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COMMUNICATION

Enantioselective synthesis of α-deuterium labelled chiral α-amino acids *via* dynamic kinetic resolution of racemic azlactones†

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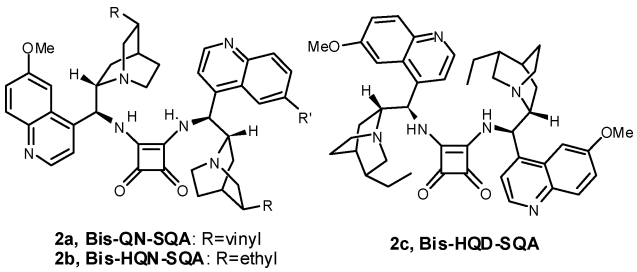
Catalytic dynamic kinetic resolution (DKR) of racemic azlactones with EtOD using squaramide-based dimeric cinchona alkaloid organocatalysts is shown to be a highly effective strategy for the preparation of enantiomerically pure α-deuterated chiral α-amino acids.

Isotopically labelled natural and unnatural amino acids and, in particular, the α-deuterated amino acids **1** are widely used in a range of bioorganic chemical studies, such as the mechanistic studies of many enzymes and various biochemical processes. In addition, their incorporation into peptides and proteins can be useful in the investigation of proteins at the atomic level.[1]

As a consequence of the importance of these studies, a number of asymmetric methods for the synthesis of α-deuterated chiral amino acids have been developed.[2] Many of these involve enzyme-catalyzed procedures[2,3] such as the enzyme mediated deuteration of amino acids,[3a–d] and enzymatic reductive amination of pyruvates.[3e,f] Recently, two chemocatalytic asymmetric approaches, *viz*. asymmetric hydrogenations using chiral rhodium catalysts[4a,b] and the chiral phase transfer catalyzed alkylation of achiral glycine equivalents,[4c] have also been efficiently utilized for the synthesis of isotopically labeled α-amino acids.

We recently developed squaramide-based dimeric cinchona alkaloid organocatalysts such as **2** (Fig. 1), in which the steric bulk of the two alkaloid moieties suppress their self-aggregation, which is an intrinsic problem of acid–base bifunctional catalysts.[5] As shown in the single crystal X-ray structure[6] of **Bis-QN-SQA** (**2a**) (Fig. 2), dimeric cinchona alkaloids do not form H-bonded self-aggregates even in the solid state. The distance between the C═O and NH moieties is *ca.* 8.8 Å. On the other hand, squaramide-based monomeric cinchona alkaloids are stacked together by intermolecular hydrogen bonding between C═O and NH.[7] Moreover,



2a, Bis-QN-SQA: R=vinyl
2b, Bis-HQN-SQA: R=ethyl

2c, Bis-HQD-SQA

Fig. 1 Typical squaramide-based cinchona alkaloid catalysts (QN = quinine; HQN = hydroquinine; HQD = hydroquinidine).

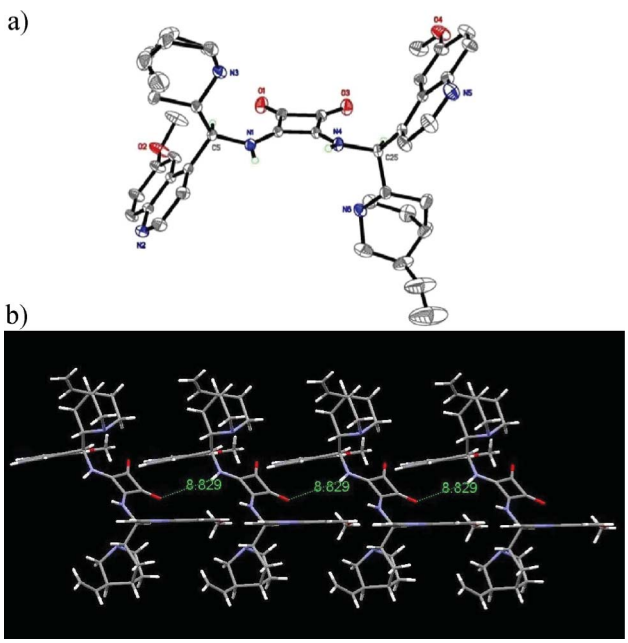


Fig. 2 (a) ORTEP diagram of **Bis-QN-SQA** (**2a**) (the solvent molecules (two H_2O) are omitted for clarity). (b) Schematic drawing of the crystal packing in **2a**.

a diffusion ordered spectroscopy (DOSY) study conducted by ourselves also confirmed the self-association free nature of dimeric catalysts in solution.[5,8] This type of dimeric cinchona alkaloid catalyst has been identified as being highly enantioselective for the dynamic kinetic resolution (DKR) reactions of a range of racemic azlactones with alcohols as nucleophiles, affording the natural and unnatural *N*-acylated α-amino acid esters with unprecedentedly

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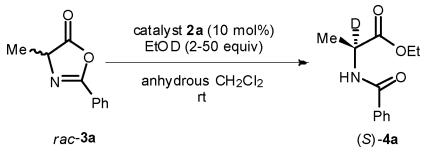
† Electronic supplementary information (ESI) available: [DETAILS]. CCDC reference number 837463. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06319g

Table 1 Catalytic DKR of the racemic valine derived azlactone **3a** with ethanol-*d*[a]



rac-**3a** (*S*)-**4a**

Entry	EtOD (equiv)	Temp	Time (h)	Yield (%)[b]	% ee[c]	D : H ratio[d]
1	2	rt	18	81	89	62 : 38
2	10	rt	10	86	88	79 : 21
3	20	rt	6	91	86	92 : 8
4	50	rt	5	92(72)[e]	85(99)[e]	97 : 3

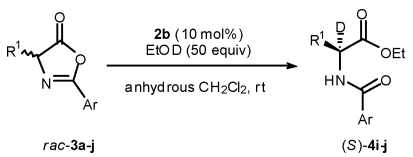
[a] The reactions were carried out with racemic **3a** (0.5 mmol), EtOD (2–50 equiv), and the catalyst **2a** (10 mol%) in CH_2Cl_2 (1.0 mL). [b] Isolated yields after chromatographic purification. [c] Determined by chiral HPLC (see ESI). [d] The D/H ratio was determined by ^{1}H NMR. [e] The yield and ee value in parentheses were obtained after a single recrystallization.

high levels of enantioselectivity (92–99% ee).[5] Moreover, due to the self-association free nature of the dimeric catalysts **1**, their enantioselectivity is not dependent on the concentration, unlike in the case of monomeric squaramide catalysts.[5,8]

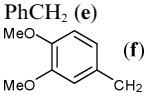
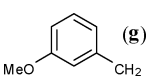
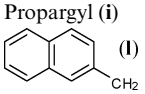
Thus, in this study, we examined the applicability of our DKR protocol in the preparation of α-carbon deuterium-labelled α-amino acids. Initially, we investigated the rate of H/D exchange for racemic alanine-derived azlactone **3a** in D_2O/acetone in the presence of an achiral base such as NEt_3. It was found that, even at room temperature, the C2 proton was rapidly deuterated at C-2 due to the acidic α-hydrogen (pK_a of α-hydrogen ~9, H_2O, 25 °C).[9] These observations suggest that it should be straightforward to access both enantiomers of α-carbon deuterium-labelled α-amino esters directly from the racemic azlactone **3**, simply by employing commercially-available deuterated alcohols such as EtOD as a nucleophile as well as a deuterium source, instead of non-deuterated alcohols, in the presence of our DKR-catalyst **2**.

Thus, we examined the DKR reactions of the racemic alanine-derived azlactone **3a** with different amounts of EtOD in the presence of the catalyst **2a** (10 mol%) in CH_2Cl_2 (0.5 M) at room temperature. As shown in Table 1, the DKR reactions of **3a** proceeded smoothly with EtOD, affording the α-deuterated amino ester (*S*)-**4a** in excellent yields. As expected, the amount of deuterium incorporated increased with increasing amount of EtOD, whereas the ee values decreased. Thus, by using 50 equiv. of

Table 2 Catalytic DKR of various azlactones *rac*-**3a–j** with ethanol-*d*[a]



rac-**3a-j** (*S*)-**4i-j**

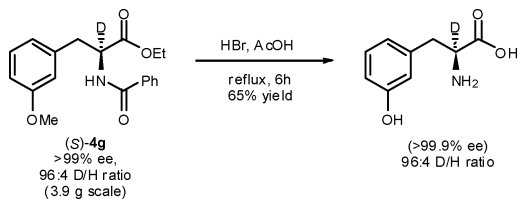
Entry	R^1	Ar	Time (h)	Yield (%)[b]	% ee[c]	D : H ratio[d]
1	Me (**a**)	Ph	5	86(66)[e]	86(99)[e]	97 : 3
2	*i*-Pr (**b**)	Ph	24	88(69)[e]	88(99)[e]	97 : 3
3	*i*-Bu (**c**)	Ph	15	86(67)[e]	83(99)[e]	97 : 3
4	Et (**d**)	Ph	9	88(70)[e]	87(99)[e]	96 : 4
5	$PhCH_2$ (**e**)	Ph	12	85(70)[e]	80(99)[e]	97 : 3
6	 (**f**)	Ph	12	88(61)[e]	84(99)[e]	97 : 3
7	 (**g**)	Ph	15	88(53)[e]	80(99)[e]	98 : 2
8	Allyl (**h**)	Tol	15	88(67)[e]	83(99)[e]	96 : 4
9	Propargyl (**i**)	Tol	12	86(65)[e]	80(99)[e]	95 : 5
10	 (**l**)	Ph	24	88(70)[e]	84(99)[e]	95 : 5

[a] The reactions were carried out with racemic **3a–j** (0.5 mmol), EtOD (25 mmol), and the catalyst **2b** (10 mol%) in CH_2Cl_2 (1.0 mL). [b] Isolated yields after chromatographic purification. [c] Determined by chiral HPLC (see ESI). [d] The D/H ratio was determined by ^{1}H NMR. [e] The yields and ee values in parentheses were obtained after a single recrystallization.

EtOD, the product (*S*)-**4a** was obtained typically with 85% ee and >95% deuterium incorporation at the α-position.[10] The optical purity was simply enriched to >99% ee by a single recrystallization from methyl cyclohexane (entry 4, Table 1).

The generality of this protocol was then demonstrated by synthesizing ten α-carbon deuterium-labelled α-*N*-acyl amino esters (*S*)-**4a–j**. As shown from the results in Table 2, in all cases, the DKR products **4a–j** were obtained typically with >95% deuterium incorporation at the α-position. In addition, high levels of asymmetric induction were also obtained with most substrates. Here again, all products **4a–j** were obtained in the enantiomerically pure form (>99% ee) after a single recrystallization from methyl cyclohexane.

The *N*-protected amino esters **4** could also be successfully transformed into the more valuable optically pure amino acids **1** by hydrolysis without any loss of their deuterium labeling or optical purity. For example, gram quantities of optically pure (>99.9% ee) α-deuterated L-*m*-tyrosine[11] could be obtained in one-step by hydrolysis of (*S*)-**4g** with HBr/AcOH (see ESI†) (Scheme 1).



Scheme 1 A gram-scale synthesis of α-deuterated L-*m*-tyrosine.

In conclusion, we have developed a convenient and general method for the synthesis of α-deuterium labelled chiral amino acids. This procedure involves the organocatalytic DKR reaction of racemic azlactones **3** with EtOD as a nucleophile as well as a deuterium source. In most cases, the *N*-protected α-deuterated amino esters **4** were obtained with a deuterium content greater than 95% and, moreover, their optical purity was enriched to >99% ee by a single recrystallization. The *N*-protected amino esters **4** could also be successfully transformed into the optically pure amino acids **1** by hydrolysis, without any loss of their deuterium labeling or optical purity. We believe that our protocol is one of the most general and effective strategies for the preparation of a variety of enantiomerically pure natural and non-natural α-deuterium labelled chiral amino acids.

Acknowledgements

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