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COMMUNICATION

A novel C-5′ substituted cinchona alkaloid-derived catalyst promotes additions of alkyl thiols to nitroolefins with excellent enantioselectivity†‡

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A new bifunctional C-5′ substituted cinchona alkaloid-based catalyst promotes the first highly enantioselective additions of alkyl thiols to nitrostyrenes.

There has been a great deal of recent interest in the catalytic asymmetric addition of thiols to Michael acceptors.[1] Much of this attention has been focused on the organocatalytic variant of the process;[2] however - despite considerable endeavour - the scope of these reactions is reasonably narrow. Specifically, the asymmetric addition of thiophenols to a range of Michael acceptors promoted by bifunctional tertiary amine-based catalysts is now relatively straight forward, however, in the majority of studies the less reactive yet considerably more versatile *aliphatic* thiols are either not utilised or are reported to undergo considerably less selective addition than their aromatic counterparts.[3,4] Outside of iminium ion catalysis (enone/enal substrates),[5] examples of the highly enantioselective addition of aliphatic thiols to Michael acceptors are very rare (Fig. 1).[6] In the case of the highly synthetically malleable 1,2-disubstituted nitroalkenes, no examples are known.[7]

A indirect solution to this problem has been identified independently by Wang and Ellman: use of thioacetic acid (2.0 equiv.) as the nucleophile allows the possibility of later cleaving the thioester adduct hydrolytically, followed by an alkylation to give the product formally derived from the addition of an aliphatic thiol to the nitroalkene. In 2006, the former group[8] devised a protocol for the catalytic asymmetric addition of thioacetic acid to nitrostyrenes, with levels of product enantiomeric excess up to a maximum of 78% possible. Later, Ellman *et al.*[9] developed chiral *N*-sulfinyl urea-based catalysts capable of promoting the reaction with up to 96% product *ee* at −78 °C. The process is complicated by product consuming Baylis-Hillman-type chemistry under the reaction conditions, which limits the product yields to 63–88%, with higher yields (up to 95%) achievable when aliphatic nitroolefins are employed.

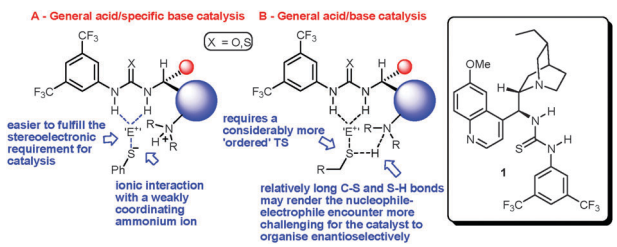

Fig. 1 Organocatalytic Michael-type additions involving thiols.

We were intrigued by and drawn to this curious general inferiority of synthetically relevant alkyl thiols in these organocatalysed Michael-type processes. While it was tempting to attribute this to the lower activity of alkyl thiols due to their reduced acidity, pronucleophiles of both similar and higher acidity have been shown to add to nitroolefins enantioselectively under similar conditions in the presence of cinchona alkaloid-based bifunctional catalysts.[10,11] We therefore postulated that the dearth of literature examples may be related to a combination of mechanistic and stereoelectronic factors: *i.e.* it is likely that catalysis by tertiary amines involving thiophenol (pK_a = 6.52[12]) occurs largely through *specific base catalysis*, while the less acidic alkane thiols (benzyl mercaptan pK_a = 9.43[12]) would require proton transfer in the transition state (*i.e. general base catalysis*), where stereocontrol over the formation and cleavage of longer bonds to a 2nd row element (relative to either carbon or other first row element based pronucleophiles) may be beyond the abilities of previously evaluated bifunctional catalyst systems (the relative positioning of the bifunctional components in which are reasonably invariant) such as **1**. In this regard we note with interest that Melchiorre *et al.* reported that the addition of the *P*-based pronucleophile diphenylphosphine (pK_a (DMSO) = 22.9[13])[14] to nitroolefins catalysed by the bifunctional catalyst **1** proceeded with moderate *ee* (36–67%).[15]

We recently[16] designed a range of C-5′-substituted cinchona alkaloid-derived catalysts devised to introduce some variation in this key catalyst attribute (*i.e.* the positioning of the bifunctional components),[17] and were naturally interested in evaluating their potential as catalysts for the problematic process outlined above. The results of this preliminary survey are presented in Table 1. First it was confirmed that no background reaction between (*E*)-β-nitrostyrene (**2**) and *t*-butyl benzyl mercaptan (**3a**)[18] in the absence of catalyst occurs (entry 1). Then, beginning with the optimum catalyst from our previous study (*i.e.* **5**) at 5 mol% levels in MTBE, we evaluated the addition of

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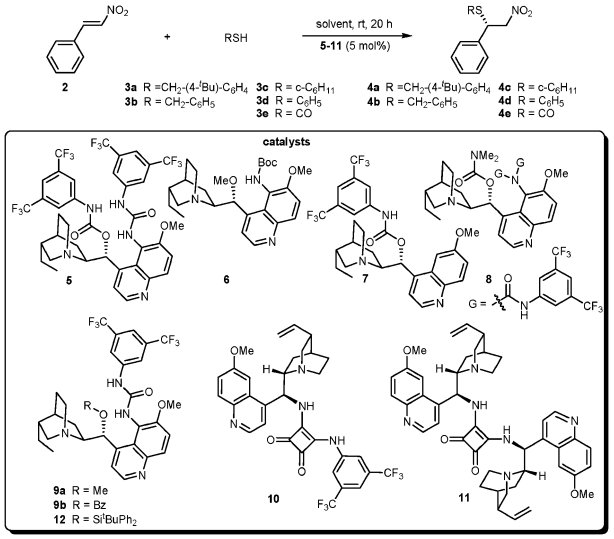
Table 1 Preliminary catalyst evaluation



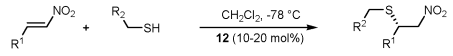
Entry	Cat. (mol%)	Prod.	Solv.	Conc. (M)	*t* (h)	Yield (%)[a]	*ee* (%)[b]
1	— (0)	**4a**	MTBE	0.37	16	0	0
2	**5** (5)	**4a**	MTBE	0.44	16	>98	32
3	**5** (5)	**4b**	MTBE	0.4	16	>98	25
4	**5** (5)	**4c**	MTBE	0.37	16	>98	4
5	**5** (5)	**4d**	MTBE	0.37	16	>98	3
6	**5** (5)	**4e**	MTBE	0.4	16	85	0
7	**5** (5)	**4d**	THF	0.37	40	>98	5
8	**5** (5)	**4d**	CH_2Cl_2	0.37	40	>98	4
9	**5** (5)	**4d**	PhMe	0.37	40	>98	7
10	**6** (5)	**4a**	MTBE	0.37	16	>98	1
11	**7** (5)	**4a**	MTBE	0.37	16	>98	8
12	**8** (5)	**4a**	MTBE	0.37	16	>98	17
13	**9a** (5)	**4a**	MTBE	0.37	16	>98	33
14	**9b** (5)	**4a**	MTBE	0.37	16	>98	−8
15	**1** (5)	**4a**	MTBE	0.37	16	>98	−1
16	**10** (5)	**4a**	MTBE	0.37	21	>98	−8
17	**11** (5)	**4a**	MTBE	0.37	21	>98	4
18	**12** (5)	**4a**	MTBE	0.37	16	>98	51
19[c]	**12** (5)	**4a**	MTBE	0.37	72	>98	71
20[c]	**12** (5)	**4a**	Et_2O	0.37	72	>98	69
21[c]	**12** (5)	**4a**	PhMe	0.37	24	>98	63
22[c]	**12** (5)	**4a**	$CHCl_3$	0.37	72	>98	75
23[c]	**12** (5)	**4a**	CH_2Cl_2	0.37	72	>98	78
24[d]	**12** (5)	**4a**	CH_2Cl_2	0.04	72	>98	88
25[d]	**12** (5)	**4a**	CH_2Cl_2	0.004	72	79	63
26[d]	**12** (10)	**4a**	CH_2Cl_2	0.02	24	>98	92

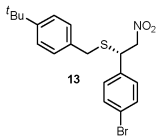
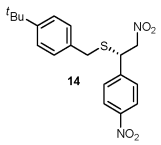
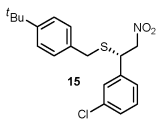
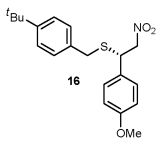
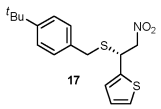
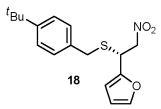
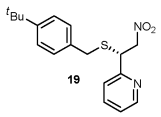
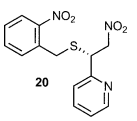
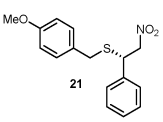
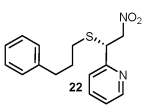
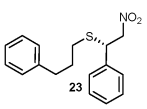
[a] Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. [b] Determined by CSP-HPLC. [c] At −30 °C. [d] At −78 °C.

a range of thiols (**3a–e**) of variable acidity to **2**. The general trend observed in previous studies is reversed in the presence of catalyst **5**: alkyl thiols **3a** and **3b** undergo moderately selective reaction (entries 2–3), while more acidic thiols **3d** and **3e** furnish either racemic or almost racemic products (entries 5–6).

Interestingly the hindered thiol **3c** proved a poor substrate (entry 4) and the failure of thiophenol to add enantioselectively to **2** is not solvent-specific (entries 7–9). Next a catalyst screen was undertaken: catalysts devoid of the C-5′ urea (*i.e.* **6** and **7**, entries 10–11) promoted efficient but unselective reactions, and while the C-5′- *bis*-urea substituted catalyst **8** fared marginally better (entry 12), it represented no improvement upon **5**. Variation of the C-9 substituent of catalyst **5** proved instructive:

Table 2 Investigation of substrate scope



Entry	Product	Loading (mol%)	Conc. (M)	*t* (h)	Yield (%)[a]	*ee* (%)[b]
1		10	0.02	20	96	90
2		20	0.01	68	98	86
3		20	0.007	68	84	91
4		20	0.01	68	97	90
5		10	0.02	20	93	92
6		20	0.01	68	99	90
7		10	0.02	20	91	96
8		10	0.02	20	82	93
9		10	0.02	20	98	90
10		20	0.01	96	56	94
11		20	0.01	96	77	89

[a] Isolated yield after chromatography. [b] Determined by CSP-HPLC.

use of the methoxy-substituted catalyst **9a** (entry 13) led to slightly higher product *ee*, whereas the corresponding benzoyl analogue **9b** is a poor catalyst from a stereoselectivity standpoint. As expected, representative traditional literature catalyst systems characterised by functionality capable of donating two hydrogen bonds at C-9 (*i.e.* **1**,[3c,10a,b,19] **10**[20] and **11**,[21] entries 15–17 respectively) failed to promote this reaction involving an alkyl thiol enantioselectively.

Given the importance of the C-9 unit in the case of catalyst **5**, it was decided to prepare an analogue with augmented steric bulk at this position. Gratifyingly, installation of a large (TBDPS) silyl-group resulted in a new catalyst (**12**) capable of generating **4a** in significantly improved enantiomeric excess (entry 18). Enantioselectivity increased further at −30 °C (entry 19) and a subsequent solvent screen (entries 20–23) and temperature/concentration optimisation experiments (entries 24–26) allowed conditions to be identified under which **12** (at 5 mol% loading) could promote the formation of **4a** in quantitative yield and 92% *ee* in 24 h.

With a useful protocol now in hand, attention turned to the question of substrate scope (Table 2). We were pleased to find that products derived from the addition of **3a** to both activated (**13–15**, entries 1–3) deactivated (**16**, entry 4) and heterocyclic (both π-excessive and π-deficient, **17–19**, entries 5–7) nitroolefins could be generated in excellent yield and enantioselectivity. Product *ee* was $\geq 90\%$ in all cases save that of the nitro-substituted **14**. Of particular synthetic utility is the use of alkane thiol derivatives which can serve as synthetic equivalents for H_2S: *i.e.* sulfides containing photo-cleavable[22] (*i.e.* **20**, entry 8) and acid/Hg^{2+}-labile[23] (*i.e.* **21**, entry 9) functionality can be prepared in excellent yield and *ee* using this methodology through the selection of the appropriate thiol. Non-benzylic alkane thiols are also compatible (**22–23**, entries 10–11).

In summary, prompted by a curious dependence of enantioselectivity on the acidity of thiol nucleophiles in many organocatalytic conjugate additions, we have developed (to the best of our knowledge) the first *general*, highly efficient and enantioselective organocatalytic system for the addition of previously problematic alkane thiols to nitrostyrenes. The process is promoted by a readily prepared novel C-5′ substituted bifunctional cinchona alkaloid catalyst and is of broad scope: a range of alkane thiols (including those containing cleavable benzyl substituents) and a variety of electron deficient, electron rich and heterocyclic nitrostyrenes are compatible. We would like to thank the Irish Research Council for Science Engineering and Technology for funding and Dr T. McCabe for X-ray analysis.

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