Published in final edited form as:

J Org Chem. 2013 June 7; 78(11): 5314–5327. doi:10.1021/jo400371x.

Asymmetric Synthesis of Nonracemic Primary Amines via Spiroborate Catalyzed Reduction of pure (*E*)- and (*Z*)-*O*-Benzyloximes: Applications toward the Synthesis of Calcimimetic Agents

Wenhua Ou, Sandraliz Espinosa, Héctor J. Meléndez, Silvia M. Farré, Jaime L. Alvarez, Valerie Torres, Ileanne Martínez, Kiara M. Santiago, and Margarita Ortiz-Marciales*

Department of Chemistry, University of Puerto Rico—Humacao, CALL BOX 860 Humacao, PR 00792

Abstract

Highly enantiopure (1-aryl)- and (1-naphthyl)-1-ethylamines were synthesized by the borane-mediated reduction of single-isomeric (*E*)- and (*Z*)-*O*-benzyloxime ethers using the stable spiroborate ester derived from (*S*)-diphenyl valinol and ethylene glycol as the chiral catalyst. Primary (*R*)-arylethylamines were prepared by the reduction of pure (*Z*)-ethanone oxime ethers in up to 99% *ee* using 15% of catalyst. Two convenient and facile approaches to the synthesis of new and known calcimimetic analogs employing enantiopure (1-naphthalen-1-yl)ethylamine as chiral precursor are described.

Introduction

Nonracemic amines are powerful pharmacophores due to their spatial arrangement and its inherent ability to form hydrogen bonds. Consequently, research on the asymmetric synthesis of small amino intermediaries has become an important field in pharmaceutical chemistry.^{1–6} It is well established that enantiomers of chiral drugs, often, differ significantly in their pharmacological, toxicological, pharmacodynamic and pharmacokinetic properties. Hence, new methods for the synthesis of both enantiomers and careful evaluation of new enantiopure drugs is of great importance.² Chiral primary amines containing an asymmetric α -benzylic carbon, are widely used as key precursors in the synthesis of a broad variety of enantiopure drugs.^{2–6} Relevant examples of chiral amino drugs illustrating the most bioactive enantiomer are shown in Figure 1. The (*S*)- α -arylalkyl amino fragments are commonly present in a variety of neuroactive drugs such as in rivastigmine (Exelon® Novartis), a well-known anticholinesterase agent used for the treatment of Alzheimer disease.^{2a,3c,d} Additionally, the active (*S*) amino enantiomer is found in the antidepressant sertraline (Zoloft® Pfizer),^{3a} and in repaglinide (Prandin® Novo Nordisk), a new drug used for the treatment of type II diabetes.^{3b} On the other hand, the

margarita.ortiz1@upr.edu.

Supporting Information Available: optimization conditions for the reduction of (*Z*)-benzyloximes, spectral and chromatographic data of starting materials and enantiopure compounds. This material is free of charge via the Internet at <http://pubs.acs.org>.

more active (*R*) isomer is found in vanilloid 1 (TRPV1), AMG 628 candidate,^{3e} a transient receptor potential antagonist used for the treatment of chronic pain, as well as, in the novel calcimimetic drug, cinacalcet (Sensipar® Amgen).⁴⁻⁵ The (*R*) enantiomer of cinacalcet is 100 times more active than is its (*S*) isomer.^{4c}

Free ionized Ca^{2+} is an important messenger in a variety of cellular functions, playing a key role in blood coagulation, neurotransmitter release, myocardial functions, and maintenance of skeletal integrity.^{4a,b} The main function of the parathyroid gland is to maintain the Ca^{2+} extra cellular level in the body by controlling the secretion of the parathyroid hormone (PTH).^{4c-f} However, when a medical condition is present, such as, chronic kidney disease (CKD) and parathyroid carcinoma, this hormone is produced excessively leading to secondary hyperparathyroidism (sHPT). If not promptly treated, sHPT can cause bone malformation, tissue calcification, and fractures as well as other disorders. Up to now, the treatment of sHPT has been accomplished by controlling the calcium levels through diet and vitamin D supplements. Surgery is the frequent treatment for patients with parathyroid carcinoma. The recent most effective treatment for the control of PTH has been the use of new drugs known as calcimimetic agents.^{4i,j} These are novel compounds which mimic the effects of extra cellular Ca^{2+} at the calcium-sensing receptor (CaSR), thereby effectively suppressing the PTH levels with a resultant decrease in blood Ca^{2+} concentrations. In 2004, cinacalcet-HCl (Fig 1) was the first calcimimetic agent approved by the FDA for the treatment of sHPT. It is presently the only drug in the market.^{4j} Other candidates, such as, calindol,^{5a} calhex 231,^{5b} NPS R-467^{5c,5d} and Amgen pyrazole^{5e} (Fig. 2) with potent and selective activity on the parathyroid calcium receptor are under pharmacokinetic studies. Although clinical studies demonstrated that NPS R-568 effectively lowered the blood level of PTH, its clinical development was discontinued owing to its low bioavailability and poor metabolism.^{4c,d,i} The synthesis and biological studies of new and more effective calcimimetic agents is presently an area of great relevance.^{5e-i}

In addition, enantiomerically pure primary arylalkyl amines are also widely used as chiral auxiliaries and ligands in catalytic and stoichiometric asymmetric synthesis, as well as, chirality transfer reagents and resolving agent.^{1,6} Hence, the development of new and convenient methods for the synthesis of these enantioenriched amino compounds continues to be an area of great importance in organic chemistry.^{1,2} Although there are a variety of chemical and enzymatic processes for the preparation of nonracemic primary amines,^{1,2,5,6} the asymmetric reduction of oxime ethers has been a preferred approach due to the availability of suitable methods to prepare pure (*E*)-oximes.^{7a-c} Since the first study by Itsuno and coworkers in 1987, the reduction of acetophenone *O*-substituted oximes by borane in the presence of chiral borane reagents, particularly, oxazaborolidines, has been broadly studied to obtain nonracemic primary phenylalkylamines.⁷ However, greater than stoichiometric amounts of these expensive chiral boron reagents were required to achieve high enantioselectivity.^{7h} The first effective catalytic method for the borane-mediated reduction of (*E*)-benzyloxime ethers was successfully developed in our laboratory using the stable spiroaminoborate ester (**1**) derived from (*S*)-diphenylvalinol and ethylene glycol (EG-DPV), as a catalytic agent. Enantiopure primary amines were obtained in high yield using low catalytic loading, usually, less than 10% of the catalyst.^{8a,b} This method was effectively applied to the asymmetric synthesis of a range of heteroaryl and heterocyclic amines^{8c} and to nicotinic analogues^{8d,e} with excellent enantioselectivity. The biological importance of nonracemic (*S*)- and (*R*)-arylethylamines, particularly, those containing halogen- and alkoxy-substituted aromatic rings, prompted us to study the synthesis and reduction of isomerically pure (*E*)- and (*Z*)-benzyloxime ethers. The product amines were investigated in their conversion to both known and new calcimimetic analogues, as is illustrated in Scheme 1. Moreover, we felt that the development of an effective catalytic asymmetric synthesis of enantiopure primary α -alkylbenzylic amines and naphthalen-1-yl-alkylamines through a

facile and environmentally friendly method would offer enormous promise for developing efficient new routes to a wide diversity of pharmaceutical products.

Results and Discussion

Asymmetric Synthesis of Nonracemic (*S*)-Primary Amines

Initially, due to the biological importance of (*S*)-arylethylamines containing F, Cl, Br, CF₃, methoxy and thiomethyl substituents as precursors for the synthesis to a wide variety of chiral drugs, in particular neuroactive compounds, such as rivastigmine, the synthesis of representative enantiopure amines was of interest.⁸ (*E*)-aryl benzyl oximes were prepared from the corresponding ketone using hydroxylamine and sodium carbonate at 65 °C at a weakly acidic pH. As indicated in Table 1, the (*E*)-oximes were obtained in moderate to high yields after recrystallization. Subsequently, the oximes were converted to their benzyloxime ethers using NaH and benzyl bromide in DMF at –30 °C. The pure (*E*)-benzyloximes were obtained in modest to good yields after careful purification by column chromatography or preparative TLC. These were characterized by ¹H and ¹³C NMR analysis and confirmed by GC/MS. Similarly, the (*E*)-1-(naphthalen-1-yl)ethanone oxime and its corresponding *O*-benzyloxime were prepared in high isomeric purity and in good yields (Table 1).

The asymmetric reduction of the previously prepared (*E*)-*O*-benzyl oximes in dioxane was conducted with 10% spiroborate ester **1** (EG-DPV) and 4 equivalents of BH₃–THF at 0 °C for 3 days.⁸ The desired pure (*S*) amines were isolated as their *N*-acetyl derivatives by the reaction of the crude product with acetic anhydride, triethylamine and DMAP in methylene chloride. The *ee*'s of the acetylated derivatives were determined by GC analysis using CP-Chirasil-Dex-CB as the stationary phase. As is illustrated in Table 1, the primary amines, isolated as their acetyl derivatives, were obtained in good to excellent yields and excellent enantiopurity (up to 98% *ee*) after column chromatography or preparative TLC. Interestingly, no significant substituent effects for either electron-donating or electron-withdrawing groups on the aromatic rings were observed in the enantioselective reduction of the (*E*)-benzyloxime ethers. The enantiomeric purities of the amine depended more on the isomeric purity of the benzyloxime ether precursor.

Asymmetric Synthesis of (*R*) Primary Amines

Contrary to the reduction of (*E*)-benzyloxime ethers with boranes in the presence of chiral catalysts, the enantioselective reduction of (*Z*)-oxime ethers has rarely been examined, possibly due to the difficulty in efficiently obtaining the (*Z*)-oxime ethers in pure form.^{6b,9} Consequently, limited information is available on the effect of (*E*)/(*Z*) isomerism on the asymmetric reduction of the imine. The stereoselectivity for both the *E* and *Z* isomers in the reduction, using the spiroborate - borane system, was therefore, of interest. Although, the (*R*)-amines can be prepared by the reduction of (*E*)-benzyloxime, using the spiroborate derived from (*S*)-diphenylvalinol as a chiral source, the high cost of this amino alcohol derived from an unnatural amino acid makes this route less attractive. Accordingly, we decided to investigate the reduction of (*Z*)-benzyloximes using the spiroborate **1** catalyst to obtain the desired (*R*)-amines.

Pure (*Z*)-oximes cannot be obtained directly from their corresponding ketones due to their thermal instability. Therefore, different approaches to the (*Z*)-isomers were studied.¹⁰ Following Sharghi and coworkers' procedure,^{10a} acetophenone was treated with hydroxylamine hydrochloride using K₂CO₃ under solvent-free conditions. However, the (*E*)-acetophenone oxime was the major product. Likewise, the (*E*)-isomer was the only product obtained by the method of Coustard and coworkers using naphthalene and

nitroethane in the presence of H₂SO₄ to obtain the 1-(naphthalen-1-yl)ethanone oxime.^{10b} However, the desired (*Z*)-isomers were conveniently prepared according to the method first developed by Smith *et al.*^{10c,d} Representative (*E*)- α -bromo acetophenone oximes and 1-(naphthalen-1-yl)ethanone oxime were synthesized from their corresponding α -bromo ketones by treatment with 3 equivalent of hydroxylamine in methanol/water solvent (Scheme 2). The corresponding (*Z*)-acetophenone oximes were then successfully prepared in excellent yield by the nucleophilic reaction of α -bromo acetophenone oximes with 1 equivalent of NaBH₄. It is interesting to note that, in the first step, no base was required for the oxime formation, and in the second step, the reaction proceeded very fast at room temperature. The (*Z*)-benzyloximes were isolated by column chromatography and obtained in moderate to high yield without isomerization from the corresponding 2-bromoketone. As indicated in Table 2, the pure (*Z*)-oximes (**6**) and (*Z*)-benzyloximes (**7**) were obtained in good yields and in high isomeric purities as determined by ¹H and ¹³C NMR analysis and GC-MS.

The borane-mediated reductions of (*Z*)-benzyloximes of acetophenone of 4-methyl- and 4-methoxy acetophenones, and 1-(naphthalen-1-yl)ethanone were initially explored to optimize the reaction conditions catalyzed by spiroborate ester **1** (see supporting information in Table 1). Similarly to the (*E*)-benzyloximes, the spiroborate ester **1**-BH₃-THF system provided better enantioselectivity than the BH₃-Me₂S complex. Interestingly, the optimal catalytic load for the enantioselective reduction of (*Z*)-oximes was 15 mol % of spiroborate **1**, slightly higher than it was required for the (*E*)-benzyloximes. Unexpectedly, the enantioselectivity was higher in THF than in dioxane at 0 °C.

Under the previous established method (0.15 equiv of spiroborate catalyst **1**, BH₃-THF, THF, 0 °C), the (*Z*)-arylethyl- and (*Z*)-1-naphthylethyl-(*O*)-benzyl oximes shown in Table 2, were efficiently reduced obtaining the desired primary amines. Representative (*R*)-(1-aryl)- and 1-(naphthalen-1-yl)ethylamines were converted to their acetamide derivatives in good yield and high enantiomeric purity (up to 99% *ee*), for all but the 4-nitro substituted phenyl ethylamine (80% *ee*).

Synthesis of Calcimimetic Analogues

As mentioned above, calcimimetic agents are small organic molecules that mimic the effects of extra cellular Ca²⁺ at the calcium sensing receptor (CaSR). These drugs are called type II calcimimetics since they decrease the plasma levels of Ca²⁺ and PTH acting as allosteric agonists by binding at sites distinct from the extra cellular Ca²⁺. Cinacalcet, shown in Figure 1, has become the only approved treatment,⁴ with only limited numbers of calcimimetic analogues presently under study.⁵ Due to the urgency in the growth of new drugs for the treatment of HPT, we were interested in developing efficient methods for the synthesis of both known and new calcimimetic agents. In general, the structure of calcimimetic compounds contains, mainly, two sections: the (*R*)-aryl- or (*R*)-naphthylalkyl amino group plus an aryl group connected through an aliphatic chain (Figure 2). Since the binding of calcimimetic agents to the CaR depends on electrostatic interactions of acidic amino acids⁴ with ionic amino compounds, changes in the structural properties of the aromatic groups are of interest to design new analogues. In addition, changes in the polarity and length of the linkers can lead to a new class of calcimimetic drugs.

Our initial efforts were directed toward the development of cinacalcet related compounds, that we call class I analogues, employing enantiopure (*R*)-1-(naphthalen-1-yl)ethylamine connected to the aryl group by a propyl linker. The cinacalcet analogs **11a** and **11b** were prepared by a two-step route, as is shown in Scheme 3. First, the racemic and chiral amines were allowed to react with 3-arylpropionic acids at room temperature using dicyclohexylcarbodiimide (DCC) and 4-(*N,N*-dimethylamino)pyridine (DMAP), as catalysts.^{5e}

The corresponding amides were obtained in excellent yield and high enantiopurities (>99% ee). Subsequent reduction of the amide with BH_3 -THF in THF under reflux conditions afforded the desired secondary amine in modest to good yield. Calcimimetic analogues and other related secondary amines can be conveniently prepared by this facile and simple approach.

As indicated in Table 3, a new family of calcimimetic analogues (class II) containing the 1-(naphthalen-1-yl)ethylamine connected by a propyl linker either to phenoxy or thiophenoxy groups was prepared. This class of analogues may provide more polar structural features that can interact with the calcium-sensing receptors. To our knowledge, there are only limited examples of this type of calcimimetic analogues.⁵ In the first step, representative (3-bromopropoxy)- and (3-bromopropylsulfanyl)-benzene **12** were prepared by the reaction of phenol or thiophenol with 1,3-dibromopropane in modest to good yield using sodium hydride as a base. Disubstituted products and a small amount of disulfide were also observed in the reaction with thiophenol. Representative calcimimetic analogues (**R**)-**13** were obtained in good yield without racemization through the nucleophilic substitution of (3-bromopropoxy)- and (3-sulfanylpropyl)benzene by the non-racemic 1-(naphthalen-1-yl)ethylamine using triethylamine and DMAP at 60 °C. Racemic compounds were also prepared in comparable yields and used for the HPLC analysis of the enantiopure isomers.

Conclusions

Enantiomerically pure (*S*) and (*R*) primary amines were conveniently prepared by the borane-mediated reduction of their corresponding (*Z*)- and (*E*)-benzyloxime ethers, respectively, employing the stable chiral spiroborate ester **1** as catalyst. In general, the stereoselectivity of the spiroborate ester **1** catalyst for the reduction of the (*Z*)-isomer was slightly lower than for the (*E*)-benzyloxime ethers and, as a consequence, these processes required somewhat higher amount of catalyst (*i.e.*, 15%) to achieve similar enantioselectivities to those from the *E* isomer which employed only a 10% catalyst loading. Overall, no substituent effects on the aromatic ring were observed in the enantioselective reduction of both *E* and *Z* isomers. The efficiency of the method depends more on the stereochemical purity of the benzyloxime ether substrates. In summary, a variety of enantioenriched *R* and *S* primary arylethyl amines were conveniently prepared in high yield using a mild and environmentally friendly method which can be applied to the synthesis of important drug intermediates. As examples, two classes of optically pure calcimimetic analogues were prepared. For the class I analogues, enantiopure 1-(naphthalen-1-yl)ethylamine was reacted with 3-arylpropionic acids to obtain the corresponding amides, which were subsequently reduced with borane to obtain the desired analogues. In addition, a new class of calcimimetic analogs (class II), containing a heteroatom in the linker, were also prepared in good yield and excellent enantiopurity (>99% ee). This work opens new avenues for the design of new calcimimetic drugs for the treatment of hyperparathyroidism.

Experimental Section

Typical Procedure for the Synthesis of *E*-Oximes

(*E*)-1-(2-Methoxyphenyl)ethanone oxime (2a).^{11a}—To a mixture of 2-methoxyacetophenone (10 g, 66 mmol, 1.0 equiv), hydroxylamine-hydrochloride (4.25 g, 1.0 equiv, 66 mmol) in ethanol (150 mL) was added dropwise sodium carbonate (0.5 equiv, 33 mmol, 3.45 g) in water (40 mL). The mixture was then heated at reflux maintaining the pH around 5 and monitoring the reaction progress by TLC. The solvent was then removed under reduced pressure and the residue extracted with ethyl acetate (4 × 40 mL). The organic phase was dried over Na_2SO_4 , filtered and concentrated under reduced pressure

obtaining the crude product (11.1 g) that was recrystallized in hexane/ethyl acetate (15:1) A white solid was obtained (8.45 g, 78%), which was analyzed by GC-MS: [10.86 min (3% *Z* isomer), 11.58 min (97 % *E* isomer)], *m/z* 165.2, 133.2, 105.2. A sample of this oxime (3.0 g) was purified by silica gel column chromatography obtaining a white crystalline solid: mp. 205 °C–206 °C; GC/MS [1.82 min (2.0% *Z*) 12.57 (98% *E*)] *m/z* 162.1, 133.1, 105.1, 77.1; ¹H NMR (400 MHz, CDCl₃) δ 2.28 (s, 3H), 3.89 (s, 3H), 7.01 (m, 2H), 7.39 (m, 2H), 9.50 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 15.2, 55.4, 111.1, 120.6, 126.8, 129.4, 130.1, 156.7, 157.4.

(*E*)-1-(3-Methoxyphenyl)ethanone oxime (2b).^{11b}—Clear Oil (3.92 g, 100%): ¹H NMR (400 MHz, CDCl₃) δ 2.33 (s, 3H), 3.89 (s, 3H), 6.98 (m, 2H), 7.50 (m, 1H), 7.33 (t, *J* = 8.4 Hz, 1H); ¹³C NMR (100 Hz, CDCl₃) δ 23.6, 55.4, 112.3, 119.3, 121.1, 129.5, 139.5, 159.9.

(*E*)-1-(4-Methylthiophenyl)ethanone oxime (2c).^{11c}—White solid (2.06 g, 98%): mp. 106–109 °C, Lit.^{11c} 118–120 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.32 (s, 3H), 2.55 (s, 3H), 7.30 (dd, *J* = 1.6, 7.4 Hz, 2H), 7.60 (dd, *J* = 1.6, 7.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 11.9, 15.5, 126.1, 126.3, 133.1, 140.1, 155.6; FT IR (ν, cm⁻¹) 2920, 1639, 1466, 1583, 1364; GC/MS *m/z* 141.0, 124.0, 83.9.

(*E*)-1-(2-Fluorophenyl)ethanone oxime (2d).^{11d}—White crystalline solid (1.59 g, 52%): mp. 72–73 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.35 (s, 3H), 7.15 (m, 2H), 7.39 (m, 1H), 7.50 (m, 1H), 9.75 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 14.7, 116.2, 124.3, 125.07, 129.4, 130.8, 154.0, 159.3, 161.7; GC/MS [9.23 min (97% *E* isomer)] *m/z* 153.1, 136.2, 111.2, 75.2.

(*E*)-1-(4-Fluorophenyl)ethanone oxime (2e).^{11e}—White solid (13.9 g, 84%): mp. 78–79 °C, Lit.^{11e} 107–108 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.33 (s, 3H), 7.12 (m, 2H), 7.66 (m, 2H), 8.92 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 12.2, 115.4, 127.9 (d, *J* = 8.0 Hz), 132.7 (d, *J* = 3.0 Hz), 155.2; 162.2, 164.7 (d, *J* = 250 Hz); FT-IR (ν, cm⁻¹) 3217, 2929, 1602, 1511; GC/MS (9.52 min) *m/z* 153.2, 112.1, 95.1, 75.1.

(*E*)-1-(2-Bromophenyl)ethanone oxime (2f).^{11e}—The product was recrystallized in hexane/ethyl acetate (9:1) obtaining a white crystalline solid (5.5 g, 89%) containing 10% of the *Z* isomer by GC/MS. A sample of 2 g of product was recrystallized in ethanol-water (3:1): mp. 129 °C–131 °C, Lit.^{11e} 112–114 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.31 (s, 3H), 7.29 (m, 1H), 7.37 (m, 2H) 7.65 (m, 1H), 78.33 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 15.9, 121.7, 127.4, 130.1, 130.1, 138.8, 158.1; GC/MS [9.23 min (97 % *E*)] *m/z* 153.1, 136.2, 111.2, 75.2.

(*E*)-1-(4-Bromophenyl)ethanone oxime (2g).^{11f}—White crystalline solid (8.9 g, 84%): mp. 119–121 °C, Lit.^{11f} 127–129 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.62 (s, 3H), 7.65 (m, 2H), 7.85 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 11.9, 123.5, 127.6, 131.6, 135.4, 155.2; GC/MS [12.65 min (*E*)] *m/z* 214, 212, 155, 106.1, 102.1.

(*E*)-1-(3,4-Difluorophenyl)ethanone oxime (2h).^{11g}—White crystalline solid (3.0, 76%): mp. 76–77 °C; ¹H NMR (400 MHz, CDCl₃, 100 MHz) δ 2.30 (s, 3H), 7.22 (m, 1H), 7.31 (s, 1H), 7.53 (m, 1H), 7.51 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 12.0, 115.2 (m, Hz), 117.3 (d, *J* = 17 Hz), 122.3 (m, *J* = 3.5 Hz, CH), 133.5 (m, *J* = 3.5 Hz), 149.5 (d, *J* = 11.5 Hz), 151.9 (d, *J* = 12 Hz), 154.3; FT-IR (ν, cm⁻¹) 31745, 3083, 2856, 1541, 1422, 1314, 1366, 891 and 813.

(E)-1-(3,5-bis(Trifluoromethyl)phenyl)ethanone oxime (2i).^{11h}—White crystalline solid (3.9, 82%): mp. 108–111 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.39 (s, 3H), 7.93 (s, 1H), 8.13 (s, 2H), 8.50 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 11.8, 126.1–119.1 (q, *J* = 271 Hz), 122.7 (m, *J* = 4 Hz), 126.1 (d, *J* = 4 Hz), 131.8 (q, *J* = 33 Hz), 138.5; GC/MS [8.84 min (*E*)] *m/z* 571.0, 254.0, 213.0, 202.2.

(E)-1-(2-Fluoro-4-methoxyphenyl)ethanone oxime (2j).¹¹ⁱ—After the above described work-up and purification, the product was isolated as a white crystalline solid (4.1 g, 93%): mp. 106–107 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.32 (s, 3H), 3.86 (s, 3H), 3.73 (m, 2H), 6.71 (m, 2H), 7.44 (t, 1H, *J* = 8.6 Hz), 9.33 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 14.6, 55.6, 102.2 (d, *J* = 21 Hz), 110.1 (d, *J* = 12 Hz), 117.5 (d, *J* = 12 Hz), 129.9 (d, *J* = 5 Hz), 153.7 (d, *J* = 3 Hz), 161.5, 162.5 (d, *J* = 249 Hz), 161; GC/MS [12.24 min, *E* isomer] *m/z* 183.2, 166.2, 151.2, 126.2, 122.2.

(E)-1-(Naphthalen-1-yl)ethanone oxime (2k).¹¹ⁱ—White crystalline solid (11.4 g, 72%): mp. 134–141 °C, Lit.^{11j} 136–138 °C; ¹H NMR (400 MHz, DMSO-*d*⁶) δ 2.3 (s, 3H), 2.4 (s, 3H), 3.9 (s, 3H), 8.2–7.4 (m, 7H), 9.2 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*⁶) δ 16.8, 125.2, 125.3, 126.0, 126.1, 126.6, 128.5, 129.2, 130.9, 133.9, 135.5, 157.5, GC/MS [14.46 min (9% *Z* isomer), 15.18 min (91 % *E* isomer)] *m/z* 185.1, 168.2, 127.2.

Typical Procedure for the Preparation of (*Z*) Oximes from the Ketone.^{10c,d}

(Z)-1-(Naphthalen-1-yl)ethanone oxime (6i).^{10d}—1-Acetylnaphthalene (3.4 g, 0.02 mol) was placed in a 125 mL round bottomed flask and dissolved in 20 mL of CH₂Cl₂. A solution of bromine (3.2 g, 1.03 mL, 0.02 mol) in 20 mL of CH₂Cl₂ was added dropwise *via* a syringe pump to the 1-acetylnaphthalene solution under stirring at 0 °C. After the addition, the mixture was stirred for 1 h and distilled under reduced pressure on a water-bath, to obtain a red viscous liquid (5.38 g, 21.3 mmol). Immediately, the 2-bromo substituted ketone was reacted with NH₂OH·HCl (4.5 g, 65 mmol) in water (6 mL) and MeOH (40 mL) until a clear solution was obtained. The reaction mixture was left stirring overnight at 25 °C or until completion was indicated by TLC. Then, the solvent was removed under vacuum to yield of dark brown viscous oil. The crude (*Z*)-2-bromo-1-(naphthalen-1-yl)ethanone oxime (10.0 g, 37.9 mmol) was dissolved in acetonitrile (60 mL) and added portion-wise to a stirred mixture of NaBH₄ (1.43 g, 37.9 mmol) in water/acetonitrile (200 mL/60 mL). Rapid evolution of gas formation was noted, and after 10 minutes the reaction was complete by TLC analysis. Water (60 mL) was added and the mixture was extracted with EtOAc (3 × 90 mL). The combined organic phase was washed with saturated NaCl solution (2 × 60 mL) and dried over anhydrous Na₂SO₄. The solvents were removed by rotary evaporation to yield the crude product (9.7 g). The crude product was purified by silica gel column chromatography, obtaining the pure product as a brown viscous liquid (4.6 g, 72% overall from 1-acetonaphthone): ¹H NMR (400 MHz, CDCl₃) δ 2.22 (s, 3H), 7.26–7.28 (m, 1H), 7.46 (m, 3H), 7.73 (m, 1H), 7.82 (m, 2H), 9.41 (s, 1H); ¹³C NMR (400 MHz, CDCl₃) δ 22.4, 123.6, 125.1, 125.2, 125.9, 126.3, 128.3, 128.5, 128.8, 133.2, 133.9, 155.7; FT-IR (ν, cm⁻¹) 775, 800, 939, 1021, 1098, 1251, 1386, 1434, 1658, 3231; GC/MS *m/z* 185.1 (M⁺).

(Z)-Acetophenone oxime (6a).^{10d}—After following the typical procedure, the crude product was purified by silica gel column chromatography affording the *Z* isomer (0.87 g, 71%) and the *E*-isomer (0.25 g). The *Z* product was a white solid: mp. 81–83 °C, Lit.^{10d} 81–83 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.20 (s, 3H), 7.35–7.39 (m, 3H), 7.42–7.43 (m, 2H), 7.44 (br s, 1H); GC/MS *m/z* 135.1 (M⁺).

(Z)-1-(p-Tolyl)ethanone oxime (6b).^{10f}—White solid (1.21 g, 87%): ¹H NMR (400 MHz, CDCl₃) δ 2.19 (s, 3H), 2.38 (s, 3H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H),

8.61 (s, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ 21.4, 21.6, 127.9, 128.9, 130.9, 139.2, 154.6, 154.7; FT-IR (ν , cm^{-1}) 673, 721, 815, 959, 1033, 1088, 1188, 1295, 1378, 1432, 1457, 1511, 1651, 2862, 3043, 3177; GC/MS m/z 149.2 (M^+).

(Z)-1-(4-Methoxyphenyl)ethanone oxime (6c).^{7k,10f}—White solid, (1.23 g, 58%): mp. 66–68 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.19 (s, 3H), 3.83 (s, 3H), 6.94 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 8.12 (br s, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ 21.5, 55.3, 113.5, 125.9, 129.9, 154.0, 160.0; FT-IR (ν , cm^{-1}) 677, 838, 945, 1021, 1121, 1184, 1249, 1311, 1406, 1509, 1572, 1603, 1631, 1978, 2837, 2997, 3176; GC/MS m/z 165.3 (M^+).

(Z)-1-(3-Methoxyphenyl)ethanone oxime (6d)—Light yellow liquid (0.72 g, 74%): ^1H NMR (400 MHz, CDCl_3) δ 2.20 (s, 3H), 3.81 (s, 3H), 6.91–6.94 (m, 1H), 7.08–7.10 (m, 2H), 7.32–7.36 (m, 1H), 8.93 (br, 1H); ^{13}C NMR (CDCl_3) δ 21.5, 55.1, 113.4, 114.4, 119.8, 129.1, 135.0, 154.4, 159.1; FT-IR (ν , cm^{-1}) 781, 855, 940, 1034, 1181, 1227, 1288, 1427, 1487, 1578, 1599, 1659, 1704, 2917, 3232; GC/MS m/z 165.3 (M^+).

(Z)-1-(4-Chlorophenyl)ethanone oxime (6e).^{7k,10f}—White solid (1.7 g, 82%): mp. 111–113 °C, Lit.^{10f} 94 °C mixture of 95% *Z* and *E*; ^1H NMR (400MHz, CDCl_3) δ 2.16 (s, 3H), 7.34 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 8.62 (s, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ 21.4, 128.5, 129.5, 132.0, 135.0, 153.5; GC/MS m/z 169.1 (M^+).

(Z)-1-(4-Bromophenyl)ethanone oxime (6f).^{10f}—White solid (1.04 g, 79% overall from α -bromo-4-bromo acetophenone): mp. 112–115 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.17 (s, 3H), 7.43 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 9.2 Hz, 2H), 8.14 (s, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ 21.4, 123.3, 129.7, 131.4, 132.5, 153.7; GC/MS m/z 213.1 (M^+).

(Z)-1-(3-Bromophenyl) ethanone oxime (6g).¹²—Light yellow liquid (0.7 g, 55%): ^1H NMR (400 MHz, CDCl_3) δ 2.18 (s, 3H), 7.25–7.30 (m, 1H), 7.44–7.51 (m, 2H), 7.69 (s, 1H), 8.68 (s, 1H); ^{13}C NMR (CDCl_3) δ 21.2, 122.1, 126.3, 129.6, 130.70, 131.87, 135.5, 153.1; FT-IR (ν , cm^{-1}) 779, 942, 1020, 1282, 1374, 1414, 1473, 1560, 1650, 1704, 2860, 3216; GC/MS m/z 213.1 (M^+).

(Z)-1-(4-Nitrophenyl)ethanone oxime (6h).¹³—Light yellow solid (0.816 g, 74%): mp. 174–175 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.24 (s, 3H), 7.51 (br s, 1H), 7.65–7.68 (m, 2H), 8.26–8.28 (m, 2H); ^{13}C -NMR (CDCl_3) δ 21.5, 123.6, 123.9, 127.0, 129.1, 140.4, 153.4; FT-IR (ν , cm^{-1}) 693, 754, 854, 945, 1026, 1084, 1109, 1340, 1395, 1514, 1602, 3189.

General Procedure for the Synthesis of (*E*) or (*Z*)-*O*-Benzyloxime Ethers 7.^{8,14–19}

To a suspension of NaH (1.1 equiv.) in DMF, a solution of oxime (1 equiv) was added dropwise by a syringe pump at 0 °C and the reaction mixture was stirred for 1 h at 0 °C. A solution of PhCH_2Br (1.05 equiv) in DMF was added dropwise *via* a syringe pump. The resulting mixture was stirred overnight at room temperature, quenched with saturated aqueous NH_4Cl solution and extracted with ether or ethyl acetate. The organic phases were combined and dried over anhydrous Na_2SO_4 . The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel or preparative TLC plates to afford the desired pure benzyloximes.

(E)-1-(2-Methoxyphenyl)ethanone O-benzyloxime (3a)—The crude product was purified by silica gel column chromatography (35.8 g, length 12.3 cm, diameter 1.6 cm) with petroleum ether/ethyl acetate (18:1). The fractions 1–9 were transferred to a round bottomed flask and concentrated to obtain a clear oil (2.38 g, 80%): ^1H NMR (400 MHz, CDCl_3) δ

2.29 (s, 3H), 3.88 (s, 3H), 5.29 (s, 2H), 6.98 (m, 1H) 7.01 (d, $J = 1.2$ Hz, 1H), 7.33 (m, 3H), 7.40 (m, 2H), 7.5 (m, 2H); ^{13}C NMR (100 MHz, CHCl_3) δ 16.37, 55.5, 75.9, 111.1, 120.6, 127.1, 128.12, 128.3, 129.7, 130.2, 138.2, 157.1, 57.5; FT-IR (ν , cm^{-1}): 1578, 1238, 919, 751, 641; HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_2$: 256.1332; Found: 256.1333.

(E)-1-(3-(Methoxyphenyl)ethanone O-benzyloxime (3b)—Clear oil (2.15 g, 93%): ^1H NMR (400 MHz, CDCl_3) δ 2.39 (s, 3H), 3.92 (s, 3H), 3.39 (s, 3H), 7.02 (m, 1H), 7.45 (m, 8H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.0, 55.3, 76.3, 111.6, 114.9, 118.8, 127.8, 128.2, 128.4, 129.4, 138.2, 154.8, 159.7; FT-IR (ν , cm^{-1}) 2834, 1598, 1229, 981, 731; HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_2$: 256.1332; Found: 256.1343.

(E)-1-(4-Methylthiophenyl)ethanone O-benzyloxime (3c)—The solid was purified by silica gel column chromatography with hexane/ethyl acetate (9:1 v/v) as eluant obtaining white crystals (1.37 g, 50%): mp. 74–75 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.30 (s, 3H), 2.54 (s, 3H), 5.29 (s, 2H), 7.29 (d, $J = 8.2$ Hz), 7.42 (m, 5H), 7.63 (d, $J = 8.4$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 12.7, 15.5, 76.2, 126.0, 126.4, 127.7, 128.1, 128.3, 133.3, 138.1, 139.8, 154.4; FT-IR (ν , cm^{-1}) 1598, 1491, 1023, 819, 699; HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{18}\text{NOS}$: 272.1104; Found: 272.1105.

1-(2-Fluoro-phenyl)ethanone O-benzyloxime (3d).^{6b}—The product was purified over silica gel (36 g) using hexane and ethyl acetate (12:1 v/v) as mobile phase obtaining an oil (1.49 g, 67%): ^1H NMR (CDCl_3 , 400 MHz) δ 2.37 (s, 3H) 5.33 (s, 2H) 7.20 (m, 2H), 7.38 (m, 7H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 15.8, 76.3, 116.2, 116.0 (d, $J = 4$ Hz) 125.2, 125.3 (d, $J = 13$ Hz), 127.8, 128.1, 128.4, 129.7, 129.7 (d, $J = 3$ Hz) 130.6, 130.5 (d, $J = 9$ Hz), 137.9, 153.7, 153.7 (d, $J = 1$ Hz), 161.9, 159.4 (d, $J = 2.49$ Hz); GC/MS (Rt 15.28 min) m/z 146.2, 138.2, 137.2, 91.2, 65.2.

(E)-1-(4-Fluorophenyl)ethanone O-benzyloxime (3e).^{7k}—The product was purified by silica gel column chromatography (50 g) using hexane/ethyl acetate (20:1 v/v) to give a white solid (4.05 g, 84%): mp. 43–45 °C, Lit.^{7k} 58–60 °C; ^1H NMR (400 MHz, CDCl_3 , 400 MHz) δ 2.31 (s, 3H), 5.29 (s, 2H), 7.10 (m, 2H), 7.43 (m, 5H), 7.67 (s, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 76.3, 115.3 (d), 127.9 (d) 154.1, 162.2, 164.7 (d, $J = 250$ Hz); FT-IR (ν , cm^{-1}) 2919, 1611, 1508, 1403; GC/MS m/z 244.2, 213.3, 136.2, 91.3;

(E)-1-(2-Bromo-phenyl)ethanone O-benzyloxime (3f).^{6b}—The product was purified by silica gel column chromatography (20 g, long 11.7 cm, diam 0.75 cm) with hexane/ethyl acetate (20:1). The fractions 2–5 were collected and concentrated to obtain a light yellow oil (1.05 g, 87%): ^1H NMR (400 MHz, CDCl_3) δ 2.33 (s, 3H), 5.31 (s, 2H), 7.25 (m, 1H), 7.33 (m, 3H), 7.46 (m, 4H), 7.64 (dd, $J = 1.2$ Hz, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CHCl_3) δ 16.92, 76.1, 121.9, 127.4, 127.8, 128.0, 130.0, 133.1, 138.0, 138.9, 157.1; FT-IR (ν , cm^{-1}) 3031, 2922, 1364, 1012, 752, 695.

(E)-1-(4-Bromophenyl)ethanone O-benzyloxime (3g).²⁰—White crystals purified by recrystallization (3.53 g, 58%): mp. 58–59 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.29 (s, 3H), 5.29 (s, 2H), 7.42 (m, 5H), 7.53 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 12.6, 123.3, 127.6, 127.8, 128.2, 128.4, 131.5, 135.5, 137.9, 153.9.

(E)-1-(3,4-Difluorophenyl)ethanone O-benzyloxime (3h)—Purified by silica gel column chromatography as a clear oil (2.52 g, 94%): ^1H NMR (400 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.31 (s, 2H), 7.20 (m, 1H), 7.43 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.5,

76.5, 115, 152; GC/MS m/z 261.3, 231.2, 91.2 [13.70 min (2% *Z*), 15.62 min (98% *E*)]; HRMS (ESI-TOF) m/z [M + H]⁺ Calcd for C₁₅H₁₃F₂NO: 262.1038; Found: 262.1041.

(*E*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethanone O-benzyloxime (3i).²¹—The crude product was purified by flash silica gel column chromatography to give a clear oil (3.2 g, 86%): ¹H NMR (400 MHz, CDCl₃) δ 2.36 (s, 3H), 5.55 (s, 2H), 7.46 (m, 5H), 7.91 (s, 1H), 8.16 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 12.5, 119–127.3 (q, *J* = 121 Hz), 122.4 (m, *J* = 4 Hz), 126.0 (d, *J* = 3 Hz), 128.1, 128.3, 128.5, 131.8 (q, *J* = 33 Hz), 137.4, 138.6, 152.1; GC/MS (Rt 14 min) m/z 362.2, 213.1, 151.1, 91.1, 77.2.

(*E*)-1-(2-Fluoro-4-methoxyphenyl)ethanone O-benzyloxime (3j).—Purified by column chromatography as an oil (3.8 g, 79%): ¹H NMR (400 MHz, CDCl₃) δ 2.33 (s, 3H), 3.85 (s, 3H), 5.30 (s, 2H), 6.70 (m, 2H), 7.4 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 15.6, 55.3, 76.1, 102.1 (d, *J* = 25 Hz), 110.1 (d, *J* = 3.0 Hz), 117.7 (d, *J* = 13 Hz), 127.8, 128.1, 128.4, 128.5, 130.2 (d, *J* = 5 Hz), 130.1, 153.5 (d, *J* = 1 Hz), 160.2, 161.5 (d, *J* = 11 Hz), 162.7; GC/MS m/z [17.87 min]: 273.1, 91.1, 65.1; HRMS (ESI-TOF) m/z [M + H]⁺ Calcd for C₁₆H₁₆NO₂F: 274.1238; Found: 274.1250.

(*E*)-1-Naphthalen-1-yl-ethanone O-benzyloxime (3k).²²—The product was purified by silica gel (60 g) flash column chromatography using hexane/ethyl acetate (17:1 V/V) as a white solid (5.12 g, 74%): mp. 36–37 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.47 (s, 3H), 5.37 (s, 2H), 7.4–7.5 (m, 9H), 7.89 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 17.6, 76.1, 76.8, 77.1, 77.4, 76.1, 125.2, 125.6, 126.0, 126.5, 127.9, 129.3, 128.4, 128.5, 129.1, 130.9, 133.9, 135.5, 138.3, 157.0.

(*Z*)-Acetophenone O-benzyloxime (7a).²³—The product was purified by preparative TLC as a yellow oil (0.785 g, 58%): ¹H NMR (C₆D₆) δ 2.07 (s, 3H), 5.23 (s, 2H), 7.14–7.23 (m, 6H), 7.27 (m, 2H), 7.39 (m, 2H); ¹³C NMR (C₆D₆) δ 21.3, 75.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.7, 134.8, 138.8, 153.2; FT-IR (ν, cm⁻¹) 692, 736, 764, 881.9, 1039, 1114, 1208, 1364, 1434, 1495, 1607, 2918, 3031; GC/MS m/z 225.2 (M⁺), 118.1, 91.1.

(*Z*)-1-(*p*-Tolyl)ethanone O-benzyloxime (7b).—The product was purified by silica gel column chromatography as a yellow oil (1.34 g, 68%): ¹H NMR (C₆D₆) δ 2.12 (s, 3H), 2.14 (s, 3H), 5.27 (s, 2H), 7.03–7.05 (m, 2H), 7.14–7.18 (m, 1H), 7.22–7.27 (m, 2H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.58 (d, *J* = 7.2 Hz, 2H); ¹³C-NMR (C₆D₆) δ 21.0, 21.2, 76.0, 76.2, 127.2, 127.5, 127.6, 127.8, 128.5, 128.7, 128.8, 128.9, 131.9, 138.5, 138.9, 153.0, 160.1; GC/MS m/z 239.3 (M⁺), 132.3 (M⁺-OBn), 91.2.

(*Z*)-1-(4-Methoxyphenyl)ethanone O-benzyloxime (7c).—The product was purified by silica gel column chromatography as a yellow oil (1.1 g, 58%): ¹H NMR (C₆D₆) δ 2.14 (s, 3H), 3.34 (s, 3H), 5.30 (s, 2H), 6.79–6.82 (m, 2H), 7.17–7.19 (m, 1H), 7.23–7.27 (m, 3H), 7.44–7.46 (m, 2H), 7.68–7.71 (m, 2H); ¹³C NMR (C₆D₆) δ 21.1, 54.5, 76.1, 113.3, 113.7, 126.7, 127.1, 127.6, 127.7, 127.8, 128.3, 128.5, 130.4, 138.9, 152.1, 160.1; FT-IR (ν, cm⁻¹) 696, 732, 830, 882, 927, 1006, 1029, 1104, 1181, 1258, 1304, 1372, 1437, 1454, 1509, 1605, 2919, 3030.7; GC/MS m/z 255.2 (M⁺), 225.2, 91.1.

(*Z*)-1-(3-Methoxyphenyl)ethanone O-benzyloxime (7d).—Yellow oil (0.67 g, 75%): ¹H NMR (CDCl₃) δ 2.16 (s, 3H), 3.73 (s, 3H), 5.09 (s, 2H), 6.84–6.87 (m, 1H), 7.02–7.06 (m, 2H), 7.25–7.30 (m, 6H); ¹³C NMR (CDCl₃) δ 21.9, 55.3, 76.0, 113.8, 114.7, 120.3, 127.7, 128.0, 128.4, 129.3, 135.9, 138.4, 154.2, 159.3; FT-IR (ν, cm⁻¹) 694, 734, 782, 875, 909, 931, 1036, 1083, 1112, 1182, 1228, 1287, 1365, 1429, 1453, 1468, 1578, 1598, 1682,

2919, 3030; GC/MS m/z 254.3 (M^+), 91.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd. for $C_{15}H_{14}BrNONa$: 396.1546; Found: 396.1546.

(Z)-1-(4-Chlorophenyl)ethanone O-benzyloxime (7e)—The product was purified by preparative TLC as a yellow oil (0.98 g, 63%): 1H NMR ($CDCl_3$) δ 2.16 (s, 3H), 5.09 (s, 2H), 7.26–7.34 (m, 7H), 7.43–7.44 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.6, 76.1, 127.7, 127.9, 128.3, 128.4, 129.6, 132.7, 134.8, 138.1, 152.8; FT-IR (ν , cm^{-1}) 733, 766, 826, 884, 931, 1012, 1038, 1091, 1104, 1208, 1289, 1307, 13645, 1398, 1433, 1454, 1489, 1593, 2918, 3032; GC/MS m/z 258.2 (M^+), 91.1

(Z)-1-(4-Bromophenyl)ethanone O-benzyl oxime (7f)²⁰—Yellow oil (0.79 g, 70%): 1H NMR (C_6D_6): δ 1.95 (s, 3H), 5.20 (s, 2H), 7.16–7.30 (m, 7H), 7.36–7.38 (m, 2H); ^{13}C NMR (C_6D_6) δ 20.9, 76.2, 122.9, 127.6, 128.0, 128.1, 128.3, 128.4, 129.9, 131.2, 133.2, 138.4, 152.0; FT-IR (ν , cm^{-1}) 732, 821, 884, 908, 1008, 1038, 1070, 1101, 1208, 1288, 1307, 1364, 1395, 1434, 1454, 1486, 1588, 2918, 3031; GC/MS m/z 303.2 (M^+), 91.1.

(Z)-1-(3-Bromophenyl)ethanone O-benzyloxime (7g)—Yellow oil (0.59 g, 71%): 1H NMR ($CDCl_3$) δ 2.21 (s, 3H), 5.22 (s, 2H), 7.17–7.36 (m, 8H), 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.9, 76.3, 122.8, 124.9, 128.1, 128.4, 128.6, 129.3, 130.1, 132.1, 138.0, 138.9, 153.8; IR (ν , cm^{-1}) 692, 733, 886, 908, 933, 996, 1038, 1070, 1116, 1209, 1281, 1364, 1433, 1454, 1472, 1559, 1591, 1723, 2922, 3031; GC/MS m/z 304.1 (M^+), 91.1; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{15}H_{15}BrNO$: 304.03370; Found: 304.03370.

(Z)-1-(4-Nitrophenyl)ethanone O-benzyloxime (7h)⁷ⁱ—Yellow oil (0.87 g, 71%): 1H NMR ($CDCl_3$) δ 2.22 (s, 3H), 5.11 (s, 2H), 7.25–7.34 (m, 5H), 7.61–7.63 (m, 2H), 8.22–8.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.6, 76.5, 123.6, 128.0, 128.1, 128.6, 129.1, 137.8, 141.0, 147.8, 152.4; FT-IR (ν , cm^{-1}) 694, 734, 750, 854, 887, 910, 933, 1012, 1038, 1113, 1179, 1209, 1302, 1344, 1433, 1454, 1493, 1517, 1596, 2924, 3033; GC/MS m/z 268.2 (M^+), 91.1.

(Z)-1-(Naphthalen-1-yl)ethanone O-benzyloxime (7i)—The crude product was first purified by column chromatography on silica gel and then recrystallized in hexane to obtain a white solid (4.1 g, 60%): mp. 56–57 °C; 1H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 5.10 (s, 2H), 7.14–7.20 (m, 3H), 7.25 (m, 4H), 7.3 (m, 2H), 7.35 (m, 1H), 7.36 (m, 1H), 7.37 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.3, 75.7, 123.7, 125.2, 125.9, 126.0, 126.2, 127.4, 127.6, 127.7, 127.8, 128.1, 128.3, 128.4, 129.5, 133.7, 135.5, 138.9, 154.7; FT-IR (ν , cm^{-1}) 777, 803, 876, 971, 1025, 1038, 1208, 1369, 1438, 1504, 1590, 1626, 3362; GC-MS m/z 274.2 (M^+), 91.2; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{19}H_{18}NO$: 276.1383; Found: 276.1388.

General Procedure for the Asymmetric Reduction of (*E*)-Benzyloximes with Spiroborate 1 as Catalyst.^{8a,17}

To an oven dried test tube under a N_2 atmosphere, 10% of catalyst EG-DPV catalyst **1** (33 mg, 0.1 mmol) was added and dissolved in anhydrous 1,4-dioxane (5 mL). A solution of BH_3 –THF (4 mL, 1 M, 4 mmol) was added and the solution was stirred for 30 min. The solution was cooled at 0 °C, and *O*-benzyloxime (1.0 mmol) dissolved in 1,4-dioxane (5 mL) was added at a slow rate *via* a syringe. After 72 h, the reaction was quenched with methanol (5 mL). The solution was refluxed for 4 h and the solvent was removed under reduced pressure. Water (10 mL) was added and the aqueous solution was extracted with diethyl ether (3 $\times$ 25 mL). The organic phase was collected, dried over potassium carbonate and the solvent removed under vacuum. To the crude product dissolved in of dry CH_2Cl_2 (10 mL) were added triethylamine Et_3N (417 μ , 3.0 mmol), acetic anhydride (284 μ , 3.0

mmol) and a small crystal of DMAP (*N,N*-dimethylamino pyridine). The reaction mixture was stirred overnight at room temperature. The mixture was transferred to a separatory funnel and extracted with water (10 mL) and brine (7 mL). The organic phase was collected, dried over Na₂SO₄, filtered and concentrate under vacuum. The crude acetamide derivative was purified by silica gel column chromatography or preparative TLC and the enantiopurity was analyzed by GC using the Chrompack Chiralsil-Dex-CB column (30 m × 25 mm × 0.25 [m]) or by HPLC with Chiral Cell OD-H or Chiral Pack AD-H columns.

(S)-N-[1-(2-Methoxyphenyl)ethyl] acetamide (5a).²⁵—The crude product was purified by preparative TLC using petroleum ether/ethyl acetate (2:1 v/v) obtaining a white solid (252 mg, 88%): mp. 155–157 °C, Lit.²⁵ 142–144 °C; chiral GC [method isothermal 120 °C, Rt 46.8 min (98.9%), 48.4 (1.1%)] 98% *ee*; [α]_D²⁰ = −9.6 (*c* 11.0, CHCl₃), Lit.²⁵ [α]_D²⁰ = −38.3 (*c* 1.69, EtOH); ¹H NMR (400 MHz, CDCl₃) δ 1.49 (d, *J* = 6.8 Hz, 3H), 2.01 (s, 3H), 3.93 (s, 3H), 5.31 (q, *J* = 7.2 Hz, 1H), 5.45 (s, 1H), 6.96 (m, 2H), 7.27 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 21.4, 23.8, 47.5, 55.3, 111.1, 120.9, 128.1, 128.4, 130.8, 157.1, 168.7; FT-IR (ν, cm^{−1}) 3313, 1642, 1436, 1240.

(S)-N-[1-(3-Methoxyphenyl)ethyl] acetamide (5b).²⁶—The crude acetamide was purified by preparative TLC using petroleum ether/ethyl acetate (3:1) as an oil (256 mg, 88%): chiral GC [method isothermal 145 °C/flow = 0.8 mL/min, Rt 20.6 (97.4), 21.1 (2.6)] 95% *ee*; [α]_D²² = −104 (*c* 0.28, CHCl₃); NMR (400 MHz, CDCl₃) δ 1.50 (d, *J* = 6.8 Hz, *J* = 7.2 Hz, 3H), 2.08 (s, 3H), 3.84 (s, 3H), 5.12 (m, *J* = 7.2 Hz, 1H), 6.0 (s, 1H), 6.83 (m, 1H), 6.93 (d, *J* = 8 Hz, 1H), 7.29 (t, *J* = 8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 21.7, 23.4, 48.8, 55.2, 112.3, 112.4, 118.4, 129.7, 144.9, 159.8, 169.1; FT-IR (ν, cm^{−1}) 3253, 3068, 2975, 1643, 1532, 827, 755.

(S)-N-[1-(4-Methylthiophenyl)ethyl] acetamide (5c).²⁷—White solid (89% yield): mp. 104–106 °C chiral GC [isothermal 120 °C/flow = 0.8 mL/min, 44.7 min (98.9%), Rt 45.0 min (1.1%)] 97.8% *ee*; [α]_D²² = −14 (*c* 1.05, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.50 (d, *J* = 6.8 Hz, 3H), 2.04 (s, 3H), 3.84 (s, 3H), 5.10 (m, *J* = 7.4 Hz, 1H), 7.26 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 16.0 (CH₃), 21.6 (CH₃), 23.4 (CH₃), 21.6 (CH), 48.3, 126.4; 127.0, 137.4, 140.2.

(S)-1-[(2-Fluorophenyl)ethyl] acetamide (5d).²⁸—White solid (0.113 g, 62%): mp. 126–128 °C; chiral GC [method isothermal 120 °C/flow = 0.80 mL/min, Rt 29.85 min (94.3 %), 30.14 min (5.7%)] 88% *ee*; ¹H NMR (400Hz, CDCl₃) δ 1.53 (d, *J* = 7.2 Hz, 3H), 2.02 (d, 3H, *J* = 20 Hz), 5.31 (q, *J* = 7.2 Hz, 1H), 7.10 (m, 1H), 7.15 (1H, m), 7.28 (2H, m); ¹³C NMR (CDCl₃, 100 Hz) δ 21.5, 23.4, 45.7, 116.0 (d, *J* = 22 Hz), 124.4, 128.3 (d, *J* = 9 Hz), 130.9 (d, *J* = 14 Hz), 162.0 (d, *J* = 244 Hz), 169.1; GC/MS (Rt 11.82 min) *m/z* 181.1, 166.2, 124.1, 122.1, 103.1, 97.1; FT IR (ν, cm^{−1}) 3253, 3069, 2974, 1650 (C=O), 1553, 1375, 1228.

(S)-1-[(4-Fluorophenyl)-ethyl] acetamide (5e).²⁹—Clear white oil. (236 mg, 87%): chiral GC [method, isothermal 120 °C/flow = 0.8 mL/min, Rt 51.24 min (97.2%) and 61.28 min (2.7%)] 95% *ee*; [α]_D²⁰ −121 (*c* 1.4, CHCl₃), Lit.²⁹ [α]_D²⁵ = −104.8 (*c* 0.28, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.53 (s, 3H), 2.03 (s, 3H), 5.16 (m, 1H), 5.71 (s, 1H), 7.07 (m, 2H), 7.32 (t, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 21.7, 23.5, 48.2, 76.7, 77.0, 77.2, 77.36, 115.4, 115.6, 127.8, 127.9, 139.0, 139.0, 160.8, 163.2, 169.0; FT-IR (ν, cm^{−1}) 3254, 3070, 2976, 1638, 1554, 1509, 831.

(S)-N-[1-(2-Bromo-phenyl)ethyl] acetamide (5f).³⁰—White solid (289 mg, 80%), mp. 155–157 °C: HPLC [Chiral Cell OD-H column, method hexane/isopropyl alcohol (85:15),

flow 0.5 mL/min, Rt 11.4 min (0.75%), 14.4 (99.25%)] 97% *ee*; $[\alpha]^{20}_{\text{D}} = -4.0$ (*c* 2.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.52 (d, *J* = 7.2 Hz, 3H), 2.04 (s, 3H), 5.39 (m, 1H), 5.90 (s, 1H), 7.16 (m, 1H), 7.36 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 21.0, 23.3, 49.2, 123.0, 127.2, 127.7, 128.8, 133.5, 142.0, 168.9; FT-IR (ν, cm⁻¹, ATR) 3277, 1647, 1546, 1374.

(S)-N-[1-(4-Bromophenyl)ethyl] acetamide (5g).³¹—White solid (301 mg, 83%): mp. 155–157 °C; chiral GC [gradient method 90 °C/10 min, 4 °C/min up to 190 °C, 190 °C/35 min (70 min), Rt 34.4 min (97.7%), 35.3 (2.3%)] 95.4% *ee*; $[\alpha]^{20}_{\text{D}} = -85$ (*c* 1.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.50 (d, *J* = 6.8 Hz, 3H), 2.03 (s, 3H), 5.12 (m, 1H), 5.73 (s, 1H), 7.24 (d, *J* = 6.8 Hz), 7.50 (d, *J* = 6.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 21.6, 23.4, 48.2, 121.1, 127.9, 131.7, 142.3, 169.1.

(S)-N-[1-(3,4-Difluorophenyl)ethyl]-acetamide (5h).³²—The crude product was purified by preparative TLC using hexane/ethyl acetate (3:2) obtaining a white solid (253 mg, 84%): mp. 88–90 °C; chiral GC [gradient method 90 °C/10 min, 4 °C/min until 190 °C, 190 °C/35 min (70 min), Rt 26.68 min. (96%), 27.2 min. (4%)] 92% *ee*; $[\alpha]^{20}_{\text{D}} = -36$ (*c* 1.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.50 (d, *J* = 6.8 Hz, 3H), 2.03 (s, 3H), 5.11 (q, *J* = 7.2 Hz, 1H), 5.84 (s, 1H), 7.07 (m, 1H), 7.15 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 21.7, 23.3, 47.9, 115.1 (d, *J* = 17 Hz), 117.3 (d, *J* = 17 Hz), 122.1 (q, *J* = 3 Hz), 140.5 (t, *J* = 4.5 Hz), 148.1–149.1 (dd *J*₁ = 13 Hz, *J*₂ = 86 Hz) 151.6–150.6 (dd, *J* = 87 Hz, *J* = 13 Hz), 169.2; FT-IR (ν, cm⁻¹) 3256, 1609, 1551, 1274, 1114; HRMS (ESI-TOF) *m/z* [M + Na]⁺ Calcd for C₁₀H₁₁F₂NNaO: 222.0701; Found: 222.0705.

(S)-N-[1-(3,5-Bistrifluoromethylphenyl)ethyl] acetamide (5i).³²—White solid (0.348 g, 78%): mp. 88–90 °C; chiral GC [method isothermal 110 °C/flow = 0.8 mL/min, Rt 25.4 min, 1.8%, 26.17 min 98.1%] 92% *ee*; $[\alpha]^{20}_{\text{D}} = -58$ (*c* 1.1, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 1.57 (d, *J* = 7.2 Hz, 3H), 2.07 (s, 3H), 5.24 (m, *J* = 7.2 Hz, 1H), 5.98 (s, 1H), 7.81 (d, *J* = 7.6 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 21.9, 23.3, 48.4, 121.3 (t, *J* = 4 Hz), 121.9, 124.6, 126.3, 131.8 (t, *J* = 34 Hz), 146.2, 169.4; GC/MS (Rt 10.83 min) *m/z* 299.2, 256.1, 242.1, 240.1, 188.2, 72.1.

(S)-N-[1-(2-Fluoro-4-methoxyphenyl)ethyl]-acetamide (5j).²⁹—White solid (258 mg, 81%): mp. 86–87 °C; chiral GC [method isothermal 130 °C/flow = 0.8 mL/min, Rt 44.65 min (96.5%), 45.92 (3.5%)] 93% *ee*; $[\alpha]^{20}_{\text{D}} = -106$ (*c* 1.4, CHCl₃), Lit.²⁹ $[\alpha]^{20}_{\text{D}} = -47.9$ (*c* 0.82, EtOH) for the *S* enantiomer; ¹H NMR (400 MHz, CDCl₃) δ 1.51 (d, *J* = 7.2 Hz, 3H), 2.01 (s, 3H), 3.83 (s, 3H), 5.38 (m, 1H), 5.98 (s, 1H), 6.67 (m, 2H), 7.22 (1H, t, *J* = 8.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.5, 23.4, 45.3, 55.6, 102.4 (d, *J* = 25 Hz); 109.7 (d, *J* = 3 Hz) 122.2 (d, *J* = 14 Hz), 128.8 (d, *J* = 7 Hz); 161 (d, *J* = 24 Hz) 169.9; HRMS (ESI-TOF) *m/z* [M + Na]⁺ Calcd for C₁₁H₁₄FNNaO₂: 234.0901; Found: 234.0909.

(S)-N-[1-(Naphthalene-1-yl)ethyl] acetamide (5k).²⁵—White solid (0.165 g, 77%): mp. 136–138 °C; HPLC [column CHIRALCEL OD-H, 70:30 hexanes/isopropanol, flow 1.0 mL/min, Rt 4.2 min (4.5%), 7.1 min (95.5%)] 91% *ee*; $[\alpha]^{20}_{\text{D}} = +49$ (*c* 1.00, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 1.67 (t, *J* = 7.2 Hz, 3H), 1.97 (s, 3H), 5.73 (s, 1H), 5.99 (t, *J* = 7.1 Hz, 1H), 7.59 (m, 4H), 7.87 (d, *J* = 8 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 8.17 (d, *J* = 8.36 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 20.7, 23.4, 44.7, 122.6, 123.5, 125.2, 125.9, 126.7, 128.5, 128.8, 131.2, 133.9, 138.2, 168.9; GC/MS (Rt 17.89 min) *m/z* 213.2, 198.2, 170.2, 156.2, 129.2, 128.2, 127.2; FT-IR (ν, cm⁻¹) 3293, 3051, 2970, 1627, 1537, 1369, 1259.

General Procedure for the Asymmetric Reduction of (*Z*)-Benzyl Oximes with Spiroborate 1 as Catalyst.^{8a}

To an oven dried 25 mL two-necked flask charged with a magnetic stirrer and under N₂ was added catalyst **1** (0.15 equiv.) and dry THF (10 mL). A solution of BH₃–THF (1 M in THF) (4 equiv) was added in one portion. The resulting mixture was stirred at 25 °C for 30 min or until complete dissolution was observed. Hydrogen gas was liberated during the process. After the solution was cooled at 0 °C, a solution of benzyloxime (1 equiv) in 5 mL of THF was added at a slow rate via a syringe pump. The resulting mixture was stirred at 0 °C for 48 to 72 h, or until conversion was completed as determined by TLC. The reaction was slowly quenched with 6N HCl and then treated with 6N NaOH until the solution was basic. It was extracted with ether and the combined organic phases were washed with saturated aqueous NaCl solution and dried over anhydrous Na₂SO₄. The solvent was removed under vacuum and the residue was analyzed by GC and used directly to prepare the stable acetamide derivatives.

(*R*)-*N*-[1-(Phenyl)ethyl] acetamide (8a).^{25,33}—White solid (0.062 g, 76%): mp. 88–91 °C, Lit.³³ 89–91 °C; [α]_D²² = +114 (*c* 1.1, CHCl₃), Lit.³³ [α]_D²⁰ = +131 (*c* 1.0, CHCl₃); chiral GC [method isothermal 120 °C/flow = 0.8 mL/min, 42.40 min, Rt (1.3%), 46.37 min (98.7%)] 97% *ee*; ¹H NMR (CDCl₃) δ 1.46–1.48 (d, *J* = 7.2 Hz), 1.97 (s, 3H), 5.08–5.15 (m, 1H), 5.92 (br, 1H), 7.23–7.35 (m, 5H); ¹³C NMR (CDCl₃) δ 21.4, 23.1, 48.6, 125.2, 126.0, 127.1, 128.4, 142.9, 169.1.

(*R*)-*N*-[1-(*p*-Tolyl)ethyl] acetamide (8b).³⁴—White solid (61.5 mg, 74%): mp. 85–86 °C, Lit.³⁴ 80–81 °C; [α]_D²² = +140 (*c* 0.5, CHCl₃), Lit.³⁴ +146 (*c* 0.5, CHCl₃); chiral GC [gradient method: 70 °C for 30 min, then 1 °C/1 min up to 190 °C, then 40 min, Rt 28.24 min (4.0%), 28.67 (96.0 %)] 92% *ee*; ¹H NMR (CDCl₃) δ 1.45–1.47 (d, *J* = 6.8 Hz, 3H), 1.95 (s, 3H), 2.32 (s, 3H), 5.06–5.11 (m, 1H), 5.67 (br, 1H), 7.13–7.25 (m, 4H); ¹³C NMR (CDCl₃) δ 20.8, 21.4, 23.3, 48.3, 125.1, 125.9, 129.1, 136.9, 139.9, 168.8.

(*R*)-*N*-[1-(4-Methoxyphenyl)ethyl] acetamide (8c).³⁴—White solid (0.067 g, 90%): mp. 83–85 °C, Lit.³⁴ 82–83 °C; [α]_D²² = +140 (*c* 0.3, CHCl₃), Lit.³⁴ [α]_D²⁰ = +145 (*c* 1.0, CHCl₃); chiral GC [gradient method: start at 80 °C, increase 5 °C/min up to 150 °C, hold for 20 min, increase 5 °C/min up to 170 °C, hold for 40 min, increase 5 °C up to 195 °C and hold for 20 min, Rt 28.13 min (4.4%), 29.20 (95.6%)] 91% *ee*; ¹H NMR (CDCl₃) δ 1.61–1.63 (d, *J* = 6.8 Hz, 3H), 3.78 (s, 3H), 4.30–4.32 (m, 1H), 6.86–6.88 (m, 2H), 7.38–7.40 (m, 2H), 8.30 (br, 1H); ¹³C NMR (CDCl₃) δ 20.6, 51.2, 55.2, 114.3, 128.1, 129.9, 159.8.

(*R*)-*N*-[1-(3-Methoxyphenyl)ethyl] acetamide (8d).³⁵—Oily liquid (0.164 g, 75%); [α]_D²² = +87 (*c* 3.4, CH₃OH), Lit.³⁵ [α]_D²⁰ = +166.13 (*c* 1.0, CH₃OH); chiral GC [gradient method: start at 80 °C, increase 5 °C/min up to 150 °C, hold for 20 min, increase 5 °C/min up to 170 °C, hold for 40 min, increase 5 °C up to 195 °C and hold for 20 min, Rt 28.78 min (3.5%), 30.16 (96.5%)] 93% *ee*; ¹H-NMR (CDCl₃) δ 1.45–1.47 (d, *J* = 6.8 Hz, 3H), 1.97 (s, 3H), 3.79 (s, 3H), 5.06–5.09 (m, 1H), 5.95 (br, 1H), 6.77–6.90 (m, 3H), 7.22–7.26 (m, 1H); ¹³C NMR (CDCl₃) δ 21.9, 23.5, 49.0, 55.4, 112.4, 112.6, 118.6, 129.9, 145.1, 160.0, 169.4.

(*R*)-*N*-[1-(4-Chlorophenyl)ethyl] acetamide (8e).²⁵—White solid (0.134 g, 69%): mp. 96–98 °C, Lit.²⁵ 97–99 °C; [α]_D²² = +126 (*c* 1.0, CHCl₃), Lit.²⁵ [α]_D²⁰ = +122.3 (*c* 1.38, EtOH); chiral GC [gradient method: start at 80 °C, increase 5 °C/min up to 150 °C, hold for 20 min, increase 5 °C/min up to 170 °C, hold for 40 min, increase 5 °C up to 195 °C and hold for 20 min, Rt 25.04 min (3.9%), 26.07 (96.1 %)] 92% *ee*; ¹H NMR (CDCl₃) δ 1.45–

1.47 (d, $J = 6.8$ Hz, 3H), 1.98 (s, 3H), 5.07–5.11 (m, 1H), 5.64 (br, 1H), 7.23–7.34 (m, 4H); ^{13}C NMR (CDCl_3) δ 21.5, 23.2, 48.0, 127.1, 127.4, 128.5, 138.6, 132.9, 141.5.

(R)-N-[1-(4-Bromophenyl)ethyl]acetamide (8f).³⁶—White solid (0.17 g, 73%); mp. 133–135 °C, Lit.³⁶ 101.5–103.2 °C; $[\alpha]_{\text{D}}^{22} = +80$ (c 1.6, CHCl_3 , Lit.³⁶ $[\alpha]_{\text{D}}^{21} = +72.2$ (c 1.02, CHCl_3); chiral GC [gradient method: start at 80 °C, increase 5 °C/min up to 150 °C, hold for 20 min, increase 5 °C/min up to 170 °C, hold for 40 min, increase 5 °C up to 195 °C and hold for 20 min, Rt 34.16 min (3.7%), 35.57 (96.3 %)] 92% *ee*; ^1H NMR (CDCl_3) δ 1.45–1.47 (d, $J = 6.8$ Hz), 1.98 (s, 3H), 5.06–5.09 (m, 1H), 5.71 (br, 1H), 7.17–7.19 (m, 2H), 7.44–7.46 (m, 2H); ^{13}C NMR (CDCl_3) δ 21.7, 23.5, 48.3, 121.2, 128.0, 131.8.

(R)-N-[1-(3-Bromophenyl)ethyl] acetamide (8g).³⁶—Light yellow liquid (0.7 g, 79%); $[\alpha]_{\text{D}}^{22} = +94$ (c 4.3, CHCl_3), Lit.³⁶ $[\alpha]_{\text{D}}^{21} = +46.7$ (c 1.05, CHCl_3); chiral GC [gradient method: start at 80 °C, increase 5 °C/min up to 150 °C, hold for 20 min, increase 5 °C/min up to 170 °C, hold for 40 min, increase 5 °C up to 195 °C and hold for 20 min, Rt 24.67 min (3.5%), 25.56 (96.5 %)] 93% *ee*; ^1H NMR (CDCl_3) δ 1.44–1.45 (d, $J = 6.8$ Hz, 3H), 1.98 (s, 3H), 5.05–5.08 (m, 1H), 5.93 (br, 1H), 7.16–7.26 (m, 2H), 7.36–7.39 (m, 2H); ^{13}C NMR (CDCl_3) δ 21.9, 23.5, 48.5, 122.9, 125.2, 129.3, 130.4, 130.6, 145.9, 169.4.

(R)-N-[1-(4-Nitrophenyl)ethyl] acetamide (8h).³⁷—White solid; (0.87 g, 71%); mp. 131–134 °C; $[\alpha]_{\text{D}}^{22} = +115$ (c 0.8, CHCl_3); Lit.³⁷ $[\alpha]_{\text{D}}^{22} = +146.7$ (c 2.97, EtOH); chiral GC [gradient method: start at 80 °C, increase 5 °C/min up to 150 °C, hold for 20 min, increase 5 °C/min up to 170 °C, hold for 40 min, increase 5 °C up to 195 °C and hold for 20 min, Rt 52.79 min (10%), 54.45 (90%)] 80% *ee*; ^1H NMR (CDCl_3) δ 1.496–1.513 (d, $J = 6.8$ Hz, 3H), 2.02 (s, 3H), 5.15–5.19 (m, 1H), 5.73 (br, 1H), 7.45–7.48 (m, 2H), 8.17–8.21 (m, 2H); ^{13}C NMR (CDCl_3) δ 22.0, 23.5, 48.8, 124.1, 127.1, 151.0, 169.5.

(R)-N-[1-(Naphthalen-1-yl)ethyl]acetamide^{24,25} (8i)—White solid (0.287 g, 79%); mp. 148–151 °C, Lit.²⁴ 153 °C, (*S* isomer), Lit.²⁵ 147–149 °C; chiral GC [gradient method: start at 80 °C, increase 5 °C/min up to 150 °C, hold for 20 min, increase 5 °C/min up to 170 °C, hold for 40 min, increase 5 °C up to 195 °C and hold for 20 min, Rt 45.59 min (100%), 44.9 min (0%)] >99% *ee* $[\alpha]_{\text{D}}^{22} = +36$ (c 0.8, CHCl_3), Lit.²⁴ $[\alpha]_{\text{D}}^{20} = -47.9$ (c 0.82, EtOH, (*S* isomer, 78% *ee*); ^1H NMR (CDCl_3) δ 1.66–1.67 (d, $J = 6.8$ Hz), 1.96 (s, 3H), 5.65 (br, 1H), 5.91–5.95 (m, 1H), 7.43–7.56 (m, 4H), 7.79–7.87 (m, 2H), 8.09–8.11 (m, 1H); ^{13}C NMR (CDCl_3) δ 20.8, 23.6, 44.8, 122.8, 123.7, 125.4, 126.1, 128.6, 129.0, 131.3, 134.1, 138.4, 169.0.

Typical procedure for the Synthesis of Class I Calcimimetics Analogues

(R)-3-(2-Chlorophenyl)-N-(1-naphthalen-1-yl-ethyl)propionamide (10b)—To an oven dried 50 mL round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet, 3-(2-chlorophenyl)propionic acid (0.188 g, 1 mmol) and anhydrous CH_2Cl_2 (4 mL) were added. Dicyclocarbodiimide (DCC) (0.229 g, 1.1 mmol) and dimethylaminopyridine (DMAP) (12.3 mg, 0.10 equiv) were added and the solution was stirred for 1 h at 25 °C. A cloudy mixture was observed. Subsequently, (*S*)-*N*-(1-naphthalene-1-yl)ethyl amine (1.0 mmol, 0.175 g) was added to the solution and stirred for 30 min. The reaction was monitored by TLC (mobile phase, hexane/ethyl acetate, 1:1). After the reaction was completed, the solution was filtered through a celite-pad (60 ml filter, 1.5 cm height) and washed with CH_2Cl_2 (50 mL). The solvent was removed under vacuum using the rotoevaporator and purified by column chromatography using silica (100–400 mesh, 60 Å 21 g, 2 cm diameter) and a mobile phase composed of $\text{CH}_3\text{Cl}/\text{MeOH}$ (1600: 9 v/v) to obtain a white solid (0.335 g, 99%); mp. 126–127 °C; chiral HPLC [column CHIRALCEL OD-H, flow rate 0.8 mL/min, MeOH 80%, hexane 20%, Rt 4.85 min (50.69%) 5.39 min (49.31%)]

>99% *ee*; $[\alpha]_D^{22} = +26$ (*c* 2.67, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.65 (d, *J* = 6.8 Hz), 2.52 (t, *J* = 7.6 Hz), 3.14 (td, *J* = 8.0 Hz, *J*₂ = 2.2 Hz, 2H), 5.66 (d, *J* = 8.0 Hz, 1H, NH), 5.96 (m *J* = 7.4 Hz, 1H), 7.15 (m, 2H), 7.25 (m, 1H), 7.46 (m, 2H), 7.57 (dd, *J* = 6.6 Hz, *J* = 2.2 Hz, 1H), 7.90 (dd, *J* = 6.6 Hz, *J* = 2.2 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 23.7, 30.4, 31.4, 53.7, 122.8, 123.0, 125.3, 125.8, 126.7, 127.2, 127.3, 129.0, 129.5, 130.4, 131.4, 133.9, 134.0, 139.8, 141.4. FT-IR (ν, cm⁻¹): 3287.59 (NH), 3055, 2928, 1698, 1631, 1538, 778, 757; HRMS (ESI-TOF) *m/z* [M + H]⁺ Calcd for C₂₁H₂₁ClNO: 338.1306; Found: 338.1317.

(*R*)-3-(2-Chlorophenyl)-*N*-1-(naphthalene-1-yl)propan-1-amine (11b).^{5l,m}—To an oven dried 50 mL round bottom flask equipped with condenser, a magnetic stirring bar and a nitrogen inlet, (*S*)-3-(2-chloro-phenyl)-*N*-(1-naphthalen-1-yl-ethyl)propionamide (**10b**) (0.606 g, 1.87 mmol) and anhydrous THF (1.82 mL) was added. Then, BH₃–THF (2.02 mL, 1 M, 2 mmol) was added and the reaction mixture was refluxed overnight. After the mixture was allowed to cool at room temperature, methanol (5 mL) was slowly added. The mixture was heated to reflux and left to cool at room temperature and concentrated under vacuum. The residue was washed with water (15 mL) and extracted with diethyl ether (15 mL × 3). The organic phase was collected and dried over potassium carbonate. After filtration and solvent removal under vacuum, the oily product was purified by column chromatography using hexane/ethyl acetate (8:2) to afford a clear oil (0.12 g, 70%). $[\alpha]_D^{22} = +27$ (*c* 2.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.56 (d, *J* = 6.4 Hz), 1.89 (t, *J* = 7.6 Hz), 2.71 (m, 2H), 2.83 (m, 4H), 4.71 (quart, *J* = 6.4 Hz, 1H), 7.18 (m, 3H), 7.38 (m, 1H), 7.54 (m, 3H), 7.73 (d, *J* = 6.8 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 20.7, 29.6, 36.3, 44.6, 122.5, 123.4, 125.2, 125.8, 126.5, 126.9, 127.0, 127.8, 127.9, 128.3, 128.7, 129.4, 129.6, 130.8, 131.1, 133.7, 133.9, 138.2, 138.2, 170.6; FT-IR (ν, cm⁻¹): 3060, 2925, 2859, 1595, 1571, 799, 679.

(*R*)-3-(2-Chlorophenyl)-*N*-1-(naphthalene-1-yl)propan-1-amine hydrochloride salt—To a stirred solution of (*R*)-3-(2-chlorophenyl)-*N*-1-(naphthalene-1-yl)propan-1-amine (0.124 mg, 0.38 mmol, 1.0 equiv) in dichloromethane (3 mL) at room temperature was added dropwise a solution of chlorotrimethylsilane (0.050 mL, 1.14 mmol, 3.0 equiv) in methanol (0.015 mL, 1.14 mmol, 3.0 equiv). The reaction was stirred overnight at room temperature and the solvent was removed under reduced pressure. The product was washed with diethyl ether obtaining white crystals (54 mg, 44%): mp. 193–195 °C; ¹H NMR (400 MHz, CDCl₃, ppm) δ 2.06 (d, *J* = 6.8 Hz, 3H), 2.33 (t, *J* = 7.8 Hz), 2.63 (m, 2H), 2.83 (s, 2H), 5.25 (s, 1H), 7.10 (m, 2H), 7.21 (m, 1H), 7.63 (m, 3H), 7.97 (m, 3H), 8.29 (d, *J* = 6.8 Hz, 1H), 10.09 (s, 1H), 10.65 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 21.4, 25.7, 30.3, 45.4, 53.3, 121.3, 125.1, 126.1, 126.2, 126.8, 127.3, 127.7, 129.4, 129.4, 130.1, 130.7, 132.2, 133.7, 133.8, 137.4; FT-IR (ν, cm⁻¹) 2963.0, 2711, 1588, 756–681.

(*R*)-*N*-(1-Naphthalen-1-yl-ethyl)-3-phenyl-propionamide (10a).^{38a}—To an oven dried 25 mL round bottom flask equipped with a magnetic stirring bar and nitrogen inlet were added 3-propionic acid (0.98 g, 0.65 mmol) and anhydrous CH₂Cl₂ (8 mL). Dicyclocarbodiimide (DCC) (0.148 g, 0.71 mmol) and dimethylaminopyridine (DMAP) (8 mg, 0.06 mmol) were added and the solution was stirred for 1 h at 25 °C. Then, (*S*)-*N*-(1-naphthalen-1-yl)ethyl amine (112 mg, 0.65 mmol) was added and the reaction mixture was stirred for additional 30 min. After the solution was filtered through a silica (20 g) and celite pad (7.3 g) and washed with a mixture CH₂Cl₂/CH₃OH (160:0.9), the solvent was removed under vacuum. (Naphthalen-1-yl-ethyl)-3-phenyl-propionamide was obtained (179 mg, 91%) as a bone white solid: mp. 166–167 °C; HPLC [column CHIRALCEL® OD-H, flow rate 0.8 mL/min, MeOH 40%, Hexane 60%, Rt 4.66 min (100%) 6.45 min (0%)] >99 % *ee*; $[\alpha]_D^{22} = +35$ (*c* 2.67, CHCl₃); ¹H NMR (100 MHz, CDCl₃) δ 1.64 (d, *J* = 6.8 Hz, 3H), 2.50

(t, $J = 7.4$ Hz, 2H), 3.02 (m, 2H), 2.59 (d, $J = 7.6$ Hz, 2H), 5.95 (t, $J = 7.4$ Hz, 1H), 7.19–7.31 (m, 5H), 7.42–7.52 (m, 2H), 7.52–7.54 (m, 2H), 7.83 (d, $J = 7.6$ Hz, 1H), 7.92 (d, $J = 7.2$ Hz, 1H), 8.11 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.6, 31.7, 38.5, 44.6, 122.5, 123.4, 125.19, 125.8, 126.2, 126.6, 128.3, 128.4, 128.5, 128.7, 131.1, 133.9, 138.1, 140.7, 170.1.

(R)-N-(1-Naphthalen-1-yl-ethyl)-3-phenyl-propionamide (10a).^{38a}—White solid (179 mg, 91%); mp. 166–167 °C; HPLC [column CHIRALCEL® OD-H, flow rate 0.8 mL/min, MeOH 40%, Hexane 60%, Rt 4.66 min (100%) 6.45 min (0%)] >99 % ee; $[\alpha]_D^{22} = +35$ (c 2.67, CHCl_3); ^1H NMR (100 MHz, CDCl_3) δ 1.64 (d, $J = 6.8$ Hz, 3H), 2.50 (t, $J = 7.4$ Hz, 2H), 3.02 (m, 2H), 2.59 (d, $J = 7.6$ Hz, 2H), 5.95 (t, $J = 7.4$ Hz, 1H), 7.19–7.31 (m, 5H), 7.42–7.52 (m, 2H), 7.52–7.54 (m, 2H), 7.83 (d, $J = 7.6$ Hz, 1H), 7.92 (d, $J = 7.2$ Hz, 1H), 8.11 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.6, 31.7, 38.5, 44.6, 122.5, 123.4, 125.19, 125.8, 126.2, 126.6, 128.3, 128.4, 128.5, 128.7, 131.1, 133.9, 138.1, 140.7, 170.1.

(R)-[(1-Naphthalen-1-yl-ethyl)-(3-phenyl)-propylamine (11a).^{38b}—After filtration and solvent removal under vacuum, the oily product was purified by preparative TLC over silica gel using hexane/ethyl acetate (5:1) and 0.4 % of Et_3N to afford a clear oil (171 mg, 59%); $[\alpha]_D^{22} = +35$ (c 2.67, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.56 (d, $J = 6.4$ Hz, 3H), 2.67–2.79 (m, 4H), 4.70 (quart, $J = 6.4$ Hz, 1H), 7.23 (m, 3H), 7.33 (t, $J = 7.0$ Hz, 2H), 7.56 (m, 3H), 7.72 (d, $J = 7.2$ Hz, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.94 (d, $J = 7.6$ Hz, 1H), 8.26 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.7, 32.1, 33.7, 47.6, 53.7, 122.7, 123.0, 125.3, 125.7, 127.1, 128.3, 128.4, 129.0, 131.4, 134.0, 141.4, 142.2.

Typical procedures for Synthesis of Class II Calcimimetics Analogues

1-(3-Bromopropoxy)-2-chlorobenzene.³⁹—To a round-bottomed flask, equipped with a magnetic stirring bar were added sodium hydride (43.2 g, 1.8 mmol) and anhydrous DMF (5 mL). The reaction mixture was cooled at 0 °C and 2-chlorophenol (257 mg, 2.0 mmol) was added using a syringe. The reaction mixture was stirred for 1.5 h at 0 °C and 1,3-dibromopropane (606 μL , 6.0 mmol) was added dropwise. The mixture was stirred at 25 °C overnight. The reaction was quenched with an aqueous solution of NH_4Cl (10 mL) and extracted with ether (3 $\times$ 15 mL). The organic phase was dried over Na_2SO_4 , filtered and concentrated to obtain 287 mg of clear oil that was purified by gradient column chromatography over silica gel (silica 8.0 g, 1.0 mm diam., 13 mm long), starting with hexane then with hexane/ethyl acetate (15:1) to obtain a clear oil (267 mg, 46 %); ^1H NMR (400 MHz, CDCl_3) δ 2.42 (m, $J = 10$ Hz, 2H), 3.72 (t, $J = 6.4$ Hz, 2H), 4.24 (t, $J = 6.0$ Hz, 2H), 6.98 (m, 2H), 7.28 (m, 1H), 7.27 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) 30.0, 32.3, 66.4, 113.6, 121.7, 123.1, 127.7, 130.3, 154.2; GC/MS (Rt 13.28 min, 80%) m/z 250, 248.1, 128.1, 102.1; (Rt 19.97 min, 20%) m/z 296.1, 169.1, 168.2, 141.1.

2-(3-Bromo-propoxy)-1,3-dimethyl-benzene.⁴⁰—The crude product was purified by preparative TLC using hexane/ethyl acetate (30:1) as mobile phase obtaining a clear oil (488 mg, 58%); GC/MS (Rt 8.42 min, 21%) m/z : 162.1, 147.2, 91.2, 72.2; (Rt 12.91 min, 73%): 242.1, 122.2, 107.3, 91.2; ^1H NMR (400 MHz, CDCl_3) δ 2.36 (s, 6H), 2.40 (m, 2H), 3.76 (t, $J = 6.6$ Hz, 2H), 3.95 (d, $J = 5.8$ Hz, 2H), 6.98–7.08 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.2, 30.3, 33.5, 69.0, 123.9, 128.8, 130.9, 155.5; FT-IR (ν , cm^{-1}) 2873, 1479, 1262.

1-(3-Bromopropoxy)-3-(trifluoromethyl)benzene.⁴¹—The product was purified by preparative TLC (20 $\times$ 20 cm, 1500 microns) using hexane/ethyl acetate (20:1) as mobile phase to give a clear oil (600 mg, 53%); ^1H NMR (400 MHz, CDCl_3) δ 2.39 (m, $J = 6$ Hz, 2H), 3.67 (t, $J = 6.4$ Hz, 2H), 4.20 (m, $J = 5.8$ Hz, 2H), 7.13 (m, $J = 8$ Hz, 1H), 7.20 (s, 1H), 7.28 (t, $J = 7.6$ Hz, 1H), 7.45 (t, $J = 8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 29.7, 32.2,

65.5, 111.3, 117.6, 117.7, 121.2 (q, $J = 271$ Hz), 130.0, 131.9 (q, $J = 32$ Hz), 158.8; FT-IR (ν , cm^{-1}) 2939, 2882, 1591, 1326, 1237, 1100, 783, 748, 563.

(3-Bromo-propylsulfanyl)-benzene.⁴²—The crude mixture was purified by silica gel column chromatography (35 g, 2.6 cm diam, 14.5 cm long) using hexane. The fractions 19–42 were combined and concentrated to obtain a clear oil (503 mg, 71%): ^1H NMR (400 MHz, CDCl_3) δ 2.20 (m, 2H), 3.12 (t, $J = 6.8$ Hz, 2H), 3.58 (t, $J = 6.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 31.8, 32.0, 126.3, 129.0, 129.6, 135.6; FT-IR (ν , cm^{-1}) 1479, 710; GC/MS (Rt, 13.12 min) m/z 232.0, 151.1, 123.1, 110.2.

1-(3-Bromo-propylsulfanyl)-4-methyl-benzene.⁴³—The product was purified by preparative TLC using hexane/ethyl acetate (65:1) as mobile phase to give a yellow oil (613 mg, 63%): ^1H NMR (400 MHz, CDCl_3) δ 2.17 (m, $J = 6.6$ Hz, 2H), 2.38 (s, 3H), 3.07 (t, $J = 6.6$ Hz), 3.57 (t, $J = 6.4$ Hz, 2H), 7.16 (d, $J = 4.4$ Hz, 2H), 7.32 (d, $J = 4.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.7, 31.9, 32.0, 33.2, 129.8, 130.5, 131.7, 136.6; FT-IR (ν , cm^{-1}) 2921.4, 1600, 1492, 1433.

(R)-N-[3-(2-Chlorophenoxy)-propyl]-N-(1-naphthalen-1-yl-ethyl)-amine (13a)—The product was purified by preparative TLC using hexane/ethyl acetate (6:1), obtaining a yellow oil (131 mg, 56%): HPLC of *N*-acetyl derivative [chiral column CHIRALPAK AD-H, method 96% hexane: 4% isopropanol, flow 1.0 ml/min, 16.4 min (100%), 18.7 min (0%)] >99% *ee*; $[\alpha]_{\text{D}}^{20} = +55$ (c 1.25, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 1.57 (d, $J = 6.4$, 3H), 2.08 (m, 2H), 2.87 (m, 2H), 4.16 (t, $J = 6.0$ Hz, 2H), 4.73 (m, 1H), 6.92 (m, 2H), 7.24 (m, 1H), 7.40 (m, 1H), 7.41 (m, 1H), 7.47 (m, 3H), 7.70 (d, $J = 7.2$ Hz, 1H), 7.78 (d, $J = 7.2$ Hz, 1H), 7.91 (m, 1H), 8.25 (t, $J = 4.8$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 23.6, 29.6, 45.1, 53.9, 67.8, 113.2, 121.3, 122.7, 122.9, 123.0, 125.3, 125.7, 127.1, 127.7, 128.9, 130.2, 131.4, 134.6, 141.2, 154.4; HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{22}\text{ClNO}$: 340.1463; Found: 340.1459.

(R)-N-[3-(2-Chlorophenoxy)propyl]-N-(1-naphthalen-1-yl-ethyl)-amine-Hydrochloride salt—White crystals (82%): mp. 145 °C; $[\alpha]_{\text{D}}^{20} = -7.0$ (c 1.0, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 2.12 (d, $J = 6.4$ Hz), 2.50 (m, 2H), 3.19 (m, 2H), 4.09 (m, 2H), 6.35 (s, 1H), 6.87 (m, 2H), 7.16 (m, 1H), 7.28 (dd, $J = 1.4$ Hz, 8 Hz, 1H), 7.61 (m, 3H), 7.95 (m, 2H), 8.08 (d, $J = 8.4$ Hz, 1H), 8.24 (d, $J = 7.2$ Hz, 1H), 9.88 (s, 1H), 10.76 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 21.3, 25.9, 43.8, 53.7, 66.2, 113.4, 121.4, 121.8, 122.8, 124.9, 126.0, 126.2, 127.3, 129.4, 129.5, 130.1, 130.7, 132.1, 133.9, 153.6; FT-IR (ν , cm^{-1} , ATR): 2787, 2726, 1589, 1584, 1487, 1278, 1065, 891.

(R)-N-[3-(2,6-Dimethyl-phenoxy)propyl]-(1-naphthalen-1-yl-ethyl)-amine (13b)—The crude product was purified by preparative TLC using hexane: ethyl acetate (6:1) and 0.4 % of triethyl amine obtaining 103 mg as a clear yellow oil (62%): HPLC of *N*-acetyl derivatives [chiral column: CHIRALCEL OD-H, hexane/isopropyl alcohol 95:5%, flow 0.7 mL/min, 20.2 min (1.0%), 23.7 min (99.0%)] 98% *ee*; $[\alpha]_{\text{D}}^{20} = +11$ (c 5.2, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 1.60 (d, $J = 6.8$ Hz, 3H), 2.08 (t, $J = 6.6$ Hz, 2H), 2.31 (s, 6H), 2.89 (d, $J = 6.8$ Hz, 2H), 3.89 (m, 2H), 4.74 (q, $J = 6.8$ Hz, 1H), 6.96 (dd, $J = 6.8$ Hz, $J = 1.2$ Hz, 1H), 7.04 (dd, $J = 16.8$ Hz, $J = 6.8$ Hz, 2H), 7.56 (m, 3H), 7.54 (d, 1H, $J = 6.8$ Hz), 7.80 (d, $J = 8.4$ Hz, 1H), 7.93 (d, $J = 1.6$ Hz, 1H), 8.31 (d, $J = 1.6$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 16.3, 23.6, 31.1, 45.4, 53.8, 70.8, 122.7, 123.0, 123.7, 125.3, 125.7, 127.2, 128.8, 129.0, 130.9, 131.3, 134.0, 141.2, 156.0; FT-IR (ν , cm^{-1}): 2924, 1474, 1263, 1200, 1129, 776, 734; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}$: 334.2165; Found: 334.2172.

(R)-3-(2,6-Dimethyl-phenoxy)-propyl-(1-naphthalen-1-yl-ethyl)-amine-

Hydrochloride salt—The crude product was obtained as a white solid (84%, 33 mg): mp. 211–213 °C; $[\alpha]_D^{20} = -6.0$ (c 1.2, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 2.02 (s, 6H, CH_3), 2.26 (d, $J = 6.4$ Hz, 3H, CH_3), 2.52 (m, 2H, CH_2), 3.16 (s, 2H, CH_2), 3.73 (d, $J = 2$ Hz, 2H, CH_2), 5.36 (s, 1H, CH), 6.9 (m, 2H), 7.15 (m, 1H), 7.65 (m, 3H), 7.96 (d, $J = 9$ Hz, 2H, CH), 8.10 (d, $J = 8.4$ Hz, 1H), 8.31 (d, $J = 8.4$ Hz, 1H), 10.1 (s, 1H, NH_2^+), 10.74 (s, 1H, NH_2^+); ^{13}C NMR (100 MHz, CDCl_3) δ 16.1, 21.2, 27.1, 44.1, 53.5, 68.9, 121.4, 123.9, 125.2, 126.1, 126.2, 127.3, 128.8, 129.5, 129.6, 130.5, 130.8, 132.1, 133.9, 155.2; FT IR (ν , cm^{-1}): 2962, 2726.3, 1590, 1471, 1260, 1198.

(R)-N-1-(Naphthalen-1-yl-ethyl)-[3-(3-trifluoromethyl-phenoxy)-propan]-1-

amine (13c)—To a stirred solution of (*R*)-1-(naphth-1-ylethyl)amine (93 mg, 0.5 mmol, 1.0 equiv), triethyl amine (84 μL , 0.6 mmol, 1.2 equiv) and dry THF (2 mL) at 25 °C was added a solution of 1-(3-bromopropoxy)-3-trifluoromethyl benzene (141 mg, 0.82 mmol, 1.0 equiv) in dry THF (2 mL). A small amount (10 mg) of 1,4-(*N,N*-dimethylamino)pyridine (DMAP) was then added. The reaction mixture was heated at reflux for 24 h and monitored by TLC. After the reaction was completed, the solvent was removed under vacuum. The reaction mixture was transferred to a separatory funnel with 10 mL of water and extracted with CH_2Cl_2 (3 $\times$ 10 mL). The organic phase was washed with brine (10 mL), dried over K_2CO_3 , filtered and concentrated to obtain 169 mg of yellow oil. The product was purified by preparative TLC (20 $\times$ 20 cm) using hexane/ethyl acetate (10:1) and 0.4% Et_3N as mobile phase to give a clear oil (129 mg, 69%); HPLC (chiral column: CHIRALCEL OD-H, method 3% IPA, 97% hex, flow 0.9 mL/min) of the *N*-acetyl derivative, R_t 26.3 min (0.4%), 31.1 min (99.6%) 99% *ee*; $[\alpha]_D^{21} +24$ (c 1.10, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.57 (d, $J = 6.4$ Hz), 2.03 (m, 2H), 2.83 (m, 2H), 4.12 (t, $J = 6.0$ Hz, 2H), 4.71 (q, $J = 6.53$ Hz, 1H), 7.06 (d, $J = 8.2$ Hz, 1H), 7.13 (s, 1H), 7.24 (d, $J = 7.6$ Hz, 1H), 7.41 (t, $J = 8$ Hz, 1H), 7.51 (m, 1H), 7.69 (d, $J = 6.8$ Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.92 (m, 1H), 8.26 (t, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.6, 29.9, 44.6, 53.9, 66.5, 111.3, 117.2, 118.0, 122.7, 122.9, 125.3, 125.6, 125.7, 127.2, 129.0, 129.9, 130.3, 131.6, 131.9, 134.0, 141.1; FT-IR (ν , cm^{-1}) 3356, 3048, 2963, 1595, 1509, 1119, 1023, 860, 798; HRMS (ESI-TOF) m/z [$\text{M} + \text{Na}$] $^+$ Calcd for $\text{C}_{22}\text{H}_{22}\text{F}_3\text{NNaO}$: 396.1546; Found: 396.1546.

(R)-N-1-(Naphthalen-1-yl-ethyl)-[3-(3-trifluoromethylphenoxy)-propan]-1-amine

Hydrochloride salt—To a solution of the amine (90 mg, 0.24 mmol, 1.0 equiv) in 3 ml of diethyl ether and 1.0 ml of hexane under nitrogen was added dropwise TMSCl (90 μL , 0.72 mmol, 30 equiv) and methanol (33 μL , 0.72 mmol, 30 equiv). After 15 min, the solvent was removed from the precipitate using a Pasteur pipette and the crystals rinsed with cold ether. The solvent was removed under reduced pressure to give a white solid (79 mg, 81%): mp. 115–117 °C; $[\alpha]_D^{21} = -5.4$ (c 1.1, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 2.12 (d, $J = 5.4$ Hz, 3H), 2.52 (s, 2H), 3.08 (s, 2H), 4.01 (s, 2H), 5.32 (s, 1H), 6.89 (d, $J = 8.4$ Hz, 2H), 7.17 (d, $J = 7.6$ Hz, 1H), 7.31 (m, 1H), 7.67–7.69 (m, 3H), 7.95 (dd, $J = 8.0$ Hz, $J = 16$ Hz, 2H), 8.06 (d, $J = 8.4$ Hz, 1H), 8.27 (d, $J = 6.4$ Hz, 1H), 10.10 (s, 1H), 10.76 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 25.9, 43.4, 53.8, 65.2, 111.3, 117.6, 117.6, 121.3, 124.9, 126.1, 126.1, 126.3, 127.4, 129.4, 129.9, 130.3, 132.1, 133.9, 159.1; FT-IR (ν , cm^{-1}) 2708, 1588, 1450, 1328, 1118, 777, 695.

(R)-1-(Naphthalen-1-yl-ethyl)-(3-phenylsulfanyl-propyl)-amine (13d)

—After the typical procedure, the crude product was purified by preparative TLC using hexane/ethyl acetate (6:1) obtaining a yellow oil (1.02 g, 61%); HPLC of *N*-acetyl derivative [chiral column CHIRALPAK AD-H, method 96% hexane, 4% isopropyl alcohol, flow 1.0 mL/min, 16.4 min (100%), 18.1 min (0%)] >99% *ee*; $[\alpha]_D^{20} = +33$ (c 2.3, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.56 (d, 3H, $J = 6.4$ Hz), 1.89 (quint., $J = 7.2$ Hz, 2H), 2.76 (m, 2H), 3.04

(m, 2H), 4.68 (m, 1H), 7.27 (t, $J = 2.0$ Hz, 1H), 7.31–7.39 (m, 4H), 7.56 (m, 3H), 7.71 (d, $J = 6.8$ Hz, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.93 (dd, $J = 2.0$ Hz, $J = 7.2$ Hz, 1H), 8.25 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.7, 29.9, 31.6, 46.7, 53.8, 122.7, 123.0, 125.3, 125.7, 125.8, 125.9, 127.2, 128.9, 129.0, 129.2, 131.3, 134.0, 136.6, 141.1; GC/MS (Rt 16.19 min) m/z 321.2, 206.2, 170.2, 155.2, 141.2; FT-IR (ν , cm^{-1}) 1734, 1438, 1264, 1130, 690; HRMS (ESI-TOI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{23}\text{NS}$: 322.1624; Found: 322.1631.

(*R*)-(1-Naphthalen-1-yl-ethyl)-(3-phenylsulfanyl-propyl)-amine-Hydrochloride salt—Beige solid (85 mg, 90%); mp. 192–194 °C; $[\alpha]_D^{20} = -29$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.73 (s, 3H), 2.29 (s, 2H), 2.95 (s, 4H), 5.24 (s, 1H), 7.17 (m, 4H), 7.62 (m, 4H), 7.99 (m, 3H), 8.26 (d, $J = 5.6$ Hz, 1H), 10.0 (s, 1H), 10.50 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 25.5, 31.2, 44.9, 53.9, 121.4, 125.0, 126.1, 126.2, 126.3, 127.3, 128.9, 129.4, 129.5, 129.7, 130.7, 132.1, 133.9, 135.2; FT-IR (ν , cm^{-1}): 953, 2785, 1585, 1450, 1250, 691.

(*R*)-(1-Naphthalen-1-yl-ethyl)-(3-*p*-tolylsulfanyl-propyl)-amine (13e).⁴⁴—The crude product was purified by preparative TLC (20 × 20 cm, 1500 microns) using hexane/ethyl acetate (5:1). The product with $R_f = 0.32$ was recovered and the sample concentrated to obtain a brown oil (128 mg, 77%); HPLC of *N*-acetyl derivative [chiral column: CHIRALCEL OD-H, hexane/IPA (92:8 v/v); flow 0.7 mL/min, 20.1 min (100%)] > 99% *ee*; $[\alpha]_D^{20} = +17$ (c 2.5, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.56 (d, $J = 6.8$ Hz, 3H), 1.87 (m, $J = 2.8$ Hz, 2H), 2.37 (s, 3H), 2.76 (m, 2H), 2.99 (m, 2H), 4.67 (quart, $J = 6.8$ Hz, 1H), 7.13 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 4.8$ Hz, 2H), 7.56 (m, 3H), 7.70 (d, $J = 6.8$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.94 (m, 1H), 8.24 (d, $J = 1.2$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 21.0, 23.6, 29.9, 39.3, 46.7, 53.7, 122.7, 129.0, 129.7, 130.1, 131.3, 132.7, 134.0, 136.0, 141.1; FT-IR (ν , cm^{-1}): 3047, 2920, 1595, 1492, 1368, 798.5, 734.

(*R*)-(1-Naphthalen-1-yl-ethyl)-(3-*p*-tolylsulfanyl-propyl)-amine-Hydrochloride salt—White solid (58 mg, 92%); $[\alpha]_D^{20} = -17.0$ (c 3.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 2.05 (d, $J = 6.8$ Hz, 3H), 2.18–2.32 (m, 2H), 2.22 (s, 3H), 2.82–2.89 (m, 2H), 2.91–2.99 (m, 2H), 5.21 (s, 1H), 6.98 (d, $J = 8.4$ Hz, 2H), 7.09 (d, $J = 8.4$ Hz, 2H), 7.60–7.66 (m, 2H), 7.66–7.71 (m, 1H), 7.94–8.00 (m, 1H), 8.27 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (100 MHz CDCl_3) δ 21.0, 23.6, 29.9, 39.3, 46.7, 53.7, 122.7, 129.0, 129.7, 130.1, 131.3, 132.7, 134.0, 136.0, 141.1; FT-IR (ν , cm^{-1}): 2780, 1585, 1449, 1235, 1118, 777, 695.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The project described was supported by Award Number U54 RR026139 from the National Center for Research Resources, and the Award Number 8U54MD 007587-03 from the National Institute on Minority Health and Health Disparities. Support for undergraduate scholars by the NIH-INBRE, NIH-RISE, NIH-MARC, and NSF-AMP programs is also gratefully acknowledged.

References and Notes

1. Nugent TC. Chiral Amine Synthesis: Methods, Developments and Applications. Wiley-VCH Verlag GmbH & CoWeinheim2010Johansson A. Contempt Org Syn. 1995; 2:393–406. and refs cited therein Jamali F. Stereochemically Pure Drugs. Drug Stereochemistry Analytical Methods and Pharmacology. Wainer W. Marcel Dekker IncNew York1993:375–384.Ojima I. Catalytic Asymmetric Synthesis. Wiley-VCH VerlagWeinheim2000Reddy IK, Mehvar R. Chirality in Drug

Design and Development. Taylor & Francis New York 2004; 1:13, 14. Aboul-Enein HY, Wainer IW. The Impact of Stereochemistry on Drug Development and Use. Wiley-Interscience. John Wiley and Sons, Inc New York 1997 Kobayashi S, Ishitani H. Chem Rev. 1999; 99:1069. [PubMed: 11749440] Enders D, Reinhold U. Tetrahedron: Asymm. 1997; 8:1895. Bandala Y, Juaristi E. Aldrichimica Acta. 2010; 43:65.

2. (a) Boezio AA, Pytdowicz J, Côte A, Charette AB. J Am Chem Soc. 2003; 125:14260. [PubMed: 14624558] (b) Kim M-J, Kim W-H, Han KY, Choi K, Park J. Org Lett. 2007; 9:1157. [PubMed: 17291005] (c) Arpin A, Manthorpe JM, Gleason JL. Org Lett. 2006; 8:1359. [PubMed: 16562891] (d) Davies NM, Teng XV. Advances in Pharmacy. 2003; 1:242. (e) Patocka J, Dvorak A. J Applied Med. 2004; 2:95. (f) Chen F, Ding Z, Qin J, Wang T, He Y, Fan QH. Org Lett. 2011; 13:4348. [PubMed: 21766831] (g) Davis FA, Zhou P, Chen BC. Chem Soc Rev. 1998; 27:13. (h) Fernández H, Hooper MW, Knight FI, Brown JM. Chem Commun. 1997:173. (i) Fernández H, Maeda K, Hooper MW, Brown JM. Chem—Eur J. 2000; 6:1840. [PubMed: 10845644] (j) Tanuwidjaja J, Peltie HM, Ellman J. J Org Chem. 2007; 72:627. (k) Lin GQ, Zhong YW, Sun XW. Acc Chem Res. 2008; 41:831. [PubMed: 18533688] (l) Wang YQ, Lu SM, Zhou YG. J Org Chem. 2007; 72:3729. [PubMed: 17444684]
3. **For recent chiral amino drugs syntheses see:** Chen CY, Reamer RA. Org Lett. 1999; 1:293. [PubMed: 10822565] Bloomgarden Z. Diabetes Care. 2000; 23:405. [PubMed: 10868872] Fuchs M, Koszelewski D, Tauber K, Kroutil W, Faber K. Chem Commun. 2010; 46:5500. Mangas-Sanchez J, Rodríguez-Mata M, Busto E, Gotor-Fernandez V, Gotor V. J Org Chem. 2009; 74:5304. [PubMed: 19555095] Thiel OR, Bernard C, King T, Dilmeghani-Seran M, Bostick R, Larsen RD, Faul MM. J Org Chem. 2008; 73:3508. [PubMed: 18351744]
4. **For studies on bioactivity of calcimimetics agents see:** Brown EM. Physiol Rev. 1991; 71:371. [PubMed: 2006218] Brown EM, Gamba G, Riccardi D, Lombardi M, Butters R, Kifor O. Nature. 1993; 366:575. [PubMed: 8255296] Nagano N, Nemeth EF. J Pharmacology Sci. 2005; 97:355. Nemeth EF, Steffey ME, Hammerland LG, Hung BCP, Van Wagenen BC, Del J, Mar EG, Balandrin MF. Proc Natl Acad Sci USA. 1998; 95:4040. [PubMed: 9520489] Nagano N. Pharmacology & Therapeutics. 2006; 109:339. [PubMed: 16102839] Franceschini N, Joy MS, Kshirsagar A. Expert Opin Invest Drugs. 2003; 12:1413. Serra, AI; Schwarz, A.; Wick, F. Nephrol Dial Transplant. 2005; 20:1315. [PubMed: 15941845] Harrington PE, Fotsch C. Curr Med Chem. 2007; 14:3027. [PubMed: 18220738] Guerra R, Auyanet I, Fernández EJ, Pérez MÁ, Bosch E, Ramírez A, Suria S, Checa MD. Nephrol. 2011; 24:78. Marquis RW, Lago AM, Callahan JF, Lee Trout RE, Gowen M, DelMar EG, Van Wagenen BC, Logan S, Shimizu S, Fox J, Nemeth EF, Yang Z, Roethke T, Smith BR, Ward KW, Lee J, Keenan RM, Bhatnagar P. J Med Chem. 2009; 52:3982. [PubMed: 19492813] Torres P. J Ren Nutr. 2006; 253. [PubMed: 16825031]
5. **For the synthesis of calcimimetics analogues see:** Kessler A, Faure H, Petrel C, Ruat M, Dauban PM, Dodd RH. Bioorg Med Chem Lett. 2004; 14:3345. [PubMed: 15149704] Kessler A, Faure H, Petrel C, Césario M, Ruat M, Dauban PM, Dodd RH. J Med Chem. 2006; 49:5119. [PubMed: 16913701] Poon SF, StJean DJ, Harrington PE, Henley C III, Davis J, Morony S, Lott FD, Reagan JD, Ying-Lin Lu J, Yang Y, Fotsch C. J Med Chem. 2009; 52:6535. [PubMed: 19835382] Fernández I, Valdivia V, Khair N. J Org Chem. 2008; 73:745. [PubMed: 18154349] Yamazaki N, Atohe M, Kibayashi C. Tetrahedron Lett. 2001; 42:5029. Wang H, Katon J, Balan C, Bannon AW, Bernard C, Doherty EM, Dominguez C, Gavva NR, Gore V, Ma V, Nishimura N, Surapaneni S, Tang P, Tamir R, Thiel OR, Treanor JS, Norman MH. J Med Chem. 2007; 50:3528. [PubMed: 17585751] Dauban P, Ferry S, Faure H, Ruat M, Dodd RH. Bioorg Med Chem Lett. 2000; 10:2001. [PubMed: 10987436] Vijayavithal TM, Gorakshanath BS, Sharad SI, Navnath CN, Panchangam R, Vankwala PJ. Synth Commun. 2011; 41:341. Gorakshanath BS, Navnath CN, Deshmukh SP, Toche RB, Mathad VT. Org Process Res & Dev. 2011; 15:455. Han K, Kim Y, Park J, Kim M-J. Tetrahedron Lett. 2010; 51:3536. Teruyuki S, Atsuya T, Rika S. WO Patent. 1998N° 9801417. Van Wagenen BC, Moe ST, Balandrin MF, Delmar EG, Nemeth EF. US Patent. 2001US 6211244 B1 20010403. Van Wagenen BC, Moe ST, Balandrin MF, Delmar EG, Nemeth EF. PCT Int Appl. 1996WO 9612697 A2 19960502.
6. (a) France S, Guerin DJ, Miller SJ, Lectka T. Chem Rev. 2003; 103:2985. [PubMed: 12914489] (b) Klingensmith LM, Nadeau KA, Moniz GA. Tetrahedron Lett. 2007; 48:4589. (c) Han K, Park J, Kim M-J. J Org Chem. 2008; 73:4302. [PubMed: 18454550] (d) Paetzold J, Bäckvall JE. J Am Chem Soc. 2005; 127:17620. [PubMed: 16351088] (e) Skupinska KA, McEachern E, Bair IR,

- Skerlj RT, Bridger GJ. *J Org Chem.* 2003; 68:3546. [PubMed: 12713358] (f) Kozma, D. *CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation.* CRC Press LLC; Boca Raton, FL: 2002.
7. (a) Itsuno S, Nakano M, Miyazaki K, Masuda H, Ito K. *J Chem Soc Perkin Trans 1.* 1985:2039.(b) Itsuno S, Sakurai Y, Ito K, Hirao A, Nakahama S. *Bull Chem Soc Jpn.* 1987; 60:395.(c) Itsuno S, Sakurai Y, Shimizu K, Ito K. *J Chem Soc Perkin Trans 1.* 1990:1859.(d) Bolm C, Felder M. *Synlett.* 1994:655.(e) Cho BT, Ryu MH. *Bull Korean Chem Soc.* 1994; 15:191.(f) Lantos I, Flisak J, Liu L, Matsunoka R, Mendelson W, Stevenson D, Tubman K, Tucker L, Zhang WY, Adams J, Sorenson M, Garigipati R, Erhardt K, Ross S. *J Org Chem.* 1997; 62:5385.(g) Itsuno S, Matsumoto T, Sato D, Inoue T. *J Org Chem.* 2000; 65:5879. [PubMed: 10970344] (h) Fontaine E, Namane C, Meneyrol J, Geslin M, Serva L, Roussey E, Tissandié S, Maftouh M, Roger P. *Tetrahedron: Asymmetry.* 2001; 12:2185.(i) Krzeminski MP, Zaidlewicz M. *Tetrahedron: Asymmetry.* 2003; 14:1463.(j) Chu YB, Shan ZX, Liu DJ, Sun NN. *J Org Chem.* 2006; 71:3998. [PubMed: 16674084] (k) Pakulski MM, Mahato SK, Bosiak MJ, Krzeminski MP, Zaidlewicz M. *Tetrahedron: Asymmetry.* 2012; 23:716–721.(l) Sailes HE, Watts JP, Whiting A. *J Chem Soc Perkin Trans 1.* 2000:3362.
8. (a) Huang X, Ortiz-Marciales M, Huang K, Stepanenko V, Merced FG, Ayala AM, De Jesús M. *Org Lett.* 2007; 9:1793–1795. [PubMed: 17397177] (b) Ortiz-Marciales, M.; Huang, X.; Huang, K.; Stepanenko, V.; De Jesús, M.; Merced, FG. *PCT/US07/76195.* Aug 17. 2007 (c) Huang K, Merced FG, Ortiz-Marciales M, Meléndez HJ, Correa W, De Jesús M. *J Org Chem.* 2008; 73:4017. [PubMed: 18447392] (d) Huang K, Ortiz-Marciales M, Stepanenko V, De Jesús M, Correa W. *J Org Chem.* 2008; 73:6928. [PubMed: 18690744] (e) Huang K, Ortiz-Marciales M. *Organic Syntheses.* 2010; 87:36.
9. (a) Demir AS. *Pure Appl Chem.* 1997; 69:105.(b) Inoue T, Sato D, Komura K, Itsuno S. *Tetrahedron Lett.* 1999; 40:5379.(c) Sakito Y, Yoneyoshi Y, Suzukamo G. *Tetrahedron Lett.* 1988; 29:223.
10. (a) Sharghi H, Sarvari MH. *Synlett.* 2001; (1):99.(b) Coustard JM, Jacquesy JC, Violeau B. *Tetrahedron Lett.* 1992; 33:8085.(c) Smith JH, Kaiser ET. *J Org Chem.* 1974; 39:728.(d) Mrlina G, Calmon JP. *J Agric Food Chem.* 1980; 28:605.(e) Jousserandot A, Boucher JL, Henry Y, Niklaus B, Clement B, Mansuy D. *J Biochem.* 1998; 37:17179.(f) Srivastava VP, Patel R, Garima Yadav LDS. *Chem Commun.* 2010; 46:5808.(g) Parthasarathy K, Cheng C. *J Org Chem.* 2009; 74:9359. [PubMed: 19894732]
11. (a) Furuya Y, Ishihara K, Yamamoto H. *J Am Chem Soc.* 2005; 127:11240. [PubMed: 16089442] (b) Liu J, Tang X, Zhang Y, Zhao W. *Molecules.* 2012; 17:2464. [PubMed: 22382525] (c) Jeyakumar K, Deepan R, Dillip C, Chand K. *Cat Commun.* 2009; 10:1948.(d) Gregory BJ, Moodie RB, Schofield K. *J Chem Soc B: Physical Org.* 1970:338.(e) Udd S, Jokela R, Franzén R, Tois J. *Tetrahedron Lett.* 2010; 5:1030.(f) Ngwerume S, Camp JE. *J Org Chem.* 2010; 75:6271. [PubMed: 20718448] (g) Truh, S.; Gantz, F. *PCT Int Appl. WO 9308183 A1* 19930429. 1993. (h) Badal MMR, Mishima M. *Bull Chem Soc Jap.* 2010; 83:58.(i) Davodov DV, Beletskaya IP. *Russ J Org Chem.* 2004; 40:124.(j) Chang ZY, Coates RM. *J Org Chem.* 1990; 55:3464.
12. Eichinger K, Wokurek M, Zauner Bernd Wischinka P. *J Prak Chem/Chem-Zeit.* 1997; 339:92.
13. Chong SS, Fu Y, Liu L, Guo QX. *J Phys Chem A.* 2007; 111:13112. [PubMed: 18034467]
14. Brunner H, Becker R, Gauder S. *Organomet.* 1986; 5:739.
15. Mona HS, Hashem S. *J Chem Res.* 2006; 3:205.
16. Geffken D, Koellner MA. *Sci Syn.* 2008; 40b:937.
17. (a) Perkins M, Beam Charles FJ, Dyer MCD, Hauser CR. *Organic Syntheses.* 1976:55, 36.(b) Jousserandot A, Boucher JL, Henry Y, Niklaus B, Clement B, Mansuy D. *Biochemistry.* 1998; 37:17179. [PubMed: 9860831]
18. Eichinger K, Wokurek M, Zauner B, Wischinka P. *J Prak Chem Chem Zeitung.* 1997; 339:92. (E isomer).
19. Uno T, Gong B, Schultz PG. *J Am Chem Soc.* 1994; 116:1145.
20. Schaefer, P.; Mangold, D. *Eur Pat Appl. EP 52744 A1* 19820602.. 1982.
21. Bloom, J.; David Curran, KJ.; Digrandi, MJ.; Dushin, RG.; Lang, SA.; Norton, EB.; Ross, AA.; O'Hara, BM. *PCT Int Appl. WO 2000034238 A1* 20000615.. 2000.

22. Summers, JB., Jr; Stewart, AO.; Brooks, DW. PCT Int Appl. WO 2000034238 A1 20000615.. 2000.
23. Rad M, Navid S, Khalafi-Nezhad A, Karimitabar F, Behrouz S. Synthesis. 2010; 10:1724.
24. Duhamel L, Ravarda A, Plaquevent JC, Davoust D. Bull Soc Chim de France. 1990:787.
25. Li G, Antilla JC. Org Lett. 2009; 11:1075. [PubMed: 19199770]
26. Horiba M, Yamamoto S, Oi N. Agric Biol Chem. 1982; 46:1219.
27. Pirkle WH, Brice LJ, Terfloth GJ. J Chrom, A. 1996; 753:109.
28. Hu, Ai-Guo; Fu, Yu; Xie, Jian-Hua; Zhou, Hai; Wang, Li-Xin; Zhou, Qi-Lin. Angew Chem, Inter Ed. 2002; 41:2348.
29. Etayo P, Nuñez-Rico JL, Fernández-Perez H, Vidal-Ferran A. Chem A Eur J. 2011; 17:13978.
30. Lotz M, Polborn K, Knochel P. Angew Chem, Inter Ed. 2002; 41:4708.
31. Pallavicini M, Bolchi C, Fumagalli L, Valoti E, Villa L. Tetrahedron: Asymm. 2002; 13:2277.
32. Imamoto T, Tamura K, Zhang Z, Horiuchi Y, Sugiya M, Yoshida K, Yanagisawa A, Gridnev ID. J Am Chem Soc. 2012; 134:1754. [PubMed: 22192064]
33. Yu L, Wang Z, Wu J, Tu S, Ding K. Angew Chem, Inter Ed. 2010; 49:3627.
34. Kim MJ, Kim WH, Han K, Choi YK, Park J. Org Lett. 2007; 9:1157. [PubMed: 17291005]
35. Mangas-Sanchez J, Rodriguez-Mata M, Busto E, Gotor-Fernandez V, Gotor V. J Org Chem. 2009; 74(15):5305310.
36. Andrade LH, Barcellos T, Santiago CG. Tetrahedron: Asymm. 2010; 21:2419.
37. Ollis WD, Rey M, Sutherland IO. J Chem Soc, Perkin Trans. 1983; 1(5):1009.
38. (a) Suh, Y-Ger; Jang, J.; Yun, H.; Han, SMi; Shin, D.; Jung, J-K.; Jung, J-W. Org Lett. 2011; 13:5920. [PubMed: 21995717] (b) Kerr DIB, Ong J, Perkins MV, Prager RH, Puspawati NM. Australian J Chem. 2006; 59:445.
39. Capuano BC, Ian T, McRobb FM, Podloucka A, Taylor DA, Vom A, Yuriev E. Australian J Chem. 2010; 6:116.
40. Ryan JP, O'Connors PR. J Am Chem Soc. 1952; 74:5866.
41. Augstein J, Stephenson O, Thomas AJ. J Med Chem. 1965; 8:356. [PubMed: 14323147]
42. (a) Cagniant P, Deluzarche A. Compt Rend. 1946; 223:677.(b) Bordwell FG. J Am Chem Soc. 1954; 76:1082.(c) Carr, Richard VC.; Williams, RV.; Paquette, LA. J Org Chem. 1983; 4:4976.
43. Blight BA, Langler RF, Thompson DB, Ross CR II. J Sulfur Chem. 2006; 27:571.
44. Sakai, T.; Takami, A.; Suzuki, R. PCT Int Appl. WO 9801417 A1 19980115.. 1998.

FIGURE 1.
Most Active Single Isomeric Drugs

FIGURE 2.
Calcium Receptor Agonists Candidates.

SCHEME 1.
Synthesis of Calcimimetic Analogues using Enantiopure Amines.

SCHEME 2.
Synthesis of (*Z*)-(*O*)-Benzyloxime Ethers.

SCHEME 3.
Synthesis of Class I Calcimimetic Analogs.

TABLE 1

Synthesis and Reduction of (*E*)-1-Aryl and 1-Naphthylethanone (*O*)-Benzyloximes

entry					
	(<i>E</i>)-oxime 2	(%) ^a	(<i>E</i>)-benzyloxime 3 (%) ^b	(<i>S</i>)-amine 4	acetamide 5 (%) ^c
1		a 78	80		98
2		b 100 ^d	93		95
3		c 98	50		98
4		d 52	58		87
5		e 84	84		97

entry	(<i>E</i>)-oxime 2	(%) ^a	(<i>E</i>)-benzyloxime 3 (%) ^b	(<i>S</i>)-amine 4	acetamide 5 (%)	<i>ee</i> (%) ^c
6		f	89		80	97
7		g	84		91	98
8		h	76		84	92
9		i	82		81	91
10		j	93		81	93
11		k	72		84	92

^a Isolated yield of pure *E* isomer.

^b Isolated yield of pure (*E*)-benzyloxime isolated by column chromatography on silica gel.

^c Enantiopurity determined by GC of acetyl derivatives on chiral column (CP-Chirasil-Dex-CB).

^d Crude product

TABLE 2

Asymmetric Reduction of Representative (*Z*)-Benzyloximes.

entry	(Z)-oxime 6	(%) ^a	(Z)-oxime ether 7 (%) ^a	(R) amine ^b	8 (%) ^c	ee (%) ^d	
1		a	71	58		76	97
2		b	87	68		74	92
3		c	58	58		90	91
4		d	74	75		75	93
5		e	82	63		69	92

entry	(Z)-oxime 6	(%) ^a	(Z)-oxime ether 7 (%) ^a	(R) amine ^b	8 (%) ^c	ee (%) ^d
6		f 79	70		73	93
7		g 55	71		79	93
8		h 74	71		77	80
9		i 72	60		79	99

^a Isolated yield..

^b Reduction conditions: 0.15 equiv of spiroborate catalyst **1**, BH₃·THF, THF, 0 °C.

^c Isolated yield of acetamide derivatives.

^d Determined by GC of acetyl derivatives on chiral column (CP-Chirasil-Dex CB)

TABLE 3

Synthesis of Class II Calcimimetic Analogues

	12	yield of 13 (%) ^a	enantiopurity of 13 (%) ee ^b
a		73	>99
b		62	98
c		68	>99
d		61	>99
e		77	>99

^a Isolated yield as hydrochloride salt derivatives.^b The ee value was determined by HPLC of the acetamide using a CHIRALCEL OD-H column.