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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 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 a D-sugar are able to generate the addition product of the phenylboronic acid to the cyclohexenone with opposite configurations, behaving thus as enantiomers.

Introduction

The synthesis of enantiopure compounds is a standing area of interest, a consequence of the significance of chirality in medicine, fragrances, agriculture and material science.[1] Among all the different approximations developed so far, enantioselective catalysis is the method of choice,[2] as it combines efficiency, versatility, atom economy, and suitability for green chemistry.[3] Enantioselective catalysis is usually achieved by using a chiral organic ligand either alone[4] or linked to a transition metal.[5] 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 appends 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.[6] 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.[7] 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.[8] Based on these premises, and within our interest in the synthesis and application of chiral sulfur compounds in organic[9] and organometallic asymmetric synthesis,[10] we have developed highly enantioselective pseudo enantiomeric mixed S/P ligands for Pd-catalyzed allylic substitution,[11] Rh(I)-catalyzed enamide hydrogenation[12] and hydrosilylation of prochiral ketones.[13] 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, Fig. 1.

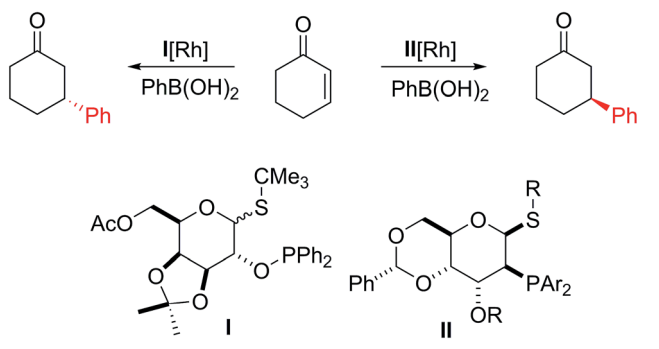

Fig. 1 General structure of mixed S/P ligands used in the Rh-catalyzed 1,4-addition of phenylboronic acid to cyclohexenone.

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† Electronic supplementary information (ESI) available: Copies of ^{1}H, ^{13}C and ^{31}P spectra of compounds **12–14**, **16–18**, and HPLC chromatograms of **6** obtained with ligand **3** and **10**. See DOI: 10.1039/c5ra10181f

Results and discussion

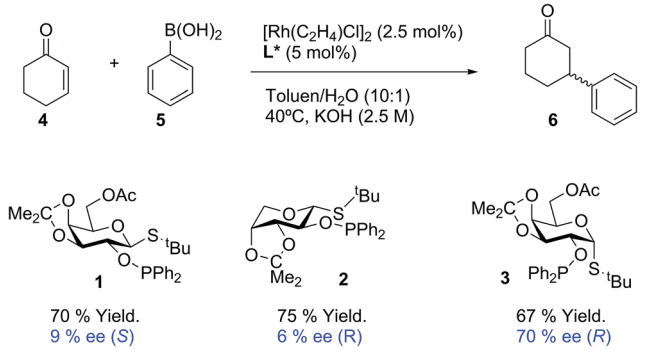
Within C–C bond formation reactions, the Rh(I)-catalyzed addition of boronic acids to activated ketones is one of the most powerful approximations.[14] Since the pioneering works of Hayashi,[15] and Miyaura[16] a wide number of methodologies have been successfully developed for this transformation and 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_2 (ref. 17) and C_1 (ref. 18) ligands with a chiral sulfinyl group (S–O) are able to generate efficient catalysts for this transformation. Surprisingly, a single type of ligands derived from carbohydrates, entailing olefin/phosphinite coordinating groups have been used in this transformation.[19] 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.[20] In our previous works we have shown that this control may be exerted, in the case of C_2-symmetric bis-thioglycosides,[21] through stereoelectronic factors, namely the exo-anomeric effect, or through steric bias in the case of C_1-symmetric phosphinite thioglycosides.[22] This stereocontrol coupled with the higher *trans* effect of phosphorus *vs.* sulfur[23] led to the discovery, of ligands **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.[12] Moreover, these ligands have also shown interesting behavior in the Rh(I)-catalyzed hydrosilylation of prochiral ketones.[13]

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 the rhodium precursor $[Rh(C_2H_4)Cl]_2$ 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 arabinose ligand **2** led to the formation of **6** in 75% yield and 6% ee in favor of the (*R*) enantiomer, Scheme 1.

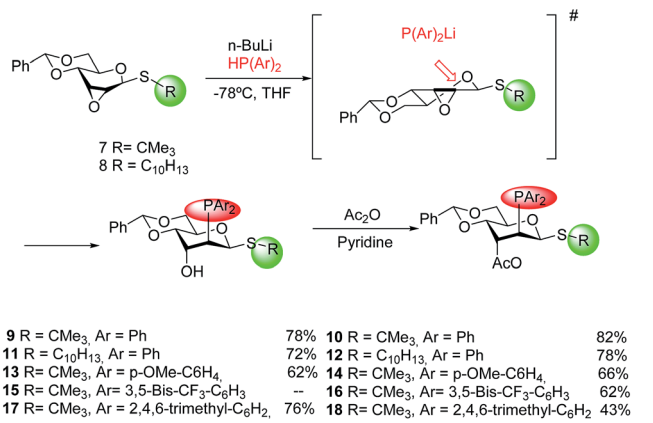
In our previous work on the Rh(I)-catalyzed hydrogenation of enamides, we have shown that the relative disposition of the coordinating sulfur and phosphorus atoms is extremely important, being the 1,2-*trans* derivative the most favored. Surprisingly, by using the galactose derivative with an α configuration at the anomeric center **3**, which was neither reactive nor enantioselective in Pd(0)-catalyzed allylic alkylation, and in the Rh(I)-catalyzed hydrogenation of enamides, 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-mannothiolglycosides and β-glucothioglycosides needed for the synthesis of 1,2-*trans* diaxial and 1,2-*trans* diequatorial 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, to evaluate the contribution of the phosphinite moiety, and the ring size in the metallacycle intermediate on the catalytic performance of ligands **1** and **2**, we have developed a method for the synthesis of β-mannothioglycosides **II**, Fig. 1, with a biphenyl phosphine moiety at C_2.[24] The approximation is based on the ring opening of an allo-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 (PPh_2H + BuLi) on a solution of epoxide **7** dissolved in a deoxygenated Et_2O : DMF (1 : 1) mixture, afforded the desired phosphine **9** as a single diastereoisomer. To study



Scheme 1 Use of phopshinite thioglycosides **1–3** as ligands in the Rh(I)-catalysed 1,4-addition of phenyl boronic acid to cyclohexenone **4**.



Scheme 2 Synthesis of phosphine thioglycoside ligands by ring opening of allo-epoxides with diarylylphosphinyl lithium.

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**, hydroxyphosphine **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 phosphine moiety were synthesized by condensation of diarylphosphinyl lithium on *tert*-butyl 4,6-*O*-benzylidene-2,3-anhydro-1-thio-β-D-allopyranosides **7**, Scheme 2.

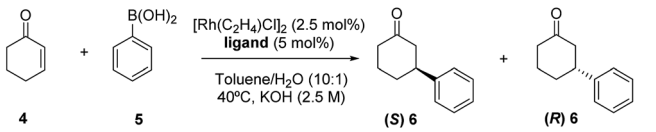
The addition of bis-(*para*-methoxyphenyl)phosphinyl lithium to the epoxide **7** afforded the electron rich hydroxyphosphine thioglycoside **13** with 62% yield, which after acetylation afforded phosphine **14** with 66% yield. The use of the hindered bis-(1,3,5-trimethylphenyl)phosphinyl lithium as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

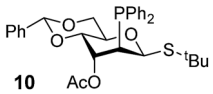
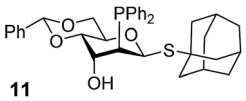
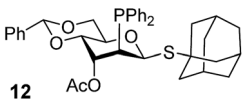
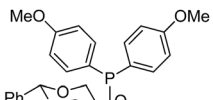
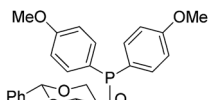
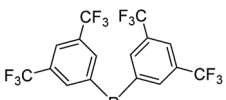
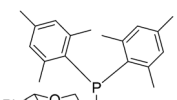
Once the ligands in hand, we assayed them in the model reaction of 2-cyclohexenone **4** and phenyl boronic acid **5** (Table 1), under the same conditions than for the phosphinite thioglycosides **1–3**.

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 the *tert*-butyl to the adamantyl group has a detrimental effect on the enantioselectivity. In this sense, ligand **10** with the *tert*-butyl group led to the desired product with 64% ee (Table 1, entry 1), while ligand **12** with the bulky adamantyl group afforded compound **6** with a lower 40% ee (Table 1, entry 3), eventhough both are equally reactive affording the addition compound in good yields (85% and 83% respectively). The protection of the hydroxyl group at the position 3 is crucial, both for the reactivity and the enantioselectivity 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 **6*S*** enantiomer as major adduct.

Table 1 Rhodium-catalyzed 1,4-addition of the phenyl boronic acid **5** to cyclohexenone **4** using chiral phosphine thioglycosides[a]

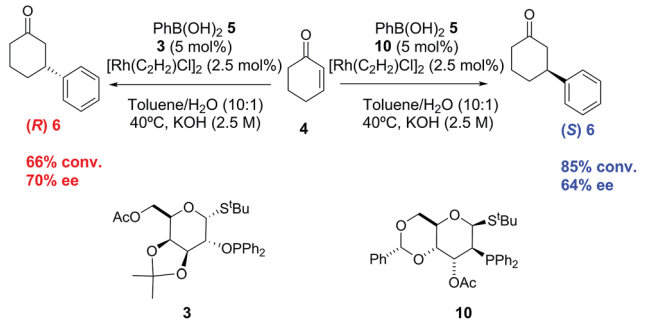


Entry	Ligand	Yield[b] (%)	e.r.[c] %*S*/%*R*	ee[c] (%)
1	 **10**	85	87/23	64
2	 **11**	0	—	—
3	 **12**	83	70/30	40
4	 **13**	23	54/46	8
5	 **14**	88	87/23	65
6	 **16**	87	88/22	66
7	 **18**	86	50/50	0

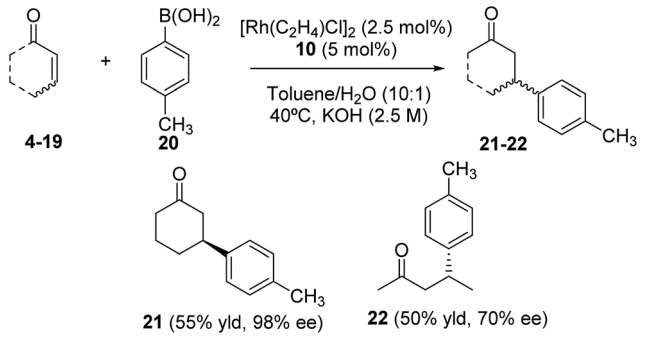
[a] All reactions were conducted using 5 mol% of the ligand together with 2.5 mol% of $[Rh(C_2H_4)Cl]_2$. [b] Isolated yields of pure compound **6** after column chromatography purification. [c] Determined by chiral stationary phase HPLC with OD-H column: hexane: iPrOH 98 : 2, flow 0.5 mL min^{-1}.

Considering that phosphinites thioglycosides type **I**, tested at the beginning of this study lead to the **6*R*** isomer, one can conclude that the two types of ligands, although structurally different behave as pseudo-enantiomers, Scheme 3.

Next we studied the addition of other boronic acid to cyclohexenone and to an acyclic α,β-unsaturated ketone, Scheme 3. The use of *p*-tolyl boronic acid **20** as nucleophile afforded the



Scheme 3 Pseudo-enantiomeric behavior of ligands **3** and **10** in the Rh-catalyzed 1,4-addition.



Scheme 4 1,4-Addition of *p*-tolyl boronic acid **20** to cyclohexenone **4** and to 3-pentenone **19** using ligand **10**.

addition compound **21*R*** in an excellent 98% enantiomeric excess albeit with low yield, Scheme 4. Surprisingly, the addition of *p*-tolyl boronic acid to the more challenging 3-pentenone **19** afforded the desired 4-phenylpentan-2-one **22*S*** in 50% yield and an interesting 70% ee.

Conclusions

In conclusion, we have reported the first application of mixed S/P ligands with a prochiral thioether group in the Rh(I)-catalyzed 1,4 addition of phenyl boronic 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 both coordinating atoms are better catalyst precursors than those with a *trans* relationship. In the case of phosphine–thioglycosides **II**, a ring opening of the allo-epoxide intermediates, obtained in 4 steps from glucose pentaacetate, with diarylphosphinyl lithium, allowed the preparation of various ligands with a 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 benzophenone 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 (^{1}H, 500 MHz) and Bruker Avance DRX500 (^{1}H, 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. 1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose, was purchased from Aldrich.

General procedure for the incorporation of the phosphinite 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 deoxygented THF/NEt_3 (1/1) solution, was added diphenyl chlorophophine (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*-isopropylidene-2-*O*-diphenylphosphinite-1-thio-β-D-galactopyranoside (1). White solid. Mp 116–120 °C. $[\alpha]_D^{20}$: +7.1 (*c* 1.05, $CHCl_3$). ^{1}H RMN (500 MHz, $CDCl_3$): δ 7.56–7.47 (m, 4H, PPh_2), 7.34–7.29 (m, 6H, PPh_2), 4.51 (d, 1H, $^3J_{H1\text{-}H2}$ = 9.5 Hz, H-1), 4.33–4.26 (m, 3H, H-3, H-4, H-6), 4.15 (dd, 1H, $^3J_{H5\text{-}H6'}$ = 1.8 Hz, $^2J_{H6\text{-}H6'}$ = 5.6 Hz, H-6′), 3.96–3.88 (m, 2H, H-2, H-5), 2.03 (s, 3H, OAc), 1.42 (s, 3H, O_2CMe_2), 1.29 (s, 3H, O_2CMe_2), 1.22 (s, 9H, $SCMe_3$). ^{13}C RMN (125 MHz, $CDCl_3$): δ 170.8 (COMe), 142.9 (d, $J_{C\text{-}P}$ = 18.4 Hz, PPh_2), 142.1 (d, $J_{C\text{-}P}$ = 15.2 Hz, PPh_2), 131.3 (d, $J_{C\text{-}P}$ = 22.1 Hz, PPh_2), 130.5 (d, $J_{C\text{-}P}$ = 21.3 Hz), 129.0 (d, $J_{C\text{-}P}$ = 32.5 Hz), 128.0 (d, $J_{C\text{-}P}$ = 6.4 Hz), 127.9 (d, $J_{C\text{-}P}$ = 7.2 Hz), 110.5 (CMe_2), 82.5 (C-1), 83.1 (d, $J_{C\text{-}P}$ = 3.3 Hz, C-2), 80.6 (C-3), 73.6 (C-4, C-5), 63.9 (C-6), 44.1 (CMe_3), 31.3 (CMe_3), 27.7 (CMe_2), 26.4 (CMe_2), 20.8 (OAc). ^{31}P RMN (121.4 MHz, $CDCl_3$): δ 119.8. HRMS calc. For $C_{27}H_{35}O_6PSNa$: 541.1792. Found: 541.1788 (−1.2 ppm).

3,4-*O*-Isopropylidene-2-*O*-diphenylphosphinite-1-thio-α-D-arabinopyranoside (2). White solid. Mp 119–125 °C. $[\alpha]_D^{20}$: +5.8 (*c* 2.22, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.54–7.46 (m, 4H, PPh_2), 7.33–7.29 (m, 6H, PPh_2), 4.76 (d, $^3J_{H1\text{-}H2}$ = 6.9 Hz, 1H), 4.28–4.26 (m, 1H, H-4), 4.22 (t, $^3J_{H3\text{-}H2}$ = 5.7 Hz, 1H, H-3), 4.08 (dd, $^3J_{H4\text{-}H5}$ = 4.8 Hz, $^2J_{H5\text{-}H5'}$ = 12.7 Hz, H-5) 3.99–4.05 (m, 1H, H-2), 3.70 (dd, $^3J_{H4\text{-}H5'}$ = 4.8 Hz, $^2J_{H5\text{-}H5'}$ = 12.7 Hz, 1H, H-5′),

1.47 (s, 3H, O_2CMe_2), 1.30 (s, 3H, O_2CMe_2), 1.19 (s, 9H, $SCMe_3$). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 131.2 (d, $J_{C\text{-}P}$ = 22.1 Hz, PPh_2), 130.5 (d, $J_{C\text{-}P}$ = 21.4 Hz, PPh_2), 129.1 (d, $J_{C\text{-}P}$ = 31.7 Hz, PPh_2), 128.1 (d, $J_{C\text{-}P}$ = 5.9 Hz, PPh_2), 128.0 (d, $J_{C\text{-}P}$ = 6.7 Hz, PPh_2), 110.1 (CMe_2), 84.5 (C-1), 82.6 (d, J_{PC} = 4.2 Hz, C-2), 80.3 (d, J_{PC} = 19.2 Hz, C-3), 72.2 (C-4), 63.2 (C-5), 44.0 (CMe_3), 31.3 (CMe_3), 27.8 (CMe_2), 26.3 (CMe_2), 17.2 (OAc). ^{31}P-NMR (121.4 MHz, $CDCl_3$): δ 118.6. Anal. Calcd for $C_{24}H_{31}O_4PS$: C, 64.55%, H, 7.00%. Found. C 64.94%, H 6.9%.

6-*O*-Acetyl-3,4-*O*-isopropylidene-2-*O*-diphenylphosphinite-1-thio-α-D-galactopyranoside (3). White solid. mp 102–104 °C. $[\alpha]_D^{20}$: +77.5 (*c* 1.65, $CHCl_3$). ^{1}H RMN (500 MHz, $CDCl_3$): δ 7.57–7.50 (m, 4H, PPh_2), 7.35–7.32 (m, 6H, PPh_2), 5.56 (d, 1H, $^3J_{H1\text{-}H2}$ = 5.1 Hz, H-1), 4.70–4.67 (m, 1H, H-5), 4.34–4.11 (m, 5H, H6, H-6′, H-2, H-3, H-4), 2.02 (s, 3H, OAc), 1.41 (s, 3H, O_2CMe_2), 1,30 (s, 12H, O_2CMe_2, $SCMe_3$). ^{13}C RMN (75 MHz, $CDCl_3$): δ 170.7 (COMe), 137.7(d, $J_{C\text{-}P}$ = 18.4 Hz, PPh_2), 132.4 (d, $J_{C\text{-}P}$ = 15.2 Hz, PPh_2), 131.1 (d, $J_{C\text{-}P}$ = 22.1 Hz, PPh_2), 130.8 (d, $J_{C\text{-}P}$ = 32.5 Hz), 130.6 (d, $J_{C\text{-}P}$ = 6.4 Hz), 129.5 (d, $J_{C\text{-}P}$ = 32.5 Hz), 128.1 (d, $J_{C\text{-}P}$ = 6.4 Hz), 110.5 (CMe_2), 88.5 (C-1), 88.4 (d, $J_{C\text{-}P}$ = 3.3 Hz, C-2), 80.4 (C-3), 80.1, 79.1, 74.0 (C-4), 73.7 (C-5), 63.7 (C-6), 38.7 (CMe_3), 27.8 (CMe_2), 27.1 (CMe_2), 26.4, 21.2 (OAc). ^{31}P RMN (121.4 MHz, $CDCl_3$): δ 117.5.

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 ($P(Ar)_2H$ + BuLi in THF) and titrated 0.6 M diphenylphosphinyl lithium solution (6 mL, 3.5 mmol). After 1 h, NH_4Cl (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 hydroxyphosphine–thioglycoside.

***tert*-Butyl 4,6-*O*-benzylidene-2-deoxy-2-diphenylphosphino-1-thio-β-D-altropyranoside (9).** $[\alpha]_D^{20}$: +13.9 (c. 0.6, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.55–7.51 (m, 5H), 7.38–7.28 (m, 10H), 5.6 (dd, $^3J_{H1\text{-}H2}$ = 3.4 and $^3J_{H1\text{-}P}$ = 24.4 Hz, 1H, H-1), 4.93 (s, 1H, CHPh), 4.22 (dd, $^3J_{H6\text{-}H5}$ = 4.8, $^3J_{H6\text{-}H6'}$ = 10.2 Hz, 1H, H-6), 3.90 (dt, $^3J_{H5\text{-}H6,6'}$ = 4.9, $^3J_{H5\text{-}H4}$ = 9.9 Hz, 1H, H-5), 3.5 (t, $^3J_{H6'\text{-}H6}$ = $^3J_{H6'\text{-}H5}$ = 10.2 Hz, 1H, H-6′), 3.08 (m, 1H, H-4), 2.85 (m, 1H, H-2), 2.05 (bs, 1H, OH), 1.38 (s, 9H, CMe_3). ^{13}C-NMR (125 MHz, $CDCl_3$): 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 (CHPh), 81.0 (d, $^2J_{C\text{-}P}$ = 14.5 Hz, C-1), 76.3 (C-4), 69.3 (C-6), 68.3 (C-5), 67.6 (C-3), 44.81 (d, $^1J_{C\text{-}P}$ = 22.3 Hz, C-2), 31.6 (CMe_3). ^{31}P-NMR (121.4 MHz, $CDCl_3$): δ −19.1.

1-Adamantyl 4,6-*O*-benzylidene-2-deoxy-2-diphenylphosphino-1-thio-β-D-altropyranoside (11). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.54–7.50 (m, 4H), 7.38–7.35 (m, 3H), 7.33–7.29 (m, 8H), 5.64 (dd, $^3J_{H1\text{-}P}$ = 24.6 and $^3J_{H1\text{-}H2}$ = 3.2 Hz, 1H, H-1), 4.91 (s, 1H, CHPh), 4.20 (dd, $^3J_{H6\text{-}H5}$ = 4.8, $^3J_{H6\text{-}H6'}$ = 10.2 Hz, 1H, H-6), 3.85 (dt, $^3J_{H5\text{-}H6,6'}$ = 4.9, $^3J_{H5\text{-}H4}$ = 9.9 Hz, 1H, H-5), 3.22 (t, $^3J_{H6'\text{-}H6}$ = $^3J_{H6'\text{-}H5}$ = 10.2 Hz, 1H, H-6′), 3.04–3.03 (m, 1H, H-4), 2.36 (m, 1H, H-2), 2.04–1.68 (m, 15H, Adam). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 137.1, 135.4, 135.2, 132.1, 129.5, 129.1, 128.4, 128.4, 128.3, 128.2, 126.0 (12C), 101.7 (CHPh), 78.6 (d, $^2J_{C\text{-}P}$ = 14.5 Hz, C-1), 78.5, 76.2 (C-4), 69.3(C-6), 68.3 (C-5), 67.5 (C-3), 47.0, 45.0 (d, $^1J_{C\text{-}P}$ = 22.3 Hz, C-2), 43.9, 36.3, 29.8 (CMe_3). ^{31}P-NMR (202 MHz, $CDCl_3$): δ −19.1. HRMS Calc. for $C_{35}H_{39}O_4NaPSNa$: 609.2204. Found: 609.2199 (−0.9 ppm).

***tert*-Butyl 4,6-*O*-benzylidene-2-deoxy-2-di(*p*-methoxy)phenylphosphine-1-thio-β-D-altropyranoside (13).** Mp 104 °C. $[\alpha]_D^{20}$: +6 (c 0.15, $CHCl_3$). ^{1}H-NMR: (500 MHz, $CDCl_3$): δ 7.48–7.44 (m, 4H), 7.32 (s, 5H), 6.92–6.87 (m, 4H), 5.58 (dd, $^3J_{H1\text{-}H2}$ = 3.0 and $^3J_{H1\text{-}P}$ = 22.9 Hz, 1H, H-1), 5.08 (brs, 1H, CHPh), 4.21(dd, $^3J_{H6\text{-}H5}$ = 4.8, $^3J_{H6\text{-}H6'}$ = 10.2 Hz, 1H, H-6), 4.15 (brs, 1H, H-3), 3.93 (dt, $^3J_{H5\text{-}H6,6'}$ = 4.9, $^3J_{H5\text{-}H4}$ = 9.9 Hz, 1H, H-5), 3.81 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.47 (t, $^3J_{H6'\text{-}H6}$ = $^3J_{H6'\text{-}H5}$ = 10.2 Hz, 1H, H-6′), 3.03–3.01 (m, 1H, H-2), 2.72 (dd, $^3J_{H4\text{-}H3}$ = 2.3, $^3J_{H4\text{-}H5}$ = 9.6 Hz, 1H, H-4), 2.35 (brs, 1H, OH), 1.36 (s, 9H, CMe_3). ^{13}C-NMR: (125 MHz, $CDCl_3$): δ 160.9, 159.9, 137.1, 136.5, 136.3, 133.8, 133.6, 129.2, 128.2, 127.5, 127.1, 126.0, 114.3, 114.2, 114.1, 114.0, 101.8 (CHPh), 80.9 (d, $^2J_{C\text{-}P}$ = 14.5 Hz, C-1), 76.3 (C-4), 69.3 (C-6), 68.4 (C-5), 67.6 (C-3), 55.3, 55.2, 45.5 (d, $^1J_{C\text{-}P}$ = 22.3 Hz, C-2), 44.7, 44.6, 31.5 (CMe_3). ^{31}P-NMR: (121.4 MHz, $CDCl_3$): δ −19.1. Anal. Calc. for $C_{31}H_{37}O_6PS$: C, 65.48%; H, 6.56%; O, 16.88%; P, 5.45%; S, 5.64%. Found: C, 64.80%, H, 6.67%, S, 5.65%.

***tert*-Butyl 4,6-*O*-benzylidene-2-deoxy-2-di(2,4,6-trimethyl) phenylphosphine-1-thio-β-D-altropyranoside (17).** ^{1}H-NMR: (500 MHz, $CDCl_3$): δ 7.33 (s, 5H), 7.05–6.77 (m, 4H), 5.52 (dd, $^3J_{H1\text{-}H2}$ = 3.0 and $^3J_{H1\text{-}P}$ = 22.9 Hz, 1H, H-1), 5.14 (brs, 1H, CHPh), 4.26 (dd, $^3J_{H6\text{-}H5}$ = 4.8, $^3J_{H6\text{-}H6'}$ = 10.2 Hz, 1H, H-6), 4.14 (brs, 1H, H-3), 3.96 (dt, $^3J_{H5\text{-}H6,6'}$ = 5, $^3J_{H5\text{-}H4}$ = 10 Hz, 1H, H-5), 3.60 (t, $^3J_{H6'\text{-}H6}$ = $^3J_{H6'\text{-}H5}$ = 10.2 Hz, 1H, H-6′), 2.99–3.01 (m, 1H, H-4), 2.85 (m, 1H, H-2), 2.24 (s, 8H), 2.22 (s, 3H), 2.16 (s, 3H), 1.36 (s, 9H). ^{13}C-NMR: (125 MHz, $CDCl_3$): δ 160.9, 159.9, 137.1, 136.5, 136.3, 133.8, 133.6, 129.2, 128.2, 127.5, 127.1, 126.0, 114.3, 114.2, 114.1, 114.0, 101.7 (CHPh), 81.1 (d, $^2J_{C\text{-}P}$ = 14.5 Hz, C-1), 76.6 (C-4), 69.1 (C-6), 68.7 (C-5), 67.7 (C-3), 55.3, 55.2, 45.5 (d, $^1J_{C\text{-}P}$ = 22.3 Hz, C-2), 44.7, 44.6, 22.6, 21.9, 31.5 (CMe_3). ^{31}P-NMR: (121.4 MHz, $CDCl_3$): δ −28 ppm.

General procedure for the acetylation of the hydroxyl group

To a solution of the corresponding hydroxyphosphine–thioglycoside (0.0924 mmol) in pyridine (0.25 mL) at r.t., was added acetic anhydride (0.1386 mmol). After 2 hours, the solvent was evaporated to give the product as a white solid.

***tert*-Butyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-diphenylphosphine-1-thio-β-D-altropyranoside (10).** White solid. Mp 141–143 °C. $[\alpha]_D^{20}$: −29.32 (c. 0.25, $CHCl_3$), ^{1}H-NMR: (500 MHz, $CDCl_3$) δ 7.68–7.64 (m, 5H, arom.), 7.42-7.34 (m, 10H, arom.), 5.45 (dd, $^3J_{H1\text{-}H2}$ = 2.6 Hz, $^3J_{H1\text{-}P}$ = 21.3 Hz, 1H, H-1), 5.37 (t, $^3J_{H3\text{-}H2}$ = $^3J_{H3\text{-}H4}$ = 2.5 Hz, 1H, H-3), 4.95 (s, 1H, CHPh), 4.20 (dd, $^3J_{H6\text{-}H5}$ = 4.8 Hz, $^3J_{H6\text{-}H6'}$ = 10.4 Hz, 1H, H-6), 3.90 (dt, $^3J_{H5\text{-}H6}$ = $^3J_{H5\text{-}H6'}$ = 4.9 Hz, $^3J_{H5\text{-}H4}$ = 9.8 Hz, 1H, H-5), 3.57 (t, $^3J_{H6'\text{-}H6}$ = $^3J_{H6'\text{-}H5}$ = 10.3 Hz, 1H, H-6′), 3.14–3.12 (m, 1H, H-2) 2.89–2.86 (m, 1H, H-4), 2.15 (s, 3H, OAc), 1.38 (s, 9H, *t*-Bu). ^{13}C-NMR: (125 MHz, $CDCl_3$) δ: 170 (COAc), 137.18, 135.59, 132.79, 129.88, 128.97, 128.70, 128.61, 128.56, 128.26, 125.98 (Ph), 101.64 (CHPh), 81.05 (d, $^2J_{C\text{-}P}$ = 14.5 Hz, C-1), 71.47 (C-4), 70.57 (C-6), 69.25 (C-5), 68.35 (C-3), 44.56 (d,

$^{1}J_{C\text{-}P}$ = 22.3 Hz, C-2), 31.46 (CMe_3), 21.21 (OAc). ^{31}P-NMR (121.4 MHz, $CDCl_3$) δ −18 ppm. Anal. Calcd for $C_{31}H_{35}O_5PS$: C, 67.62%; H, 6.41%. Found: C, 67.20%, H, 6.19%.

Adamantyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-diphenylphosphine-1-thio-β-D-altropyranoside (12). ^{1}H-NMR (500 MHz, $CDCl_3$): 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, $^{3}J_{H1\text{-}P}$ = 22.9 Hz, $^{3}J_{H1\text{-}H2}$ = 2.6 Hz, H-1), 5.36–5.35 (m, 1H, H-3), 4.93 (s, 1H, CHPh), 4.19 (dd, $^{3}J_{H6\text{-}H5}$ = 4.8 Hz, $^{3}J_{H6\text{-}H6'}$ = 10.4 Hz, 1H, H-6), 3.92 (dt, $^{3}J_{H5\text{-}H6}$ = $^{3}J_{H5\text{-}H6'}$ = 4.9 Hz, $^{3}J_{H5\text{-}H4}$ = 9.8 Hz, 1H, H-5), 3.44 (t, $^{3}J_{H6'\text{-}H6}$ = $^{3}J_{H6'\text{-}H5}$ = 10.3 Hz, 1H, H-6′), 3.09–3.07 (m, 1H, H-2), 2.83 (dd, $^{3}J_{H4\text{-}H3}$ = 2.3, $^{3}J_{H4\text{-}H5}$ = 9.6 Hz, 1H, H-4), 2.14 (s, 3H, OAc), 2.03–1.64 (m, 15H, Adam.). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 170.0 ($O\underline{C}OCH_3$), 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 (CHPh), 78.6 (d, $^{2}J_{C\text{-}P}$ = 14.5 Hz, C-1), 74.4 (C-4), 70.6 (C-6), 69.2 (C-5), 68.2 (C-3), 47.0 (Adam.), 44.6 (d, $^{1}J_{C\text{-}P}$ = 22.3 Hz, C-2), 44.0, 36.2, 29.7 (Adam.), 21.2 (OAc). ^{31}P-NMR (121.4 MHz, $CDCl_3$): δ −18.2. HRMS calc. for $C_{37}H_{41}O_5NaPSNa$: 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-β-D-altropyranoside (14).** White solid. Mp 94 °C. $[\alpha]_D^{20}$: +5.71 (c 0.175, $CHCl_3$). ^{1}H-NMR: (400 MHz, $CDCl_3$): δ 7.63–7.57 (m, 4H, arom.), 7.30 (s, 5H, arom.), 6.92–6.87 (m, 4H, arom.), 5.43 (dd, $^{3}J_{H1\text{-}H2}$ = 2.6 Hz, $^{3}J_{H1\text{-}P}$ = 21.3 Hz, 1H, H-1), 5.31 (t, $^{3}J_{H3\text{-}H2}$ = $^{3}J_{H3\text{-}H4}$ = 2.5 Hz, 1H, H-3), 5.09 (s, 1H, CHPh), 4.23 (dd, $^{3}J_{H6\text{-}H5}$ = 4.8 Hz, $^{3}J_{H6\text{-}H6'}$ = 10.4 Hz, 1H, H-6), 4.95 (dt, $^{3}J_{H5\text{-}H6}$ = $^{3}J_{H5\text{-}H6'}$ = 4.9 Hz, $^{3}J_{H5\text{-}H4}$ = 9.8 Hz, 1H, H-5), 3.81 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.58 (t, $^{3}J_{H6'\text{-}H6}$ = $^{3}J_{H6'\text{-}H5}$ = 10.3 Hz, 1H, H-6′), 3.13–3.10 (m, 2H, H-2 and H-4), 2.16 (s, 3H, OAc), 1.36 (s, 9H, CMe_3). ^{13}C-NMR: (125 MHz, $CDCl_3$): δ 170.1, 160.9, 160.12, 137.13, 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 (CHPh), 81.0 (d, $^{2}J_{C\text{-}P}$ = 14.5 Hz, C-1), 80.8, 74.5, 74.4 (C-4), 70.8 (C-6), 69.2 (C-5), 68.2(C-3), 55.2 (OMe), 44.8 (d, $^{1}J_{C\text{-}P}$ = 22.3 Hz, C-2), 31.4 (CMe_3), 21.2 (OAc). ^{31}P-NMR: (121.4 MHz, $CDCl_3$): δ −22.3.

***tert*-Butyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-bis[3,5 bis(trifluoromethyl)phenyl]phosphine-1-thio-β-D-altropyranoside (16).** ^{1}H-NMR: (500 MHz, $CDCl_3$): 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 (dd, $^{3}J_{H1\text{-}H2}$ = 2.6 Hz, $^{3}J_{H1\text{-}P}$ = 21.3 Hz, 1H, H-1), 5.29 (s, 1H, CHPh), 5.0 (s, 1H, H-3), 4.31 (dd, $^{3}J_{H6\text{-}H5}$ = 4.8 Hz, $^{3}J_{H6\text{-}H6'}$ = 10.4 Hz, 1H, H-6), 4.09 (dt, $^{3}J_{H5\text{-}H6}$ = $^{3}J_{H5\text{-}H6'}$ = 4.9 Hz, $^{3}J_{H5\text{-}H4}$ = 9.8 Hz, 1H, H-5), 3.67 (t, $^{3}J_{H6'\text{-}H6}$ = $^{3}J_{H6'\text{-}H5}$ = 10.3 Hz, 1H, H-6′), 3.55 (dd, $^{3}J_{H4\text{-}H3}$ = 2.3, $^{3}J_{H4\text{-}H5}$ = 9.6 Hz, 1H, H-4), 3.39 (s, 1H, H-2), 2.19 (s, 3H, OAc), 1.31 (s, 9H, CMe_3). ^{13}C-NMR: (125 MHz, $CDCl_3$): 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 (CHPh), 79.7 (d, $^{2}J_{C\text{-}P}$ = 14.5 Hz, C-1), 78.2, 74.6 (C-4), 70.0 (C-6), 69.0 (C-5), 68.4 (C-3), 44.9 (d, $^{1}J_{C\text{-}P}$ = 22.3 Hz, C-2), 31.2 (CMe_3), 21.0 (OAc). ^{31}P-NMR: (121.4 MHz, $CDCl_3$): δ −17.0. HRMS calc. for $C_{35}H_{31}O_5F_{12}$-PSNa: 845.1314. Found: 845.1330 (−1.97 ppm).

***tert*-Butyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-di(2,4,6-trimethyl)phenylphosphine-1-thio-β-D-altropyranoside (18).** ^{1}H-NMR: (400 MHz, $CDCl_3$): δ 7.29 (s, 5H), 6.96–6.67 (m, 4H), 5.33 (dd, $^{3}J_{H1\text{-}H2}$ = 2.6 Hz, $^{3}J_{H1\text{-}P}$ = 21.3 Hz, 1H, H-1), 5.10 (s, 1H, CHPh), 5.08 (s, 1H), 4.37 (s, 1H, H-3), 4.29 (dd, $^{3}J_{H6\text{-}H5}$ = 4.8 Hz, $^{3}J_{H6\text{-}H6'}$ = 10.4 Hz, 1H, H-6), 3.94 (dt, $^{3}J_{H5\text{-}H6}$ = $^{3}J_{H5\text{-}H6'}$ = 4.9 Hz, $^{3}J_{H5\text{-}H4}$ = 9.8 Hz, 1H, H-5), 3.69 (t, $^{3}J_{H6'\text{-}H6}$ = $^{3}J_{H6'\text{-}H5}$ = 10.3 Hz, 1H, H-6′), 3.15 (dd, $^{3}J_{H4\text{-}H3}$ = 2.3, $^{3}J_{H4\text{-}H5}$ = 9.6 Hz, 1H, H-4), 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, CMe_3). ^{13}C-NMR: (125 MHz, $CDCl_3$): δ 170.0, 137.2, 128.9, 128.1, 126.0, 101.7 (CHPh), 81.6 (d, $^{2}J_{C\text{-}P}$ = 14.5 Hz, C-1), 75.0 (C-4), 71.5 (C-6), 69.5 (C-5), 68.0 (C-4), 42.4 (d, $^{1}J_{C\text{-}P}$ = 22.3 Hz, C-2), 31.4 (CMe_3), 21.2, 20.9 (OAc), 20.5. ^{31}P-NMR: (121.4 MHz, $CDCl_3$): δ −27.5. HRMS calc. for $C_{37}H_{48}O_5PS$: 635.2942. Found: 635.2955 (−1.93 ppm).

General procedure for the 1,4-addition of boronic acids to activated ketones

A mixture of ligand **10** (0.03 mmol, 5 mol%) and $[Rh(C_2H_4)Cl]_2$ (6.0 mg, 0.015 mmol, 2.5 mol%) was stirred for 0.5 h in 1.2 mL of degassed toluene. Arylboronic acid (1.2 mmol) was added over the catalyst and sequentially the activated ketone (0.6 mmol) and an aqueous solution of KOH (120 μL, 2.5 M). The reaction was followed by TLC, stopped at 24 h, the crude reaction mixtures were purified by column chromatography.

(*S*)-3-Phenylcyclohexanone (6). Colorless oil. $[\alpha]_D^{20}$: +11.2° (c 0.9, $CHCl_3$). HPLC: 64%, Chiralcel OD-H column (*n*-hexane/2-propanol, 90/10), 0.5 mL min^{-1}; t_R = 19.5 min (*S*-isomer), 22.4 min (*R*-isomer). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33–7.36 (m, 2H), 7.21–7.26 (m, 3H), 3.05–2.95 (m, 1H), 2.37–2.59 (m, 4H), 2.07–2.16 (m, 2H), 1.80–1.89 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 210.9, 144.3, 128.6, 126.6, 126.5, 48.9, 44.7, 41.1, 32.7, 25.5. HRMS calc. for $C_{12}H_{15}O$: 175.1113. Found: 175.1117 (−2.34 ppm.).

(*S*)-3-(*p*-Tolyl)cyclohexanone (21). Colorless oil. $[\alpha]_D^{20}$ = +21.3 (c. 0.5, CH_2Cl_2). HPLC: 98% ee, Chiralcel® AS-H column (*n*-hexane/2-propanol, 60/40, 0.6 mL min^{-1}); t_R: 12.6 min. (*R*-isomer), 14.8 min. (*S*-isomer). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10–7.01 (m, 4H), 2.93–2.84 (m, 1H), 2.51–2.29 (m, 4H), 2.22 (s, 3H), 2.08–1.96 (m, 2H), 1.82–1.64 (m, 2H). ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.0, 141.4, 136.2, 129.3 (CH × 2), 126.4 (CH × 2), 49.0, 44.3, 41.1, 32.8, 25.5, 20.9. HRMS calc. for $C_{13}H_{17}O$: 189.1628. Found: 189.1274 (−2.96 ppm.).

(*R*)-4-(*p*-Tolyl)pentan-2-one (22). Colorless oil. $[\alpha]_D^{20}$ = −15.4 (*c* 0.3, $CHCl_3$). HPLC: 70% ee, Chiralcel AS-H column (*n*-hexane/2-propanol, 98 : 2, 1 mL min^{-1}); t_R: 11.2 min (major), 12.9 min (minor). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14–7.12 (m, 4H), 3.32–3.28 (m, 1H), 2.80–2.60 (m, 2H), 2.34 (s, 3H), 2.09 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.02, 143.20, 135.84, 129.27, 126.68, 52.16, 35.15, 30.60, 22.18, 21.03. HRMS calc. for $C_{12}H_{16}ONa$: 199.1093. Found: 199.1089 (−2.32 ppm.).

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