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Highly Enantioselective Borane Reduction of Heteroaryl and Heterocyclic Ketoxime Ethers Catalyzed by Novel Spiroborate Ester Derived from Diphenylvalinol: Application to the Synthesis of Nicotine Analogues

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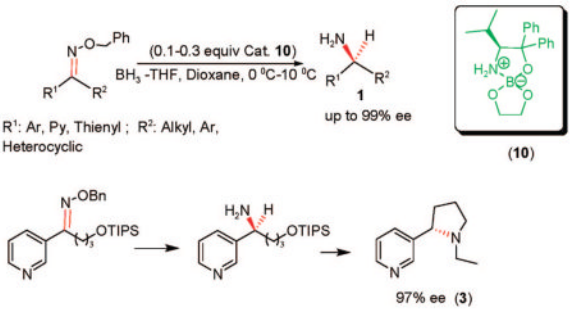
Abstract



An asymmetric synthesis for the preparation of nonracemic amines bearing heterocyclic and heteroaromatic rings is described. A variety of important enantiopure thionyl and arylalkyl primary amines were afforded by the borane-mediated enantioselective reduction of *O*-benzyl ketoximes using 10% of catalyst **10** derived from (*S*)-diphenylvalinol and ethylene glycol with excellent enantioselectivity, in up to 99% ee. The optimal condition for the first asymmetric reduction of 3- and 4-pyridyl-derived *O*-benzyl ketoxime ethers was achieved using 30% of catalytic loading in dioxane at 10 °C. (*S*)-*N*-ethylnornicotine (**3**) was also successfully synthesized from the TIPS-protected (*S*)-2-amino-2-pyridylethanol in 97% ee.

Introduction

Nicotinic acetylcholine receptors (nAChRs) are a group of ligand-gated ion channel receptors that play a vital role in different biological processes, in particular, those related to the electrical transmission at the neuromuscular junction and central nervous system (CNS) functions.[1–6] Several studies have demonstrated that (*S*)-nicotine (**2** in Figure 1) and analogues display potent biological activity in mammals by modulation of nAChRs[2] which, in addition, regulate the release of other important neurotransmitters, such as catecholamines (dopamine, norepinephrine), glutamate, γ-aminobutyric acid (GABA), and serotonin (5-

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Supporting Information Available: Experimental procedures, physical properties and spectral data for all oximes, data characterization for known benzyl oximes and acetamides, and enantiomeric determination by chromatography for all racemic and nonracemic acetamides. This material is available free of charge via the Internet at http://pubs.acs.org.

hydroxytriptamine). In the past decade, intense research efforts in the area of neurobiology and pharmacology of nicotine and related nAChR agonists and antagonists have led to exciting developments in drug discovery for the treatment of Parkinson's and Alzheimer's (AD) diseases, schizophrenia, attention deficit/hyperactivity, and Tourette's syndrome.[3,4] Agonist SIB-1508Y (**5**) and ABT-418 (**6**), as well as other potentially active drugs, are presently in clinical trial for AD and Parkinson's diseases.[5] Several nicotine-derived drug candidates are also being developed for the treatment of nicotine addition, as analgesic and anesthetic agents.[1c,6] Novel competitive antagonist *N*-*n*-nicotinium analogues (**7**) have been, recently, found to possess selective binding to nAChR subtypes depending on the lipophilicity of the alkyl groups, opening a new area of selective antagonists.[7] Moreover, (*S*)-nicotine has been, recently, demonstrated to inhibit amyloid formation by *β*-peptides.[5a,8] Consequently, new nonaddictive nicotine analogues that can prevent or retard the development of Alzheimer's disease will be of interest in the future. (*S*)-Nicotine is more bioactive than the (*R*) enantiomer,[9] as it is also observed for related alkaloid compounds. Surprisingly, appropriate methods for the enantioselective synthesis of nicotinic derivatives are scarce,[3e,f] and usually, the desired enantiomer is obtained by costly resolution methods.[2a] Hence, convenient and versatile asymmetric synthetic methods that permit the introduction of a chiral pyrrolidine-based ring skeleton, offering diverse structural features in the design of new enantiopure nicotinic compound, are needed.

In general, enantioenriched compounds with a stereogenic carbon center α to the amino group are being extensively used as key intermediaries in the synthesis of a large variety of pharmaceuticals,[10] chiral auxiliaries,[11] catalysts,[12] and resolving agents.[13] Accordingly, the development of facile and efficient synthetic strategies that provide highly enantiopure amines at low cost has received, recently, an increasing amount of attention.[14] Organoborane reagents, especially oxazaborolidine–borane complexes, have achieved wide recognition for the asymmetric reduction of ketones due to their outstanding enantioselectivity, predictable absolute stereochemistry, and low environmental impact.[12] Noteworthy, the use of these chiral boron-based reagents for the C=N reduction under catalytic conditions remains limited due to their relatively modest enantioselectivity and lack of reproducibility in some cases.[12–17] Although the asymmetric reduction of oxime ethers with borane-based catalysts offers a facile and direct approach to obtain enantioenriched primary amines, more than an stoichiometric amount of in situ prepared oxazaborolidine has been employed to obtain a high degree of enantioselectivity.[12,14–17] Itsuno et al.[16] described the first catalytic reduction of acetophenone *O*-benzyl oxime using the B-H oxazaborolidine–borane complex prepared in situ by the reaction of 10 mol % of (*S*)-diphenylvalinol with 1 equiv of borane, achieving only 52% ee of (*S*)-1-phenylethanamine. Fontaine et al.[17c] used 2.5 equiv of diphenylvalinol–B-H oxazaborolidine for the reduction of arylalkyl ketoxime *O*-benzyl ethers, achieving excellent enantioselectivity and good yield. When the amount of diphenylvalinol was lowered to 1 equiv in the reduction of *p*-fluoro-2-cyclopropylacetophenone *O*-benzyl oxime, the yield of the corresponding amine decreased to 52%. In addition, previous reports in the literature have demonstrated that the in situ prepared B-H oxazaborolidines present unusual side products that can affect the enantioselectivity of the catalyst.[18] Recently, stable spiroborate esters, derived from (*R*)- or (*S*)-1,1′-bi-2-naphthol and (*S*)-proline, were employed as chirality transfer agents in the borane-mediated reduction of arylalkyl ketoxime ethers.[17e] Nevertheless, 1 equiv of the expensive chiral reagents was necessary to achieve a high degree of stereoselectivity.

We recently disclosed a series of air- and moisture-stable crystalline spiroborate esters, derived from nonracemic 1,2-amino alcohols and ethylene glycol, for the enantioselective reduction of ketones that were fully characterized by optical and spectroscopic methods.[19] Catalysts **8**–**12** (Figure 2) provide a high degree of enantioselectivity in the borane–DMS reduction of aromatic and aliphatic prochiral ketones, at room temperature, in less than 1 h.[19b] In a related

study, enantiopure alcohols containing pyridyl and other heterocyclic fragments were obtained with an excellent yield in up to 99% ee using, in some cases, only 1 mol % of catalyst **12**.[19c]

A preliminary study of catalysts **8**–**12** (Figure 2) in the borane-mediated reduction of aryl ketoximes as catalytic systems for the synthesis of enantiopure primary amines was recently reported.[20] After several optimization studies using different equivalents of borane and borane sources, in addition to a variety of solvents and different temperatures, the asymmetric reduction of (*E*)-acetophenone *O*-benzyl oxime ether was accomplished, with only 10 mol % of catalyst **10** and 4 equiv of borane–THF in dioxane at 0 °C, affording α-methylbenzylamine with an excellent yield and 97% ee. After screening the catalysts presented in Figure 2, it was observed that the reactivity of catalysts **8**, **9**, and **11** was rather low at 0 °C. At room temperature, complete reduction was achieved with catalysts **8** and **9** but provided only 59 and 65% ee, respectively, while catalyst **11** derived from 1-amino-2-indanol afforded the (*R*)-benzylamine enantiomer in 88% ee. Interestingly, 10% of spiroborate **12** derived from diphenylprolinol offers outstanding enantioselectivity for acetophenone reduction, affording the 1-phenylethanol in 99% ee, while it provides modest enantioselectivity (77% ee) for the reduction of its corresponding benzyl oxime ether to the primary amine. Substituents at the ketoxime oxygen play a key role in the reduction stereoselectivity, as illustrated in Table 1. The (*E*)-acetophenone *O*-4-(trifluoromethy)benzyl oxime imparts outstanding enantioselectivity (99% ee), although with a modest yield (entry 4). Excellent enantioselectivity and good chemical yield (entry 5) were achieved for the 2-nitrobenzyl oxime. Unfortunately, *N*-2-nitrobenzyl diphenylvalinol was also isolated from the reaction mixture, possibly formed by the reaction of the 2-nitrobenzylic borate intermediate with the amino group, destroying the expensive amino alcohol. Consequently, benzylic oximes were selected as more adequate substrates since they can also provide excellent enantioselectivity (entry 2) and their synthesis affords pure products using the less expensive benzyl bromide. Besides, the diphenylvalinol can be recovered almost quantitatively after the reduction process. Other representative aromatic and cyclic *O*-benzyl oximes were prepared and reduced, giving excellent enantioselectivities (up to 99% ee) and demonstrating the capability of our developed spiroborate–borane method for an effective asymmetric catalytic reduction of oxime ethers.

As mentioned previously, asymmetric synthesis of nonracemic amines with heterocyclic and heteroaromatic fragments is a key step in the preparation of many biological active compounds. Optically active pyridine-derived amines have attracted a strong interest,[1–9] primarily, due to their existence in naturally occurring compounds, such as tobacco alkaloids,[3a] or as potential drug candidates.[4] To our knowledge, there is a lack of direct methods for the enantioselective synthesis of these compounds. Herein, we describe the first catalytic asymmetric reduction of pyridyl alkyl and heterocyclic *O*-benzyl oxime ethers to obtain amino derivatives with a high degree of enantiopurity and good yield using a simple and convenient process and a further application of the method to the stereoselective synthesis of *N*-ethylnornicotine.

Results and Discussion

It is well-known that the enantioselectivity in the reduction of C=N bonds depends not only on the chirality's transfer agent but also on the *E*/*Z* isomeric purity.[14,15] In a comparative study, Sakito and co-worker[15i] studied the borane-mediated reduction of *E* and *Z* aromatic and aliphatic ketoxime ethers in the presence of (−)-norephedrine, demonstrating that each geometric isomer affords the chiral amine with the opposite absolute configuration (Scheme 1). Since (*E*)-ketoximes are easier to purify by crystallization or column chromatography than their benzylated ethers, our first aim was to prepare pure (*E*)-oximes. Most ketoximes were initially prepared using Na_2CO_3 in EtOH/water at 60–70 °C (method A), affording, mainly, the *E* isomer (>99%). However, in the case of certain pyridyl ketoximes, a significant amount of the *Z* isomer was observed, about 25% for oxime of compound **19** (Scheme 2), possibly

formed by *E*/*Z* isomerization under the heating conditions. To obtain enriched (*E*)-pyridyl ketoxime isomers, pyridine was used as base at room temperature, attaining high yields of the product (90% for oxime of **19**) in a relative short time (3 h) (method B).[21] These oximes were carefully purified by recrystallization or column chromatography to obtain only the *E* isomer.

Excellent yields of the desired (*E*)-oxime benzyl ethers (Scheme 2) were obtained after oxime treatment with NaH and benzyl bromide at low temperature (0 °C) and purified by column chromatography on silica. We have observed that some benzylic oximes isomerize or decompose under vacuum distillation at temperatures over 150 °C.[22,23] Oxime and benzyl oxime isomeric purity was carefully assessed by TLC, NMR, and GC/MS analysis.

(*E*)-Heteroaryl and Heterocyclic *O*-Benzyl Oxime Reduction

The heteroaryl and heterocyclic benzyl oximes (**15a**–**f**, Table 2) were reduced at 0 °C with 0.1 equiv of catalyst **10** and 4 equiv of borane in dioxane until the conversion was completed. After an acidic work up, the corresponding (*S*) primary amines were acetylated with acetic anhydride in the presence of triethylamine and DMAP in dichloromethane. All of the products (**20a**–**f**) were purified by column chromatography, and the enantiomeric excess was determined by GC with a Crompack Chirasil-Dex-CB column, using the optimal condition established with the racemic amide derivative. The enantioselectivity of the reactions was excellent, up to 99% ee for thiochroman-4-amine (entry 5), and with good to high yields of the isolated pure amides.

Pyridyl Ethanone *O*-Benzyl Oximes Reduction

Initially, the reduction of (*E*)-1-(3-pyridyl)ethanone *O*-benzyl oxime (**16a**) in THF with 0.1 mol % of catalyst **10** and 5 equiv of $BH_3 \cdot THF$ for 72 h at 0 °C was carried out according to our previously developed protocol.[20] One equivalent of borane was required for the boron coordination to the pyridyl nitrogen. The extraction of (*S*)-1-(3-pyridyl)ethylamine (**21a**) in ether was unsuccessful, due to the high solubility of the amine in water, and hence the workup procedure was modified. The reaction was first quenched with methanol at 0 °C and then refluxed overnight to hydrolyze the boron amino complex. The desired product **21a** was obtained by a simple solvent removal under vacuum and purification by column chromatography. However, the amine's chemical yield and optical purity were assessed from the acetylated derivative due to the amides' stability and facile resolution by GC. Initially, the corresponding amide (**22a**) was obtained in 92% ee, but the isolated yield was low (entry 1, Table 3). This result encouraged us to further optimize the reaction conditions to improve both the enantioselectivity and chemical yield. Dioxane was the best solvent, although THF and *t*-butyl methyl ether afforded also good selectivity (entries 1–4). By increasing the amount of catalyst to 0.3 equiv and the temperature at 10 °C in dioxane, the reaction time decreased and, fortunately, the amine **22a** was obtained with 75% yield and 98% ee (entry 6). Under similar conditions, the reduction of the 1-(4-pyridyl)ethanone *O*-benzyl oxime (**18a**) gave excellent enantioselectivity (99% ee), with 84% yield of amine **24a** (entry 10). A larger catalytic load did not improve the enantioselectivity or the chemical yield (entry 11).

Our attention was directed to the synthesis of 2-pyridylalkylamine. Initially, 1-(2-pyridyl) ethanone *O*-benzyl oxime was reduced in the presence of 10 mol % of catalyst and THF as solvent, with 5 equiv of $BH_3 \cdot THF$, but the reaction provided a low enantioselectivity (entry 1, Table 4), due to the uncatalyzed reaction that takes place by hydrogen transfer from the borane coordinated to the pyridine nitrogen (Scheme 3). Increasing the amount of borane and catalyst produced modest results. In the presence of 1.0 equiv of catalyst and 4.0 equiv of borane–THF in dioxane at 10 °C, compound **27** was achieved in 73% ee and 79% yield. Attempts to protect the pyridine nitrogen with BEt_3 provided unsatisfactory results (entry 6), and protection with BF_3 afforded only 54% ee, although the yield increased to 73% (entry 7).

Under optimized conditions, a variety of other pyridylalkyl and pyridylphenyl *O*-benzyl oxime ethers were tested to investigate the generality of the reaction. The asymmetric reduction of **16**–**19** was conducted with 30 mol % of catalyst and 5 equiv of borane in dioxane at 10 °C for 2 days. As illustrated in Table 5, excellent enantioselectivities (95–99% ee) were obtained with good to excellent yields of isolated pure products by column chromatography. The enantiomeric excess values of the amine or their acetylated derivatives were determined by GC or HPLC analysis, using suitable chiral stationary phases. The (*S*)-cyclopropyl 3- and 4-pyridyl methanamines (entries 4 and 8) were afforded in 96 and 98% ee, respectively. Noteworthy, the reduction of the 3-pyridyl phenyl oxime ether provided the (*S*)-amine **31** (entry 5) in excellent enantiopurity (95% ee), with the pyridine ring being the larger group and the phenyl the smaller group in the face selectivity. In addition, both *E* and *Z* isomers of cyclopropyl-4-pyridyl *O*-benzylketoxime (**18c**) were separated by chromatography on a silica column and reduced by our established protocol. The *E* isomer produced the (*S*)-amine in 98% ee (entry 8); however, the minor *Z* isomer afforded the (*R*)-amine in only 71% ee.

To demonstrate the capability of our methodology for the synthesis of (*S*)-nicotine analogues, we decided to prepare (*S*)-*N*-ethylnornicotine (**3**) for its biological activity as a potential selective nAChR agonist. Initially, an attempt was made to synthesize racemic nornicotine (**4**) from amine **35** by first removing the protecting TIPS group using TBAF in THF at 0 °C to obtain the amino alcohol **36**, followed by an intramolecular Mitsunobu[24] reaction, as indicated in Scheme 4. However, the cyclization step gave a complex mixture of products. As an alternative, (*S*)-*N*-ethylnornicotine (**3**) was successfully prepared from compound (*S*)-**34**, previously synthesized in 95% ee (HPLC analysis). The amino alcohol (*S*)-**37** was afforded in 89% yield, after deprotection with TBAF in THF at 0 °C and subsequent reduction with borane providing *N*-ethylamine **38** in 86% yield. The desired pyrrolidine derivative **3** was furnished in 84% yield after a successful intramolecular cyclization of (*S*)-**38** with Ph_3P/DIAD.[25] In summary, the synthesis of (*S*)-*N*-ethylnornicotine was achieved with excellent enantiopurity (97% ee determined by GC) and 64% overall yield. This approach opens the door to the highly enantioselective synthesis of other important biological targets in a facile and efficient way.

Conclusion

We have investigated the effect of heteroaryl and heterocyclic groups in the asymmetric borane reduction of *O*-benzyl oxime ethers with the novel spiroborate **10** derived from diphenylvalinol and ethylene glycol as catalyst. A true catalytic and practical synthesis of a variety of chiral primary amines containing heterocyclic and heteroaryl rings with a high degree of enantioselectivity with only 10% of spiroborate **10** was developed. After several optimization studies, the first borane reduction of a variety of pyridyl benzyl oximes afforded enantiopure amines in up to 99% ee, using 30% of **10** at 10 °C. The (*S*)-nicotine analogue **3** was prepared in 97% ee from enantiopure **34** with 64% overall yield. Considering the convenience and generality of the method and the abundance of natural products that contain the heterocyclic amine functionality, this method should find wide interest in both academic research and industry.

Experimental Section

Catalyst, [19] (*R*)-2-amino-1,1,2-triphenylethanol,[26] (*S*)-2-amino-1,1,2-triphenylethanol, [26] (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol,[27] cyclopropylpyridin-3yl methanone,[28] cyclopropylpyridin-4yl methanone,[28] and 4-hydroxy-1-pyridin-3-yl butan-1-one[29] were synthesized according to literature procedures. $BH_3 \cdot THF$ (1 M solution in THF, stabilized with <0.005 M $NaBH_4$) and other starting materials and chemical reagents were purchased and used without purification unless otherwise noted.

General Procedure for the Preparation of *O*-Benzyl Oximes

To a suspension of NaH (1.1 equiv) in DMF was added dropwise a solution of hydroxyl oxime (1.0 equiv) and maintaining the temperature at 0 °C. After the addition, the reaction mixture was stirred for 1 h. Then, BnBr (1.05 equiv) in DMF was added dropwise at 0 °C. The resulting mixture was stirred overnight at rt and then quenched with saturated aqueous NH_4Cl solution and extracted with ether. The organic phases were combined and dried over anhydrous Na_2SO_4. The solvents were evaporated under vacuum, and the residue was purified by flash silica gel column chromatography.

(*E*)-1-(Thiophen-3-yl)ethanone *O*-Benzyl Oxime (15a)

Purified by column chromatography on silica gel/hexane: AcOEt (30:1) as a colorless oil; 94% (6.1 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 5.27 (s, 2H), 7.3–7.5 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 76.7, 123.4, 125.4, 126.1, 127.8, 128.2, 128.4, 138.2, 139.0, 151.3 ppm; IR ν (cm^{-1}) 3031, 2922, 1601, 1454, 1363, 1015, 734, 755; GC-MS *m*/*z* 231.0 (M^+). Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found: C, 67.67; H, 5.71; N, 6.17.

(*E*)-1-(2,5-Dimethylthiophen-3-yl)ethanone *O*-Benzyl Oxime (15b)

Purified by column chromatography on silica gel/hexane: AcOEt (30:1) as a colorless oil; yield 92% (2.10 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.44 (s, 3H), 2.46 (s, 3H), 5.24 (s, 2H), 6.72 (s, 1H), 7.3–7.5 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 15.1, 15.2, 75.9, 125.5, 127.7, 128.1, 128.3, 133.3, 135.4, 135.8, 138.5, 153.0 ppm; IR ν (cm^{-1}) 3031, 2919, 2857, 1604, 1496, 1454, 1364, 1266, 1208, 1181, 1143, 1081, 1048, 1012, 985, 924, 882, 833, 733, 696; GC-MS *m*/*z* 259.0 (M^+). Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found: C, 69.71; H, 6.66; N, 5.41.

(*E*)-6-Chlorochroman-4-one *O*-Benzyl Oxime (15d)

Purified by column chromatography on silica gel/hexane: AcOEt (9:1) as an oil with a slight yellow color; yield: 84% (1.62 g);^{1}H NMR (400 MHz, $CDCl_3$) δ 2.98 (t, 2H, J = 6.0 Hz), 4.24 (t, 2H, J = 6.0 Hz), 5.29 (s, 2H), 6.9 (m, 1H), 7.39 (m, 1H), 7.43 (m, 5H), 7.92 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 24.0, 65.1, 76.7, 119.1, 119.8, 123.8, 126.6, 128.0, 128.2, 128.4, 130.7, 137.6, 147.7, 155.1 ppm; IR ν (cm^{-1}) 3031, 2928, 1618, 1475, 1452, 1425, 1364, 1284, 1250, 1216, 1094, 1068, 1039, 1014, 962, 814, 732; GC/MS *m*/*z* 287.0 (M^+), 91.1 ($PhCH_2^+$). Anal. Calcd for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; N, 4.87. Found: C, 67.03; H, 4.89; N, 4.85.

(*E*)-Thiochroman-4-one *O*-Benzyl Oxime (15e)

Purified by column chromatography on silica gel/hexane: AcOEt (9:1) as an oil with a slight yellow color; yield 84% (1.89 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99 (t, 2H, J = 6.0 Hz), 3.21 (t, 2H, J = 6.0 Hz), 5.32 (s, 2H), 7.2 (m, 1H), 7.3 (m, 2H), 7.44 (m, 5H), 8.0 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 26.9, 76.6, 25.4, 126.2, 127.9, 128.2, 128.3 128.4, 129.1, 129.8, 135.9, 137.9, 152.3 ppm; IR ν (cm^{-1}) 3059, 2921, 1598, 1495, 1468, 1433, 1364, 1330, 1286, 1245, 1208, 1007, 931, 907, 751, 695; GC/MS *m*/*z* 269.0 (M^+), 91.1 ($PhCH_2^+$). Anal. Calcd for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.21. Found: C, 71.45; H, 5.66; N, 5.30.

(*E*)-6-Chlorothiochroman-4-one *O*-Benzyl Oxime (15f)

Purified by column chromatography on silica gel/hexane: AcOEt (9:1) as an oil with a slight yellow color; yield 82% (2.82 g);^{1}H NMR (400 MHz, $CDCl_3$) δ 2.98 (t, 2H, J = 6.0 Hz), 3.18 (t, 2H, J = 6.0 Hz), 5.32 (s, 2H), 7.32 (m, 2H), 7.41 (m, 5H), 8.06 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 26.4, 77.0, 125.8, 128.1, 128.2, 128.5, 129.0, 129.4, 131.1, 131.2, 134.2, 137.6, 151.2 ppm; IR ν (cm^{-1}) 2922, 1573, 1496, 1455, 1394, 1364, 1305, 1240, 1099, 1048,

1009, 940, 889, 796, 725, 695; GC/MS *m*/*z* 303.0 (M^+), 91.1 ($PhCH_2^+$). Anal. Calcd for $C_{16}H_{14}ClNOS$: C, 63.25; H, 4.64; N, 4.61. Found: C, 63.50; H, 4.66; N, 4.67.

(*E*)-1-(Pyridine-3-yl)propan-1-one *O*-Benzyl Oxime (16b)

Purified by column chromatography on silica gel/hexane: AcOEt (2: 1) as a colorless oil; yield 80% (0.96 g); ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, 3H, J = 7.6 Hz), 2.86 (q, 2H, J = 7.6 Hz), 5.29 (s, 2H), 7.3–7.5 (m, 6H), 7.98 (m, 1H), 8.6 (m, 1H), 8.9 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 19.9, 76.5, 123.3, 127.9, 128.2, 128.4, 131.3, 133.5, 137.9, 147.7, 150.0, 157.6 ppm; IR ν (cm^{-1}) 3032, 2972, 2937, 2877, 1604, 1454, 1412, 1365, 1018, 982, 951, 905, 876, 808, 747; GC-MS *m*/*z* 240.2 (M^+). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.06; H, 6.76; N, 11.63.

(*E*)-1-(6-Methoxypyridin-3-yl)ethanone *O*-Benzyl Oxime (16c)

Purified by column chromatography on silica gel/hexane: AcOEt (2:1) as a colorless oil; yield 90% (1.41 g); ^1H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 4.00 (s, 3H), 5.27 (s, 2H), 6.8 (m, 1H), 7.4–7.5 (m, 5H), 7.97 (m, 1H), 8.4 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 53.6, 76.0, 110.7, 125.9, 127.8, 128.2, 128.4, 136.2, 138.0, 144.8, 152.4, 164.6 ppm; IR ν (cm^{-1}) 3026, 2947, 2897, 1726, 1601, 1499, 1452, 1376, 1285, 1020, 928, 900, 833, 738, 698; GC-MS *m*/*z* 256.1 (M^+). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.01; H, 6.27; N, 10.56.

(*E*)-Cyclopropyl(pyridine-3-yl)methanone *O*-Benzyl Oxime (16d)

Purified by column chromatography on silica gel/hexane: AcOEt (2:1) as a colorless oil; yield 88% (0.89 g); ^1H NMR (400 MHz, $CDCl_3$) δ 0.69 (m, 2H), 1.0 (m, 2H), 2.3 (m, 1H), 5.28 (s, 2H), 7.3–7.5 (m, 6H), 7.8 (m, 1H), 8.6 (m, 1H), 8.7 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.8, 9.77, 76.3, 122.9, 127.9, 128.1, 128.4, 130.5, 135.6, 137.8, 149.3, 149.7, 158.2 ppm; IR ν (cm^{-1}) 3087, 3031, 2924, 2869, 1592, 1564, 1497, 1475, 1455, 1412, 1365, 1327, 1083, 1022, 981, 938, 808,734; GC-MS *m*/*z* 252.1 (M^+). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.02; H, 6.39; N, 11.00.

(*E*)-1-(Pyridine-4-yl)propan-1-one *O*-Benzyl Oxime (18b)

Purified by column chromatography on silica gel/hexane: AcOEt (2:1) as a colorless oil; yield 90% (1.08 g); ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, 3H, J = 7.6 Hz), 2.8 (q, 2H, J = 7.6 Hz), 5.31 (s, 2H), 7.4–7.5 (m, 5H), 7.6 (m, 2H), 8.7 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 19.5, 76.7, 120.4, 128.0, 128.2, 128.4, 137.7, 142.9, 150.2, 157.7 ppm; IR ν (cm^{-1}) 3031, 2976, 2936, 2877, 1591, 1454, 1409, 1366, 1015, 992, 979, 922, 824, 740; GC-MS *m*/*z* 240.2 (M^+). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.21; H, 6.78; N, 11.65.

(*E*)-Cyclopropyl(pyridine-4-yl)methanone *O*-Benzyl Oxime ($18c_E$)

Purified by column chromatography on silica gel/hexane: AcOEt (2:1) as a colorless oil; yield 94% (1.32 g); ^1H NMR (400 MHz, $CDCl_3$) δ 0.73 (m, 2H), 1.0 (m, 2H), 2.2 (m, 1H), 5.29 (s, 2H), 7.3–7.5 (m, 7H), 8.6 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.1, 9.4, 77.0, 122.5, 127.9, 128.1, 128.4, 137.7, 142.6, 149.8, 158.1 ppm; IR ν (cm^{-1}) 3066, 3031, 2930, 2876, 1588, 1541, 1496, 1454, 1408, 1365, 1210, 1083, 984, 940, 909, 820, 697; GC-MS *m*/*z* 252.2 (M^+). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.08; H, 6.40; N, 11.04.

(*E*)-1-(Pyridine-3-yl)-4-(triisopropylsilyloxy)butan-1-one *O*-Benzyl Oxime (19)

Purified by column chromatography on silica gel/hexane: AcOEt (2:1) as a colorless oil; yield 93% (1.98 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04–1.14 (m, 21H), 1.85 (m, 2H), 2.93 (m, 2H), 3.77 (t, 2H, J = 6.4 Hz), 5.29 (s, 2H), 7.3–7.5 (m, 6), 8.02 (m, 1H), 8.63 (m, 1H), 8.96 (d, 1H, J = 2.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 18.0, 23.2, 29.7, 62.8, 76.3, 123.2, 127.8, 128.2, 128.4, 131.6, 133.6, 137.9, 147.8, 149.9, 156.5 ppm; IR v (cm^{-1}) 3065, 3031, 2928, 2877, 1619, 1475, 1455, 1425, 1283, 1250, 1216, 1095, 1040, 1014, 962, 815, 696. Anal. Calcd for $C_{25}H_{38}N_2O_2Si$: C, 70.38; H, 8.98; N, 6.57. Found: C, 70.11; H, 9.02; N, 6.38.

General Procedure for Asymmetric Reduction of Thiofuranyl and Heterocyclic *O*-Benzyl Oximes with Spiroborate 10

To a 25 mL two-necked flask under N_2 was added catalyst **10** (33 mg, 0.1 mmol). Then, anhydrous dioxane (10 mL) was introduced, and $BH_3 \cdot THF$ (4 mL, 1 M in THF stabilized with <0.005 M $NaBH_4$) was added in one portion. The resulting mixture was stirred at rt for 30 min until a transparent solution was observed. The solution was cooled at 0 °C, and the benzyl oxime (1 mmol) in dioxane (5 mL) was added dropwise during 1.5 h by a syringe pump. The resulting mixture was stirred at 0 °C until the conversion was completed in about 48 h. Then, the reaction was quenched with 6 N HCl and then 6 N NaOH until the solution was basic. It was extracted with ether, and the combined organic phase was washed with a saturated NaCl solution and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was analyzed by GC for amine conversion and then used directly to form the acetylated derivatives for GC analysis on a chiral column. The acetamide derivatives of racemic amines were first prepared by reduction of the benzyl oximes with borane and used as standard samples for chiral GC analysis. Generally, the ee was determined using a Crompack Chirasil-Dex-CB GC column (30 m × 0.25 mm × 0.25μm), with a He flow at a 1.0 mL/min rate and an initial temperature of 70 °C for 10 min, followed by a 5 °C/min ramp until 190 °C, and maintaining this temperature for about 25 min, depending on the particular compound.

(*S*)-*N*-(1-(Thiophen-3-yl)ethyl)acetamide (20a)

Purified by column chromatography on silica gel/hexane: AcOEt (1:1) as a white solid; yield 85% (144 mg); mp 69–71 °C; 98% ee; $[\alpha]^{20}_D$ = −120° (c 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (d, 3H J = 6.8 Hz), 2.03 (s, 3H), 5.3 (m, 1H), 5.73 (s, 1H), 7.19 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 23.5, 44.1, 120.7, 126.3, 126.5, 144.4, 169.0 ppm; IR v (cm^{-1}) 3285, 3095, 3079, 2968, 1629, 1545, 1446, 1417.18, 1367, 1274, 1214, 1167, 1121, 1050 971, 862, 784, 731, 693; GC/MS m/z 169.0 (M^+); HRMS m/z 170.0631 $(M + H)^+$.

(*S*)-*N*-(1-(2,5-Dimethylthiophen-3-yl)ethyl)acetamide (20b)

Purified by column chromatography on silica gel/hexane: AcOEt (1: 1) as a white solid; yield 92% (169 mg); mp 102–104 °C; 96% ee; $[\alpha]^{20}_D$ = −117.5° (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, 3H, J = 6.8 Hz), 1.99 (s, 3H), 2.41 (s, 3H), 2.45 (s, 3H), 5.1 (m, 1H), 5.58 (s, 1H), 6.62 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 15.2, 21.7, 23.4, 43.0, 123.1, 132.7, 136.4, 138.3, 168.7; IR v (cm^{-1}) 3278, 3064, 2972, 2919, 2869, 1635, 1544, 1442, 1368, 1334, 1311, 1274, 1222, 1132, 1108, 1035, 968, 824, 733; GC-MS m/z 197.0 (M^+). HRMS m/z 198.0944 $(M + H)^+$.

(*S*)-*N*-(6-Chlorochroman-4-yl)acetamide (20d)

Purified by column chromatography on silica gel/hexane: AcOEt (1:1) as a white solid; yield 73% (0.161 g); mp 188–190 °C; 95% ee; $[\alpha]^{20}_D$=−56.4° (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.0–2.1 (m, 1H), 2.09 (s, 3H), 2.1 (m, 2H), 4.2–4.3 (m, 2H), 5.2 (m, 1H), 5.80 (s, 1H), 6.8 (m, 1H), 7.2 (m, 1H), 7.19 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 28.8, 43.6, 63.6, 118.7, 123.6, 125.6, 128.6, 129.3, 153.8, 169.4 ppm; IR v (cm^{-1}) 3265, 3083, 2984,

1634, 1537, 1483, 1411, 1370, 1261, 1222, 1193, 1107, 1022, 993, 878, 814, 751, 677; GC/MS *m*/*z* 225.1 (M^+), 167.0 (M^+ – NHAc); HRMS *m*/*z* 226.0627 $(M + H)^+$.

(*S*)-*N*-(Thiochroman-4-yl)acetamide (20e)

Purified by column chromatography on silica gel/hexane: AcOEt (1:1) as a white solid; yield 71% (0.150 g); mp 186–188 °C; 99% ee; $[\alpha]^{20}_D = -134.6°$ (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.15 (m, 1H), 2.4 (m, 1H), 3.0–3.14 (m, 2H), 5.22 (s, 1H), 5.91, (s, 1H), 7.1 (m, 1H), 7.26 (m, 2H), 7.2 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 22.7, 23.4, 28.1, 46.8, 124.5, 125.5, 126.8, 130.5, 132.6, 133.5, 169.1 ppm; IR *v* (cm^{-1}) 3191, 3034, 2944, 2837, 1632, 1532, 1476, 1431, 1369, 1322, 1277, 1199, 1095, 944, 796, 753; GC/MS 207.0 (M^+), 149.0 (M^+ – NHAc); HRMS *m*/*z* 208.0788 $(M + H)^+$.

(*S*)-*N*-(6-Chlorothiochroman-4-yl)acetamide (20f)

Purified by column chromatography on silica gel/hexane: AcOEt (1:1) as a white solid; yield 70% (0.167 g); mp 190–192 °C; 94% ee; $[\alpha]^{20}_D = -107.6°$ (*c* 1.00, $CHCl_3$);^1H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.1–2.3 (m, 1H), 3.0 (m, 2H), 5.2 (m, 1H), 5.91 (s, 1H), 7.1(m, 1H), 7.14 (m, 1H), 7.3 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 23.4, 28.1, 46.6, 76.7, 128.1, 128.3, 129.9, 132.1, 134.2, 169.2; IR *v* (cm^{-1}) 3269, 3048, 2940, 1635, 1532, 1463, 1427, 1367, 1186, 1098, 1054, 944, 887, 811, 730; GC/MS *m*/*z* 241.1 (M^+), 183.0 (M^+ – NHAc); HRMS *m*/*z* 242.0399 $(M + H)^+$.

General Procedure for Asymmetric Reduction of Pyridyl *O*-Benzyl Oximes with Catalyst 10

To a dried 50 mL reaction tube under N_2 was added catalyst **10** (50 mg, 0.15 mmol, 0.3 equiv) at room temperature. Then, anhydrous dioxane (4 mL) was introduced, and $BH_3 \cdot THF$ (2.5 mL, 1.0 M in THF stabilized with <0.005 M $NaBH_4$) was added. The resulting mixture was stirred at room temperature for 1 h until a clear solution formed. The oxime benzyl ether (0.5 mmol, 1.0 equiv) in 4 mL of dioxane was added dropwise by syringe pump for 1 h. The resulting mixture was stirred for 2 days at 10 °C under nitrogen. The reaction mixture was quenched with methanol (5 mL) at 0 °C and then refluxed overnight. The solvents were evaporated under vacuum, and the residue was directly acetylated, in most cases, to form the amide derivatives. To a solution of crude amine in anhydrous CH_2Cl_2 (10 mL) were added DMAP (13 mg, 10%), Et_3N (0.2 mL, 1 mmol, 2.0 equiv) and acetic anhydride (0.11 mL, 1.0 mmol, 2.0 equiv). The resulting mixture was stirred for 3 h. The solvent was removed under water pump and then under high vacuum. The residue was purified directly by flash chromatography on a silica gel column, eluted first by ether and then by CH_2Cl_2/CH_3OH (10/1), giving the corresponding products. As indicated previously, the enantiomeric excess was determined by GC with a chiral column, using a Crompack Chirasil-Dex-CB GC column (30 m × 0.25 mm × 0.25 μm), with He flow at a 1.0 mL/min rate isothermal at 140–160 °C or with a gradient at an initial temperature of 80–120 °C for 5–15 min, followed by a 2–5 °C/min ramp until 130–170 °C, and maintaining this temperature for about 35–100 min, depending on the particular compound. Generally, the HPLC enantiomeric analysis was carried out with a Chiralcel-IB or OD-H columns (0.46 cm × 25 cm) with a 0.5 mL/min flow of 90% hexane/10% 2-propanol for 100 min or at 0.4 mL/min flow with 95% hexane/5% 2-isopropanol for 60 min, using a UV detector at 254 nm.

(*S*)-*N*-(1-(Pyridine-3-yl)propyl)acetamide (28)

Purified by column chromatography on silica gel/CH_2Cl_2: CH_3OH (10:1) as a colorless oil; yield 89% (80 mg); 99% ee; $[\alpha]^{20}_D = -109.7°$ (*c* 1.30, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J* = 7.6 Hz), 1.88 (m, 2H, *J* = 7.6 Hz), 2.05 (s, 3H), 4.95 (m, 1H, *J* = 7.6 Hz), 6.10 (s, 1H), 7.29 (m, 1H), 7.6 (m, 1H), 8.5 (m, 1H), 8.60 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7, 23.3, 28.8, 53.0, 123.5, 134.5, 137.8, 148.4, 148.7, 169.5; IR *v* (cm^{-1}) 3259,

3060, 2968, 2933, 2877, 1647, 1544, 1373, 1301, 1137, 1027, 795, 693 ppm; GC-MS *m*/*z* 178.1 (M^+); HRMS *m*/*z* 179.1175 $(M + H)^+$.

(*S*)-*N*-(1-(6-Methoxypyridine-3-yl)ethyl)acetamide (29)

Purified by column chromatography on silica gel/CH_2Cl_2: CH_3OH (10: 1) as a white solid; yield 88% (85 mg); mp 66–67 °C; 98% ee; $[\alpha]^{20}_D = -63.5°$ (*c* 1.85, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, 3H, *J* = 6.8 Hz), 2.01 (s, 3H), 3.95 (s, 3H), 5.1 (m, 1H), 5.92 (s, 1H), 6.7 (m, 1H), 7.6 (m, 1H), 8.16 (d, 1H, *J* = 2.0 Hz) ppm; ^{13}CNMR (100 MHz, $CDCl_3$) δ 21.3, 23.4, 46.3, 53.5, 110.9, 131.4, 137.2, 144.6, 163.6, 169.2 ppm; IR *v* (cm^{-1}) 3277, 2988, 1629, 1539, 1500, 1430, 1384, 1293, 1258, 1120, 1019, 972, 826, 744; GC-MS *m*/*z* 194.1 (M^+); HRMS *m*/*z* 195.1123 $(M + H)^+$.

(*S*)-*N*-(Cyclopropyl(pyridine-3-yl)methyl)acetamide (30)

Purified by column chromatography on silica gel/CH_2Cl_2: CH_3OH (10: 1) as a white solid; yield 83% (157 mg); mp 122–123 °C; 96% ee; $[\alpha]^{20}_D = -32.5°$ (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.41 (m, 1H), 0.52 (m, 1H), 0.69 (m, 2H), 1.19 (m, 1H), 2.07 (s, 3H), 4.4 (m, 1H, CH), 6.2 (s, 1H), 7.3 (m, 1H), 7.7 (m, 1H), 8.5 (d, 1H, *J* = 3.6 Hz), 8.68 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.9, 4.2, 16.4, 23.3, 55.5, 123.4, 134.4, 137.7, 148.3, 148.6, 169.4 ppm; IR *v* (cm^{-1}) 3244, 3062, 3004, 2928, 2849, 1630, 1546, 1426, 1372, 1298, 1194, 1162, 1104, 1091, 1020, 948, 845, 807, 715; GC-MS *m*/*z* 190.1 (M^+); HRMS *m*/*z* 191.1174 $(M + H)^+$.

(*S*)-*N*-(1-(Pyridine-4-yl)propyl)acetamide (32)

Purified by column chromatography on silica gel/CH_2Cl_2: CH_3OH (10:1) as a colorless oil; yield 85% (76 mg); 96% ee; $[\alpha]^{20}_D = -114°$ (*c* 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, 3H, *J* = 7.6 Hz), 1.84 (m, 2H, *J* = 7.6 Hz), 2.08 (s, 3H), 4.93 (m, 1H, *J* = 7.6 Hz), 5.87 (s, 1H), 7.23 (dd, 2H, *J* = 1.6, 6.0 Hz), 8.6 (dd, 2H, *J* = 1.6, 6.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 23.3, 28.6, 54.0, 121.7, 150.1, 169.8 ppm; IR *v* (cm^{-1}) 3259, 3056, 2968, 2936, 2877, 1648, 1601, 1543, 1415, 1372, 1299, 1178, 999, 825, 789; GC-MS *m*/*z* 178.1 (M^+); HRMS *m*/*z* 179.1175 $(M + H)^+$.

(*S*)-*N*-(Cyclopropyl(pyridine-4-yl)methyl)acetamide (33)

Purified by column chromatography on silica gel/CH_2Cl_2: CH_3OH (10: 1) as a white solid; yield 91% (176 mg); mp 78–80 °C; 98% ee; $[\alpha]^{20}_D = -15.6°$ (*c* 1.25, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 0.49 (m, 2H), 0.72 (m, 2H), 1.14 (m, 1H), 2.10 (s, 3H), 4.37 (m, 1H), 6.20 (s, 1H), 7.32 (d, 2H, *J* = 6.0 Hz), 8.60 (dd, 2H, *J* = 1.6, 6.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.77, 4.42, 16.3, 23.3, 56.7, 121.7, 150.0, 151.0, 169.5 ppm; IR *v* (cm^{-1}) 3276, 3080, 3006, 1649, 1598, 1542, 1432, 1410, 1371, 1312, 1289, 1221, 1200, 1105, 1052, 1023, 957, 850, 820, 808, 737; GC-MS *m*/*z* 190.2 (M^+); HRMS *m*/*z* 191.1174 $(M + H)^+$.

(*S*)-*N*-(1-(Pyridine-3-yl)-4-(triisopropylsilyloxy)butyl)acetamide (34)

Purified by column chromatography on silica gel/CH_2Cl_2: CH_3OH (10:1) as a colorless oil; yield 91% (331 mg); 95% ee by HPLC; $[\alpha]^{20}_D = -109.7°$ (*c* 1.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.07–1.18 (m, 21H), 1.56 (m, 2H), 1.94 (m, 2H), 2.04 (s, 3H), 3.75 (m, 2H), 5.04 (m, 1H), 6.15 (s, 1H), 7.3 (m, 1H), 7.6 (m, 1H), 8.53 (t, 1H), 8.6 (d, 1H, *J* = 2.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 18.0, 23.3, 29.3, 32.1, 51.4, 62.5, 123.5, 134.3, 138.0, 148.3, 148.6, 169.4 ppm; IR *v* (cm^{-1}) 3278, 3054, 2942, 2865, 1648, 1546, 1463, 1428, 1372, 1292, 1099, 1068, 1012, 995, 881, 796, 714, 680; GC-MS *m*/*z* 364.2 (M^+); HRMS m/z 365.2614 $(M + H)^+$, calcd for $C_{20}H_{37}O_2N_2$28Si *m*/*z* 365.2619.

(*S*)-*N*-(4-Hydroxy-1-(pyridine-3-yl)butyl)acetamide (37)

To a round-bottom flask was added a solution of **34** (364 mg, 1.0 mmol) in THF (10 mL). The solution was cooled with an ice-bath, and Bu_4NF (1.5 mL, 1.0 M in THF) was added dropwise. The mixture was stirred for 2 h until **37** was consumed. Solvents were removed under vacuum, and the residue was purified by chromatography on a silica gel column, eluted with CH_2Cl_2: CH_3OH (5: 1). The product was obtained as a colorless oil; yield 89% (186 mg); $[\alpha]^{20}_D = -92°$ (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (m, 2H), 1.92 (m, 2H), 1.99 (s, 3H), 3.41 (br, 1H), 3.67 (m, 2H), 5.01 (m, 1H), 7.28 (m, 2H), 7.68 (d, 1H, *J* = 7.6 Hz), 8.47 (d, 1H, *J* = 4.0 Hz), 8.57 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 29.0, 32.5, 51.3, 61.7, 123.7, 134.8, 138.5, 148.0, 148.2, 170.2 ppm; IR *v* (cm^{-1}) 3265, 3056, 2931, 2861, 1647, 1543, 1479, 1428, 1372, 1299, 1102, 1058, 1041, 806, 747, 713; GC-MS *m*/*z* 208.1 (M^+); HRMS *m*/*z* 209.1281 $(M + H)^+$, calcd for $C_{11}H_{17}O_2N_2$ *m*/*z* 209.1284.

(*S*)-4-(*N*-Ethylamino)-4-(pyridin-3-yl)butan-1-ol (38)

To a dried two-neck flask at room temperature under nitrogen was added **37** (180 mg, 0.87 mmol) in 10 mL of THF and $BH_3 \cdot THF$ (2.6 mL, 1.0 M in THF, stabilized with <0.005 M $NaBH_4$). The solution was refluxed for 3.5 h. Then, the mixture was cooled with an ice-bath, and 5 mL of MeOH was added dropwise to quench the borane. The resulting mixture was refluxed overnight. The solvents were evaporated under reduced pressure, and the residue was directly purified by chromatography on a silica gel column eluted with CH_2Cl_2:CH_3OH (4:1). The product was obtained as a colorless oil; yield 86% (145 mg); $[\alpha]^{20}_D = -37°$ (*c* 2.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, 3H, *J* = 7.2 Hz), 1.67 (m, 2H), 1.85 (m, 2H), 2.53 (q, 2H, *J* = 7.2 Hz), 3.0 (br, 1H), 3.7 (m, 3H), 7.32 (m, 1H), 7.6 (m, 1H), 8.5 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 30.5, 36.2, 41.6, 60.9, 62.7, 123.6, 134.3, 139.3, 148.7, 148.9 ppm; IR *v* (cm^{-1}) 3268, 2932, 2861, 1655, 1578, 1426, 1379, 1320, 1268, 1104, 1060, 1027, 928, 808, 715; GC-MS *m*/*z* 194.0 (M^+); HRMS *m*/*z* 195.1490 $(M + H)^+$, calcd for $C_{11}H_{19}O_1N_2$ 195.1492.

(*S*)-3-(1-Ethylpyrrolidin-2-yl)pyridine[30] (3)

To a dried three-neck round-bottom flask containing PPh_3 (393 mg, 1.5 mmol), $Et_3N \cdot HCl$ (104 mg, 0.75 mmol), and compound **38** (145 mg, 0.75 mmol) in anhydrous CH_2Cl_2 (30 mL) under nitrogen was added a solution of diisopropyl azodicarboxilato (DIAD) (303 mg, 1.5 mmol) in anhydrous CH_2Cl_2 (10 mL) dropwise at −20 °C. The reaction was monitored by TLC until the starting material was totally consumed (around 3 h). When the reaction was completed, water (15 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4. The solvents were removed under vacuum, and the residue was purified by chromatography on silica gel eluted with CH_2Cl_2:CH_3OH (95:5). The product was obtained as a colorless oil; yield 84% (110 mg); 97% ee by GC; $[\alpha]^{20}_D = -139°$ (*c* 2.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, 3H, *J* = 7.2 Hz), 1.73 (m, 1H), 1.85 (m, 1H), 2.0 (m, 1H), 2.12 (m, 1H), 2.25 (m, 2H), 2.64 (m, 1H), 3.27 (m, 1H), 3.4 (m, 1H), 7.28 (m, 1H), 7.7 (m, 1H), 8.5 (m, 1H), 8.6 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.5, 35.1, 48.2, 53.2, 67.5, 123.5, 134.9, 139.6, 148.5, 149.6 ppm; GC-MS *m*/*z* 176.1 (M^+).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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22. Purification of oxime benzyl ethers by vacuum distillation should be avoided since they isomerize and decompose under heating by a reverse radical disproportionation.23

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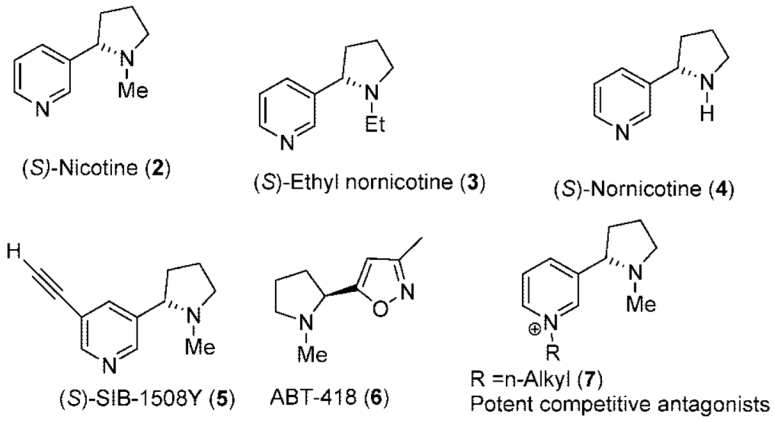


Figure 1.
Nicotine and analogues.

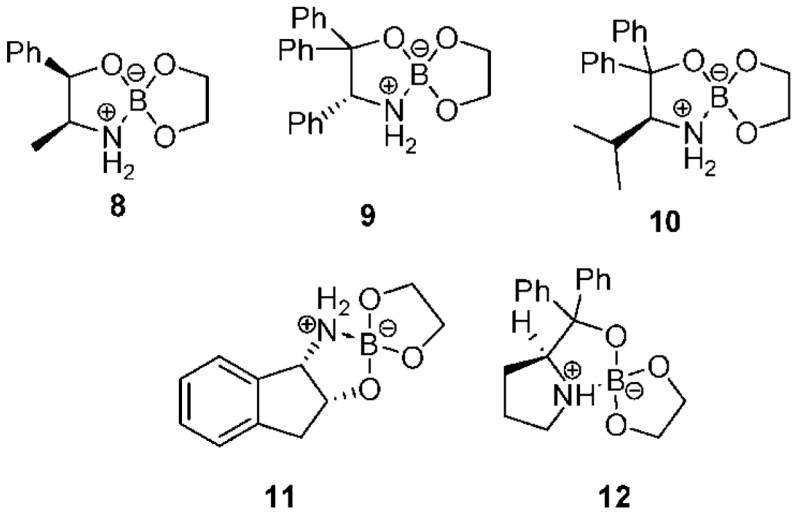
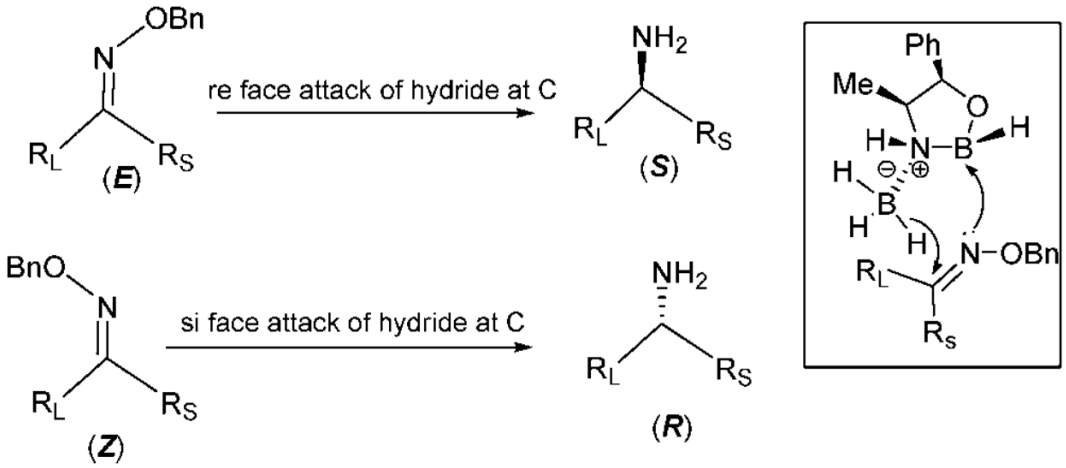
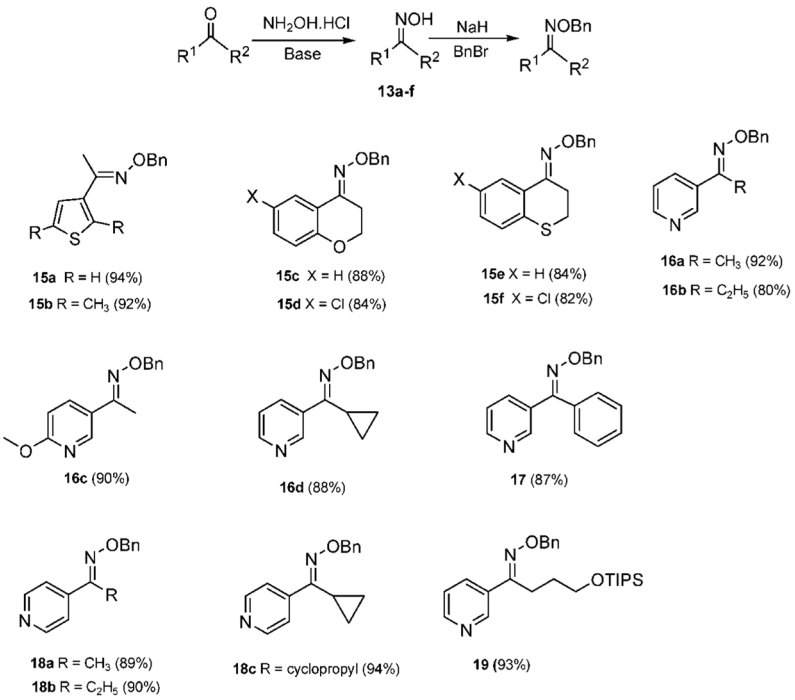


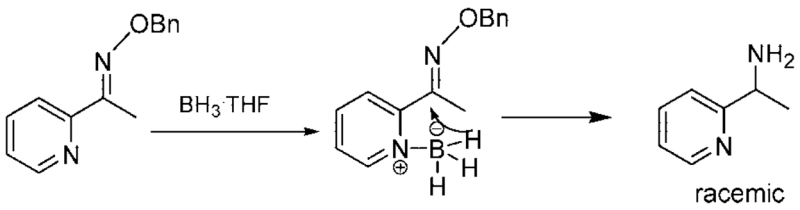
Figure 2.
Spiroborate esters derived from nonracemic amino alcohols and ethylene glycol.



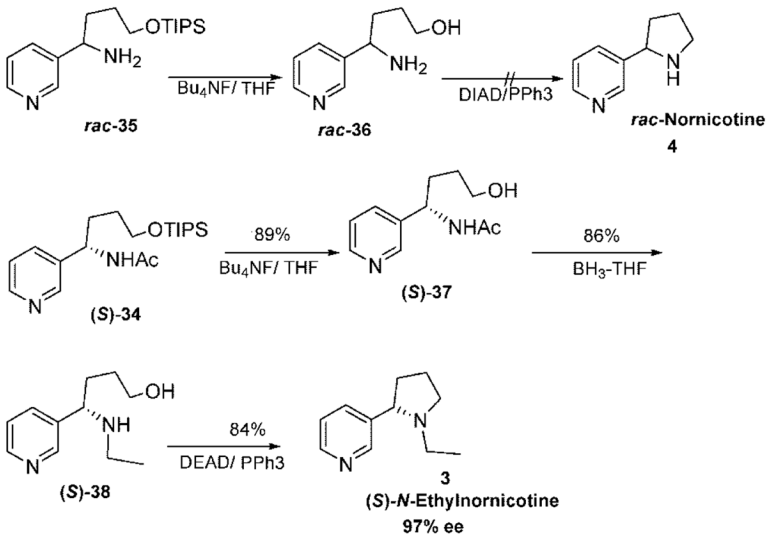
Scheme 1.
Stereoselectivity in the Borane Reduction of Oxime Ethers with (*S*)-Norephedrine



Scheme 2.
Synthesis of (*E*)-*O*-Benzyl Ketoxime Ethers



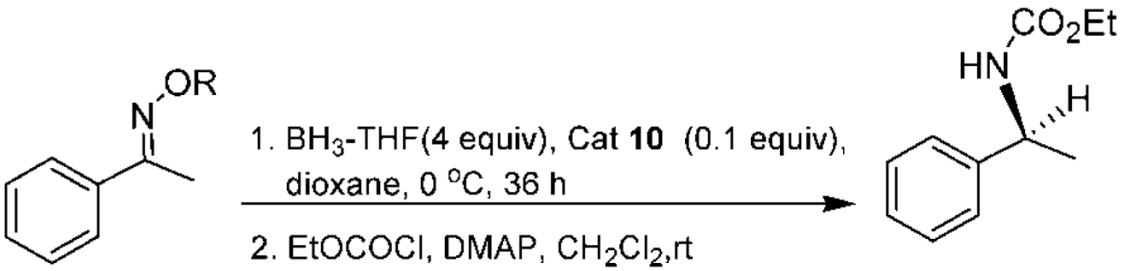
Scheme 3.
Intramolecular Uncatalyzed Reduction of 25



Scheme 4.
Enantioselective Synthesis of the (*S*)-Nicotine Analogue

Table 1

Catalyzed Asymmetric Reduction of Acetophenone *O*-Substituted Oxime Ethers



entry	oxime	R	yield (%)[a,b]	ee (%)[c]
1	**a**	Me	85	95
2	**b**	Bn	77	97
3	**c**	4-MeOBn	70	97
4	**d**	4-CF_3Bn	60	99
5	**e**	2-NO_2Bn	95	97

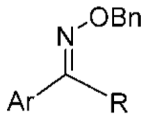
[a] Borane was stabilized with <0.005 M *N*-isopropyl *N*-methyl *tert*-butylamine.

[b] Isolated yield after purification by column chromatography.

[c] The ee was analyzed using a Crompack Chirasil-Dex-CB GC column.

Table 2

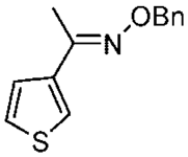
Asymmetric Reduction of (*E*)-Heteroaryl and Heterocyclic *O*-Benzyl Oximes

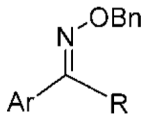


15a-f

1. cat. **10** (0.1
dioxane, 0 °

2. Ac_2O, DM

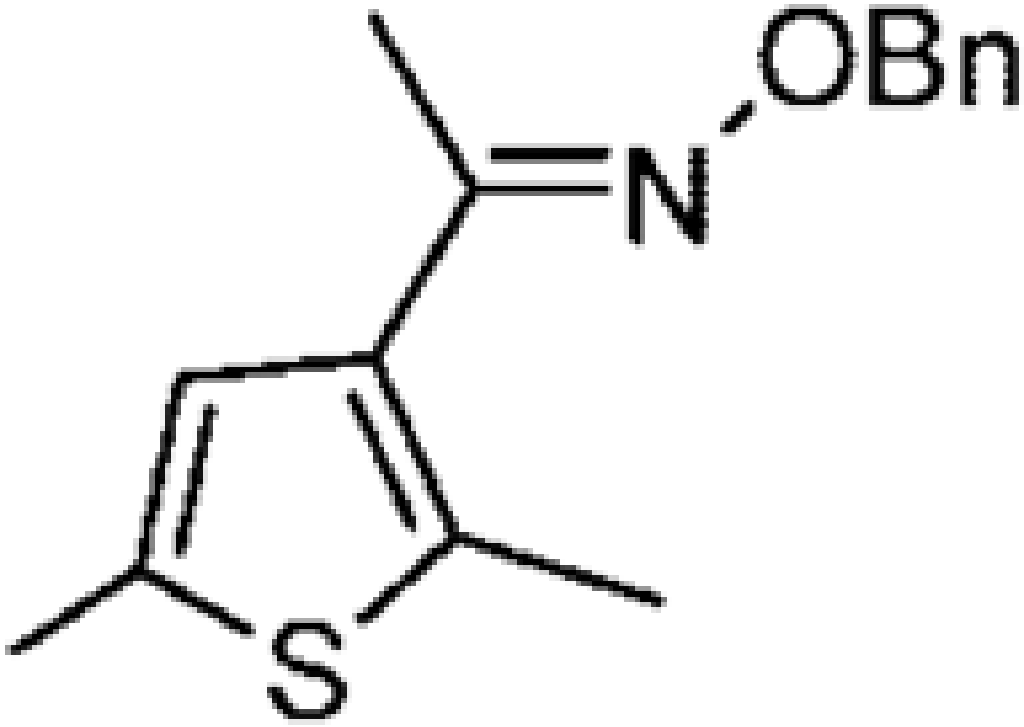
entry	15
1	 **15a**



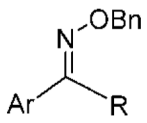
15a-f

1. cat. **10** (0.1
dioxane, 0 °

2. Ac_2O, DM

entry	15
2	

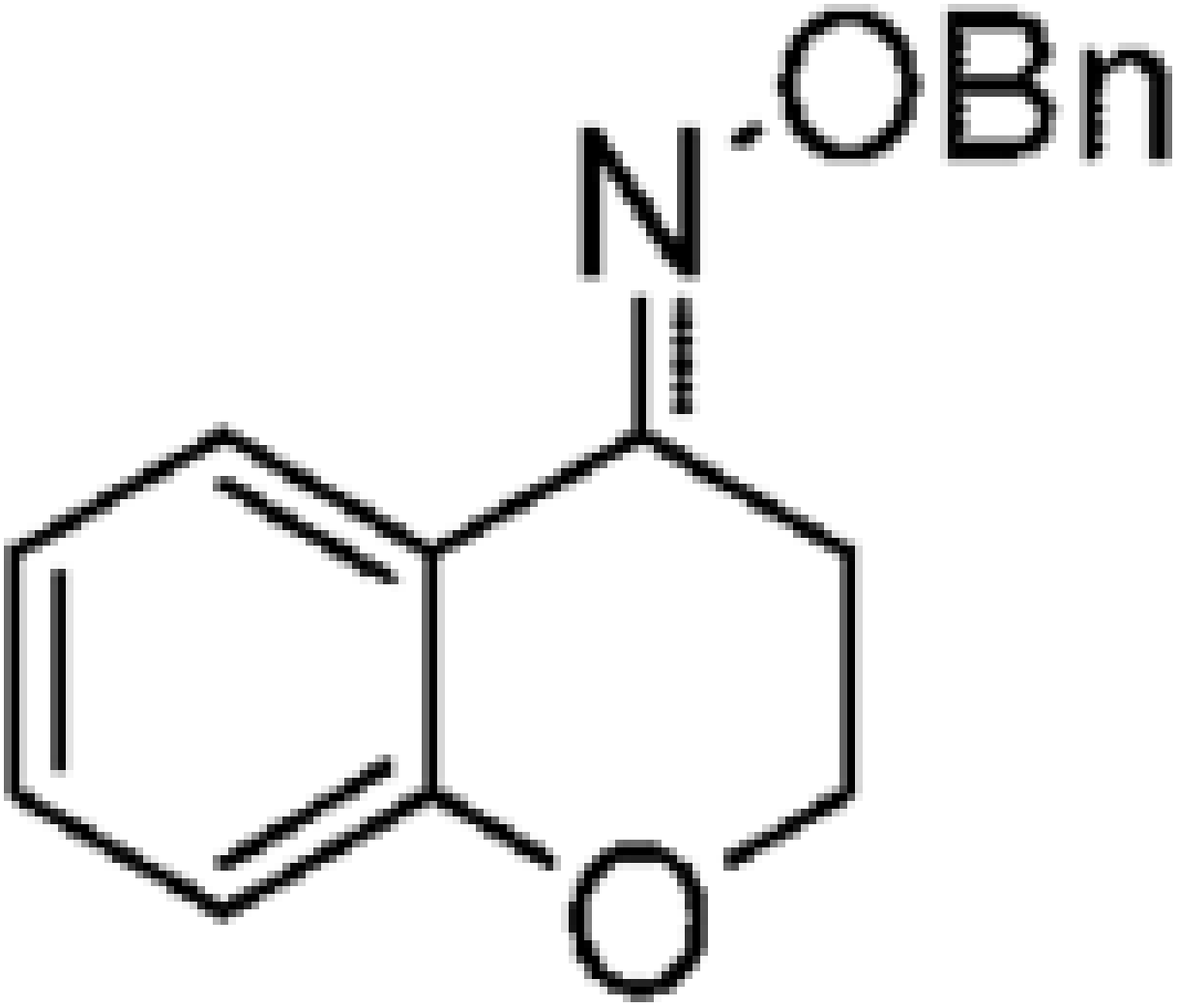
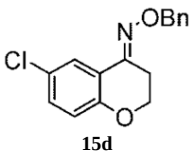
15b

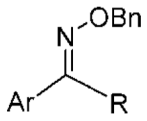


15a-f

1. cat. **10** (0.1
dioxane, 0 °

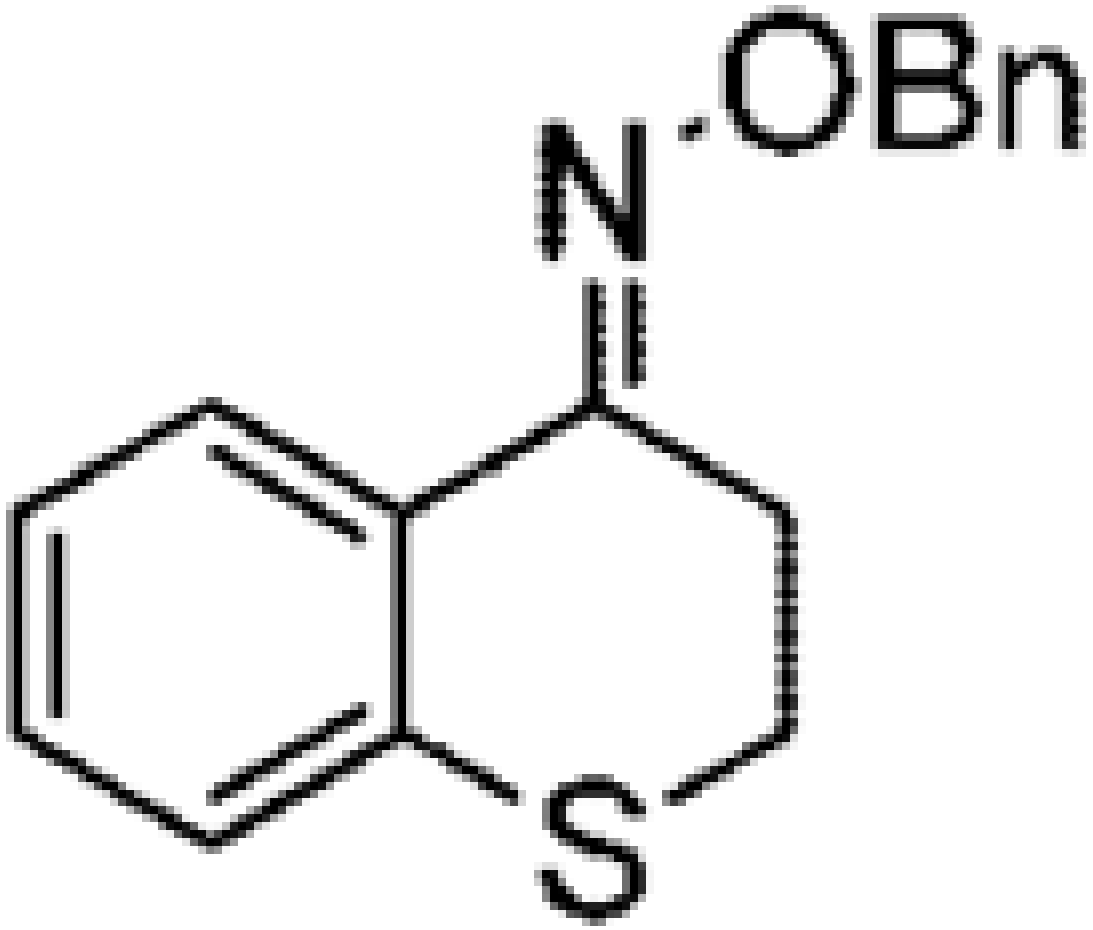
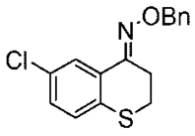
2. Ac_2O, DM

entry	15
3	
	15c
4	
	15d



15a-f

1. cat. **10** (0.1
dioxane, 0 °
2. Ac_2O, DMA

entry	15
5	 **15e**
6	 **15f**

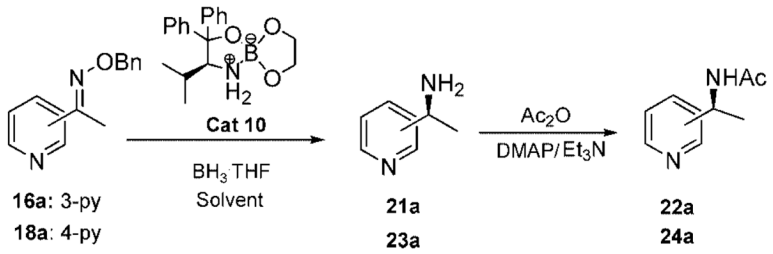
[a]The reactions were carried out using 4 equiv of borane stabilized with $NaBH_4$.

[b] Isolated yield of amides purified by column chromatography.

[c] Determined by GC of acetyl derivatives on chiral column (CP-Chirasil-Dex-CB).

Table 3

Optimization Studies for the Asymmetric Reduction of Pyridyl Ethanone O-Benzyl Oximes



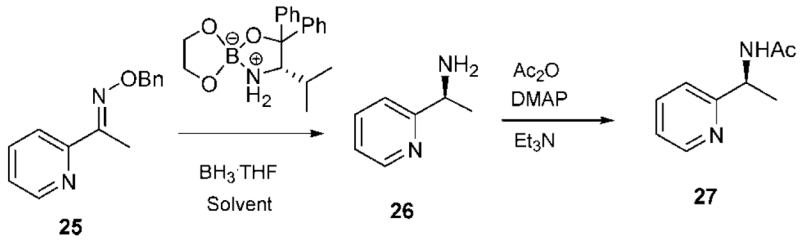
entry	benzyl oxime	cat 10 (equiv)	*T* (°C)	solvent	time (h)	yield (%)[a]	ee (%)[b]
1	**16a**	0.1	0	THF	72	46	92
2	**16a**	0.1	25	THF	48	53	89
3	**16a**	0.1	0	*t*-BuOMe	72	42	93
4	**16a**	0.1	0	dioxane	72	38	98
5	**16a**	0.3	0	dioxane	72	50	99
6	**16a**	0.3	10	dioxane	48	75	98
7	**18a**	0.1	0	THF	72	38	99
8	**18a**	0.2	10	dioxane	72	64	94
9	**18a**	0.1	25	THF	48	63	90
10	**18a**	0.3	10	dioxane	48	84	99
11	**18a**	0.5	10	dioxane	48	79	98

[a] The reactions were carried out using 5 equiv of borane stabilized with $NaBH_4$. Isolated yield of amides by column chromatography.

[b] Determined by GC of acetyl derivatives on a chiral column (CP-Chirasil-Dex-CB).

Table 4

Asymmetric Reduction of 25 under Different Reaction Conditions



entry	cat 10 (equiv)	BH_3–THF (equiv)[a]	*T* (°C)	solvent	time (h)	isolated yield (%)[b]	ee (%)[c]
1	0.1	5.0	0	THF	72	50	8
2	1.0	5.0	0	THF	96	46	13
3	1.0	2.0	10	dioxane	72	57	60
4	1.0	3.0	10	dioxane	48	71	57
5	1.0	4.0	10	dioxane	48	79	73
6	0.3	5.0	10	dioxane	72	34	4[d]
7	1.0	2.0	10	dioxane	48	73	54[e]

[a] Stabilized with $NaBH_4$.

[b] Isolated yield of amide.

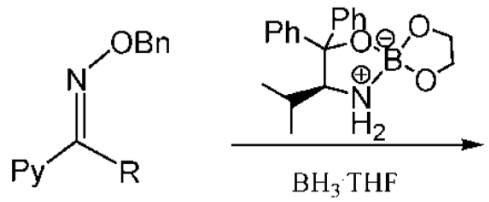
[c] Determined by GC of acetyl derivatives on a chiral column (CP-Chirasil-Dex-CB).

[d] Triethyl borane (1.0 equiv) was added.

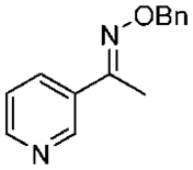
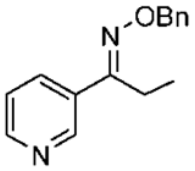
[e] BF_3 (1.0 equiv) was added.

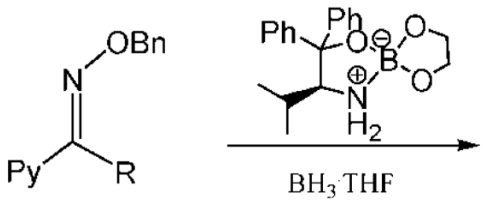
Table 5

Asymmetric Reduction of Representative Pyridyl *O*-Benzyl Oxime Ethers

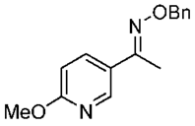


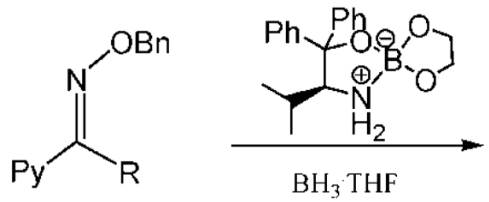
16- 19

entry	benzyloxime
1	 **16a**
2	 **16b**

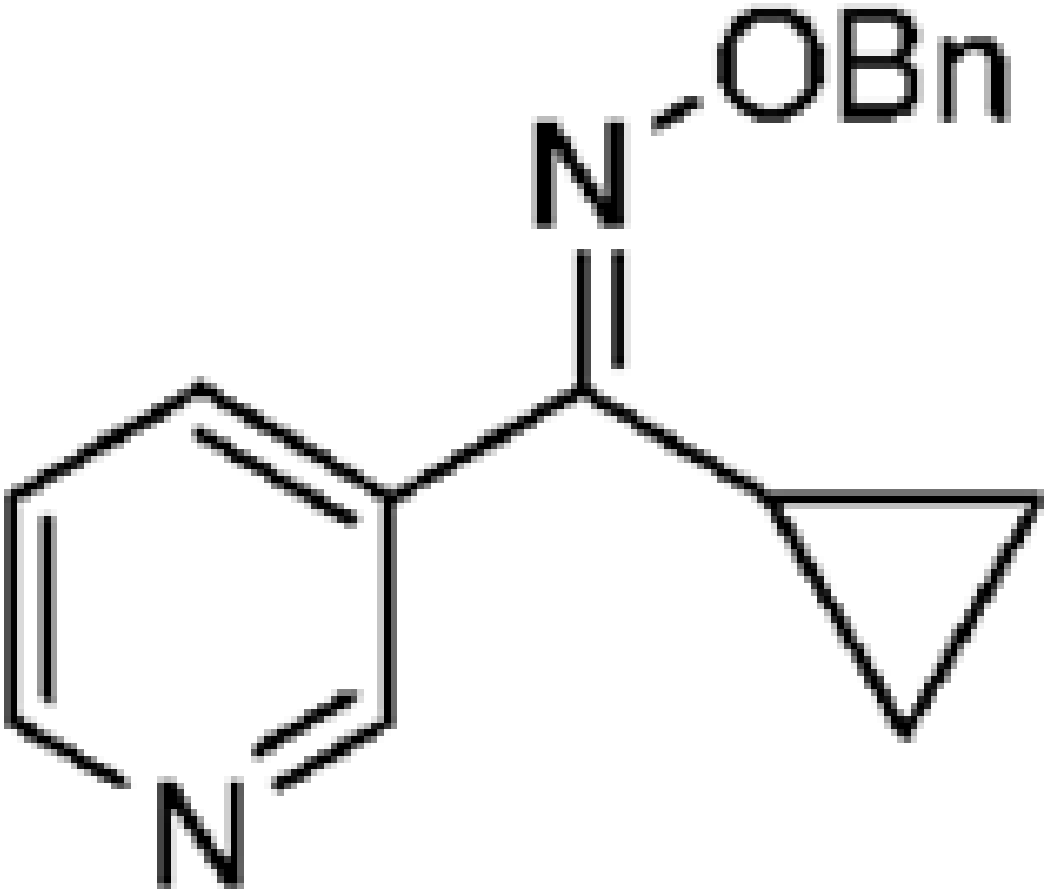
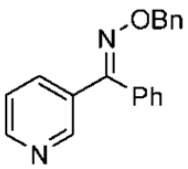


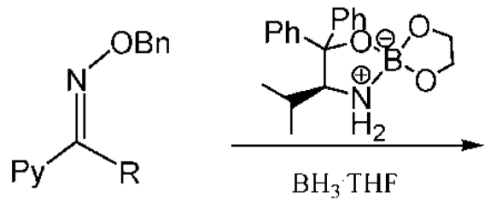
16- 19

entry	benzyloxime
3	 **16c**

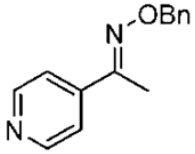
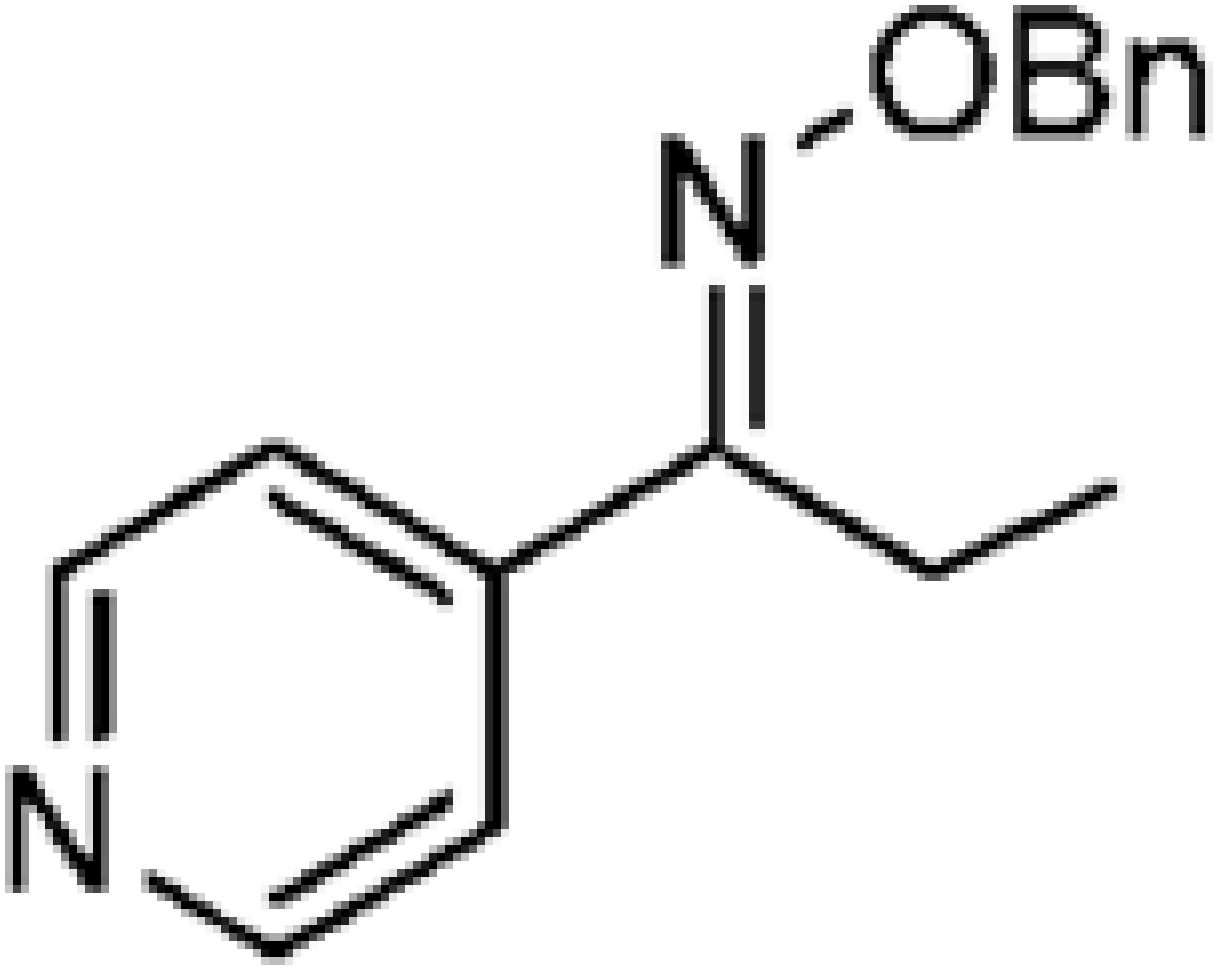


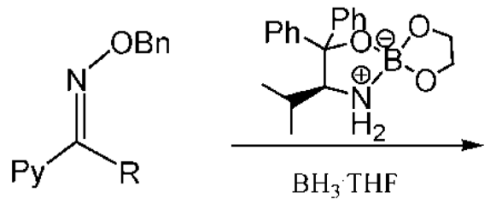
16- 19

entry	benzyloxime
4	 **16d**
5	 **17**

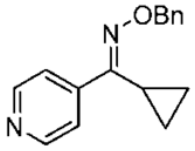
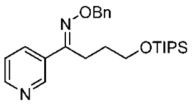


16- 19

entry	benzyloxime
6	 **18a**
7	 **18b**



16- 19

entry	benzyloxime
8	 **18c**
9	 **19**

[a]The reactions were carried out using 1 equiv of oxime ether, 0.3 equiv of catalyst **10** and 5 equiv of borane stabilized with $NaBH_4$ in dioxane at 10 °C until 100% amine conversion.

[b]Isolated yield of products after column chromatography.

[c]Determined by GC of acetyl derivatives on a chiral column (CP-Chirasil-Dex-CB).

[d]Determined by chiral HPLC (Chiralcel OD-H column).

[e]Determined by chiral HPLC (Chiralcel IB column).