Enantioselective organocatalytic Michael addition of malonate esters to nitro olefins using bifunctional cinchonine derivatives†‡

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A family of 9-amino(9-deoxy) epicinchonine derivatives, possessing a range of mono- and bidentate hydrogen bond donor groups at the 9-position, were synthesised and evaluated for asymmetric organocatalytic activity in the dimethyl malonate Michael addition to β-nitrostyrene; thiourea derivative 1e was identified as the most effective bifunctional organic catalyst and found to induce high enantioselectivity in the malonate ester Michael addition reaction to a range of nitro olefins.

The Michael addition of carbon-centred nucleophiles to nitro olefin acceptors is a powerful reaction for the synthesis of functionally dense, stereochemically defined molecules with the generation of up to three new stereogenic centres in the carbon chain.[1] When 1,3-dicarbonyl compounds are used as the carbon-centred nucleophile, the reaction provides rapid access to versatile chiral building blocks for the synthesis of important, nitrogen-containing bioactive agrochemical and pharmaceutical compounds.[2] This has resulted in much interest from within the synthetic community, and in particular from groups engaged in the development of catalytic asymmetric methodologies. Thus, reactions of this type have been reported to proceed in high yield and with good enantioselectivity by the employment of various asymmetric catalysts containing metal ions.[3] Additionally, with the interest in the use of organic catalysts[4] for the asymmetric α-functionalisation of aldehyde and ketone substrates, many researchers have explored the cyclic secondary amine catalysed addition of carbonyl compounds to nitro olefins and good levels of enantiocontrol have been reported.[5]

Asymmetric bifunctional organic catalysts, which possess a combination of suitably separated Lewis base and Brønsted acid functionalities attached to a fairly rigid chiral scaffold, have emerged as powerful tools for the asymmetric construction of carbon–carbon and carbon–heteroatom bonds in reactions of carbon acids with aldehyde,[6] imine,[7] electron poor alkene[5,8] and other[9] substrates. As with their asymmetric Lewis base–Lewis acid bifunctional catalyst counterparts,[10] the capacity of these compounds to mutually activate and template electrophilic substrates and nucleophilic (or pro-nucleophilic) reagents can provide excellent levels of stereocontrol in efficient reactions at low catalyst loadings and at reasonable reaction rates. However, these organic counterparts are more easily prepared, are user-friendly (no need for glovebox techniques), often have little or no sensitivity to moisture and air in the reaction solvents, are less toxic, and can be available at a reasonable cost.

In search of new organic, asymmetric Lewis base–Brønsted acid bifunctional catalysts we reasoned that a versatile, powerful and readily accessible *family* of bifunctional organic catalysts could be created from a 9-amino(9-deoxy) *epi-Cinchona* alkaloid skeleton. This structure would combine a basic bridgehead nitrogen with a readily tunable hydrogen bond donor group originating from the 9-amino functionality. Thus attachment of suitable electron withdrawing groups (with or without additional hydrogen bond donor groups) would allow for subtle or dramatic changes to the type, structure and electronics of the Brønsted acid group of the catalyst and thus provide a platform for rapid catalyst synthesis, identification and optimisation in the reaction of interest.

Herein we report the performance of a family of 9-amino(9-deoxy) epicinchonine-derived bifunctional catalysts **1**, in the nitro olefin Michael addition reaction with malonate esters.

9-Amino(9-deoxy) epicinchonine (AECN) was prepared from cinchonine on a 15 g scale in one step following the literature method.[11] Conversion of this material to test catalysts **1a–f**, bearing a range of monodentate hydrogen bond donor groups (carboxamides and sulfonamides)[11b,e] and bidentate hydrogen bond donor groups (thiourea) was readily accomplished (Fig. 1).[12]

These compounds were screened for performance in the dimethyl malonate Michael addition to β-nitrostyrene in dichloromethane at room temperature (Table 1). With monodentate hydrogen bond donor catalysts **1a–c**, the reactions were sluggish and required 72 h to go to completion. Benzoylamide **1a** gave rise to virtually no enantioselectivity but methanesulfonamide **1b** and *p*-toluenesulfonamide **1c** gave moderate to good enantiocontrol (70% and 60% ee respectively).

With bidentate hydrogen bond donor catalysts **1d** and **1e** bearing a phenyl thiourea and 3,5-bis(trifluoromethyl) phenyl thiourea, the room temperature reactions in dichloromethane were complete in 44 and 22 h respectively. This enhanced catalytic activity was mirrored by a significant increase in the enantiocontrol

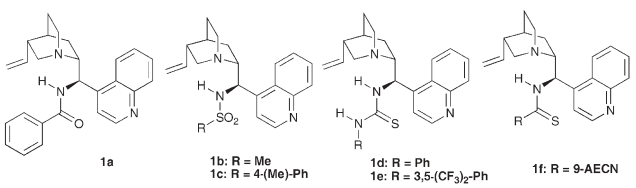

Fig. 1 A family of cinchonine-derived bifunctional catalysts.

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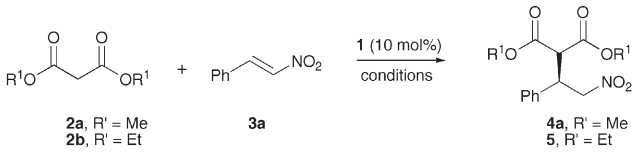
‡ Dedicated with respect to Professor Steven V. Ley on the occasion of his 60th birthday.

Table 1 Screen of reaction conditions in malonate Michael addition reactions to β-nitrostyrene using bifunctional catalyst **1**[a]



2a, R' = Me
2b, R' = Et

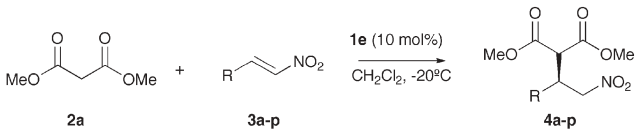
3a

4a, R' = Me
5, R' = Et

Entry	Catalyst	R^1	Temp./°C	Solvent	Time/h	Conv. (%)[b]	ee (%)[c]
1	**1a**	Me	r.t.	CH_2Cl_2	72	93	8
2	**1b**	Me	r.t.	CH_2Cl_2	72	99	70
3	**1c**	Me	r.t.	CH_2Cl_2	72	88	60
4	**1d**	Me	r.t.	CH_2Cl_2	44	96	87
5	**1e**	Me	r.t.	CH_2Cl_2	22	98	87
6	**1f**	Me	r.t.	CH_2Cl_2	44	99	17
7	**1e**	Et	−20	Toluene	48	83	92
8	**1e**	Me	−20	Toluene	48	94	94
9	**1e**	Me	−20	CH_2Cl_2	40	98	94
10	**1e**	Me	−20	Et_2O	40	97	94
11	**1e**	Me	−20	TBME	48	98	93
12	**1e**	Me	−20	THF	48	93	89
13	**1e**	Me	−20	*n*-Hexane[d]	22	<30	89
14	**1e**	Me	−20	—	30	97	92

[a] Reactions performed with 0.2 mmol of nitro olefin and 2 eq. of malonate in 0.2 mL of solvent. [b] Determined by HPLC analysis. [c] Determined by chiral HPLC analysis. [d] Catalyst insoluble in hexane at room temperature.

Table 2 Scope of the Michael addition of methyl malonate to nitro olefins catalysed by bifunctional catalyst **1e**[a]



2a

3a-p

4a-p

Entry	R	Time/h	Product	Yield (%)[b]	ee (%)[c]
1	Ph	30	**4a**	95	94
2	2-Naphthyl	48	**4b**	83	89
3	2-Cl phenyl	30	**4c**	99	94
4	2-Br phenyl	30	**4d**	95	92
5	3-Br phenyl	30	**4e**	85	90
6	4-Br phenyl	48	**4f**	87	90
7	4-Me phenyl	48	**4g**	82	92
8	3-Me phenyl	52	**4h**	92	91
9	4-MeO phenyl	30	**4i**	96	92
10	3-MeO phenyl	30	**4j**	96	91
11	2-MeO phenyl	30	**4k**	96	97
12	2-Furyl	30	**4l**	93	95
13	2-Thienyl	30	**4m**	87	94
14	*n*-Pen	72	**4n**	81	87
15	*c*-Hex[d]	31	**4o**	82	82
16	*t*-Bu[d]	48	**4p**	—	—

[a] Reactions performed with 0.4 mmol of nitro olefin and 3 eq. of dimethyl malonate in 0.4 mL of CH_2Cl_2. [b] Yield after purification by flash column chromatography on silica gel. [c] Determined by chiral HPLC analysis. [d] Performed in neat dimethyl malonate (5 eq.) at room temperature.

in the reactions (87% ee in both cases). Interestingly however, the reaction with C_2-symmetric thiourea catalyst **1f** gave the Michael adduct in only 17% ee.

Having identified the thiourea catalyst **1e** as the champion of the family, a screen of solvents in the Michael reaction of dimethyl and diethyl malonate (2.0 eq.) with β-nitrostryene (1.0 eq.) at −20 °C was performed. Initially, diethyl and dimethyl malonate were compared, using toluene as the solvent, for a reaction time of 48 h. Dimethyl malonate proved to be more reactive than the diethyl analogue (94% *vs.* 83% conversion) and afforded the product in the highest enantiomeric excess (94% *vs.* 92% ee). The stereochemistry of the major product was confirmed as (*R*).† The excellent enantiocontrol was maintained in all non-hydroxylic solvents tested. These included chlorinated (CH_2Cl_2, 94% ee), ethereal (diethyl ether, 94% ee; TBME, 93% ee and THF 89% ee) and non-ethereal (*n*-hexane 89% ee). Additionally, good reaction rates and enantiocontrol were observed when the reaction was performed without solvent (97% conversion, 30 h and 92% ee). Notably, in all cases shown in Table 1, the solvents were used directly from the bottle and no attempt was made to exclude moisture or oxygen from the reaction mixture.

Although it was clear that most solvents could be used for the reaction without significant detriment to the yield or enantioselectivity, it was decided to scope the reaction using **1e** in dichloromethane. This solvent gave rise to the highest enantiocontrol, fastest reaction rate and invariably offered the best solubilising properties for substrates and products.

A range of *ortho*-, *meta*- and *para*-substituted aryl, heteroaryl and alkyl β-substituted nitro olefins were synthesised according to the literature methods. These were then treated with dimethyl malonate (3 eq.) and catalyst **1e** (10 mol%) in dichloromethane at −20 °C and the reactions monitored by TLC. On completion, the reaction mixtures were evaporated and the crude products purified by flash column chromatography. The results are presented in Table 2.

With aromatic and heteroaromatic substrates, typical reaction times ranged from 1 to 2 days with 30 h being common. The reaction yields were good to excellent (82–99%). Enantioselectivities were good and ranged from 89 to 97% ee. In general, the lowest selectivities were found with *meta*- and *para*-substituted aryl ring systems (89–92% ee). Conversely, the highest enantiocontrol was witnessed in Michael acceptors derived from *ortho*-substituted aryl aldehydes and aromatic heterocyclic aldehydes (92–97% ee).

Aliphatic nitro olefins reacted more slowly than their aromatic counterparts and slight erosion in enantioselectivity was witnessed. Thus, with *E*-1-nitro-1-heptene the reaction required 72 h at −20 °C and the product was isolated in 81% yield and 87% ee. With *E*-2-cyclohexyl-1-nitroethene as the Michael acceptor, the reaction was impractically slow at −20 °C in dichloromethane and thus alternative reaction conditions were sought. Pleasingly, reaction in neat dimethyl malonate (5 eq.) at room temperature was fast (31 h) and gave the product in respectable yield (82%) and good enantioselectivity (82% ee). Unsurprisingly, with *E*-2-*tert*-butyl-1-nitroethene little reaction product (<5%) was observed in the reaction at room temperature in neat dimethyl malonate for 48 h and the reaction was abandoned.

In conclusion, we have demonstrated that catalyst **1e** is representative of a new class of asymmetric bifunctional organic catalysts originating from the privileged *Cinchona* alkaloid scaffold.[12,13] This structure has provided the necessary positioning of Lewis basic and Brønsted acidic functional groups to allow desirable activation and organisation of malonate nucleophiles and nitro olefin Michael acceptors leading to the adducts in good yield and enantioselectivity. Further work to explore the scope of this

and related catalysts is ongoing in our group and the results will be reported in due course.

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