Novel phosphite-thiother ligands derived from carbohydrates allow the enantioswitchable hydrogenation of cyclic β-enamides using either Rh- or Ir-catalysts

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Abstract: Phosphite-thioether ligands with a simple modular architecture, derived from inexpensive L-(+)-tartaric acid and D-mannitol, have been for the first time successfully applied (ee's up to 99%) in the synthesis of 2-aminotetralines and 3-aminochromanes via metal-catalyzed asymmetric hydrogenation of cyclic β-enamides. The ligands have the advantages of the robustness of the thioether/phosphite moieties and the extra control provided by the flexibility of the chiral pocket through the presence of a biaryl phosphite group and a modular carbohydrate derived backbone. Moreover, they are solid and stable to air and they are therefore easy to handle, manipulate and store. Usefully, both enantiomers of the hydrogenated products were obtained by simply switching from Rh to Ir. Low hydrogen pressure and environmentally friendly propylene carbonate can be used, with no loss of selectivity.

Introduction

Asymmetric hydrogenation of prochiral olefins is a widely used process for preparing optically active compounds. It is highly efficient, has a perfect atom economy, requires low catalyst loadings and is operationally simple.[1] Over the last decades the substrate scope has been substantially expanded and commercial processes have been developed.[2] However, there are substrate classes such as the cyclic β-enamides whose hydrogenation is still a challenge. Whilst the hydrogenation of related α-enamides can be carried out with acceptable success, the asymmetric hydrogenation of β-enamides remains one of the most puzzling transformations, albeit the corresponding hydrogenated products, i.e. 2-aminotetralines and 3-aminochromanes, are key units for many drugs and biologically active natural products (Figure 1).[3]

Most of the catalysts, predominantly based on Rh- and Ru-, provide unsatisfactory enantioselectivities in the asymmetric hydrogenation of cyclic β-enamides.[4] Among the most successful examples (Figure 2),[4a,c,e,f,j,k] Ratovelomanana et al. reported the synthesis 3-aminochromanes with enantioselectivities up to 96% ee using Ru-diphosphine catalysts.[4f] More recently, Tang et al reported similar high enantioselectivities in the hydrogenation of enamides derived from 2-tetralones (ee's up to 96%) and enamides derived from 3-chromanones (ee's in the range 94-98%), using a Rh-catalyst modified with WingPhos, a specially designed P-stereogenic

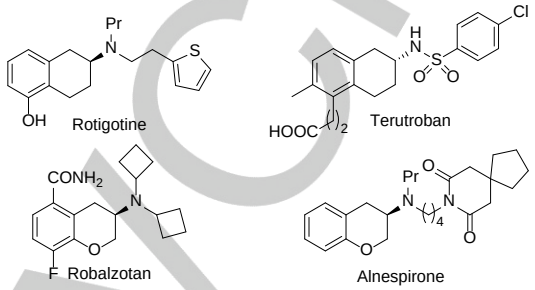

Figure 1. Examples of chiral 2-aminotetralines and 3-aminochromanes with pharmaceutical applications.

diphosphine ligand synthesized in nine steps (Figure 2).[4k] Very recently, Verdaguer et al. have shown for the first time that Ir-P,N catalysts, which have been mainly applied to hydrogenate minimally functionalized olefins,[5] are also able to hydrogenate these elusive substrates.[6] In particular, they were able to hydrogenate cyclic β-enamides derived from 2-tetralones with an Ir-catalyst modified with MaxPHOXs, a P-stereogenic aminophosphine-oxazoline ligand (Figure 2), with enantioselectivities up to 99% ee.[6] Just afterwards, our group showed that Ir-catalysts modified with PHOX-based phosphite-oxazoline ligands can also be successfully used to reduce cyclic β-enamides derived from both, 2-tetralones and 3-chromanones (ee's up to 99%).[7] Despite these advances, the use of alternative Ir-P,X catalysts in that process remains unexplored, and the performance of Ir-P,X catalysts must be further studied by screening new accessible Ir-heterodonor catalysts. Therefore, the need for easy to synthesize, easy to handle (air-stable, solid and robust) and highly efficient P,X ligands for the metal-catalyzed asymmetric hydrogenation of cyclic β-enamides, derived from both 2-tetralones and 3-chromanones, continues.

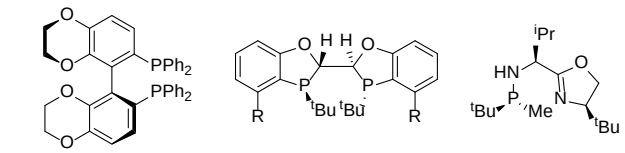

Figure 2. Selection of most successful ligands applied in the asymmetric hydrogenation of the cyclic β-enamides.

A simple way to prepare chiral ligands is to transform or derivatize natural chiral compounds (chiral pool) such as carbohydrates. These are extremely useful not only because they are available at low price, but also because they can be

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easily modulated, with a well-established chemistry.[8] An inconvenience of using natural products as precursors is that only one enantiomer (in the case of carbohydrates, the D-series) is readily accessible from the chiral pool. This makes their use more difficult when both enantiomers are demanded for biological and medical applications, although pseudo-enantiomeric ligands[9] and different transition metals[10] have been used to overcome this limitation. For example, it was shown that for asymmetric hydrosilylation and asymmetric hydroboration,[10a,b,e,h] both enantiomers can be accessible by switching from Rh- to Ir-catalysts.

Our group has wide expertise in the design of easy to handle phosphite-containing ligand families prepared from readily available starting materials.[11] In this context, we have shown the benefits of using heterodonor biaryl phosphite-oxazoline ligand families for the Ir-catalyzed hydrogenation of minimally functionalized olefins, which in the last decades have become the state of art for the reduction of these challenging substrates.[12] We have also recently found that the previously mentioned PHOX-based phosphite-oxazoline ligands can be considered privileged ligands not only for their ability to control the stereochemistry in the Ir-catalyzed hydrogenation,[7] with a exceptionally broad substrate scope, but also because they work well in a variety of processes, such as Pd-catalyzed Heck[13a] and allylic substitution[13b] reactions and Ir-catalyzed hydroboration[13c]. The reason for this exceptional performance is the flexible biaryl phosphite group that allows the chiral pocket of the catalyst to accommodate itself according to the steric demands of the substrate.[11, 13b] Moreover, phosphite ligands are less sensitive to air and other oxidizing agents and also easier to prepare than the most commonly used phosphines, which have dominated the field of asymmetric hydrogenation. More recently, our research progressed toward mixed ligands, with groups more robust than oxazolines. The thioether group adds the advantages of higher stability and easier synthesis than oxazolines.[14] In addition, the intrinsic stereogenic sulphur chirality upon coordination can benefit the reaction stereocontrol since the chiral center is adjacent to the metal centre. This allows the thioether-containing ligands to have a simple structure. In this respect, we have recently identified the successful use of two simple families of heterodonor phosphite-thioether ligands for hydrogenation of minimally functionalized olefins[15] with results comparable to the best ones reported to date.

Inspired by the pioneering work of Verdaguer, the success of P-S ligands in hydrogenation and the similarities of the elementary steps involved in hydrosilylation/hydroboration and hydrogenation, we reasoned that both enantiomers of the 2-aminotetralines and 3-aminochromanes might be accessed for the first time using either Rh- or Ir-catalysts modified with the same ligand. To prove this, we developed a new carbohydrate-derived phosphite-thioether ligand library (**L1**-**L5a**-**c**) with a very simple architecture (Figure 3). The new ligands are easily prepared in a large scale from L-tartaric acid (**L1**) and D-mannitol (**L2**-**L5**) and their advantageous properties derive from the sugar core, the biaryl phosphite group and the thioether moiety.

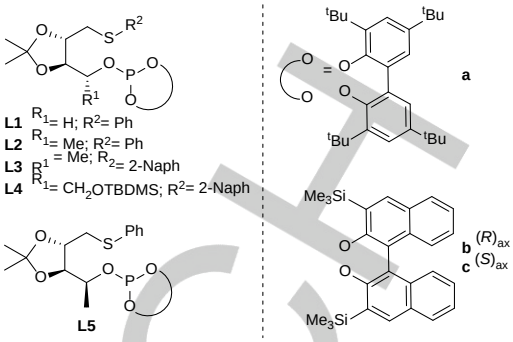
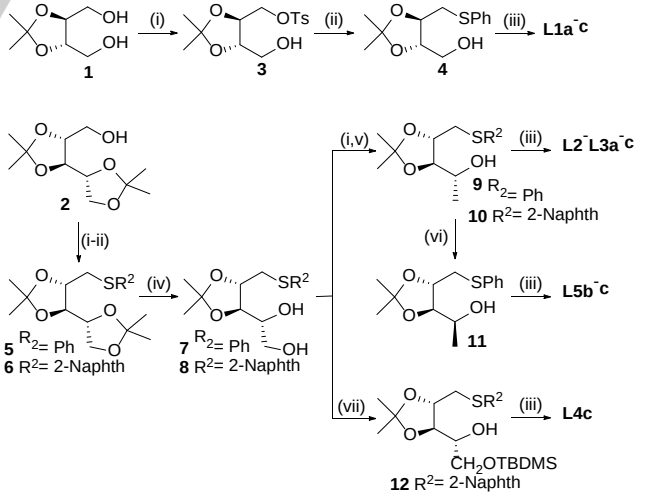


Figure 3. Phosphite-thioether ligands **L1**-**L5a**-**c** derived from carbohydrates.

Results and Discussion

Synthesis of ligands L1-L5a-c

The synthesis of phosphite-thioether ligands **L1**-**L5a**-**c** is straightforward (Scheme 1). They were efficiently synthesized from the corresponding easily accessible hydroxyl-thioether compounds **4** and **9**-**12**. Compounds **4** and **9**-**12** are easily prepared in a multrigram scale by highly effective methods from compounds **1**[16] and **2**[17], which are obtained in a few steps from inexpensive natural L-(+)-tartaric acid and D-(+)-mannitol. Compounds **4** and **9**-**12** were chosen as intermediates for the preparation of ligands because they easily allow incorporating the desired diversity in the ligand structure. For the preparation of hydroxyl-thioether compound **4**,[18] compound **1** was treated with 1 equiv of *p*-toluenesulfonyl chloride to produce the desired monotosylated compound **3** (Scheme 1, step (i)). Subsequent reaction with in situ formed sodium thiophenolate provided hydroxyl-thioether **4** (Scheme 1, step (ii)).



Scheme 1. Synthesis of phosphite-thioether ligands **L1**-**L5a**-**c**. (i) TsCl, Py, CH_2Cl_2; (ii) $NaSR^2$, THF; (iii) $ClP(OR)_2$; $(OR)_2$ = **a**-**c**, Py or NEt_3, toluene; (iv) AcOH (dil); (v) $LiAlH_4$, THF; (vi) DIAD, *p*NBA, PPh_3, THF then MeOH, NaOH; (vii) TBDMSCl, imidazole, DMF.

For the preparation of hydroxyl-thioethers **9**-**12**, that differ from **4** in the substituent on the carbon adjacent to the alcohol group, compound **2** was transformed to the desired thioether compounds **5** and **6** by treatment of **2** with 1 equiv of *p*-toluenesulfonyl chloride followed by reaction with the corresponding $NaSR^2$ (Scheme 1, steps (i-ii)). Subsequent standard acid catalyzed acetal deprotection provided compounds **7** and **8** (Scheme 1, step (iv)). From this point, the syntheses followed different pathways depending of the ligand to be prepared. Hydroxyl-thioethers **9** and **10** were easily obtained by treating compounds **7** and **8** with 1 equiv of *p*-toluenesulfonyl chloride followed by reaction with $LiAlH_4$ (Scheme 1, steps (i and v)). For the preparation of hydroxyl-thioether **11**, which differs from **9** in the configuration of the carbon adjacent to the alcohol group, the methyl group was inverted using Mitsunobu methodology (Scheme 1, step (vi)). Finally, treatment of **8** with 1 equiv of *tert*-butyldimethylsilyl chloride gave access to the desired hydroxyl-thioether **12** (Scheme 1, step (vii)).

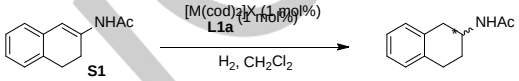
The last step in the ligand synthesis is common for all the ligands (Scheme 1, step (iii)). Treating the corresponding hydroxyl-thioethers (**9**-**12**) with 1.1 equiv of the desired in situ formed phosphorochloridite ($ClP(OR)_2$; $(OR)_2$ = **a**-**c**) in the presence of base provided easy access to the desired ligands (Scheme 1, step (iii)). All the ligands were purified on neutral alumina under argon atmosphere and were isolated in moderate-to-good yields as white solids. Advantageously, they were stable in air and very stable to hydrolysis, so further manipulation/storage was carried out in air. HRMS-ESI spectra agreed with the assigned structures. The ^1H, ^{31}P and ^{13}C NMR spectra were as expected for these ligands. One singlet for each compound was observed in the ^{31}P NMR spectrum. Rapid ring inversions (tropoisomerization) in the biphenyl-phosphorus moiety (**a**) occurred in the NMR time scale because the expected diastereoisomers were not detected by low-temperature ^{31}P NMR.[19]

Asymmetric hydrogenation of N-(3,4-dihydronaphthalen-2-yl)acetamide

Initially, we evaluated carbohydrate-derived phosphite-thioether ligands **L1**-**L5a**-**c** in the asymmetric Rh- and Ir-catalyzed hydrogenation of model *N*-(3,4-dihydronaphthalen-2-yl)acetamide **S1** (Table 1). For initial reaction conditions, we tested **L1**-**L5a**-**c** using the same optimal reaction conditions found in our previous studies with related Ir-P,S catalytic systems for the hydrogenation of minimally functionalized olefins[15] and related Rh-P,S catalysts for the hydrogenation of dehidroaminoacid derivatives[20]. The reactions were therefore performed at room temperature in dichloromethane using 1 mol % of the corresponding catalyst under 30 bar of H_2 for Rh-catalysts and 100 bar for Ir-catalysts. In both cases, the catalysts were prepared in situ by adding the corresponding ligands to the appropriate catalyst precursor (either $[Rh(cod)_2]BF_4$ or $[Ir(cod)_2]BAr_F$).

Concerning the ligand architecture, the results with ligands **L1a-c,** derived from L-(+)-tartaric acid, indicated that the presence of a chiral biaryl phosphite moiety increases the enantioselectivity (entry 1 vs 2 and 3). The ligand backbone is therefore not able to control the tropoisomerism of the biphenyl phosphite group (**a**). There is also a cooperative effect between the configuration of the biaryl phosphite moiety and the ligand backbone (entries 2-3), which results in a matched combination for ligand **L1b** that contains an *R*-biaryl phosphite. This cooperative effect is more significant for Rh-**L1b**, allowing us to increase enantioselectivity up to 84% ee (entry 2), than for the Ir-catalyst (entry 2, ee's only up to 59%). Advantageously, both enantiomers of the hydrogenated products could be obtained with the same ligand by simply exchanging Rh for Ir.

Table 1. Asymmetric metal-catalyzed hydrogenation of *N*-(3,4-dihydronaphthalen-2-yl)acetamide **S1** using ligand **L1**-**L4a**-**c**[a]



		[Rh(cod)$_2$]BF$_4$/**L**		[Ir(cod)$_2$]BAr$_F$/**L**	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L1a**	100	16 (*R*)	100	11 (*S*)
2	**L1b**	100	84 (*R*)	100	59 (*S*)
3	**L1c**	100	73 (*S*)	100	34 (*R*)
4	**L2a**	100	13 (*S*)	100	35 (*R*)
5	**L2b**	100	83 (*R*)	100	50 (*S*)
6	**L2c**	100	86 (*S*)	100	90 (*R*)
7	**L3c**	100	87 (*S*)	100	89 (*R*)
8	**L4c**	100	90 (*S*)	100	97 (*R*)
9	**L5b**	100	81 (*R*)	95	80 (*S*)
10	**L5c**	100	59 (*S*)	92	6 (*R*)

[a] Reactions conditions: $[M(cod)_2]X$ (1 mol%), ligand (1 mol%), **S1** (0.5 mmol), CH_2Cl_2 (2 mL), H_2 (30 bar for Rh-catalysts and 100 bar for Ir-catalysts), 12 h (for Rh-catalyst) or 24 h (for Ir-catalyst) at rt. [b] Conversion determined by ^1H NMR. [c] Enantiomeric excesses determined by chiral HPLC.

Ligands **L2** differ from **L1** in that they contain a methyl group next to the phosphite moiety that generates a new chiral center. The introduction of the methyl group does not affect significantly the ee for Rh-catalyst, that keep being high (entry 6), but has a remarkable positive effect in Ir-catalysts and makes the ee's increase to 90% (**L2c**, entry 6) from 59% (**L1b**, entry 2). The results also indicates a new cooperative effect in **L2** between the configuration of the biaryl phosphite moiety and the ligand backbone (entries 5-6 vs 2-3), that is larger in Ir-catalysts than in Rh-catalysts and that results in a matched combination for ligand **L2c** with a *S*-biaryl phosphite (entry 6).

Ligands **L4** differ from **L1** in that they contain a $CH_2OTBDMS$ group next to the phosphite moiety. The introduction of this new group also had a positive effect on enantioselectivity compared to **L1** (entry 8 vs 2) but also the high ee's (up to 97%) surpassed those obtained with **L2** that contain

a methyl group (entry 8 vs 6). Like for **L1** and **L2**, both enantiomers can be obtained by using either Rh or Ir.

Ligands **L5** differ from **L2** in the configuration of the carbon adjacent to the phosphite moiety that is *S* instead of *R*. This change affected the enantioselectivity negatively (entries 6 vs 9). Finally the effect of the thioether group was studied with ligands **L2c** and **L3c**. The nature of the thioether group had little effect on enantioselectivity (entries 6 and 7).

In summary, the highest enantioselectivities (ee's up to 90% with Rh and ee's up to 97% with Ir) were achieved using phosphite-thioehter ligand **L4c**, which contains the optimal combination of ligand parameters.

We next studied the effect of several experimental parameters on the catalytic performance with the best ligand **L4c** (Table 2). We started our investigations testing different temperatures (entries 1, 3-5 for Rh-**L4c** and entries 7-9 for Ir-**L4c**). Lowering the reaction temperature to 5 ºC increased the enantioselectivity to 94% (from 90% at rt) for Rh-**L4c**, combined with good activity (entry 4). Lower temperatures did not improve enantioselectivities further. We next evaluated the effect of lowering the pressure (entries 1 and 2 for Rh-**L4c** and 7 and 10 for Ir-**L4c)**. The catalytic performance was maintained regardless of the lower hydrogen pressure and, advantageously, high enantioselectivities were still obtained for both catalysts at 10 bar of H_2 (entries 2 and 10). Finally, the use of preformed catalyst precursors [Rh(cod)(**L4c**)]BF_4 and [Ir(cod)(**L4c**)]BAr_F provided the same results (entries 4 vs 6 and 11 vs 7). There is no need therefore to synthesize and isolate the precatalysts prior to use.

Table 2. Asymmetric metal-catalyzed hydrogenation of *N*-(3,4-dihydronaphthalen-2-yl)acetamide **S1** using ligand **L4c**. Optimization studies[a]

Entry	Catalyst precursor	P_{H2}[b]	T[c]	% Conv (h)[d]	%ee[e]
1	$[Rh(cod)_2]BF_4$	30	25	100 (12)	90 (*S*)
2	$[Rh(cod)_2]BF_4$	10	25	89 (12)	88 (*S*)
3	$[Rh(cod)_2]BF_4$	30	40	100 (8)	84 (*S*)
4	$[Rh(cod)_2]BF_4$	30	5	100 (36)	94 (*S*)
5	$[Rh(cod)_2]BF_4$	30	-5	48 (36)	93 (*S*)
6	[Rh(cod)(**L4c**)]BF_4	30	5	100 (36)	94 (*S*)
7	$[Ir(cod)_2]BAr_F$	100	25	100 (24)	97 (*R*)
8	$[Ir(cod)_2]BAr_F$	100	40	100 (18)	89 (*R*)
9	$[Ir(cod)_2]BAr_F$	100	5	23 (24)	96 (*R*)
10	$[Ir(cod)_2]BAr_F$	10	25	89 (24)	97 (*R*)
11	[Ir(cod)(**L4c**)]BAr_F	100	25	100 (24)	97 (*R*)

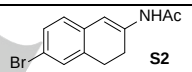
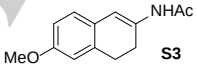
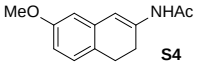
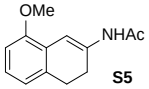
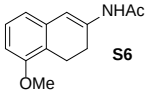
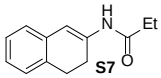
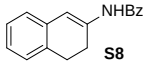
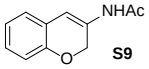
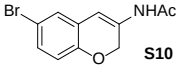
[a] Reactions conditions: $[M(cod)_2]X$ (1 mol%), ligand (1 mol%), **S1** (0.5 mmol), CH_2Cl_2 (2 mL). [b] Hydrogen pressure in bars. [c] Reaction temperature in °C. [d] Conversion determined by ^1H NMR. [e] Enantiomeric excesses determined by chiral HPLC.

As a summary, under these new mild reaction conditions we were therefore able to obtain both enantiomers of the hydrogenated product by simply choosing the metal centre in enantioselectivities (up to 97% ee) comparable to the best ones reported.

Substrate scope

In the optimal conditions found, we next studied the substrate scope using [Rh(cod)(**L4c**)]BF_4 and [Ir(cod)(**L4c**)]BAr_F catalyst precursors. For this purpose a range of cyclic β-enamides, which contemplate all possible monosubstitution patterns as well as different substituents at position 6 of the 3,4-dihydronaphthalene core, were investigated (Table 3). We were pleased to discover that not only the replacement of the metal gave access to both enantiomers of the hydrogenated products with enantioselectivity comparable to the best one reported, but also that the [M(cod)(**L4c**)]X (M=Rh or Ir) were very tolerant to the electronic properties and to variations in the substitution pattern of the 3,4-dihydronaphthalene core. Several substituted cyclic enamides derived from β-tetralones were therefore hydrogenated in high yields and high enantioselectivities (ee's up to 99%; entries 1-10).

Table 3. Asymmetric Rh- and Ir-catalyzed hydrogenation of cyclic β-enamides **S2**-**S10** using ligand **L4c**[a]

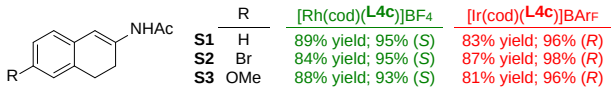
Entry	Substrate	% Conv (% Yield)[b]	% ee[c]
1	 **S2**	100 (83)	95 (*S*)
2		100 (86)	99 (*R*)
3	 **S3**	100 (91)	92 (*S*)
4		100 (92)	97 (*R*)
5	 **S4**	100 (86)	91 (*S*)
6		99 (85)	95 (*R*)
7	 **S5**	100 (87)	90 (*S*)
8		100 (86)	97 (*R*)
9	 **S6**	100 (91)	91 (*S*)
10		100 (90)	97 (*R*)
11	 **S7**	100 (80)	94 (*S*)
12		100 (83)	98 (*R*)
13	 **S8**	100 (85)	93 (*S*)
14		99 (82)	97 (*R*)
15	 **S9**	100 (91)	92 (*R*)
16		98 (90)	97 (*S*)
17	 **S10**	100 (86)	92 (*R*)
18		99 (84)	98 (*S*)

[a] Reactions conditions: [Rh(cod)(**L4c**)]BF_4 (1 mol%) or [Ir(cod)(**L4c**)]BAr_F (1 mol%), substrate (0.5 mmol), CH_2Cl_2 (2 mL), H_2 (10 bar), 36 h at 5 °C (for Rh-catalyst) or at rt (for Ir-catalyst). [b] Conversion determined by ^1H NMR. Isolated yields shown in parentheses [c] Enantiomeric excesses determined by chiral HPLC.

Advantageously, the nature of the amido group had no effect on conversion and enantioselectivities. Therefore, cyclic β-enamides **S7** and **S8** were also hydrogenated to the desired

amines in similar high enantioselectivities than **S1** (entries 11-14; ee's up to 98%). We could also efficiently reduce enamides derived from 3-chromanones **S9** and **S10** in high yields and enantioselectivities (entries 15-18; ee's up to 98%). Among all these results, it should be pointed out the successful hydrogenation of *N*-(5-methoxy-3,4-dihydronaphthalen-2-yl)acetamide **S6** and *N*-(2H-chromen-3-yl)acetamide **S9** (ee's up to 97%) that give access to key chiral intermediates for the synthesis of rotigotine and alnespirone. The former is a dopamine agonist used for the treatment of Parkinson's disease,[3a] while alnespirone is a selective 5-HT1A receptor with antidepressant and anxiolytic properties[3d].

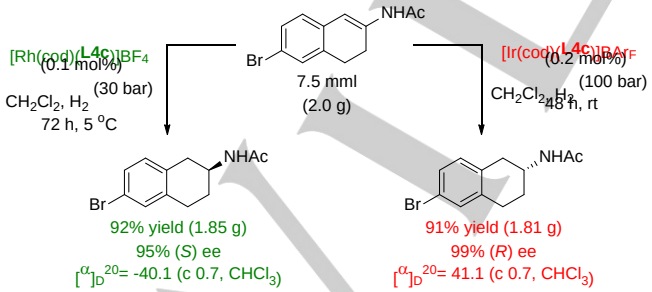
Encouraged by these excellent results we decided to go one step further and study the metal-catalyzed hydrogenation of various cyclic β-enamides **S1**-**S3** using 1,2-propylene carbonate (PC) as solvent (Scheme 2). PC has emerged as a sustainable "green" alternative to standard organic solvents because of its high boiling point, low toxicity and environmentally friendly synthesis.[21] We were pleased to see that the enantioselectivities with PC remained as high as those observed with dichloromethane.



	R	[Rh(cod)(**L4c**)]BF$_4$	[Ir(cod)(**L4c**)]BAr$_F$
S1	H	89% yield; 95% (*S*)	83% yield; 96% (*R*)
S2	Br	84% yield; 95% (*S*)	87% yield; 98% (*R*)
S3	OMe	88% yield; 93% (*S*)	81% yield; 96% (*R*)

Scheme 2. Asymmetric hydrogenation of cyclic β-enamides **S1**-**S3** using 1,2-propylene carbonate. Reaction conditions: catalyst precursor (1 mol%), substrate (0.5 mmol), PC (2 mL), H_2 (30 bar for Rh-catalyst and 100 bar for Ir-catalyst), 5 °C (for Rh-catalyst) or rt (for Ir-catalyst) for 36 h.

To demonstrate the potential usefulness of these Rh- and Ir-catalyst processors modified with simple carbohydrate-derived phosphite-thioether ligand **L4c** we performed the hydrogenation of *N*-(6-bromo-3,4-dihydronaphthalen-2-yl)acetamide **S2** at 7.5 mmol scale and at a low catalyst loading. Both isomers of the desired *N*-(6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide were achieved in high yields and enantioselectivities (Scheme 3).



Scheme 3. Practical synthesis of *N*-(6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide.

Conclusions

A novel class of phosphite-thioether ligands with a simple modular architecture has been successfully applied for the first time in the Rh- and Ir-catalyzed hydrogenation of cyclic β-enamides. The ligands can be easily prepared on large scale from inexpensive L-(+)-tartaric acid and D-mannitol, and they have the advantages of the robustness of the thioether/phosphite moieties and the extra control provided by the flexibility of the chiral pocket through the presence of a biaryl phosphite group and a modular carbohydrate derived backbone. Moreover, they are solid and stable to air and they are therefore easy to handle, manipulate and store. These ligands allowed to obtain 2-aminotetralines and 3-aminochromanes in high yields and enantioselectivities comparable to the best ones reported (ee's up to 99%). Three novel features of these ligands are that both enantiomers are accessible in high enantioselectivities by simple switching from Rh to Ir, excellent yields and enantioselectivities are obtained also at low pressure and that the environmentally friendly propylene carbonate can be used as solvent, with no loss of selectivity. These results open up the use of phosphite-thioether ligands to the challenging enantioselective M-catalyzed hydrogenation of cylic β-enamides.

Experimental Section

General considerations

All syntheses were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[22] Compounds **1**[16] and **2**[17] were easily prepared on a multigram scale from L-(+)-tartaric acid and D-(+)-mannitol, respectively. Hydroxyl-thioether **4** was prepared following previously described methodology by Chida and coworkers.[18] Cylic β-enamides **S1**-**S10**[23] were prepared following literature procedures. All other reagents were used as commercially available. ^{1}H, ^{13}C{^{1}H}, ^{31}P{^{1}H} NMR spectra experiments were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of SiMe$_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H and ^{13}C assignments were done based on ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments.

Typical procedure for the preparation of phosphite-thioether ligands L1-L5a-c

The corresponding phosphorochloridite (1.1 mmol) produced in situ was dissolved in toluene (5 mL), and pyridine (0.3 mL, 3.9 mmol) was added. The corresponding thioether-hydroxyl compound (1 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in toluene (5 mL) to which pyridine (0.3 mL, 3.9 mmol) was added. The alcohol solution was transferred slowly to a solution of phosphorochloridite. The reaction mixture was stirred at 80 °C for 90 min, after which the pyridine salts were removed by filtration. In the case of ligands **L4b**-**c**, triethylamine was added instead of pyridine (0.5 ml, 3.9 mmol) and the reaction mixture was stirred overnight at 80 °C. In the case of ligands **L5b**-**c**, triethylamine (0.5 ml, 2.8 mmol) and DMAP (0.11 mmol, 13.4 mg) were added and the reaction mixture was stirred overnight at room temperature. Evaporation of the solvent gave a white foam, which was purified by flash chromatography (see Supporting Information for copies of the NMR spectra).

L1a. Yield: 413 mg (65%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 135.7 (s). ^1H NMR (C_6D_6), δ: 1.27 (s, 9H, CH_3, *t*Bu), 1.28 (s, 9H, CH_3, *t*Bu), 1.29 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.57 (s, 9H, CH_3, *t*Bu), 1.59 (s, 9H, CH_3, *t*Bu), 2.88 (dd, 1H, $^2J_{H\text{-}H}$= 13.6 Hz, $^3J_{H\text{-}H}$= 6.4 Hz, CH_2-S), 3.03 (dd, 1H, $^2J_{H\text{-}H}$= 13.6 Hz, $^3J_{H\text{-}H}$= 5.6 Hz, CH_2-S), 3.93-3.96 (m, 1H, C*H*CH_2O), 4.02 (m, 1H, C*H*CH_2S), 4.08-4.11 (m, 2H, CH_2-O), 6.87-7.60 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 26.9 (CH_3), 27.1 (CH_3), 30.8 (CH_3, *t*Bu), 30.9 (CH_3, *t*Bu), 31.2 (CH_3, *t*Bu), 34.3 (C, *t*Bu), 35.3 (C, *t*Bu), 35.3 (C, *t*Bu), 36.5 (CH_2-S), 64.6 (CH_2-O), 76.5 (*C*HCH_2S), 79.7 (d, *C*HCH_2O, $J_{C\text{-}P}$= 3.8 Hz), 109.4 (CMe_2), 124.1 (CH=), 125.3 (C), 125.7 (CH=), 126.7 (CH=), 128.1 (CH=), 128.7 (CH=), 128.9 (CH=), 129.0 (CH=), 133.2 (C), 136.4 (C), 140.1 (C), 140.2 (C), 146.5 (C), 146.6 (C). MS HR-ESI [found 715.3556, $C_{41}H_{57}O_5PS$ (M-Na)$^+$ requires 715.35.57].

L1b. Yield: 335.2 mg (47%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=134.1 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.51 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 1.27 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 2.77 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.2 Hz, $^3J_{H\text{-}H}$ =6.0 Hz), 2.95 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^2J_{H\text{-}H}$ =5.2 Hz), 3.39-3.44 (m, 1H, CH_2-O), 3.72-3.76 (m, 1H, C*H*CH_2O), 3.94-3.99 (m, 1H, C*H*CH_2S), 4.29-4.35 (m, 1H, CH_2-O), 6.85-7.16 (m, 9H, CH=), 7.23 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.4 Hz), 7.34 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.4 Hz), 7.70 (d, 2H, CH=, $^3J_{H\text{-}H}$ =8.0 Hz), 8.11 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.5 (CH_3, $SiMe_3$), -0.3 (d, CH_3, $SiMe_3$, $J_{C\text{-}P}$ =4.6 Hz), 26.8 (CH_3), 26.9 (CH_3), 36.5 (CH_2-S), 63.9 (CH_2-O), 75.9 (*C*HCH_2S), 79.6 (*C*HCH_2O), 109.2 (CMe_2), 122.3-152.6 (aromatic carbons). MS HR-ESI [found 735.2154, $C_{39}H_{45}O_5PSSi_2$ (M-Na)$^+$ requires 735.2156].

L1c. Yield: 289.7 mg (41%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=132.1 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.51 (s, 9H, CH_3, $SiMe_3$), 0.57 (s, 9H, CH_3, $SiMe_3$), 1.22 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 2.73 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =6.0 Hz), 2.92 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^2J_{H\text{-}H}$ =4.8 Hz), 3.57-3.62 (m, 1H, CH_2-O), 3.77-3.81 (m, 2H, C*H*CH_2S, C*H*CH_2O), 4.10-4.14 (m, 1H, CH_2-O), 6.84-7.16 (m, 9H, CH=), 7.23 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.4 Hz), 7.35 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.4 Hz), 7.69 (t, 2H, CH=, $^3J_{H\text{-}H}$ =6.8 Hz), 8.10 (s, 1H, CH=), 8.14 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.4 (CH_3, $SiMe_3$), -0.2 (d, CH_3, $SiMe_3$, $J_{C\text{-}P}$ =5.4 Hz), 26.7 (CH_3), 26.9 (CH_3), 36.5 (CH_2-S), 64.4 (d, CH_2-O, $^2J_{C\text{-}P}$ = 5.1 Hz), 75.5 (*C*HCH_2S), 79.5 (d, *C*HCH_2O, $^3J_{C\text{-}P}$ =3.1 Hz), 109.3 (CMe_2), 122.2-152.9 (aromatic carbons). MS HR-ESI [found 735.2155, $C_{39}H_{45}O_5PSSi_2$ (M-Na)$^+$ requires 735.2156].

L2a. Yield: 415.1 mg (58%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=145.3 (s). ^1H NMR (400 MHz, C_6D_6): δ=1.26 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 2.83 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =14.2 Hz, $^3J_{H\text{-}H}$ =5.6 Hz), 3.08 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =14.4 Hz, $^3J_{H\text{-}H}$ =4.4 Hz), 3.94 (pt, 1H, C*H*CHO, $^3J_{H\text{-}H}$ =7.3 Hz), 4.35-4.39 (m, 1H, C*H*CH_2S), 4.57-4.62 (m, 1H, CH-O), 6.86-7.15 (m, 3H, CH=), 7.28-7.33 (m, 4H, CH=), 7.57 (d, 1H, CH=, $^4J_{H\text{-}H}$ =2.4 Hz), 7.60 (d, 1H, CH=, $^4J_{H\text{-}H}$ =2.8 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=19.2 (d, CH_3, $^3J_{C\text{-}P}$ =3.0 Hz), 26.9 (CH_3), 27.1 (CH_3), 31.1 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$ =3.1 Hz), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.4 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 36.5 (CH_2-S), 73.0 (d, CH-O, $^2J_{C\text{-}P}$ =6.1 Hz), 78.4 (*C*HCH_2S), 82.6 (d, *C*HCHO, $^3J_{C\text{-}P}$ = 3.8 Hz), 109.4 (CMe_2), 124.0-146.7 (aromatic carbons). MS HR-ESI [found 729.3712, $C_{42}H_{59}O_5PS$ (M-Na)$^+$ requires 729.3719]. Anal. calc (%) for $C_{42}H_{59}O_5PS$: C 71.36, H 8.41, S 4.53; found: C 70.98, H 8.36, N 4.50.

L2b. Yield: 429 mg (59%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=147.4 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.52 (s, 9H, CH_3, $SiMe_3$), 0.56 (s, 9H, CH_3, $SiMe_3$), 1.22 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.49 (d, 3H, CH_3, $^3J_{H\text{-}H}$ =6.4 Hz), 2.33 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^2J_{H\text{-}H}$ =4.3 Hz), 2.40 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =14.0 Hz, $^2J_{H\text{-}H}$ =3.6 Hz), 3.83 (pt, 1H, C*H*CHO, $^3J_{H\text{-}H}$ =7.6 Hz), 4.08 (m, 1H, C*H*CH_2S), 4.49 (m, 1H, CH-O), 6.84-7.16 (m, 9H, CH=), 7.28 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.8 Hz), 7.33 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.4 Hz), 7.69 (dd, 2H, CH=, $^3J_{H\text{-}H}$ =10.8 Hz, $^3J_{H\text{-}H}$ =8.4 Hz), 8.11 (s, 1H, CH=), 8.16 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.9 (d, CH_3, $SiMe_3$, $J_{C\text{-}P}$ =4.6 Hz), 0.7 (CH_3, $SiMe_3$), 18.3 (CH_3), 26.0 (CH_3), 26.2 (CH_3), 37.4 (CH_2-S), 72.1 (d, CH-O, $^2J_{C\text{-}P}$ = 4.6 Hz), 77.4 (*C*HCH_2S), 81.2 (d, *C*HCHO, $^3J_{C\text{-}P}$ =2.7 Hz), 111.2 (CMe_2), 124.0-136.4 (aromatic carbons). MS HR-ESI [found 749.2313, $C_{40}H_{47}O_5PSSi_2$ (M-Na)$^+$ requires 749.2318]. Anal. calc (%) for $C_{40}H_{47}O_5PSSi_2$: C 66.08, H 6.52, S 4.41; found: C 65.89, H 6.49, N 4.39.

L2c. Yield: 480 mg (66%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=140.9 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.50 (s, 9H, CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 0.78 (d, 3H, CH_3, $^3J_{H\text{-}H}$ =6.8 Hz), 1.32 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.00 (d, 2H, CH_2-S, $^3J_{H\text{-}H}$ =5.6 Hz), 3.93 (dd, 1H, C*H*CHO, $^3J_{H\text{-}H}$ =5.6 Hz, $^3J_{H\text{-}H}$ =1.1 Hz), 4.20 (m, 1H, C*H*CH_2S), 4.66 (m, 1H, CH-O), 6.83-7.22 (m, 10H, CH=), 7.34 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.8 Hz), 7.69 (dd, 2H, CH=, $^3J_{H\text{-}H}$ =6.4 Hz, $^4J_{H\text{-}H}$ =3.6 Hz), 8.10 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.1 (d, CH_3, $SiMe_3$, $J_{C\text{-}P}$ =4.0 Hz), 0.1 (CH_3, $SiMe_3$), 17.8 (CH_3), 26.9 (CH_3), 27.1 (CH_3), 37.5 (CH_2-S), 72.4 (d, CH-O, $^2J_{C\text{-}P}$ = 6.9 Hz), 77.1 (*C*HCH_2S), 82.9 (d, *C*HCHO, $^3J_{C\text{-}P}$ =4.6 Hz), 109.3 (CMe_2), 122.5-137.3 (aromatic carbons). MS HR-ESI [found 749.2314, , $C_{40}H_{47}O_5PSSi_2$ (M-Na)$^+$ requires 749.2318]. Anal. calc (%) for $C_{40}H_{47}O_5PSSi_2$: C 66.08, H 6.52, S 4.41; found: C 65.91, H 6.50, N 4.39.

L3c. Yield: 396.0 mg (51%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=141.0 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.48 (s, 9H, CH_3, $SiMe_3$), 0.53 (s, 9H, CH_3, $SiMe_3$), 0.80 (d, 3H, CH_3, $^3J_{H\text{-}H}$ =6.0 Hz), 1.34 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 3.11 (d, 2H, CH_2-S, $^3J_{H\text{-}H}$ =5.6 Hz), 3.97 (dd, 1H, C*H*CHO, $^3J_{H\text{-}H}$ =7.2 Hz, $^3J_{H\text{-}H}$ =5.6 Hz), 4.26-4.31 (m, 1H, C*H*CH_2S), 4.66-4.71 (m, 1H, CH-O), 6.81-6.87 (m, 2H, CH=), 6.99-7.23 (m, 5H, CH=), 7.31-7.53 (m, 5H, CH=), 7.67-7.70 (m, 3H, CH=), 8.10 (s, 1H, CH=), 8.12 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.8 (d, CH_3, $SiMe_3$, $J_{C\text{-}P}$ =4.7 Hz), 0.9 (CH_3, $SiMe_3$), 18.8 (CH_3), 28.1 (CH_3), 28.3 (CH_3), 38.6 (CH_2-S), 73.6 (d, CH-O, $^2J_{C\text{-}P}$ = 6.5 Hz), 78.3 (*C*HCH_2S), 84.1 (d, *C*HCHO, $^3J_{C\text{-}P}$ =3.8 Hz), 110.5 (CMe_2), 123.6-153.2 (aromatic carbons). MS HR-ESI [found 799.2473, $C_{44}H_{49}O_5PSSi_2$ (M-Na)$^+$ requires 799.2475]. Anal. calc (%) for $C_{44}H_{49}O_5PSSi_2$: C 68.01, H 6.36, S 4.13; found: C 67.88, H 6.33, N 4.09.

L4c. Yield: 535 mg (58%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=143.6 (s). ^1H NMR (400 MHz, C_6D_6): δ=-0.38 (s, 3H, CH_3, OTBDMS), -0.33 (s, 3H, CH_3, OTBDMS), 0.45 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 0.75 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.43 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.10 (dd, 1H, CH_2-OTBDMS, $^2J_{H\text{-}H}$ =10.4 Hz, $^3J_{H\text{-}H}$ =5.2 Hz), 3.24 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =6.4 Hz), 3.38 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =3.6 Hz), 3.51 (dd, 1H, CH_2-OTBDMS, $^2J_{H\text{-}H}$ =10.8 Hz, $^3J_{H\text{-}H}$ =8.0 Hz), 4.48 (dd, 1H, C*H*CHO, $^3J_{H\text{-}H}$ =7.2 Hz, $^3J_{H\text{-}H}$ =4.0 Hz), 4.69-4.74 (m, 1H, C*H*CH_2S), 4.83-4.90 (m, 1H, CH-O), 6.83-6.88 (m, 2H, CH=), 7.02-7.23 (m, 3H, CH=), 7.32 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.4 Hz), 7.45 (s, 2H, CH=), 7.50-7.53 (m, 2H, CH=), 7.69 (t, 2H, CH=, $^3J_{H\text{-}H}$ =7.2 Hz), 7.82 (s, 1H, CH=), 8.08 (s, 1H, CH=), 8.10 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-5.5 (CH_3, OTBDMS), -5.2 (CH_3, OTBDMS), 0.55 (d, CH_3, $SiMe_3$, $J_{C\text{-}P}$ =4.6 Hz), 0.7 (CH_3, $SiMe_3$), 18.5 (C, ^{t}Bu, OTBDMS), 26.3 (CH_3, ^{t}Bu, OTBDMS), 28.1 (CH_3), 38.4 (CH_2-S), 63.2 (CH_2-OTBDMS), 75.3 (d, CH-

O, $^2J_{C\text{-}P}$ =7.3 Hz), 76.9 (*C*HCH$_2$S), 80.4 (d, *C*HCHO, $^3J_{C\text{-}P}$ =3.4 Hz), 110.4 (CMe$_2$), 125.5-152.7 (aromatic carbons). MS HR-ESI [found 949.2968, $C_{52}H_{59}O_6PSSi_3$ (M-Na)$^+$ requires 949.2970]. Anal. calc (%) for $C_{50}H_{63}O_6PSSi_3$: C 66.19, H 7.00, S 3.53; found: C 66.12, H 6.96, N 3.50.

L5b. Yield: 237.1 mg (32%); SiO_2-flash chromatography (toluene/hexane/NEt$_3$ = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=143.6 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.53 (s, 9H, CH$_3$, SiMe$_3$), 0.54 (s, 9H, CH$_3$, SiMe$_3$), 0.78 (d, 3H, CH$_3$, $^3J_{H\text{-}H}$ =6.4 Hz), 1.31 (s, 3H, CH$_3$), 1.34 (s, 3H, CH$_3$), 2.96 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =6.4 Hz), 3.10 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =4.0 Hz), 3.97 (dd, 1H, C*H*CHO, $^3J_{H\text{-}H}$ =4.8 Hz, $^3J_{H\text{-}H}$ =7.2 Hz), 4.13 (m, 1H, C*H*CH$_2$S), 4.55 (m, 1H, CH-O), 6.83-7.15 (m, 7H, CH=), 7.23-7.34 (m, 4H, CH=), 7.68-7.71 (m, 2H, CH=), 8.10 (s, 1H, C=H), 8.14 (s, 1H, C=H). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.1 (d, CH$_3$, SiMe$_3$, $J_{C\text{-}P}$ =4.5 Hz), 0.1 (CH$_3$, SiMe$_3$), 17.6 (CH$_3$), 27.0 (CH$_3$), 27.2 (CH$_3$), 37.3 (CH$_2$-S), 71.6 (CH-O), 75.8 (*C*HCH$_2$S), 82.2 (d, *C*HCHO, $^3J_{C\text{-}P}$ =4.6 Hz), 109.5 (CMe$_2$), 122.5-152.3 (aromatic carbons). MS HR-ESI [found 749.2316, $C_{40}H_{47}O_5PSSi_2$ (M-Na)$^+$ requires 749.2318]. Anal. calc (%) for $C_{40}H_{47}O_5PSSi_2$: C 66.08, H 6.52, S 4.41; found: C 65.87, H 6.48, N 4.38.

L5c. Yield: 289.0 mg (39%); SiO_2-flash chromatography (toluene/hexane/NEt$_3$ = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=151.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.51 (s, 9H, CH$_3$, SiMe$_3$), 0.53 (s, 9H, CH$_3$, SiMe$_3$), 1.15 (s, 3H, CH$_3$), 1.25 (m, 6H, CH$_3$), 2.53 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =14.0 Hz, $^3J_{H\text{-}H}$ =6.0 Hz), 2.69 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =2.6 Hz), 3.95-4.00 (m, 2H, C*H*CHO, C*H*CH$_2$S), 4.50-4.55 (m, 1H, CH-O), 6.85-6.86 (m, 3H, CH=), 6.92-6.96 (m, 2H, CH=), 6.98-7.00 (m, 1H, CH=), 7.09-7.15 (m, 5H, CH=), 7.24 (d, 1H, C=H, $^3J_{H\text{-}H}$ =8.4 Hz), 7.31 (d, 1H, C=H, $^3J_{H\text{-}H}$ =8.4 Hz), 7.69 (d, 1H, C=H, $^3J_{H\text{-}H}$ =8.4 Hz), 8.10 (d, 1H, C=H, $^3J_{H\text{-}H}$ =8.4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.1 (d, CH$_3$, SiMe$_3$, $J_{C\text{-}P}$ =4.6 Hz), 0.2 (CH$_3$, SiMe$_3$), 17.6 (CH$_3$), 26.8 (CH$_3$), 27.1 (CH$_3$), 36.3 (CH$_2$-S), 70.1 (d, CH-O, $^2J_{C\text{-}P}$ =10.0 Hz), 75.1 (*C*HCH$_2$S), 81.0 (*C*HCHO), 109.1 (CMe$_2$), 122.5-152.1 (aromatic carbons). MS HR-ESI [found 749.2317, $C_{40}H_{47}O_5PSSi_2$ (M-Na)$^+$ requires 749.2318]. Anal. calc (%) for $C_{40}H_{47}O_5PSSi_2$: C 66.08, H 6.52, S 4.41; found: C 65.92, H 6.50, N 4.40.

Preparation of compounds 7 and 8

A suspension of NaH (3.1 mg, 77.4 mmol), washed three times in hexane, in THF (25 mL) was cooled to -15 °C, and the corresponding thiol (37.5 mmol) in THF (8 mL), at -15 °C was added. After 10 min a solution of 1-deoxy-2,3-*O*-isopropylidene-1-tosyl-D-arabinitol[24] (16.3 mmol) in THF (25 ml) was added at -15 °C. The reaction was stirred for 72 h at room temperature. The reaction was quenched with water and extracted with dichloromethane for three times. The extract was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by SiO_2-column chromatography (PE/EtOAc = 1/6) to produce the corresponding thioether-derived compound as colorless oil (see Supporting Information for copies of the NMR spectra).

1-Deoxy-2,3:4,5-di-*O*-isopropylidene-1-phenylthio-D-arabinitol (5). Yield: 3.6 g (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.35 (s, 3H, CH$_3$), 1.37 (s, 3H, CH$_3$), 1.40 (s, 3H, CH$_3$), 1.42 (s, 3H, CH$_3$), 3.09 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =6.8 Hz), 3.46 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =3.2 Hz), 3.78 (pt, 1H, CHCHO, $^3J_{H\text{-}H}$ =7.3 Hz), 3.95 (dd, 1H, CH$_2$-O, $^2J_{H\text{-}H}$ =8.4 Hz, $^3J_{H\text{-}H}$ =4.8 Hz), 4.04-4.08 (m, 1H, CH-O), 4.13 (dd, 1H, CH$_2$-O, $^2J_{H\text{-}H}$ =8.0 Hz, $^3J_{H\text{-}H}$ =6.0 Hz), 4.16-4.19 (m, 1H, CHCH$_2$S), 7.15-7.19 (m, 1H, CH=), 7.25-7.29 (m, 2H, CH=), 7.39-7.41 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 25.5 (CH$_3$), 26.9 (CH$_3$), 27.3 (CH$_3$), 27.4 (CH$_3$), 36.8 (CH$_2$-S), 68.0 (CH$_2$-O), 77.3 (CH-O), 79.3 (CHCH$_2$S), 80.3 (CHCHO), 109.9 (CMe$_2$), 110.1 (CMe$_2$), 126.0 (CH=), 129.0 (CH=), 129.1 (CH=), 136.8 (C=).

1-Deoxy-2,3:4,5-di-*O*-Isopropylidene-1-(2-naftylthio)-D-arabinitol (6). Yield: 5.3 g (87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.39 (s, 6H, CH$_3$), 1.45 (s, 6H, CH$_3$), 3.19 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =7.6 Hz), 3.60 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =14.4 Hz, $^3J_{H\text{-}H}$ =3.2 Hz), 3.83 (pt, 1H, CHCHO, $^3J_{H\text{-}H}$ =8.4 Hz), 4.00 (dd, 1H, CH$_2$-O, $^2J_{H\text{-}H}$ =8.4 Hz, $^3J_{H\text{-}H}$ =3.2 Hz), 4.07-4.11 (m, 1H, CH-O), 4.14-4.17 (m, 1H, CH$_2$-O), 4.23-4.27 (m, 1H, CHCH$_2$S), 7.41-7.49 (m, 3H, CH=), 7.24-7.80 (m, 3H, CH=), 7.84 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 25.6 (CH$_3$), 27.1 (CH$_3$), 27.4 (CH$_3$), 27.5 (CH$_3$), 36.7 (CH$_2$-S), 68.0 (CH$_2$-O), 77.4 (CH-O), 79.3 (CHCH$_2$S), 80.5 (CHCHO), 110.0 (CMe$_2$), 110.2 (CMe$_2$), 125.8 (CH=), 126.4 (CH=), 126.8 (CH=), 127.2 (CH=), 127.3 (CH=), 128.0 (CH=), 128.6 (CH=), 131.9 (C=), 134.1 (C=), 134.3 (C=).

Compounds **5** and **6** (1.0 mmol) were stirred overnight at room temperature in 70% aq. acetic acid (3.5 mL). Then, the reaction mixture was neutralized with aq. $NaHCO_3$, and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by SiO_2-column chromatography (EtOAc/PE = 1/1) to afford the desired deprotected compounds as colorless oils.

1-Deoxy-2,3-*O*-isopropylidene-1-phenylthio-D-arabinitol (7). Yield: 2.1 g (67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.38 (s, 3H, CH$_3$), 1.43 (s, 3H, CH$_3$), 2.08 (b, 1H, OH), 2.65 (b, 1H, OH), 3.20 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =6.0 Hz), 3.33 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =4.8 Hz), 3.68 (dd, 1H, CH$_2$-O, $^2J_{H\text{-}H}$ =10.8 Hz, $^3J_{H\text{-}H}$ =5.2 Hz), 3.72-3.76 (m, 1H, CH-O), 3.80 (dd, 1H, CH$_2$-O, $^2J_{H\text{-}H}$ =10.4 Hz, $^3J_{H\text{-}H}$ =3.2 Hz), 3.87 (pt, 1H, CHCH-O, $^3J_{H\text{-}H}$ =6.8 Hz), 4.18-4.22 (m, 1H, CHCH$_2$S), 7.17-7.21 (m, 1H, CH=), 7.26-7.31 (m, 2H, CH=), 7.39-7.41 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 27.4 (CH$_3$), 27.5 (CH$_3$), 37.5 (CH$_2$-S), 64.2 (CH$_2$-O), 72.9 (CH-O), 78.5 (CHCH$_2$S), 80.7 (CHCHOH), 110.0 (CMe$_2$), 126.6 (CH=), 129.3 (CH=), 129.6 (CH=), 136.1 (C=).

1-Deoxy-2,3-*O*-Isopropylidene-1-(2-naftylthio)-D-arabinitol (8). Yield: 3.0 g (63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.35 (s, 3H, CH$_3$), 1.41 (s, 3H, CH$_3$), 3.22 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =7.2 Hz), 3.46 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =14.0 Hz, $^3J_{H\text{-}H}$ =4.4 Hz), 3.65 (dd, 1H, CH$_2$-O, $^2J_{H\text{-}H}$ =11.6 Hz, $^3J_{H\text{-}H}$ =6.0 Hz), 3.67-3.73 (m, 1H, CH-O), 3.79 (dd, 1H, CH$_2$-O, $^2J_{H\text{-}H}$ =10.8 Hz, $^3J_{H\text{-}H}$ =2.8 Hz), 3.86 (pt, 1H, CHCHO, $^3J_{H\text{-}H}$ =7.6 Hz), 4.24-4.29 (m, 1H, CHCH$_2$S), 7.36-7.44 (m, 3H, CH=), 7.69-7.74 (m, 3H, CH=), 7.81 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 27.1 (CH$_3$), 27.2 (CH$_3$), 37.0 (CH$_2$-S), 63.9 (CH$_2$-O), 72.8 (CH-O), 78.3 (CHCH$_2$S), 80.2 (CHCHOH), 109.8 (CMe$_2$), 125.7 (CH=), 126.6 (CH=), 126.7 (CH=), 127.1 (CH=), 127.7 (CH=), 128.5 (CH=), 131.7 (C=), 133.4 (C=), 133.7 (C=).

Synthesis of hydroxyl-thioether compounds 9 and 10

To a cooled solution (-15 °C) of compound **2** and **3** (1 mmol) in pyridine (0.27 mL. 3.4 mmol), a solution of *p*-toluenesulfonyl chloride (190.0 mg, 1 mmol) in DCM (2 mL) was slowly added. After stirring overnight, water was added and the reaction mixture was extracted with DCM (3 x 50 mL). The organic extract was washed with a solution of HCl 0.1 M (x1). The organic layer was dried over $MgSO_4$, evaporated to dryness and purified by SiO_2-flash chromatography (EtOAc/PE = 1/2) to produce the product as a white solid (see Supporting Information for copies of the NMR spectra).

1-Deoxy-2,3-*O*-Isopropylidene-1-phenylthio-5-*O*-tosyl-D-arabinitol. Yield: 3.0 g (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.21 (s, 3H, CH$_3$), 1.27 (s, 3H, CH$_3$), 2.35 (s, 3H, CH$_3$, OTs), 2.58 (d, 1H, OH, $^3J_{H\text{-}H}$ =4.4 Hz), 3.02 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =14.0 Hz, $^3J_{H\text{-}H}$ =6.8 Hz), 3.24 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =4.4 Hz), 3.62 (dd, 1H, CHCHO, $^3J_{H\text{-}H}$ =8.0 Hz, $^3J_{H\text{-}H}$

=6.4 Hz), 3.71-3.78 (m, 1H, CH-O), 3.94 (dd, 1H, CH_2-OTs, $^2J_{H-H}$ =10.4 Hz, $^3J_{H-H}$ =6.8 Hz), 4.06-4.09 (m, 1H, $CHCH_2S$), 4.18 (dd, 1H, CH_2-OTs, $^2J_{H-H}$ =10.4 Hz, $^3J_{H-H}$ =2.4 Hz), 7.06-7.10 (m, 1H, CH=), 7.15-7.19 (m, 2H, CH=), 7.24-7.28 (m, 4H, CH=), 7.69-7.71 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 21.9 (CH_3, OTs), 27.2 (CH_3), 27.4 (CH_3), 37.4 (CH_2-S), 71.8 (CH-O), 72.1 (CH_2-OTs), 78.8 (CHCHO), 79.2 ($CHCH_2S$), 110.3 (CMe_2), 126.4 (CH=), 128.2 (CH=), 129.2 (CH=), 129.4 (CH=), 130.2 (CH=), 132.6 (C=), 136.1 (C=), 145.4 (C=).

1-Deoxy-2,3-*O*-Isopropylidene-1-(2-naftylthio)-5-*O*-tosyl-D-arabinitol. Yield: 3.6 g (83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.42 (s, 3H, CH_3, OTs), 3.20 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.4 Hz, $^3J_{H-H}$ =7.2 Hz), 3.47 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =4.4 Hz), 3.76 (dd, 1H, CHCHO, $^3J_{H-H}$ =8.4 Hz, $^3J_{H-H}$ =6.8 Hz), 3.83-3.88 (m, 1H, CH-O), 4.06 (dd, 1H, CH_2-OTs, $^2J_{H-H}$ =10.8 Hz, $^3J_{H-H}$ =6.8 Hz), 4.22-4.26 (m, 1H, $CHCH_2S$), 4.29 (dd, 1H, CH_2-OTs, $^2J_{H-H}$ =10.4 Hz, $^3J_{H-H}$ =2.4 Hz), 7.31 (d, 2H, CH=, $^3J_{H-H}$ =8.8 Hz), 7.42-7.46 (m, 3H, CH=), 7.72-7.81 (m, 6H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 21.7 (CH_3, OTs), 27.0 (CH_3), 27.2 (CH_3), 36.9 (CH_2-S), 71.6 (CH-O), 72.0 (CH_2-O), 78.6 (CHCHOH), 78.9 ($CHCH_2S$), 110.2 (CMe_2), 125.7 (CH=), 126.5 (CH=), 126.6 (CH=), 127.1 (CH=), 127.7 (CH=), 128.0 (CH=), 128.5 (CH=), 130.0 (CH=), 131.7 (C=), 132.3 (C=), 133.4 (C=), 133.8 (C=), 145,2 (C=).

To a cooled solution (0 °C) of the corresponding thioether-tosyl compound (1.0 mmol) in THF (2.5 mL), $LiAlH_4$ (56.9 mg, 1.5 mmol) was added portion-wise. The solution was stirred at reflux for 2 h. Then, drops of water were carefully added and a white precipitate appeared which was filtered and clean three times with ethyl acetate. The organic phase was dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by SiO_2-column chromatography (EtOAc/PE = 1/3) yielding the corresponding compounds as colorless oils.

1,5-Dideoxy-2,3-*O*-isopropylidene-5-methyl-1-phenylthio-D-arabinitol (9). Yield: 1.2 g (67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.18 (d, 3H, CH_3, $^3J_{H-H}$ =6.8 Hz), 1.38 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.03 (b, 1H, OH), 3.15 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =6.8 Hz), 3.26 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =4.8 Hz), 3.74 (dd, 1H, CHCHO, $^3J_{H-H}$ =7.2 Hz, $^3J_{H-H}$ =5.2 Hz), 3.87-3.90 (m, 1H, CH-O), 4.13-4.18 (m, 1H, $CHCH_2S$), 7.14-7.18 (m, 1H, CH=), 7.23-7.28 (m, 2H, CH=), 7.36-7.39 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.5 (CH_3), 27.5 (CH_3), 27.6 (CH_3), 38.2 (CH_2-S), 68.2 (CH-O), 77.0 ($CHCH_2S$), 84.0 (CHCHO), 109.7 (CMe_2), 126.6 (CH=), 129.3 (CH=), 129.7 (CH=), 136.3 (C=).

1,5-Dideoxy-2,3-O-isopropylidene-5-methyl-1-(2-naftylthio)-D-arabinitol (10). Yield: 1.1 g (54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.22 (d, 3H, CH_3, $^3J_{H-H}$ =6.8 Hz), 1.39 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.91 (b, 1H, OH), 3.26 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =6.4 Hz), 3.39 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =4.4 Hz), 3.79 (dd, 1H, CHCHO, $^3J_{H-H}$ =7.6 Hz, $^3J_{H-H}$ =5.6 Hz), 3.90-3.93 (m, 1H, CH-O), 4.21-4.24 (m, 1H, $CHCH_2S$), 7.40-7.48 (m, 3H, CH=), 7.72-7.82 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.3 (CH_3), 27.2 (CH_3), 27.3 (CH_3), 37.7 (CH_2-S), 68.0 (CH-O), 77.4 ($CHCH_2S$), 83.8 (CHCHO), 109.4 (CMe_2), 125.8 (CH=), 126.6 (CH=), 126.9 (CH=), 127.1 (CH=), 127.3 (CH=), 127.7 (CH=), 128.5 (CH=), 131.8 (C=), 133.5 (C=), 133.7 (C=).

***Synthesis of hydroxyl-thioether compound 11 with inversion of configuration*[25]**

DIAD (3.1 mL, 16 mmol) was added dropwise to a solution of thioether-hydroxyl **4** (1.1 g, 4 mmol), *p*-nitrobenzoic acid (2.7 g, 16 mmol), and PPh_3 (4.2 g, 16 mmol) in THF (33 mL) at 0 °C. After being stirred overnight at room temperature, the reaction mixture was concentrated and the residue was purifief by SiO_2-column chromatography (EtOAc/PE = 1/6) to yield the product as a colorless oil.

1,5-Dideoxy-2,3-*O*-isopropylidene-5-methyl-*O*-4-(*p*-nitrobenzoate)-1-phenylthio-D-xylitol. Yield: 1.4 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.39 (d, 3H, CH_3, $^3J_{H-H}$ =6.0 Hz), 1.43 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.13 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =5.6 Hz), 3.24 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =5.6 Hz), 4.02-4.09 (m, 2H, $CHCH_2S$, CHCHOpNBA), 5.32-5.35 (m, 1H, CH-OpNBA), 7.07-7.09 (m, 1H, CH=), 7.15-7.20 (m, 2H, CH=), 7.29-7.32 (m, 2H, CH=), 8.10-8.12 (m, 2H, CH=), 8.20-8.23 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.7 (CH_3), 27.2 (CH_3), 27.5 (CH_3), 36.9 (CH_2-S), 70.9 (CH-O*p*NBA), 75.2 ($CHCH_2S$), 82.1 (CHCHO*p*NBA), 109.9 (CMe_2), 123.5 (CH=), 126.4 (CH=), 129.0 (CH=), 129.5 (CH=), 130.7 (CH=), 135.2 (C=), 135.3 (C=), 150.5 (C=), 163.9 (C=O, pNBA).

1,5-Dideoxy-2,3-*O*-isopropylidene-5-methyl-*O*-4-(*p*-nitrobenzoate)-1-phenylthio-D-xylitol (1.4 g, 3.6 mmol) was dissolved in MeOH (48.5 mL) and treated with NaOH (1.1 g, 26.9 mL) at room temperature. After being stirred overnight, the reaction mixture was concentrated and extracted with diethyl ether. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by SiO_2-column chromatography (EtOAc/PE = 1/1) to yield the product as a colorless oil.

1,5-Dideoxy-2,3-*O*-isopropylidene-5-methyl-1-phenylthio-D-xylitol (11). Yield: 850 mg (87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.17 (d, 3H, CH_3, $^3J_{H-H}$ =6.0 Hz), 1.40 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.29 (s, 1H, OH, $^3J_{H-H}$ =10.4 Hz), 3.10-3.23 (m, 2H, CH_2-S), 3.72-3.79 (m, 2H, CHCHO, CH-O), 4.11 (q, 1H, $CHCH_2S$, $^3J_{H-H}$ =6.0 Hz), 7.16-7.20 (m, 1H, CH=), 7.27 (t, 2H, CH=, , $^3J_{H-H}$ =7.2 Hz), 7.36-7.38 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 20.0 (CH_3), 27.4 (CH_3), 27.5 (CH_3), 37.3 (CH_2-S), 67.2 (CH-O), 76.0 ($CHCH_2S$), 84.1 (CHCHO), 109.7 (CMe_2), 126.4 (CH=), 129.1 (CH=), 129.5 (CH=), 135.7 (C=).

Synthesis of thioether-hydroxyl compound 12

Diol **7** (1 mmol) was solved in DMF (2 mL) in the presence of imidazole (2.5 mmol) and was cooled to -15 °C. A solution of *tert*-butyldimethylsilylchloride (1.2 mmol) in DMF (1 mL) was added and the reaction was stirred for 1.5 h. When chlorotrimethylsilane was used, the solution was cooled to -75 °C and the reaction mixture was stirred only 30 min. Then, water was added and the reaction mixture was extracted with Et_2O (x3). The organic layer was dried over $MgSO_4$, evaporated to dryness and purified by SiO_2-column chromatography (EtOAc/PE = 1/4) to produce the product as a colorless oil (see Supporting Information for copies of the NMR spectra).

5-*O*-(*tert*-Butyldimethylsilyl)-1-deoxy-2,3-*O*-isopropylidene-1-phenylthio-D-arabinitol (12). Yield 263.3 mg (61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.09 (s, 6H, CH_3, OTBDMS), 0.91 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.38 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.62 (d, 1H, OH, $^3J_{H-H}$ =5.2 Hz), 3.12 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =7.2 Hz), 3.46 (dd, 1H, CH_2-S, $^2J_{H-H}$ =10.4 Hz, $^3J_{H-H}$ =6.8 Hz), 3.62-3.68 (m, 2H, CH-O, CH_2-OTBDMS), 3.76-3.81 (m, 2H, CHCHO, CH_2-OTBDMS), 4.26 (m, 1H, $CHCH_2S$), 7.14-7.18 (m, 1H, CH=), 7.25-7.29 (m, 2H, CH=), 7.39-7.42 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-5.2 (CH_3, OTBDMS), -5.1 (CH_3, OTBDMS), 18.5 (C,, ^{t}Bu, OTBDMS), 26.1 (CH_3, ^{t}Bu, OTBDMS), 27.4 (CH_3), 27.5 (CH_3), 37.4 (CH_2-S), 64.5 (CH_2-OTBDMS), 73.3 (CH-O), 79.1 ($CHCH_2S$, CHCHO), 109.8 (CMe_2), 126.0 (CH=), 129.1 (CH=), 136.8 (C=).

Synthesis of [Rh(cod)(L4c)]BF_4 catalyst precursor

Ligand **L4c** (55.6, 0.05 mmol) was dissolved in CH_2Cl_2 (1 mL) and $[Rh(cod)_2]BF_4$ (20.3 mg, 0.05 mmol) was added. The reaction was stirred for 10 min at room temperature. The product was precipitated by adding cold hexane (5 mL). The product was then filtered and washed with cold hexane (3 x 5 mL). The solid was then dried to afford the catalyst precursor as a yellow solid (see Supporting Information for copies of the NMR spectra). Yield: 53 mg (89%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ=119.9 (d, $^1J_{P\text{-}Rh}$= 261.5 Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.59 (s, 9H, CH_3, $SiMe_3$), 0.72 (s, 9H, CH_3, $SiMe_3$), 0.84 (b, 6H, CH_3), 1.04 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.20 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.79 (m, 2H, CH_2, cod), 1.95 (m, 1H, CH_2, cod), 2.12 (m, 1H, CH_2, cod), 2.27 (m, 1H, CH_2-OTBDMS), 2.37 (m, 2H, CH_2, cod), 2.49 (m, 1H, CH_2, cod), 2.69 (m, 1H, CH_2, cod), 3.16 (m, 2H, CH_2-OTBDMS and CH_2-S), 4.16 (b, 1H, CH=, cod), 4.27 (m, 3H, CH_2-S, CH= cod, CH), 4.64 (m, 2H, CH), 5.50 (m, 2H, CH= cod), 6.918-8.21 (m, 17H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-0.1 (CH_3-Si), 0.4 (CH_3-Si), 14.3 (CH_3), 18.4 (C, ^{t}Bu-Si), 22.9 (CH_3), 26.8 (CH_3, ^{t}Bu-Si), 29.7 (b, CH_2 cod), 30.4 (b, CH_2 cod), 31.9 (CH_3), 34.5 (b, CH_2 cod), 34.9 (b, CH_2 cod), 42.5 (CH_2-S), 62.2 (CH_2-OTBDMS), 75.6 (CH), 75.7 (CH), 81.1 (CH), 82.7 (CH=, cod), 94.0 (CH=, cod), 112.1 (CMe_2), 112.3 (CH=, cod), 114.6 (CH=, cod), 114.6-151.4 (aromatic carbons). MS HR-ESI [found 1117.3383, $C_{58}H_{75}O_6PRhSSi_3$ $(M)^+$ requires 1117.3379]. Anal. calc (%) for $C_{58}H_{75}BF_4O_6PRhSSi_3$: C 57.80, H 6.27, S 2.66; found: C 57.89, H 6.31, N 2.64

Synthesis of [Ir(cod)(L4c)]BAr$_F$ catalyst precursor

Ligand **L4c** (41.1 mg, 0.037 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and $[Ir(\mu\text{-}Cl)(cod)]_2$ (12.5 mg, 0.0185 mmol) was added. The reaction was refluxed at 50 °C for 1 hour. After 5 min at room temperature, $NaBAr_F$ (38.6 mg, 0.041 mmol) and water (2.5 mL) were added and the reaction mixture was stirred vigorously for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered through a plug of celite and the solvent was evaporated to give the product as a red-orange solid (see Supporting Information for copies of the NMR spectra). Yield: 71 mg (93%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ=101.0 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=-0.09 (s, 3H, CH_3, OTBDMS), -0.02 (s, 3H, CH_3, OTBDMS), 0.63 (s, 9H, CH_3, $SiMe_3$), 0.71 (s, 9H, CH_3, $SiMe_3$), 0.86 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.27 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.72-2.07 (m, 6H, CH_2, cod), 2.05 (d, 1H, CH_2-OTBDMS, $^2J_{H\text{-}H}$ =12.0 Hz), 2.17-2.21 (m, 1H, CH_2, cod), 2.29-2.32 (m, 1H, CH_2, cod), 3.18 (d, 1H, CH_2-OTBDMS, $^2J_{H\text{-}H}$ =11.6 Hz), 3.55-3.60 (m, 1H, CH_2-S), 3.69 (b, 1H, CH=, cod), 4.03 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =11.2 Hz, $^3J_{H\text{-}H}$ =3.2 Hz), 4.30 (m, 2H, CH-O, CH=, cod), 4.44 (pt, 1H, C*H*CHO, $^3J_{H\text{-}H}$ =8.4 Hz), 4.57 (b, 1H, C*H*CH_2S), 4.93 (b, 1H, CH=, cod), 5.30 (b, 1H, CH=, cod), 6.98-8.18 (m, 29H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-5.9 (CH_3, $SiMe_3$, OTBDMS), -5.3 (CH_3, $SiMe_3$, OTBDMS), 0.0 (CH_3, $SiMe_3$), 0.9 (CH_3, $SiMe_3$), 18.4 (C, ^{t}Bu, OTBDMS), 25.8 (CH_3, ^{t}Bu, OTBDMS), 26.2 (CH_3), 26.8 (CH_3), 27.8 (CH_2, cod), 29.6 (d, CH_2, cod, $J_{C\text{-}P}$ =13.0 Hz), 31.9 (CH_2, cod), 33.4 (CH_2, cod), 45.6 (CH_2-S), 61.2 (CH_2-OTBDMS), 69.5 (CH=, cod), 76.2 (d, *C*HCHO, $^3J_{C\text{-}P}$ =5.3 Hz), 76.6 (*C*HCH_2S), 79.2 (CH=, cod), 82.5 (d, CH-O, $^2J_{C\text{-}P}$ =14.5 Hz), 102.6 (d, CH=, cod, $J_{C\text{-}P}$ =17.6 Hz), 105.5 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 112.4 (CMe_2), 117.4-151.6 (aromatic carbons), 162.2 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =63.4 Hz). MS HR-ESI [found 1207.3964, $C_{58}H_{75}IrO_6PSSi_3$ $(M)^+$ requires 1207.3959]. Anal. calc (%) for $C_{90}H_{87}BF_4IrO_6PSSi_3$: C 52.20, H 4.23, S 1.55; found: C 52.29, H 4.25, N 1.52.

General procedure for the asymmetric hydrogenation of cyclic β-enamides S1-S10

The enamide (0.25 mmol), catalyst precursor $[M(cod)_2]X$ (M= Rh, X= BF_4 or M= Ir, X= BAr_F; 1 mol%) and the corresponding ligand (1 mol%) were dissolved in CH_2Cl_2 (1 mL) and placed in a high-pressure autoclave, which was purged four times with hydrogen. It was then pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short celite plug. Conversions were determined by ^{1}H NMR. The enantiomeric excesses of hydrogenated products were determined using the conditions previously described (see Supporting Information for details).

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Keywords: asymmetric hydrogenation • cyclic β-enamides • rhodium • iridium • phosphite-thioether ligands

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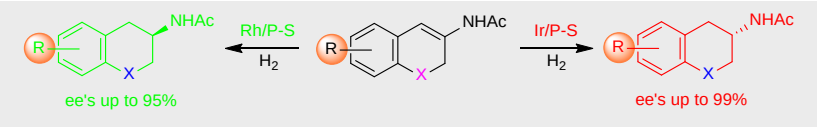
Entry for the Table of Contents

FULL PAPER



Phosphite-thioether ligands with a simple modular architecture derived from carbohydrates have been successfully applied (ee's up to 99%) in the synthesis of 2-aminotetralines and 3-aminochromanes via metal catalysed asymmetric hydrogenation of cyclic β-enamides. Both enantiomers were obtained by using either Rh- or Ir-catalyst precursors.

Jèssica Margalef, Oscar Pàmies and Montserrat Diéguez**

Page No. – Page No.

Novel phosphite-thiother ligands derived from carbohydrates allow the enantioswitchable hydrogenation of cyclic β-enamides using either Rh- or Ir-catalysts