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Spiroborate Ester-Mediated Asymmetric Synthesis of β-Hydroxy Ethers and Its Conversion to Highly Enantiopure β-Amino Ethers

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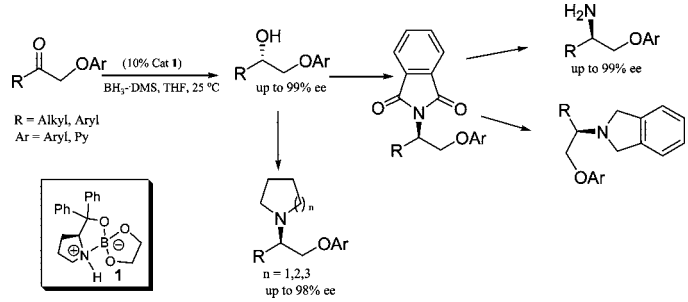

Borane-mediated reduction of aryl and alkyl ketones with α-aryl- and α-pyridyloxy groups affords β-hydroxy ethers in high enantiomeric purity (up to 99% ee) and in good yield, using as catalyst 10 mol % of spiroborate ester **1** derived from (*S*)-diphenylprolinol. Representative β-hydroxy ethers are successfully converted to β-amino ethers, with minor epimerization, by phthalimide substitution under Mitsunobu's conditions followed by hydrazinolysis to obtain primary amino ethers or by imide reduction with borane to afford β-2,3-dihydro-1*H*-isoindol ethers. Nonracemic Mexiletine and nAChR analogues with potential biological activity are also synthesized in excellent yield by mesylation of key β-hydroxy pyridylethers and substitution with five-, six-, and seven-membered ring heterocyclic amines.

Introduction

Optically active β-hydroxy ethers are valuable building blocks in organic synthesis, in particular for their transformation to enantiopure β-amino ethers, which are important precursors in the preparation of a wide variety of pharmaceutical compounds.[1] Accordingly, various methods have been sought for the asymmetric synthesis of β-hydroxy ethers, such as the enantioselective ring opening of epoxides catalyzed by chiral Salen complexes[2] and ring opening of optically active aryl oxiranes.[1a] However, the steric and electronic factors controlling the regioselectivity of the nucleophilic ring opening, usually, can generate a mixture of products producing modest yields.[3] Furthermore, the classic method of ring opening, usually, requires high temperature and longer reaction time associated with side reactions, such as isomerization, epimerization, and/or rearrangement.[1a,4] Recently, Wills and co-workers[5] studied the asymmetric transfer hydrogenation of functionalized acetophenone by a ruthenium(II) catalyst with a tethering group attachment from the basic nitrogen atom to the arene ligand. They applied the method to the reduction of a ketone ether obtaining the corresponding β-hydroxy ether in 95% ee. The environmentally benign asymmetric reduction of functionalized ketones mediated by 1,3,2-oxazaborolidines (OB) and other chiral borane reagents has been extensively investigated by

(1) (a) Franchini, C.; Carocci, A.; Catalano, A. A.; Cavalluzzi, M. M.; Corbo, F.; Lentini, G.; Scilimati, A.; Scilimati, A.; Tortorella, P.; Camerino, D. C.; Luca, A. *J. Med. Chem.* **2003**, *46*, 5238. (b) Wright, J. T.; Gregory, T. F.; Heffner, T. G.; Mackenie, R. G.; Pugsley, T. A.; Meulen, S. V.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1997**, 1377. (c) Baker, N. R.; Byrne, N. R.; Byrne, N. G.; Economide, A. P.; Javeld, T. *Chem. Pharm. Bull.* **1995**, 1045. (d) Kirkup, M. P.; Rizvi, R.; Shankar, B. B.; Duggar, S.; Clader, J.; McCombie, S. W.; Lin, S.; Yumibe, N.; Huie, K.; Heek, M.; Compton, D. S.; Davis, H. R.; Mcphail, A. T. *Bioorg. Med. Chem. Lett.* **1996**, 2069. (e) Cavalluzzia, M. M.; Catalanoa, A.; Brunoa, C.; Lovecea, A.; Caroccia, A.; Corboa, F.; Franchinia, C.; Lentini, G.; Tortorellaa, V. *Tetrahedron: Asymmetry* **2007**, *18*, 2409.

(2) (a) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086. (b) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 2687.

(3) Guy, A.; Dubuffet, T.; Doussot, J.; God Froy-Falguieres, A. *Synlett* **1991**, 403.

(4) (a) Fringuelli, F.; Pizzo, F.; Vittoriani, C.; Vaccaro, L. *Chem. Commun.* **2004**, 2756. (b) Kleiner, C. M.; Schreiner, P. R. *Chem. Commun.* **2006**, 4315. (c) Chen, J.; Shum, W. *Tetrahedron Lett.* **1995**, *36*, 2379–2382. (d) Fan, R. H.; Hou, X. L. *J. Org. Chem.* **2003**, *68*, 726.

(5) Morris, D. J.; Hayes, A. M.; Wills, M. *J. Org. Chem.* **2006**, *71*, 7035.

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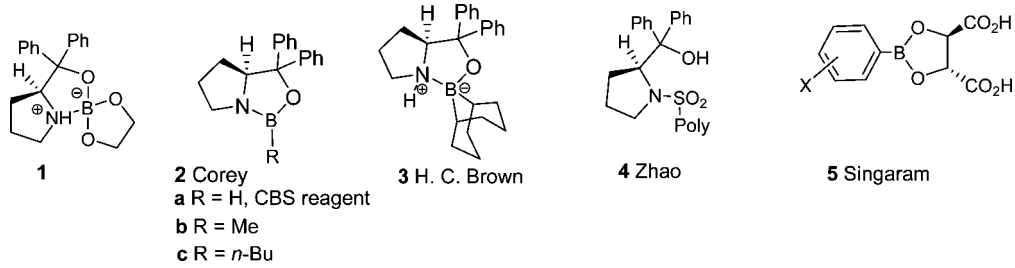
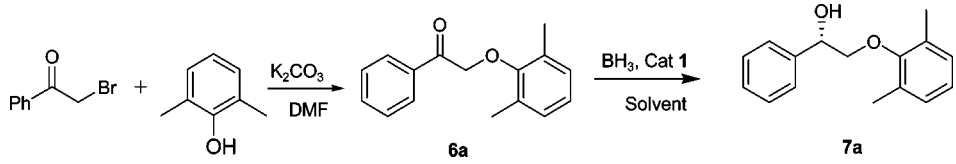


FIGURE 1. Spiroborate ester **1**, Corey's oxazaborolidines **2**, Brown's reagent **3**, Zhao's reagent **4**, and TarB-X Singaram's reagent **5**.

SCHEME 1. Asymmetric Synthesis of Model β-Hydroxy Ether 7a



Corey[6] and other groups (Figure 1).[7,8] The *B*-H oxazaborolidine (**2a**)-catalyzed reduction has been widely applied with high enantioselectivity and predictable configuration to α-haloketones,[9] α-[(triorganosilyl)oxy] ketones,[10a] α-(2-pyranyl)oxy ketones,[10b] α-sulfonyloxy ketones,[10c] α-amido ketones,[10d] diketones,[11] α-keto acetals,[12] α,β-enones and ynones,[13] α-azido ketones,[7h,j] ketone esters,[7f] ketophosphonates,[14] β-keto sulfides, and sulfones.[15] However, the in situ prepared *B*-H oxazaborolidines may possibly form side products that can diminish the efficiency of the catalyst.[16] Although *B*-Me and *B*-*n*-Bu oxazaborolidines (**2b**, **2c**) could overcome these disadvantages, the use of relatively expensive trialkylboroxine or alkylboronic acid and the careful purification procedure required for their preparation make these reagents expensive for multigram syntheses. The enantioselective reduction of β-keto ethers using affordable and environmentally friendly chiral boron catalysts is expected to be one of the most convenient methods for the synthesis of optically active β-hydroxy ethers.

Recently, a series of air- and moisture-stable crystalline spiroborate esters have been easily synthesized in our laboratory from nonracemic 1,2-amino alcohols, ethylene glycol, and inexpensive triisopropyl borate.[17a,b] Spiroborate ester **1** (Figure 1) derived from diphenyl prolinol, which was isolated and characterized by X-ray, optical, and spectroscopical methods, has demonstrated outstanding enantioselectivity for ketone reductions.[17c,d] The facile and successful use of spiroborate ester **1** has prompted us to investigate its application for the reduction of key β-keto ethers. Herein, we wish to report a highly efficient synthesis of β-hydroxy ethers with excellent enantiomeric purity in high yield and study its conversion to a wide variety of β-amino ethers, Mexiletine and nAChR analogues.

Results and Discussion

The reduction of ketone ether **6a**, as shown in Scheme 1, was initially selected as a model substrate. Ketone **6a** was readily prepared in high yield by the treatment of 2-bromoacetophenone

(6) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012, and references cited therein. (c) Sing, V. K. *Synthesis* **1992**, 605.

(7) (a) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *12*, 1475–1504. (b) Kanth, J. V. B.; Brown, H. C. *Tetrahedron* **2002**, *58*, 1069. (c) Liu, D.; Shan, Z.; Zhou, Y.; Wu, X.; Qin, J. *Helv. Chim. Acta* **2004**, *87*, 2310. (d) Shan, Z.; Zhou, Y.; Liu, D.; Ha, W. *Synth. React. Inorg. Met.Org. Nano-Met. Chem.* **2005**, *35*, 275. (e) Yang, S.-D.; Shi, Y.; Sun, Z.-H.; Zhao, Y.-B.; Liang, Y.-M. *Tetrahedron: Asymmetry* **2006**, *17*, 1895. (f) Wang, G.; Hu, J.; Zhao, G. *Tetrahedron: Asymmetry* **2004**, *15*, 807. (g) Gamble, M. P.; Studle, J. R.; Wills, M. *Tetrahedron Lett.* **1992**, *37*, 2853. (h) Reddy, M. S.; Narender, Rao, M. K. R. *Tetrahedron* **2007**, *63*, 331. (i) Eagon, S.; Kim, J.; Yan, K.; Haddenham, D.; Singaram, B. *Tetrahedron Lett.* **2007**, *48*, 9025. (j) Bolm, C.; Felder, M. *Tetrahedron Lett.* **1993**, *34*, 6041. (k) Bolm, C.; Seger, A.; Felder, M. *Tetrahedron Lett.* **1993**, *34*, 8079. (l) Yadav, J. S.; Reddy, P. T.; Hashim, S. R. *Synlett* **2000**, 1049. (m) Hu, J.; Zhao, G.; Yang, G.; Ding, Z. *J. Org. Chem.* **2001**, *66*, 303.

(8) (a) Cho, B. T. *Tetrahedron* **2006**, *62*, 7621. (b) Cho, B. T. *Chem. Soc. Rev.* **2009**, *38*, 443. (c) Cho, B. T. *Aldrichimica Acta* **2002**, *35*, 3.

(9) (a) Hett, R.; Senanayake, C. H.; Wald, S. A. *Tetrahedron Lett.* **1998**, *39*, 1705. (b) Hett, R.; Fang, Q. K.; Gao, Y.; Wald, S. A.; Senanayake, C. H. *Org. Process Res. Dev.* **1998**, *2*, 96. (c) Wilkinson, H. S.; Tanoury, G. J.; Wald, S. A.; Senanayake, C. H. *Org. Process Res. Dev.* **2002**, *6*, 146.

(10) (a) Cho, B. T.; Chun, Y. S. *J. Org. Chem.* **1998**, *63*, 5280. (b) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1999**, *10*, 1843. (c) Cho, B. T.; Yang, W. K.; Choi, O. K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1204. (d) Cho, B. T.; Shin, S. H. *Bull. Korean Chem. Soc.* **2004**, *25*, 747.

(11) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1996**, *61*, 3888.

(12) Cho, B. T.; Chun, Y. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2095.

(13) (a) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153–9156. (b) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214.

(14) Meier, C.; Laux, W. H. G. *Tetrahedron: Asymmetry* **1995**, *6*, 1089.

(15) (a) Cho, B. T.; Choi, O. K.; Kim, D. J. *Tetrahedron: Asymmetry* **2002**, *13*, 697. (b) Cho, B. T.; Shin, S. H. *Tetrahedron* **2005**, *61*, 6959. (c) Cho, B. T.; Kim, D. J. *Tetrahedron: Asymmetry* **2001**, *12*, 2043.

(16) (a) Lang, A.; Noth, H.; Schmidt, M. *Chem. Ber.* **1997**, *130*, 241. (b) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880. (c) Tlahuext, H.; Santiesteban, F.; García-Báez, E.; Contreras, R. *Tetrahedron: Asymmetry* **1994**, *5*, 1579. (d) Santiesteban, F.; Mancilla, T.; Klaébe, A.; Contreras, R. *Tetrahedron Lett.* **1983**, *24*, 759. (e) Brown, J. M.; Guy, C.; Lloyd-Jones, G. C.; Layzell, T. P. *Tetrahedron: Asymmetry* **1993**, *4*, 2151. (f) Stepanenko, V.; Ortiz-Marciales, M.; Barnes, C. E.; Garcia, C. *Tetrahedron Lett.* **2006**, *47*, 7603. (g) Ortiz-Marciales, M.; De Jesus, M.; Gonzales, E.; Raptis, R. G.; Baran, P. *Acta Crystallogr.* **2004**, *C60*, 173.

(17) (a) Stepanenko, V.; Ortiz-Marciales, M.; Correa, W.; De Jesús, M.; Espinosa, S.; Ortiz, L. *Tetrahedron: Asymmetry* **2006**, *17*, 112. (b) Ortiz-Marciales, M.; Stepanenko, V.; Correa, W.; De Jesús, M.; Espinosa, S. U.S. Patent Application 11/512,599, August 30, 2006. (c) Stepanenko, V.; De Jesús, M.; Correa, W.; Vázquez, C.; Guzman, I.; Vazquez, C.; De la Cruz, W.; Ortiz-Marciales, M.; Barnes, C. L. *Tetrahedron Lett.* **2007**, *48*, 5799. (d) Stepanenko, V.; Ortiz-Marciales, M.; De Jesús, M.; Correa, W.; Vázquez, C.; Ortiz, L.; Guzmán, I.; De la Cruz, W. *Tetrahedron: Asymmetry* **2007**, *18*, 2738.

(18) (a) Huang, K.; Ortiz-Marciales, M.; Merced, F. G.; Meléndez, H. J.; De Jesús, M.; Correa, W. *J. Org. Chem.* **2008**, *73*, 4017. (b) Huang, K.; Ortiz-Marciales, M.; Stepanenko, V.; De Jesús, M.; Correa, W. *J. Org. Chem.* **2008**, *73*, 6928.

(19) (a) De Luca, A.; Natuzzi, F.; Desaphy, J.-F.; Loni, G.; Lentini, G.; Franchini, C.; Tortorella, V.; Conte Camerino, D. *Mol. Pharmacol.* **2000**, *57*, 268. (b) De Luca, A.; Natuzzi, F.; Duranti, A.; Lentini, G.; Franchini, C.; Tortorella, V.; Conte Camerino, D. *Arch. Pharmacol.* **1997**, *356*, 777. (c) De Luca, A.; Pierno, S.; Natuzzi, F.; Franchini, C.; Duranti, A.; Lentini, G.; Tortorella, V.; Jockush, H.; Conte Camerino, D. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 93. (d) Cannon, S. C. *Trends Neurosci.* **1996**, *19*, 3. (e) Lehmann-Horn, F.; Rüdel, R. *Rev. Physiol. Biochem. Pharmacol.* **1996**, *128*, 195. (f) Liu, H.; Gao, Z. B.; Yao, Z.; Zheng, S.; Li, Y.; Zhu, W.; Tan, X.; Luo, X.; Shen, J.; Chen, K.; Hu, G. Y.; Jiang, H. *J. Med. Chem.* **2007**, *50*, 83–93.

TABLE 1. Optimization Studies for the Asymmetric Reduction of β-Keto Ether 6a[a]

entry	borane	cat **1** (equiv)	solvent	yield (%)[b]	ee (%)[c]
1	BH_3·DMS	0.01	THF	71	23
2	BH_3·DMS	0.05	THF	83	66
3	BH_3·DMS	0.1	THF	96	98
4	BH_3·DMS	0.1	dioxane	96	65
5	BH_3·BACH	0.1	THF	67	99
6	BH_3·THF	0.1	THF	91	98

[a] Unless otherwise stated, reactions were performed on a 2 mmol scale: 1 equiv of ketone, 0.7 equiv of BH_3 in THF at 25 °C for 1 h. [b] Purified by flash column chromatography. [c] Determined by chiral HPLC (Chiralcel OD-H column).

with K_2CO_3 (1.5 equiv) and 2,6-dimethylphenol (1.5 equiv) in DMF at room temperature for 24 h.[18] To establish the most advantageous conditions, different catalytic loads (Table 1, entries 1−3), dioxane as an alternative solvent and the use of other borane sources (entries 4−6), were evaluated. Initially, the reduction of ketone **6a** with BH_3·DMS in THF at 25 °C using 1, 5, and 10% of catalyst **1** was investigated. A remarkable increase in enantioselectivity and eficiency of the reaction was achieved with 10% of catalyst, providing the alcohol **7a** in 98% ee and 96% isolated yield. Dioxane was found as an unsuitable solvent for the reaction, giving only 65% ee. Although BH_3·BACH-EI (borane *N*-ethyl-*N*-isopropylaniline complex) and BH_3·THF provided 99 and 98% ee, respectively, BH_3·DMS was more attractive due to its low price and stability.

Having optimized the reaction conditions, the reduction of a variety of β-keto aryl and pyridyl ethers with aliphatic and aromatic substituents was accomplished. Table 2 illustrates the optical rotation, yield, and enantiomeric excess for the prepared enantiopure secondary alcohols. In general, the β-hydroxy ethers were afforded in 92−99% ee and with excellent yield. Generally, steric and electronic effects of the substituents attached to both aromatic rings on the enantioselectivity of the reaction were not observed. For example, β-aryl keto ethers bearing both electron-withdrawing and electron-donating groups on the aryl groups afford excellent enantioselectivities (entries 1−7). It is important to note that the reduction of aliphatic β-keto ethers containing cyclohexanyl and adamantyl groups provides the desired alcohols in 93 and 99% ee, respectively, and in high yield (entries 8 and 9). It should be pointed out that 1.7 equiv of BH_3·DMS is needed for the reduction of pyridyl ethers because one borane molecule coordinates to the pyridine nitrogen. Surprisingly, the β-keto 2-pyridyl ethers (entries 10, 11, and 13), which could bring forth a nonselective intramolecular borane reduction, afford excellent enantioselectivities in good to high yields. The 3-pyridyl ethers also offered high enantiopurity and excellent yields (entries 12−14). The absolute configuration of products was determined by comparison with the optical rotations of corresponding known compounds.[1a]

Optically active β-amino aryl ethers display a key role in the treatment of neuromuscular disorders (Figure 2).[1] The commercial Mexiletine, as a racemate **8**, is used as an anti-arrhythmic and analgesic oral drug,[1a] but due to side effects, such as dizziness, heartburn, nausea, nervousness, trembling, and unsteadiness, its use is limited. The optically active Mexiletine analogue (*R*)-**9** is more potent than the more active (*R*)-Mexiletine isomer.[1a,e] The racemic potent β-blocker of voltage-gated K^+ channels **10** was recently discovered, using structure-based virtual screening in combination with electrophysiological assays in rat hippocampal neurons.[19f] In addition, other important β-amino ethers are neuronal nicotinic acetylcholine receptor (nAChRs) agonists, which are a group of ligand-gated ion channels that hold significant promise as therapeutic targets for the treatment of central nervous system (CNS) and peripheral nervous system disorders.[20] As shown in Figure 2, the β-amino pyridyl ethers A-84534 (**11**),[21] ABT-594 (**12**),[22] NIDA52189 (**13**),[23] and related compounds have been investigated as potential drug candidates. Recently, we reported a new methodology for the synthesis of novel Mexiletine analogues by the reduction of benzylated oxime ethers with excellent enantiopurity.[18b] As part of our ongoing programs, we are interested in developing alternative methodologies for the synthesis of a variety primary β-amino pyridyl ethers with possible neurobiological activity. Since β-hydroxy ethers are easily converted into β-amino ethers employing the Mitsunobu reaction[24] with only slight decrease in enantioselectivity,[25] we were interested in the synthesis of Mexiletine and nAChRs analogues from the previously prepared optically pure β-hydroxy pyridyl ethers.

As outlined in Table 3, the optically pure alcohols **7** were readily transformed into **14** by a stereospecific substitution reaction of the hydroxyl group with phthalimide employing a typical Mitsunobu procedure. After hydrazinolysis of phthalimido ethers **14**, the desired bioactive β-amino ethers were obtained with inversion of configuration at the stereogenic center in moderate to good yields. Chiral HPLC analysis indicated high enatiomeric purity of the β-amino ethers **14** (95−99% ee) (Table 3 entries 1−6), with only a slight racemization. Interestingly, adamantyl and pyridyl ethers are also suitable substrates for this transformation, demonstrating the efficiency and the functional tolerance of this reaction toward phenoxy and pyridyl groups.

On the basis of similar structural features present in the nAChRs agonist, we investigated the reduction of phthalimide ethers **14** to obtain 2,3-dihydro-1*H*-isoindol derivatives (Scheme 2). BH_3·DMS in THF (8 equiv) was employed for the imide reduction. After the mixture was refluxed for 1.5 h, the reaction was quenched with MeOH at 0 °C. As evidenced by TLC analysis, the starting material was consumed and only one compound was observed. Surprisingly, amide **16j**, formed by monoreduction of the phthalimide ether, was identified by NMR analysis as the initial partial reduction product. After the reaction time was extended to 8 h, the target product **17j** was obtained in 71% yield.

Under the previous optimized conditions, representative substrates were reduced to 2,3-dihydro-1*H*-isoindol derivatives

(20) (a) Karlin, A. *Nat. Rev. Neurosci.* **2002**, *3*, 102. (b) Lloyd, G. K.; Williams, M. *J. Pharmacol. Exp. Ther.* **2000**, *29*, 2–461. (c) Tonder, J. E.; Olesen, P. H. *Curr. Med. Chem.* **2001**, *8*, 651. (d) Jensen, A. A.; Frolund, B.; Liljefors, T.; Krogsgaard- Larsen, P. *J. Med. Chem.* **2005**, *48*, 4705.

(21) Tonder, J. E.; Olesen, P. H. *Curr. Med. Chem.* **2001**, *8*, 651.

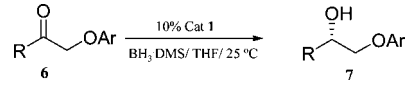
(22) (a) Bannon, A. W.; Decker, M. W.; Holladay, M. W.; Curzon, P.; Donnelly-Roberts, D.; Puttfarcken, P. S.; Bitner, R. S.; Diaz, A.; Dickenson, A. H.; Porsolt, R. D.; Williams, M.; Arneric, S. P. *Science* **1998**, *279*, 77. (b) Holladay, M. W.; Wasicak, J. T.; He, Y.; Ryther, K. B.; Bannon, A. W.; Buckley, M. J.; Kim, D. B.; Decker, M. W.; Anderson, D. J.; Campbell, J. E.; Kuntzweiler, T. A.; Donnelly-Roberts, D. L.; Piattoni-Kaplan, M.; Briggs, C. A.; Williams, M.; Arneric, S. P. *J. Med. Chem.* **1998**, *41*, 407. (c) Abreo, M. A.; Lin, N.-H.; Garvey, D. S.; Gunn, D. E.; Hettinger, A.-M.; Wasicak, J. T.; Pavlik, P. A.; Martin, Y. C.; Donnelly-Roberts, D. L.; Anderson, D. J.; Sullivan, J. P.; Williams, M.; Arneric, S. P.; Holladay, M. W. *J. Med. Chem.* **1996**, *39*, 817.

(23) Gao, Y.; Horti, A. G.; Kuwabara, H.; Ravert, H. T.; Hilton, J.; Holt, D. P.; Kumar, A.; Alexander, M.; Enres, C. J.; Wong, D. F.; Dannals, R. F. *J. Med. Chem.* **2007**, *50*, 3814.

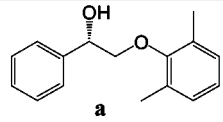
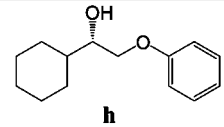
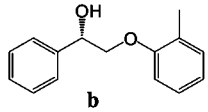
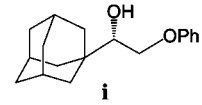
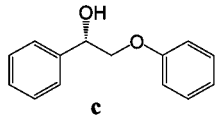
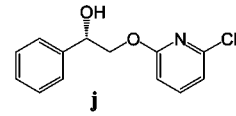
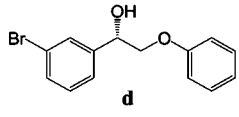
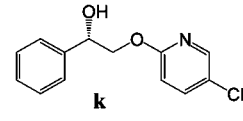
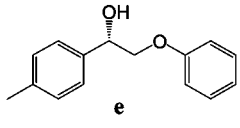
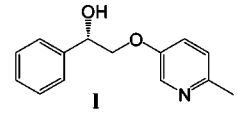
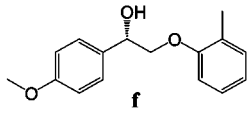
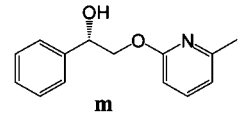
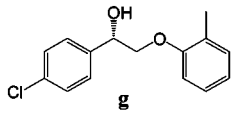
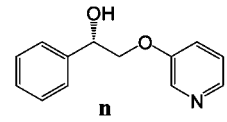
(24) Mitsunobu, O. *Synthesis* **1981**, 1.

(25) (a) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886. (b) Chen, C.-P.; Prasad, K.; Repic, O. *Tetrahedron Lett.* **1991**, *32*, 7175.

TABLE 2. Asymmetric Reduction of β-Keto Aryl and Pyridyl Ethers[a]



6 → 7

entry	β-hydroxy ethers 7	$[\alpha]^{20}_D$ [b]	yield (%)[c]	ee (%)[d]	entry	β-hydroxy ethers 7	$[\alpha]^{20}_D$ [b]	yield (%)[c]	ee (%)[d]
1	 a	+17 (1.9)	96	98	8	 h	+12 (1.2)	93	93
2	 b	+50 (1.5)	94	98	9	 i	+41 (1.5)	96	>99
3	 c	+50 (1.7)	93	98	10	 j	+48 (1.0)	88[f]	99
4	 d	+24 (1.6)	95	98	11	 k	+59 (1.1)	75[f]	92[e]
5	 e	+43 (1.2)	96	98	12	 l	+46 (1.3)	90[f]	97
6	 f	+43 (1.6)	94	98	13	 m	+99 (1.0)	89[f]	99
7	 g	+41 (1.8)	92	99	14	 n	+57 (1.2)	93[f]	96[e]

[a] Unless otherwise stated, reactions were performed on a 2 mmol scale: 1 equiv of ketone, 0.7 equiv of BH_3·DMS in THF at 25 °C for 1 h. [b] Optical rotation in $CHCl_3$. [c] Purified by flash chromatography column. [d] Determined by chiral HPLC analysis on a Chiralcel OD-H column. [e] Determined by HPLC analysis of acetyl derivative on a Chiralcel OD-H column. [f] It used 1.7 equiv of BH_3·DMS.

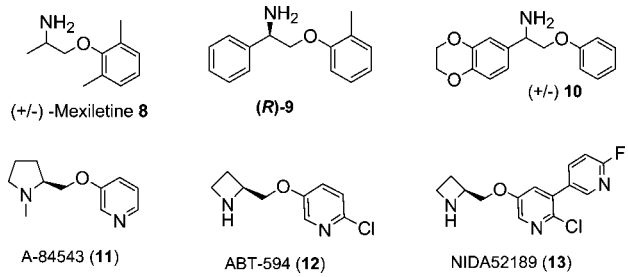


FIGURE 2. Mexiletine and neuronal nicotinic acetylcholine receptors agonist.

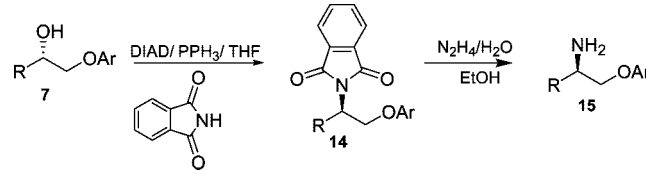
17 using 8 equiv of BH_3·DMS in anhydrous THF for 10 h. As shown in Table 4, various chiral 2,3-dihydro-1*H*-isoindol derivatives were provided in good to high yields. Moreover, by control of the reaction time, selective reduction can provide a rapid access to novel amides and amino acids with potential biological applications.

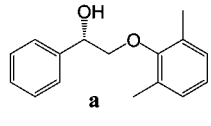
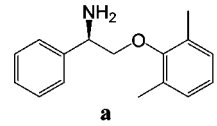
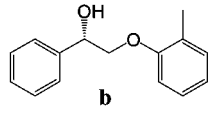
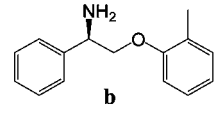
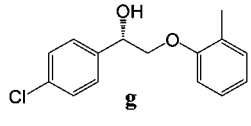
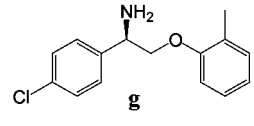
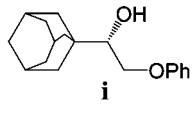
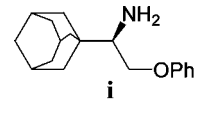
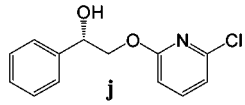
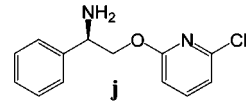
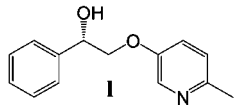
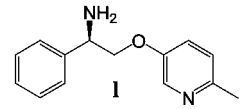
Many biologically important compounds contain a heterocyclic ring in their structure, and many piperidine derivatives are also in clinical and preclinical studies.[26] Our interest in the synthesis of nicotinic analogues prompted us to investigate the direct substitution of the hydroxyl group with secondary cyclic amines, such as pyrrolidine, piperidine, or azepane. Considering the efficiency and convenience of the Mitsunobu reaction, we initially explored this procedure (Scheme 3). Unfortunately, no product was observed even by increasing the reaction temperature and time, and only starting materials were observed by TLC. Consequently, an alternative route was searched.

One of the most common methods for the preparation of tertiary heterocyclic amine is the displacement of a sulfonated

(26) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679.

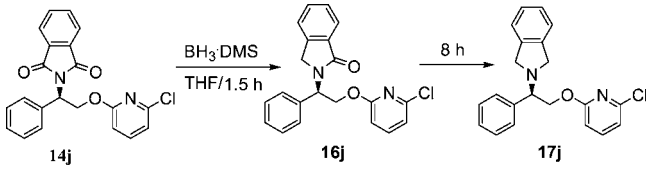
TABLE 3. Asymmetric Synthesis of β-Amino Ethers from Optically Pure Alcohols



entry	Substrate **7**	Phthalimide **14** yield (%)[a]	β-amino ether **15**	yield (%)[a]	*ee* (%)[b]
1	 **a**	79	 **a**	85	96[c]
2	 **b**	84	 **b**	88	98[c]
3	 **g**	77	 **g**	62	95
4	 **i**	91	 **i**	86	>99[c]
5	 **j**	86	 **j**	85	97
6	 **l**	90	 **l**	66	97[c]

[a] Purified by flash chromatography column. [b] Determined by chiral HPLC (Chiralcel OD-H column). [c] Determined by HPLC analysis of acetyl derivative on a chiral Chiralcel OD-H column.

SCHEME 2. Reduction of Representative Phthalimide 14j

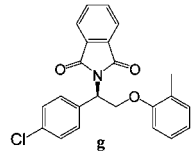
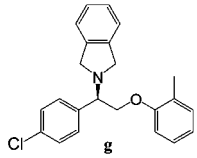
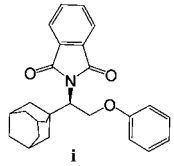
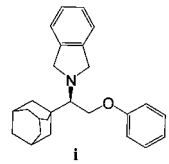
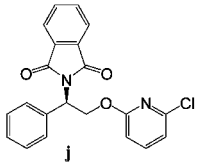
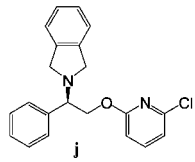
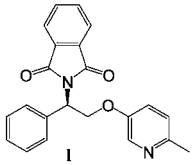
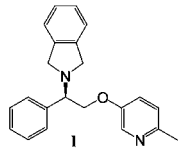
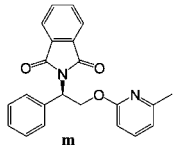
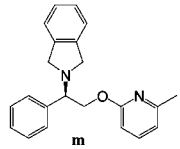


intermediate with the secondary aliphatic amines. To investigate the possibility of this transformation with complete inversion of configuration, optically active alcohol **7a** (Table 5) was chosen as a model. The mesylate (*S*)-**18a** was prepared by conventional treatment of alcohol with mesyl chloride in the presence of Et_3N. Considering the instability of mesylate **18a** on the chromatographic columm, this intermediate was used without further purification and was treated directly with pyrrolidine in acetonitrile. To our delight, the desirable product **19a** was obtained in 83% yield for the two steps. A baseline separation of the racemic sample was not satisfactory for chiral GC and HPLC analysis; however, a good baseline separation was achieved for the chiral HPLC analysis of racemic compound **19b**. As indicated in Table 5 (entry 3), the optical purity of this product was 98% ee. As desired, the reaction took place stereoselectively via an S_N2 process as the optical purity of **19b** is even higher than the enantiopurity of the starting alcohol (*S*)-**7l** (97% ee). Under similar condition, various secondary aliphatic amines and substrates were examined. As shown in Table 5, pyrrolidine, piperidine, and azepane derivatives are obtained in good yields, providing a rapid access to new nicotinic acetylcholine receptor (nAChRs) analogues in high optical purity.

Conclusions

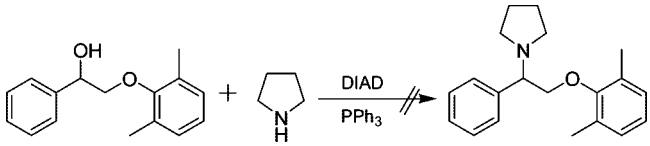
Spiroborate ester **1** demonstrated to be an excellent catalyst for the facile enantioselective borane reduction of representative β-keto aryl and pyridylethers using 10% of catalytic load in THF at room temperature. A wide range of aliphatic and aromatic β-hydroxy ethers were afforded in optically pure form in up to 99% ee and in high yield. Electronic factors or steric effects in the aryl or pyridyl rings do not affect significantly the enantioselectivity of the spiroborate ester-mediated reduction. The nonracemic β-hydroxy ethers were successfully converted to β-amino ethers with negligible epimerization by phthalimide substitution under Mitsunobu's conditions. By a facile imide hydrazinolysis, representative primary aryl and alkyl amino

TABLE 4. Synthesis of Novel nAChRs Analogues by Reduction of Optically Active Lactame 14

entry	substrate **14**	product **17**	yield (%)[a]
1			82
2			65
3			71
4			88
5			86

[a] Purified by column chromatography on silica gel.

SCHEME 3. Attempted Substitution of the Hydroxyl Group with Pyrrolidine by Mitsunobu's Method

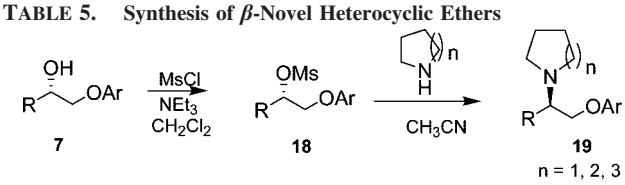


ethers were achieved in good yield. Complete phthalimide reduction with borane provided the corresponding β-2,3-dihydro-1*H*-isoindol derivatives in good yield. In addition, the partial imide reduction can afford important β-amide ethers, which by hydrolysis can be transformed to aromatic ortho-secondary amino acids with a β-aryl and pyridyloxy moiety. In addition, nonracemic novel Mexiletine and nAChR analogues with potential biological activity were synthesized in enantiopure form and excellent yields by mesylation of key β-hydroxy pyridylethers and in situ substitution with pyrrolidine, piperidine, and azepane to form, respectively, five-, six-, and seven-membered ring heterocyclic amino ethers.

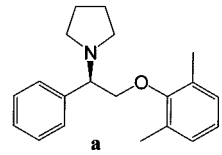
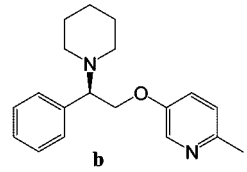
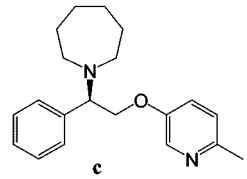
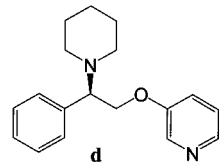
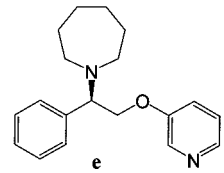
Experimental Section

General Procedure for the Reduction of β-Keto Ethers (6a−6i). To a dried 50 mL reaction tube under N_2 were added catalyst **1**[17a] (65 mg, 0.2 mmol) and anhydrous THF (4 mL). Then, BH_3·DMS (0.14 mL, 10.0 M) was added in one portion. The resulting mixture was stirred at room temperature for 30 min until a transparent solution was observed. A solution of β-keto ether[18] (2 mmol) in THF (3 mL) was added dropwise during 1 h by a syringe pump. The resulting mixture was stirred for another 1 h. Then, the reaction mixture was cooled with an ice-bath and quenched with MeOH (3 mL). The solvents were removed under reduced pressure, and to the residue was added 1 N HCl (10 mL). The aqueous phase was extracted with ether (3 × 30 mL), and the combined organic phases were washed with brine and dried over Na_2SO_4. After solvent removal under reduced pressure and purification by silica gel column chromatography, the corresponding β-hydroxy ethers (**7**) were provided.

TABLE 5. Synthesis of β-Novel Heterocyclic Ethers



7 **18** **19** n = 1, 2, 3

entry	product **19**	$[\alpha]^{20}_D$[a]	yield (%)[b]
1		-15 (1.7)	83
2		-13 (1.2)	87 (98)[c]
3		+5 (2.1)	85
4		-7 (1.4)	91
5		+6 (1.1)	86

[a] $CHCl_3$ as solvent. [b] Purified by flash chromatography column. [c] Determined by chiral HPLC (Chiralcel AD-H column).

(*S*)-1-Adamantan-1-yl-2-phenoxyethanol (7i): White solid; mp 65−66 °C; yield 96% (262 mg); >99% ee; $[\alpha]^{20}_D = +41$ (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.7−1.83 (m, 12H), 2.08 (m, 3H), 2.38 (br s, 1H, OH), 3.58 (m, 1H), 3.98 (m, 1H), 4.19 (m, 1H), 6.97−7.04 (m, 3H), 7.32−7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 35.7, 37.2, 38.4, 68.6, 114.7, 121.1, 129.5, 158.7; IR ν (cm^{-1}) 3454, 2912, 2893, 2848, 1600, 1585, 1497, 1450, 1298, 1241, 1172, 1086, 1048, 1034, 1022, 986, 895, 880, 814, 749, 688; ESI HRMS *m/z* calcd for $C_{18}H_{24}NaO_2$ $(M + Na)^+$ 295.1674, found 295.1666. Enantiomeric excess was determined by HPLC with a

Chiralpak OD-H column (95:5 hexane/2-propanol), 0.5 mL/min, 254 nm, minor enantiomer t_R = 16.65 min, major enantiomer t_R = 26.69 min.

General Procedure for the Reduction of β-Keto Pyridyl Ethers (6j−6m). To a dried 50 mL reaction tube under N_2 were added catalyst **1** (65 mg, 0.2 mmol) and anhydrous THF (4 mL). Then, BH_3·DMS (0.34 mL, 10.0 M) was added in one portion. The resulting mixture was stirred at room temperature for 30 min until a transparent solution was observed. A solution of β-keto pyridyl ethers (2 mmol) in THF (4 mL) was added dropwise during 1 h by a syringe pump. The resulting mixture was stirred overnight. Then, the reaction mixture was cooled with an ice-bath and quenched with MeOH (5 mL). After the mixture was refluxed for 3 h, the solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography.

(*S*)-2-(6-Chloropyridin-2-yloxy)-1-phenylethanol (7j): White solid; mp 85−86 °C; yield 88% (659 mg); 99% ee; $[\alpha]^{20}_D$ = +48 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 (br s, 1H), 4.41 (m, 1H), 4.60 (m, 1H), 5.19 (m, 1H), 6.78 (m, 1H), 6.98 (m, 1H), 7.35 (m, 1H), 7.44 (m, 2H), 7.53 (m, 2H), 7.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.2, 72.9, 109.4, 116.9, 126.3, 128.1, 128.6, 140, 141, 148.3, 163.2; IR ν (cm^{-1}) 3368, 2988, 2941, 1588, 1559, 1493, 1433, 1407, 1296, 1261, 1159, 1082, 1056, 1021, 1006, 983, 921, 899, 788, 756, 701; ESI HRMS *m*/*z* calcd for $C_{13}H_{12}ClNNaO_2$ $(M + Na)^+$ 272.0454, found 272.0454. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (9:1 hexane/2-propanol), 0.5 mL/min, 254 nm, major enantiomer t_R = 16.72 min, minor enantiomer t_R = 20.54 min.

General Procedure for the Synthesis of Compounds 14 via a Mitsunobo Reaction. To a mixture of the optically pure alcohol (2 mmol), phthalimide (441 mg, 3 mmol), and triphenylphosphine (786 mg, 3 mmol) in 20 mL of anhydrous THF under N_2 at room temperature was added dropwise a solution of DIAD (603 mg, 3 mmol) in anhydrous THF (10 mL). The resulting mixture was stirred until TLC indicated that the alcohol was consumed. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography, affording the corresponding imide.

(*R*)-2-(1-Adamantan-1-yl-2-phenoxyethyl)isoindole-1,3-dione (14i): Colorless oil; yield 86% (345 mg); reaction time 72 h; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.7−1.77 (m, 9H), 1.82−1.88 (m, 3H), 2.06 (m, 3H), 4.43 (m, 2H), 5.02 (m, 1H), 6.88 (m, 2H), 6.96 (m, 1H), 7.26 (m, 2H), 7.77 (m, 2H), 7.84 (m, 1H), 7.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 28.4, 36.8, 37.1, 37.2, 38.4, 40.1, 60.8, 63.0, 115, 121, 123.1, 123.4, 129.4, 131.6, 133.8, 134.0, 158.6, 169.5; IR ν (cm^{-1}) 3512, 3039, 2900, 2847, 1773, 1710, 1599, 1587, 1496, 1450, 1392, 1345, 1241, 1171, 1076, 1032, 1013, 986, 874, 751, 736, 716, 690; ESI HRMS *m*/*z* calcd for $C_{26}H_{28}NO_3$ $(M + H)^+$ 402.2069, found 402.2079.

General Procedure for the Synthesis of β-Amino Ether 15 via Hydrazinolysis. To a stirred solution of **14** (1 mmol) in 5 mL of EtOH was added 50−60% N_2H_4 (256 mg, 8 mmol). The resulting mixture was refluxed for 3 h. The precipitated solid was filtered off, and the solvent was removed under reduced pressure. The residue, dissolved in ether, was extracted with 2 N HCl, and the aqueous phase was treated with 2 N NaOH until pH >12. The aqueous phase was extracted with ether (3 × 20 mL), and the combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure to give the target product. For the amine of **15i**, **15j**, and **15l**, because of their water solubility, the desired products were obtained, directly, by silica gel column chromatography.

(*R*)-1-Adamantan-1-yl-2-phenoxyethylamine (15i): White solid; mp 61−62 °C; yield 86% (465 mg); >99% ee; $[\alpha]^{20}_D$ = −29 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (br s, 2H), 1.72−1.81 (m, 12H), 2.07 (m, 3H), 2.78 (m, 1H), 3.82 (m, 1H), 4.22 (m, 1H), 4.50 (m, 1H), 6.96−7.01 (m, 2H), 7.31−7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 35.3, 37.3, 38.9, 59.5, 69.5, 114.7, 120.8, 129.5, 159.0; IR ν (cm^{-1}) 3371, 3308, 2901, 2893, 2849, 1727, 1599, 1587, 1498, 1467, 1449, 1301, 1285, 1243, 1179, 1077, 1038, 1031, 1018, 990, 960, 900, 879, 815, 755, 691; ESI HRMS *m*/*z* calcd for $C_{18}H_{26}NO$ $(M + H)^+$ 272.2009, found 272.2015. Enantiomeric excess was determined by HPLC for acetyl derivative with a Chiralpak OD-H column (96:4 hexane/2-propanol), 0.4 mL /min, 254 nm, major enantiomer t_R = 43.11 min, minor enantiomer t_R = 47.73 min.

(*R*)-2-(6-Methylpyridin-3-yloxy)-1-phenylethylamine (15l): Colorless oil; yield 66% (136 mg); 97% ee; $[\alpha]^{20}_D$ = −37 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (br s, 2H), 2.52 (s, 3H), 3.98 (m, 1H), 4.13 (m, 1H), 4.47 (m, 1H), 7.07−7.15 (m, 2H), 7.33−7.50 (m, 5H), 8.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 55.2, 74.5, 122.1, 123.3, 126.9, 127.9, 128.7, 136.9, 141.6, 150.8, 152.9; IR ν (cm^{-1}) 3368, 3291, 3060, 3026, 2923, 2866, 1599, 1572, 1484, 1454, 1387, 1287, 1265, 1240, 1212, 1122, 1023, 825, 759, 702; ESI HRMS *m*/*z* calcd for $C_{14}H_{17}N_2O$ $(M + H)^+$ 229.1341, found 229.1351. Enantiomeric excess was determined by HPLC for acetyl derivative with a Chiralcel OD-H column (9:1 hexane/2-propanol), 0.5 mL /min, 254 nm, major enantiomer t_R = 46.32 min, minor enantiomer t_R = 55.8 min.

General Procedure for the Synthesis of Compounds 16 and 17 via Borane Reduction. To a stirred solution of **14** (1 mmol) in anhydrous THF under nitrogen was added BH_3·DMS (0.8 mL, 10 M, 8 mmol). Compound **16** was produced after the mixture was refluxed for 1.5 h. Compound **17** was formed by complete reduction when the mixture was refluxed overnight. In both cases, the reaction mixtures were slowly quenched with 5 mL of MeOH at 0 °C. The corresponding products were isolated after the solvents were evaporated under reduced pressure, and the residue was purified by silica gel column chromatography.

(*R*)-2-(1-Adamantan-1-yl-2-phenoxyethyl)-2,3-dihydroisoindol-1-one (16i): White solid; mp 148−150 °C; yield 81% (313 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70−1.82 (m, 9H), 1.88 (m, 3H), 2.09 (m, 3H), 4.37 (m, 2H), 4.58 (m, 3H), 6.89−7.0 (m, 3H), 7.29 (m, 2H), 7.45−7.60 (m, 3H), 7.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 36.9, 40.3, 64.5, 114.8, 121.1, 122.5, 123.9, 127.9, 129.5, 131.2, 141.6, 158.6; IR ν (cm^{-1}) 3039, 2918, 2899, 2875, 2850, 1731, 1676, 1597, 1498, 1483, 1448, 1401, 1303, 1288, 1246, 1218, 1175, 1164, 1018, 989, 947, 896, 879, 834, 815,796, 753, 735, 688; ESI HRMS *m*/*z* calcd for $C_{26}H_{30}NO_2$ $(M + H)^+$ 388.2277, found 388.2299.

(*R*)-2-(1-Adamantan-1-yl-2-phenoxyethyl)-2,3-dihydro-1*H*-isoindole (17i): Colorless oil; yield 65% (121 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72−1.77 (m, 9H), 1.88 (m, 3H), 2.06 (m, 3H), 2.89 (m, 1H), 4.36 (m, 6H), 6.89−6.99 (m, 3H), 7.21 (m, 4H), 7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 37.3, 38.2, 40.2, 57.7, 64.9, 67.7, 114.6, 120.6, 122.1, 126.2, 129.4, 140.6, 158.8; IR ν (cm^{-1}) 2961, 2899, 2846, 1693, 1598, 1587, 1495, 1468, 1448, 1360, 1344, 1300, 1258, 1240, 1170, 1152, 1135, 1077, 1031, 1017, 858, 796, 739, 689; ESI HRMS *m*/*z* calcd for $C_{26}H_{32}NO$ $(M + H)^+$ 374.2484, found 374.2491.

General Procedure for the Synthesis of 18. To a two-neck round-bottom flask under nitrogen was added a solution of the nonracemic alcohol (2 mmol) in anhydrous CH_2Cl_2 (20 mL) and Et_3N (1.7 mL, 10 mmol). The mixture was cooled to 0 °C, and MsCl (0.46 mL, 6 mmol) was added dropwise for 0.5 h by a syringe pump. The resulting solution was stirred until TLC indicated that the starting material was consumed (about 30 min). Water (20 mL) was added to quench the reaction, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure at 25 °C, affording the crude product.

General Procedure for the Synthesis of 19. To the crude sulfonate intermediate **18** (2 mmol) in 10 mL of CH_3CN at room temperature was added the corresponding heterocyclic amine (5 equiv). The resulting mixture was stirred overnight. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography.

(*R*)-2-Methyl-5-(2-phenyl-2-piperidin-1-ylethoxy)pyridine (19b): Colorless oil; yield 87% (259 mg); 98% ee; $[\alpha]^{20}_{D} = -13$ (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (m, 2H), 1.62 (m, 4H), 2.52 (m, 7H), 3.80 (m, 1H), 4.32 (m, 1H), 4.42 (m, 1H), 7.05−7.13 (m, 2H), 7.33−7.40 (m, 5H), 8.2 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 24.5, 26.3, 52.2, 69.2, 70.4, 122.4, 123.3, 127.5, 128.3, 128.5, 137.2, 150.5, 152.9; IR ν (cm^{-1}) 3374, 3059, 3028, 2931, 2853, 2799, 2755, 1600, 1572, 1485, 1471, 1452, 1387, 1266, 1239, 1212, 1175, 1118, 1027, 992, 912, 827, 758, 723, 699; ESI HRMS *m*/*z* calcd for $C_{19}H_{25}N_2O$ $(M + H)^+$ 297.1967, found 297.1968. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (95:5 hexane/2-propanol), 0.5 mL/min, 254 nm, major enantiomer $t_R = 17.65$ min, minor enantiomer $t_R = 19.62$ min.

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Supporting Information Available: Experimental data and full characterization of new and known compounds, and spectral and chromatographic data of starting materials and enantiopure compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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