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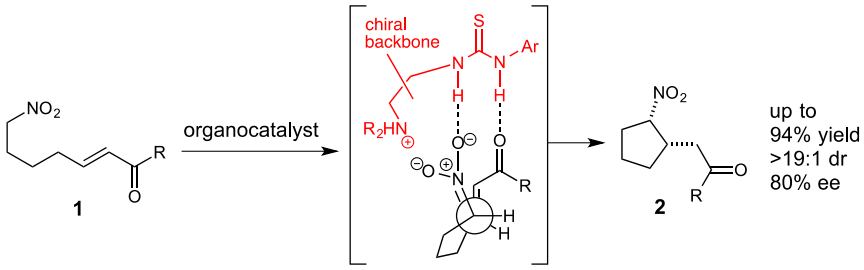
Dedicated to Professor Steven V. Ley CBE FRS on the occasion of his 70th birthday



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Abstract This paper described the use of bifunctional thiourea catalysts in the intramolecular reaction of a nitronate with conjugated ketones to generate the corresponding γ-nitroketones. In contrast to our previous studies in this area, we obtained the *cis*-functionalised systems as the major diastereoisomer in good yield and reasonable selectivities.

Key words organocatalysis, nitronate, cyclization, Michael addition, γ-nitroketone

The formation of new carbon-carbon bonds in a stereoselective and efficient manner is central to organic chemistry. In particular, methods that have an ease of utility, and that are environmentally benign have rightly become a focus of these studies. As such, organocatalysis has become a rapidly growing field which has shown a broad spectrum of behavior and utility.[1] Our interest in this area originated in our desire to construct novel amino acid precursors in a rapid and highly selective manner. As such, we have described the synthesis of a number of unnatural γ-amino acids, which have been constructed using hydrogen-bonding catalysis using either a nitro-group or a sulfone as the nucleophilic handle.[2] However, attempts at constructing the corresponding five-membered systems have been met with much lower selectivities, despite the attempted use of alternate catalyst methods.[3] In an attempt to improve upon this, we decided to change the nature of the electrophilic component from conjugated esters to conjugated ketones **1** (Figure 1A). Although this would not easily lead to amino acid precursors, we felt that the resulting adducts were interesting frameworks in their own right, and could be used in the construction of bicyclic pyrrolidine systems (Figure 1B). Examples of compounds that contain this functionality include the antihypertensive, ramipril and the DE ring system of the *Solanum* class of alkaloids (Figure 1B, highlighted in red).[4]

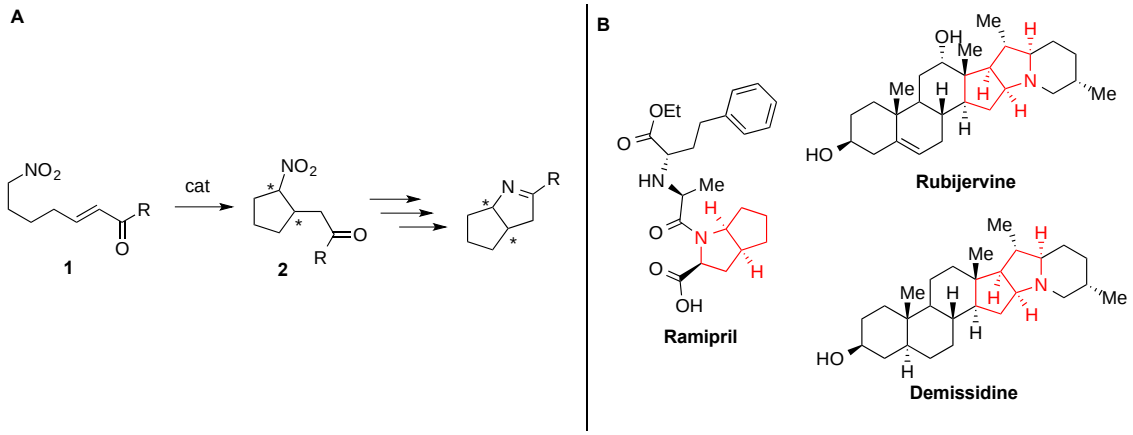
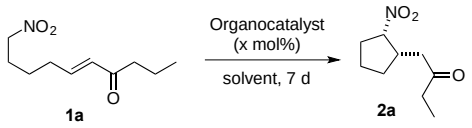


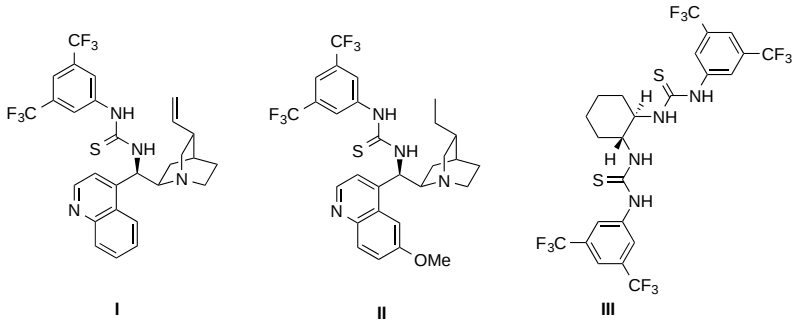
Figure 1(A) Concept : Synthesis of γ-nitroketone **(B)** Example occurances of the bicyclic pyrrolidine framework

Our starting point was the simple substrate (*E*)-10-nitrodec-5-en-4-one **1a**, which was made in two steps *via* standard formation of the β-ketophosphonate and subsequent Horner-Wadsworth-Emmons reaction according to literature procedure.[5] With this test substrate in hand, we subjected it to a number of thiourea catalysts (Table 1, representative examples shown),[6] using conditions we found to be favourable for a similar reaction in another study,[2a] and discovered that the cinchonine derived system **I** fared best in terms of enantioselectivity (Table 1, Entry 1). The related hydroquinine system **II** gave reduced enantioselectivities (Entry 2), and the C_2-symmetric catalyst **III**,[7] lacking an internal Lewis base, gave only a stoichiometric amount of product at a reduced enantioselectivity (Entry 3). A subsequent screen of solvent and catalyst load confirmed that organocatalyst **I**, when used at 20 mol% in

acetonitrile was indeed the best option. Intriguingly, the diastereoselectivity of the process was hugely dependent upon solvent, and could even be moderately reversed in some cases (Entries 7 and 8). Also of note, is the fact that a lower loading of organocatalyst leads to lower selectivities (Entries 1, 4 and 5).

Table 1. Catalyst and solvent screen for the asymmetric formation of γ-nitroketones





Entry	Catalyst	Mol%	Solvent	Yield, %[a]	Dr[b]	ee % (major)[c]
1	**I**	20	MeCN	60	>19:1	80
2	**II**	20	MeCN	73	2:1	64
3	**III**	20	MeCN	20	17:1	40
4	**I**	10	MeCN	56	6:1	64
5	**I**	5	MeCN	76	3:1	49
6	**I**	20	CH_2Cl_2	80	6:1	29
7	**I**	20	DCE	77	1:2	43
8	**I**	20	MeOH	83	1:3	25
9	**I**	20	THF	60	11:1	51
10	**I**	20	MeOH:MeCN, 1:1	65	5:1	45

[a]Isolated yield.

[b]Determined by 1H NMR spectroscopy.

[c]Determined by chiral-phase HPLC using a Chiralpak AD-H column and detection by UV at 280nm

We then examined the scope of the process using a variety of different conjugated ketones, and pleasingly found that each of them generated the corresponding cyclized compound in good yield and with reasonable enantiomeric excess (Table 2). The alkyl ketones (Entries 1-3) in particular performed well under our conditions with excellent diastereoselectivity and useful enantioelectivities, which were certainly an improvement upon the related conjugated ester systems using similar catalytic conditions. Indeed diastereoselectivity was generally good, except for the pivaloyl system **2e** (Entry 6), which also suffered from (relatively) reduced yield and enantioselectivity – presumably due to the steric constraints within this system. We also succeeded in preparing an adduct containing three contiguous stereocentres – the yield in this case was much reduced, but nevertheless the enantioselectivity was very pleasing (Entry 9).

In order to ascertain the relative stereochemistry of the adducts, a single crystal of compound **2d** was grown and a crystal structure obtained by X-ray diffraction using copper incident radiation. The crystal structure itself (CCDC deposition 1406015), in the centrosymmetric space group *Pbca*, is unremarkable but fascinatingly shows the relative configuration on the ring to be *cis* in nature (Figure 2). In many of the related systems that we have studied, we observe that under the reaction conditions, the *cis* system tends to equilibrate to the thermodynamically more favourable *trans* adduct. However in this case, such equilibration does not seem to occur to the same extent. This could well be to do with the reversibility of conjugate additions into conjugated esters *vs* the corresponding conjugated ketone systems in this study. The configuration of the other substrates was assigned by analogy.

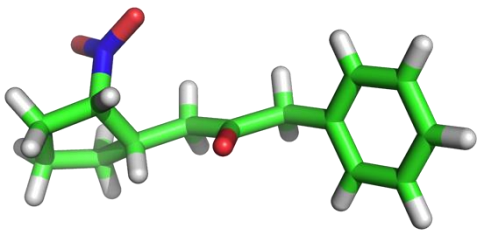


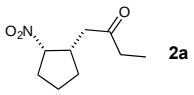
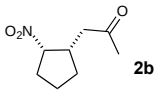
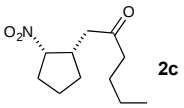
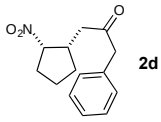
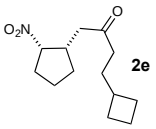
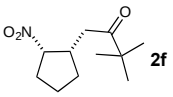
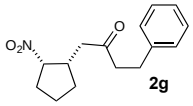
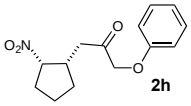
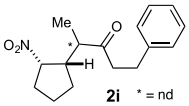
Figure 2 : The relative configuration of the adduct **2d,** as determined by single-crystal X-ray crystallography. CCDC no: 1406015, http://www.ccdc.cam.ac.uk.

The rationale for the formation of the *cis*-adduct follows on from our conjucture[2a,b] that in order to have reasonable reactivity, both the electrophilic ketone and the nucleophilic nitronate must be co-ordinated simultaneously. A third interaction between the protonated tertiary amine and the other nitronate

anion cements the chiral environment, leading to the transfer of stereochemical information (Figure 3).

Table 2 : Substrate scope for the asymmetric formation of γ-nitroketones.[8]

1 2

Entry, **product**	Yield, %[a]	Dr,[b] ee% (major)[c]
1  **2a**	2  **2b**	3  **2c**
60%, >19:1, 80%	65%, >19:1, 61%	65%, >19:1, 67%
4[8,9]  **2d**	5  **2e**	6  **2f**
94%, >19:1, 65%	80%, 3:1, 66%	50%, 4:1, 30%
7  **2g**	8  **2h**	9  **2i** * = nd
86%, 9:1, 30%	80%, 15:1, 8%	20%, 4:1:<1, 51%

[a]Isolated yield.

[b]Determined by 1H NMR spectroscopy.

[c]Determined by chiral-phase HPLC using a Chiralpak AD-H column and detection by UV at 280nm

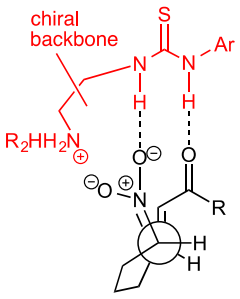


Figure 3 : Proposed transition state showing the preferred co-ordination of the catalyst (red) to the substrate, leading to the *cis*-configured cyclopentane system.

In conclusion, we have briefly demonstrated that we can extend our catalytic methodology to conjugated ketones in the formation of five-membered ring systems. These constructs are of *cis*-stereochemistry, and represent an improvement in the selectivity for nitrocyclopentane formation using the bifunctional thiourea catalyst class. This promising data has inspired us to design modified catalyst structures that should be more bespoke for this type of system, and we shall disclose these results in the near future.

Acknowledgment

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(8) Representative procedure : To a solution of (*E*)-8-nitro-1-phenyloct-3-en-2-one (150 mg, 0.6 mmol) in acetonitrile (5 mL) was added catalyst I (60.1 mg, 20 mol%) in one portion. The resulting mixture was stirred at room temperature for 7 days, whereupon the solvent was removed under reduced pressure, and the residue purified by column chromatography (diethyl ether:hexane, 1:3) to afford *cis*-1-(2-nitrocyclopentyl)-3-phenylpropan-2-one **2d** as a colourless oil (140 mg, 94%).

(9) Data for **2d** : The enantiomeric excess was determined by chiral HPLC analysis at 20 °C to be 65% (Chiralpak AD-H [0.46cm x 25cm] : t_1 32.7 min, t_2 39.2 min). 1H NMR (400MHz, $CDCl_3$) : 1.45 – 1.48 (2H, m, $C\underline{H}_2CH_2CHNO_2$), 1.65 – 1.68 (2H, m, $C\underline{H}_2CHRCHNO_2$), 2.10 (1H, m, $C\underline{H}HCHNO_2$), 2.34 (1H, m, $CH\underline{H}CHNO_2$), 2.48 (2H, m, cp$C\underline{H}_2$C(O)), 2.70 (1H, m, $CHNO_2C\underline{H}R$), 3.80 (2H, s, CH_2Ph), 5.04 (1H, dt, J 6.6 2.2, $C\underline{H}NO_2$), 7.17-7.30 (5H, m, Ar$\underline{H}$). IR (cm^{-1}) : 1260, 2973, 1714, 1544, 1458. HRMS required for ($C_{14}H_{18}O_3N$, MH^+) : 248.1132; Found 248.1133.