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Stereoselective synthesis of 4-substituted-cyclic sulfamidate-5-carboxylates by asymmetric transfer hydrogenation accompanied by dynamic kinetic resolution and applications to concise stereoselective syntheses of (−)-*epi*-cytoxazone and the taxotere side-chain†

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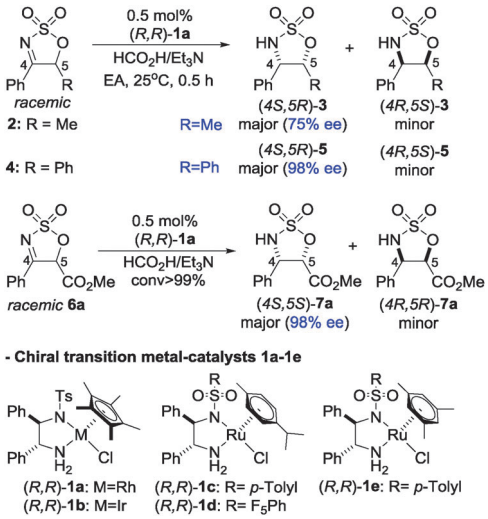
Dynamic kinetic resolution driven, asymmetric transfer hydrogenation reactions of cyclic sulfamidate imine-5-carboxylate esters were developed. Applications of the new methodology to stereoselective syntheses of the taxotere side-chain and (−)-*epi*-cytoxazone are described.

1,2-Amino alcohol motifs, including those found in β-amino-α-hydroxy acids, are present in a vast range of natural products and pharmaceutically related compounds.[1] In addition, the relative and absolute stereochemistry of the 1,2-amino alcohol moiety generally governs the biological activities of these substances. Therefore, the development of methods for stereoselective synthesis of members of this family has received considerable attention.[1a,2]

Transition metal catalyzed-asymmetric transfer hydrogenation reactions (ATH)[3] of carbonyl compounds containing configurationally labile stereogenic C–H centers, accompanied by dynamic kinetic resolution (DKR), have become efficient and powerful techniques for controlling the stereochemistry at two contiguous stereogenic centers. Examples of processes of this type include ATH of α-substituted-β-ketoesters,[4] β-ketoamides,[5] α-alkoxy-β-keto phosphonates,[6] 1,2-diketones,[7] α-ketoesters,[8] and α-ketophosphonates.[9] However, only a few reports exist describing ATH reactions of imines that are accompanied by DKR.[10] In this context, we recently described a highly efficient procedure for ATH–DKR of prochiral cyclic sulfamidate imines, using HCO_2H/Et_3N as the hydrogen source and chiral Rh-catalysts (Scheme 1).[10a,b] In this early effort, we showed that ATH of 4,5-disubstituted cyclic sulfamidate imines **2**, possessing configurationally labile stereogenic centers (C5), is accompanied by DKR. It was also observed that DKR is caused by rapid racemization at the acidic stereogenic C_5 position adjacent to the imine carbon under the reaction conditions. In fact, introduction of an aryl in place of a methyl group at C-5 of **2** leads to drastic improvement in the stereoselectivity of the ATH reaction (*e.g.*, from 75% ee for **3** to 98% ee for **5**), an obvious consequence of the enhanced acidity of H-5 (Scheme 1).[10a]



Scheme 1

While considering other strategies to improve the stereoselectivity of ATH–DKR reactions of cyclic imine **2**, we envisioned that introduction of a carboxylate group at C-5 would also enhance the acidity of H-5 and, as a result, would promote high levels of stereoselectivity in the ATH–DKR reaction.

Below, we describe the results of an investigation exploring this proposal, which led to the first examples of highly efficient ATH reactions of cyclic imines **6**, which are accompanied by

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† Electronic supplementary information (ESI) available: Experimental procedures and characterization data with the copies of ^{1}H-, ^{13}C-NMR spectra, chiral HPLC chromatograms of all chiral compounds and X-ray crystallography data of (*S*,*S*)-**7j**. CCDC 1007235. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc06395c

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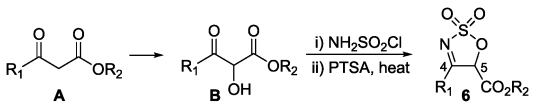


Scheme 2 Synthesis of 4-substituted sulfamidate imine-5-carboxylates **6**.

DKR and can be applied in the synthesis of stereochemically enriched, chiral cyclic sulfamidate-5-carboxylate esters **7**.

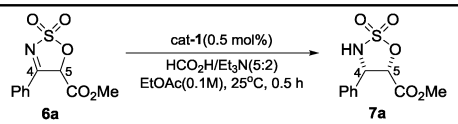
The racemic cyclic imine-5-carboxylate esters **6**, used in this work, were prepared from α-hydroxy-β-keto ester (**B**) and sulfamoyl chloride by modification of a previously described procedure (Scheme 2).[11]

Racemic 4-phenyl-5-methoxycarbonyl cyclic imine **6a** was selected as the model substrate in initial efforts aimed at the identification of the most suitable catalyst systems for the ATH reactions. Reactions of **6a** were performed using the known chiral transition metal catalysts **1a–e** (0.5 mol%) and employing HCO_2H/Et_3N as the hydrogen source in EtOAc at rt (Table 1).

As the results given in Table 1 show, the efficiencies and stereochemical outcomes of ATH reactions of **6a** are strongly affected by both the nature of the transition metal and the diamine ligands. For example, reaction of this substrate using Ru-catalysts with diamine ligands bearing electron rich or electron deficient arylsulfonyl groups (**1c**,[3c] **1d**,[12] **1e**[4a]) proceed to very low conversions (Table 1, entries 3–5). However, ATH of **6a** using Ir-catalyst **1b**[13] reaches completion in 0.5 h (conversion > 99%) but takes place with a low level enantioselectivity (30% ee). Finally, the results reveal that ATH–DKR of **6a** with Rh-catalyst (*R,R*)-**1a**,[14] which possesses TsDPEN and pentamethylcyclopentadienyl ligands, for 0.5 h at rt produces (*S,S*)-**7a** in the highest conversion (>99%) and level of stereoselectivity (>25 : 1 dr, 98% ee).

The influence of solvent on the ATH reaction of **6a** catalyzed by (*R,R*)-**1a** was investigated. In most of the solvents tested (EtOAc, CH_2Cl_2, $Cl(CH_2)_2Cl$, $CHCl_3$, toluene, DMF, MeOH, THF, and 2-propanol), ATH of **6a** takes place completely to form (*S,S*)-**7a** with high levels of stereoselectivity (>25 : 1 dr, 84–99% ee) (see, Table S2 in ESI†). For the purpose of experimental convenience and based on optimization of stereoselectivity, further ATH reactions were carried out in EtOAc as solvent.

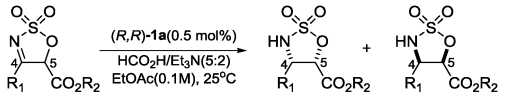
Table 1 Optimization of chiral catalysts **1a–e** for ATH–DKR of **6a**[a]



Entry	Cat.**1**	Convn[b] (%)	dr (*syn* : *anti*)	ee[d] (%)	Config.[e]
1	(*R,R*)-**1a**	>99	>25 : 1[c]	98	*S,S*
2	(*R,R*)-**1b**	>99	>25 : 1[c]	30	*S,S*
3	(*R,R*)-**1c**	13	—	95	*S,S*
4	(*R,R*)-**1d**	6	—	—	—
5	(*R,R*)-**1e**	17	—	83	*S,S*

[a] Reaction conditions: **6a** (0.5 mmol), cat-**1** (0.5 mol%), HCO_2H/Et_3N (5 : 2, 0.5 mL), EtOAc (5 mL), rt, 0.5 h. [b] Determined by ^1H NMR analysis of crude products. [c] Only 4,5-*cis* products were detected by using ^1H NMR analysis of crude product mixtures. [d] Determined by chiral HPLC. [e] See Scheme S1 in ESI.

Table 2 ATH–DKR of cyclic sulfamidate imine-5-carboxylates **6**[a]



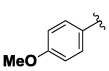
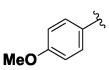
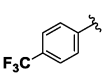
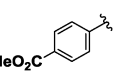
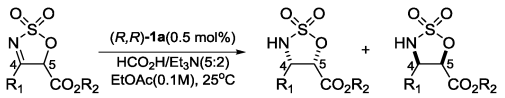
Entry	Substrate **6**, **7**	R_1	R_2	Time (h)	Conv.[b] (%)	ee[c] (%)	Conf.[d]
1	**a**		Me	0.5	>99(92)	98	*S,S*[e]
2	**b**		i-Pr	0.5	>99(85)	98	*S,S*
3	**c**		Bn	0.5	>99(87)	98	*S,S*
4	**d**		*t*-Bu	0.5	>99(87)	>99	*S,S*
5[f]	**a**		Me	0.5	>99(94)	98	*R,R*[f]
6	**e**		Me	12	20	—	—
7[g]	**e**		Me	12[g]	>99(95)[g]	92[g]	—
8	**f**		Me	0.5	>99(99)	99	*S,S*
9	**g**		Me	0.5	>99(99)	99	*S,S*
10	**h**		Me	0.5	>99(99)	97	*S,S*
11	**i**		Me	0.75	>99(92)	97	*S,S*
12	**j**		Me	0.5	>99(99)	>99	*S,S*[h]
13[i]	**j**		Me	3.5[i]	>99[i]	99[i]	*S,S*[h]
14	**k**		Me	0.5	>99(96)	97	*S,S*
15	**l**		Me	0.5	>99(88)	99	*S,S*
16	**m**		Me	0.5	>99(95)	96	*S,S*
17	**n**		Me	0.5	>99(92)	97	*S,S*
18	**o**		Me	0.5	>99(91)	97	*S,S*
19	**p**		Me	1.0	>99(92)	95	*S,S*
20	**q**		Me	2.0	>99(94)	99	*S,S*
21	**r**	*n*-Pr–	Me	1.5	>99(69)	91[j]	ND[k]
22	**s**	$Ph(CH_2)_2$–	Me	12	>99(54)	76	ND[k]

Table 2 (*continued*)



Entry	Substrate 6, 7	R_1	R_2	Time (h)	Conv.[b] (%)	ee[c] (%)	Conf.[d]
23	**t**		Me	24	50	—	ND[k]
24[g]	**t**		Me	48[g]	>99(67)[g]	47[j]	ND[k]

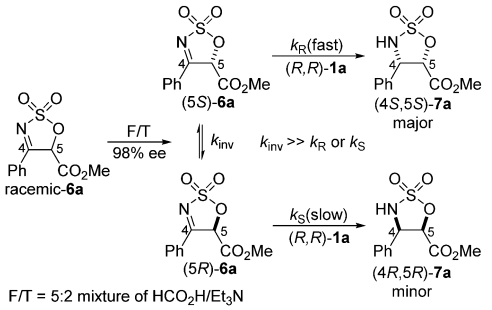
[a] Reaction conditions: **6** (0.5 mmol), (*R,R*)-**1a** (0.5 mol%), HCO_2H/Et_3N (5 : 2, 0.5 mL), EtOAc (5 mL), rt. [b] Determined by ^1H NMR analysis of the crude product mixtures (isolated yields in parentheses). [c] Determined by using chiral HPLC. Only 4,5-*cis* products were detected by using ^1H NMR analysis of crude product mixtures. [d] Absolute configuration of **7b–i**, **7k–q** was determined by analogy to **7a** and **7j**. [e] See, Scheme S1 in ESI. [f] (*S,S*)-**1a** (0.5 mol%) was used. [g] 1 : 1 mixture of HCO_2H/Et_3N was used as the hydrogen source. [h] Determined by using X-ray crystallographic analysis (CCDC 1007235). [i] 0.1 mol% of (*R,R*)-**1a** (*S*/*C* = 1000) was used. [j] ee of ring-opened derivatives derived from **7r** and **7t** respectively (see, Scheme S2 in ESI). [k] Not determined.

The scope and limitations of the ATH–DKR reaction were explored using a variety of cyclic sulfamidate imine-5-carboxylates (**6**). All reactions were carried out in EtOAc (25 °C) under the optimized reaction conditions employing (*R,R*)-**1a** (0.5 mol%) as the catalyst and a 5 : 2 mixture of HCO_2H/Et_3N as the hydrogen source. The results are summarized in Table 2.

ATH of **6a** with (*R,R*)-**1a** under the optimized reaction conditions produces a mixture of stereoisomeric 4,5-*cis* sulfamidates, in which the (4*S*,5*S*)-**7a** isomer predominates (98% ee, 92% yield, Table 2, entry 1). None of the 4,5-*trans* sulfamidates are detected in the crude product mixture by using ^1H-NMR spectroscopic analysis. These results show that hydrogen addition to **6a** occurs exclusively from the less hindered face of the cyclic imine moiety.[10a] In addition, ATH–DKR reactions of 4-phenyl-cyclic imine-5-carboxylates containing different ester moieties, such as isopropyl (**6b**) and benzyl (**6c**), also produce the corresponding cyclic sulfamidates (**7b**, **7c**) with excellent efficiencies and stereoselectivities. Moreover, ATH–DKR of the *t*-butyl ester **6d** forms nearly a single stereoisomer of the corresponding cyclic sulfamidate **7d**.

ATH reaction of **6a** under the optimized conditions, except in this case using the (*S,S*)-**1a** as catalyst, produces the antipodal sulfamidate (*R,R*)-**7a** with efficiency and stereoselectivity (98% ee, 94% yield) that match those of accompanying reaction using (*R,R*)-**1a** (Table 2, entry 5). These observations demonstrate that the source of dynamic kinetic resolution in this process is the configurational ability of the C-5 stereogenic center in **6a** caused by rapid racemization under the reaction conditions[10a] (Scheme 3). As a result, the absolute stereochemistry of the major reduction product depends on the enantiomer of the Rh-catalyst employed in a manner such that (5*S*)-**6a** is preferentially reduced with (*R,R*)-**1a** to form sulfamidate (*S,S*)-**7a** and (5*R*)-**6a** is preferentially reduced with (*S,S*)-**1a** to give sulfamidate (*R,R*)-**7a**.

ATH–DKR of cyclic sulfamidate imines possessing either electron-withdrawing or -donating groups at the *meta*- or *para*-positions on the phenyl ring leads to production of the corresponding sulfamidates in high yields and stereoselectivites. However, ATH of the cyclic imine **6e** possessing an *ortho*-methyl substituted phenyl group is sluggish, reaching only 20% conversion even after 12 h. Based on the results of recent studies which show that the HCO_2H/Et_3N (F/T) ratio has a significant effect on both the ATH rate and the level of enantioselectivity,[5b,6,15] we employed the 1 : 1 instead of a 5 : 2 mixture of F/T as the hydrogen source for ATH of **6e**. This reaction proceeds to completion in 12 h and is attended by a slightly decreased level of stereoselectivity (92% ee) (Table 2, entries 6 and 7). Cyclic imines containing heteroaromatic moieties also serve as suitable substrates for the ATH–DKR reaction, as exemplified by the results of reactions of furan **6p** and thiophene **6q** (Table 2, entries 19 and 20). Importantly, we also found that the catalyst loading can be reduced to 0.1 mol% (*S*/*C* = 1000) in the ATH–DKR reaction of **6j** without deterioration of optical purity when the process is carried out using a longer reaction time (Table 2, entry 13). ATH reaction of 4-alkyl substituted cyclic sulfamidate imine-5-carboxylates was also explored. The results show that the efficiencies and stereoselectivities of the processes are sensitive to the steric bulkiness of the 4-alkyl group. Thus, ATH–DKR reaction of 4-(*n*-propyl) cyclic imine **6r** is complete in 1.5 h (91% ee) but that of the 4-phenethyl containing cyclic imine **6s** requires 12 h for completion and occurs with a lower level of stereoselectivity (76% ee) (Table 2, entries 21 and 22). ATH–DKR reaction of 4-cyclohexyl-substituted cyclic imine **6t** is more sluggish resulting in only 50% conversion after 24 h. However, by employing a 1 : 1 mixture of HCO_2H/Et_3N as the hydrogen source, reaction of **6t** reaches completion in 48 h but it takes place with a lower level of stereoselectivity (47% ee) (Table 2, entries 23 and 24).



Scheme 3 Proposed mechanism for DKR in ATH of **6a**.

The cyclic sulfamidates **7** produced in these reactions are valuable intermediates for the synthesis of various chiral β-amino-α-hydroxy carboxylic acids or 1,2-functionalized amines[16] such as those present in the side chain of the anticancer drug taxotere (**10**)[17] and the potent cytokine modulator (−)-*epi*-cytoxazone (**12**)[2b,18] (Fig. 1).

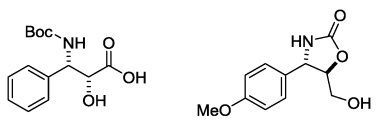
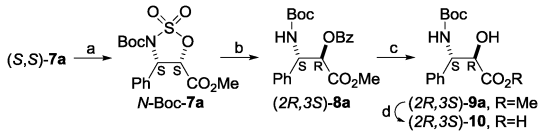
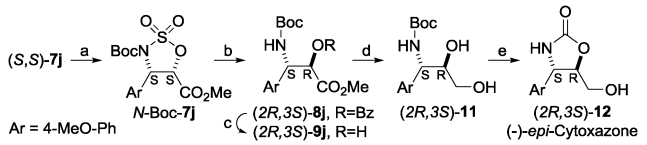


Fig. 1 Examples of biologically important 1,2-amino alcohol compounds.



Scheme 4 Reaction conditions: (a) $(Boc)_2O$, Et_3N, cat. DMAP, CH_2Cl_2, 100%; (b) (i) $PhCO_2NH_4$, DMF, 55 °C, 12 h; (ii) 1N HCl, CH_2Cl_2, 6 h, rt, 82%; (c) KCN, MeOH, 65 °C, 85%; (d) 1N NaOH, MeOH–THF, rt, 88%.



Scheme 5 Reaction conditions: (a) $(Boc)_2O$, Et_3N, cat. DMAP, CH_2Cl_2, 94%; (b) (i) $PhCO_2NH_4$, DMF, 55 °C, 12 h; (ii) 1N HCl, CH_2Cl_2, 6 h, rt, 100%; (c) KCN, MeOH, 65 °C, 86%; (d) $NaBH_4$, MeOH, rt, 92%; (e) NaH, THF, rt, 95%.

In order to demonstrate the utility of the methodology developed in this effort, we employed it in the synthesis of the taxotere side-chain **10**[17] (Scheme 4).

Accordingly, (*S*,*S*)-**7a** formed by ATH–DKR reaction of **6a** is converted to its *N*-Boc derivative, which upon treatment with $PhCO_2NH_4$ undergoes ring opening[10a,19] to form (2*R*,3*S*)-**8a**. Selective removal of the *O*-benzoyl group in **8a** using KCN[11] in MeOH and subsequent hydrolysis of methyl ester **9a** produce the taxotere side-chain **10**[17] (*ca.* 61% overall yield over 4 steps from (*S*,*S*)-**7a**).

An additional example demonstrating the usefulness of the methodology is found in the synthesis of (−)-*epi*-cytoxazone (**12**) starting with (*S*,*S*)-**7j** (Scheme 5)[2b,18] (*ca.* 70% overall yield over 5 steps from (*S*,*S*)-**7j**).

In summary, a convenient and highly stereoselective method for the preparation of 4-substituted cyclic sulfamidate-5-carboxylate esters **7** was developed in this investigation. The process, involving asymmetric transfer hydrogenation accompanied by dynamic kinetic resolution (ATH–DKR), uses HCO_2H/Et_3N as the hydrogen source and chiral Rh catalysts (*S*,*S*)- or (*R*,*R*)-Cp*RhCl(TsDPEN). Most of the ATH–DKR reactions probed in this study occur rapidly (30 min) and highly stereoselectively under mild and experimentally convenient conditions (rt, without the need for solvent degassing or an inert atmosphere). The utility of this methodology was demonstrated by its application to stereoselective syntheses of the taxotere side-chain and (−)-*epi*-cytoxazone.

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