A new asymmetric organocatalytic nitrocyclopropanation reaction

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Using 5-(pyrrolidin-2-yl)-1*H*-tetrazole as an organic catalyst, the nitrocyclopropanation of 2-cyclohexen-1-one has been achieved, proceeding in high yield and with good enantioselective control.

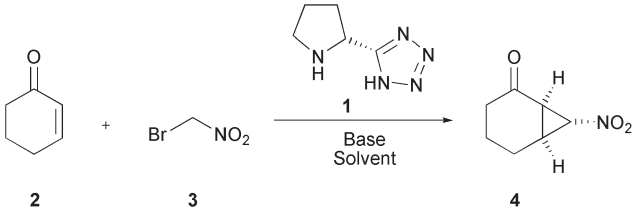
Cyclopropane containing structures are compounds of interest within organic chemistry as they display the potential for considerable stereogenic change over a small, rigid framework of just three carbon atoms. They serve as versatile synthetic intermediates in a variety of reactions[1] and are widely distributed in a range of naturally occurring compounds[2] and peptidomimetics.[3] Consequently, their stereoselective preparation is a valuable goal and to date, several methods have been developed towards this aim.[4]

In particular, nitro substituted cyclopropanes may be converted to a wide range of functionalities,[5] and are prepared by a variety of methods.[6] Among these, a diastereoselective nitrocyclopropanation reaction, in which bromonitromethane was reacted with a range of electrophilic alkenes,[7] was interesting and sparked the idea that the process could be rendered enantioselective through the use of an organocatalyst.

The use of pyrrolidine-based catalysts in enantioselective synthesis is now widely accepted,[8] and one of the best studied reaction types is the enantioselective addition of nucleophiles to α,β-unsaturated ketones.[9–11] Indeed, among other reaction processes investigated in this laboratory,[12] it was found that conjugate addition of malonate esters and nitroalkanes proceeded well,[9,10] producing both high yields and enantioselectivities in the presence of proline tetrazole **1** and its enantiomer as a catalyst.[13]

In view of these observations, we speculated that by using an unsaturated carbonyl compound and bromonitromethane in the presence of the same asymmetric organocatalyst, the desired enantioselective nitrocyclopropanation would ensue, setting up three new stereogenic centers in a single operation (Scheme 1).

To the best of our knowledge, currently in the literature the only example of a one-step *enantioselective* nitrocyclopropanation is through the phase transfer catalysed reaction of α-bromocyclopentenone with nitromethane. In this isolated example, the yield (50%) and the enantioselectivity (62%) are moderate.[14]



Scheme 1 Enantioselective nitrocyclopropanation.

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Thus the project aims were firstly to demonstrate that the organocatalytic reaction would be successful, secondly to provide a good yield and enantioselectivity through optimisation procedures and thirdly to demonstrate the generality of the reaction process. Studies to date are reported below.

Initially, using conditions similar to those developed earlier for the nitroalkylation of enones,[10] a range of solvents for the reaction was investigated (Table 1). It was most encouraging to see that in each case, some of the desired product was formed and in all cases, only one diastereomer was observed and the reaction was clearly enantioselective. Closer examination of the results revealed that dimethyl sulfoxide and water gave poor yields and low enantioselectivities (Entries 1 and 2), while methanol, tetrahydrofuran and acetonitrile (Entries 3–5) provided a noticeable improvement. Dichloromethane, however, proved to be the optimal solvent in terms of both yield and enantioselectivity in this initial screen (Entry 6).

It was then necessary to investigate the stoichiometry of the reaction partners and where possible only use the minimum excess of reagents. The only known synthesis of compound **4**, although diastereoselective, was not enantioselective, and a 15-fold excess of nitromethane was used, giving only a 51% yield of product.[15]

Thus, it was pleasing to find that in our case the best yields were obtained when the enone was in slight excess, and that yields and enantioselectivities hardly changed, even when ten equivalents of enone were added (Table 2). Thus, the remainder of this study was conducted with just 1.2 equivalents of enone.

Given the vast amount of literature now published in the area of organocatalysis, we believed it was also necessary to screen alternative catalytic species. Therefore, the reaction was carried out using a selection of known catalysts, shown in Fig. 1. No attempt was made to optimise the reaction for the individual catalysts.

L-proline **5** (Table 3, Entries 2 and 3) gave a lower yield and reduced enantioselectivity when compared with the tetrazole

Table 1 Solvent screen[a]

Entry	Solvent	Yield (%)[b]	ee (%)[c]
1	DMSO	23	5
2	H_2O	40	4
3	MeOH	51	10
4	THF	50	48
5	MeCN	48	59
6	**CH_2Cl_2**	**75**	**59**

[a] Conditions: **2** (2.5 mmol), **3** (0.5 mmol), *trans*-2,5-dimethylpiperazine (0.5 mmol), **1** (15 mol%), solvent (2 mL), 24 h, rt. [b] Isolated yield. [c] Determined by chiral GC.

Table 2 Equivalent screen[a]

Entry	Equiv. of **2**	Equiv. of **3**	Yield (%)[b]	ee (%)[c]
1	1	2	16	68
2	**1.2**	**1**	**77**	**64**
3	2	1	72	61
4	5	1	70	59
5	10	1	75	57

[a] Conditions: **3** (0.5 mmol), *trans*-2,5-dimethylpiperazine (0.5 mmol), **1** (15 mol%), CH_2Cl_2 (2 mL), 24 h, rt. [b] Isolated yield. [c] Determined by chiral GC.

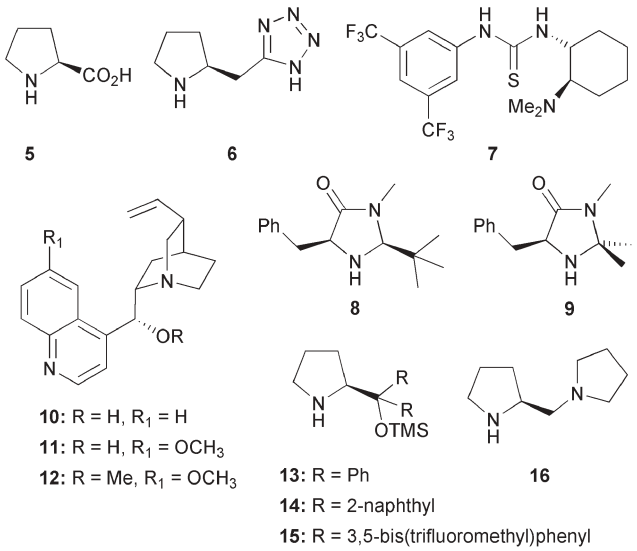

Fig. 1 Catalysts used for nitrocyclopropanation.

catalyst (Entry 1) both in dichloromethane and dimethyl sulfoxide. Homo-tetrazole catalyst **6** (Entry 4)[16] did not affect the yield greatly but completely destroyed any enantioselectivity and the thiourea catalyst **7** (Entry 5)[17] produced product but in very low yield and stereoselectivity. The MacMillan catalysts **8** and **9**

Table 3 Catalyst screen[a]

Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**1**	**77**	**64**
2	**5**	49	49[d]
3	**5**[e]	14	5[d]
4	**6**	68	0
5	**7**	20	6[d]
6	**8**	24[f]	0
7	**9**	26[f]	0
8	**10**	38[f]	0
9	**11**	34[f]	0
10	**12**	24[f]	0
11	**13**	Trace	—
12	**14**	Trace	—
13	**15**	Trace	—
14	**16**	75	16
15	**None**	6[f]	0
16[g]	**1**[g]	0	—

[a] Conditions: **2** (0.6 mmol), **3** (0.5 mmol), *trans*-2,5-dimethylpiperazine (0.5 mmol), catalyst (15 mol%), CH_2Cl_2 (2 mL), 24 h, rt. [b] Isolated yield. [c] Determined by chiral GC. [d] Opposite enantiomer. [e] 2 mL DMSO as solvent. [f] Yield based on ^{1}H-NMR integration of side-product **17**[20] and product **4**, formed as an inseparable mixture. [g] No base present.

Table 4 Time and temperature screen[a]

Entry	Temperature (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	25	2	21	57
2	25	4	49	63
3	25	8	53	65
4	**25**	**24**	**77**	**64**
5	25	48	68	67
6	−78	24	1	24
7	−40	24	13	23
8	0	24	48	58
9	40	24	33	62

[a] Conditions: **2** (0.6 mmol), **3** (0.5 mmol), **1** (15 mol%), *trans*-2,5-dimethylpiperazine (0.5 mmol), CH_2Cl_2 (2 mL). [b] Isolated yield. [c] Determined by chiral GC.

(Entries 6 and 7)[18] and cinchona alkaloids **10**, **11** and **12** (Entries 8–10)[19] were also examined but surprisingly did not demonstrate any enantioselectivity and the product yields were poor due to significant side-product formation.[20] The bulky pyrrolidine catalysts **13**, **14** and **15** were also tested (Entries 11–13),[21] but disappointingly gave only trace amounts of product and multiple side-products and although the (1-pyrrolidinylmethyl)pyrrolidine **16**[22] gave a good yield (Entry 14), the enantioselectivity was quite low. It is interesting to note that there was also a background reaction occurring in the absence of catalyst, but no enantioselection was demonstrated (Entry 15) and in the absence of base, no reaction occurred at all (Entry 16). Ultimately, it was found that our initial reaction, using the tetrazole catalyst **1** remained our best result so the following reactions were performed using this catalyst, but altering time and temperature of the reaction.

Yield and enantioselectivity were found to be at their best after 24 hours at room temperature (Table 4, Entry 4). Any decrease in reaction time brought about an unacceptable decline in yield (Entries 1–3) and doubling it only provided a comparable result (Entry 5), with enantioselectivity essentially constant throughout. Any change in temperature gave a concomitant loss in yield and, counterintuitively, enantioselectivity decreased at lower temperature (Entries 6–8) and remained constant at reflux (Entry 9).

In the final round of screening, a broad range of bases were evaluated, providing some interesting data (Table 5). Typically,

Table 5 Base screen[a]

Entry	Base	Yield (%)[b]	ee (%)[c]
1	None	0	—
2	pyridine	17	0
3	2,6-lutidine	3	8
4	2,6-di-*tert*-butyl-pyridine	0	—
5	DBU	14	11
6	Et_3N	28	28
7	*N*,*N*′-dimethyl-ethylenediamine	44	46
8	Et_2NH	59	43
9	iPr_2NH	61	31
10	2,2,6,6-tetramethyl-piperidine	48	30
11	pyrrolidine	64	8
12	piperazine	44	74
13	*N*-methylpiperazine	55	76
14	2-methylpiperazine	69	64
15	*trans*-2,5-dimethylpiperazine	77	64
16	**morpholine**	**80**	**77**

[a] Conditions: **2** (0.6 mmol), **3** (0.5 mmol), **1** (15 mol%), base (0.5 mmol), CH_2Cl_2 (2 mL), 24 h, rt. [b] Isolated yield. [c] Determined by chiral GC.

aromatic bases gave poor results (Entry 2–4), and with non-aromatic, tertiary bases (Entries 5–7), the yield and the enantioselectivity were generally lower than those for all the secondary amine bases tried (Entries 8–16). Gratifyingly, however, morpholine (Entry 16) gave the desired improvement, finally now providing the product in 80% yield and 77% enantiomeric excess.

Work is now underway to explore the scope of the reaction for other substrates. Preliminary indications suggest that for the five and seven ring congeners, while yields of product are high (73% and 93% respectively), the enantioselectivities are only moderate (40% and 35%). However, while these results suggest that further optimisation and catalyst development will be necessary to discover a general nitrocyclopropanation procedure, they do set a bench mark for catalysis of this cyclopropanation process.

In summary, a new organocatalytic nitrocyclopropanation reaction has been developed and conditions optimised using cyclohexenone as the substrate. The reaction is scaleable[23] and a single recrystallisation takes the 77% ee up to $>$ 98%. Relative stereochemistry has been proven by X-ray crystallography† and derivatisation should provide absolute stereochemistry. Current work is now concerned with the application of this method to other cyclic and acyclic aliphatic and aromatic substrates, in the quest for a general method to facilitate transformations of this type with even higher enantioselectivity.

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Notes and references

† *Crystal data*: for **4**: $C_7H_9NO_3$, M = 155.15, orthorhombic, space group $P2_12_12_1$ (no. 19); a = 5.4987(3), b = 9.8391(5), c = 13.5025(6) Å; U = 730.52(6) Å^3; Z = 4; μ(Mo-Kα) = 0.111 mm^{-1}; 5667 reflections measured at 120(2) K using an Oxford Cryosystems Cryostream cooling apparatus; 997 unique (R_{int} = 0.068); R_1 = 0.044, wR_2 = 0.081 [$I > 2\sigma(I)$]; goodness-of-fit on F^2, S = 1.06. The absolute configuration is unknown, 666 Friedel pairs were averaged for the refinement. The structure was solved with *SHELXS-97** and refined with *SHELXL-97**. CCDC 618771. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b612436b

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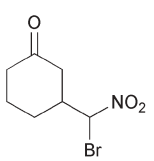

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