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PAPER

Self-association free bifunctional thiourea organocatalysts: synthesis of chiral α -amino acids *via* dynamic kinetic resolution of racemic azlactones[†]Joong-Suk Oh,^a Ji-Woong Lee,^a Tae Hee Ryu,^a Jae Heon Lee^a and Choong Eui Song^{*a,b}

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Concentration-independent high enantioselectivity in the dynamic kinetic resolution (DKR) of racemic azlactones affording chiral α -aminoesters has been achieved using self-association free thiourea-based dimeric cinchona alkaloid organocatalysts. Detailed experimental studies and single crystal X-ray analysis confirmed that these bifunctional organocatalysts **I** do not form H-bonded self-aggregates in either solution or solid state.

Introduction

At present, there is much interest in organocatalysts, because they tend to be less toxic and more environmentally friendly than traditional metal-based catalysts.¹ Although much progress has been made, the development of chiral organocatalysts that are as reactive and stereoselective as some of the best transition-metal catalysts remains a considerable challenge. To attain reasonable reaction rates and stereoselectivity with organocatalysts, large catalyst loading is often required. One way to address this difficulty is to design bifunctional or multifunctional organocatalysts with functional groups that work cooperatively to stabilize the transition state and accelerate the rate of the reaction.² It has been shown that urea- or thiourea-based bifunctional organocatalysts are effective in facilitating a variety of useful organic reactions.³ However, we showed recently that urea- and thiourea-based organocatalysts can form hydrogen-bonded aggregates, which result in a strong dependence of reactivity and enantioselectivity on concentration and temperature.⁴ Due to the self-association phenomena of this type of catalysts, in general, enantioselectivity dramatically decreases with increasing concentration,^{4a,4c} which can hamper their practical use. X-Ray crystal structures of monofunctional and bifunctional (thio)urea derivatives show that they form aggregates through hydrogen bonding between the (thio)urea NH groups and the (thio)urea sulfur or oxygen atom in an intermolecular fashion.⁵ Recent NMR spectroscopic studies conducted independently by us and by the Soós research group also showed that cinchona-derived thioureas exist as dimers, even in solution and at room temperature.^{4a,6}

Results and discussion

In this paper, we report that C₂-symmetric bis-cinchona-alkaloid-based thiourea catalysts **Ia–d** (Fig. 1)^{7,8} are self-association free since the steric bulk of the two alkaloid moieties of **I** prevent their self-aggregation, and, thus, showed concentration-independent enantioselectivity in the dynamic kinetic resolution (DKR)^{7,9,10} of racemic azlactones, affording chiral α -amino esters with high ee values even under highly concentrated conditions (1 M). Moreover, as anticipated, experimental and NMR spectroscopic studies and single crystal X-ray analysis confirmed that these bifunctional organocatalysts **I** do not form H-bonded self-aggregates in either solution or solid state.

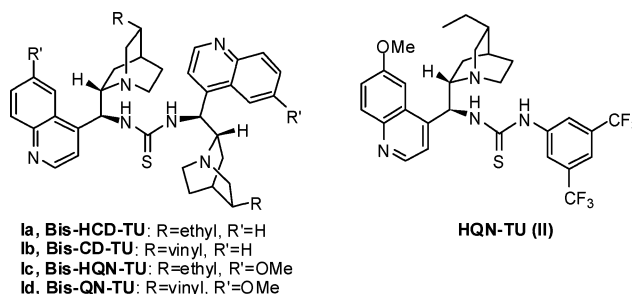


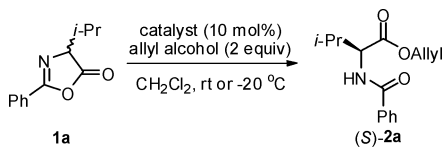
Fig. 1 Cinchona-based organocatalysts tested in our study (HCD = hydrocinchonidine; CD = cinchonidine; HQN = hydroquinine; QN = quinine).

To investigate the catalytic activity and enantioselectivity of the bis-cinchona-alkaloid-based thiourea catalysts, we conducted DKR of the racemic valine-derived azlactone **1a**¹¹ in the presence of catalysts **Ia–d** (10 mol%) in CH₂Cl₂ (0.5 M) at room temperature. The results are summarized in Table 1, with the data obtained using monomeric thiourea **II**. As shown in Table 1, DKR of racemic azlactone **1a** proceeded smoothly, and, thus, all reactions were completed within 24 h to afford the chiral amino ester **2a** at excellent yields and high enantioselectivity (entries 1, 3, 4 and 5).¹² The enantioselectivity could be further increased

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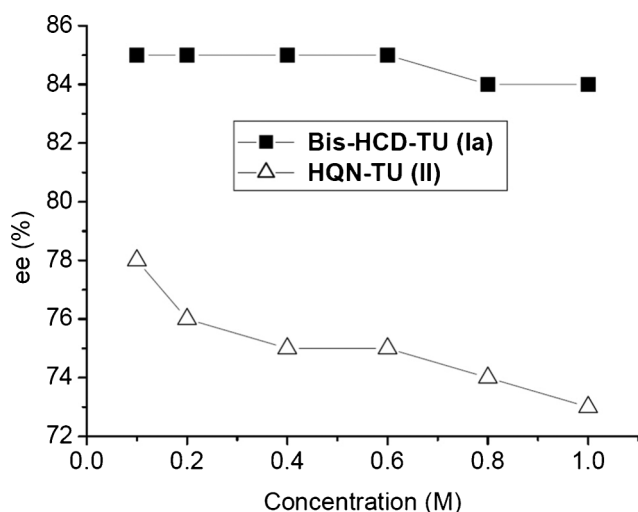
Table 1 Catalytic DKR of the racemic valine-derived azlactone **1a** with allyl alcohol^a


Entry	Catalyst	Temp. (°C)	Time (h)	Yield (%) ^b	ee (%) ^c
1	1a	20	8	95(76)	85(>99) ^d
2	1a	-20	48	96(85)	91(>99) ^d
3	1b	20	18	96	82
4	1c	20	10	96	84
5	1d	20	24	97	82
6	11	20	12	95	75

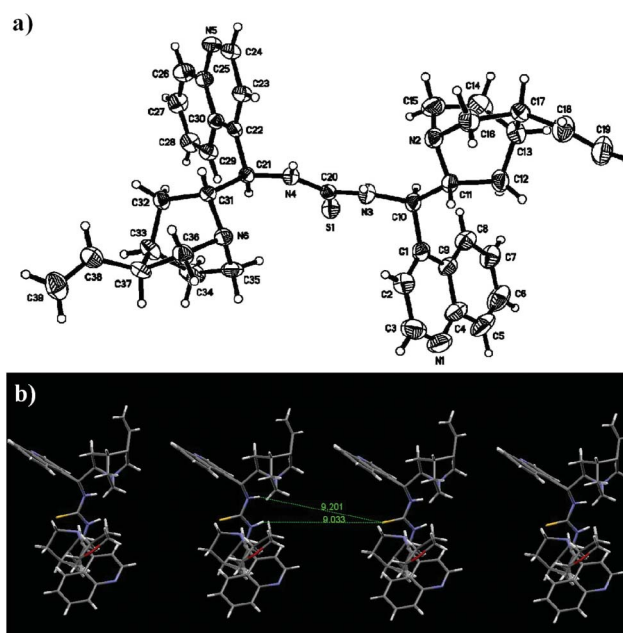
^a The reactions were carried out with **1a** (0.5 mmol), allyl alcohol (2 equiv., 1 mmol), and the catalyst (10 mol%) in CH₂Cl₂ (1.0 mL). ^b Isolated yields after chromatographic purification. ^c Determined by chiral HPLC (see ESI). ^d The values in parentheses were obtained after single recrystallization.

to 91% ee by lowering the reaction temperature to -20 °C (entry 2). Moreover, the optical purity was enriched to >99% ee by a single recrystallization (entries 1 and 2). In contrast, the previously reported cinchona-based monomeric thiourea catalyst **11** (entry 6) showed inferior enantioselectivity (75% ee) compared to the dimeric ones **1a–1d**.

We next conducted DKR reactions of the azlactone **1a** with allyl alcohol (2 equiv.) in the presence of the hydrocinchonidine derived dimeric catalyst **1a** (10 mol%) and the corresponding monomeric catalysts **11** (10 mol%) at various concentrations ([**1a**] = 0.1–1.0 M in CH₂Cl₂). As depicted in Fig. 2, the enantioselectivity of the dimeric catalyst **1a** (square symbols) was not significantly dependent on the concentration, unlike the corresponding monomeric catalyst **11** (triangle). Even under highly concentrated conditions (1 M), the ee value can almost be retained, which is highly desirable for practical purposes. On the basis of these experimental results, it is clear that the thiourea-based dimeric catalysts **1a** do not self-aggregate to any appreciable extent, as was anticipated.



**Fig. 2** Effect of concentration on the enantioselectivity in the DKR of racemic **1a**.

Moreover, NMR spectroscopy also showed that the catalyst **1a** does not form aggregates in solution. In the ¹H NMR dilution experiments of **1a** in CDCl₃, any significant concentration dependencies were not observed for the chemical shift of –C(=S)N(H)–Ar proton. The chemical shift ($\delta = ca.$ 6.9 ppm) of this proton was maintained at concentrations ranging from 0.1 M to 1.0 M. In contrast, marked concentration dependencies were observed for the chemical shift of the thiourea proton of monomeric analogue **QN-TU**,^{4c} strongly indicating the hydrogen-bonded self-association of this type of monomeric catalyst.¹³ Furthermore, the single crystal X-ray structure of **Bis-CD-TU (1b)** revealed that this type of catalyst cannot form H-bonded self-aggregates even in the solid state.¹⁴ As shown in Fig. 3, there is no intermolecular H-bond interaction between the thiourea NH group and the thiourea sulfur atom. The distance between the C=S and NH moieties is *ca.* 9.0–9.2 Å.

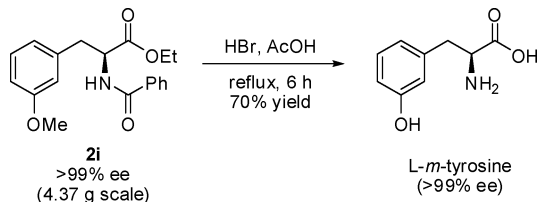
**Fig. 3** (a) ORTEP diagram of **Bis-CD-TU (1b)** (the solvent molecule (toluene) is omitted for clarity). (b) Schematic drawing of the crystal packing in **1b**.

Having established that the thiourea-based dimeric cinchona alkaloids **1** act as highly enantioselective and self-association free catalysts, we explored the scope of the substrate. All reactions were conducted in one pot starting from the *N*-protected racemic amino acids **3**, which were derived from valine (**3a–3d**), alanine (**3e**), 2-aminobutyric acid (**3f**), allylglycine (**3g**), propargylglycine (**3h**), *m*-tyrosine (**3i**) and 3-(2-naphthyl)alanine (**3j**) in the presence of 10 mol% of the catalyst **1a** in CH₂Cl₂ (0.5 M) at -20 °C (for experimental details, see ESI).[†] As shown in Table 2, a range of racemic azlactones **1a–j** were smoothly converted into the corresponding amino esters (**S**)-**2a–j** in high yields and ee values. Moreover, in most cases, a single recrystallization provides the enantiomerically pure form (> 99% ee). For example, after a single recrystallization from methyl cyclohexane, the enantiomerically pure *N*-benzoyl amino ester (**S**)-**2i** was obtained in multigram-scale, which can be transformed in one step into highly valuable optically pure *L*-*m*-tyrosine¹⁵ by hydrolysis with HBr without any

Table 2 Catalytic DKR of racemic azlactones **1a–1j**^a

Entry	R ¹	R ²	R ³	Time (h)	Yield (%) ^b	ee (%) ^c
1	<i>i</i> -Pr (3a)	Ph	allyl	36	95	90
2	<i>i</i> -Pr (3b)	4-Me-C ₆ H ₄	allyl	36	95(82) ^d	90(99) ^d
3	<i>i</i> -Pr (3c)	4-F-C ₆ H ₄	allyl	36	90	91
4	<i>i</i> -Pr (3d)	2-naphthyl	allyl	32	86(75) ^d	91(98) ^d
5	Me (3e)	Ph	allyl	15	95	89
6	Et (3f)	Ph	allyl	18	93	91
7	Allyl (3g)	4-Me-C ₆ H ₄	ethyl	36	88(75) ^d	91(99) ^d
8	Propargyl (3g)	4-Me-C ₆ H ₄	ethyl	36	86(70) ^d	89(99) ^d
9	 (3i)	Ph	ethyl	48	89(61) ^d	73(99) ^d
10	 (3j)	Ph	ethyl	48	90(76) ^d	88(99) ^d

^a Unless otherwise indicated, the reactions were carried out with **3a–h** (0.5 mmol), alcohol (2 equiv., 1 mmol), and the catalyst **Ia** (10 mol%) in CH₂Cl₂ (1.0 mL) at –20 °C. ^b Isolated yields after chromatographic purification. ^c Determined by chiral HPLC (see ESI). ^d The values in parentheses were obtained after single recrystallization from methylcyclohexane. DCC: dicyclohexylcarbodiimide.

**Scheme 1** A multigram-scale synthesis of *L-m*-tyrosine by hydrolysis of **2i**.

loss of optical purity (Scheme 1) (see ESI).[†] It should also be noted that this DKR protocol can be applied to the stereoinversion of chiral α -amino acids. For example, the optically pure *N*-benzoyl-(*R*)-valine ((*R*)-**3a**) produced the *N*-benzoyl-(*S*)-valine allyl ester ((*S*)-**2a**) with 90% ee after alcoholic DKR with the catalyst **Bis-HCD-TU (Ia)**.

Conclusions

In summary, concentration-independent high enantioselectivity in the dynamic kinetic resolution (DKR) of racemic azlactones affording a variety of non-natural chiral α -aminoesters has been achieved using self-association free thiourea-based dimeric cinchona alkaloid organocatalysts. Detailed experimental and NMR spectroscopic studies and single crystal X-ray analysis confirmed that these bifunctional organocatalysts **I** do not form H-bonded self-aggregates in either solution or solid state. We are currently investigating the application of these self-association free dimeric catalysts to other asymmetric catalytic reactions.

Experimental section

General information

All chemicals used in this study were obtained from commercial sources and used without further purification. The chromatographic

purification of the products was carried out by flash chromatography using Merck silica gel 60 (230–400 mesh). Thin-layer chromatography was carried out on Merck silica gel 60 F plates. HPLC analyses were performed on a Varian Pro Star Series instrument equipped with an isostatic pump using a CHIRALCEL OD-H Column (250 × 4.6 mm). The ¹H and ¹³C NMR spectra were recorded on Varian 300 and Varian 500 spectrometers. The IR spectra were obtained using a Bruker Vertex 70 spectrometer with MIRacle Micro ATR accessory. The HRMS spectra were recorded on a Jeol JMS-700 M station. The melting points (mp's) were determined on a Buchi B-540 melting point apparatus and were uncorrected. The optical rotation was measured on a Perkin Elmer Polarimeter 343 plus.

Representative procedure for synthesis of catalysts **I**

A round bottom flask was charged with 9-amino(9-deoxy)*epi*-dihydroquinine (4.2 g, 12.9 mmol) and CH₂Cl₂ (60 mL) as a solvent. Thiocarbonyl diimidazole (1.16 g, 6.5 mmol) was added in one portion, and the reaction mixture was stirred at room temperature. After 18 h, the reaction mixture was concentrated under reduced pressure, and the crude product was purified by column chromatography (EtOAc: MeOH = 1:1) to afford **Bis-HQN-TU (Ic)** (3.3 g, 73%) as a white solid. The characterization data of thiourea-based dimeric alkaloid catalysts **Ia–d** are as follows.

Bis-HCD-TU (Ia). mp 183 °C; $\alpha_D = -155.9$ (c = 0.1 in CHCl₃); ¹H NMR (400 MHz, *d*₆-DMSO, 80 °C) δ 0.74 (t, *J* = 7.2 Hz, 3H), 0.80–0.84 (m, 1H), 0.97–1.21 (m, 3H), 1.24–1.36 (m, 2H), 1.41–1.57 (m, 2H), 2.27–2.37 (m, 1H), 2.50–2.58 (m, 1H), 2.85–3.17 (m, 3H), 5.60 (d, *J* = 10.4 Hz, 1H), 7.33 (d, *J* = 4.4 Hz, 1H), 7.54 (pseudo t, 1H), 7.69 (pseudo t, 1H), 7.90 (br s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 8.38 (d, *J* = 8.4 Hz, 1H), 8.80 (d, *J* = 4.4 Hz, 1H); ¹³C NMR (100 MHz, *d*₆-DMSO, 80 °C) δ 11.16, 24.54, 24.64, 26.21, 27.59, 36.46, 40.16, 55.57, 56.44, 59.56, 119.60, 123.84, 125.48, 126.57, 128.14, 129.15, 147.18, 147.55, 149.38, 181.83; HRMS (FAB) calcd for [C₃₉H₄₈N₆S+H]⁺: 633.3739 (100.0%); found: 633.3739 (100.0%); IR (powder) 3255, 3054, 2929, 2867, 1511, 1302, 1240, 1048, 844, 758 cm⁻¹.

Bis-CD-TU (Ib). mp 240 °C; $\alpha_D = -162.3$ (c = 0.1 in CHCl₃); ¹H NMR (400 MHz, *d*₆-DMSO, 80 °C) δ 0.78–0.86 (m, 1H), 1.06–1.19 (m, 1H), 1.40–1.58 (m, 3H), 2.20–2.24 (m, 1H), 2.52–2.66 (m, 2H), 2.87–3.20 (m, 3H), 4.85–4.96 (m, 2H), 5.62–5.78 (m, 2H), 7.34 (d, *J* = 4.4 Hz, 1H), 7.54 (pseudo t, 1H), 7.70 (pseudo t, 1H), 7.92 (br s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 8.40 (d, *J* = 8.4 Hz, 1H), 8.81 (d, *J* = 4.4 Hz, 1H); ¹³C NMR (100 MHz, *d*₆-DMSO, 80 °C) δ 24.78, 26.58, 26.82, 38.45, 40.11, 54.79, 55.48, 59.61, 113.47, 119.59, 123.85, 125.51, 126.56, 128.18, 129.15, 141.33, 147.08, 147.55, 149.38, 181.86; HRMS (FAB) calcd for [C₃₉H₄₄N₆S+H]⁺: 629.3426 (100.0%); found: 629.3426 (100.0%); IR (powder) 3706, 3669, 3361, 3232, 2944, 2869, 1507, 1306, 1240, 1056, 1009, 916, 845, 754 cm⁻¹.

Bis-HQN-TU (Ic). mp 188 °C; $\alpha_D = -176.3$ (c = 0.1 in CHCl₃); ¹H NMR (300 MHz, *d*₆-DMSO, 80 °C) δ 0.75 (t, *J* = 7.2 Hz, 3H), 0.78–0.83 (m, 1H), 1.05–1.23 (m, 3H), 1.24–1.43 (m, 2H), 1.46–1.53 (m, 2H), 2.29–2.36 (m, 1H), 2.90–3.14 (m, 4H), 3.90 (s, 3H), 5.61 (d, *J* = 10.5 Hz, 1H), 7.29 (d, *J* = 4.5 Hz, 1H), 7.37 (dd, *J* = 2.6 and 9.2 Hz, 1H), 7.81 (d, *J* = 2.3 Hz, 1H), 7.90 (d, *J* = 9.2 Hz,

1H), 7.95 (br s, 1H), 8.64 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR (100 MHz, d_6 -DMSO, 80 °C) δ 11.30, 24.57, 24.84, 26.21, 27.69, 36.45, 40.28, 55.12, 55.74, 56.52, 59.25, 102.96, 119.96, 120.43, 127.56, 130.57, 143.72, 145.59, 146.86, 156.54, 181.77; HRMS (FAB) calcd for $[\text{C}_{41}\text{H}_{52}\text{N}_6\text{O}_2\text{S}+\text{H}]^+$: 693.3951 (100.0%); found: 693.3951 (100.0%); IR (powder) 3307, 2935, 2870, 1622, 1508, 1454, 1363, 1226, 1080, 1030, 853, 827, 716 cm^{-1} .

Bis-QN-TU (Id). mp 170 °C, α_D : -145.4 ($c = 0.1$ in CHCl_3). ^1H NMR (400 MHz, d_6 -DMSO, 80 °C) δ 0.78–0.85 (m, 1H), 1.13–1.23 (m, 1H), 1.44–1.55 (m, 3H), 2.15–2.25 (m, 1H), 2.59–2.68 (m, 1H), 2.90–3.18 (m, 4H), 3.92 (s, 3H), 4.87–4.97 (m, 2H), 5.64 (d, $J = 10.5$ Hz, 1H), 5.69–5.81 (m, 1H), 7.31 (d, $J = 4.5$ Hz, 1H), 7.37 (dd, $J = 2.6$ and 9.2 Hz, 1H), 7.81 (d, $J = 2.6$ Hz, 1H), 7.93 (d, $J = 9.2$ Hz, 1H), 7.94 (br s, 1H), 8.65 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR (100 MHz, d_6 -DMSO, 80 °C) δ 24.98, 26.62, 26.90, 38.46, 40.22, 54.86, 55.14, 55.72, 59.28, 102.95, 113.45, 119.98, 120.48, 127.53, 130.58, 141.37, 143.73, 145.41, 146.86, 156.58, 181.80; HRMS (FAB) calcd for $[\text{C}_{41}\text{H}_{48}\text{N}_6\text{O}_2\text{S}+\text{H}]^+$: 689.3638 (100.0%); found: 689.3638 (100.0%); IR (powder) 3255, 2938, 2870, 1623, 1510, 1468, 1350, 1231, 1031, 915, 847, 676 cm^{-1} .

General procedure for DKR of racemic azlactones

To a stirred solution of azlactone **1** (0.5 mmol) and catalyst (0.05 mmol) in CH_2Cl_2 (1 mL), allyl alcohol (1 mmol) was added at room temperature. The resulting mixture was vigorously stirred at room temperature until the reaction was complete by TLC. The mixture was extracted with ethyl acetate (3×5 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column with EtOAc–hexanes (1 : 6) to afford the desired ester **2**.

One-pot procedure for the DKR reactions starting from the racemic *N*-acylated α -amino acids

The *N*-acylated α -amino acids **3** (0.5 mmol) was added to a stirred solution of DCC (108.3 mg, 0.53 mmol) in CH_2Cl_2 (1 mL) at rt. After the complete conversion (*ca.* 2 h) of the *N*-acylated α -amino acids **3** to the corresponding azlactones **1**, the catalyst (**1a**, 0.05 mmol) and alcohol (1 mmol) were added to the reaction mixture. The reaction mixture was stirred at -20 °C and the reaction progress was monitored by TLC. After completion of the reaction, 2 M HCl (10 mL) was added to the reaction mixture. The heterogenous reaction mixture was then filtered to remove the dicyclohexylurea. The filtrate was extracted with CH_2Cl_2 (2×10 mL). The combined organic extract was dried over anhydrous MgSO_4 and concentrated. The obtained crude product was purified by column chromatography on silica gel (EtOAc:hexane = 1 : 4) to give the *N*-acylated α -amino ester **2**. ^1H and ^{13}C NMR spectra for the obtained products **2a–j** were in agreement with previously reports (see ESI).[†]

Acknowledgements

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- CCDC 836783 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44)-1223-336-033.
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