49%) was obtained using cyclohexenone and this catalyst.[10] Reaction times were typically between 110 and 300 hours. In addition, the nitroalkanes were employed as the reaction solvent, and thus were used in approximately 20-fold excess.[10]

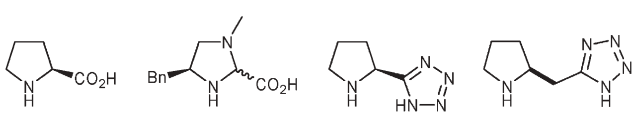

Fig. 1 Proline and related organocatalysts.

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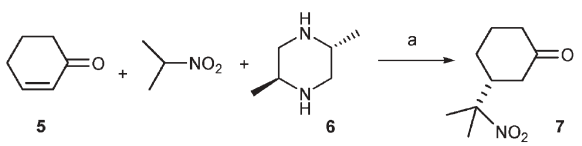
We and others have previously reported on the tetrazole analogue of proline (**3**) as a more soluble and effective catalyst in a variety of transformations.[11] Using this catalyst, we sought to establish reaction conditions that were applicable to a wider range of enone substrates and that were amenable to large-scale organic synthesis. Initial results using the conditions Hanessian *et al.*[9] developed for proline with achiral *meso* base additive **6** were promising. The reaction of cyclohexenone with only 2 equivalents of 2-nitropropane in chloroform afforded the product **7** in 70% yield and 98% ee (Table 1, entry 2), a significant improvement over the results with proline (entry 1). Without the base additive, the reaction proceeded slowly and with poor enantioselectivity (entry 3); with no catalyst present, no background reaction was observed (entry 4). While the homologated tetrazole **4** was effective as a catalyst in the asymmetric Michael addition of ketones to nitro-olefins,[12] in the Michael addition of nitroalkanes to enones, it provided the product **7** in only poor yield and enantioselectivity (entry 5). Two of the chiral imidazolidinone catalysts developed by MacMillan were also screened, but gave none of the expected product under these reaction conditions.[13]

With an effective catalyst for addition to cyclic enones in hand, optimisation of reaction conditions was undertaken using catalyst **3** and less reactive acyclic enones as coupling partners. Although 4-phenyl-3-buten-2-one (**8**) generated the product **9** in good ee, the isolated yield was low using chloroform as solvent (Table 2, entry 1). Proline (**1**) was found to give the product in higher yield but only moderate enantioselectivity (entry 2). In dichloromethane, an enhanced rate of reaction was observed, with a 79% isolated yield after 2.5 days (entry 3). The best enantioselectivity was obtained in THF, but the reaction was too slow to be useful, presumably due to low solubility of the catalyst in this solvent

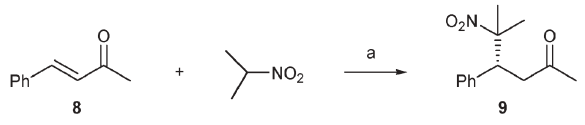
Table 1 Initial results with cyclohexenone



Entry	Catalyst	Base eq	Yield (%)[b]	Ee (%)[c]
1	**1**	1	64	88
2	**3**	1	70	98
3	**3**	—	4	53
4	—	1	0	—
5	**4**	1	17	28

[a] **5** (0.5 mmol), catalyst (15 mol%), 2-nitropropane (1 mmol), **6** (0.5 mmol), $CHCl_3$ (2 mL), 2 d, oven-dried glassware, rt. [b] Isolated yield. [c] Determined by chiral GC.

Table 2 Further optimisation



Entry	Conditions[a]	Time (d)	Yield (%)[b]	Ee (%)[c]
1	$CHCl_3$	2.5	27	76
2	$CHCl_3$[d]	2.5	49	58
3	CH_2Cl_2	2.5	79	70
4	MeCN	2.5	38	66
5	THF	2.5	10	84
6	MeOH	2.5	58	7
7	DMSO	2.5	39	0
8	5 mol% catalyst **3**	2	55	72
9	1.1 eq 2-nitropropane	2	57	71
10	0.25 eq H_2O	2	46	74
11	Non dried glassware	3	61	82
12	0 °C	4	30	79
13	40 °C	1	68	46
14	0.5 eq **6**	2	20	78
15	2 eq **6**	1	48	67
16	1 eq Et_2NH	2	72	62
17	1 eq piperidine	2	86	53
18	1 eq piperazine	2	30	76

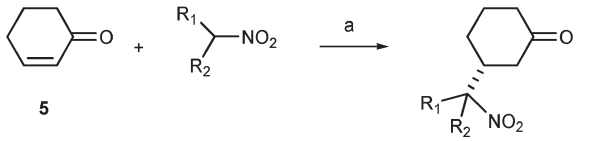
[a] **8** (0.5 mmol), **3** (15 mol%), 2-nitropropane (1 mmol), **6** (0.5 mmol), entries 1–7 solvent (2 mL) as indicated, entries 8–18 CH_2Cl_2 (2 mL), oven-dried glassware, rt, unless otherwise stated. [b] Isolated yield. [c] Determined by chiral GC. [d] Using 15 mol% catalyst **1**.

(entry 5). More polar solvents led to a decrease in enantioselectivity (entries 6, 7). The absolute stereochemistry of both **7** and **9** was confirmed by a comparison of the optical rotation with literature values.[7,10]

Using only 5 mol% catalyst **3**, the reaction proceeded more slowly giving a 55% isolated yield of the product, with no change in the ee (entries 3, 8). Reducing the nitroalkane loading led to a similar decrease in reaction rate (entry 9). Although standard reactions were not run under an inert atmosphere, when 0.25 equivalents of water was added to a reaction run under argon, the product **9** was isolated in only 46% yield (entry 10). An important factor in reaction reproducibility was found to be small variations in the amount of water present; when the reaction was run under standard reaction conditions, but in non oven-dried glassware, a lower isolated yield but slightly higher enantioselectivity was obtained (entry 11). Lowering the temperature improved the enantioselectivity, but decreased the reaction rate (entry 12). Unsurprisingly, increasing the temperature led to a drop in enantioselectivity (entry 13). Varying the loading of additive **6** revealed the optimal level of base additive was 1 equivalent (entries 14, 15). Improved yields were obtained with both diethylamine and piperidine (entries 16, 17), and slightly improved enantioselectivity was observed with piperazine (entry 18), accordingly use of amine **6** was found to be optimal. Monitoring of the reaction by HPLC over 4 days (conditions as for entry 11) showed that the reaction did not progress significantly after 3 days.

Next we examined the addition of a range of nitroalkanes to cyclohexenone under the optimised conditions, and all gave excellent enantioselectivities (Table 3, 94–98%). A similar trend of faster reaction rates but lower enantioselectivities in dichloromethane compared to chloroform was observed, although differences in reaction rate were less pronounced. Using

Table 3 Addition of various nitroalkanes to cyclohexenone



Entry	Nitroalkane	Conditions[a]	Yield (%)[b]	Ee (%)[c]
1	$R_1 = R_2 = H$	A	47	94
2		B	49	95
3	$R_1 = H$, $R_2 = Me$	A	84	95/94, 1.1 : 1
4		B	74	95, dr 1.2 : 1
5	$R_1 = R_2 = Me$	A	84	96
6		B	70	98
7	$R_1 = R_2 = (CH_2)_5$	A	63	94
8		B	53	97

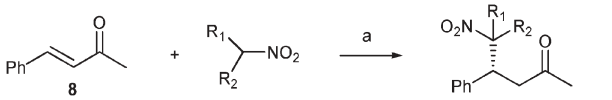
[a] Conditions A) **5** (0.5 mmol), **3** (15 mol%), nitroalkane (1 mmol), **6** (0.5 mmol), CH_2Cl_2 (2 mL), 1 d, rt. Conditions B) as A except $CHCl_3$ (2 mL), 2 d. [b] Isolated yield. [c] Determined by chiral GC.

nitroethane, the high stereoselectivity at the β-position was maintained, but the product was a mixture of diastereomers arising from the exocyclic stereocenter of the nitroalkyl side chain (entries 3, 4). The reactions of cyclohexenone did not exhibit the same sensitivity to water, as identical yields and ee's were obtained using both oven-dried and non oven-dried glassware. Excellent enantioselectivity was obtained for all nitroalkanes examined; whereas with proline poorer selectivity was reported for the addition of the less sterically hindered nitroethane and nitromethane nucleophiles.[9]

We then examined the addition of a range of nitroalkanes to 4-phenyl-3-buten-2-one. Reactions were generally slower relative to those for cyclohexenone and did not proceed to completion. Again, substrate **8** showed different results with oven and non-oven dried glassware. Moderate to good yields and good enantioselectivities were obtained in all cases (Table 4). However, it was necessary to use 10 equivalents of nitromethane to obtain a good yield of product (entries 1, 2).

The substrate scope was next demonstrated with a range of acceptors. Generally these substrates were not found to be as sensitive to small amounts of water. Excellent enantioselectivity

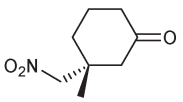
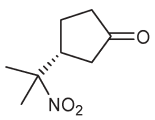
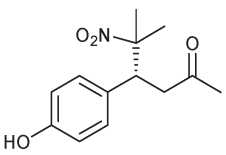
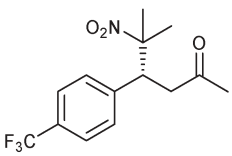
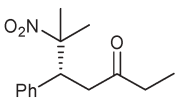
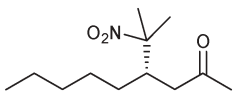
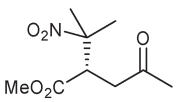
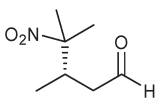
Table 4 Addition of various nitroalkanes to 4-phenyl-3-buten-2-one



Entry	Nitroalkane	Conditions[a]	Yield (%)[b]	Ee (%)[c]
1	$R_1 = R_2 = H$	A	46	89
2		A[d]	76	77
3	$R_1 = H$, $R_2 = Me$	A	67	80, dr 1.3 : 1
4		C	40	82/80, 1.3 : 1
5	$R_1 = R_2 = Me$	A	79	70
6		C	61	82
7	$R_1 = R_2 = (CH_2)_5$	A	80	73
8		C	59	77

[a] Conditions A) **8** (0.5 mmol), **3** (15 mol%), nitroalkane (1 mmol), **6** (0.5 mmol), CH_2Cl_2 (2 mL), 3 d, oven-dried glassware, rt. Conditions C) as A except non oven-dried glassware. [b] Isolated yield. [c] Determined by chiral GC/HPLC. [d] 5 mmol nitroalkane used.

Table 5 Addition of nitroalkane to various enones

Entry	Product	Conditions[a]	Yield (%)[b]	Ee (%)[c]
1		A	64	91
2		C	59	91
3		A[d]	62	80
4		B	63	75
5		A	72	61
6		C	70	62
7		A	73	66
8		C	66	68
9		A	21	83
10		A[e]	78	78
11		A	23	55
12		A[f]	44	58
13		A	88	82
14		C	96	82
15		A[d]	40	42
16		C[d]	39	46

[a] Conditions A) Enone (0.5 mmol), **3** (15 mol%), nitroalkane (1 mmol), **6** (0.5 mmol), CH_2Cl_2 (2 mL), 3 d, oven-dried glassware, rt; Conditions B) as A except $CHCl_3$ (2 mL); Conditions C) as A except non oven-dried glassware. [b] Isolated yield. [c] Determined by chiral GC/HPLC. [d] Reaction time 21 h. [e] Reaction time 12 d. [f] 1 mmol **6** used.

was observed for 3-methylcyclohexenone (Table 5, entries 1, 2). Cyclopentenone also gave good enantioselectivities (entries 3, 4). Substituted 4-phenyl-3-buten-2-ones were examined: both electron-donating (entries 5, 6) and electron-withdrawing (entries 7, 8) groups led to comparable yields but lower selectivity relative to the unsubstituted substrate. The ethyl ketone reacted considerably more slowly than the methyl ketone and thus required longer reaction times (entries 9, 10). Non-3-en-2-one was found to be less reactive, and also to give poorer enantioselectivities, although use of 2 equivalents of **6** gave improved results (entries 11, 12). However, (*E*)-methyl-4-oxopent-2-enoate gave both good yield and enantioselectivity (entries 13, 14). Aldehydes gave, at best, modest enantioselectivities and yields (entries 15, 16). However, the 46% enantioselectivity obtained for crotonaldehyde (entry 16) is, to our knowledge, the highest reported to date for addition of a nitroalkane to an α,β-unsaturated aldehyde (*cf.* 29% ee for hexenal[8]). Studies on cinnamaldehyde (data not shown) showed significant levels of background reaction with base additive but no catalyst.

The mechanism for these reactions has not been rigorously established, although it is plausible that the catalyst initially forms an iminium complex with the enone. The exact role of the base is not clear, as the nature of the base affects not only yield but enantioselectivity. Kinetic studies are presently underway to elucidate these pathways. Also, investigations are ongoing concerning the asymmetric addition of other nucleophiles into enone acceptors.

In conclusion, it has been shown that tetrazole **3** performs as an improved catalyst for the asymmetric addition of a range of nitroalkanes to both cyclic and acyclic enones. This reaction is scaleable,[14] providing enantiomeric excesses of up to 98% in comparatively short reaction times of 24 to 72 hours, and using only 2 equivalents of the coupling nitroalkane.

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14 The reaction was run on a 15 mmol scale (enone).

