Enantioselective construction of quaternary carbon centre catalysed by bifunctional organocatalyst†

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The bifunctional thiourea–tertiary amine derivatives of simple chiral diamines serve as highly enantioselective catalysts for the Michael addition of α-substituted cyanoacetates to vinyl sulfones, giving an efficient protocol for the construction of an all-carbon substituted quaternary stereocentre.

In recent years the development of organic molecules capable of the efficient and enantioselective promotion of carbon–carbon bond-forming reactions has triggered ongoing interest.[1] In particular, bifunctional catalysts[2] possessing a combination of thiourea (or urea)[3] and amine groups have received special attention.[4] The double hydrogen-bonding interaction of the N–H of thiourea (or urea) and a reactant has been generally realized to have a specific role in efficient catalysis and high enantiocontrol.[5] Several functionalities, including nitro, carbonyl and imine groups, have been successfully applied.[3–5] Nevertheless, expanding the scope of reactants would be a welcome advance to the insight of the general synthetic utilities of the thiourea-based catalysts.

Nowadays, sulfones are still recognized as significant intermediates in organic synthesis, especially when behaving as the activating group for C–C bond forming reactions.[6] Therefore, it is not surprising that considerable efforts have been devoted to the development of enantioselective Michael addition to vinyl sulfones. However, compared to the extensively studied α,β-unsaturated carbonyl compounds or nitroolefins, the enantioselective catalytic reaction of vinyl sulfones is still in its infancy.[7,8] In addition, the application of hydrogen-bonding interactions of S=O functionalities in asymmetric synthesis is also rare.[9] In 1998 Gong *et al.* reported that a robust 2D sheet could be formed from *N*,*N*′-dibenzylsulfamides through intermolecular hydrogen-bonding of O=S–N–H units (Fig. 1a).[10] We envision that an efficient double hydrogen-bonding interaction might also be possible between the N–H of thiourea catalyst and the S=O of vinyl sulfone compounds,[11] as has been observed for nitro groups (Fig. 1b *vs* c).[4a,b,h,j] As part of our continuous study on thiourea-based organocatalysis,[4d] here we wish to report the highly enantioselective Michael addition of α-substituted cyanoacetates[12] and vinyl sulfones synergistically promoted by bifunctional thiourea–tertiary amine organocatalysts, giving an efficient protocol for the construction of an all-carbon substituted quaternary stereocentre[13] at the prochiral nucleophiles.[8c] More importantly, the addition products could be smoothly converted to the enantiomerically pure $\beta^{2,2}$-amino acids, which still represent a challenge for synthetic chemists.[14]

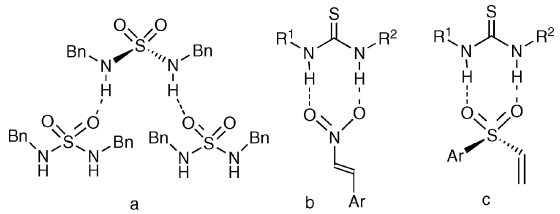

Fig. 1 Proposed hydrogen-bonding interaction of NH of thiourea with functional groups.

Bifunctional catalysts **1a**–**e** (Fig. 2, 20 mol%) with various chiral scaffolds, which have been previously reported by us[4d] and other chemists,[4] were screened in the Michael addition of ethyl α-phenyl cyanoacetate **2a** and phenyl vinyl sulfone **3** in toluene at room temperature. As summarized in Table 1, all catalysts could smoothly promote this Michael reaction to give the addition product **4a**. Good to quantitative yields with moderate enantioselectivities (43–68% ee) were observed for structurally variable bifunctional catalysts (Table 1, entries 1–5). Catalyst **1e** derived from the more flexible (*R*,*R*)-1,2-diphenylethylenediamine exhibited much better enantioselectivity (68% ee, entry 5), while the catalytic activity was inferior to the other catalysts **1a**–**d**. Notably this was the first example that the acyclic catalyst **1e** was superior to the other thiourea–tertiary amine bifunctional analogues with more rigid scaffolds.[4a–l] Similar results were obtained for the modified catalysts **1f** and **1g** (entries 6 and 7). Subsequently various solvents were tested (entries 8–11). The

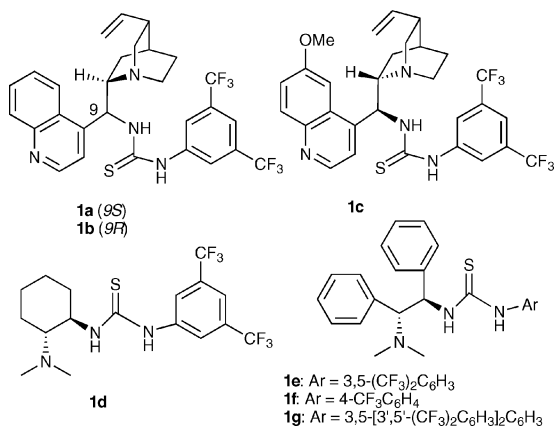

Fig. 2 Structures of various chiral thiourea–tertiary amine catalysts.

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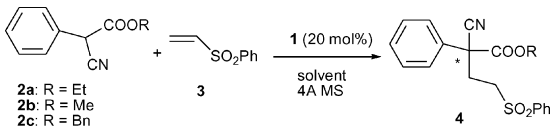
† Electronic supplementary information (ESI) available: Experimental procedures, structural proofs, NMR, HRMS and HPLC spectra of the products. See DOI: 10.1039/b605871j

Table 1 Screening studies of the Michael addition of α-phenyl cyanoacetates **2** to phenyl vinyl sulfone **3**[a]



Entry	Catalyst	Solvent	T (°C)	Time/h	Yield[b] (%)	ee[c] (%)
1	**1a**	Toluene	20	5	95	54
2	**1b**	Toluene	20	5	96	43
3	**1c**	Toluene	20	5	95	53
4	**1d**	Toluene	20	6	94	52
5	**1e**	Toluene	20	8	75	68
6	**1f**	Toluene	20	8	75	66
7	**1g**	Toluene	20	6	81	62
8	**1e**	DCM	20	10	62	48
9	**1e**	THF	20	13	47	31
10	**1e**	CH_3CN	20	13	61	8
11	**1e**	Benzene	20	8	73	66
12[d]	**1e**	Toluene	20	7	76	64
13[e]	**1e**	Toluene	20	10	77	63
14	**1a**	Toluene	−40	48	90	72
15	**1d**	Toluene	−40	48	89	81
16	**1e**	**Toluene**	**−40**	**96**	**83**	**94**
17	**1f**	Toluene	−40	96	75	81

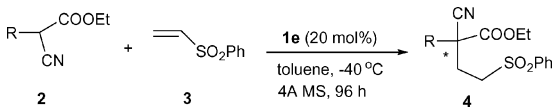
[a] Reaction conditions: **2** (0.2 mmol), **3** (0.1 mmol) and catalyst **1** (0.02 mmol) were stirred in a solvent (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] **2b** was used. [e] **2c** was used.

enantioselectivities decreased dramatically in non-arene solvents (entries 8–10). In addition, similar results were gained for the other cyanoacetates **2b** and **2c** (entries 12 and 13). Finally, we conducted the Michael reaction at lower temperature in order to improve the enantioselectivity. It was quite inspiring that the ees were greatly elevated at −40 °C in the reactions catalysed by organocatalysts **1a**, **1d**–**f** (entries 14–17), and up to 94% ee was obtained in good isolated yield after 96 h in the case of **1e** (entry 16).

With the optimised reaction conditions in hand, the scope and limitation of the bifunctional organocatalyst **1e** promoted asymmetric Michael reactions were explored. A series of α-aryl substituted ethyl cyanoacetates were reacted with phenyl vinyl sulfone **3** in the presence of 20 mol% **1e** at −40 °C for 96 h. As summarised in Table 2, excellent enantioselectivities with high yields were obtained for α-aryl cyanoacetates with various halide substituents (Table 2, entries 2–4). For *m*-trifluoromethyl substrate **2g**, better ee could be received at lower temperature (entry 5). In addition, high enantioselectivity was achieved for aryl substrate **2h** with electron-donating substituent (entry 6). Heteroaryl derivative **2i** also gave excellent results under the same conditions (entry 7).

Having presented the reaction scope of α-aryl cyanoacetates with vinyl sulfone **3**, we further investigated the reaction of α-alkyl cyanoacetates. Unfortunately, very poor reactivity was observed in the reaction of α-methyl cyanoacetate **2j** and **3** even at ambient temperature in the presence of **1e** (20 mol%, 24 h, <30% conversion, 45% ee). However, the reaction could be considerably accelerated by employing the highly electrophilic 1,1-bis(benzenesulfonyl)ethylene **5**[8d] as the Michael acceptor. Quantitative yield was obtained in the reaction of **2j** and **5** catalysed by **1d** or **1e** (20 mol%) after 1 h at ambient temperature, but very poor enantioselectivity was obtained (<30% ee).[15] Gratifyingly, the result could be greatly improved when the reaction was conducted

Table 2 Asymmetric Michael addition of α-aryl cyanoacetates **2** to phenyl vinyl sulfone **3**[a]



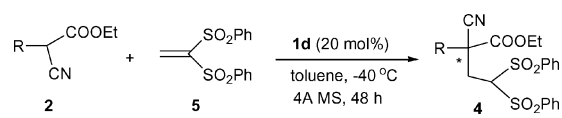
Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	Ph (**2a**)	**4a**	83	94
2	*p*-Cl–Ph (**2d**)	**4d**	90	95
3	*p*-Br–Ph (**2e**)	**4e**	93	96
4	*p*-F–Ph (**2f**)	**4f**	92	93
5[d]	*m*-CF_3–Ph (**2g**)	**4g**	92	91
6	*p*-CH_3O–Ph (**2h**)	**4h**	73	94
7	2-thienyl (**2i**)	**4i**	96	95

[a] Reaction conditions: **2** (0.2 mmol), **3** (0.1 mmol) and catalyst **1e** (0.02 mmol) were stirred in toluene (1 mL) for 96 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. The absolute configurations have not been assigned yet. [d] At −50 °C for 96 h.

at −40 °C, and up to 73% ee was received in excellent isolated yield in the presence of the more rigid catalyst **1d** (Table 3, entry 1).[16] Nevertheless, the enantioselectivity could not been further increased at lower temperature. When α-*n*-butyl cyanoacetate **2k** was applied, the enantioselectivity was elevated to 82% ee (entry 2). In addition, good ee was obtained in the case of α-benzyl substrate **2l** (entry 3), and almost enantiomerically pure product was received after recrystallization (data in bracket). Notably the acetal-functionalised cyanoacetate **2m** gave excellent ee at −50 °C while the isolated yield was moderate (entry 4).

Deng *et al.* have successfully developed an approach for the synthesis of chiral α,α-disubstituted α-amino acids from the addition products of vinyl sulfone.[8c] Here the α,α-disubstituted cyanoacetates were smoothly converted to the biologically important $\beta^{2,2}$-amino acids, which have not been easily accessible in an enantioselective catalytic way to date.[14] As illustrated in Scheme 1, the protected $\beta^{2,2}$-amino acid **6a** was obtained in one pot in the presence of Boc_2O, employing Raney-Ni catalysed hydrogenation at 50 psi H_2 pressure. In addition, the protected $\beta^{2,2}$-amino acid **6b** was also prepared from the α-benzyl bis(pehnylsulfone) **4l** under the same conditions, while a slight decrease in ee was observed in the product. The remaining sulfone could behave as the activating

Table 3 Asymmetric Michael addition of α-alkyl cyanoacetates **2** to vinyl sulfone **5**[a]



Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	Me (**2j**)	**4j**	96	73
2	*n*-Butyl (**2k**)	**4k**	98	82
3	Benzyl (**2l**)	**4l**	98 (70)[d]	72 (99)[d]
4[e]	$(EtO)_2CH_2$ (**2m**)	**4m**	52	96

[a] Reaction conditions: **2** (0.2 mmol), **5** (0.1 mmol) and catalyst **1d** (0.02 mmol) were stirred in toluene (1 mL) for 48 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. The absolute configurations have not been assigned yet. [d] After recrystallization from 2-propanol–hexane. [e] At −50 °C for 96 h.

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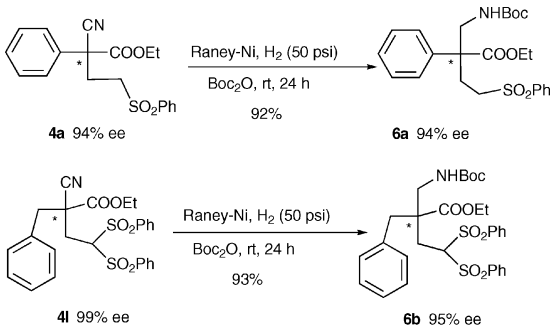

Scheme 1 Synthesis of optically active $\beta^{2,2}$-amino acids.

group for the further C–C bond forming reactions, thus variously structured $\beta^{2,2}$-amino acids might be accessible from the well established procedures.[6,8c,d]

In conclusion, we have described a highly efficient organocatalytic method for the asymmetric Michael addition of α-substituted cyanoacetates to vinyl sulfones. This reaction was synergistically promoted by readily available bifunctional thiourea–tertiary amine organocatalysts, and an all-carbon substituted quaternary stereocentre was constructed. To the best of our knowledge, this is the first enantioselective catalytic reaction which might involve a double-hydrogen bonding interaction between the NH of thiourea and a sulfone functionality. In addition, the reaction scope is substantial and α-aryl or alkyl cyanoacetates could be successfully applied, and excellent enantioselectivities (72–96% ee) were achieved. Moreover, the biologically important $\beta^{2,2}$-amino acids could be smoothly prepared from the addition products. Currently, studies are actively underway to investigate the reaction mechanism and expand the synthetic utility of the optically active addition products.

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