DOSY NMR for monitoring self aggregation of bifunctional organocatalysts: increasing enantioselectivity with decreasing catalyst concentration†

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In this report, we demonstrate that self-aggregation is an intrinsic problem of bifunctional organocatalysts, especially in the case when the substrates do not have functional groups which are able to bind strongly with catalyst. Due to their self-association phenomena, the enantioselectivity of bifunctional catalysts dramatically decreases with increasing catalyst concentration or decreasing temperature. Thus, when the substrate concentration is kept constant, the enantioselectivity of bifunctional catalysts dramatically increases with decreasing catalyst loading. The ee values obtained at different catalyst concentrations are fairly consistent with the diffusion coefficients (*D*) of the catalysts, strongly indicating that their degree of self-association plays a crucial role in determining their enantioselectivity.

Introduction

Cooperative catalysis,[1] the simultaneous binding and activation of the reacting partners resulting in both the pre-organization of the substrates and stabilization of the transition state structures, is a fundamental principle in enzymatic catalysis.[2] As predicted by Wynberg in 1981,[3] chemists have recently started to recognize "the advantages of bifunctional catalysis in the preparation of enantiomers by catalytic chiral synthesis". Indeed, over the past several years, a wide variety of catalytic asymmetric reactions promoted by small chiral organocatalysts[4] have been deemed to operate *via* cooperative mechanisms. For cooperative catalysis using small organic molecules, the engineering of synthetic organocatalysts has mainly focused on the introduction of tunable H-bond donor and acceptor groups to induce high levels of stereoselectivity *via* the dual activation mechanism.[5] Particularly prominent among bifunctional organocatalysts are tertiary amino-thioureas such as **1–3**[5,6] and tertiary amino-squaramides such as **4**[7] (Fig. 1), which represent one of the most versatile and useful classes of enantioselective bifunctional catalysts that have been successfully applied to a series of synthetically important asymmetric reactions.

Although the bifunctionality of the catalysts enables cooperative catalysis to be achieved, it is also a potential source of self-recognition of the catalysts, resulting in their self-aggregation. The X-ray crystal structures of bifunctional (thio)ureas[8] and cinchonine-based squaramide[9] show that they can form H-bonded aggregates in the solid state. A recent NMR spectroscopic study conducted by Soós and co-workers also showed that the quinine thiourea **3a** exists as a dimeric form in solution through H-bond and T-type π–π interactions in an intermolecular fashion.[10] Its self association constants (K in D_8-toluene = $[\mathbf{3a}_{dimer}]/[\mathbf{3a}_{monomer}]^2$) are

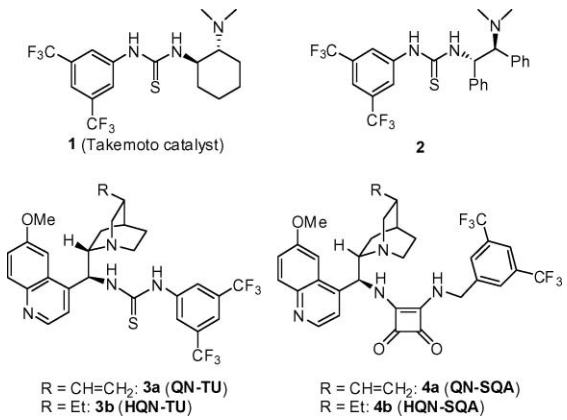

Fig. 1 Representative examples of bifunctional chiral organocatalysts.

23381, 11091 and 4307 mol L^{-1} at –60 °C, –50 °C and –40 °C, respectively. The extrapolated *K* values suggest that dimeric self-assembly is abundant near room temperature (K at 20 °C = *ca.* 92 mol L^{-1}). Notably, in the self-assembled dimeric structure of **3a**,[10] however, only in one of the two thiourea moieties are the two N–H bonds in an *anti* conformation with respect to the C=S bond that is essential for the effective bifurcate H-bonding activation of a reactant.

Upon the self-association of catalysts, the monomer and dimer (or higher aggregates) must act as a distinct catalyst species giving different selectivities. Thus, their enantioselectivity can often be strongly dependent on the concentration and temperature, as well as the solvent. In the case where it is negatively affected by the aggregates in catalytic reactions, the enantioselectivity usually decreases with increasing concentration or decreasing temperature.[11,12a] Therefore, to maximize the enantioselectivity of bifunctional catalysts, an understanding of their self-association phenomena in solution is required. Detailed information on the monomer/dimer (or higher aggregates) equilibrium would make it possible to optimize the catalytic conditions (concentration, temperature, catalyst loading, *etc.*).

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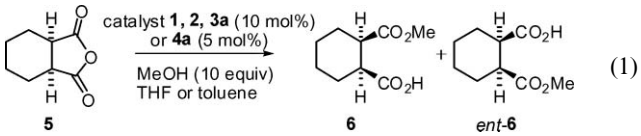
In this report, we demonstrate that self-aggregation is an intrinsic and general problem of bifunctional organocatalysts such as **1**–**4**. Due to their self-association phenomena, the enantioselectivity of bifunctional organocatalysts usually decreases with increasing concentration or decreasing temperature. Thus, when the substrate concentration is kept constant, the enantioselectivity of bifunctional catalysts dramatically increases with decreasing catalyst loading. The ee values obtained at different catalyst concentrations are fairly consistent with the diffusion coefficients (*D*) of the catalysts, strongly indicating that their degree of self-association plays a crucial role in determining their enantioselectivity. In this paper, we also demonstrate that the self-aggregation problem of bifunctional organocatalysts can be overcome by well-designing the catalysts.

Results and discussion

First, to demonstrate that self-association is a general problem affecting the efficiency of bifunctional catalysts, three model catalytic reactions (the methanolytic desymmetrization[12,13] of *meso*-1,2-cyclohexanedicarboxylic anhydride (**5**) (eqn (1)); the DKR reaction[14,18d] of racemic valine-derived azlactone (**7**) with allyl alcohol (eqn (2)); the enantioselective conjugate addition[15] of thiophenol to 2-cyclohexene-1-one (**9**) (eqn (3)) promoted by bifunctional catalysts **1**–**4** (5–10 mol%) were selected and conducted at various concentrations and reaction temperatures. In all reactions examined in this study (Fig. 2–4 and Tables S1–S8 in the ESI†) the strong dependence of the enantioselectivity on the concentration and temperature was observed. The enantioselectivity decreased with increasing concentration or decreasing temperature. The experimental results obtained for the methanolytic desymmetrization of *meso*-1,2-cyclohexanedicarboxylic anhydride **5** using 10 mol% of Takemoto's catalyst **1** serves to highlight the importance of the effect of self-association on the enantioselectivity. Under dilute conditions at room temperature ([**5**] = 0.0125 M in THF), excellent enantioselectivity (95% ee) was observed, while concentrated conditions at lower temperatures (0.2 M in toluene at −20 °C)



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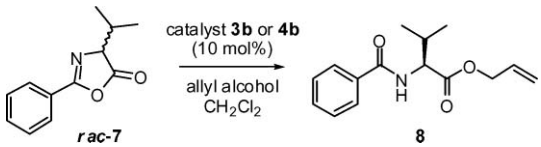

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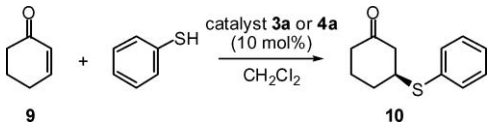

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gave a dramatically decreased ee value (11% ee). These results indicate how important the optimization of the reaction conditions is when employing bifunctional catalysts (see Fig. 2).

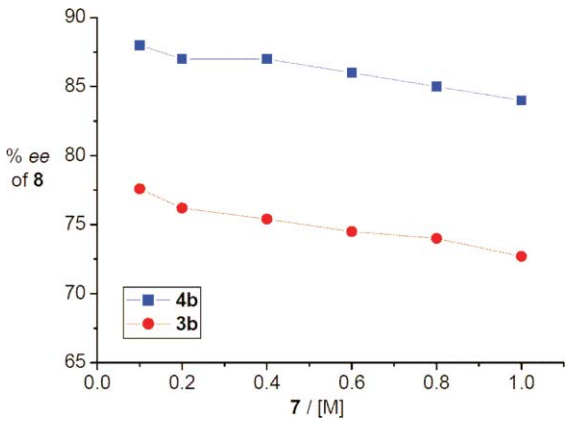


Fig. 3 Effect of concentration on enantioselectivity in the DKR reaction of racemic valine-derived azlactone (**7**) with allyl alcohol (eqn (2)) catalyzed by **3b** or **4b**.[17,18d]

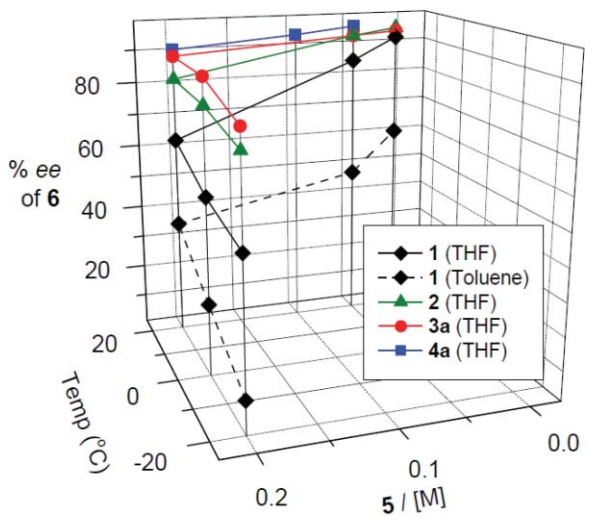


Fig. 2 Effects of concentration and temperature on enantioselectivity in the methanolytic desymmetrization of *meso*-1,2-cyclohexanedicarboxylic anhydride (**5**) (eqn (1); **6** was obtained as the major isomer using **2**, **3a** and **4a**,[16] while **1** gave *ent*-**6** as the major isomer).

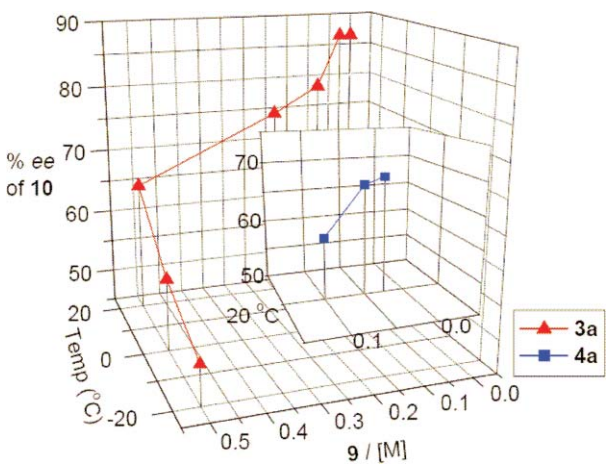
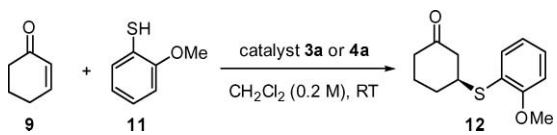


Fig. 4 Effects of concentration and temperature on enantioselectivity in the conjugate addition of thiophenol to 2-cyclohexene-1-one (**9**) (eqn (3)) catalyzed by **3a** or **4a**.[16]

Having observed that self-association is a general problem affecting the efficiency of bifunctional catalysts, we turned our attention to the development of a simple tool to determine the range of concentrations in which bifunctional organo- catalysts exist mainly in their monomeric form, on the assumption that, in such concentration ranges, the enantioselectivity of bifunctional catalysts such as **1–4** would be maximized. The DOSY (diffusion ordered spectroscopy) NMR technique has recently been regarded as an invaluable tool for studying self-association phenomena in solution.[18] The monomer/dimer (or higher aggregates) equilibrium can be monitored by measuring the diffusion coefficients, *D*, at different concentrations. Thus, ^{19}F-DOSY experiments were carried out to determine the range of concentrations in which the bifunctional organocatalysts do not self-aggregate.

As shown in Table 1, the diffusion coefficients of the quinine thiourea catalyst **3a** and quinine squaramide catalyst **4a** significantly decreased upon increasing their concentration, strongly indicating the existence of the dimer at concentrations higher than 0.002 M. However, at concentrations lower than 0.002 M, their diffusion coefficients did not show any appreciable dependence on the concentration ($\Delta D \sim 0.01$ and 0.03 for **3a** and **4a**, respectively), in contrast to those obtained at concentrations higher than 0.002 M. On the basis of these ^{19}F-DOSY results, it is now clear that at concentrations lower than 0.002 M, the catalysts **3a** and **4a** exist mainly in the monomeric form, indicating that the maximum enantioselectivity might be achieved in this range of catalyst concentrations. It is therefore reasonable to expect that the enantioselectivity of bifunctional catalysts could be increased by decreasing the catalyst loading, if the substrate concentration were kept constant. To confirm this hypothesis, the conjugate addition of 2-methoxybenzene thiol (**11**) (1.2 equiv.) to 2-cycloalken-1-one (0.5 mmol, **9**) in CH_2Cl_2 (2.5 mL) at room temperature was conducted as a model reaction by varying the catalyst loading (for **3a**, 0.5–100 mol%; for **4a**, 0.5–10 mol%), while keeping the substrate concentration constant (0.2 M). To our delight, as shown in Table 1, Table S11 and Table S12 (ESI†), the enantioselectivity of the thiol addition reaction significantly increased with decreasing catalyst loading. The highest enantioselectivity (94% and 91% ee) was obtained when 1.0 mol% ([**3a**] = 0.002 M) of catalyst **3a** and 0.5 mol% ([**4a**] = 0.001 M) of catalyst **4a** were used. However, a higher catalyst loading gave a dramatically lower enantioselectivity (*e.g.*, 61% ee using 100 mol% of **3a** and 67% ee using 10 mol% of **4a**). These experimental results strongly suggest that the bifunctional catalysts **3a** and **4a** exist in monomer/dimer equilibrium at catalyst loadings higher than *ca.* 1.0 mol% ([cat] = 0.002 M), in accordance with the DOSY data. On the basis of all these experimental results, it can be concluded that increasing the catalyst loading reduced the enantioselectivity, due to the increasing degree of self-association, and, moreover, that the enantioselectivity was dependent only on the concentration of the bifunctional catalysts. The possibility that the variation in the enantioselectivity might also be caused by a concentration-dependent change in the conformational composition cannot be excluded. However, at least in the cases of the present study, the degree of self-association played a crucial role in determining the enantioselectivity, since the ee values obtained at different concentrations were fairly consistent with the DOSY data (see Table 1, Table S-9 and Table S-10†).

Table 1 Diffusion coefficients D [10^{-10}m^{2}s^{-1}] (500 MHz, $CDCl_3$, 25 °C) of **3a** and **4a** at different concentrations *versus* enantioselectivities in asymmetric addition of thiol **11** to cyclohexenone **9** (Eq. 4) catalyzed by **3a** or **4a** at different catalyst concentrations.[a]

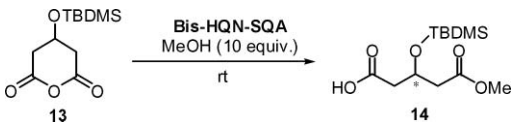


9 11 12

Cat. loading (mol%)	Cat. conc./M	QN-TU(3a)		QN-SQA(4a)	
		$D/10^{-10}$m^{2}s^{-1}[19]	% ee	$D/10^{-10}$m^{2}s^{-1}[19]	% ee
100	0.2	3.97	61	n.d.[20]	n.d.[16]
20	0.1	4.52	71	n.d.[20]	n.d.[16]
10	0.02	5.47	86	3.04	67
5	0.01	5.62	90	3.69	79
1	0.002	5.85	94	4.82	90
0.5	0.001	5.86	92	4.85	91

[a] Reactions were carried out on a 0.5 mmol scale in CH_2Cl_2 (2.5 mL, [**9**] = 0.2 M) at room temperature.

To solve the intrinsic self-aggregation problem of bifunctional organocatalysts such as **1–4**, we quite recently developed the self-association-free, bifunctional, squaramide-based dimeric cinchona alkaloid, **Bis-HQN-SQA** (Fig. 5) ,[18d] in which the steric bulk of the two alkaloid moieties can suppress their self-aggregation. As can be expected, in the DKR reactions of the racemic valine-derived azlactone by allyl alcohol[18d] and methanolytic desymmetrization of glutaric anhydride (**13**) (eqn (4) and Fig. 6) at various concentrations, the enantioselectivity of the dimeric catalyst **Bis-HQN-SQA** was not significantly dependent on the concentration, unlike in the case of the corresponding monomeric catalyst **4b**. Moreover, the diffusion coefficients of the dimeric catalyst, **Bis-HQN-SQA**, did also not show any appreciable dependence on the concentration ($\Delta D = -0.04 \times 10^{-10}$ m^{2}s^{-1}), in contrast to the monomeric catalyst **4b**.[18d]



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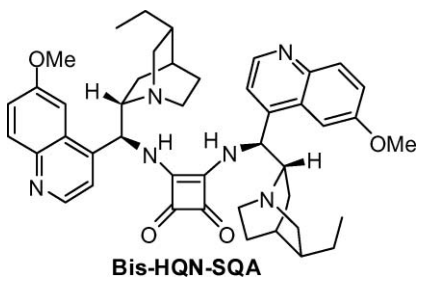

Bis-HQN-SQA

Fig. 5 Structure of the squaramide-base dimeric cinchona alkaloid (**Bis-HQN-SQA**).

Conclusions

Bifunctional organocatalysts such as **1–4** are of broad interest, as they have been shown to catalyze a wide range of organic reactions. However, the results described herein strongly indicate that

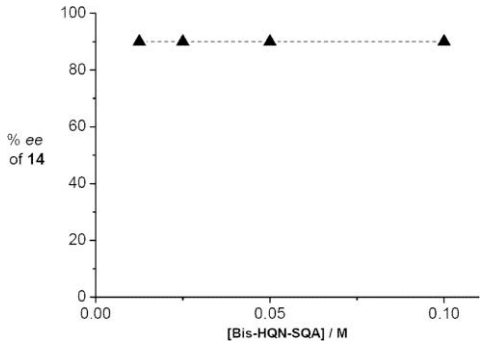

Fig. 6 Effects of concentration on enantioselectivity for eqn (4).

self-aggregation is an intrinsic problem of bifunctional catalysts. Due to their self-association phenomena, the enantioselectivity of bifunctional organocatalysts usually decreases with increasing concentration or decreasing temperature. Thus, when the substrate concentration is kept constant, the enantioselectivity of bifunctional catalysts dramatically increases with decreasing catalyst loading. The DOSY NMR technique has been shown to be an easy and powerful tool for determining the range of catalyst concentrations (*i.e.*, the catalyst loading) in which catalysts exist mainly as a monomeric form that would give the maximum enantioselectivity. Our future work will be directed at gaining a detailed understanding of how the monomer and dimer act as distinct catalyst species giving different selectivities.

Experimental section

General remarks

meso-1,2-Cyclohexanedicarbolyic anhydride (**5**), 2-cylclohexene-1-one (**9**) were purchased from Aldrich and used without further purification. The racemic valine-derived azlactone (**7**) was prepared from racemic valine according to the literature procedure.[21] Alcohols (methanol and allyl alcohol) and thiols (thiophenol and 2-methoxy thiophenol) were purchased from Aldrich and used without further purification. Thiourea catalysts (**1**,[8a]**2**,[8a]**3a**,[15,22]**3b**[15,22]) and squaramide catalysts (**4a**,[7]**4b**[7]) were prepared according to the literature procedure.

General procedure for the methanolysis of meso-1,2-cyclohexanedicarboxylic anhydride (5)

Methanol (202 μL, 5 mmol) was added dropwise to a stirred solution of anhydrides (**5**, 0.5 mmol) and catalysts (**1**, **2**, **3a** and **4a**) (10 mol%) in appropriate solvents (2.5 mL–40 mL) at the temperature indicated in Fig. 2 (Table S1, S2, S3 and S4†). The reaction mixture was stirred at that temperature until the starting material was consumed, as indicated by TLC analysis. The reaction was quenched by adding HCl (1 N, 3 mL) in one portion. The aqueous phase was extracted with EtOAc (2 × 100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the crude product. Purification by column chromatography (EtOAc : Hexane = 1 : 4) gave hemiester product **6**.

General procedure for the DKR reaction of racemic valine-derived azalactone (7)

Allyl alcohol (68 μL, 1 mmol) was added to a stirred solution of the azalactones (**7**, 0.5 mmol) and catalyst (**3b** and **4b**) (10 mol%) in CH_2Cl_2 (5 mL–50 mL) (Table S5 and S6†). The reaction mixture was stirred at that temperature until the starting material was consumed, as indicated by TLC analysis. The reaction was quenched by adding HCl (1 N, 3 mL) in one portion. The aqueous phase was extracted with EtOAc (2 × 100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the crude product. Purification by column chromatography (EtOAc:Hexane = 1 : 4) gave *N*-benzoylated α-amino allyl ester (**8**).

General for the conjugate addition of aryl thiol to 2-cyclohexene-1-one (9)

Thiophenol (61 μL, 0.6 mmol) or 2-methoxybenzenethiol (73 μL, 0.6 mmol) was added in one portion to a stirred solution of 2-cylclohexene-1-one (**9**, 0.5 mmol) and thiourea catalyst **3a** (0.25 mol%–100 mol%) and squaramide catalyst **4a** (0.25 mol%–10 mol%) in CH_2Cl_2 (0.6 mL–20 mL) at the temperature indicated in Fig. 3 (Table S7 and S8†) and Table 1 (Table S11 and S12†). The reaction mixture was stirred at that temperature until the starting material was consumed, as indicated by TLC analysis. The reaction was quenched by adding HCl (1 N, 3 mL) in one portion. The aqueous phase was extracted with EtOAc (2 × 100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the crude product. Purification by column chromatography (EtOAc:Hexane = 1 : 4) gave thiol added products (**10** and **12**)

Acknowledgements

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