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Modular optimization of enantiopure epoxide-derived P,S-ligands for rhodium-catalyzed hydrogenation of dehydroamino acids

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ABSTRACT

The optimization of P,S-ligands derived from enantiopure (2*S*,3*S*)-phenylglycidol for asymmetric rhodium-catalyzed hydrogenation of dehydroamino esters is described. The exceptionally high modular character of the (2*S*,3*S*)-phenylglycidol platform is demonstrated by systematic modification of the ether and thioether moieties, the skeletal aryl substituent and the stereo and regiochemistry of the ligands. An experimentally useful method for the monitoring of hydrogenation reactions is also described and used for obtaining relevant data of the catalytic systems studied.

1. Introduction

Asymmetric catalysis is one of the most active research fields in chemistry, having experienced an enormous growth in the last decades. The huge and permanently growing number of chemical processes suitable for asymmetric catalysis, as well as the large variety of substrates to which they can be applied represent a permanent need for the discovery of new catalysts.

Preparation of combinatorial libraries of modular ligands for asymmetric catalysis has been for years one of the key strategies for fast progress towards high catalytic activity and enantioselectivity for a broad variety of processes and substrates.[1] In this context, however, attention has been usually focused on enantioselectivity only, prioritizing it over any other variable. Despite the undeniable importance of methodologies for obtaining enantiopure compounds for fine chemicals and pharmaceutical industries, catalytic activity is a variable frequently overlooked by asymmetric catalysis academic researchers. When a catalytic enantioselective process is analyzed from the perspective of its potential application as a production tool a different parameter; i.e., catalytic activity and its translation into productivity, needs to be simultaneously considered. In this respect, it is pertinent to recall here that enantiopurity of a synthetic material (measured as either enantiomeric excess or enantiomeric ratio) can in many cases[2] be brought to levels far superior to those intrinsically arising from the enantioselectivity of the employed reaction by simple recrystallization,[3] while the consequences of poor catalytic activity (in terms of reactor/plant occupation) or inconvenient reaction conditions (in terms of energy consumption) have unavoidable, potentially very negative impacts on production costs.

From this perspective, comparison between very similar ligands, which do not afford significant differences in terms of enantioselectivity should take into account their catalytic activity as a key factor, which strongly influences the economic viability of a determined process, by saving time (and thus energy) and allowing lower catalyst loadings to be used, which represents a very important contribution to the global costs.

Recently, we have reported on the preparation and application in Pd-catalyzed allylic substitution reactions[4] of a family of modular P,S-ligands[5,6] derived from enantiopure (2*S*,3*S*)-phenylglycidol **1** (Fig. 1). This readily available, purely synthetic chiral edduct has demonstrated in the last years to be an exceptionally versatile platform for the preparation of diverse types of ligands.[7] Encouraged by these results, we envisioned to further study the behaviour of these ligands by optimization of their structural parameters for their application in Rh-catalyzed hydrogenation[8] paying particular attention to the accurate comparison of their catalytic activities, represented by the turnover frequency measured at half conversion ($TOF_{1/2}$). Herein we report the results from this systematic study, together with an experimentally useful methodology for monitoring the hydrogenation reactions based on the measurement of the gas consumed.

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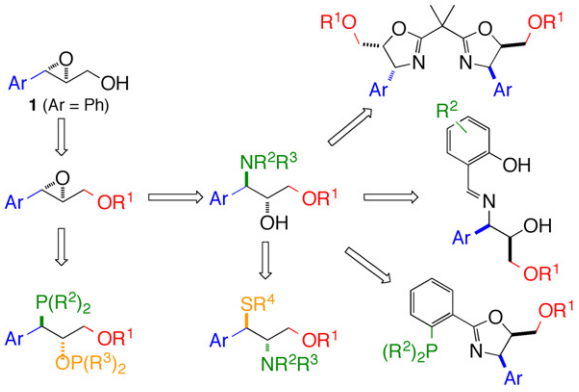
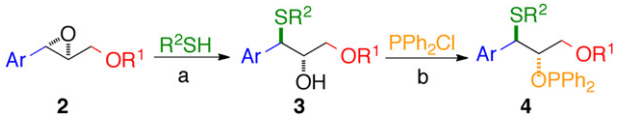


Fig. 1. Modular construction of diverse ligands from a simple epoxide precursor.

2. Results and discussion

2.1. General strategy for the preparation of the ligands

The modular P,S-ligands (**4**) employed in this study were prepared in a straightforward manner by ring opening with thiols of different epoxyethers (**2**) derived from (2*S*,3*S*)-phenylglycidol, followed by phosphinylation of the resulting alcohols **3** (Scheme 1), as has been already described.[4] This approach demonstrated to be very reliable, allowing preparation of a wide variety of compounds with good yields with little dependence on the particular structure of the different building blocks.



Scheme 1. Preparation of P,S-ligands from chiral enantiopure epoxides.

The structure of the ligands was modified (see below) as to provide optimal catalytic activity and enantioselectivity in the hydrogenation of methyl *Z*-α-acetamidocinnamate (*Z*-MAC). This reaction was used as a benchmark for the structural optimization of P,S-ligands **4**, performed systematically according to their catalytic performance (expressed in terms of turnover frequency measured at half conversion ($TOF_{1/2}$) and enantiomeric excess of the product obtained).

2.2. Monitoring of the hydrogenation reactions by the gas uptake data. Determination of $TOF_{1/2}$

With the purpose of accurately comparing the different ligands tested, a measure of the catalytic activity was necessary. Since in almost all the cases (see below) the reactions proceeded to completion in relatively short reaction times (most frequently ranging 5–100 min), simply measuring conversion at a fixed time did not constitute a practical method. Thus, we decided to use the hydrogen gas uptake in order to closely monitor the reactions. For this purpose, computer-controlled reactors equipped with a pressure probe where used (see Experimental section), this allowing accurate measurements of the gas consumed.

Considering this accurate pressure measurement together with the total amount of gas consumed (Fig. 2, left), corrected gas uptake data in which non chemical gas expense (i.e., flushing reactors, pressurizing, etc.) was excluded could be calculated (Fig. 2, right). This data constitute a rough representation of the time interval in which the reaction took place, allowing determination of the reaction starting and ending points.

For transforming this data into a conversion against time plot, a series of assumptions were made: (i) The dissolution of hydrogen gas in the reaction medium is faster than the reaction (so the gas consumed in the solution is immediately replaced and this is thus reflected in a small decrease in the gas phase pressure, which is measured); (ii) the catalyst loading is small enough for neglecting the gas consumed in reducing the catalyst; (iii) the pressure variations throughout the hole process are small enough to neglect the variation in the amount of hydrogen dissolved in the reaction medium. These considerations allow us to directly relate the gas uptake to conversion. Having in mind the 1:1 hydrogen to substrate stoichiometry, conversion can be expressed as described in Eq. 1.

$$\text{Conversion}(\%) = \frac{n_t - n_0}{n_f - n_0} \cdot 100 \qquad (1)$$

where n_t is the gas uptake (corrected) at a given time and n_0 and n_f are the gas uptake data at the reaction starting and ending points, respectively.

In this way, a conversion to time plot could be generated (Fig. 3). From this graph, the time for half conversion could be determined by linear interpolation (for accuracy, interpolation was done with all the data between 40 and 60% conversion). Finally, the $TOF_{1/2}$ was determined by Eq. 2.

$$TOF_{1/2} = \frac{50}{l \cdot t_{1/2}} \qquad (2)$$

where l is the catalyst loading expressed in percentage respect to the substrate and $t_{1/2}$ is the time for half conversion previously determined.

In addition to serving for the determination of reaction times and TOFs, the conversion versus time plots obtained allowed observation of the kinetics of the process. In all the cases herein

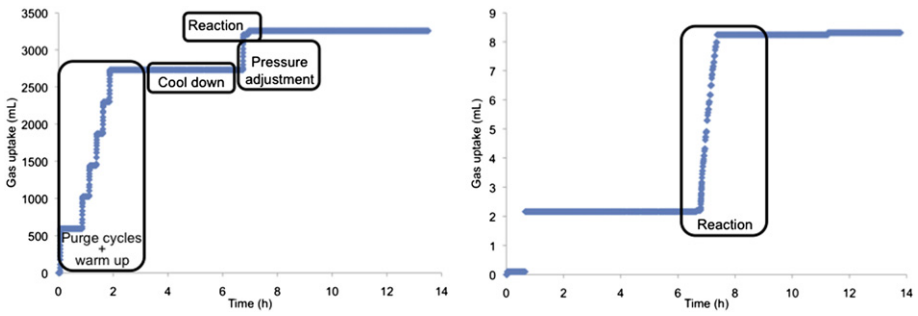


Fig. 2. Raw (left) and corrected (right) gas uptake versus time plots for a model hydrogenation reaction.

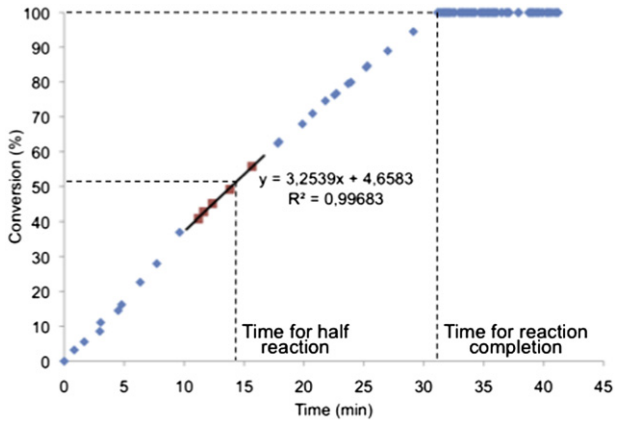
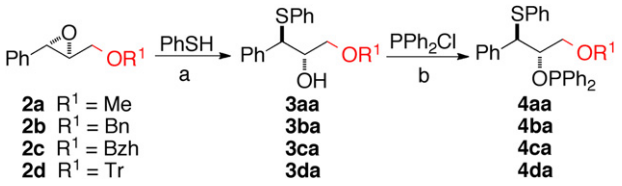


Fig. 3. Conversion versus time plot for a model hydrogenation reaction and linear regression calculated with the central points (red).

studied, except when alcohol type solvents were used (see Section 3.3), the curves obtained were close to perfectly linear. This implies the reaction rate is independent of the substrate concentration. On the other hand, the rates were linearly dependent on the hydrogen pressure. This rate equation (order 0 on the substrate, order 1 on hydrogen) is consistent with the oxidative addition being the rate limiting step of the reaction.

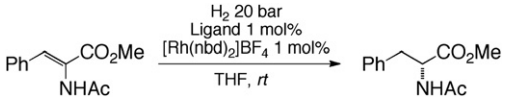
2.3. Modification of the alkoxy group

As an entry to our investigation in rhodium-catalyzed hydrogenation, we tested a series of P,S-ligands of the general structure **4** bearing alkoxy substituents (OR^1) with increasing size (Scheme 2). For the catalytic tests, *Z*-MAC was chosen as a reference substrate,[8] and the reactions were carried out under standard conditions in THF, with the catalysts generated in situ from cationic bisnorbornadiene rhodium (I) tetrafluoroborate and under 20 atm of hydrogen. The results obtained are summarized in Table 1.



Scheme 2. Variation of the ether R^1 substituent in epoxide-derived P,S-ligands **4**.

Table 1
Rhodium-catalyzed asymmetric hydrogenation of *Z*-MAC with P,S-ligands **4**. Effect of the ether R^1 substituent[a]



Ligand	t [b] (min)	$TOF_{1/2}$ [c] (h^{-1})	ee[d] (%)
4aa	69	109	79
4ba	63	120	75
4ca	36	198	77
4da	36	208	77

[a] All the reactions run with 50 mg of substrate and 0.1 M concentration.
[b] Time for reaction completion, monitored by the gas uptake data.
[c] TOF calculated at 50% conversion.
[d] Determined by HPLC with a chiral stationary phase.

In all the cases, the reaction proceeded cleanly to complete conversion in short reaction times, giving place to the pure hydrogenated product in quantitative yield. Ligands **4ca** and **4da**, bearing more bulky benzhydryl and trityl substituents, showed higher catalytic activities than the less hindered **4aa** and **4ba**. On the other hand, little influence on the ee was observed, ligand **4aa** affording the highest.

2.4. Optimization of the reaction conditions

With these results in hand, we set on to optimize the reaction conditions before going on with the study of the different modules in the ligands. With this aim, some experiments were run in order to identify the best metal precursor. A series of cationic rhodium complexes of the general formula $[Rh(diene)_2]X$ were studied, varying independently the diene ligands and the counterion (X). The results of these tests are summarized in Table 2.

Table 2
Influence of the precursor rhodium species on the hydrogenation of *Z*-MAC with ligand **4aa**[a]

Entry	Diene	X	t (min)	$TOF_{1/2}$ (h^{-1})	ee (%)
1	nbd	BF_4^-	69	109	79
2	cod	OTf^-	100	68	74
3	cod	BF_4^-	56	137	79
4	cod	PF_6^-	19	318	79
5	cod	SbF_6^-	20	291	82

[a] All the reactions performed under the conditions described in Table 1, with the appropriate metallic complex and ligand **4aa**.

Not surprisingly, the diene ligand in the precursor complex seemed to have little influence on activity and enantioselectivity of the resulting catalysts (entries 1 and 3), which is consistent with these ligands not being present in the catalytic species. No induction period was observed in any case, indicating that both dienes are readily hydrogenated and dissociated.

On the other hand, remarkable variations were registered when the counterion was changed (entries 2–5). The best enantioselectivity was registered using the SbF_6^- anion (82% ee, entry 5), with only a moderate decrease in activity respect to that recorded with PF_6^- (entry 4).

Thus, using SbF_6^- as the counterion, the influence of variables as solvent, hydrogen pressure and temperature were studied, with the results shown in Table 3.

Table 3
Optimization of the reaction conditions for the rhodium-catalyzed hydrogenation of *Z*-MAC with ligand **4aa**[a]

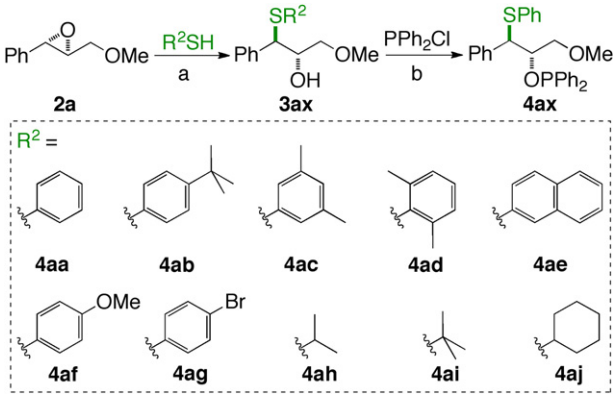
Entry	Solvent	P (bar)	T (°C)	t (min)	$TOF_{1/2}$ (h^{-1})	ee (%)
1	Toluene	20	30	116	59	53
2	CH_2Cl_2	20	30	16	367	76
3	THF	20	30	20	291	82
4	MeCN	20	30	—[b]	~3[c]	36
5	IPA	20	30	116	85[d]	63
6	MeOH	20	30	110	124[d]	20
7	THF	5	30	75	79	79
8	THF	10	30	38	156	82
9	THF	50	30	8	773	77
10	THF	10	50	15	563	63
11	THF	10	75	6.7	1706	58
12	THF	10	100	3.5	4680	55

[a] All the reactions performed under the conditions described in Table 1, with $[Rh(cod)_2]SbF_6$ and ligand **4aa.**
[b] The reaction proceeded to 23% conversion in 8 h, and reduction of the solvent to ethylamine was observed by ^1H NMR.
[c] TOF at 23% conversion.
[d] The reaction rate was not constant in these cases, but it fastly decayed with time, in contrast with that observed for aprotic solvents. This suggests alcoholysis of the phosphinite taking place in the reaction medium.

The nature of the solvent turned out to be an important factor, the results obtained for the reaction in THF being optimal. In acetonitrile, conversion was very low even after 8 h, due to hydrogenation of the solvent as a competitive process. Alcohols, such as ^{i}PrOH or MeOH resulted also detrimental for the reaction. On the other hand, no improvement was obtained by changing pressure or temperature.

2.5. Variation of the thioether moiety

With these results in hand, we turned our attention back to the optimization of the different structural variables on the phosphinyloxy thioether P,S-ligands. With this purpose, a series of ligands was prepared by using different thiols as nucleophiles in the ring opening step (Scheme 3).



Scheme 3. Modification of the thioether R^2 group in epoxide-derived P,S-ligands **4**.

All these ligands were tested in the reference reaction using the conditions described in Table 3, entry 3 (i.e., $[Rh(cod)_2]SbF_6$ as the metal source, in THF, at 30 °C and under 20 bar hydrogen pressure). The results obtained are shown in Table 4.

Table 4
Influence of the modification of the R^2 thioether substituent on the catalytic performance of epoxide-derived P,S-ligands **4** on the rhodium-catalyzed hydrogenation of *Z*-MAC[a]

Ligand	*t* (min)	$TOF_{1/2}$ (h^{-1})	ee (%)
4aa	20	291	82
4ab	40	182	76
4ac	17	284	84
4ad	13	620	59
4ae	17	349	73
4af	5	2249	64
4ag	40	148	80
4ah	17	397	82
4ai	18	432	72
4aj	19	331	74

[a] All the reactions performed under the conditions described in Table 3, entry 3, with the appropriate ligand in each case.

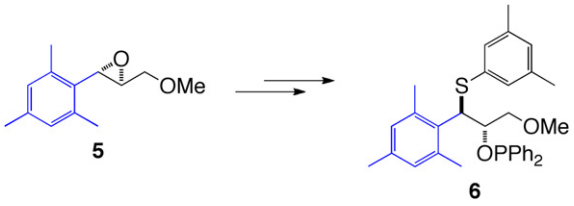
Ligands bearing aryl substituents with different substitution patterns were tested and compared to the original **4aa**. A most favourable compromise of different steric parameters was attained with ligand **4ac**, bearing a 3,5-dimethylphenyl substituent on sulfur, which afforded complete conversion to the hydrogenated product in short time and with 84% ee.

Regarding the operation of electronic effects, it is worth to note the extremely fast reaction recorded with ligand **4af**, bearing an electron-rich 4-methoxyphenyl substituent. Unfortunately, this dramatic increase in catalytic activity was associated with a significant decrease in enantioselectivity.

Finally, ligands resulting from the incorporation of alkyl thiols were tested (**4ah**, **4ai** and **4aj**). All of them showed a catalytic activity in the same order of that observed with **4ac**. In terms of enantioselectivity, the ligand bearing an ^{i}Pr group (**4ah**) turned out to be the best one, affording the product in 82% ee. Interestingly, **4ah** showed also a rather high (397) $TOF_{1/2}$ value.

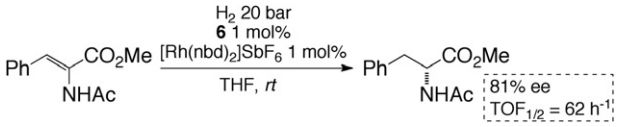
2.6. Modification of the skeletal carbon substituent

Having in mind that the sulfur atom becomes a stereogenic centre upon coordination, whose configuration is mainly controlled by steric repulsion between the thioether (R^2) and the skeletal aryl (Ar) substituents,[5b,9] we thought that a bulkier aryl substituent was likely to increase the enantioselectivity by more strongly fixing the configuration of this newly formed chiral centre. With this in mind, ligand **6** was prepared from epoxide **5**[9] by the same sequence described before for ligands of type **4** (Scheme 4).



Scheme 4. Modification of the skeletal aryl (Ar) substituent.

Test of this ligand in hydrogenation (Scheme 5), unfortunately, showed no improvement respect to the phenyl-substituted analogue **4ac**. The product of hydrogenation was obtained with slightly decreased ee (81%) in a significantly longer reaction time.



Scheme 5. Rhodium-catalyzed hydrogenation of *Z*-MAC with ligand **6**.

2.7. Variation of regio- and relative stereochemistry

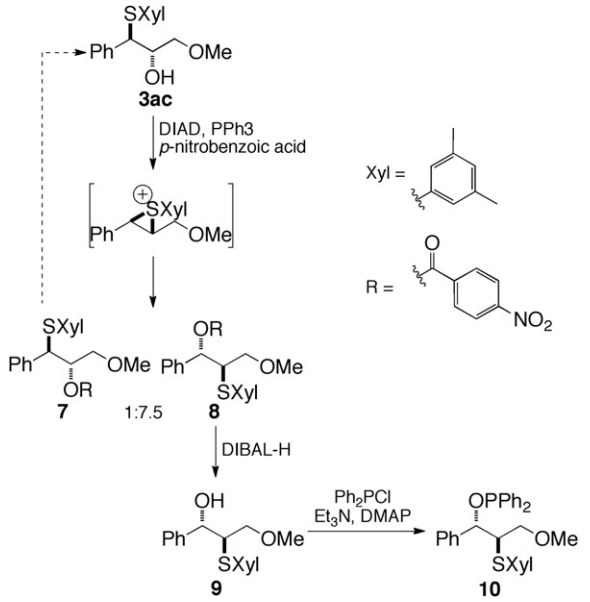
Finally, as another approach for introducing diversity in our ligands, we decided to modify the relative configuration of the ligands, as well as their regiochemistry. Thus, the *syn* diastereoisomer of **4ac** was prepared, as well as both diastereoisomers of the C_2-opening regioisomeric product **10**.

For the preparation of **10**, a sulfur 1,2–migration was used, through formation and opening of an episulfonium ion under Mitsunobu conditions (Scheme 6).[7c,10]

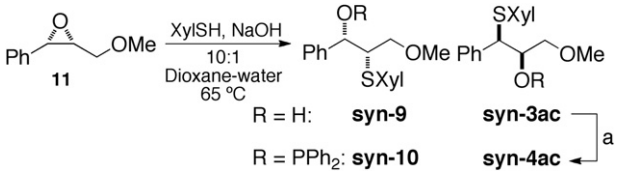
On the other hand, *syn*-**10** and *syn*-**4ac** were prepared from the *cis* epoxide **11**[12] (Scheme 7). Although the opening of the *trans* epoxide **2a** proceeded in a completely regioselective manner, as explained before, the situation was completely different with the cis stereoisomer. Thus, opening of the *cis* epoxide **11** afforded a mixture of both regioisomers *syn*-**9** and *syn*-**3ac**. After separation, phosphinylation gave place to the desired ligands *syn*-**10** and *syn*-**4ac**.

All three ligands gave place to rhodium complexes that were active as catalysts for the model reaction (Table 5).

Although all the ligands were active in the reaction, particularly *syn*-**4ac**, which afforded a ~6-fold increase in reaction rate compared to **4ac**, in all the cases the enantioselectivities were also significantly reduced. It is worth to note that with ligand *syn*-**10**, with *S* configuration in the chiral centre in position α to sulfur, the



Scheme 6. Preparation of regioisomeric ligand **10** through formation of an episulfonium intermediate.



Scheme 7. Preparation of epoxide-derived P,S-ligands with *syn* relative configuration.

Table 5
Effect of the regiochemistry and relative configuration on the catalytic performance of P,S-ligands for rhodium-catalyzed hydrogenation of *Z*-MAC[a]

Ligand	*t* (min)	$TOF_{1/2}$ (h^{-1})	ee (%)
4ac	17	284	84
10	11	1139	38
syn-**4ac**	7	1765	61
syn-**10**	17	629	45[b]

[a] All the reactions performed under the conditions described in Table 3, entry 3, with the appropriate ligand in each case.
[b] The product was obtained with opposite absolute configuration (*S*).

product was obtained with the opposite absolute configuration. Thus, it is this centre the one controlling the stereochemical outcome of the reaction.

2.8. Analysis of the (2*S*,3*S*)-phenylglycidol-derived P,S-ligands structural space

All the data collected in the former sections (3.1–3.6) afford a comprehensive sight on the structural space available for P,S-ligands derived from (2*S*,3*S*)-phenylglycidol. A representation of the $TOF_{1/2}$ and ee obtained in the hydrogenation reaction with each individual ligand (Fig. 4) allows us to determine the main structural variables leading to high enantioselectivity or catalytic activity. Thus, the higher enantioselectivities where those registered for some of the **4ax**-type ligands, derived from direct ring opening of epoxide **2a** with thiols, followed by phosphinylation, bearing a xylyl (**4ac**), phenyl (**4aa**) or 2-propyl (**4ah**) substituents on the sulfur atom. On the other hand, the results make obvious the dramatic effect on catalytic activity of two main variables, i.e., the relative stereochemistry of the two stereogenic centres in the ligand and the electronic properties of the sulfur substituent, as shown by the very high catalytic activities registered with ligands *syn*-**4ac** (presenting a 10-fold increase respect to its *anti* analogue **4ac**) and **4af**, bearing an electron-donating substituent on sulfur.

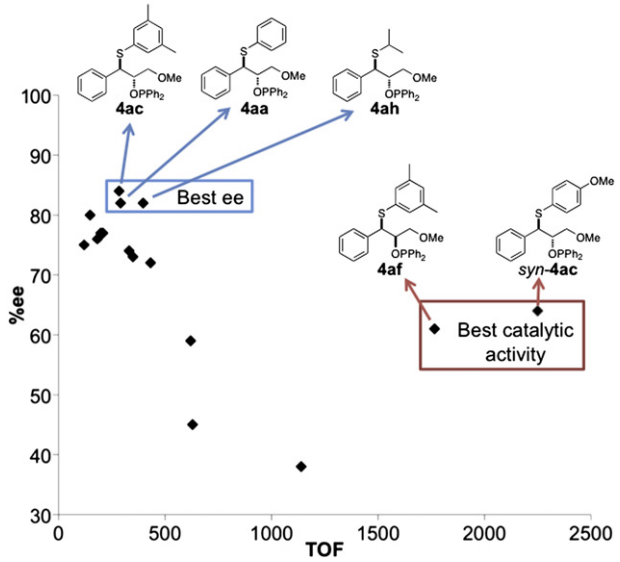


Fig. 4. Data dispersion of % ee versus $TOF_{1/2}$ for the rhodium-catalyzed hydrogenation of *Z*-MAC with all the ligands studied under the optimized conditions.

3. Conclusion

In summary, a complete, systematic study on the influence of the different structural parameters of epoxide-derived P,S-ligands family **4** has been done, demonstrating the extremely modular nature of these ligands. Catalytic activity and kinetics data obtained by monitoring the reactions gas uptake, together with the enantioselectivity data, have allowed determination of the key structural variables (steric and electronic properties of the sulfur substituent and relative stereochemistry), which will lead to the development of new and more efficient ligand families.

4. Experimental section

4.1. Materials

Unless otherwise stated, all commercial reagents were used as received and all reactions were carried out directly under open air. Reactions under inert atmosphere were performed using standard Schlenk techniques with oxygen and water free solvents and reagents, obtained as follows: DMF, THF, DCM, toluene and acetonitrile were obtained from a solvent purification system, with <5 ppm of water (Karl-Fischer analysis); methanol, 2-propanol, hexane and ethyl acetate were dried by prolonged contact with activated 4 Å molecular sieves and degassed by bubbling argon; deuterated chloroform was dried by prolonged contact with 4 Å molecular sieves, distilled and degassed by vacuum–argon cycles at low temperature, then stored under inert atmosphere protected from light; triethylamine was dried by prolonged contact with powdered calcium hydride, distilled, degassed by bubbling argon and stored over pieces of calcium hydride under inert atmosphere; chlorodiphenylphosphine was degassed prior to use by high vacuum–argon cycles to remove hydrochloric acid; hydroxythioethers were dried prior to phosphinylation by azeotropic distillation of toluene.

4.2. Instrumentation

All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. Catalytic tests in hydrogenation were performed in a computer-controlled AMTEC SPR-16 parallel reactor, equipped with a pressure probe that allows registering the gas uptake data from the reaction. NMR spectra were registered in a Bruker Advance 400 Ultrashield spectrometer in $CDCl_3$ at room temperature, operating at 400.13 MHz for ^1H (100.63 MHz for ^{13}C and 162.18 MHz for ^{31}P). Chemical shifts are reported in parts per million referred to TMS (^1H and ^{13}C) or 85% phosphoric acid (^{31}P). IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses were performed on a LECO CHNS 932 microanalyzer at the Universidad Complutense de Madrid, Spain. Melting points were determined using a Büchi melting point apparatus. FAB mass spectra were obtained on a Fisons V6-Quattro instrument, ESI mass spectra were obtained on a Waters LCT Premier instrument and CI and EI spectra were obtained on a Waters GCT spectrometer. Optical rotations were measured on a Jasco P-1030 polarimeter. High performance liquid chromatography (HPLC) was performed on Agilent Technologies chromatographs (Serie1200), using Chiralpak OJ-H column and guard column.

4.3. Experimental procedures for the preparation of P,S-ligands

4.3.1. General procedure for the ring opening of epoxides by thiols[4]. To a solution of the epoxide (1 mmol) and sodium hydroxide (2 mmol) in dioxane–water (10:1 v/v) the corresponding thiol (2 mmol, 2 equiv) was added. The mixture was heated at the indicated temperature, and reaction progress was monitored by TLC until disappearance of the starting epoxide was observed (ca. 20–90 min). The mixture was then allowed to reach room temperature, when 10 mL of water were added, and the mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel, eluting with hexane–ethyl acetate mixtures to give the desired product in pure form.

4.3.2. General procedure for the phosphinylation of β-hydroxy thioethers[4]. To a Schlenk flask containing β-hydroxy thioether (0.55 mmol) and DMAP (0.055 mmol, 0.1 equiv) in toluene (0.28 M) at room temperature, NEt_3 (0.66 mmol, 1.2 equiv) and chlorodiphenylphosphine (0.55 mmol, 1.01 equiv) were added via syringe and the reaction was stirred for 20 min. The solvent was removed under reduced pressure and the reaction crude was diluted with 95:5 hexane–ethyl acetate mixture (0.5 mL). The resulting slurry was loaded onto a plug of silica and purified by flash chromatography (1×3 cm, 95% hexane, 5% ethyl acetate).

4.4. Preparation and characterization of new compounds

*4.4.1. (2S,3S)-2-Mesityl-3-(methoxymethyl)oxirane (**5b**).* A solution of the epoxide **5**[9] (300 mg, 1.56 mmol) in DMF (3 mL) was added via cannula to a suspension of sodium hydride (44 mg, 1.81 mmol) in DMF (2 mL) at −20 °C under inert atmosphere. The mixture was stirred for 20 min, and methyl iodide (126 μl, 2.03 mmol) was syringed into the mixture. After being stirred for 4 h at −20 °C, the mixture was allowed to reach room temperature and stirred for a further hour. MeOH (10 mL) and brine (10 mL) were added. The aqueous solution was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried and concentrated in vacuo. The residual oil was purified by flash chromatography using hexane–Et_2O (9:1 to 7:3) as eluent to give 300 mg (93%) of the epoxyether (**5b**) as an oil. $[\alpha]_{D^{27}}$ −13.4 (*c* 0.44, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) 6.82 (s, 2H), 3.88 (d×d, 1H, ^2J=11.4 Hz, ^3J=2.9 Hz), 3.81 (d, 1H, ^3J=2.3 Hz), 3.56 (d×d, 1H, ^2J=11.4 Hz, ^3J=5.3 Hz), 3.46 (s, 3H), 3.13–3.16 (m, 1H), 2.35 (s, 6H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 137.4 (C), 137.0 (C), 130.3 (C), 128.6 (CH), 72.6 (CH_2), 59.3 (CH_3), 58.3 (CH), 54.4 (CH), 20.8 (CH_3), 19.6 (CH_3). HRMS (ES^+): *m*/*z* found: 229.1205 (M+Na), calculated for $C_{13}H_{18}O_2Na^+$: 229.1204. IR 2977, 2887, 1729, 1615, 1453, 1374, 1315, 1199, 954, 850, 816, 703.

*4.4.2. (1R,2S)-1-(3,5-Dimethylphenylthio)-1-mesityl-3-methoxypropan-2-ol (**6b**).* To a solution of the epoxyether **5b** (30 mg, 0.15 mmol) and sodium hydroxide (30 mg, 0.75 mmol) in dioxane–water (10:1 v/v) was added the corresponding thiol (113 μl, 0.75 mmol). The mixture was warmed up to 80 °C and stirred at this temperature for 120 min while monitoring the progress of the reaction by TLC. After disappearance of the epoxide, the mixture was allowed to cool down to room temperature; 10 mL of water was added and the mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried with Na_2SO_4, the solvent was removed under vacuum and the crude was purified by flash chromatography on SiO_2 eluting with 9:1 hexane–ethyl acetate to obtain the title product as a white solid (42 mg, 81% yield). ^1H NMR (400 MHz, $CDCl_3$) 6.98 (s, 2H), 6.87 (s, 1H), 6.84 (s, 1H), 6.78 (s, 1H), 4.77 (d, 1H, ^3J=10,3 Hz), 4.33–4.38 (m, 1H), 3.82 (d×d, 1H, ^2J=9.7 Hz, ^3J=2.6 Hz), 3.63 (d×d, ^2J=9.7 Hz, ^3J=5 Hz), 3.32 (s, 3H), 2.52 (s, 3H), 2.24 (s, 9H), 2.16 (s, 3H), 2.03 (d, ^3J=4.43 Hz, OH). ^{13}C NMR (100 MHz, $CDCl_3$) 138.3 (C), 137.4 (C), 136.9 (C), 136.7 (C), 135.7 (C), 134.5 (C), 133.0 (C), 131.2 (CH), 129.6 (CH), 129.1 (CH), 128.9 (CH), 74.0 (CH_2), 72.6 (CH), 58.9 (CH_3), 50.7 (CH), 21.3 (CH_3), 21.3 (CH_3), 21.1 (CH_3), 20.8 (CH_3). HRMS (ES^+): *m*/*z* found: 367.1710 (M+Na), calculated for $C_{21}H_{28}O_2NaS^+$: 367.1708. $[\alpha]_{D^{26}}$ −266.73 (*c* 0.2, $CHCl_3$). IR 3444, 2916, 2859, 1599, 1579, 1450, 1376, 1191, 1121, 1097, 1062, 1032, 848, 689.

*4.4.3. ((1R,2S)-1-(3,5-Dimethylphenylthio)-1-mesityl-3-methoxypropan-2-yloxy)diphenylphosphine (**6**).* Under inert atmosphere, β-hydroxysulfide **6b** (20 mg, 60 μmol) and DMAP (0.7 mg, 6 μmol) were dissolved in toluene (0.28 M) at room temperature. Then, triethylamine (10 μl, 70 μmol) and chlorodiphenylphosphine (11 μl, 60 μmol) were sequentially added via syringe. The reaction was stirred for 20 min before the solvent was removed under vacuum, and the reaction was diluted with 95:5 hexane–ethyl acetate (0.5 mL, dried over 4 Å molecular sieves and degassed with argon). The resulting slurry was loaded onto a plug of silica and purified by flash chromatography (1×3 cm, 95% hexane, 5% ethyl acetate) to yield product **6** as a clear oil (23 mg, 75% yield). ^1H NMR (400 MHz, $CDCl_3$) 7.35–7.40 (m, 2H), 7.23–7.28 (m, 3H), 7.10–7.14 (m, 1H), 6.97–7.01 (m, 4H), 6.82 (s, 1H), 6.62–6.70 (m, 4H), 4.96 (d, 1H, ^3J=10,8 Hz), 4.64–4.7 (m, 1H), 3.83 (d×d, 1H, ^2J=10 Hz, ^3J=1.03 Hz), 3.69 (d×d, ^2J=10 Hz, ^3J=4.4 Hz), 3.01 (s, 3H), 2.44 (s, 3H), 2.23 (s, 6H), 2.20 (s, 3H), 2.14 (s, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) 117.9. ^{13}C NMR (100 MHz, $CDCl_3$) 143.6 (C, d, *J*=17.9 Hz), 142.2 (C, d, *J*=14 Hz), 138.3 (C), 136.9 (C), 136.6 (C), 136.0 (C), 136.0 (C), 134.2 (C), 130.9 (CH), 130.0 (CH, d, *J*=21.9 Hz), 130.0 (CH, d, *J*=21.9 Hz), 129.5 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 127.9 (CH, d, *J*=7.1 Hz), 127.5 (CH, d, *J*=6.6 Hz), 82.1 (CH, d, *J*=19.1 Hz), 73.6 (CH_2, d, *J*=2.9 Hz), 58.2 (CH_3), 50.1 (CH, d, *J*=6 Hz), 21.5 (CH_3), 21.4 (CH_3, d, *J*=2.5 Hz), 21.1 (CH_3), 20.8 (CH_3). HRMS (ES^+): *m*/*z* found: 529.2313 (M), calculated for $C_{33}H_{38}O_2PS^+$: 529.2330. $[\alpha]_{D^{26}}$ −123.7 (*c* 0.33, $CHCl_3$). IR 2970, 2920, 1738, 1435, 1375, 1229, 1217, 1127, 1094, 1053, 739, 697.

*4.4.4. (1S,2R)-2-(3,5-Dimethylphenylthio)-3-methoxy-1-phenylpropan-1-ol (**9**).* A solution of **3ac** (150 mg, 0.5 mmol), PPh_3 (657 mg, 2.48 mmol) and 4-nitrobenzoic acid (93 mg, 0.55 mmol) in toluene (4.5 mL) and THF (4.5 mL) under inert atmosphere was cooled down to −20 °C. Then, DEAD (403 μl, 2.48 mmol) was

syringed into the solution. The mixture was stirred at −20 °C for 3 h, allowed to reach room temperature and stirred for further 14 h at room temperature. The solvents were removed in vacuo, and the residual oil was chromatographed using hexane–EtOAc (95:5) as eluent to give 157 mg (80% yield) of a mixture of regioisomers **7** and **8** with a 1:7.5 ratio.

To this mixture (141 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) at −20 °C under inert atmosphere, DIBAL-H 1 M in hexanes (2.5 mL, 2.5 mmol) was added dropwise. After stirring at −20 °C for 19 h, brine (20 mL) and CH_2Cl_2 (30 mL) were added carefully, and the mixture was stirred vigorously. The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (2×30 mL). The combined organic extracts were dried and concentrated in vacuo. The residual oil was chromatographed using hexane–EtOAc mixture (99:1 to 95:5) as eluent to give 55 mg (58% yield) of **9**. ^{1}H NMR (400 MHz, $CDCl_3$) 7.32–7.35 (m, 4H), 7.26–7.29 (m, 1H), 6.99 (s, 2H), 6.87 (s, 1H), 4.93–4.96 (m, 1H), 3.73 (d, 1H, ^3J=5.2 Hz), 3.61–3.66 (m, 1H), 3.47–3.54 (m, 1H), 3.35 (s, 3H), 2.27 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) 141.4 (C), 138.7 (C), 133.6 (C), 130.0 (CH), 129.3 (CH), 128.2 (CH), 127.6 (CH), 126.4 (CH), 75.0 (CH), 73.0 (CH_2), 59.1 (CH_3), 55.5 (CH), 21.1 (CH_3). HRMS (ES^+): *m*/*z* found: 325.1239 (M+Na), calculated for $C_{18}H_{22}O_2NaS^+$: 325.1238. IR 3438, 2914, 1599, 1579, 1491, 1451, 1190, 1120, 1074, 962, 847, 748, 699, 686.

*4.4.5. ((1S,2R)-2-(3,5-Dimethylphenylthio)-3-methoxy-1-phenylpropoxy)diphenylphosphine (**10**).* A procedure analogous to that described for compound **6** was applied, using **9** (50 mg, 0.165 mmol), DMAP (2 mg, 0.016 mmol), NEt_3 (28 μl, 0.2 mmol) and chlorodiphenylphosphine (31 μl, 0.165 mmol). After purification, compound **10** was obtained as a clear oil (53 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) 7.56–60 (m, 2H), 7.3–7.36 (m, 7H), 7.17–7.26 (m, 6H), 6.8 (s, 2H), 6.78 (s, 1H), 5.18–5.21 (m, 1H), 3.61–3.67 (m, 2H), 3.44–3.49 (m, 1H), 3.23 (s, 3H), 2.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) 142.2 (C, d, *J*=15.9 Hz), 142.2 (C, d, *J*=18.9 Hz), 139.1 (C, d, *J*=2.23 Hz), 138.2 (C), 134.6 (C), 131.0 (CH, d, *J*=22.7 Hz), 130.3 (CH, d, *J*=21.5 Hz), 130.0 (CH), 129.4 (CH), 128.9 (CH), 128.8 (CH), 128.2 (CH, d, *J*=7.1 Hz), 128.0 (CH, d, *J*=6.6 Hz), 127.9 (CH), 127.9 (CH), 127.8 (CH), 81.4 (CH, d, *J*=21.6 Hz), 72.0 (CH_2), 58.6 (CH_3), 56.0 (CH, d, *J*=6.3 Hz), 21.1 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) 114.9. HRMS (ES^+): *m*/*z* found: 509.1673 (M+Na), calculated for $C_{30}H_{31}O_2NaPS^+$: 509.1680. IR 3052, 3027, 2916, 2893, 1599, 1580, 1492, 1480, 1466, 1453, 1434, 1129, 1094, 1074, 1026, 967, 848, 741.

*4.4.6. (2R,3S)-2-(Methoxymethyl)-3-phenyloxirane (**11**).* A solution of ((2*R*,3*S*)-3-phenyloxiran-2-yl)methanol[11b] (150 mg, 1 mmol) in DMF (1.4 mL) was added via cannula to a suspension of sodium hydride (44 mg, 1.1 mmol) in DMF (2 mL) at −20 °C under inert atmosphere. The mixture was stirred for 20 min before methyl iodide (82 μL, 1.3 mmol) was syringed into the mixture. After being stirred for 4 h at −20 °C, the mixture was allowed to reach room temperature and stirred for further 2 h. MeOH (10 mL) and brine (10 mL) were then added, the aqueous solution was extracted with CH_2Cl_2 (3×15 mL) and the combined organic extracts were dried and concentrated in vacuo. The residual oil was chromatographed using hexane–Et_2O (9:1 to 7:3) as eluent to give 140 mg (86% yield) of epoxyether **11** as a clear oil. All the spectroscopic data matched those previously described.[11a]

^{1}H NMR (400 MHz, $CDCl_3$) 7.28–7.37 (m, 5H), 4.14 (d, 1H, ^3J=4.3 Hz), 3.40–3.44 (m, 1H), 3.33 (d×d, 1H, ^2J=11.4 Hz ^3J=4.4 Hz), 3.28 (s, 3H), 3.22 (d×d, 1H, ^2J=11.4 Hz ^3J=6.5 Hz).

*4.4.7. Thiolate ring opening of cis epoxide **11**.* A procedure analogous to that described for compound **6b** was applied, using the *cis* epoxide **11** (75 mg, 0.46 mmol), 3,5-dimethylbenzenethiol (192 μl, 1.37 mmol) and NaOH (55 mg, 1.37 mmol) at 55 °C for 2 h. After purification by flash chromatography (9:1 hexane–ethyl acetate), both regioisomers could be separately isolated (*syn*-**3ac**, 80 mg, 57% yield, *syn*-**9**, 53 mg, 38% yield).

*4.4.8. (1R,2R)-1-(3,5-Dimethylphenylthio)-3-methoxy-1-phenylpropan-2-ol (syn-**3ac**).* ^{1}H NMR (400 MHz, $CDCl_3$) 7.19–7.29 (m, 5H), 6.89 (s, 2H), 6.82 (s, 1H), 4.27 (d, 1H, ^3J=8.4 Hz), 4.04–4.09 (m, 1H), 3.4 (d×d, 1H, ^2J=9.8 Hz, ^3J=3.1 Hz), 3.27 (s, 3H), 3.17 (d×d, 1H, ^2J=9.8 Hz, ^3J=6 Hz), 3.00 (br s, OH), 2.20 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) 139.7 (C), 138.3 (C), 133.2 (C), 130.3 (CH), 129.3 (CH), 128.4 (CH), 128.2 (CH), 127.4 (CH), 73.6 (CH_2), 72.9 (CH), 59.1 (CH_3), 58.1 (CH), 21.1 (CH_3). HRMS (ES^+): *m*/*z* found: 325.1241 (M+Na), calculated for $C_{18}H_{22}O_2NaS^+$: 325.1238. IR 3438, 2914, 1599, 1579, 1491, 1451, 1190, 1120, 1074, 962, 847, 748, 699, 686.

*4.4.9. (1S,2S)-2-(3,5-Dimethylphenylthio)-3-methoxy-1-phenylpropan-1-ol (syn-**9**).* ^{1}H NMR (400 MHz, $CDCl_3$) 7.27–7.43 (m, 5H), 6.92 (s, 2H), 6.84 (s, 1H), 4.98 (m, 1H), 3.51–3.56 (m, 1H), 3.4–3.47 (m, 3H), 3.35 (s, 3H), 2.24 (s, 6H), 1.56 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 141.1 (C), 138.6 (C), 133.7 (C), 129.8 (CH), 129.2 (CH), 128.2 (CH), 127.7 (CH), 126.6 (CH), 74.0 (CH), 73.2 (CH_2), 59.0 (CH_3), 57.5 (CH), 21.1 (CH_3). HRMS (ES^+): *m*/*z* found: 325.1241 (M+Na), calculated for $C_{18}H_{22}O_2NaS^+$: 325.1238. IR 3052, 3027, 2916, 2893, 1599, 1580, 1492, 1480, 1466, 1453, 1434, 1129, 1094, 1074, 1026, 967, 848, 741.

*4.4.10. ((1R,2R)-1-(3,5-Dimethylphenylthio)-3-methoxy-1-phenylpropan-2-yloxy)diphenylphosphine (syn-**4ac**).* A procedure analogous to that described for compound **6** was applied, using *syn*-**3ac** (48 mg, 0.16 mmol), DMAP (2 mg, 0.016 mmol), NEt_3 (26 μl, 0.19 mmol) and chlorodiphenylphosphine (29 μl, 0.16 mmol). After purification, *syn*-**4ac** was obtained as a clear oil (55 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) 7.46–7.55 (m, 4H), 7.24–7.36 (m, 8H), 7.16–7.18 (m, 3H), 6.82 (s, 2H), 6.74 (s, 1H), 4.55 (d, 1H, ^3J=5.6 Hz), 4.38–4.44 (m, 1H), 3.63 (d×d, 1H, ^2J=10 Hz, ^3J=4.4 Hz), 3.27 (d×d, 1H, ^2J=10 Hz, ^3J=5.6 Hz), 3.09 (s, 3H), 2.16 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) 143.1 (C, d, *J*=18.3 Hz), 142.2 (C, d, *J*=14.8 Hz), 140.0 (C), 138.1 (C), 134.9 (C), 130.8 (CH, d, *J*=22.5 Hz), 130.2 (CH, d, *J*=22.3 Hz), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 128.4 (CH), 128.1 (CH, d, *J*=5.1 Hz), 128.1 (CH), 128.0 (CH, d, *J*=5.8 Hz), 127.1 (CH), 82.9 (CH, d, *J*=19.1 Hz), 73.4 (CH_2, d, *J*=3.5 Hz), 58.7 (CH_3), 56.3 (CH, d, *J*=5.9 Hz), 21.1 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) 117.9. HRMS (ES^+): *m*/*z* found: 487.1838 (M−H), calculated for $C_{30}H_{32}O_2PS^+$: 487.1868. IR 3052, 3027, 2916, 2893, 1599, 1580, 1492, 1480, 1466, 1453, 1434, 1129, 1094, 1074, 1026, 967, 848, 741.

*4.4.11. ((1S,2S)-2-(3,5-Dimethylphenylthio)-3-methoxy-1-phenylpropoxy)diphenylphosphine (syn-**10**).* A procedure analogous to that described for compound **6** was applied, using *syn*-**9** (38 mg, 0.13 mmol), DMAP (1.6 mg, 0.013 mmol), NEt_3 (21 μl, 0.15 mmol) and chlorodiphenylphosphine (23 μl, 0.13 mmol). After purification, *syn*-**10** was obtained as a clear oil (45 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) 7.5–7.54 (m, 2H) 7.27–7.4 (m, 7H), 7.17–7.23 (m, 6H), 6.67 (s, 1H), 6.63 (s, 1H), 5.29 (d×d, 1H, *J*=9.4, 2.9 Hz), 3.38–3.46 (m, 1H), 3.27–3.34 (m, 2H), 3.02 (s, 3H), 2.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) 142.1 (C), 141.9 (C, d, *J*=4.1 Hz), 140.4 (C, d, *J*=2.1 Hz), 138.3 (C), 135.3 (C), 131.2 (CH, d, *J*=23.2 Hz), 130.3 (CH, d, *J*=22.0 Hz), 129.5 (CH), 129.0 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH, d, *J*=7.3 Hz), 128.1 (CH, d, *J*=7.0 Hz), 127.9 (CH), 128.6 (CH), 127.3 (CH), 80.1 (CH, d, *J*=21.2 Hz), 72.3 (CH_2), 58.4 (CH_3), 57.4 (CH, d, *J*=6 Hz), 21.1 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) 115.4. HRMS (ES^+): *m*/*z* found: 509.1665 (M+Na), calculated for $C_{30}H_{31}O_2NaPS^+$:

509.1680. IR 3052, 3027, 2916, 2893, 1599, 1580, 1492, 1480, 1466, 1453, 1434, 1129, 1094, 1074, 1026, 967, 848, 741.

4.5. General procedure for the asymmetric hydrogenation of *Z*-MAC

Under inert atmosphere, ligand **4aa** (1.38 mg, 3.0 μmol) and $[Rh(cod)_2]SbF_6$ (1.67 mg, 3.0 μmol) were dissolved in dry, degassed THF (1.2 mL). The mixture was stirred at room temperature for 30 min to obtain a yellow solution. Separately, also under inert atmosphere, another solution was prepared containing methyl *Z*-MAC (62 mg, 0.28 mmol) in dry, degassed THF (1.7 mL).

A stainless steel reactor was conditioned by warming it up to 110 °C and pressurizing with N_2 to 50 bar, followed by venting (9 cycles) and cooling down again to room temperature. Then, the catalyst solution was introduced (1 mL, 2.5 μmol, 1 mol %) via syringe, immediately followed by the substrate solution (1.5 mL, 0.25 mmol). The system was flushed with H_2 and pressurized to 20 bar.

The reaction was monitored by the gas uptake data. When no more H_2 was consumed, the reactor was vented and opened to air and the reaction solution was concentrated under reduced pressure to obtain a pale brown solid identified by ^1H NMR as pure product.

This crude could be purified by a filtration through silica gel, eluting with hexane–ethyl acetate mixtures. After removal of the solvents, the product was obtained in quantitative yield as a colourless crystalline solid. A sample (1 mg/mL in hexane–IPA 93:7) was analyzed by HPLC on a chiral stationary phase (82% ee).

^1H NMR ($CDCl_3$, 400 MHz): δ 1.99 (s, 3H), 3.09 (dd, J=13.9, 5.7 Hz, 1H), 3.15 (dd, J=13.9, 6.0 Hz, 1H), 3.73 (s, 2H), 4.89 (dt, J=7.8, 5.7 Hz, 1H), 5.91 (br s, 1H), 7.09 (m, 2H), 7.28 (m, 3H). HPLC: Chiralpak OJ-H column, hexane–IPA 93:7, 1 mL/min, 216 nm; t_R=18.1 min (*S*), 28.8 min (*R*).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.04.050. These data include MOL file and InChiKey of the most important compounds described in this article.

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