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# Enantioselective Synthesis of Cyclic Sulfamidates by Using Chiral Rhodium-Catalyzed Asymmetric Transfer Hydrogenation

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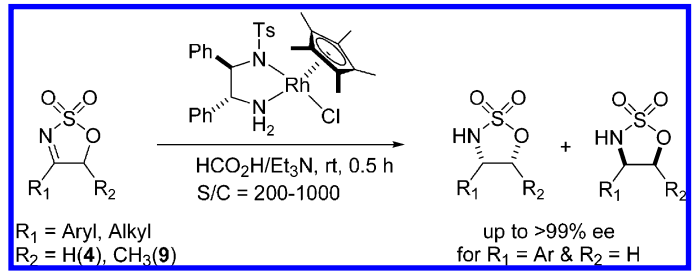
## ABSTRACT




**Asymmetric transfer hydrogenation (ATH) of cyclic sulfamidate imines 4 and 9, using a $HCO_2H/Et_3N$ mixture as the hydrogen source and well-defined chiral Rh catalysts (*S*,*S*)- or (*R*,*R*)-2, Cp*RhCl(TsDPEN), effectively produces the corresponding cyclic sulfamidates with excellent yields and enantioselectivities at room temperature within 0.5 h. ATH of 4,5-disubstituted imines 9, having preexisting stereogenic centers, is shown to take place with dynamic kinetic resolution.**

Asymmetric transfer hydrogenation (ATH) involves the reduction of prochiral compounds with a hydrogen source other than hydrogen gas in the presence of a chiral catalyst. In general, ATH offers operational simplicity since the reaction does not involve (high pressure) molecular hydrogen and can be carried out under areobic conditions. Owing to its excellent selectivity, wide substrate scope, and operational simplicity, ATH of ketones is one of the most powerful and practical methods to access chiral alcohols in both academic and industrial environments.[1] Among the various chiral catalysts used for ATH, transition metal complexes based on Ru(II), Rh(III), or Ir(III) with chiral bidentate ligands, such as *N*-monosulfonylated 1,2-diamines (e.g., **1**−**3**), have been used most frequently.[1a] However, compared to the reactions of ketones, ATH-promoted conversion of imines to chiral amines is more challenging owing to the fact that two additional variables come into play, including the nature of the nitrogen substituent and stereochemistry about the C=N double bond (Scheme 1). Generally, ATH of acyclic imines using catalysts **1**−**3** provides the corresponding amines with relatively low enantioselectivities compared to

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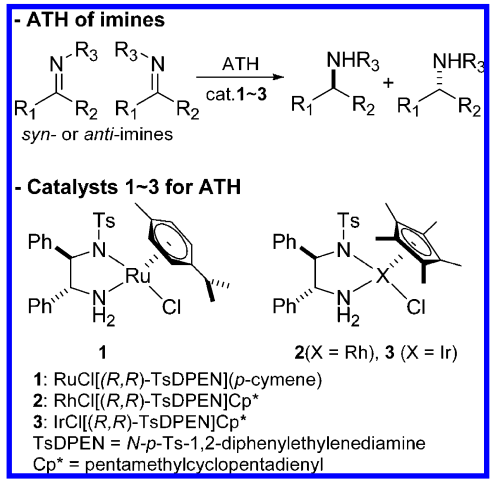
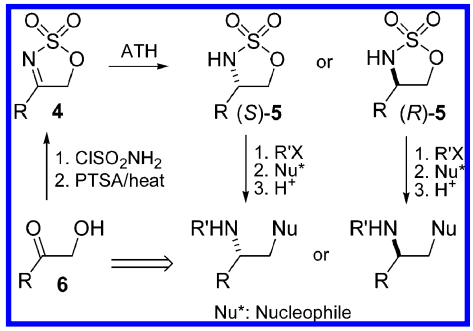
those observed for analogous reaction of ketones.[1c,e,2−4] This is likely a result of the different rates and selectivities of reduction of the *anti* and *syn* isomers.[1c,2] However, five- or six-membered cyclic imines, which lack this stereochemical issue, undergo ATH induced by catalysts **1**−**3** with excellent enantioselectivities.[1f,3,5,6] In addition, ATH of acyclic imines possessing sterically bulky N-substituents, such as *N*-(diphenylphosphinoyl) that causes a predominance of the *anti* geometry, leads to the corresponding *N*-(diphenylphosphinoyl)amines with high degrees of enantioselectivity.[7]

**Scheme 1**




On the basis of the factors described above, we envisioned that the cyclic sulfamate imines **4**, which are activated by the electron-withdrawing sulfamidate group and are free of *syn*- and *anti*-isomerism, would be good substrates for highly enantioselective ATH reactions. Moreover, cyclic sulfamidates (**5**), possessing both a chiral carbon that bears an amine moiety and a reactive cyclic sulfamidate group, are valuable precursors in the syntheses of various chiral 1,2-functionalized amine derivatives including 1,2-amino alcohols, α-amino acids, and nitrogen-containing heterocycles (Scheme 2).[8,9] Typically, cyclic sulfamidates are prepared from chiral amino alcohols and diols through routes that involve several steps.[10,11] Catalytic asymmetric intramolecular amidation of prochiral sulfamate esters using chiral Ru(II)−pybox and valerolactam-derived Rh(II) catalysts has also been employed to generate chiral cyclic sulfamidates with high enantioselectivities.[12] Recently, an efficient enantioselective synthesis of cyclic sulfamidates (**5**) employing chiral Pd-catalyzed asymmetric hydrogenation of corresponding cyclic imines (**4**) has been reported.[10] Although this method provides cyclic sulfamidates **5** in high yields and ee's, it requires the use of high (600 psi) $H_2$ pressures, only trifluoroethanol as the solvent, and 2.4 mol % of the expensive chiral (*S*,*S*)-*f*-binaphane ligand, of which only the (*S*,*S*) isomer is commercially available.

**Scheme 2.** 1,2-Functionalized Chiral Amines through ATH of Cyclic Imines **4** to Form Cyclic Sulfamidate **5**




In investigations aimed at the development of new methods for the preparation of functionalized chiral amines, we have uncovered a highly efficient and practical ATH-based procedure for the synthesis of chiral cyclic sulfamidates (**5**) starting with the corresponding cyclic imines (**4**). This methodology uses a 5:2 mixture of $HCO_2H$ and $Et_3N$ as the hydrogen source along with the chiral Rh catalysts (*S*,*S*)- or (*R*,*R*)-**2**, Cp*RhCl(TsDPEN) (Cp* = pentamethylcyclopentadienyl and TsDPEN = (1*S*,2*S*)- or (1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine). The cyclic imines employed in these processes are conveniently prepared from hydroxyl ketones (**6**) and sulfamoyl chloride by using previously described procedures.[10]

The cyclic imine **4a**, (*R*,*R*)-**2** catalyst (0.5 mol %, S/C = 200), and 5:2 mixture of $HCO_2H/Et_3N$ (azeotropic mixture)[13] in various solvents (EtOAc, $CH_2Cl_2$, THF, DMF, MeOH, toluene, $CH_3CN$) were employed in an effort aimed at optimizing the ATH reaction conditions. The results (see Supporting Information) show that in each case **4a** is completely converted to the cyclic sulfamidate (**5a**) with high enantioselectivity within 1 h at room temperature. In addition, ATH of **4a** in ethyl acetate takes place completely in 0.5 h even using 0.1 mol % of catalyst (*R*,*R*)-**2** (S/C = 1000), while the reaction with 0.1 mol % of (*R*,*R*)-**2** in dichloromethane solvent requires 3.5 h. Therefore, ethyl acetate was selected as the solvent for all of the ATH reactions of imines **4**.

The preformed chiral Rh(III) complex (*R*,*R*)-**2**[5] with a 5:2 mixture of $HCO_2H$ and $Et_3N$ as the hydrogen source was found to be the best condition for performing the ATH reactions of the imines **4**. The ATH of **4a** (0.1 M in ethyl

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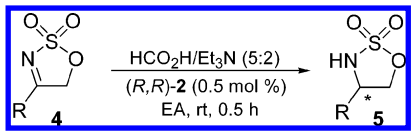
**Table 1.** Rh-Catalyzed ATH of Cyclic Imines **4**[a]




| entry | R | yield(%)[b] | ee(%)[c] | config[d] |
|---|---|---|---|---|
| 1 | Ph (**4a**) | 98 | 99 | *S* |
| 2 | Ph (**4a**) | 99 | 96 | *R*[e] |
| 3 | 4-MeOC$_6$H$_4$ (**4b**) | 98 | 99 | *S* |
| 4 | 3-MeOC$_6$H$_4$ (**4c**) | 92 | 98 | *S* |
| 5 | 2-MeOC$_6$H$_4$ (**4d**) | 95[f] | 16 | *S* |
| 6 | 4-MeC$_6$H$_4$ (**4e**) | 98 | 99 | *S* |
| 7 | 3-MeC$_6$H$_4$ (**4f**) | 99 | 98 | *S* |
| 8 | 2-MeC$_6$H$_4$ (**4g**) | 99 | 83 | *S* |
| 9 | 4-ClC$_6$H$_4$ (**4h**) | 94 | 98 | *S* |
| 10 | 3-ClC$_6$H$_4$ (**4i**) | 99 | 99 | *S* |
| 11 | 2-ClC$_6$H$_4$ (**4j**) | 97 | 62 | *S* |
| 12 | 4-FC$_6$H$_4$ (**4k**) | 99 | 99 | *S* |
| 13 | 4-CNC$_6$H$_4$ (**4l**) | 91 | 94 | *S* |
| 14 | 4-MeO$_2$CC$_6$H$_4$ (**4m**) | 91 | 98 | *S* |
| 15 | 4-NO$_2$C$_6$H$_4$ (**4n**) | 93 | 98 | *S* |
| 16 | *n*-C$_6$H$_{13}$ (**4o**) | 96 | 93[g] | *S* |
| 17 | *t*-Bu (**4p**) | –[h] | – | – |
| 18 | Ph (**4a**)[i] | 98 | 99 | *S* |

[a] 0.5 mmol scale in 5.0 mL of EtOAc (0.1 M) with 0.5 mL of HCO$_2$H/Et$_3$N (5:2) mixture and (*R*,*R*)-**2** catalyst (0.5 mol %) at 25 °C for 0.5 h. [b] Isolated yields. [c] ee was determined by HPLC analysis. [d] Absolute configuration was determined by the sign of rotation of the isolated product for the known compounds (**4a**, **4c**, **4g**, **4k**, **4o**) or by analogy for the unknown compounds. [e] (*S*,*S*)-**2** catalyst was used. [f] Reaction time 24 h. [g] ee of *N*-*cbz* derivative of **5o** (see Supporting Information). [h] No reaction was observed even at an extended reaction time (5 h). [i] Reaction was conducted under air.

acetate) is completed in 0.5 h with 0.5 mol % of (*R*,*R*)-**2** (S/C = 200) (98% yield, 99% ee). Under essentially the same reaction conditions, but instead using the chiral Ru(II) catalyst (*R*,*R*)-**1**,[14] ATH of **4a** is completed in 12 h (95% yield, 87% ee). Reaction of **4a** promoted by the analogous Ir(III) catalyst (*R*,*R*)-**3**[15] also takes place smoothly but with poor enantioselectivity (2 h, 99% yield, 28% ee).

A variety of imines **4** were subjected to the optimized ATH reaction conditions (ethyl acetate, room temperature) to examine the scope and limitations of the process. Most of these ATH reactions take place completely within 30 min (Table 1).

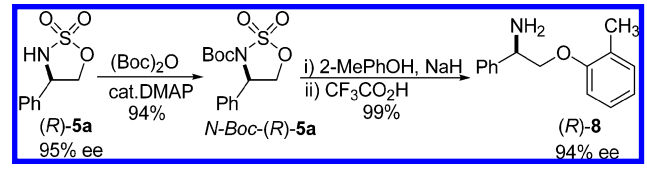
Cyclic imines **4** bearing *meta* or *para* electron-donating or -withdrawing group substituted aryl substituents are smoothly converted to the corresponding cyclic sulfamidates **5** in excellent yields and enantioselectivites (91−99% yields and 94−99% ee) within 30 min. However, imines with *ortho*-substituted aryl groups (**4d**, **4g**, **4j**) react to afford the corresponding cyclic sulfamidates with high yields but with low or even poor enantioselectivity. This observation suggests that through steric or electronic effects *ortho*-substituents might perturb the formation of the chiral catalyst−substrate complex. ATH of imine **4a**, employing the (*S*,*S*)-**2**, produces the (*R*)-**5a** enantiomer with almost the same efficiency and enantioselectivity as is observed for formation of (*S*)-**5a** in the reaction promoted by (*R*,*R*)-**2** catalyst (Table 1, entry 2). It should be emphasized that most of the ATH reactions desribed above take place rapidly (ca. 30 min) under mild conditions (room temperature, without degassing or drying of the solvent, and in air (Table 1, entry 18)) and yield products with high efficiencies and enantioselectivities (except for the *ortho*- aryl-substituted imines **4d**, **4g**, and **4j**).

ATH of the alkyl-substituted imine **4o** also occurs to produce the corresponding sulfamidate **5o** in high yield (96%) and enantioselectivity (93% ee) (Table 1, entry 16). However, the efficienies of reactions of alkyl imines are sensitive to the steric bulk of the alkyl group, as is exemplified by the *t*-butyl-containing imine **4p** that is inert under the ATH reaction conditions even over extended reaction times (Table 1, entry 17).

To test the practicality of the method described above, ATH of cyclic imine **4a** was carried out on a two gram scale (10 mmol) using 0.1 mol % of (*R*,*R*)-**2** catalyst (S/C = 1000) at room temperature. After 1.5 h, the cyclic sulfamate (*S*)-**5a** was generated in 99% isolated yield with 98% ee.

To demonstrate the synthetic utility of the current methodology, facile conversion of the cyclic sulfamidate (*R*)-**5a** to the optically active mexiletine analogue (*R*)-**8** was carried out. Mexiletine (**7**) is an effective sodium channel blocker used in its racemic form as an antiarrhythmic and analgesic oral drug even though (*R*)-Mexiletine is more active than its (*S*)-enantiomer. The results of recent studies revealed that the optically active mexiletine analogue (*R*)-**8** is 27-fold more potent than (*R*)-mexiletine **7** in producing a tonic block and 23-fold more potent under high frequency stimulation conditions (phasic block).[16] Therefore, efficient routes for the preparation of the enantiomerically pure mexiletine analogue (*R*)-**8** are highly desirable.[16,17]

**Scheme 3.** Enantioselective Synthesis of Mexiletine Analogue (*R*)-**8**




In the pathway for synthesis of (*R*)-**8**, the cyclic sulfamidate (*R*)-**5a** (95% ee) is converted to *N*-Boc-(*R*)-**5a** which is then reacted with 2-methylphenol in the presence of base at room temperature for 2 h. After treatment of the reaction

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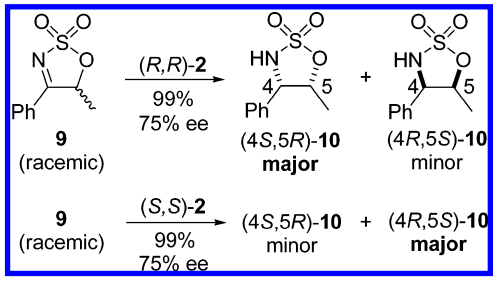
mixture with $CF_3CO_2H$, (*R*)-**8** is obtained in high yield (99%) with almost no loss of the optical purity (94% ee) (Scheme 3).

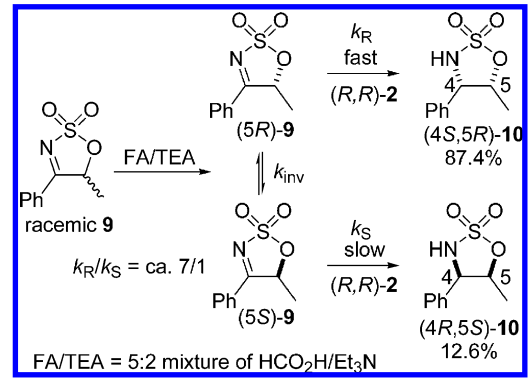
**Scheme 4.** ATH of Racemic 4,5-Disubstituted Cyclic Imine **9**[a]




[a] For reaction conditions, see footnote of Table 1.

ATH reaction of the 4,5-disubstituted imines **9**, containing a preexisting stereogenic center, can take place to form diastereomeic sulfamidates **10** (Scheme 4). In fact, treatment of **9** with the (*R*,*R*)-**2** catalyst (S/C = 200) under the conditions described above produces only a 4,5-*cis*-sulfamidate with the major isomer being (4*S*,5*R*)-**10** (75% ee, 99% yield, Scheme 4). No 4,5-*trans*-sulfamidates are detected by $^1$H NMR analysis of the crude reaction mixture. Authentic samples of 4,5-*cis*- and 4,5-*trans*-sulfamidates were independently synthesized by using known procedures and compared with the ATH products of **9** (see Supporting Information). The result shows that hydrogen addition takes place preferentially from the less hindered face of the cyclic imine **9**. In a similar manner, reduction of the racemic imine **9**, using (*S*,*S*)-**2**, yields only a 4,5-*cis*-sulfamidate, but in this case, (4*R*,5*S*)-**10** is the major isomer produced with 75% ee (99% yield). These observations suggest that the stereogenic center of imine **9** 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, representing an example of dynamic kinetic resolution. In fact, treatment of optically active imine (5*S*)-**9** (89% ee) with a $HCO_2H/Et_3N$ (5:2) mixture in the absence of (*R*,*R*)- or (*S*,*S*)-**2** catalyst (room temperature, 5 min) does not cause formation of a reduction product, and imine (5*S*)-**9** is recovered in nearly quantitative yield with a 0.2% ee, demonstrating that rapid racemization of imine (5*S*)-**9** occurs under the reaction conditions. The stereochemical results also suggest that reactions of the imine (5*R*)-**9** with the (*R*,*R*)-**2** catalyst and imine (5*S*)-**9** with the (*S*,*S*)-**2** catalyst take place most rapidly. An analysis of stereoisomer product distributions generated in these processes indicates that the rate of reduction of imine (5*R*)-**9** with (*R*,*R*)-**2** proceeds ca. 7 times (87.4:12.6) faster than that of the (5*S*)-**9** isomer with (*R*,*R*)-**2** catalyst (Scheme 5).[18]

**Scheme 5.** Dynamic Kinetic Resolution in ATH of Racemic 4,5-Disubstituted Cyclic Imine **9**




This effort has provided the first example of a reductive transformation of unsymmetrically disubstituted cyclic imines to the corresponding optically active cyclic sulfamidates.

In conclusion, the investigation described above has led to the development of an asymmetric transfer hydrogenation (ATH) reaction of cyclic sulfamidate imines **4** that uses a $HCO_2H/Et_3N$ mixture as the hydrogen source and well-defined chiral Rh catalysts (*S*,*S*)- or (*R*,*R*)-**2**, Cp*RhCl(TsDPEN), and that occurs at room temperature in ca. 0.5 h. This process effectively produces the corresponding cyclic sulfamidates in excellent yields and enantioselectivities. The ATH reaction of 4-aryl imines **4** is practical, mild, rapid, and enantioselective except in the cases of imines (e.g., **4d**, **4 g, 4j**) that have *ortho*-substituted aryl groups. ATH of 4,5-disubstituted imines **9**, which contain a preexisting stereogenic center, was found to be accompanied by dynamic kinetic resolution that causes the stereochemical outcome of the ATH reaction to be mainly controlled by the stereochemistry of the Rh catalysts used.

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**Supporting Information Available:** Experimental procedures for the asymmetric transfer hydrogenation and characterization data for all new compounds including the copies of $^1$H and $^{13}$C NMR spectra and chromatograms for the determination of enantiomeric excess of all chiral compounds on chiral HPLC. This material is available free of charge via the Internet at http://pubs.acs.org.

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