

Kinetic Resolution Driven Diastereo- and Enantioselective Synthesis of $cis-\beta$ -Heteroaryl Amino Cycloalkanols by Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation

Vijyesh K. Vyas and Bhalchandra M. Bhanage*

Department of Chemistry, Institute of Chemical Technology, Mumbai 400019, India

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.

D ynamic 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 $cis-\beta$ -heteroaryl amino cycloalkanols. Herein, we report an efficient protocol for the synthesis of $cis-\beta$ 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-\beta*-heteroaryl amino cycloalkanols with up to 99.9%

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

Previous work

A) DKR-AH of α -amino cycloalkanones



enantiomeric excess (ee) and a diastereomer ratio (dr) up to 99/1.

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-diamines⁷ with various ruthenium complexes was examined for hydrogenation of the model substrate (Table 1). A high ee was observed with catalyst

Received: November 7, 2016

Table 1. Catalyst and Solvent Screening^a



^{*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.

(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-workers⁸ with excellent diastereoand 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 diasteroand 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

Table 2. Catalyst Loading, Temperature, and Time Screening^a

	O N=N N Ph	condit	ions	OH N=N Ph 2b	1
entry	catalyst loading (mol %)	temp (°C)	time (h)	conv (%) (cis/ trans) ^b	ee (%) (cis)
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.



^{*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 CH₂Cl₂ (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.

Organic Letters

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_rR)-D with **1h** is shown in Figure 1. The transition



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

state [Ts-S] of (R,R)-**D** with S-1**h** is unfavored because of steric hindrance, whereas [Ts-R] is favored due to lack of steric hindrance, thereby producing the **2h** with *cis*-selectivity ((1S,2R)-isomer).

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 (1R,2S)-2-(1H-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-((1R,2S)-2-((3-chlorobenzyl)oxy)cyclohexyl)-1H-imidazole was isolated with 52% yield (SI).

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).



To determine the stereochemistry of the stereogenic centers, the compound with anomalous scatterer [5-bromo-2-(4phenyl-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 $cis-\beta$ -heteroaryl amino cycloalkanols by DKR-ATH was developed for the first time. Through this protocol, a range of $cis-\beta$ -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 1S, 2R.

ASSOCIATED CONTENT

Supporting Information

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

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

Crystallographic data for compound 2s (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: bm.bhanage@gmail.com.

ORCID ©

Bhalchandra M. Bhanage: 0000-0001-9538-3339

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

V.K.V. is thankful to the Department of Science and Technology (DST), New Delhi, India, for providing a Senior Research Fellowship (SRF).

REFERENCES

 Representative papers and reviews for DKR-AH: (a) Bai, W.; Xie,
 J.; Li, Y.; Liu, S.; Zhou, Q. Adv. Synth. Catal. 2010, 352, 81–84.
 Perez, M.; Echeverria, P.; Martinez-Arripe, E.; Zoubir, M.; Touati,
 R.; Zhang, Z.; Genet, J.; Phansavath, P.; Ayad, T.; Ratovelomanana-Vidal, V. Eur. J. Org. Chem. 2015, 2015, 5949–5958. (c) Echeverria, P.-G.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. Synthesis 2016, 48, 2523–2539. (d) Horiguchi, K.; Yamamoto, E.; Saito, K.; Yamanaka, M.; Akiyama, T. Chem. - Eur. J. 2016, 22, 8078–8083.

(2) Representative papers and reviews for DKR-ATH (a) Mohar, B.;
Valleix, A.; Desmurs, J.-R.; Felemez, M.; Wagner, A.; Mioskowski, C. *Chem. Commun.* 2001, 0, 2572-2573. (b) Alcock, N.; Mann, I.; Peach, P.; Wills, M. *Tetrahedron: Asymmetry* 2002, 13, 2485-2490. (c) Ding, Z.; Yang, J.; Wang, T.; Shen, Z.; Zhang, Y. *Chem. Commun.* 2009, 0, 571-573. (d) Cartigny, D.; Püntener, K.; Ayad, T.; Scalone, M.; Ratovelomanana-Vidal, V. Org. Lett. 2010, 12, 3788-3791. (e) Steward, K.; Corbett, M.; Goodman, C.; Johnson, J. J. Am. Chem. Soc. 2012, 134, 20197-201206. (f) Son, S.-M.; Lee, H.-K. J. Org. Chem. 2013, 78, 8396-8404. (g) Corbett, M.; Johnson, J. J. Am. Chem. Soc. 2013, 135, 594-597. (h) Son, S.-M.; Lee, H.-K. J. J. Org. Chem. 2014, 79, 2666-2681. (i) Monnereau, L.; Cartigny, D.; Scalone, M.; Ayad, T.; Ratovelomanana-Vidal, V. Chem. - Eur. J. 2015, 21, 11799-11806. (j) Cheng, T.; Ye, Q.; Zhao, Q.; Liu, G. Org. Lett. 2015, 17, 4972-4975. (k) Wang, D.; Astruc, D. Chem. Rev. 2015, 115, 6621-6686.

(3) Representative paper for DKR of amino ketones: (a) Ros, A.; Magriz, A.; Dietrich, H.; Fernández, R.; Alvarez, E.; Lassaletta, J. Org. Lett. 2006, 8, 127–30. (b) Liu, S.; Xie, J.; Wang, L.; Zhou, Q. Angew. Chem., Int. Ed. 2007, 46, 7506–7508. (c) Liu, S.; Xie, J.-H.; Li, W.; Kong, W.-L.; Wang, L.-X.; Zhou, Q.-L. Org. Lett. 2009, 11, 4994– 4997. (d) Xie, J.-H.; Liu, S.; Kong, W.-L.; Bai, W.-J.; Wang, X.-C.; Wang, L.-X.; Zhou, Q.-L. J. Am. Chem. Soc. 2009, 131, 4222–4223. (e) Seashore-Ludlow, B.; Villo, P.; Häcker, C.; Somfai, P. Org. Lett. 2010, 12, 5274–5277. (f) Limanto, J.; Krska, S.; Dorner, B.; Vazquez, E.; Yoshikawa, N.; Tan, L. Org. Lett. 2010, 12, 512–515. (g) Hu, Q.; Chen, J.; Zhang, Z.; Liu, Y.; Zhang, W. Org. Lett. 2016, 18, 1290– 1293.

(4) (a) Marrapu, V.; Srinivas, N.; Mittal, M.; Shakya, N.; Gupta, S.; Bhandari, K. Bioorg. Med. Chem. Lett. 2011, 21, 1407–1410. (b) Yousuf, S.; Majeed, R.; Ahmad, M.; Sangwan, P.; Purnima, B.; Saxsena, A. K.; Suri, K. A.; Mukherjee, D.; Taneja, S. Steroids 2011, 76, 1213–1222. (c) Fehér, K.; Balogh, J.; Csók, Z.; Kégl, T.; Kollár, L.; Skoda-Földes, R. Steroids 2012, 77, 738–44. (d) Anastasopoulou, P.; Kythreoti, G.; Cosmidis, T.; Pyrkotis, C.; Nahmias, V.; Vourloumis, D. Bioorg. Med. Chem. Lett. 2014, 24, 1122–1126. (e) Saikia, P.; Kaishap, P.; Goswami, J.; Singh, A.; Boruah, H.; Gogoi, S.; Boruah, R. Steroids 2014, 84, 36–45.

(5) (a) Busto, E.; Gotor-Fernández, V.; Ríos-Lombardía, N.; García-Verdugo, E.; Alfonso, I.; García-Granda, S.; Menéndez-Velázquez, A.; Burguete, M.; Luis, S.; Gotor, V. *Tetrahedron Lett.* **2007**, 48, 5251– 5254. (b) Ríos-Lombardía, N.; Busto, E.; Gotor-Fernández, V.; Gotor, V.; Porcar, R.; García-Verdugo, E.; Luis, S. V.; Alfonso, I.; García-Granda, S.; Menéndez-Velázquez, A. *Chem. - Eur. J.* **2010**, *16*, 836– 847. (c) Ríos-Lombardía, N.; Porcar, R.; Busto, E.; Alfonso, I.; Montejo-Bernardo, J.; García-Granda, S.; Gotor, V.; Luis, S.; García-Verdugo, E.; Gotor-Fernández, V. *ChemCatChem* 2011, 3, 1921–1928.
(d) Paul, C.; Gotor-Fernández, V.; Lavandera, I.; Montejo-Bernardo, J.; García-Granda, S.; Gotor, V. RSC Adv. 2012, 2, 6455–6463.
(e) Porcar, R.; Ríos-Lombardía, N.; Busto, E.; Gotor-Fernández, V.; Gotor, V.; Garcia-Verdugo, E.; Burguete, M.; Luis, S. *Catal. Sci. Technol.* 2013, 3, 2596–2601. (f) Vasiloiu, M.; Gaertner, P.; Zirbs, R.; Bica, K. *Eur, I. Org. Chem.* 2015, 2015, 2374–2381.

(6) (a) Kotsuki, H.; Hayashida, K.; Shimanouchi, T.; Nishizawa, H. J. Org. Chem. **1996**, *61*, 984–990. (b) Torregrosa, R.; Pastor, I.; Yus, M. Tetrahedron **2007**, *63*, 469–473. (c) Bhanushali, M.; Nandurkar, N.; Bhor, M.; Bhanage, B. Tetrahedron Lett. **2008**, *49*, 3672–3676. (d) Lu, H.-F.; Sun, L.-L.; Le, W.-J.; Yang, F.-F.; Zhou, J.-T.; Gao, Y.-H. Tetrahedron Lett. **2012**, *53*, 4267–4272. (e) Shinde, S. S.; Said, M. S.; Surwase, T. B.; Kumar, P. Tetrahedron Lett. **2015**, *56*, 5916–5919.

(7) (a) Gladiali, S.; Alberico, E. Chem. Soc. Rev. 2006, 35, 226–236.
(b) Ikariya, T.; Blacker, A. Acc. Chem. Res. 2007, 40, 1300–1308.
(c) Wang, C.; Wu, X.; Xiao, J. Chem. - Asian J. 2008, 3, 1750–1770.
(d) Morris, R. H. Chem. Soc. Rev. 2009, 38, 2282–2291. (e) Chen, F.; Wang, T. L.; He, Y. M.; Ding, Z. Y.; Li, Z. W.; Fan, Q. H. Chem. - Eur. J. 2011, 17, 1109. (f) Ding, Z. Y.; Chen, F.; Qin, J.; He, Y. M.; Fan, Q. H. Angew. Chem., Int. Ed. 2012, 51, 5706. (g) Li, Y.-Y.; Yu, S.-L.; Shen, W.-Y.; Gao, J.-X. Acc. Chem. Res. 2015, 48, 2587–2598. (h) Liu, R.; Zhou, G.; Hall, T.; Clarkson, G.; Wills, M.; Chen, W. Adv. Synth. Catal. 2015, 357, 3453–3457. (i) Vyas, V. K.; Bhanage, B. M. Org. Chem. Front. 2016, 3, 614–619.

(8) Representative paper for Ru-tethered catalysts: (a) Hannedouche, J.; Clarkson, G. J.; Wills, M. J. Am. Chem. Soc. 2004, 126, 986-987. (b) Cheung, F. K.; Hayes, A. M.; Hannedouche, J.; Yim, A. S. Y.; Wills, M. J. Org. Chem. 2005, 70, 3188-3197. (c) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. J. Am. Chem. Soc. 2005, 127, 7318-7319. (d) Morris, D. J.; Hayes, A. M.; Wills, M. J. Org. Chem. 2006, 71, 7035-7044. (e) Cheung, F. K.; Lin, C.; Minissi, F.; Crivillé, A. L.; Graham, M. A.; Fox, D. J.; Wills, M. Org. Lett. 2007, 9, 4659-4662. (f) Martins, J. E. D.; Morris, D. J.; Tripathi, B.; Wills, M. J. Organomet. Chem. 2008, 693, 3527-3532. (g) Soni, R.; Collinson, J.-M.; Clarkson, G. C.; Wills, M. Org. Lett. 2011, 13, 4304-4307. (h) Jolley, K. E.; Hancock, A. Z.-G. F.; Dyke, A.; Grainger, D. M.; Medlock, J. A.; Nedden, H. G.; Paih, J. J. M. L.; Roseblade, S. J.; Seger, A.; Sivakumar, V.; Morris, D. J.; Wills, M. Adv. Synth. Catal. 2012, 354, 2545-2555. (9) (a) Wu, X.; Li, X.; Hems, W.; King, F.; Xiao, J. Org. Biomol. Chem. 2004, 2, 1818-1821. (b) Wu, X.; Li, X.; King, F.; Xiao, J. Angew. Chem. 2005, 117, 3473-3477. (c) Peach, P.; Cross, D. J.; Kenny, J. A.; Mann, I.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. Tetrahedron 2006, 62, 1864-1876.