rayny ER

CHO

Enantioselective One-Pot Synthesis of Ring-Fused Tetrahydroquinolines via Aerobic Oxidation and 1,5-Hydride Transfer/Cyclization Sequences

Chang Won Suh and Dae Young Kim*

Department of Chemistry, Soonchunhyang Uni[ver](#page-2-0)sity, Asan, Chungnam 336-745, Korea

S Supporting Information

[AB](#page-2-0)STRACT: [Enantioselect](#page-2-0)ive organocatalytic synthesis of tetrahydroquinolines has been achieved via an aerobic oxidation and a 1,5-hydride transfer/cyclization sequence. The feature of this research is a one-pot transformation of 3-arylprop-2-en-1-ol derivatives into tetrahydroquinolines using a Ru(VII)-catalyzed aerobic oxidation and highly efficient internal redox reactions. The synthetically useful ring-fused tetrahydroquinoline derivatives are obtained in moderate yields and high levels of enantioselectivity.

up to 20:1 dr, 98% ee I, Ar = 3,5-(CF₃)₂C₆H₃

 R^1

The direct functionalization of relatively unreactive C−H
bonds has recently received considerable attention owing
to its intrinsic notatiol for stam and stan economy and to its intrinsic potential for atom and step economy and environmental sustainability. A number of efforts have been devoted to the synthesis of structurally complex and biologically active organic molecules via C−H functionalization to avoid tedious synthetic procedures.¹ C(sp³)-H bond functionalization by a hydride shift/cyclization has attracted much interest for its application in [t](#page-2-0)he synthesis of heterocyclic compounds.² The key feature of this transformation is the 1,5-hydride shift of the C(sp³)–H bond α to the heteroatom and sub[se](#page-2-0)quent 6-endo cyclization to afford heterocycle compounds.^{3,4} In particular, the C(sp³)–H functionalization via the 1,5-hydride transfer/cyclization sequence of o-(dialkyla[min](#page-2-0)o)aryl derivatives has attracted much attention to their ability to afford structurally diverse heterocycles including tetrahydroquinolines.⁵ Chiral tetrahydroquinoline derivatives have emerged as attractive synthetic targets because of their prevalence in a num[be](#page-3-0)r of biologically active compounds and natural products.⁶ Therefore, the development of a new and efficient synthetic method for the preparation of chiral tetrahydroquinoli[ne](#page-3-0) analogues is of importance to both organic and medicinal chemistry.⁷ Recently, several groups reported the enantioselective synthesis of tetrahydroquinolines via an intramolecular redo[x](#page-3-0) process involving direct $C(sp^3) - H$ functionalization at a position α to nitrogen atom.⁸

Enantioselective multicomponent cascade reactions are useful synthetic transformati[on](#page-3-0)s, as they allow expedient and efficient construction of chiral complex molecules. Because such protocols achieve time, cost, and environmental savings, and desirable experimental operations including tedious isolation procedures for each reaction, much effort has been devoted to the development of new asymmetric cascade reactions and the conversion of already existing multistep syntheses into the one-pot procedures.⁹ A well-established method is the tandem oxidation process involving oxidative enamine catalysis and oxidative imi[ni](#page-3-0)um catalysis.^{10−12} Recently, direct oxidative β -functionalization of simple aldehydes to β -substituted ones has been achieved th[rough](#page-3-0) oxidative enamine catalysis.¹¹ In this, oxidants convert the enamines to iminium ions in the presence of the amine catalyst, which facilitates [fur](#page-3-0)ther nucleophilic addition to afford β-functionalized products. Related asymmetric oxidative iminium activation has gained increasing attention.¹² This strategy involves oxidation of an allylic alcohol and subsequent enantioselective prolinol ether catalyzed [im](#page-3-0)inium reactions.

TPAP (5 mol %), O₂

DNBS (20 mol %)

 R^2

cat. I (20 mol %)

OН

As part of a research program related to the enantioselective construction of stereogenic centers, 13 we recently reported an intramolecular version of oxidative enamine catalysis and 1,5-hydride transfer/cyclization a[s a](#page-3-0)n approach to the asymmetric synthesis of tetrahydroquinolines (Scheme $1a)^{14}$ However, organocatalytic enantioselective hydride transfer/cyclization reaction cascade reactions involving the in situ [o](#page-1-0)xi[da](#page-3-0)tion of allylic alcohols have not been reported (Scheme 1b). Herein, we report an aerobic oxidation and 1,5-hydride transfer/cyclization sequences allied for the asymmetric [sy](#page-1-0)nthesis of ring-fused tetrahydroquinolines (Scheme 2).

To determine suitable reaction conditions for the in situ oxidation and intramolecular redox reactions of ([E](#page-1-0))-3-(2- (dialkylamino)phenyl)prop-2-en-1-ol derivatives 1, we initially investigated the reaction system with (E) -3- $(2-(azocan-1$ yl)phenyl)prop-2-en-1-ol (1d) in the presence of an oxidant and prolinol derivatives in chloroform at room temperature. The results of representative intramolecular redox reactions are summarized in Table 1. The advantages of the TPAP

Received: September 2, 201[4](#page-1-0) Published: October 3, 2014

Scheme 1. Strategies for the Synthesis of Tetrahydroquinolines via Oxidative Catalysis/Internal Redox Reaction

Scheme 2. Oxidation and Organocatalytic Intramolecular Redox Reaction Sequence

oxidation process include the use of a catalytic amount of Ru(VII) and oxygen which is an ideal oxidant. We studied the effect the amount of tetrapropylammonium perruthenate (TPAP) as a metal oxidant has on the oxidative coupling reaction of (E) -3- $(2-(azocan-1-yl)phenyl)prop-2-en-1-ol (1d)$ using 20 mol % of TPAP with oxygen (balloon), catalyst I (20 mol %), and 2,4-dinitrobenzenesulfonic acid (DNBS) in chloroform. The reaction gave a moderate yield (50%) of product 2d with high enantioselectivity (92% ee) (Table 1, entry 1). The present catalytic system tolerates a TPAP loading down to 5 mol % without compromising both the yield and enatioselectivity (Table 1, entries 1−4). At high temperature (40 \degree C), the yield can be elevated to 70%, but this slightly decreases the enantioselectivity. To improve the yield and enantioselectivity, we examined a one-pot two-step process involving oxidation of (E) -3- $(2-(azocan-1-yl)$ phenyl)prop-2-en-1-ol (1d) with 5 mol % of TPAP with oxygen (balloon) at 40 °C in toluene, followed by 1,5-hydride transfer/cyclization sequences in the presence of catalyst I (20 mol %) with DNBS (20 mol %). The reaction gave a high yield (70%) of 2d with high enantioselectivity (95% ee) (Table 1, entry 6). Screening analogues II−IV of catalyst I revealed that the reactivity and enantioselectivity were decreased (Table 1, entries 8−10) and III and IV did not promote the process at all (Table 1, entries 9−10). In addition, the solvent was found to have an important effect on the reactivity and enantioselectivity. Among different solvents, toluene emerged as the best solvent with regard to the yield, diastereoselectivity, and enantioselectivity (Table 1, entry 15). Further optimization of reaction conditions was performed by screening additives. The best result was achieved when the

Table 1. Optimization of Aerobic Oxidation and Organocatalytic Intramolecular Redox Reaction Conditions

^aMethod A: Reactions were carried out with (E) -3- $(2-(azocan-1-d)$ yl)phenyl)prop-2-en-1-ol (1d, 0.1 mmol), TPAP, catalyst I (20 mol %), and DNBS (20 mol %) under O_2 (balloon) at room temperature. b Method B: Reactions were carried out with (E) -3-(2-(azocan-1yl)phenyl)prop-2-en-1-ol (1d, 0.2 mmol) and TPAP (5 mol %) under O_2 (balloon) at 40 °C for 1 d, and then catalyst I (20 mol %) and DNBS $(20 \text{ mol } %)$ were added at rt. Combined yield of both diastereomers. ^dDiastereomeric ratio was determined by ¹H NMR spectroscopic analysis of the crude reaction mixture. ^{*e*}Enantiopurity of major diastereomer was determined by HPLC analysis using chiralpak AS-H. ^fReactions were carried out at 40 $^{\circ}$ C. g (−)-CSA was used instead of DNBS. ${}^{h}TsOH$ was used instead of DNBS. ${}^{h}TsOH$ was used instead of DNBS. ^j TFA was used instead of DNBS.

reaction was conducted with 2,4-dinitrobenzenesulfonic acid (DNBS, Table 1, entry 15). Consequently, the best result was obtained through a one-pot process involving oxidation of (E)-3-(2-(azocan-1-yl)phenyl)prop-2-en-1-ol (1d) with 5 mol % of TPAP and oxygen (balloon) at 40 °C in toluene, followed by 1,5-hydride transfer/cyclization in the presence of I (20 mol %) with DNBS (20 mol %).

With the optimized conditions in hand, we proceeded to investigate the scope of the aerobic oxidation and 1,5-hydride transfer/cyclization sequence with various (E) -3- $(2-(\text{dialkyl}$ amino)phenyl)prop-2-en-1-ol derivatives 1. All of the reactions were conducted in toluene to give the corresponding ring-fused tetrahydroquinolines 2 in moderate yields and high enantioselectivities (Scheme 3). Products 2a−2p, which incorporated five- to nine-membered azacycles, were formed with moderate yields, and mo[de](#page-2-0)rate-to-high diastereoselectiv-

 a Reactions were carried out with 3-arylprop-2-en-1-ol 1 (0.2 mmol) and TPAP (3.5 mg, 0.01 mmol, 5 mol %) under O_2 (balloon) at 40 °C for 1 d, and then catalyst I (23.9 mg, 0.04 mmol, 20 mol %) and DNBS (9.9 mg, 0.04 mmol, 20 mol %) were added at rt. ^b Combined yield of both diastereomers. ^c Diastereomeric ratio was determined by H NMR spectroscopic analysis of the crude reaction mixture. d Enantiopurity of the major diastereomer was determined by HPLC analysis using chiralpak AS-H (for 2d, 2e, 2f, 2g, 2i, 2j, 2l, and 2p), IC (for 2a, 2b, 2c, 2h, and 2o), IB (for 2k and 2n), and ID (for 2m) columns. e 40 mol % of catalyst I and DNBS were used.

ities and excellent enantioselectivities (33−95% yield, 3:1− 20:1 dr, and 80−98% ee) were also observed. A range of electron-withdrawing and -donating substitutents on the aryl ring of 3-arylpropanal derivatives 1 provided the corresponding products 2 in excellent enantioselectivities (90−99% ee). The absolute configuration of the products 2 was determined by comparison of the optical rotation and chiral HPLC data with literature values.^{8b,14}

To illustrate synthetic utility, we also carried out functional group transformatio[ns of](#page-3-0) tetrahydroquinolines 2. Reductive amination and Wittig reactions led to 3 and 4 without any erosion of optical purities (Scheme 4).

In summary, we have developed an enantioselective synthesis of ring-fused tetrahydroquinolines via Ru(VII) catalyzed aerobic oxidation and a 1,5-hydride transfer/ cyclization sequence. The desired products were obtained in moderate yields and high enantioselectivities through a onepot transformation from 3-arylprop-2-en-1-ol derivatives. Current studies are aimed at developing a related internal

Scheme 4. Transformation of Tetrahydroquinoline Derivative 2e

redox reaction cascade for the efficient buildup of molecular complexity.

B ASSOCIATED CONTENT

S Supporting Information

Detailed experimental procedure and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dyoung@sch.ac.kr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Soonchunhyang University Research Fund and Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2014006224).

■ REFERENCES

(1) For recent reviews on C−H activation, see: (a) Lyons, T. W.; Sanford, M. S. Chem. Rev. 2010, 110, 1147. (b) Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. *Chem. Soc. Rev.* **2011**, 40, 1855. (c) Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. Acc. Chem. Res. 2012, 45, 826. (2) For recent reviews on the internal redox process, see: (a) Pan, S. C. Beilstein J. Org. Chem. 2012, 8, 1374. (b) Wang, M. ChemCatChem 2013, 5, 1291. (c) Peng, B.; Maulide, N. Chem. Eur. J. 2013, 19, 13274. (d) Wang, L.; Xiao, J. Adv. Synth. Catal. 2014, 356, 1137. (e) Haibach, M. C.; Seidel, D. Angew. Chem., Int. Ed. 2014, 53, 5010.

(3) For selected reviews on the tert-amino effect, see: (a) Quintela, J. M. Recent Res. Dev. Org. Chem. 2003, 7, 259. (b) Matyus, P.; Elias, O.; Tapolcsanyi, P.; Polonka-Balint, A.; Halasz-Dajka, B. Synthesis 2006, 2625.

(4) For recent selected examples, see: (a) Pastine, S. J.; McQuaid, K. M.; Sames, D. J. Am. Chem. Soc. 2005, 127, 12180. (b) McQuaid, K. M.; Sames, D. J. Am. Chem. Soc. 2009, 131, 402. (c) Vadola, P. A.; Sames, D. J. Am. Chem. Soc. 2009, 131, 16525. (d) Haibach, M.; Deb, I.; De, C. K.; Seidel, D. J. Am. Chem. Soc. 2011, 133, 2100. (e) Mori, K.; Sueoka, S.; Akiyama, T. J. Am. Chem. Soc. 2011, 133, 2424. (f) Mori, K.; Kawasaki, T.; Akiyama, T. Org. Lett. 2012, 14, 1436. (g) Vadola, P. A.; Carrera, I.; Sames, D. J. Org. Chem. 2012, 77, 6689. (h) Jiao, Z.-W.; Zhang, S.-Y.; He, C.; Tu, Y.-Q.; Wang, S.- H.; Zhang, F.-M.; Zhang, W.-Q.; Li, H. Angew. Chem., Int. Ed. 2012, 51, 8811.

(5) For selected examples, see: (a) Zhang, C.; Kanta De, C.; Mal, R.; Seidel, D. J. Am. Chem. Soc. 2008, 130, 416. (b) Shikanai, D.; Murase, H.; Hata, T.; Urabe, H. J. Am. Chem. Soc. 2009, 131, 3166. (c) Mahoney, S. J.; Moon, D. T.; Hollinger, J.; Fillion, E. Tetrahedron Lett. 2009, 50, 4706. (d) Mori, K.; Ohshima, Y.; Ehara, K.; Akiyama, T. Chem. Lett. 2009, 38, 524. (e) Zhang, C.; Murarka, S.; Seidel, D. J. Org. Chem. 2009, 74, 419. (f) Murarka, S.; Zhang, C.; Konieczynska, M. D. Org. Lett. 2009, 11, 129. (g) Mori, K.; Kawasaki, T.; Sueoka, S.; Akiyama, T. Org. Lett. 2010, 12, 1732. (h) Kwon, Y. K.; Kang, Y. K.; Kim, D. Y. Bull. Korean Chem. Soc. 2011, 32, 1773. (i) Kim, D. Y. Bull. Korean Chem. Soc. 2013, 34, 3463. (j) Kim, M. H.; Kim, D. Y. Bull. Korean Chem. Soc. 2013, 34, 3891.

(6) (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. Tetrahedron 1996, 52, 15031. (b) Zhou, Y.-G. Acc. Chem. Res. 2007, 40, 1357.

(7) (a) Akiyama, T.; Morita, H.; Fuchibe, K. J. Am. Chem. Soc. 2006, 128, 13070. (b) Rueping, M.; Antonchick, A. P.; Theissmann, T. Angew. Chem., Int. Ed. 2006, 45, 3683. (c) Guo, Q. S.; Du, D. M.; Xu, J. Angew. Chem., Int. Ed. 2008, 47, 759. (d) Wang, X. B.; Zhou, Y. G. J. Org. Chem. 2008, 73, 5640. (e) Glushkov, V. A.; Tolstikov, A. G. Russ. Chem. Rev. 2008, 77, 137. (f) O'Byrne, A.; Evans, P. Tetrahedron 2008, 64, 8067. (g) Kouznetsov, V. V. Tetrahedron 2009, 65, 2721. (h) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. P. J. Am. Chem. Soc. 2009, 131, 4598. (i) Bergonzini, G.; Gramigna, L.; Mazzanti, A.; Fochi, M.; Bernardi, L.; Ricci, A. Chem. Commun. 2010, 46, 327. (j) Mori, K.; Kurihara, K.; Yabe, S.; Yamanaka, M.; Akiyama, T. J. Am. Chem. Soc. 2014, 136, 3744.

(8) (a) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. J. Am. Chem. Soc. 2009, 131, 13226. (b) Kang, Y. K.; Kim, S. M.; Kim, D. Y. J. Am. Chem. Soc. 2010, 132, 11847. (c) Cao, W.; Liu, X.; Wang, W.; Lin, L.; Feng, X. Org. Lett. 2011, 13, 600. (d) Zhou, G.; Liu, F.; Zhang, J. Chem.-Eur. J. 2011, 17, 3101. (e) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. J. Am. Chem. Soc. 2011, 133, 6166. (f) He, Y.-P.; Du, Y.- L.; Luo, S.-W.; Gong, L.-Z. Tetrahedron Lett. 2011, 52, 7064. (g) Zhang, L.; Chen, L.; Lv, J.; Cheng, J.-P.; Luo, S. Chem.—Asian J. 2012, 7, 2569. (h) Chen, L.; Zhang, L.; Lv, J.; Cheng, J.-P.; Luo, S. Chem.-Eur. J. 2012, 18, 8891. (i) Kang, Y. K.; Kim, D. Y. Adv. Synth. Catal. 2013, 355, 3131. (j) Wang, M. ChemCatChem 2013, 5, 1291.

(9) (a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Angew. Chem., Int. Ed. 2006, 45, 7134. (b) Chapman, C. J.; Frost, C. G. Synthesis 2007, 1. (c) Enders, D.; Grondal, C.; Huttl, M. R. M. Angew. Chem., Int. Ed. 2007, 46, 1570. (d) Yu, X.; Wang, W. Org. Biomol. Chem. 2008, 6, 2037. (e) Grondal, C.; Jeanty, M.; Enders, D. Nat. Chem. 2010, 2, 167. (f) Albrecht, Ł.; Jiang, H.; Jorgensen, K. A. Angew. Chem., Int. Ed. 2011, 50, 8492.

(10) (a) Taylor, R. J. K.; Reid, M.; Foot, J.; Raw, S. A. Acc. Chem. Res. 2005, 38, 851. (b) Xiao, J. ChemCatChem 2012, 4, 612.

(11) (a) Zhang, S.-L.; Xie, H.-X.; Zhu, J.; Li, H.; Zhang, X.-S.; Li, J.; Wang, W. Nat. Commun. 2011, 2, 211. (b) Zhu, J.; Yu, S.-T.; Lu, W.- C.; Deng, J.; Li, J.; Wang, W. Tetrahedron Lett. 2012, 53, 1207. (c) Xie, H.-X.; Zhang, S.-L.; Li, H.; Zhang, X.-S.; Zhao, S.-H.; Xu, Z.; Song, X.-X.; Yu, X.-H.; Wang, W. Chem.-Eur. J. 2012, 18, 2230. (d) Hayashi, Y.; Itoh, T.; Ishikawa, H. Angew. Chem., Int. Ed. 2011, 50, 3920. (e) Zhao, Y.-L.; Wang, Y.; Hu, X.-Q.; Xu, P.-F. Chem. Commun. 2013, 49, 7555. (f) Zeng, X.; Ni, Q.; Raabe, G.; Enders, D. Angew. Chem., Int. Ed. 2013, 52, 2977.

 (12) (a) Rueping, M.; Sundén, H.; Sugiono, E. Chem.-Eur. J. 2012, 18, 3649. (b) Rueping, M.; Sundén, H.; Hubener, L.; Sugiono, E. Chem. Commun. 2012, 48, 2201. (c) Quintard, A.; Alexakis, A.; Mazet, C. Angew. Chem., Int. Ed. 2011, 50, 2354. (d) Miyamura, H.; Choo, G. C. Y.; Yasukawa, T.; Yoo, W.-J.; Kobayashi, S. Chem. Commun. 2013, 49, 9917. (e) Ho, X.-H.; Oh, H.-J.; Jang, H. Y. Eur. J. Org. Chem. 2012, 5655.

(13) For our selected work on synthetic methodology using organocatalysts, see: (a) Kim, D. Y.; Park, E. J. Org. Lett. 2002, 4, 545. (b) Kim, D. Y.; Kim, S. M.; Koh, K. O.; Mang, J. Y.; Lee, K. Bull. Korean Chem. Soc. 2003, 24, 1425. (c) Park, E. J.; Kim, M. H.; Kim, D. Y. J. Org. Chem. 2004, 69, 6897. (d) Jung, S. H.; Kim, D. Y. Tetrahedron Lett. 2008, 49, 5527. (e) Lee, J. H.; Kim, D. Y. Adv.

Synth. Catal. 2009, 351, 1779. (f) Kang, Y. K.; Kim, D. Y. J. Org. Chem. 2009, 74, 5734. (g) Oh, Y.; Kim, S. M.; Kim, D. Y. Tetrahedron Lett. 2009, 50, 4674. (h) Moon, H. W.; Cho, M. J.; Kim, D. Y. Tetrahedron Lett. 2009, 50, 4896. (i) Moon, H. W.; Kim, D. Y. Tetrahedron Lett. 2010, 51, 2906. (j) Lee, J. H.; Kim, D. Y. Synthesis 2010, 1860. (k) Lee, H. J.; Kang, S. H.; Kim, D. Y. Synlett 2011, 1559. (l) Yoon, S. J.; Kang, Y. K.; Kim, D. Y. Synlett 2011, 420. (m) Moon, H. W.; Kim, D. Y. Tetrahedron Lett. 2012, 53, 6569. (n) Lee, H. J.; Woo, S. B.; Kim, D. Y. Tetrahedron Lett. 2012, 53, 3374. (o) Lee, J. H.; Kim, D. Y. Bull. Korean Chem. Soc. 2013, 34, 1619. (p) Suh, C. W.; Han, T. H.; Kim, D. Y. Bull. Korean Chem. Soc. 2013, 34, 1623. (q) Lim, Y. J.; Kim, D. Y. Bull. Korean Chem. Soc. 2013, 34, 1955. (r) Suh, C. W.; Chang, C. W.; Choi, K. W.; Lim, Y. J.; Kim, D. Y. Tetrahedron Lett. 2013, 54, 3651. (s) Suh, C. W.; Kim, D. Y. Bull. Korean Chem. Soc. 2014, 35, 98.

(14) (a) Kang, Y. K.; Kim, D. Y. Chem. Commun. 2014, 50, 222. (b) Suh, C. W.; Woo, S. B.; Kim, D. Y. Asian J. Org. Chem. 2014, 3, 399.