Kinetic Resolution Driven Diastereo- and Enantioselective Synthesis of *cis*-*β*-Heteroaryl Amino Cycloalkanols by Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation

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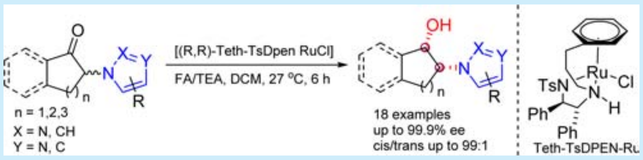
Supporting Information

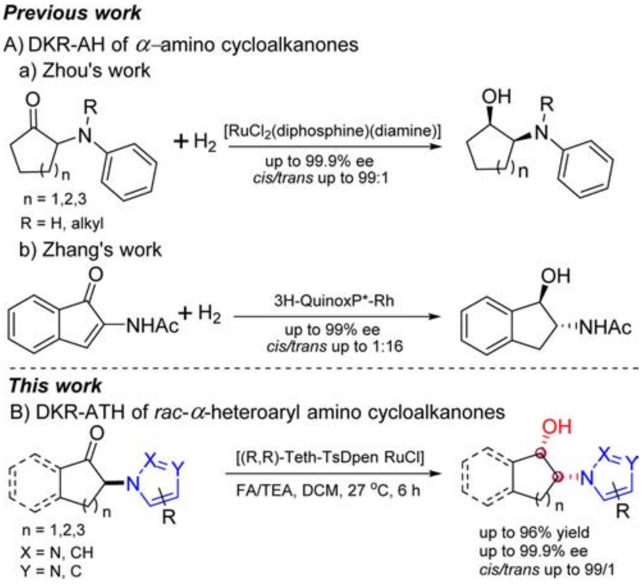


ABSTRACT: The utility of tethered Ru-TsDPEN catalyst has been demonstrated for the asymmetric transfer hydrogenation of *rac*-*α*-heteroaryl amino cycloalkanones to construct biologically important *cis*-*β*-heteroaryl amino cycloalkanols with two contiguous chiral centers via dynamic kinetic resolution. The stated (*R*,*R*)-Teth-TsDPEN-Ru-catalyzed transformation is carried out under mild conditions using formic acid/triethylamine as a hydrogen source with excellent diastereo- and enantioselectivities. Further, this methodology has been applied for the synthesis of an antileishmanial agent and chiral ionic liquid.

Dynamic kinetic resolution (DKR) effected by asymmetric hydrogenation (AH)[1] as well as by asymmetric transfer hydrogenation (ATH)[2] has sparked extensive interest and has found endless application in the field of academics as well as in the pharmaceutical industry. Recently, DKR-ATH of *rac*-*α*-substituted ketones was extensively studied to produce optically active *β*-substituted alcohols. In particular, the synthesis of chiral *β*-amino alcohol with two contiguous chiral centers has attracted considerable interest as a building block in pharmaceutical drug synthesis and as a ligand in asymmetric synthesis.[3]

Enantiopure vicinal *β*-amino cycloalkanols along with triazole and the imidazole nucleus at the *β*-position have emerged as important structural motifs in pharmaceutical and carbohydrate chemistry.[4] In addition, these *β*-heteroaryl amino cycloalkanols with an imidazole ring at the *β*-position show excellent chiral ionic liquid properties.[5] In general, efforts have been made to synthesize optically active *β*-amino cycloalkanols via AH-DKR by Zhou et al.[3b,c] (Scheme 1Aa) and more recently by Zhang et al.[3g] (Scheme 1Ab). However, to the best of our knowledge, there is no report for the catalytic asymmetric hydrogenation or asymmetric transfer hydrogenation to produce optically active *β*-heteroaryl amino cycloalkanols. Previously, these scaffolds were synthesized by ring opening of *meso* epoxides, which produces the *trans* isomer.[6] Therefore, there is an urgent need for the development of an efficient route that can be applied for the synthesis of *cis*-*β*-heteroaryl amino cycloalkanols. Herein, we report an efficient protocol for the synthesis of *cis*-*β*-heteroaryl amino cycloalkanols by ruthenium-catalyzed DKR-ATH of *rac*-*α*-heteroaryl amino cycloalkanones. Additionally, the substrate scope was extended by altering heteroaryl nucleus at *α*-position. Triazole, imidazole, and pyrazole as heterocycles were successfully investigated. This protocol provides access to *cis*-*β*-heteroaryl amino cycloalkanols with up to 99.9% enantiomeric excess (ee) and a diastereomer ratio (dr) up to 99/1.

Scheme 1. Asymmetric Hydrogenation/Transfer Hydrogenation of *α*-Amino Cycloalkanones



We began our optimization study with *rac*-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-3,4-dihydronaphthalen-1(2*H*)-one (**1a**) as a model substrate. First, a unique and well-documented chiral ligand in ATH *N*-sulfonylated 1,2-diamines[7] with various ruthenium complexes was examined for hydrogenation of the model substrate (Table 1). A high ee was observed with catalyst

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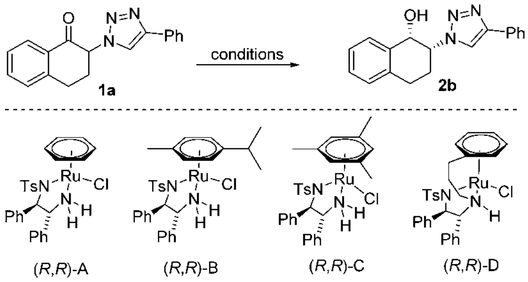
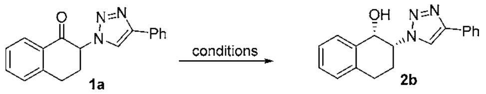
Table 1. Catalyst and Solvent Screening[a]



entry	catalyst	solvent	conv (%) (*cis*/*trans*)[b]	ee (%) (*cis*)[b]
1	A	CH_2Cl_2	15/05	93
2	B	CH_2Cl_2	18/02	95
3	C	CH_2Cl_2	28/02	97
4	D	CH_2Cl_2	99/01	94
5	D	CH_3OH	80/20	91
6	D	C_2H_5OH	82/18	92
7	D	$(CH_3)_2CHOH$	78/22	90
8	D	toluene	96/04	92
9	D	CH_3CN	94/06	90
10	D	THF	98/02	91
11	D	DMF	85/15	88
[c]12	D	CH_2Cl_2	50/04	92
[d]13	D	CH_2Cl_2	99/01	94

[a]Conditions: 0.5 mmol of **1a**, 2 mol % of catalyst, and 0.5 mL of FA/TEA (5:2) were added to the solvent (3.0 mL), and the mixture was stirred at 27 °C for 48 h. [b]Conversions and ee were calculated from chiral HPLC. [c]FA/TEA (0.2:1) was used. [d]FA/TEA (5:2) was added in portions over 2 h.

Table 2. Catalyst Loading, Temperature, and Time Screening[a]



entry	catalyst loading (mol %)	temp (°C)	time (h)	conv (%) (*cis*/*trans*)[b]	ee (%) (*cis*)[b]
1	2	27	48	99/1	94
2	1	27	48	99/1	>99
3	0.5	27	48	58/1	>99
4	1	40	48	99/1	94
5	1	60	48	99/1	93
6	1	27	24	99/1	>99
7	1	27	12	99/1	>99
8	1	27	06	99/1	>99
9	1	27	03	87/1	>99
10	1	27	01	50/1	99

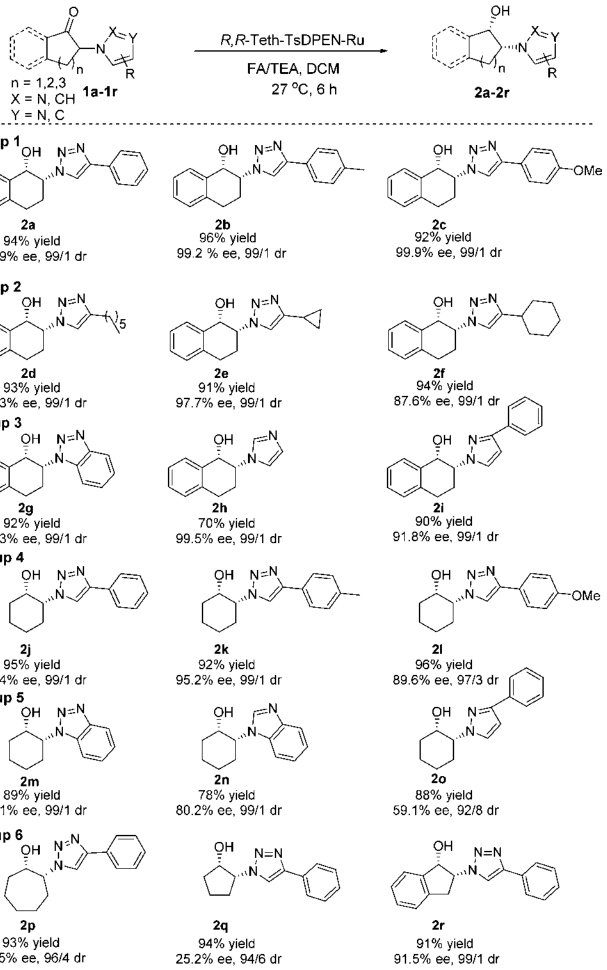
[a]Conditions: 0.5 mmol of **1a**, respective mol % of (*R*,*R*)-D, and 0.5 mL of FA/TEA (5:2) were added into DCM (3.0 mL), and the mixture was stirred at the respective time and temperature. [b]Conversions and ee were calculated from chiral HPLC.

(*R*,*R*)-A, (*R*,*R*)-B, and (*R*,*R*)-C in DCM, but conversion was on the lower side (Table 1, entries 1−3). The complete conversion was obtained by using tethered Ru−TsDPEN catalyst (*R*,*R*)-D developed by Wills and co-workers[8] with excellent diastereo- and enantioselectivity (Table 1, entry 4). A solvent study was carried out using tethered complex (*R*,*R*)-D (Table 1, entries 4−11). It was found that polar protic solvents were able to give high % ee, but the dr ratio was low (Table 1, entries 5−7). However, aprotic solvents were able to furnish high % ee and dr (Table 1, entries 4, 8−11). We observed that DCM gave the highest % ee and dr (Table 1 entry 4). Thus, DCM was selected as the optimized solvent for further studies. Next, the ratio of FA/TEA was altered to check its effect on % ee. When the ratio of FA/TEA was taken as 0.2/1, a lower conversion was observed with no effect on % ee (Table 1, entry 12). Prolonged addition of hydrogen source did not show any improvement in % ee and dr (Table 1, entry 13).

In order to increase enantioselectivity of *cis*-isomer, the effect of catalyst loading was examined (Table 2, entries 1−3). Delightfully, a catalyst loading of 1 mol % is sufficient enough to produce the highest % ee with no loss in conversion (Table 2, entry 2). Decreasing the catalyst loading to 0.5 mol % resulted in a lower conversion (Table 2, entry 3). An increase in temperature leads to a decrease in diasteroselectivity as well as enantioselectivity (Table 2, entries 4 and 5). A detailed time study revealed that 6 h is enough to achieve maximum diastero- and enantioselectivity (Table 2, entries 6−10).

With the optimized reactions conditions in hand, a range of different substrates were hydrogenated in the presence of tethered Ru−TsDPEN catalyst by using FA/TEA as the hydrogen source (Scheme 2). For a better understanding, the

Scheme 2. Substrate Scope[a]



[a]Conditions: 0.5 mmol of **1a**, 1 mol % of (*R*,*R*)-D, and 0.5 mL of FA/TEA (5:2) were added into CH_2Cl_2 (3.0 mL), and the mixture was stirred at 27 °C for 6 h. The yields were for the mixture of *cis*/*trans*-isomers isolated by preparative chromatography. The dr and ee values were determined by chiral HPLC.

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substrates were divided in different groups depending on the substitution pattern. In group 1, the substrates **1a**, **1b**, and **1c** having phenyl and substituted phenyl groups on the triazole nucleus, gave **2a**, **2b**, and **2c** in excellent % ee and dr. In group 2, we studied the effect of substitution on the triazole nucleus by replacing the phenyl group with alkyl chains and alicyclic counterparts. This resulted in a marginal decrease in % ee in the case of **2d** and **2e**, whereas **2f** was obtained with 87.6% ee. However, no effect on dr was observed in group 2. To extend the substrates scope and considering the pharmacological importance of imidazole and the pyrazole nucleus at the β-position of cycloalkanols, we further included the benzotriazole (**1g**), imidazole (**1h**), and pyrazole (**1i**) nucleus at the α-position of the substrates. The corresponding cycloalkanols **2g**, **2h**, and **2i** were obtained in 88.3%, 99.5%, and 91.8% ee, respectively, with uniform dr of 99/1 in group 3. In group 4, the tetralone functionality was replaced by cyclohexanone functionality. Substrates **1j**, **1k** and **1l** were efficiently reduced by a marginal decrease in % ee and dr. In group 5, we combined the cyclohexanone functionality with different heterocyclic nuclei. As compared to group 3, we observed a decrease in % ee, especially in the case of **2n** and **2o**. We observed that varying the cycloalkanone ring size in group F results in 95.5% ee in the case of cycloheptanone (**2p**) and 91.5% ee in the case of indanone (**2r**). However, the cyclopentanone (**2q**) functionality brings down the % ee to 25.2.

The ruthenium-catalyzed-transfer hydrogenation proceeds through the well-known catalytic cycle for the hydrogenation of ketones.[2j,8g,9] The proposed catalytic cycle in this case is shown in the Supporting Information. The plausible transition states for this DKR-ATH catalyzed by the tethered Ru−TsDPEN complex (*R*,*R*)-**D** with **1h** is shown in Figure 1. The transition state [Ts-*S*] of (*R*,*R*)-**D** with *S*-**1h** is unfavored because of steric hindrance, whereas [Ts-*R*] is favored due to lack of steric hindrance, thereby producing the **2h** with *cis*-selectivity ((1*S*,2*R*)-isomer).

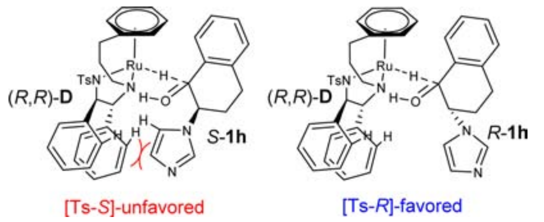
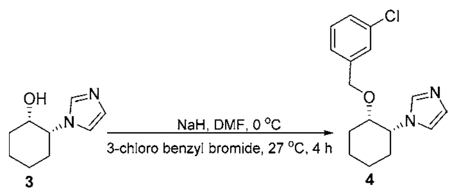


Figure 1. Plausible transition states ([Ts-*S*] and [Ts-*R*]) for the DKR-ATH of **1h** with (*R*,*R*)-**D**.

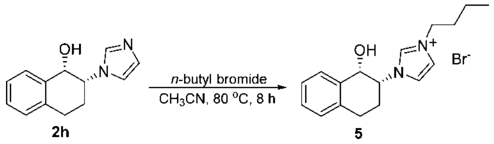
The synthetic utility of this methodology was demonstrated by carrying out the synthesis of the antileishmanial agent **4** (Scheme 3). This was carried out by preparing (1*R*,2*S*)-2-(1*H*-imidazol-1-yl)cyclohexanol (**3**) followed by the alkylation of the hydroxyl group in **3** using 3-chlorobenzyl bromide in the presence of sodium hydride in DMF. The product 1-((1*R*,2*S*)-2-((3-chlorobenzyl)oxy)cyclohexyl)-1*H*-imidazole was isolated with 52% yield (SI).

Scheme 3. Synthesis of Antileishmanial Drug



In continuation, considering the ability of chiral ionic liquid in inducing chirality in organic transformations, substrate **2h** was *n*-alkylated with *n*-butyl bromide to afford chiral ionic liquid **5** in 65% yield (Scheme 4 and SI).

Scheme 4. Synthesis of Chiral Ionic Liquid



To determine the stereochemistry of the stereogenic centers, the compound with anomalous scatterer [5-bromo-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-2,3-dihydro-1*H*-inden-1-one] (**1s**) was synthesized. DKR-ATH of **1s** with optimized reaction conditions afforded **2s** in 78% yield with 99% ee (99/1 dr). Recrystallization from *n*-hexane/DCM and subsequent X-ray crystallographic analysis revealed that the absolute configuration at the vicinal carbon atoms was determined to be 1*S*,2*R* (Figure 2) (see the SI).

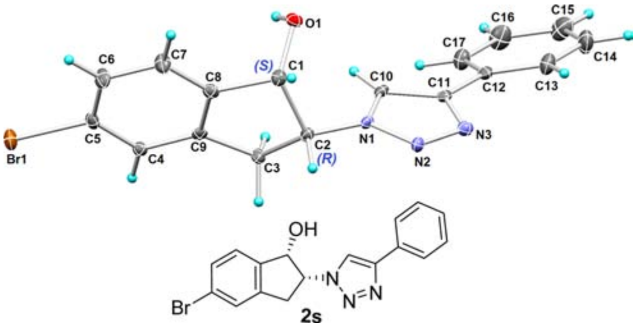


Figure 2. X-ray structure of **2s** (CCDC 15122464).

In conclusion, tethered Ru−TsDPEN complex catalyzed synthesis of *cis*-β-heteroaryl amino cycloalkanols by DKR-ATH was developed for the first time. Through this protocol, a range of *cis*-β-heteroaryl amino cycloalkanols with two contiguous chiral centers could be synthesized with excellent diastereo- and enantioselectivities. The established methodology was applied for the synthesis of an antileishmanial agent and a chiral ionic liquid. The absolute configuration of the vicinal chiral centers was determined by single-crystal X-ray analysis and was found to be 1*S*,2*R*.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03334.

Synthetic details for substrates; typical procedures for asymmetric transfer hydrogenation reactions; NMR spectra; HPLC data (PDF)

Crystallographic data for compound **2s** (CIF)

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Notes

The authors declare no competing financial interest.

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