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COMMUNICATION

Dynamic kinetic resolution in the stereoselective synthesis of 4,5-diaryl cyclic sulfamidates by using chiral rhodium-catalyzed asymmetric transfer hydrogenation†

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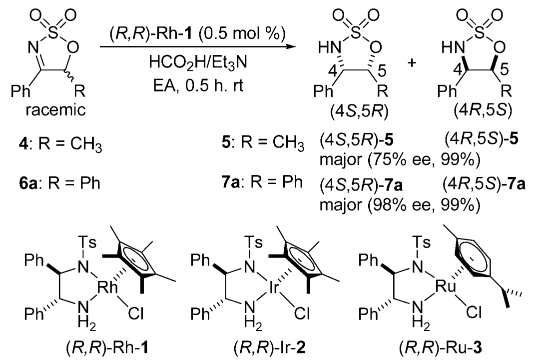
The dynamic kinetic resolution of 4,5-diaryl cyclic sulfamidate imines was achieved *via* asymmetric transfer hydrogenation using a HCO_2H/Et_3N mixture as the hydrogen source and chiral Rh catalysts (*R*,*R*)- or (*S*,*S*)-RhCl(TsDPEN)Cp* affording the corresponding cyclic sulfamidates in good yields with up to >20 : 1 dr and up to >99% ee.

Dynamic kinetic resolution (DKR), which combines a kinetic resolution step with an *in situ* equilibration or racemization of a configurationally labile substrate, serves as an efficient method to generate optically pure compounds from racemic substrates.[1]

Asymmetric transfer hydrogenation (ATH), using hydrogen sources other than molecular hydrogen, has proven to be one of the most powerful general procedures for asymmetric reduction of ketones or imines, which yields the corresponding chiral alcohols and amines because of its operational simplicity, the easy availability of hydrogen sources, and ability to use readily accessible and less sensitive catalysts.[2] In this context, transition metal-catalyzed asymmetric transfer hydrogenation of configurationally labile carbonyl compounds *via* DKR has emerged as an efficient and powerful technique for controlling the stereochemistry at two contiguous stereogenic centers formed in the process. Examples of this application include ATH of α-substituted β-keto esters,[3] β-keto amides,[4] β-keto sulfones,[5] 2-substituted cycloalkanones,[6] 1,3-diketones[7] and 1,2-diketones.[8] However, to our knowledge only one report exists describing ATH reactions of imines that are accompanied by DKR.[9]

Recently we described a highly efficient procedure for ATH of prochiral cyclic sulfamidate imines with HCO_2H/Et_3N as the hydrogen source and well-defined chiral Rh complexes as catalysts.[10] In this earlier effort, we demonstrated that ATH of 4-phenyl-5-methyl cyclic imine **4**, having a configurationally labile stereogenic center, is accompanied by DKR although the levels of stereoselectivity were not high (**5**: 75% ee, 99% yield, Scheme 1). In considering ways to improve the stereochemical performance of ATH–DKR reactions of cyclic sulfamidate imines, we envisioned that introduction of aryl groups at the 5-positon of **4** instead of an alkyl group would enhance the lability of the hydrogen at the stereogenic center and that this might lead to more rapid racemization and an improved level of stereoselectivity.



Scheme 1 DKR in the Rh-catalyzed ATH reaction of racemic 4,5-disubstituted cyclic imine **4** and **6a**.

In this communication, we describe the results of a recent effort guided by this proposal, which has led to the first examples of highly efficient and practical ATH-based DKR reactions of cyclic imines **6** for the synthesis of chiral 4,5-diaryl substituted cyclic sulfamidates **7**. The resulting 4,5-diaryl cyclic sulfamidates **7** possess both an amine substituted chiral carbon and a reactive cyclic sulfamidate group, and are valuable precursors in the synthesis of various chiral 1,2-functionalized amine derivatives.[11] The requisite 4,5-diaryl cyclic imines **6**, probed in this study, are conveniently prepared from readily available benzoins and sulfamoyl chloride by using a modification of a previously described procedure.[10]

Reduction of racemic imine **6a** employing a mixture of HCO_2H/Et_3N in the presence of the (*R*,*R*)-Rh-**1** catalyst (S/C = 200) in EtOAc for 0.5 h at room temperature produces a mixture of stereoisomeric 4,5-*cis*-sulfamidates, in which the (4*S*,5*R*)-**7a** isomer predominates (98% ee, 99% yield, Scheme 1). No 4,5-*trans*-sulfamidates were detected in the crude product mixture by using ^{1}H-NMR analysis. Therefore,

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the results show that hydrogen addition occurs only from the less hindered face of the cyclic imine moiety in **6a**.[3d]

To optimize the reaction conditions the influence of solvents on ATH–DKR reaction of **6a** was investigated. The cyclic imine **6a** (0.1 M) in the solvents tested (EtOAc, CH_2Cl_2, THF, DMF, MeOH, toluene, CH_3CN) is completely converted to the cyclic sulfamidate **7a** within 0.5 h at room temperature, with high levels of stereoselectivity.[12] The exception to this trend is the reaction in MeOH which takes place more slowly than in the other solvents (2 h, 66% yield). Interestingly, **6a** is completely converted to **7a**, employing HCO_2H/Et_3N (**6a** : HCO_2H : Et_3N = 1 : 2 : 2) as the hydrogen source with excellent stereoselectivity (97% ee, 89%) even when no solvent is used. For the sake of experimental convenience, all further reactions were carried out in EtOAc as solvent. The ATH–DKR reaction of **6a**, promoted by different transition metal catalysts, was also explored.[12] ATH reaction of **6a** in EtOAc (0.1 M) occurs to completion (98% ee, 99%) in 0.5 h when 0.5 mol% of (*R*,*R*)-Rh-**1** is used as the catalyst. Under essentially the same conditions, the chiral Ru(II) catalyst (*R*,*R*)-Ru-**3** promotes complete reaction of **6a** in 12 h with a slightly lower enantioselectivity (90% ee, 86% yield). The Ir(III) catalyst (*R*,*R*)-Ir-**2** also brings about complete conversion of **6a**, but with a low level of enantioselectivity (2 h, 91% yield, 28% ee). The results show that the preformed (*R*,*R*)-Rh-**1** is the best catalyst for the ATH reaction of imine **6a**.[13]

Under the optimized reaction conditions, ATH reactions with various imines **6**, possessing both electron-donating and electron-withdrawing substituents on the 4,5-phenyl groups, were carried out to examine the scope and limitations of the ATH process and the results are summarized in Table 1.

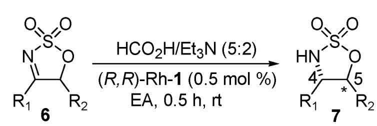
ATH reaction of **6a** employing the (*S*,*S*)-Rh-**1** catalyst produced the antipodal sulfamidate (4*R*,5*S*)-**7a** with almost same efficiency and stereoselectivity (97% ee, 99%) as with the (*R*,*R*)-Rh-**1** catalyst (Table 1, entries 1 and 2). These observations suggest that the stereogenic center of imine **6a** is configurationally labile, undergoing rapid racemization under the ATH reaction conditions. As a consequence, the absolute stereochemistry of the reduction products depends on the chirality of the Rh-catalysts used.[14] In addition, the results in Table 1 show that substituents on the 5-phenyl group of cyclic imine **6** greatly influence the rate and stereoselectivity of the ATH–DKR process. Cyclic imines **6** bearing electron-withdrawing groups, such as chloro (**6c**, **6d**), fluoro (**6e**), or trifluoromethyl (**6f**), at the *meta*- or *para*-positions of the 4,5-diaryl moiety are smoothly converted to the corresponding cyclic sulfamidates **7** in excellent yields and stereoselectivities. However, imine with the *ortho*-chloro phenyl (**6b**) group reacts to afford the corresponding cyclic sulfamidate (**7b**) with high yield but with very low enantioselectivity (22% ee, Table 1, entry 3).

Cyclic imines **6i** and **6j** bearing electron-donating methyl group at the *meta*- or *para*-positions of the 5-aryl moiety, although forming the corresponding cyclic sulfamidates **7i** and **7j** in excellent yields, display slightly low levels of stereoselectivity.[15]

Strong electron-donating groups at the *para*-position of the 5-phenyl group in **6** retard the ATH–DKR reaction. For example, the 4,5-bis-(4-methoxy-phenyl) substituted cyclic imine **6h** is inert under the ATH reaction conditions even over extended time periods up to 24 h. In this case, **6h** is recovered nearly quantitatively (Table 1, entry 9). In sharp contrast to **6h**, the 4,5-bis-(3-methoxy-phenyl) substituted cyclic imine **6g** is smoothly reduced within 0.5 h to form the corresponding cyclic sulfamidate **7g** in excellent yield but with a slightly lower enantioselectivity[15] (94% ee, Table 1, entry 8).

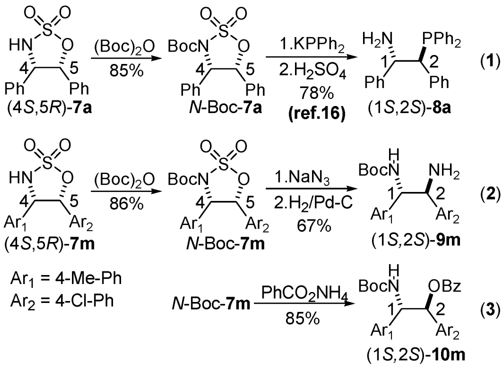
ATH–DKR reactions of cyclic imines having different aromatic groups at the 4 and 5 positions of imine **6** were also investigated. ATH reactions of 4-(4-chloro-phenyl)-5-phenyl

Table 1 Rh-catalyzed ATH–DKR reaction of cyclic imines **6**[a]



Entry	Imine	R_1	R_2	Amine	Yield[b] (%)	dr[c]	ee[d] (%)	Config.[e]
1	**6a**	Ph	Ph	**7a**	99	> 20 : 1	98	4*S*,5*R*
2	**6a**	Ph	Ph	**7a**	99	> 20 : 1	97	4*R*,5*S*[f]
3	**6b**	2-Cl-Ph	2-Cl-Ph	**7b**	99	> 20 : 1	22	4*S*,5*R*
4	**6c**	3-Cl-Ph	3-Cl-Ph	**7c**	99	> 20 : 1	99	4*S*,5*R*
5	**6d**	4-Cl-Ph	4-Cl-Ph	**7d**	99	> 20 : 1	99	4*S*,5*R*
6	**6e**	4-F-Ph	4-F-Ph	**7e**	94	> 20 : 1	99	4*S*,5*R*
7	**6f**	4-CF_3-Ph	4-CF_3-Ph	**7f**	99	> 20 : 1	99	4*S*,5*R*
8	**6g**	3-MeO-Ph	3-MeO-Ph	**7g**	99[g]	> 20 : 1	94	4*S*,5*R*
9	**6h**	4-MeO-Ph	4-MeO-Ph	**7h**	—[h]	—	—	—
10	**6i**	3-Me-Ph	3-Me-Ph	**7i**	99[g]	> 20 : 1	89	4*S*,5*R*
11	**6j**	4-Me-Ph	4-Me-Ph	**7j**	99[g,i]	> 20 : 1	87	4*S*,5*R*
12	**6k**	4-Cl-Ph	Ph	**7k**	98	> 20 : 1	97	4*S*,5*R*
13	**6l**	4-Cl-Ph	4-Me-Ph	**7l**	99[g,i]	> 20 : 1	99	4*S*,5*R*
14	**6m**	4-Me-Ph	4-Cl-Ph	**7m**	94	> 20 : 1	99	4*S*,5*R*

[a] **6** (0.2 mmol), 2.0 mL of EtOAc, 0.2 mL of HCO_2H/Et_3N (5 : 2) mixture, (*R*,*R*)-Rh-**1** catalyst (0.5 mol%) at 25 °C for 0.5 h. [b] Isolated yields. [c] Only a single diastereomer was detected in the ^{1}H-NMR of the crude reaction mixture. [d] ee was determined by using chiral HPLC. [e] Absolute configuration of **7a** was determined by X-ray crystallographic analysis (CCDC 803456†) and those of the others are assigned by analogy of **7a**. [f] (*S*,*S*)-Rh-**1** catalyst was used. [g] Crude yields. [h] No reaction. [i] Reaction time: 15 min.



Scheme 2 Conversion of cyclic sulfamidates to 1,2-functionalized amines.

cyclic imine (**6k**), 4-(4-chloro-phenyl)-5-(4-methyl-phenyl) cyclic imine (**6l**) or 4-(4-methyl-phenyl)-5-(4-chloro-phenyl) cyclic imine (**6m**) all take place smoothly to generate the corresponding cyclic sulfamidates **7k**, **7l** and **7m** with excellent yields and enantioselectivities (Table 1, entries 12–14).

The nature of substituents on the 5-aryl group of the cyclic imines **6** greatly influences not only the reactivity and stereoselectivity of the ATH reaction but also the stability of the ATH products. For example, cyclic sulfamidates **7g**, **7i**, **7j** and **7l**, having electron donating groups on the *meta*- or *para*-positions of their 5-phenyl moieties, are unstable under the reaction conditions on the extended reaction time (>0.5 h at rt) or when subjected to silica-gel column chromatographic purification.[15]

The cyclic sulfamidates **7** produced in these reactions are valuable precursors for the synthesis of various chiral 1,2-functionalized amine derivatives.[11] An example of the usefulness of **7a** was shown by the facile conversion of its *N*-Boc derivative (4*S*,5*R*)-**7a** (Scheme 2, eqn (1)) to the chiral aminophosphine **8a**, which is a potentially valuable chiral ligand for transition metal catalyzed asymmetric transformations.[16] To further demonstrate the usefulness of the methodology developed in this effort, the 4,5-differentially substituted cyclic sulfamidate **7m** was transformed into the corresponding 1,2-differentially substituted diaryl ethylenediamine **9m** and diaryl aminoethanol **10m**, substances that are difficult to prepare by using alternative routes (Scheme 2, eqn (2) and (3)).

In summary, a convenient and highly stereoselective methodology for the preparation of 4,5-diaryl cyclic sulfamidates **7** has been developed. This process, involving asymmetric transfer hydrogenation accompanied by dynamic kinetic resolution (ATH–DKR), uses HCO_2H/Et_3N as the hydrogen source and the well-defined chiral Rh catalysts (*S*,*S*)- or (*R*,*R*)-Rh-**1**, Cp*RhCl(TsDPEN). Most of the 4,5-diaryl cyclic imine substrates **6** probed undergo highly stereoselective ATH–DKR reactions rapidly (within 30 min) under mild and experimentally convenient conditions (room temperature, without the need for solvent degassing or an inert atmosphere). The exception to this general rule is imine **6h** that has a strong electron-donating group at the *para*-position of the 5-phenyl group. Moreover, in the ATH–DKR reactions of cyclic imines **6**, two contiguous stereogenic centers are produced simultaneously with excellent levels of diastereoselectivity (>20 : 1) and enantioselectivity (as high as >99% ee). Finally, the absolute configurations of the stereocenters formed in ATH–DKR reactions of imines **6** are controlled by the stereochemistry of the Rh-catalysts employed.

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12 See ESI†.
13 The amount of catalyst loading can be reduced to 0.05 mol% (S/C = 2000) with longer reaction time to complete the reaction without loss of the optical purity (15 h, 98% ee, 94% yield).
14 Optically active (5*S*)-**6a** (85% ee) was prepared and allowed to stir in an EtOAc solvent in the presence of only Et_3N at room temperature. After 0.5 h, no reduction products were obtained and racemic **6a** (0.4% ee) was recovered quantitatively with almost complete loss of the optical purity (see ESI†, 6-1 and 6-2).
15 We assume that the relatively lower enantioselectivities of **7g**, **7i** and **7j** partially come from the instability of **7g**, **7i** and **7j** under the chiral HPLC column conditions for measurement of ee. In fact, the ee's of chromatographically stable *N*-Boc-**7g** (98% ee), *N*-Boc-**7i** (91% ee) and *N*-Boc-**7j** (93% ee), which were prepared from the corresponding **7g**, **7i** and **7j**, are higher than those of **7g**, **7i** and **7j**[12].
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