Tetrahedron: *Asymmetry* 20 (2009) 2234–2239

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A convenient synthesis of new diamine, amino alcohol and aminophosphines chiral auxiliaries based on limonene oxide

Cristina Cimarelli, Davide Fratoni, Gianni Palmieri *

Dipartimento di Scienze Chimiche, v. S. Agostino 1, 62032 Camerino, Italy

ARTICLE INFO

Article history:
Received 24 July 2009
Accepted 12 August 2009
Available online 14 September 2009

ABSTRACT

A strategy for the synthesis of new chiral auxiliaries based upon vicinal diamines, amino alcohols and aminophosphines, obtained from limonene oxide, has been developed. The methodology allows the preparation of (1*R*,2*R*,4*S*)-1-methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diamine starting from a commercially available mixture of *cis*/*trans* (4*S*)-(−)-limonene oxides, through a stereoconvergent synthetic sequence. The process starts from an inexpensive naturally occurring material, is amenable to scale-up and allows easy access to highly useful enantiopure building blocks and ligands, employed in asymmetric catalysis.

1. Introduction

Chiral vicinal diamines, amino alcohols and aminophosphines are important molecules that find application in several fields.[1] For instance, several synthetic diamine derivatives have been employed as chemotherapeutics as substitutes of cisplatin. Chiral 1,2-diamines are also used in organic synthesis as chiral auxiliaries. The large use of enantiomerically pure *trans*-1,2-diaminocyclohexane derivatives as broad-range chiral reagents and ligands for catalytic cycles in the field of asymmetric synthesis is well known in the literature.[1c] They can be used as chelants[1c] or organocatalysts[1e,f] to obtain enantiopure coordination compounds useful in homogeneous catalytic asymmetric synthesis.

The stereoselective synthesis of β-diamines and β-amino alcohols, without the need for enantiomer separation, was made starting from naturally occurring, inexpensive and readily available chiral materials, such as terpenes.[2] Limonene is a terpene widely used in the organic synthesis of enantiomerically pure molecules, as the chiral core of auxiliaries or ligands employed in stereoselective synthesis.[3]

2. Results and discussion

Herein, we report the synthesis of new chiral vicinal diamines, amino alcohols and derivatives obtained starting from limonene which is an inexpensive enantiomerically pure natural compound, easily obtained from the 'chiral pool' in both enantiomers. Moreover, we have chosen limonene because its structure allows for the preparation diamines containing a *trans*-1,2-diamminocyclohexane skeleton, widely fused in chiral reagents, scaffolds and ligands for catalysis.

The *cis*/*trans*-epoxides **1** of (4*S*)-(−)-limonene were converted to enantiomerically pure diamino limonene **8** through the intermediate azido-alcohols **2** and **3**, aziridines **4** and **5** and azido-amines **6** and **7** (Scheme 1).

The synthetic sequence begins with the opening of the (4*S*)-(−)-limonene oxides **1**, commercially available as a 47:53 mixture of the *cis*- and the *trans*-epoxides, with sodium azide in the presence of ammonium chloride as catalyst. Due to the difficulty involved in the separation of the two diastereomers of limonene oxide by physical means, even by gas chromatographic methods, synthetic routes to pure limonene oxide have been attempted by the kinetic separation of commercially available *cis* and *trans* mixture.[3f,g] The opening of the epoxides of each isomer is regio- and diastereoselective. The *trans*-diaxial approach of the nucleophile has long been established.[3a,f,4] The regioselectivity observed in this step can be explained by the inherent conformation difference between the *cis*- and *trans*-limonene oxide. For the *trans*-**1** isomer, an S_N2-type reaction can be envisioned to occur at the less hindered secondary carbon C-2 to afford azido-alcohol **2**.[5] For the *cis*-**1** isomer, there is evidence that an S_N1-type reaction takes place on the tertiary carbon C-1 with inversion of configuration at the C-1 centre to obtain derivate **3**.[6] Contrary to limonene oxide, the mixture of the azido-alcohols **2** and **3** can be separated quantitatively by silica gel column chromatography. The second step involves the formation of aziridines **4** and **5**. This reaction takes place with triphenylphosphine by a pseudo-Staudinger mechanism.[7] The Staudinger reaction on the secondary azide **2** is much faster; the azido-alcohol **2** is converted into *cis*-aziridine **4** at room temperature over a period of 48 h. Conversely, azido-alcohol **3** is changed to the corresponding *trans*-aziridine **5**, in 1,4-dioxane at reflux for 24 h[8] (to the best

* Corresponding author. Tel.: +39 0737 402241; fax: +39 0737 637345.
E-mail address: gianni.palmieri@unicam.it (G. Palmieri).

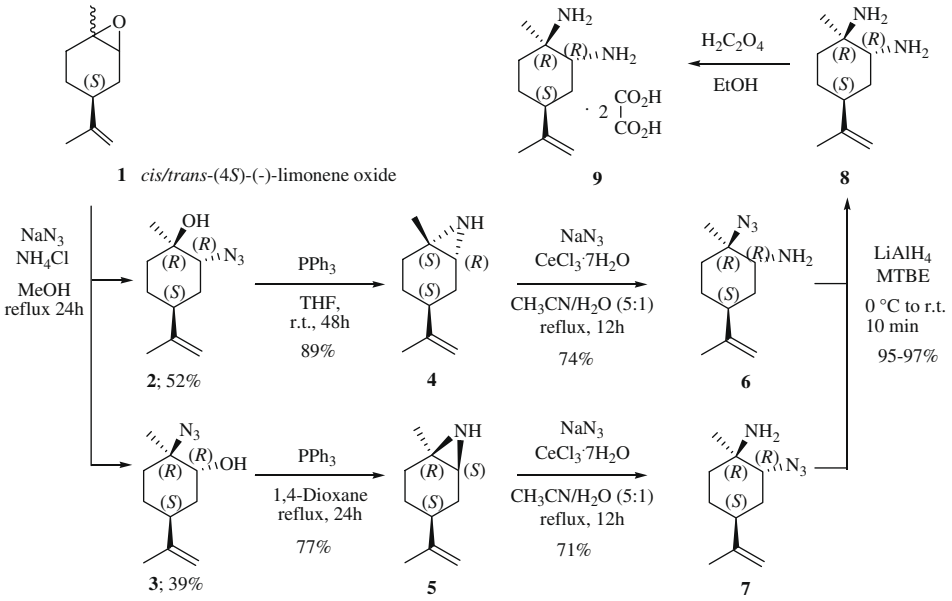
0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.08.012

of our knowledge, the spectroscopic data in Ref. 8 of these aziridines diastereomer are reversed). The different reactivities of the two azido-alcohols **2** and **3** provide an additional possibility in the stereoselective and scaleable synthesis of the two aziridine diastereomers from the commercially available mixture of limonene oxides.[8] The subsequent step is the formation of azido-amines **6** and **7** from the corresponding aziridines **4** and **5**. The reaction takes places with sodium azide and $CeCl_3 \cdot 7H_2O$ as a catalyst in acetonitrile. The nucleophilic ring opening of the limonene aziridines **4** and **5** is both regio- and diastereoselective and proceeds with the same stereochemical constraints that dictate the opening of the corresponding epoxides. Therefore, the reaction of *cis*-aziridine **4** with NaN_3 occurs at the more sterically hindered tertiary carbon C-1, forming the azido amine **6**. Instead, nucleophilic attack on *trans*-aziridine **5** occurs only at the less sterically hindered secondary carbon C-2 to give the adduct **7**.[9] The last reaction is the separate reduction of azido-amines **6** and **7** with $LiAlH_4$. In both the reduction reactions, the same enantiomerically pure *trans*-(1*R*,2*R*,4*S*)-diamino limonene **8** is formed. The liquid diamine **8** is purified by reaction with oxalic acid to form the crystalline solid **9**. Then, starting from a 1:1 mixture of *cis*- and *trans*-limonene oxides **1** we obtained enantiopure **8** by a diastereoconvergent synthesis. Therefore, we synthesized successively the *trans*-1,2-diamine **8**, on a multigram scale starting from a (4*S*)-(−)-limonene oxide mixture following the same passages as shown in Scheme 1, without splitting of the intermediates **2–7**, with an overall final yield of 52%.

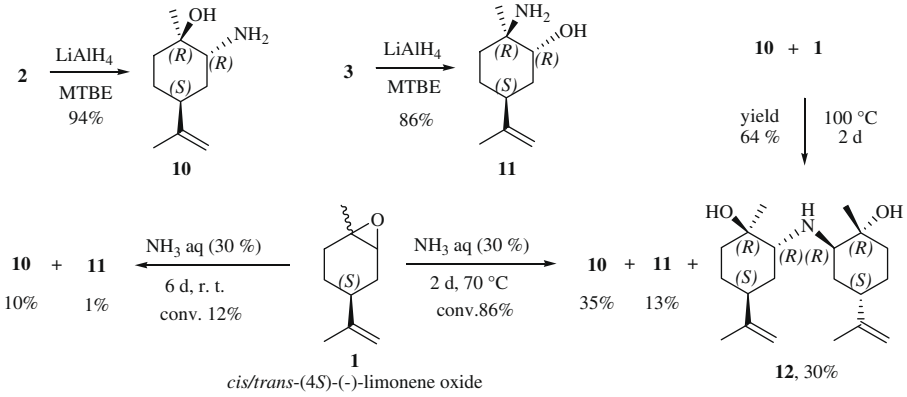
It is important to note that this sequence of reactions allows the preparation of *trans*-(1*S*,2*S*,4*R*)-diaminolimonene, an enantiomer of **8**, starting from the commercially available (+)-(4*R*)-limonene (the availability of both enantiomers of a chiral auxiliary is an important requirement in asymmetric synthesis).

The reduction of azido-alcohols **2** and **3**, obtained as pure stereoisomers in the procedure described above, leads to the corresponding amino alcohols **10** and **11**, respectively, via reduction with $LiAlH_4$ (see Scheme 2).

These compounds, which find important applications in asymmetric catalysis,[3a,10] were previously prepared from limonene oxide with good results when secondary amines were used. When dimethylamine or butylamine is used, more complex mixtures of amino alcohol stereoisomers, which are difficult to separate, were obtained.[3b] We have found that *cis*/*trans*-limonene oxide reacts



Scheme 1. Stereoconvergent synthesis of (1*R*,2*R*,4*S*)-1-methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diamine **8** starting from a commercially available mixture of *cis*/*trans* (4*S*)-(−)-limonene oxides **1**.



Scheme 2. Synthesis of amino alcohols **10–12**.

slowly at room temperature with aqueous ammonia at 30% with selective formation of the amino alcohol **10** (see Scheme 2). When the reaction was carried out at 70 °C, it led to high conversion of limonene oxide with the formation of various isomers of amino alcohols with poor selectivity (see Scheme 2) differently from what was reported in the literature.[3a] Under these conditions major amine **12** was isolated and characterized. The structure of this molecule corresponds to amino alcohol **12** with *C*2 symmetry, on the basis of the observation on the ^{1}H NMR spectrum that the H-2 at δ = 2.55 ppm (geminal to the amino group), is in an equatorial position showing the multiplicity of a dd (J = 5.1, 3.0 ppm). This is in agreement with the most stable conformation calculated for compounds **12** and **10** via stochastic methods (semiempirical PM3 minimization),[11] where the cumbersome isopropenyl group, is in the equatorial position, constraining the molecule in the conformation shown in Figure 1.[12] The same behaviour was observed for most compounds described in this work albeit with coupling constants that were very small for the ^{1}H NMR signal for the gauche equatorial H-2 proton.

To confirm the structure of amine **12** the conditions for its preparation from amine **10** in the presence of (4*S*)-(−)-limonene oxides **1** were optimized.

Since there is high demand for new chiral functionalized phosphine ligands for application in transition metal-catalyzed asymmetric synthesis,[1a,13] we have developed the synthesis of enantiopure N,P-ligands derived from limonene. Amines **8** and **10** give selectively an aza-Michael addition on diethyl vinylphosphonate (Scheme 3).

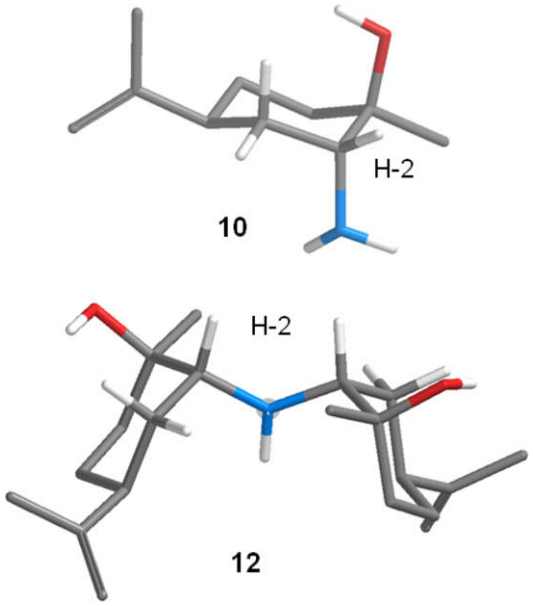
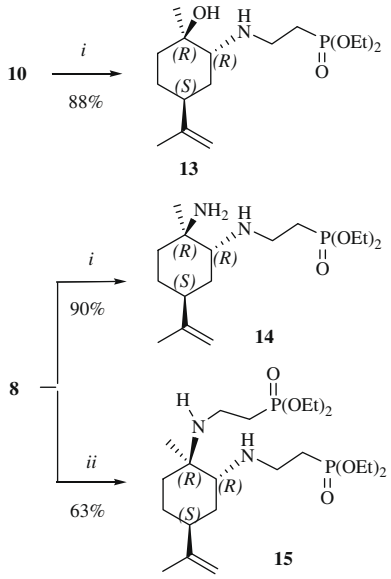


Figure 1. The more stable conformations for amino alcohols **10** and **12**.



Scheme 3. Reagents and conditions: (i) ethyl vinylphosphonate, 1 equiv, EtOH, reflux, 15 h; (ii) ethyl vinylphosphonate, 2 equiv, EtOH, reflux, 70 h.

3. Conclusion

Starting from *cis*/*trans* (4*S*)-(−)-limonene oxides, an inexpensive enantiomerically pure natural compound commercially available in both the enantiomeric form, we carried out the synthesis of new chiral vicinal diamines, amino alcohols and other derivatives. The methodology allows the straightforward preparation of (1*R*,2*R*,4*S*)-1-methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diamine, a useful chelant unknown in the literature, via a practical stereoconvergent synthetic sequence, without the need to separate the *cis*/*trans* mixture of the starting limonene oxide and the intermediate diastereomers. These compounds, conveniently prepared on a multigram scale as single enantiomers, without having to resort to resolution, are widely used in organic synthesis of enantiomerically pure molecules, as the chiral core of auxiliaries or ligands employed in asymmetric catalysis.

4. Experimental

4.1. General experimental

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with $CDCl_3$ as a solvent at ambient temperature and were calibrated using residual undeuterated solvents as the internal reference. Coupling constants (*J*) are given in hertz. When necessary, assignments of the structures of compounds prepared were aided by a self-consistency check using the ^{1}H NOESY correlation spectrum and decoupling experiments. IR spectra were recorded using FTIR apparatus. Optical rotations were measured in a 1 dm cell at 20 °C. All melting points are uncorrected. Where only the major diastereomer was obtained pure, the ^{1}H NMR signals for the minor diastereomer were deduced from the spectra of the crude reaction mixture or of enriched chromatographic fractions. All reagents were commercially available, were purchased at the highest quality, and were purified by distillation when necessary.

4.2. Synthesis of (1*R*,2*R*,4*S*)-2-azido-1-methyl-4-(prop-1-en-2-yl)cyclohexanol 2 and (1*R*,2*R*,5*S*)-2-azido-2-methyl-5-(prop-1-en-2-yl)cyclohexanol 3

To a solution of (4*S*)-(−)-limonene oxides **1** (3.04 g, 20.00 mmol) in methanol (8 mL) were added NaN_3 (2.60 g, 40.00 mmol) and NH_4Cl (1.08 g, 20.00 mmol). The solution was heated at reflux for 32 h. The reaction was monitored by GC. The mixture was allowed to cool to room temperature, then the solvent was removed in vacuo. The resulting mixture was diluted with DCM and filtered on Na_2SO_4. The azido-alcohols **2** and **3** were separated by silica gel column chromatography with cyclohexane/AcOEt 95:5 mixture as eluent (**2**: 2.03 g, 10.4 mmol, 52%; **3**: 1.52 g, 7.80 mmol, 39%).

4.2.1. (1*R*,2*R*,4*S*)-2-Azido-1-methyl-4-(prop-1-en-2-yl) cyclohexanol 2

Yellow oil; $[\alpha]_D^{20} = -107.55$ (*c* 1.1, $CHCl_3$); ν_{max} (liquid film): 3392, 2097, 1454, 1263, 1004, 890 cm^{-1}; NMR (400 MHz, $CDCl_3$): δ_H 1.23 (s, 3H), 1.45–1.65 (m, 4H), 1,70 (s, 3H), 1.77 (dtd, 1H, *J* = 17.5, 3.8, 1.9 Hz), 1.96 (ddd, 1H, *J* = 13.7, 12.0, 3.0 Hz), 2.09–2.17 (m, 1H), 2.37 (s, 1H), 3.50–3.56 (m, 1H), 4.68–4.73 (m, 2H); δ_C 21.2, 26.1, 27.8, 30.9, 34.1, 38.2, 66.7, 70.8, 109.3, 149.1. Anal. Calcd for $C_{10}H_{17}N_3O$, MW 195.261: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.69; H, 8.59; N, 21.42.

4.2.2. (1*R*,2*R*,5*S*)-2-Azido-2-methyl-5-(prop-1-en-2-yl)cyclohexanol 3

Yellow oil; $[\alpha]_D^{20} = -75.5$ (*c* 1.2, $CHCl_3$); ν_{max} (liquid film): 3435, 1645, 1452, 1375, 1261, 1030, 890 cm^{-1}; NMR (400 MHz, $CDCl_3$): δ_H 1.37 (s, 3H), 1.42–1.80 (m, 6H), 1,72 (s, 3H), 1.86 (ddd, 1H, *J* = 13.7, 12.4, 3.0 Hz), 2.25 (tt, 1H, *J* = 12.0, 3.8 Hz), 3.63–3.66 (m, 1H), 4.73–4.76 (m, 2H); δ_C 21.0, 22.9, 26.7, 31.1, 34.4, 37.4, 63.4, 72.2, 109.4, 149.2. Anal. Calcd for $C_{10}H_{17}N_3O$, MW 195.261: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.73; H, 8.56; N, 21.31.

4.3. Synthesis of (1*S*,4*S*,6*R*)-1-methyl-4-(prop-1-en-2-yl)-7-azabicyclo-[4.1.0]heptane 4

A solution of **2** (1.91 g, 9.80 mmol) in THF (3.5 mL) was magnetically stirred at room temperature with triphenylphosphine (3.08 g, 11.76 mmol) for 48 h. The reaction was monitored by GC. The solvent was removed in vacuo and the resulting crude was diluted with DCM. The solution was washed with citric acid (2.96 g, 10% aqueous solution, 14.11 mmol), then, the organic layer was washed with Na_2CO_3 (1.79 g, 10% aqueous solution, 16.93 mmol), dried over Na_2SO_4 and concentrated under reduced pressure to give **4** as a colourless oil (1.32 g, 8.72 mmol, 89%).

4.3.1. (1*S*,4*S*,6*R*)-1-Methyl-4-(prop-1-en-2-yl)-7-aza-bicyclo-[4.1.0]heptane 4

Colourless oil; $[\alpha]_D^{20} = -40.1$ (*c* 1.9, $CHCl_3$); ν_{max} (liquid film): 3279, 1776, 1644, 1442, 886 cm^{-1}; NMR (400 MHz, $CDCl_3$): δ_H 0.40 (br s, 1H), 1.17 (dtd, 1H, *J* = 12.8, 10.7, 6.8 Hz), 1.24 (s, 3H), 1.42–1.49 (m, 1H), 1.60–1.69 (m, 1H), 1.67 (s, 3H), 1.73 (qd, 1H, *J* = 9.7, 4.9 Hz), 1.78 (ddd, 1H, *J* = 14.3, 6.7, 4.1 Hz), 1.92–2.02 (m, 2H), 2.06–2.09 (m, 1H), 4.67 (s,1H), 4.68–4.70 (m, 1H); δ_C 20.5, 25.0, 26.5, 30.7, 31.1, 35.4, 37.8, 41.7, 108.9, 149.9. Anal. Calcd for $C_{10}H_{17}N$, MW 151.249: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.63; H, 11.46; N, 9.03.

4.4. Synthesis of (1*R*,4*S*,6*S*)-methyl-4-(prop-1-en-2-yl)-7-azabicyclo-[4.1.0]heptane 5

Aziridine **5** was prepared starting from azido-alcohol **3** (1.48 g, 9.79 mmol) according to the procedure followed for aziridine **4**, stirring at reflux for 24 h instead of at room temperature for 48 h (1.14 g, 7.54 mmol, 77%).

4.4.1. (1*R*,4*S*,6*S*)-Methyl-4-(prop-1-en-2-yl)-7-aza-bicyclo-[4.1.0]heptanes 5

Colourless oil; $[\alpha]_D^{20} = -88.3$ (*c* 1.2, $CHCl_3$); ν_{max} (liquid film): 3255, 1644, 1442, 1379, 834 cm^{-1}; NMR (400 MHz, $CDCl_3$): δ_H 1.15–2.07 (m, 6H), 1.24 (s, 3H), 1.48 (dd, 1H, *J* = 14.1, 12.0 Hz), 1.63 (s, 3H), 1.80 (tdd, 1H, *J* = 12.0, 6.0, 2.6 Hz), 1.95 (ddd, 1H, 13.7, 3.8, 2.6 Hz), 4.62 (s, 2H); δ_C 21.2, 26.6, 27.7, 29.7, 30.6, 35.1, 36.8, 39.4, 109.0, 149.4. Anal. Calcd for $C_{10}H_{17}N$, MW 151.249: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.63; H, 11.44; N, 9.09.

4.5. Synthesis of (1*R*,2*R*,5*S*)-2-azido-2-methyl-5-(prop-1-en-2-yl)cyclohexanamine 6

A solution of aziridine **4** (2.16 g, 14.32 mmol) in CH_3CN/H_2O 10:1 (11 mL) was added of NaN_3 (1.11 g, 17.16 mmol) and $CeCl_3 \cdot 7H_2O$ (2.67 g, 7.16 mmol) then it was heated at reflux for 12 h. The reaction was monitored by GC. After cooling, the reaction mixture was concentrated in vacuo to remove the solvent. The crude was diluted with DCM and the mixture resulting was dried with Na_2SO_4. The solution was further filtered on a thin pad of Na_2SO_4. The azido-amine **6** was purified by column chromatography with cyclohexane/AcOEt 80:20 mixture as eluent to obtain **6** (2.06 g, 10.59 mmol, 74%).

4.5.1. (1*R*,2*R*,5*S*)-2-azido-2-methyl-5-(prop-1-en-2-yl)cyclohexanamine 6

Colourless oil; $[\alpha]_D^{20} = -58.3$ (*c* 1.8, $CHCl_3$); ν_{max} (liquid film): 2105, 1644, 1453, 1256, 888 cm^{-1}; NMR (400 MHz, $CDCl_3$): δ_H 1.17 (br s, 2H), 1.31 (s, 3H), 1.44–1.62 (m, 4H), 1.71 (s, 3H), 1.75 (ddd, 1H, *J* = 13.7, 11.5, 3.8 Hz), 1.88 (ddd, 1H, *J* = 13.7, 12.0, 3.8 Hz), 2.21 (tt, 1H, *J* = 11.5, 3.4 Hz), 2.89 (t, 1H, *J* = 3.4 Hz), 4.70 (br s, 2H); δ_C 21.2, 23.0, 26.8, 30.7, 34.6, 37.2, 53.4, 64.4, 109.3, 149.3. Anal. Calcd for $C_{10}H_{18}N_4$, MW 194.277: C, 61.82; H, 9.34; N, 28.84. Found: C, 61.99; H, 9.09; N, 28.96.

4.6. Synthesis of (1*R*,2*R*,4*S*)-2-azido-1-methyl-4-(prop-1-en-2-yl) cyclohexanamine 7

Starting from aziridine **5** (2.17 g, 14.34 mmol) and following the same procedure followed to prepare product **6**, product **7** was obtained (1.97 g, 10.18 mmol, 71%).

4.6.1. (1*R*,2*R*,4*S*)-2-Szido-1-methyl-4-(prop-1-en-2-yl) cyclohexanamine 7

Colourless oil; $[\alpha]_D^{20} = -96.8$ (*c* 1.2, $CHCl_3$); ν_{max} (liquid film): 2099, 1644, 1451, 1374, 1258, 889 cm^{-1}; NMR (400 MHz, $CDCl_3$): δ_H 1.15 (s. 3H), 1.20–1.94 (m, 8H), 1.73 (s, 3H), 2.18 (tt, 1H, *J* = 11.1, 4.3 Hz), 3.40 (m, 1H), 4.68–4.76 (m, 2H); δ_C 21.4, 26.2, 28.5, 30.9, 34.8, 38.2, 51.4, 68.4, 109.4, 148.9. Anal. Calcd for $C_{10}H_{18}N_4$, MW 194.277: C, 61.82; H, 9.34; N, 28.84. Found: C, 61.60; H, 9.52; N, 28.61.

4.7. Synthesis of (1*R*,2*R*,4*S*)-1-methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diamine 8

Azido-amine **6** or **7** (2.00 g, 10.29 mmol) was dissolved in anhydrous MTBE (12 mL) and was magnetically stirred at 0 °C in an ice-water bath. The solution was treated with $LiAlH_4$ (0.47 g, 13.87 mmol) and stirred for 10 min until room temperature. The reaction was monitored by GC. The excess of $LiAlH_4$ was destroyed adding some drops of Na_2SO_4 saturated water solution. The mixture was then dried with anhydrous Na_2SO_4, filtered, washed with DCM and evaporated under reduced pressure to give diamine **8** (from **6**, 1.68 g, 9.99 mmol, 97%; from **7**, 1.65 g, 9.78 mmol, 95%).

4.7.1. (1*R*,2*R*,4*S*)-1-Methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diamine 8

Colourless oil; $[\alpha]_D^{20} = -28.5$ (*c* 0.4, $CHCl_3$); ν_{max} (liquid film): 3365, 1643, 1453, 1372, 886, 834 cm^{-1}; NMR (400 MHz, $CDCl_3$): δ_H 0.85 (s, 3H), 0.95–1.68 (m, 10H), 1.50 (s, 3H), 2.02 (tt, 1H, *J* = 10.3, 4.7 Hz), 2.50 (t, 1H, *J* = 4.1 Hz), 4.51 (s, 2H); δ_C 21.2, 26.1, 26.6, 34.2, 34.3, 37.4, 51.3, 56.1, 108.8, 148.9. Anal. Calcd for $C_{10}H_{20}N_2$, MW 168.279: C, 71.37; H, 11.98; N, 16.65. Found: C, 71.52; H, 12.18; N, 16.58.

4.8. Preparation of (1*R*,2*R*,4*S*)-1-methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diamine oxalate 9

Oxalic acid (1.83 g, 20.34 mmol) was dissolved in EtOH (5 mL) on heating. The solution was added slowly to diamine **8** (1.63 g, 9.68 mmol). After few minutes crystal of **9** appeared. The crystals were collected, washed with EtOH and dried (2.93 g, 8.42 mmol, 87%).

White crystals; mp 202–206 °C (methanol); $[\alpha]_D^{20} = -76.2$ (*c* 1.2, $CHCl_3$); ν_{max} (liquid film): 1600, 1453, 1422, 992, 751, 694 cm^{-1}; NMR (400 MHz, DMSO-d_6): δ_H 1.28 (s, 3H), 1.50–2.27 (m, 7H), 1.68 (s, 3H), 3.40–3.45 (m, 1H), 4.78 (s, 1H), 4.82 (s, 1H), 7.40 (br s, 8H); δ_C 20.9, 21.5, 23.9, 29.3, 31.0, 36.7, 51.5, 54.3, 111.0, 146.8, 164.4, 164.9. Anal. Calcd for $C_{14}H_{24}N_2O_8$, MW 348.35: C, 48.27; H, 6.94; N, 8.04. Found: C, 48.07; H, 6.82; N, 8.22.

4.9. Scaleable preparation of (1*R*,2*R*,4*S*)-1-methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diamine 8 starting from (4*S*)-(−)-limonene oxides 1

To a solution of (4*S*)-(−)-limonene oxides **1** (76.11 g, 0.50 mol) in methanol (200 mL) were added NaN_3 (65.01 g, 1.00 mol) and NH_4Cl (26.74 g, 0.50 mol). The solution was heated at reflux for 32 h. The reaction was monitored by GC. The mixture was allowed to cool to room temperature then the solvent was removed in vacuo. The resulting mixture was diluted with DCM (200 mL) and filtered on Na_2SO_4. The residue obtained from evaporation of the solvent was purified by filtration on a short column of silica gel eluting with a mixture of cyclohexane/AcOEt 80:20 to give **2** and **3** azido-alcohol mixture (87.80 g, 0.45 mol, 90%)

A solution of **2** and **3** azido-alcohol mixture (87.80 g, 0.45 mol) in dioxane (190 mL) was heated at reflux with triphenylphosphine (141.6 g, 0.54 mol) for 24 h. The reaction was monitored by GC. The solvent was removed in vacuo and the resulting crude was diluted with DCM (200 mL). The solution was washed with citric acid (124.5 g , 20% aqueous solution, 0.648 mol), then the organic layer was washed with Na_2CO_3 (82.4 g, 10% aqueous solution , 0.778 mol), dried over Na_2SO_4 and concentrated under reduced pressure to give a mixture of aziridines **4** and **5** as a colourless oil (56.00 g, 0.37 mol, 83%).

To a solution of a mixture of aziridines **4** and **5** (56.00 g, 0.37 mol) in CH_3CN/H_2O 5:1 (280 mL) were added NaN_3 (28.60 g, 0.44 mol) and $CeCl_3{\cdot}7H_2O$ (68.93 g, 0.18 mol) and heated at reflux for 12 h. The reaction was monitored by GC. After cooling, the reaction mixture was concentrated in vacuo to remove the solvent. The crude was diluted with DCM (200 mL) and added of Na_2SO_4. The mixture of the azido-amines **6** and **7** was obtained as a brown residue (58.34 g) by filtration and evaporation of the DCM. The mixture of azido-amines **6** and **7** was purified by a short column chromatography, eluting with a mixture of cyclohexane/AcOEt 60:40 (51.77 g, 0.27 mol, 72%).

The mixture of azido-amines **6** and **7** (51.77 g, 0.27 mol) was dissolved in anhydrous MTBE (300 mL) and magnetically stirred at 0 °C in an ice-water bath. The solution was treated with $LiAlH_4$ (12.14 g, 0.32 mol) which was added in portions over 2 h. The reaction was stirred for 10 min until room temperature. The reaction was monitored by GC. The excess of $LiAlH_4$ was destroyed adding some millilitre of Na_2SO_4 saturated water solution. The mixture was then added of DCM (300 mL), dried, filtered and evaporated under reduced pressure to give the diamine **8** (43.68 g, 0.26 mol, 96%).

This synthetic sequence affords the final (1*R*,2*R*,4*S*)-1-methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diamine (**8**) in 52% overall yield.

4.10. Synthesis of (1*R*,2*R*,4*S*)-2-amino-1-methyl-4-(prop-1-en-2-yl)cyclohexanol 10

The azido-alcohol **2** (1.00 g, 5.12 mmol) was dissolved in MTBE anhydrous (5 mL) under magnetic stirring at 0 °C in an ice-water bath. The solution was treated with $LiAlH_4$ (0.26 g, 6.80 mmol) and stirred for 1 h until room temperature. The excess of $LiAlH_4$ was destroyed adding some drops of Na_2SO_4 saturated water solution. The mixture was then added of DCM (10 mL), dried, filtered and evaporated under reduced pressure to give amino alcohol **10** (0.81 g, 4.81 mmol, 94%).

4.10.1. (1*R*,2*R*,4*S*)-2-Amino-1-methyl-4-(prop-1-en-2-yl)cyclohexanol 10

Colourless oil; $[\alpha]_D^{20} = -14.6$ (*c* 1.2, $CHCl_3$); IR (Nujol): ν_{max} 3350, 1621, 1439, 1203, 875 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.18 (s, 3H), 1.38–1.72 (m, 8H), 1,70 (s, 3H), 1.94 (ddd, 1H, *J* = 13.7, 10.7, 3.8 Hz), 2.20 (tt, 1H, *J* = 10.3, 3.8 Hz), 2.82 (t, 1H, *J* = 4.3 Hz), 4.70 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 26.5, 27.1, 33.8, 34.7, 37.7, 55.7, 74.8, 109.2, 149.3. Anal. Calcd for $C_{10}H_{19}NO$ (169.26): C, 70.96; H, 11.31; N, 8.28. Found: C, 70.81; H, 11.49; N, 8.07.

4.11. Synthesis of (1*R*,2*R*,5*S*)-2-amino-2-methyl-5-(prop-1-en-2-yl)cyclohexanol 11

Amino alcohol **11** was prepared starting from azido-alcohol **3** (1.00 g, 5.12 mmol), according to the same procedure followed for amino alcohol **10** (0.75 g, 4.40 mmol, 86%).

4.11.1. (1*R*,2*R*,5*S*)-2-Amino-2-methyl-5-(prop-1-en-2-yl)cyclohexanol 11

White crystals ; mp 39–41 °C (hexane); $[\alpha]_D^{20} = -17.9$ (*c* 1.2, $CHCl_3$); IR (Nujol): ν_{max} 3360, 1643, 1452, 1196, 1049, 887 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.08 (s, 3H), 1.32 (dt, 1H, *J* = 13.2, 4.3 Hz), 1.38–1.95 (m, 7H), 1,69 (s, 3H), 1.76 (ddd, 1H, *J* = 14.1, 10.7, 3.0 Hz), 2.25 (tt, 1H, *J* = 10.5, 4.1 Hz), 3.46 (t, 1H, *J* = 3.8 Hz), 4.66–4.72 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 26.4, 26.7, 34.0, 34.8, 37.8, 51.8, 74.7, 109.2, 149.3. Anal. Calcd for $C_{10}H_{19}NO$ (169.26): C, 70.96; H, 11.31; N, 8.28. Found: C, 71.13; H, 11.42; N, 8.13.

4.12. Reaction of (4*S*)-(−)-limonene oxide with ammonium hydroxide

The commercial mixture of *cis*/*trans*-(4*S*)-(−)-limonene oxides **1** (0.5 g, 3.29 mmol) was added to a 30% aqueous solution of ammonia (4 mL, 64.8 mmol). The heterogeneous mixture was left under magnetic stirring at room temperature for six days, leading to a conversion of 12% of limonene oxide with formation of amino alcohol **10** as a major product (0.05 g, 10.6%). If the reaction is conducted at 70 °C under magnetic stirring, after two days it shows a conversion of 86% with formation of the amino alcohols **10–12**. The reaction mixture was extracted with DCM (3 × 10 mL). The organic phase was dried with Na_2SO_4 and evaporated, leaving a residue which was purified by column chromatography on silica gel, with cyclohexane/AcOEt 1:1 mixture as eluent, giving the amino alcohols **10** (0.195 g, 1.15 mmol, 35%), **11** (0.072 g, 0.43 mmol, 13%) and **12** (0.317 g, 0.98 mmol, 30%).

4.12.1. (1*S*,1′*S*,2*R*,2′*R*,4*S*,4′*S*)-2,2′-Azanediylbis(1-methyl-4-(prop-1-en-2-yl)cyclohexanol 12

Yellow oil ; $[\alpha]_D^{20} = -46.8$ (*c* 1.4, $CHCl_3$); IR (Nujol): ν_{max} 3370, 1642, 1452, 1188, 885 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 6H), 1.48–1.70 (m, 11H), 1,71 (s, 6H), 1.75–1.87 (m, 4H), 2.25 (m, 2H), 2.55 (dd, 2H, *J* = 5.5, 3.0 Hz), 4.69–4.75 (m, 4H) ppm; ^{13}C

NMR (100 MHz, $CDCl_3$): δ 21.7, 25.9, 26.2, 29.9, 34.7, 38.0, 58.7, 72.1, 109.4, 149.1. Anal. Calcd for $C_{20}H_{35}NO_2$ (321.50): C, 74.72; H, 10.97; N, 4.36. Found: C, 74.86; H, 11.12; N, 4.11.

4.13. Preparation of diethyl 2-((1*R*,2*R*,5*S*)-2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexylamino)ethylphosphonate 13

To a solution of *trans*-aminoalcohol **10** (0.50 g, 2.96 mmol) in ethanol (3 mL) was added diethyl vinylphosphonate (0.49 g, 3.00 mmol). The mixture was heated at reflux for 15 h. then was cooled until room temperature and the solvent was evaporated under reduced pressure. The product was purified by column chromatography with EtOH/AcOEt, 1:1 mixture as eluent giving **13** as colourless oil (0.86 g, 2.60 mmol, *Y* = 88%).

4.13.1. Diethyl 2-((1*R*,2*R*,5*S*)-2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexylamino) ethylphosphonate 13

Colourless oil; $[\alpha]_D^{20} = -28.0$ (*c* 1.1, $CHCl_3$); IR (Nujol): ν_{max} 3411, 1455, 1228, 1099, 962 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 3H), 1.18 (t, 6H, *J* = 7.1 Hz), 1.32–1.60 (m, 5H), 1.58 (s, 3H), 1.79 (t, 2H, *J* = 6.8 Hz), 1.84 (t, 2H, *J* = 6.8 Hz), 2.05 (br m, 1H), 2.39 (dd, 1H, *J* = 6.0, 3.4 Hz), 2.63 (ddt, 1H, *J* = 18.8, 12.0, 6.0 Hz), 2.66 (br s, 1H), 2.90 (ddt, 1H, *J* = 15.4, 12.0, 6.8 Hz), 3.89–4.03 (m, 4H), 4.52 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3, 16.4, 21.3, 25.4, 25.5, 26.1, 28.2, 30.2, 34.5, 37.8, 41.7, 61.4, 61.5, 71.6, 109.1, 148.8. Anal. Calcd for $C_{16}H_{32}NO_4P$ (333.4): C, 57.64; H, 9.67; N, 4.20. Found: C, 57.69; H, 9.51; N, 4.04.

4.14. Preparation of diethyl 2-((1*R*,2*R*,5*S*)-2-amino-2-methyl-5-(prop-1-en-2-yl)cyclohexylamino) ethylphosphonate 14

Product **14** was prepared starting from *trans*-diaminolimonene **8** (0.50 g, 2.97 mmol), according to the procedure followed for product **13** (0.89 g, 2.67 mmol, 90%).

4.14.1. Diethyl 2-((1*R*,2*R*,5*S*)-2-amino-2-methyl-5-(prop-1-en-2-yl)cyclohexylamino) ethylphosphonate 14

Yellow oil; $[\alpha]_D^{20} = -24.0$ (*c* 0.7, $CHCl_3$); IR (liquid film): ν_{max} 3435, 1642, 1454, 1226, 1055, 1028, 962 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.03 (s, 3H), 1.27 (t, 6H, *J* = 7.3 Hz), 1.42–1.68 (m, 8H), 1.68 (s, 3H), 1.78 (ddd, 1H, *J* = 12.8, 9.8, 3.0 Hz), 1.89 (t, 1H, *J* = 7.3 Hz), 1.93 (t, 1H, *J* = 7.3 Hz), 2.11–2.21 (m, 1H), 2.33 (dd, 1H, *J* = 5.6, 3.2 Hz), 2.70 (ddt, 1H, *J* = 16.7, 12.0, 7.3 Hz), 2.97 (ddt, 1H, *J* = 15.4, 12.0, 7.3 Hz), 3.98–4.12 (m, 4H), 4.68–4.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 16.6, 21.7, 26.2, 27.5, 30.1, 35.7, 37.8, 37.9, 41.9, 42.0, 51.9, 61.7, 62.6, 109.3, 148.9. Anal. Calcd for $C_{16}H_{33}N_2O_3P$ (332.42): C, 57.81; H, 10.01; N, 8.43. Found: C, 57.63; H, 10.21; N, 8.21.

4.15. Preparation of tetraethyl 1,2-((1*R*,2*R*,4*S*)-1-methyl-4-(prop-1-en-2-yl)cyclohexyldiamino)-*N*^{1},*N*^{2}-diethyl-phosphonate 15

Product **15** was prepared according to the procedure followed for product **14**, starting from *trans*-diaminolimonene **8** (0.50 g, 2.97 mmol) and using 6 mmol of diethyl vinylphosphonate, and stirring for 70 h. (0.93 g, 1.87 mmol, 63%).

4.15.1. 1,2-((1*R*,2*R*,4*S*)-1-Methyl-4-(prop-1-en-2-yl)cyclohexyldiamino)-*N*^{1},*N*^{2}-diethyl-phosphonate 15

Yellow oil ; $[\alpha]_D^{20} = -20.5$ (*c* 0.6, $CHCl_3$); IR (liquid film): ν_{max} 3436, 1445, 1392, 1237, 1098, 1028, 962 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 3H), 1.30 (t, 12H, *J* = 6.8 Hz), 1.43–1.58 (m, 5H), 1.71 (s, 3H), 1.83–2.04 (m, 7H), 2.13–2.21 (m, 1H), 2.49 (dd, 1H, *J* = 6.0, 3.2 Hz), 2.67–2.85 (m, 3H), 3.00 (ddt, 1H, *J* = 14.5, 12.0, 7.3 Hz), 4.05–4.16 (m, 8H), 4.71–4.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 16.7, 21.6, 22.0, 25.8, 26.3, 28.5, 29.1, 29.8, 32.0, 35.1, 35.2, 38.0, 42.1, 42.2, 55.4, 59.8, 61.6, 61.7, 109.2, 149.2; MS (API-ES) *m/z*: 497.2 (MH^+, 100), 498.2 (26), 519.2 (MNa^+). Anal. Calcd for $C_{22}H_{46}N_2O_6P_2$ (496.56): C, 53.21; H, 9.34; N, 5.64. Found: C, 52.98; H, 9.46; N, 5.41.

Acknowledgements

The financial support of this research by a grant from University of Camerino and from MIUR-PRIN is gratefully acknowledged.

References

1. (a) Fache, F.; Schulz, E.; Tommassino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159–2232; (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627; (c) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161–3196; (d) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed.* **1994**, *33*, 497–526; (e) Yang, Y.-Q.; Zhao, G. *Chem. Eur. J.* **2008**, *14*, 10888–10891; (f) Rasappan, R.; Reiser, O. *Eur. J. Org. Chem.* **2009**, 1305–1308; (g) Amoroso, D.; Graham, T. W.; Rongwei, G.; Tsang, C.-W.; Kamaluddin, A.-R. *Aldrichim. Acta* **2008**, *41*, 15–26.
2. (a) Paquette, L. A.; Kang, H.-J. *J. Am. Chem. Soc.* **1991**, *113*, 2610–2621; (b) Baudouy, R.; Prince, P. *Tetrahedron* **1989**, *45*, 2067–2074; (c) Marron, B. E.; Nicolaou, K. C. *Synthesis* **1989**, 537–541; (d) Tius, M. A.; Kerr, M. A. *Synth. Commun.* **1988**, *18*, 1905–1911; (e) Baker, R.; Borges, M.; Cooke, N. G.; Herbert, R. H. *J. Chem. Soc., Chem. Commun.* **1987**, 414–416; (f) Mori, K.; Kato, M. *Tetrahedron Lett.* **1986**, *27*, 981–982; (g) Łączkowsky, K. Z.; Kmieciak, A.; Kozakiewicz, A. *Tetrahedron: Asymmetry* **2009**. doi:10.1016/j.tetasi.2009.06.007.
3. (a) Watts, C. C.; Thoniyot, P.; Hirayama, L. C.; Romano, T.; Singaram, B. *Tetrahedron: Asymmetry* **2005**, *16*, 1829–1835; (b) Steiner, D.; Sethofer, S. G.; Goralski, C. T.; Singaram, B. *Tetrahedron: Asymmetry* **2002**, *13*, 1477–1483; (c) Xu, Q.; Wu, X.; Pan, X.; Chan, A. C. S.; Yang, T.-K. *Chirality* **2002**, *14*, 28–31; (d) Pu, L.; Hong-Bin, Y. *Chem. Rev.* **2001**, *101*, 757–824; (e) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; (f) Steiner, D.; Ivison, L.; Goralski, C. T.; Appel, R. B.; Gojkovic, J. R.; Singaram, B. *Tetrahedron: Asymmetry* **2002**, *13*, 2359–2363; (g) Andrews, P. C.; Blair, M.; Fraser, B. H.; Junk, P. C.; Massi, M.; Tuck, L. *Tetrahedron: Asymmetry* **2006**, *17*, 2833–2838.
4. (a) Royals, E. E.; Leffingwell, J. C. *J. Org. Chem.* **1966**, *31*, 1937–1944; (b) Newhall, W. F. *J. Org. Chem.* **1964**, *29*, 185–187.
5. Alcaraz, L.; Cridl, A.; Kinchin, E. *Org. Lett.* **2001**, *3*, 4051–4053.
6. Royals, E. E.; Leffingwell, J. C. *Tetrahedron Lett.* **1965**, *43*, 3829–3837.
7. (a) Sommerdijk, N. A. J. M.; Buynsters, P. J. J. A.; Akdemir, H.; Geurts, D. G.; Nolte, R. J. M.; Zwanenburg, B. *J. Org. Chem.* **1997**, *62*, 4955–4960; (b) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437–472.
8. Voronkov, M. V.; Gontcharov, A. V.; Kanamarlapudi, R. C.; Richardson, P. F.; Wang, Z.-M. *Org. Proc. Res. Dev.* **2005**, *9*, 221–224.
9. Voronkov, M. V.; Kanamarlapudi, R. C.; Richardson, P. *Tetrahedron Lett.* **2005**, *46*, 6907–6910.
10. (a) Brown, H. C.; Suzuki, A. *J. Am. Chem. Soc.* **1967**, *89*, 1933–1941; (b) Watts, C. C.; Thoniyot, P.; Cappuccio, F.; Verhagen, J.; Gallagher, B.; Singaram, B. *Tetrahedron: Asymmetry* **2006**, *17*, 1301–1307.
11. Spartan′ 06, Wavefunction, Inc., Irvine, CA.
12. Partal Ureña, F.; Avilés Moreno, J. R.; López González, J. J. *Tetrahedron: Asymmetry* **2009**, *20*, 89–97.
13. (a) Uenishi, J.; Hamada, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2999–3006; (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*;; John Wiley and Sons: New York, 1994.