Pseudo Enantiomeric Mixed S/P Ligands Derived from Carbohydrates for the 1,4-Addition of Phenyl Boronic Acid to Cyclohexenone

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The application of phosphinite-thioglycosides and phosphine-thioglycosides ligands in the Rh(I)-catalyzed 1,4-addition of phenylboronic acid to cyclohexenone is reported. Among the ligands tested, phosphinite-thioglycoside 3 and phosphine-thioglycoside 10, bearing a 1,2-cis arrangement of the two heteroatoms, have exhibited the best results in terms of reactivity and enantioselectivity. Interestingly, ligands 3 and 10, both derived from D-sugars are able to generate the addition product of the phenylboronic acid to the cyclohexenone with opposite configuration, behaving thus as enantiomers.

Introduction

The synthesis of enantiopure compounds is a standing area of interest, consequence of the significance of chirality in medicine, fragrances, agriculture and material science. Among all the different approximations developed so far, enantioselective catalysis is the method of choice, as it combines efficiency, versatility, atom economy, and suitability for green chemistry. Enantioselective catalysis is usually achieved by using a chiral organic ligand either alone or linked to a transition metal. The difficulties to predict the structural requirements of a ligand for generating an efficient catalyst, explain the continuous need of new modular ligands with different coordinating or activation modes. To develop such ligands, the first step is the search of interesting scaffolds, and sequentially append the ligating group. Ideally, the scaffold must be easily obtained in optically pure form, and equipped with orthogonal functions which allow optimization of the ligating groups individually. Among the different compounds which can be used in this task, carbohydrates hold a prominent role. Indeed, carbohydrates account for the 93% of the renewable biomass on earth, are the cheapest enantiopure compounds in the market, possess various hydroxyl groups in different orientations, and compared to other biomolecules, their chiral coding information capacity is by far the most significant. However, usually both enantiomers of a target compound are required, imposing the need to easily access to both enantiomeric ligands, which in the case of carbohydrates is highly challenging. This drawback has been solved by developing the concept of pseudo-enantiomeric ligands, which consist in the use of D-sugars as starting material for the synthesis of two structurally different ligands, yet able to generate both enantiomers. Based on these premises, and within our interest in the synthesis and application of chiral sulfur compounds in organic and organometallic asymmetric synthesis, we have developed highly enantioselective pseudo enantiomeric mixed S/P ligands for Pd-catalyzed allylic substitution, Rh(I)-catalyzed enamide hydrogenation and hydrosilylation of prochiral ketones. In the present work, we report our preliminary results directed toward the development of two pseudo-enantiomeric ligands I and II for the Rh(I)-catalyzed 1,4 addition of phenyl boronic acid to cyclohexenone, Figure 1.

Results and Discussion

Within C-C bond formation reactions, the Rh(I)-catalyzed addition of boronic acids to activated ketone is one of the most powerful approximation. Since the pioneering works of Hayashi and Miyaura a wide number of methodologies have been successfully developed for this transformation and very high levels of sophistication and efficiency have been achieved so far. Among the most important contributions recently developed it is interesting to highlight the discovery that C, and C, ligands with a chiral...
sulfanyl group (S-O) are able to generate efficient catalysts for this transformation. Surprisingly, a single type of ligand derived from carbohydrates, entailing olefin/phosphinite coordinating groups have been used in this transformation.\(^9\) Moreover, as far as we know no example using mixed S/P ligand with a prochiral thioether (S-R) group has been reported yet. In this sense, one of the most important features in the sulfur-based ligands derived from carbohydrates is that the sugar acts as a chiral rely to the nascent stereogenic sulfur center upon coordination to the metal. Consequently, an efficient control of the stereochemical outcome in the coordination step will lead to a well-defined chiral environment in a very close proximity to the coordination sphere of the metal.\(^9\) In our previous works we have shown that this control may be exerted, in the case of C₂-symmetric bis-thioglucosides,\(^\^{10}\) through stereoelectronic factors, namely the exo-anomeric effect, or through steric bias in the case of C₃-symmetric phosphinite thioglucosides.\(^\^{10}\) This stereocoupling coupled with the higher trans effect of phosphorus vs sulfur led to the discovery, of ligand 1 and 2 derived from D-sugars galactose and arabinose as excellent catalyst precursors for the synthesis of L- and D-amino esters, scheme 1.\(^\^{11}\) Moreover, these ligands have also shown interesting behavior in the Rh(I)-catalyzed hydrogenolysis of prochiral ketones.\(^\^{12}\)

In order to enhance the reaction scope of these ligands, we assayed them in the model reaction of 2-cyclohexenone 4 and phenylboronic acid 5. Employing Hayashi initial conditions in the presence of 2.5 mol% of rhodium precursor [Rh(C₂H₅)Cl]₂ and 5 mol% of ligand, the adduct was generally obtained with good yields but with very low enantioselectivities. The galactose derivative ligand 1, led to the addition compound 6 with 70% yield and 9% enantioselectivity in favor of the (S) enantiomer, while the arabino ligand 2 led to the formation of 6 in 75% yield and 6% ee in favor of the (R) enantiomer, Scheme 1.

In our previous work on the Rh(I)-catalyzed hydrogenation of enamides, we have shown that the relative disposition of the coordinating sulfur and phosphorus atoms is extremely important, being the 1,2-trans derivative the most favored. Surprisingly, by using the galactose derivative with an α configuration at the anomeric center 3, which was neither reactive nor enantioselective in Pd(0)-catalyzed alkylation, and in the Rh(I)-catalyzed hydrogenation in enamide, led to a significant increase in the enantioselectivity. Indeed using ligand 3 enabled the production of the addition product 6 with 67% yield and an interesting 70% ee in favor of the (R) enantiomer.

Based on these preliminary results, we decided to apply other ligands with a 1,2-cis disposition of both heteroatoms. At this point, it is worth of mention that while the synthesis of α-mannothioglycosides and β-glucothioglycosides needed for the synthesis of 1,2 trans-diaxial and 1,2 trans diecuatorial mixed S/P ligands can be easily performed, the synthesis of the corresponding 1,2 cis-counterpart is more challenging. In order to address this problem, and to evaluate the contribution of the phosphinite moiety, and the ring size in the metallacyclic intermediate on the catalytic performance of ligands 1 and 2, we have developed a method for the synthesis of β-manno-thioglycosides II, figure 1, with a biphenyl phosphine moiety at C5.\(^\^{24}\) The approximation is based on the ring opening of an alko-epoxide intermediate by biphenyl phosphinyl lithium. Based on the modularity of the approximation, we decided to apply it for the synthesis of a small library of ligands in order to unravel the effect of sulfur and phosphorus substituents on their catalytic behavior. Therefore, tert-Butyl and adamantyl 4,6-O-benzylidene-2,3-anhydro-1-thio-β-D-allopyranosides 7 and 8, prepared in four steps from glucose pentaacetate were used as starting materials, scheme 2.\(^\^{25}\)

Addition of freshly prepared and titrated diphenylphosphinyl lithium (PPh₂H + BuLi) on a solution of epoxide 9 dissolved in a deoxygenated Et₂O:DMF (1:1) mixture, afforded the desired phosphine 9 as a single diastereoisomer. To study the influence of the hydroxyl group on the position 3 of the sugar on its catalytic behavior, the corresponding acetylated ligand 10 was synthesized by treatment of 9 with acetic anhydride in pyridine. Similarly, starting from epoxide 8, hydroxophosphine 11 was obtained as a single diastereoisomer, which after acetylation led to the fully protected ligand 12. Homo- and heteronuclear NMR analyses indicate that the opening of the epoxide takes place as predicted at the 2 position in accord with the Fürst-Plattner rule (1,2-trans diaxial opening).\(^\^{26}\) Next, different ligands with varied electronic and steric phosphate moiety were synthesized by condensation of diarylphosphinyl...
lithium on tert-butyl 4,6-O-benzylidene-2,3-anhydro-1-thio-Δ6-D-allopyranosides 7, Scheme 2.

The addition of bis-(para-methoxyphenyl) phosphinyl lithium to the epoxide 7 afforded the electron rich hydroxyphosphine thioglycoside 13 with 62% yield, which after acetylation afforded phosphine 14 with 66% yield. The use of the hindered bis-(1,3,5) trimethylphenyl phosphinyl lithium as nucleophile, led to the opening product 17 with 76% yield, which gave ligand 18 with 43% yield after acetylation. In the case of the electronically deficient phosphine, bis (1,3-bis-trifluorophenyl)phosphine, the corresponding hydroxyphosphine 15, could not be isolated, however, an in situ acetylation led to the ligand 16 with 62% yield.

Once the ligands in hand, we assayed them in the model reaction of 2-cyclohexenone 4 and phenyl boronic acid 5 (Table 1), under the same conditions than for the phosphinite thioglycosides 1-3.

As shown in Table 1, the enantioselectivity depends mainly on the steric substituent of the sulfur and the phosphine. Surprisingly, enhancing the steric hindrance of the sulfur substituent from a tert-butyl to an adamantyl group has a detrimental effect on the enantioselectivity. In this sense, ligand 10 with a tert-butyl group led to the desired product with 64% ee (Table 1, entry 1), while ligand 12 with a bulky adamantyl group afforded compound 6 with a lower 40% ee (Table 1, entry 3), eventhough both are equally reactive affording the addition compound with good yields (85% and 83% respectively). The protection of the hydroxyl group at the position 3 is crucial both for the reactivity and enantioselctivity of the process. As a general trend, ligands with a free hydroxyl group generate unreactive and unselective catalysts compared with the acetylated counterparts (compare entry 2 with 3 and 4 with 5). Ligand 14 with an electron rich phosphine moiety led to the desired compound with an excellent 88% yield and a good 65% enantioselectivity (Table 1, entry 5). Practically the same results 88% yield and 65% ee were obtained with ligand 16 with an electron deficient phosphine group (Table 1, entry 6), highlighting that the electronic factor are not determinant.
in the reactivity of the ligands. At the contrary, enhancing the steric hindrance of the phosphine has a detrimental effect on the enantioselectivity, as shown by the result obtained by ligand 18 which affords compound 6 with 86% yield but in racemic form (Table 1, entry 7). The most interesting feature that emerges from the analysis of the results obtained with mixed ligand type II, is that without exception all lead to the S enantiomer as major adduct. Considering that phosphinites thioglycosides type I, tested at the beginning of this study lead to the R-isomer, one can conclude that the two types of ligands, although structurally different behave as pseudo-enantiomers, Scheme 3.

Conclusions

In conclusion, we have reported the first application mixed S/P ligand with a prochiral thioether group in the Rh(I)-catalyzed 1,4 addition of phenylboronic acid to cyclohexenone. The obtained results showed that, contrary to the behavior of phosphinite thioglycosides I in Pd(0)-catalyzed allylic substitution and Rh(I)-catalyzed hydrogenation of enamides, the ligands with a cis relationship of the both coordinating atoms are better catalyst precursors than those with a trans relationship. In the case of phosphine-thioglycosides II, a ring opening of allo-epoxide intermediates, obtained in 4 steps from glucose pentaacetate, with dialkylphosphinyl lithium, allowed the preparation of ligands with different substituent at sulfur, and with diverse sterically and electronically phosphine moiety at C2. Despite the structural dissimilarity of ligands I and II, they behave as pseudoenantiomers affording as major isomer R- and S-3-Phenylcyclohexanone 6 respectively, in the Rh-catalyzed addition of phenylboronic acid to cyclohexenone.

Experimental Section

General Methods

All reactions were run under an atmosphere of dry argon using oven-dried glassware and freshly distilled and dried solvents. THF and diethyl ether were distilled from sodium benzenophene ketyl. Dichloromethane was distilled from calcium hydride. TLC was performed on Silica Gel GF254 (Merck) with detection by charring with phosphomolybdic acid/EtOH. For flash chromatography, silica Gel (Merck 230-400 mesh) was used. Columns were eluted with positive air pressure. Chromatographic eluents are given as volume to volume ratios (v/v). NMR spectra were recorded with a Bruker AMX500 (1H, 500 MHz) and Bruker Avance DRX500 (1H, 500 MHz) spectrometers. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. Routine spectra were referenced to the residual proton or carbon signals of the solvent. High-resolution mass spectra were recorded on a Kratos MS-80RFA 241-MC apparatus. Optical rotations were determined with a Perkin-Elmer 341 polarimeter. 1,2,3,4,5-Penta-O-acetyl-β-D-gluco pyranose, was purchased from Aldrich.

General procedure for the incorporation of the phosphine moiety for the preparation of phosphinite-thioglycosides 1, 2 and 3.

To a solution of the monoalcohol (1.4 mmol) in 7 mL of dry and deoxygenated THF / NEt$_3$ (1 / 1 solution), was added diphenyl chlorophosphine (276 µL, 1.54 mmol) followed by a catalytic amount of DMAP (30 mg). After 30 min, the suspension was directly loaded on a short pad of silica and eluted with the corresponding eluent previously deoxygenated. The phosphinite thioglycosides are usually obtained as white solids and immediately stored in a dry glove box.

6-O-Acetyl-3,4-O-Isopropyliden-2-O-diphenylphosphinophenyl-1-thio-β-D-galactopyranoside (1).

1H RMN (500 MHz, CDCl$_3$): δ 7.56–7.47 (m, 4 H, Ph$_2$H), 7.34–7.29 (m, 6 H, Ph$_2$H), 4.51 (d, 1 H, J = 9.5 Hz, H-1), 4.33–4.26 (m, 3 H, H-3, H-4, H-6), 4.15 (dd, 1 H, J = 1.8 Hz, 5.6 Hz, H-6’), 3.96–3.88 (m, 2 H, H-2, H-5), 2.03 (s, 3 H, OAc), 1.42 (s, 3 H, O$_2$CMe$_2$), 1.29 (s, 3 H, O$_2$CMe$_2$), 1.22 (s, 9 H, SCMe$_3$). $^{13}$C RMN (125 MHz, CDCl$_3$): δ 170.8, 142.9 (d, J$_{PC}$ = 18.4 Hz), 142.1 (d, J$_{PC}$ = 15.2 Hz), 131.3 (d, J$_{EC}$ = 22.1 Hz), 130.5 (d, J$_{EC}$ = 21.3Hz), 129.0 (d, J$_{EC}$ = 32.5 Hz), 128.0 (d, J$_{EC}$ = 6.4 Hz), 127.9 (d, J$_{EC}$ = 7.2 Hz), 110.5, 83.1 (d, J$_{EC}$ = 3.3 Hz), 80.6 (d, J$_{EC}$ = 18.7 Hz), 79.3 (d, J$_{EC}$ = 2.7 Hz), 73.6 (2C), 63.9, 44.1, 31.3, 27.7, 26.4, 20.8. $^{31}$P RMN (121.4 MHz, CDCl$_3$): δ 119.8.

3,4-O-Isopropyliden-2-O-diphenylphosphinophenyl-1-thio-β-D-arabinopyranoside (2).

1H-NMR (500 MHz, CDC13): δ 7.54–7.46 (m, 4 H), 7.33–7.29 (m, 6 H), 4.76 (d, J = 6.9 Hz, 1H), 4.28–4.26 (m, 1 H), 4.22 (t, J = 5.7 Hz, 1H), 4.10–4.01 (m, 1 H), 3.70 (dd, J = 4.4 and 12.7 Hz 1H), 1.47 (s, 3 H), 1.30 (s, 3 H), 1.19 (s, 9 H). $^{13}$C-NMR (125 MHz, CDC13): δ 131.2 (d, JPC = 22.1 Hz), 130.5 (d, JPC = 21.4 Hz), 129.1 (d, JPC = 31.7 Hz), 128.1 (d, JPC = 5.9 Hz), 128.0 (d, JPC = 6.7 Hz), 110.1, 84.5, 82.6 (d, JPC = 4.2 Hz), 80.3 (d, JPC = 19.2 Hz), 72.2, 63.2, 44.0, 31.3, 27.8, 26.3. $^{31}$P-NMR (121.4 MHz, CDC13): δ 118.6. Anal. Calcd. for C$_{34}$H$_{32}$O$_5$PS: C, 64.55%, H, 7.00%. Found. C 64.94%, H 6.9%.
6-O-Acetyl-3,4-O-Isoprenylidene-2-O-diphenylphosphinite-1-thio-α,δ-D-galactopyranoside (3).

1H RMN (500 MHz, CDCl₃): δ 7.55-7.51 (m, 5H), 7.38-7.28 (m, 10H), 5.6 (dd, J = 3.4 and 24.4 Hz, 1H), 4.93 (s, 1H), 4.19-4.10 (m, 2H), 3.90-3.85 (m, 1H), 3.35 (t, J = 10.2 Hz, 1H), 3.08 (dd, J = 2.9 and 3.9 Hz, 1H), 2.5 (bs, 1H), 2.40 (dd, J = 2.9 and 9.6 Hz, 1H), 1.38 (s, 9H). 13C-NMR (125 MHz, CDCl₃): δ 137.1, 136.9 (d, J=19.7 Hz), 135.8 (d, J=10.9 Hz), 135.3 (d, J=21.9 Hz), 132.2 (d, J=18.3 Hz), 129.4 (d, J=51.4 Hz), 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 126.1, 101.8, 81.0 (d, J = 14.5 Hz), 76.3, 69.3, 68.3 (d, J=14.6 Hz), 67.6, 44.81 (d, J = 22.3 Hz), 31.6. 31P-NMR (121.4 MHz): δ -19.1.

General procedure of the opening epoxide reaction.

To a solution of the corresponding epoxide (575 mg, 1.8 mmol) in a 1:1 mixture of THF: DMF (8 mL) at -10 °C was added a freshly prepared (Ph2ArH + BuLi in THF) and titrated 0.6 M diphenylphosphinite lithium solution (6 mL, 3.5 mmol). After 1 h, NH₄Cl (200 mg, 3.7 mmol) was added and stirring was continued for 30 min more before evaporating the solvent. After coevaporation with toluene, the crude mixture was purified by column chromatography (EtOAc : Hexanes, 1:6), affording the corresponding hydroxypyranosyl-thioglycoside.

tert-Butyl 6,0-Benzylidene-2-deoxy-2-diphenylphosphino-1-thio-δ-D-altropyranoside (9).

[α]D: +13.9 (c 0.6, CHCl₃). 1H-NMR (500 MHz, CDCl₃): δ 7.55-7.51 (m, 5H), 7.38-7.28 (m, 10H), 5.6 (dd, J = 3.4 and 24.4 Hz, 1H), 4.93 (s, 1H), 4.19-4.10 (m, 2H), 3.90-3.85 (m, 1H), 3.35 (t, J = 10.2 Hz, 1H), 3.08 (dd, J = 2.9 and 3.9 Hz, 1H), 2.5 (bs, 1H), 2.40 (dd, J = 2.9 and 9.6 Hz, 1H), 1.38 (s, 9H). 13C-NMR (125 MHz, CDCl₃): δ 137.1, 136.9 (d, J=19.7 Hz), 135.8 (d, J=10.9 Hz), 135.3 (d, J=21.9 Hz), 132.2 (d, J=18.3 Hz), 129.4 (d, J=51.4 Hz), 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 126.1, 101.8, 81.0 (d, J = 14.5 Hz), 76.3, 69.3, 68.3 (d, J=14.6 Hz), 67.6, 44.81 (d, J = 22.3 Hz), 31.6. 31P-NMR (121.4 MHz): δ -19.1.

1-Adamantyl 6,0-Benzylidene-2-deoxy-2-diphenylphosphino-1-thio-δ-D-altropyranoside (10).

1H-NMR (500 MHz, CDCl₃): δ 7.54-7.50 (m, 4H), 7.38-7.35 (m, 3H), 7.33-7.29 (m, 8H), 5.64 (dd, J = 24.6 and 3.2 Hz, 1H), 4.91 (s, 1H), 4.20-4.15 (m, 2H), 3.90-3.85 (m, 1H), 3.22 (t, J = 10.3 Hz, 1H), 3.04-3.03 (m, 1H), 2.36-2.34 (m, 2H), 2.04-2.16 (m, 15H). 13C-NMR (125 MHz, CDCl₃): δ 137.1, 135.4, 135.2, 132.1, 129.1, 128.4, 128.3, 128.2, 126.0 (12C), 101.7, 78.6, 78.5, 76.2, 69.3, 68.3, 67.5, 47.0, 45.0, 43.9, 36.3, 29.8.

[t]D: -29.32 (c 0.25, CHCl₃). 1H-NMR (500 MHz) δ 7.68-7.64 (m, 5H, arom.), 7.42-7.34 (m, 10H, arom.), 5.45 (d, J = 2.9 Hz, H-1), 5.37 (t, 1H, J = 2.5 Hz, H-3), 4.95 (s, 1H, Charom.), 4.21-4.18 (m, 1H, H-6'), 3.93-3.89 (m, 1H, H-5'), 3.57 (t, 1H, J = 10.0 Hz, H-6), 3.14-3.12 (m, 1H, H-2), 2.86 (dd, 1H, J = 2.9 Hz, J = 9.6 Hz, H-4), 2.15 (s, 3H, Ac), 1.38 (s, 9H, t-Bu). 13C-NMR (125 MHz) δ 170 (COCH₃), 137.18, 135.59, 132.79, 129.88, 128.97, 128.70, 128.61, 128.56, 128.26, 125.98 (Ph), 101.64 (Charom.), 81.05 (C-1), 71.47 (C-4), 70.57 (C-3), 69.25 (C-6), 68.35 (C-5), 44.56 (C-2), 31.46 (CH₂(C₃H₇)), 21.27 (Ac), 17.59(C(CH₃)₃). 31P-NMR (121.4 MHz) δ -18 ppm. Anal. Calcld. for C₃₃H₃₄O₇NaPsNa: C, 67.62%; H, 6.41%. Found: C, 67.20%, H, 6.19%.

Adamantyl 3-O-acetyl-4,6-O-benzylidene-2-deoxy-diphenylphosphino-1-thio-δ-D-altropyranoside (12).

1H-NMR (500 MHz): δ 7.66-7.63 (m, 4H, arom.), 7.37-7.29 (m, 6H, arom.), 7.28-7.25 (m, 5H, arom.), 5.50 (dd, 1H, J = 22.9 y 2.6 Hz, H-1), 5.36-5.35 (m, 1H, H-3), 4.93 (s, 1H, PhOCH₂), 4.19 (dd, 1H, J = 10.1 y 1.46 Hz, H₆'), 3.93-3.88 (m, 1H, H-5'), 3.44 (t, 1H, J = 10.2 Hz, H-6'), 3.09-3.07 (m, 1H, H-2), 2.83 (dd, 1H, J = 8.9 y 2.3 Hz, H-4), 2.14 (s, 3H, OCOCH₃), 2.03-1.64 (m, 15H, Adam.). 13C-NMR (125 MHz): δ 170.0 (OCOCH₃), 137.2, 135.7, 135.6, 132.7, 132.6, 129.8, 128.9, 128.6, 128.5, 128.1, 126.0 (12C arom.), 101.6 (CHOPh), 78.6 (C-1), 74.4 (C-4), 70.6 (C-3), 69.2 (C-6), 68.2 (C-5), 47.0 (Adam.), 44.6 (C-2), 44.0, 36.2, 29.7 (Adam.), 21.2 (OCOCH₃). 31P-NMR (121.4 MHz): δ -18.2.
HRMS calc. For C₉H₄O₂NaPSNa: 651.2310. Found: 651.2331 (3.2 ppm).

tert-Butyl 3-O-acetyl-4,6-O-benzylidene-2-deoxy-2-di(p-methoxy)phenylphosphine-1-thio-/D-altropropanside (14).

White solid. M.p: 94°C. [α]D° = +5.71 (c 0.175, CHCl₃). ¹H-NMR (400 MHz): δ 7.63-7.57 (m, 4H), 7.30 (s, 5H), 6.92-6.87 (m, 4H), 5.43 (dd, J = 2.6 and 21.3 Hz, 1H), 5.31 (t, J = 2.5 Hz, 1H), 5.09 (s, 1H), 4.23 (dd, J = 4.8 and 10.4 Hz, 1H), 4.95 (dt, J = 4.9 y 9.8 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.58 (t, J = 10.3 Hz, 1H), 3.13 (d, J = 3.0 Hz, 1H), 3.10 (dd, J = 2.7 and 5.4 Hz, 1H), 2.16 (s, 3H), 3.36 (s, 3H). ¹³C-NMR: δ 170.1, 160.9, 160.1, 137.1, 136.8, 136.6, 134.4, 134.1, 128.9, 128.1, 127.7, 127.6, 126.6, 126.4, 126.0, 114.3, 114.2, 114.1, 101.7, 81.0, 80.8, 74.5, 74.4, 70.8, 69.2, 68.2, 55.2, 55.1, 45.0, 44.8, 44.6, 44.5, 31.4, 21.2. ³¹P-NMR: (121.4 MHz): δ -22.3.

terc-Butyl 3-O-acetyl-4,6-O-benzylidene-2-deoxy-2-bis[(3,5 bis(trifluoromethyl)phenyl)phosphine-1-thio-/D-altropropanside (16).

³¹H-NMR: (500 MHz): δ 8.17 (dd, J = 6.8 and 27.5 Hz, 4H), 7.92 (d, 28.2 Hz, 2H), 7.33 (s, 5H), 5.50 (s, J = 18.5 Hz, 1H), 5.29 (s, 1H), 5.0 (s, 1H), 4.31 (dd, J = 4.7 and 10.4 Hz, 1H), 4.09 (dt, J = 5.0 and 9.6 Hz, 1H), 3.67 (t, J = 10.5 Hz, 1H), 3.55 (dd, J = 2.2 y 9.6 Hz, 1H), 3.39 (s, 1H). ¹³C-NMR: δ 170.0, 137.7, 136.6, 134.9, 133.5, 129.7, 129.3, 128.9, 128.3, 126.0, 124.4, 123.9, 121.9, 102.3, 79.7, 78.2, 74.6, 70.0, 69.0, 68.4, 45.7, 44.7, 31.2, 21.0. ³¹P-NMR: (121.4 MHz): δ -17.0.

tert-Butyl 3-O-acetyl-4,6-O- benzylidene-2- deoxy-2-di(2,4,6-trimethyl)phenylphosphine-1-thio-/D-altropropanside (18).

³¹H-NMR: (400 MHz): δ 7.29 (s, 5H), 6.96-6.67 (m, 4H), 5.33 (d, J = 26.0 Hz, 1H), 5.10 (s, 1H), 5.08 (s, 1H), 4.37 (s, 1H), 4.29 (dd, J = 4.6 and 10.2 Hz, 1H), 3.98-3.91 (m, 1H), 3.69 (t, J = 10.1 Hz, 1H), 3.15 (d, J = 8.5 Hz, 1H), 2.92 (s, 3H), 2.71 (s, 3H), 2.35 (s, 3H), 2.21 (s, 6H), 2.14 (s, 3H), 2.10 (s, 3H), 1.37 (s, 9H). ¹³C-NMR: (125 MHz): δ 170.0, 137.2, 128.9, 128.1, 126.0, 101.7, 81.7, 81.5, 75.0, 71.5, 69.5, 68.0, 42.7, 42.3, 31.4, 21.2, 20.9, 20.5. ³¹P-NMR: (121.4 MHz): δ -27.5.

Procedure for the 1,4-Addition of phenyloronic acid to cyclohexenone.

A mixture of ligand (0.03 mmol, 5 mol %) and [Rh(C₅H₄Cl)₂] (6.0 mg, 0.015 mmol, 2.5 mol %) was stirred for 0.5 h in 1.2 mL of degassed toluene. Phenyloronic acid 2 (146 mg, 1.2 mmol) was added over the catalyst and sequentially the cyclohexenone 1 (0.6 mmol) and an aqueous solution of KOH (120 μL, 2.5 M). The reaction was followed by TLC, and once the starting material was consumed, the crude reaction mixture was charged into a column chromatography (AcOEt : Hexane 1:7).

3-Phenylcyclohexanone (6).


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