Self-association-free dimeric cinchona alkaloid organocatalysts: unprecedented catalytic activity, enantioselectivity and catalyst recyclability in dynamic kinetic resolution of racemic azlactones†

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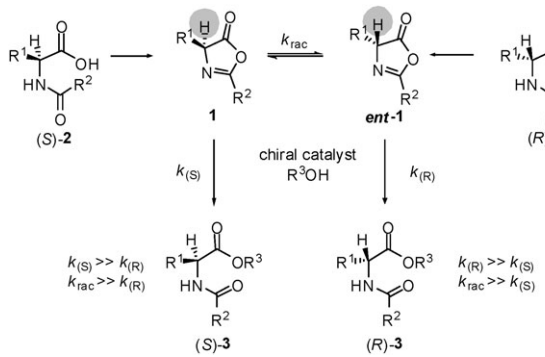
Self-association-free, bifunctional, squaramide-based dimeric cinchona alkaloid organocatalysts show unprecedented catalytic activity, enantioselectivity and catalyst recyclability in the dynamic kinetic resolution (DKR) reaction of a broad range of racemic azlactones.

The development of practical methods for the synthesis of enantiomerically pure natural and non-natural α-amino acids is a challenge of considerable practical importance, due to their numerous applications in the synthesis of chiral drugs, peptides, chiral ligands, chiral catalysts and many other valuable target molecules. Besides the (bio)catalytic enantioselective approach employing prochiral substrates, the catalytic dynamic kinetic resolution (DKR) of racemic α-amino acid derivatives is another potentially very practical route for the preparation of enantiomerically pure amino acid derivatives.[1] Azlactones **1** are attractive substrates for the DKR process due to their configurational lability (pK_a of α-hydrogen ~9, H_2O, 25 °C).[2] In the presence of chiral catalysts with sufficient basicity to enable the rapid racemization of azlactones, the asymmetric alcoholytic ring opening of racemic azlactones leads to the formation of the enantiomerically enriched *N*-acyl amino esters **3** in 100% theoretical yield (Scheme 1).

Several strategies involving enzymes,[3] Ti-based complexes,[4] cyclic dipeptides,[5] and chiral DMAP nucleophilic catalysts[6] have been employed to bring about the efficient DKR of azlactones. However, all of these methods suffer from either a narrow substrate scope and/or very long reaction times and unsatisfactory enantioselectivity. Recently, the groups of Berkessel[7] and Connon[8] demonstrated that the use of bifunctional (thio)ureas as organic chiral catalysts can promote the DKR reactions of a range of azlactones using an alcohol nucleophile, affording the corresponding *N*-protected amino esters. However, their catalytic activity and enantioselectivity are still unsatisfactory for synthetic use for the preparation of enantiomerically pure α-amino acids. Moreover, it is known that these urea or thiourea based organocatalysts can form H-bonded aggregates, due to their bifunctional nature, resulting in the strong dependency of the reactivity and enantioselectivity on the concentration and temperature.[9,10] Due to the self-association phenomena of this type of catalysts, the enantioselectivity generally decreases with increasing concentration or decreasing temperature, which can hamper their practical use.[9] This may well be a general problem, since such organocatalysts are used for a wide variety of reactions.[11] Thus, it would be highly desirable to develop a new class of highly active and enantioselective bifunctional organocatalysts that do not self aggregate in the solution state.

To prevent self-aggregation, we designed the squaramide-based dimeric cinchona alkaloids **4** (Fig. 1), in the hope that the steric bulk of the two alkaloid moieties would suppress their self-aggregation. The squaramide-based (**4a–e**) dimeric cinchona alkaloid catalysts were simply prepared in one step by the reaction of the corresponding 9-amino-(9-deoxy)-*epi*-cinchona alkaloids[12] with dimethyl squarate (see ESI†).



Scheme 1

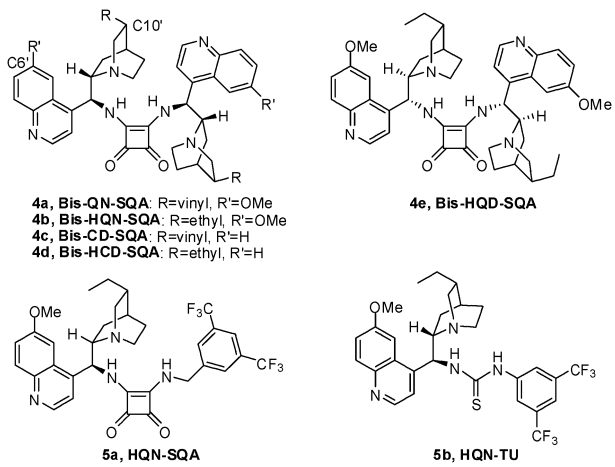


Fig. 1 Structures of *Cinchona* alkaloid organocatalysts.

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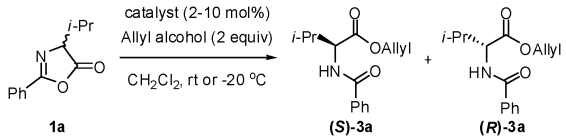
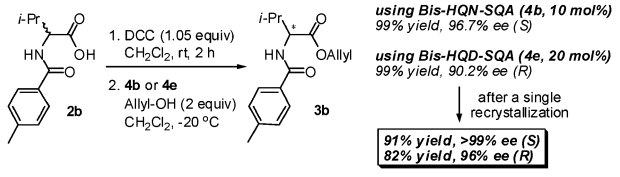
Table 1 Catalytic DKR of the racemic valine-derived azlactone **1a** with allyl alcohol[a]



Entry	Catalyst (mol%)	T/°C	Time	Yield[b] (%)	ee[c] (%)	Main product
1	**4a** (10)	rt	6 h	99	93	(*S*)-**3a**
2	**4b** (10)	rt	3 h	95	94	(*S*)-**3a**
3	**4b** (5)	rt	6 h	92	94	(*S*)-**3a**
4	**4b** (2)	rt	24 h	98	94	(*S*)-**3a**
5	**4b** (10)	−20	8 h	98	97	(*S*)-**3a**
6	**4c** (10)	rt	6 h	96	93	(*S*)-**3a**
7	**4d** (10)	rt	3 h	98	94	(*S*)-**3a**
8	**4e** (20)	rt	48 h	97	91	(*R*)-**3a**
9	**5a** (10)	rt	24 h	86	86	(*S*)-**3a**
10	**5b** (10)	rt	12 h	95	75	(*S*)-**3a**

[a] The reactions were carried out with **1a** (0.5 mmol), allyl alcohol (2 equiv., 1 mmol) in the presence of catalyst in CH_2Cl_2 (1.0 mL). [b] Isolated yields after chromatographic purification. [c] Determined by chiral HPLC (see the ESI†).

To investigate the catalytic activity and enantioselectivity of the readily synthesized, new dimeric alkaloid catalysts (**4**), we initially examined the DKR reactions of the racemic valine-derived azlactone **1a** in the presence of the catalyst (2–10 mol%) and allyl alcohol (2 equiv.) in CH_2Cl_2 (0.5 M). The results are summarized in Table 1, together with the data obtained using the previously reported monomeric catalysts, **HQN-SQA** (**5a**)[13] and **HQN-TU** (**5b**)[12] (Fig. 1). As shown in entries 1, 2, 6 and 7 in Table 1, regardless of the substituent at the C6' and C10' positions of alkaloids **4a–d**, the DKR reactions of **1a** proceeded unprecedentedly fast, with the reaction being completed within 3–6 h affording the (*S*)-α-amino allyl ester in nearly quantitative yields and excellent ees (93–94% ee).[14] A lower catalyst loading of up to 2 mol% still resulted in excellent enantioselectivity (94% ee, entries 3 and 4). The enantioselectivity could be further increased to 97% ee by lowering the reaction temperature to −20 °C (entry 5). The non-natural (*R*)-configured α-amino ester (*R*)-**3a** could also be obtained using the hydroquinidine-derived catalyst, **Bis-HQD-SQA** (**4e**), in 97% yield and with 91% ee (entry 8). To the best of our knowledge, this level of enantioselectivity is unprecedented in the organocatalytic DKR of racemic azlactones. In contrast to these results, the previously reported cinchona-based monomeric catalysts **5a** and **5b** (entries 9 and 10, respectively) showed much inferior reactivity and enantioselectivity (75–86% ee) compared to the squaramide-based dimeric ones **4a–e**.



Scheme 2

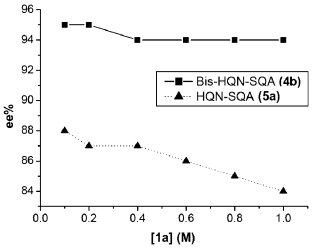


Fig. 2 Effect of concentration on enantioselectivity of dimeric catalyst **4b** (squares) *versus* that of monomeric catalyst **5a** (triangles).

Furthermore, the robust nature of the squaramide-based dimeric catalysts, (**Bis-HQN-SQA** (**4b**) and **Bis-HQD-SQA** (**4e**)), toward chemicals allowed for a convenient "one-pot" process starting from the *N*-toluoyl racemic valine **2b**, which gave the corresponding *enantio*-enriched allyl ester **3b** in nearly quantitative yields and excellent enantioselectivities (97% ee for (*S*)-**3b** and 90% ee for (*R*)-**3b**) (Scheme 2). It is noteworthy that the product was obtained in almost pure form after the filtration of the produced dicyclohexyl urea, followed by the treatment of the filtrate with aqueous HCl and subsequent evaporation of the volatiles in the organic layer. Moreover, after a single recrystallization (from methyl cyclohexane), the product *N*-toluoyl amino acid allyl ester (*S*)-**3b** was obtained in enantiomerically pure form (>99% ee) in 91% yield.

We assumed that the unprecedented catalytic efficiency of the squaramide-based dimeric catalysts **4** was due to the efficient suppression of their self-aggregation. To prove this assumption, we conducted DKR reactions of the azlactone **1a** with allyl alcohol (2 equiv.) in the presence of the hydroquinine derived dimeric catalyst **4b** (10 mol%) and the corresponding monomeric catalysts **5a** (10 mol%) at various concentrations ([**1a**] = 0.1–1.0 M in CH_2Cl_2). As depicted in Fig. 2, the enantioselectivity of the dimeric catalyst **4b** (square symbols) was not significantly dependent on the concentration, unlike in the case of the corresponding monomeric catalyst **5a** (triangle). On the basis of these experimental results, it is clear that the squaramide-based dimeric catalysts **4** do not self aggregate to any appreciable extent, as was anticipated.

Further direct evidence was obtained by experiments using the DOSY (Diffusion Ordered Spectroscopy) technique, which is regarded as an invaluable tool for studying self-association phenomena in solution.[15] The monomer/dimer (or higher aggregates) equilibrium can be monitored by measuring the diffusion coefficients D at different concentrations.

As shown in Table 2, the diffusion coefficients of the monomeric catalyst, **HQN-SQA** (**5a**), significantly decreased on increasing the concentration from 10 mM to 20 mM (from 4.33×10^{-10} m^2 s^{-1} to 3.50×10^{-10} m^2 s^{-1}).[17] However, in studies using the same concentration gradient, the diffusion

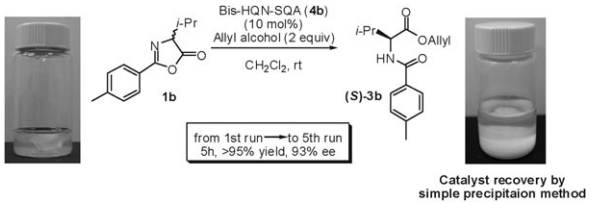
Table 2 Diffusion coefficients D [10^{-10} m^2s^{-1}] (500 MHz, $CDCl_3$, 25 °C) of **4b** and **5a** at different concentrations c_M[16]

c_M	$D/10^{-10}$ m^2 s^{-1} of **Bis-HQN-SQA** (**4b**)	$D/10^{-10}$ m^2 s^{-1} of **HQN-SQA** (**5a**)
10 mM	5.12	4.33
20 mM	5.08	3.50

coefficients of the dimeric catalyst, **Bis-HQN-SQA** (**4b**), did 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 **5a**. On the basis of the experimental (Fig. 2) and DOSY (Table 2) results, it is now clear that the self-association phenomenon is negligible in the case of the dimeric catalyst **Bis-HQN-SQA** (**4b**).

Having established **Bis-HQN-SQA** (**4b**) and **Bis-HQD-SQA** (**4e**) as the highly enantioselective and self-association free catalysts for the preparation of both enantiomers of α-amino acids *via* the DKR process, we undertook to explore the scope of the substrate and nucleophile (R^3OH) (Table S-3 in ESI†). All reactions were carried out in one-pot starting from the *N*-protected racemic amino acids **2**, derived from valine, leucine, *tert*-leucine, 2-aminobutyric acid, 2-amino-4-pentenoic acid, cyclohexylalanine, alanine, phenylalanine, DOPA, tyrosine and phenylglycine in the presence of the catalyst **4b** or **4e** in CH_2Cl_2 (0.5 M) at rt or −20 °C (for experimental details, see ESI†). As shown in Table S-3, in all cases (entries 1–15 of Table S-3) except phenylglycine, the squaramide-based dimeric catalyst, **Bis-HQN-SQA** (**4b**), was insensitive to the substituents (R^1 and R^2) of **2** as well as the nucleophiles R^3OH, thus allowing the DKR reaction to proceed with nearly quantitative yields and unprecedentedly high levels of enantioselectivity. Highly enantioenriched (*R*)-configured amino esters (up to 92% ee) could also be obtained using the hydroquinidine derived catalyst **Bis-HQD-SQA** (**4e**) (entries 17–20 of Table S-3). It should also be noted that our DKR protocol can be applied to the stereoinversion of chiral α-amino acids. For example, the optically pure *N*-benzoyl-(*R*)-valine ((*R*)-**2a**) gave the *N*-benzoyl-(*S*)-valine allyl ester ((*S*)-**3a**) with 96% ee after alcoholytic DKR with catalyst **Bis-HQN-SQA** (**4b**) (entry 22 of Table S-3). The corresponding *R*-isomer was also obtained in 91% ee with the catalyst **Bis-HQD-SQA** (**4e**) from *N*-benzoyl-(*S*)-valine ((*S*)-**2a**) (entry 21 of Table S-3). Our DKR products, *N*-protected amino esters, was also successfully transformed into more valuable *N*-protected amino acids without racemization by hydrolysis with LiOH, showing the utility of the DKR products.

Finally, the recyclability of the catalysts was also examined. The squaramide-based dimeric cinchona alkaloid catalysts **4a–e** are poorly soluble in all organic solvents,[14] and thus could readily be recovered using a simple precipitation method. Upon the completion of the reaction, the addition of hexane induced the complete precipitation of the catalysts, allowing their repeated recycling without any loss of turnover time or enantioselectivity (experimental details, see ESI†) (Scheme 3).



Scheme 3 Catalyst recycling experiments.

In summary, we developed self-association-free, bifunctional, squaramide-based dimeric cinchona alkaloid organocatalysts which showed unprecedented catalytic activity and the highest levels of enantioselectivity reported to date in the dynamic kinetic resolution (DKR) reaction of a broad range of racemic azlactones, affording a variety of natural and non-natural α-amino acid derivatives. We also showed that our DKR protocol can be applied to the stereoinversion of chiral α-amino acids. Moreover, the robust nature of these catalysts toward chemicals allowed for a convenient "one-pot" process starting from the racemic *N*-protected α-amino acids. Furthermore, the poor solubility of these catalysts in organic solvents enabled their easy recovery by a simple precipitation method, allowing their repeated recycling without any loss of turnover time or enantioselectivity.

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