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New developments in the synthesis of heterotopic atropisomeric diphosphines via diastereoselective aryl coupling reactions

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Abstract—The new heterotopic atropisomeric diphosphine (*R*)-5,6-benzo-2,2′-bis(diphenylphosphino)-4′,5′,6′-trimethylbiphenyl has been prepared. The key step of this synthesis is a diastereoselective, intramolecular aryl–aryl coupling reaction via oxidation of a suitable, chiral diarylcuprate. The catalytic properties of the diphosphine in ruthenium promoted hydrogenations of model substrates and in rhodium promoted 1,4-additions of boronic acids to α,β-unsaturated ketones are fully comparable to those of reference ligands such as BINAP. This seems to indicate that C_2-symmetry is not a structural prerequisite for atropisomeric chiral diphosphines to obtain high enantioselectivities in 1,4-addition reactions as well as in hydrogenation reactions.

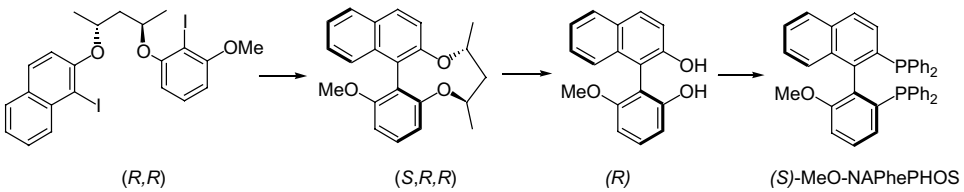
1. Introduction

The utility of enantiomerically pure diphosphines with atropoisomeric structures has been undeniably established by their outstanding properties in a number of significant catalytic processes.[1] Nevertheless, the search for new derivatives in these series still represents an extremely active research field as fine tuning of the structure of the phosphorus ligands significantly affects their catalytic properties. Thus, for instance, the enantioselectivities are highly dependent on the steric, conformational and electronic properties of the chiral atropisomeric ligands, with an optimal selectivity attained by using highly specific substrate/ligand pairs.[2–6]

In this context, we devised recently the synthesis of a new chiral atropisomeric diphosphine, called MeO–NAPhePHOS, which bears an unsymmetric biaryl moiety.[7] Despite the lack of C_2-symmetry, this ligand induces high enantioselectivity in the ruthenium-promoted hydrogenations of functionalised carbonyl derivatives.

The key step for the preparation of MeO–NAPhePHOS was an intramolecular aryl–aryl coupling reaction, according to Lipshutz's method.[8,9] The 2,4-pentanediol tether, first introduced by Sugimura and co-workers,[10–13] was used as the chiral auxiliary to induce high diastereoselectivity in the coupling reaction. The resulting macrocyclic bis-ether derivative was then converted successively into the corresponding biphenol and diphosphine through known methods (Scheme 1).

The same approach, which allows the synthesis of highly modular ligands, has been extended here to the synthesis of a new unsymmetric diphosphine where naphthyl and



Scheme 1. Synthetic approach to the unsymmetric diphosphine MeO–NAPhePHOS.

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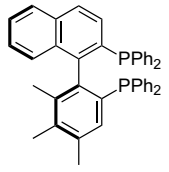
3,4,5-trimethylphenyl units constitute the biaryl framework.

2. Results and discussion

2.1. Synthesis of the heterotopic atropisomeric diphosphine TriMe-NAPhePHOS

In designing the first heterotopic atropisomeric diphosphine of the series above, we envisioned the use of the 2-naphthyl and 2-methoxyphenyl fragments, which form the structures of BINAP and MeO–BIPHEP,[14] respectively, two of the most known and successful atropisomeric diphosphines.

Of course, a number of other aromatic and heteroaromatic fragments could be considered for the synthesis of new biphenols and diphosphines by the same synthetic approach. As the second target in this study, we choose diphosphine **5** where a naphthyl group is associated with the 2,3,4-trimethylphenyl fragment. The 3,4,5-trimethylphenyl moiety has already been used for the synthesis of C_2-symmetric atropisomeric diphosphines.[15]

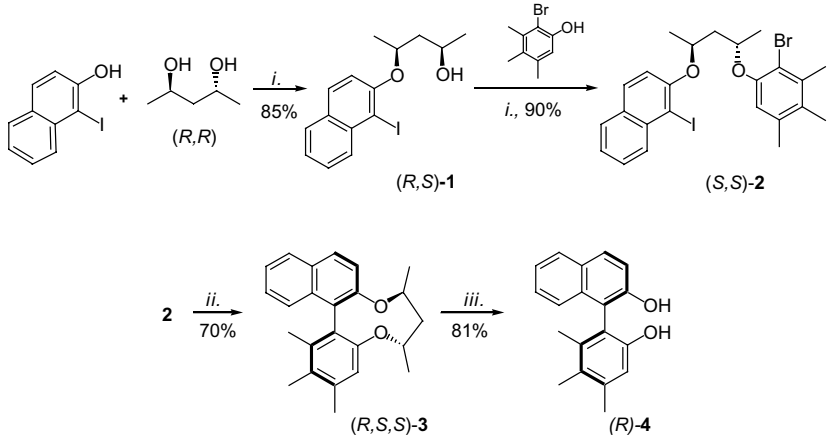


5

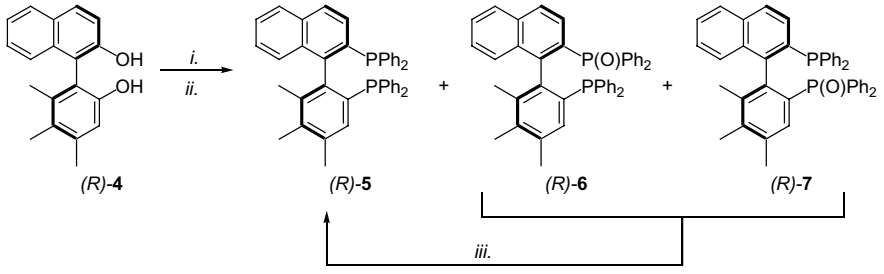
The methyl substituents of **5** should modulate mainly the steric properties and the dihedral angle of the biaryl framework, while it should only slightly affect the electronic properties, with respect to the previously prepared MeO–NAPhePHOS ligand.

As shown in Schemes 2 and 3, the synthesis of the biaryl framework of **5** follows exactly the same approach used for the preparation of MeO–NAPhePHOS. The halogenated aromatic fragments, for example, 1-iodo-2-naphthol and 2-bromo-3,4,5-trimethylphenol, have been connected to the chiral tether, (*R*,*R*)-2,4-pentanediol, through ether bonds, which are formed by two successive Mitsunobu reactions. Diisopropyl azodicarboxylate is preferably used as the reagent. High yields of the desired ethers **1**[7] and **2** are obtained in optimised conditions.

The biaryl coupling reaction has been performed according to Lipshutz's method:[8,9] after halogen–lithium exchange with *sec*-BuLi, the mixed cuprate is formed by addition of 1.5 equiv of CuCN. Finally, oxidation of the cuprate with molecular oxygen affords the macrocyclic bis-ether derivative **3** as a single diastereoisomer after purification by column chromatography. In this case as well, the chiral tether induces very high diastereoselectivity. The configuration of the biaryl frame obtained by using (*R*,*R*)-2,4-pentanediol as starting material, is assumed to be (*R*) by analogy to the stereochemical course of the biaryl coupling reaction in the synthesis of MeO–NAPhePHOS. In that case the



Scheme 2. Synthesis of the unsymmetric diphenol(*R*)-**4**. Reagents and conditions: (i) PPh_3, *i*-$PrO_2CN{=}NCO_2$*i*-Pr (DIAD), THF, 0–25 °C, 48 h; (ii) *sec*-BuLi, −78 °C, THF, CuCN, O_2, 70% yield; (iii) BBr_3, CH_2Cl_2, −50 °C, 81% yield.



Scheme 3. Synthesis of (*R*)-TriMe–NAPhePHOS, **5**. Reagents and conditions: (i) Tf_2O, pyridine, CH_2Cl_2, rt., 12 h, 95% yield; (ii) $HPPh_2$, $NiCl_2$ (dppe), DABCO, DMF, 100 °C, 3 days: 72% total yield (phosphine + monooxides); (iii) $HSiCl_3$/*n*-Bu_3N, xylene, 140 °C, 18 h, 97% yield.

absolute configuration of the biaryl moiety had been established by X-ray crystallography.

The chiral auxiliary was removed by reacting **3** with an excess BBr_3. The biphenol **4** was thus obtained in 81% yield, with a total 42% yield over four steps. The enantiomeric purity (ee >99%) was determined by HPLC on a Chiralcel OD-H column, flow rate: 1 mL/min, eluent: hexane/propan-2-ol (99:1), $t = 35.1$ min (*R*-assumed configuration), $t = 43.0$ (*S*).

The diphenylphosphino groups were then introduced on the biaryl framework by nickel catalysed coupling of the bis-triflate of **4** with diphenylphosphine (Scheme 3).[16]

The diphosphine **5**, was obtained in low yield, but a significant amount of the corresponding diphosphine-monooxides were recovered after column chromatography. Even under rigorously inert gas atmosphere this partial oxidation could not be avoided. However, the phosphine oxides were quantitatively reduced to the targeted diphosphine **5** by reduction with an $HSiCl_3$/n-Bu_3N mixture, according to the usual procedure. Finally, the diphosphine (*R*)-**5**, called TriMe–NAPhePHOS, was recovered in a total 66% yield from diol **4**. The (*S*)-enantiomer of the same ligand has been obtained by the same procedure, starting from (*S*,*S*)-2,4-pentanediol.

Thus, the preparation of TriMe–NAPhePHOS, **5**, affords a new example of the synthesis of unsymmetric biaryl–diphosphines based on the diastereoselective, copper mediated, biaryl coupling reaction.

2.2. Ruthenium promoted hydrogenation reactions

With the unsymmetric ligands (*R*)-MeO–NAPhePHOS[17] and (*R*)-TriMe–NAPhePHOS in hand, we started a systematic study of their catalytic properties, in comparison with those of the C_2-symmetric BINAP and MeO–BIPHEP ligands. We have at first expanded our previous work on ruthenium promoted hydrogenations and we have then considered rhodium promoted 1,4-addition reactions on model substrates.

Both unsymmetric NAPhePHOS diphosphines, namely (*R*)-**5** and (*R*)-MeO–NAPhePHOS, have been engaged in ruthenium promoted hydrogenations of carbonyl and olefin derivatives. The usual model β-ketoesters as well as other functionalised carbonyl derivatives have been used as substrates. The ruthenium catalyst has been generated from a mixture of (COD)Ru(2-Me-allyl)$_2$ and the diphosphine, by addition of 2 equiv of HBr, according to the usual procedure.[18] For comparative purposes, the same hydrogenation reactions have been performed in parallel experiments by using (*R*)-BINAP and (*R*)-MeO–BIPHEP. Results are reported in Table 1.

Ligand **5** affords very high enantiomeric excesses in the hydrogenation reactions where other atropoisomeric ligands also perform successfully (entries 1,3,7). In the case of more challenging substrates such as α-ketoesters (entry 8), olefins (entries 9 and 10) and halogenated β-ketoesters (entries 4–6) the enantioselectivity levels attained by the unsymmetrical ligands MeO–NAPhePHOS and TriMe–NAPhePHOS lie always between those given by BINAP and MeO–BIPHEP under analogous conditions.

In previous work, small but significant differences in the catalytic performances of atropoisomeric ligands have been tentatively related to small changes in the dihedral angles of the biaryl framework.[3,19] An analogous structure–enantioselectivity relationship could roughly hold here: the calculated dihedral angle values (θ) for MeO–NAPhePHOS and TriMe–NAPhePHOS in their ruthenium complexes (P*P)Ru(H)Br(MeCOCH$_2$CO$_2$Me) are of 77.2° and 77.0°, respectively[20] (Fig. 1).

These values are very close to each other and are intermediate between those of BINAP (79.5°) and MeO–BIPHEP (75.7°), which parallels the observed variations in enantiomeric excesses. Nevertheless, comparison of the four ligands based only on geometrical parameters can't be fully significant, as the four ligands don't represent a homogeneous series with respect to their electronic properties.

Evaluation of their relative basicity, as well as of their electron donating properties towards a transition metal, has been attempted by comparing the $^1J(^{31}P–^{77}Se)$ coupling constants of the diphosphine diselenides[21] and the ν (CO) stretching frequencies of their RhCl(CO)(P*P) complexes[21], respectively. Results are shown in Table 2.

The $^1J_{P–Se}$ coupling constants values for MeO–NAPhePHOS fit well with those of BINAP and MeO–BIPHEP, and suggest a similar basicity.

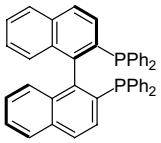
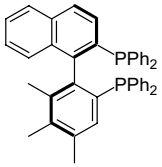
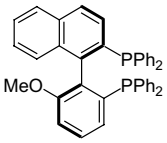
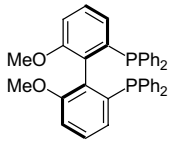
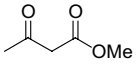
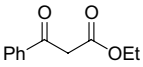
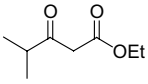
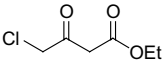
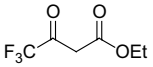
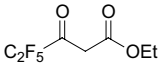
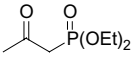
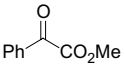
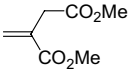
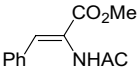
The observed IR stretching frequencies of the rhodium complexes of heterotopic diphosphines are probably not fully significant and can be hardly compared to those of BINAP and MeO–BIPHEP. This is mainly because mixtures of two isomeric, undistinguishable complexes are formed from unsymmetrical diphosphines and a single, averaged ν (CO) stretching frequency is observed. Moreover, the observed frequencies are out of the expected range, at lower frequency than that of the MeO–BIPHEP complex. The unsymmetrical nature of the ligands might affect the IR spectra and prevent the direct comparison with complexes containing C_2-symmetric ligands.

Finally, the observed trends in enantioselectivities seem to correlate roughly with the geometric features of these ligands, nevertheless the small but significant differences in their electronic properties could affect their behaviours as well.

2.3. Rhodium promoted 1,4-additions of boronic acids to enones

For a second series of catalytic tests we considered a C–C bond forming reaction, the rhodium promoted

Table 1. Hydrogenation of functionalised carbonyl and olefin derivatives by ruthenium–diphosphine complexes

Entry	Substrate	Conditions	Ee (config)				
							
1		4 bar, 50 °C, 24 h, MeOH	99	99	99	99	(*R*)
2		10 bar, 80 °C, 24 h, EtOH	90	93	92	97	(*S*)
3		4 bar, 50 °C, 24 h, EtOH	98	98	99	99	(*S*)
4		10 bar, 110 °C, 3 h, EtOH	90	86	83	78	(*S*)
5		10 bar, 110 °C, 1 h, EtOH	25	32	32	42	(*S*)
6		10 bar, 110 °C, 1 h, EtOH	45	48	51	58	(*S*)
7		10 bar, 50 °C, 24 h, EtOH	99	99	99	99	(*R*)
8		20 bar, 50 °C, 24 h, MeOH	72	85	75	90	(*R*)
9		4 bar, 50 °C, 24 h, MeOH	89	90	89	90	(*S*)
10		10 bar, 50 °C, 24 h, EtOH	75	70	69	68	(*R*)

Reactions were conducted on a 1 mmol scale, using 1 mol% of in situ prepared $RuBr_2$[(*R*)-ligand] as catalyst. All conversions were quantitative, according to ^1H NMR spectroscopy. Enantiomeric excesses (ee) were determined by chiral liquid and gas chromatography.

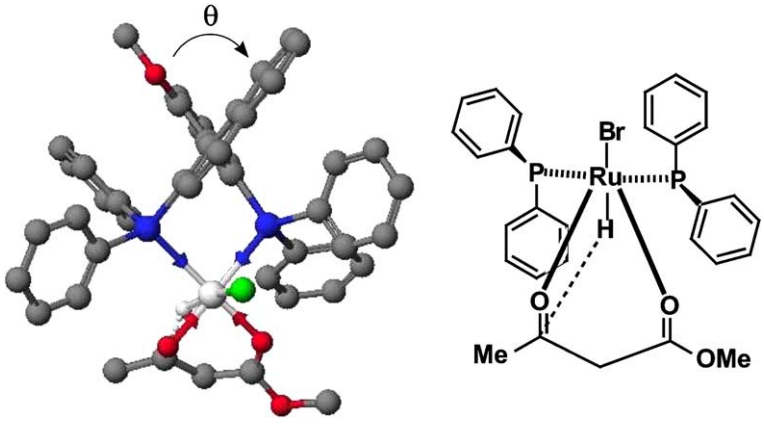
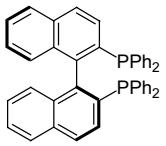
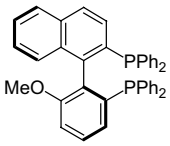
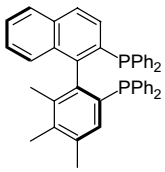
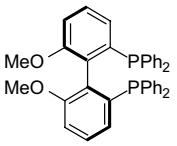


Figure 1. CAChe MM2 representation of the (MeO–NAPhePHOS)Ru(H)Br-($MeCOCH_2CO_2Me$) complex (unsymmetric atropisomeric biaryl backbone not represented for clarity, blue = P, red = O, green = Br, white = Ru and H, grey = C).

1,4-addition of boronic acids to unsaturated ketones.[22] As shown in the pioneering work of Hayashi and co-workers,[23] atropisomeric diphosphines behave as highly efficient chiral auxiliaries in these reactions.

Table 2. $^{1}J(^{31}P–^{77}Se)$ coupling values in diphosphines diselenides. Carbonyl stretching frequencies of RhCl(CO)(P*P) complexes

				
$^{1}J(^{31}P–^{77}Se)$ (Hz)	738	739; 742	723; 736	742
ν (CO) (cm^{-1})	2016	2009	2011	2014

Cyclohexenone and 3-nonen-2-one was reacted with arylboronic acids in standard conditions, by using a dioxane/H_2O mixture as the solvent and 3% of the rhodium complex Rh(acac)$(C_2H_4)_2$ as the catalyst precursor (Scheme 4). The rhodium-phosphine complexes were formed in situ by using the (*S*) configured ligands. Results are shown in Table 3.

Results in Table 3 are issued from parallel screening of the four ligands. For comparison, literature data (ees and isolated yields) are given in brackets. Conversion rates and enantiomeric excesses obtained with the unsymmetric ligands are fully comparable to those obtained with BINAP and MeO–BIPHEP in analogous conditions. This shows that the C_2-symmetry of the chiral diphosphine is not a prerequisite in these reactions and that diphosphines with unsymmetric biaryl framework are well suited ligands. This is in agreement with the Hayashi's mechanism[24] and stereochemical model where the diphosphine is supposed to chelate the metal in the key intermediate of the catalytic cycle (Fig. 2).

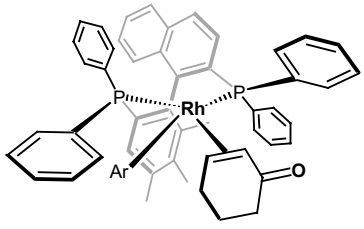


Figure 2. Key intermediate in the catalytic cycle of the rhodium-(*S*)-TriMe-NAPhePHOS promoted 1,4-addition reactions, according to the Hayashi's stereochemical model.

The chiral discrimination should come mainly from the three dimensional arrangement of the phenyl groups bound to phosphorus and the exact nature of the biaryl moiety hardly affects the stereochemical course of these reactions. These preliminary data do not exclude that more pronounced effects of the biaryl moieties on the enantioselectivity could be evidenced by comparing atropisomeric diphosphines with stereoelectronic properties markedly different from each other.

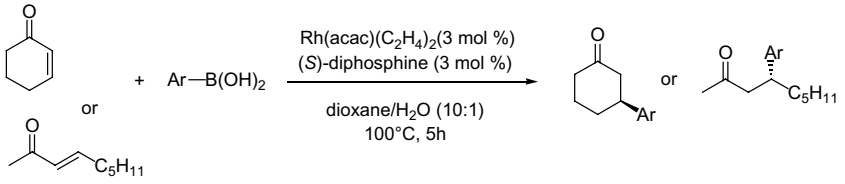
3. Conclusion

Finally, these preliminary catalytic tests show that the new ligand **5** is an efficient, unsymmetric atropisomeric diphosphine, whose catalytic properties in ruthenium promoted hydrogenations and rhodium catalysed 1,4-addition reactions are fully comparable to those of the reference ligands BINAP and MeO–BIPHEP. Fine-tuning of the reaction conditions, including the choice of the catalyst precursors, is beyond the objectives of the present preliminary work. It will be performed in the future, on selected and synthetically relevant substrates.

4. Experimental section

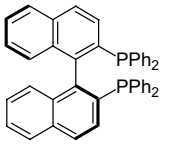
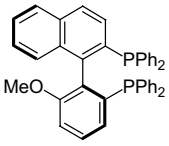
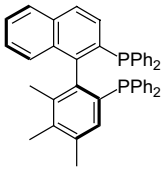
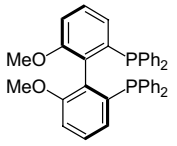
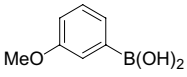
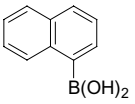
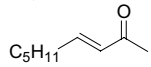
4.1. General methods

NMR spectra were recorded on a Bruker AC 200 (at 50 MHz for ^{13}C), on a Bruker AC 300 (at 75 MHz for ^{13}C) or on a Bruker Avance 400 (at 100 MHz for ^{13}C, at 162 MHz for ^{31}P, at 376 MHz for ^{19}F). Chemical shifts (δ) are reported in ppm downfield relative to external Me_4Si, H_3PO_4 (85%) or $CFCl_3$ (1% in $CDCl_3$). Mass spectra were recorded on a Ribermag instrument. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Melting points (mp) were determined on a Kofler melting point apparatus. Enantiomeric excesses



Scheme 4. Rhodium/diphosphine promoted 1,4-additions of boronic acids to unsaturated ketones.

Table 3. Asymmetric 1,4-addition of $ArB(OH)_2$ to enones catalyzed by diphosphine–rhodium complexes

Substrates		 (%) Ee (conv.)	 (%) Ee (conv.)	 (%) Ee (conv.)	 (%) Ee (conv.)
	$PhB(OH)_2$	98 (95) [97 (64)][23]	98 (95)	98 (95)	98 (97)
		96 (98) [96 (97)][23]	95 (98)	98 (96)	96 (98)
		98 (50)	96 (48)	96 (46)	97 (45)
	$PhB(OH)_2$	90 (98) [92 (88)][23]	88 (97)	87 (96)	87 (98)

Reactions were conducted on a 0.4 mmol scale, using 3 mol% of $Rh(acac)(C_2H_4)_2$ as catalyst. Reactions were performed in dioxane/water (10:1) at 100 °C, for 5 h. Conversions were measured by ^1H NMR spectroscopy. Enantiomeric excesses (ee) were determined by chiral HPLC.

were determined by GC on a Lipodex A and Chirasil-L-Val capillary columns or by HPLC analyses on a Waters 600 system, using Daicel chiral columns. All reactions were carried out under an atmosphere of argon unless otherwise specified.

4.2. (2*S*,4*S*)-4-(α-Iodo-β-naphthyloxy)-2-(2-bromo-3,4,5-trimethylphenyloxy)pentane 2

Has been prepared by two successive Mitsunobu's reactions. The first step of the synthesis as well as spectral data for (2*R*,4*S*)-4-(α-iodo-β-naphthyloxy)-2-pentanol **1** have been reported previously. 2-Bromo-3,4,5-trimethylphenol[25] has been obtained in 95% yield by bromination of the corresponding phenol with *N*-bromosuccinimide in DMF at 0 °C. It was engaged then with **1** in the second Mitsunobu-type reaction: a THF solution (200 mL) containing 2-bromo-3,4,5-trimethylphenol (10.1 g, 47 mmol) and diisopropylazodicarboxylate (9 mL, 56 mmol) was cooled to 5 °C. A solution of alcohol **1** (16.7 g, 47 mmol) and PPh_3 (14.7 g, 56 mmol) in THF was then added slowly. The mixture was stirred at room temperature for 24 h. After evaporation of the solvent, cyclohexane (200 mL) was poured into the residue. The insoluble by-products were removed by filtration and the residue was purified by chromatography on a silica gel column with cyclohexane/ethyl acetate (90:10 mixture) as the eluent ($R_f = 0.8$). The bis-ether **2** was isolated in 90% yield (23 g) as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.40$ (d, $J = 6.2$ Hz, Me), 1.46 (d, $J = 6.2$ Hz, Me), 1.78 (s, Me), 1.82 (s, Me), 2.1 (m, 2H, CH_2), 2.28 (s, Me), 4.7–4.8 (m, 1H, CH–O), 4.8–4.9 (m, 1H, CH–O), 6.34 (s, 1H), 6.98 (d, $J = 9.0$ Hz, 1H), 7.3–7.6 (4H), 8.8 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 15.8$ (Me), 20.3 (Me), 20.6 (Me), 20.8 (Me), 21.0 (Me), 45.3 (CH_2), 73.4 (CH–O), 73.8 (CH–O), 89.5 (C-I), 113.7 (C–Br), 114.8 ($CH_{ortho\text{-}O}$), 115.4 ($CH_{ortho\text{-}O}$), 124.0, 127.7, 127.9, 128.5 (C), 129.7, 129.8, 131.2, 135.5 (C), 135.7 (C), 136.5 (C), 152.1 (C–O), 155.5 (C–O) ppm. MS (EI) m/z (^{81}Br, %): 554 (M, 17%), 270 (53%), 41 (100%). Anal. Calcd for $C_{24}H_{26}BrIO_2$: C, 52.10; H, 4.74. Found: C, 52.26, H, 4.66. $[\alpha]_D = +107$ (c 1, $CHCl_3$).

4.3. Synthesis of (*R*,*S*,*S*)-3 via oxidative coupling of (*S*,*S*)-2

The dihalogenated substrate **2** (19.5 g, 35 mmol) was dissolved in anhydrous THF (200 mL) and the solution cooled to −78 °C. An excess *sec*-BuLi (108 mL, 1.3 M solution in hexane) was added dropwise and the reaction mixture was stirred at −78 °C for 1 h. Then, CuCN (3.2 g, 39 mmol) was added and the reaction mixture was stirred vigorously for about 2 h at the same temperature. Dry oxygen was bubbled through the solution for 2 h at −78 °C. After warming to room temperature, the reaction mixture was hydrolyzed with a saturated solution of aqueous ammonium chloride. The organic phase was extracted with diethyl ether and dried over $MgSO_4$. The final product was purified by column chromatography with cyclohexane/ethyl acetate (85:15 mixture) as eluent ($R_f = 0.4$). The macrocyclic ether **3** was thus obtained as a single diastereoisomer in 70% yield (8.9 g), as a colourless solid. Mp 55 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (d, $J = 6.5$ Hz, Me), 1.42 (d, $J = 6.4$ Hz, Me), 1.72 (m, AB, $J_{AB} = 15.3$ Hz, $J = 4.4$ Hz, $J = 2.8$ Hz, 1H, CH_2), 1.8–2.0 (m, 1H, CH_2), 1.91 (s, Me), 2.23 (s, Me), 2.37 (s, Me), 4.6 (m, 2H, CH–O), 6.90 (s, 1H), 7.3–7.4 (4H), 7.8 (2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 15.6$ (Me), 18.3 (Me), 21.0 (Me), 22.2 (Me), 22.8 (Me), 41.5 (CH_2), 74.8 (CH–O), 75.4 (CH–O), 117.4 ($CH_{ortho\text{-}O}$), 119.1 ($CH_{ortho\text{-}O}$), 123.8, 125.5 (C), 125.9, 126.1, 126.2

(C), 128.0, 128.7, 129.4 (C), 130.2 (C), 133.2 (C), 136.4 (C), 136.5 (C), 154.4 (C–O), 155.0 (C–O) ppm. MS (EI) m/z (%): 346 (M, 100%), 278 (87%). Anal. Calcd for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56. Found: C, 82.81; H, 7.57. $[\alpha]_D = -120$ (c 1, $CHCl_3$).

4.4. (*R*)-5,6-Benzo-4′,5′,6′-trimethyl-2,2′-biphenol 4

A solution of boron tribromide in CH_2Cl_2 (12 mL, 1 M solution) was added to a cooled solution (0 °C) of **3** (1.4 g, 4 mmol) in CH_2Cl_2 (10 mL). After stirring for 3 h at 0 °C, an aqueous solution of HCl (20 mL, 10% solution) was added at the same temperature. Extraction of the organic phase with ethyl acetate, drying over $MgSO_4$ and purification by column chromatography with cyclohexane/ethyl acetate (70:30) as the eluent gave **4** as a colourless solid (81% yield, 890 mg). The enantiomeric purity was determined by HPLC analysis: Chiralcel OD-H column, flow rate:1 mL/min, eluent: hexane/propan-2-ol (99:1), detection at 254 nm, retention times 35.1 min (*R*) and 43.0 min (*S*), ee >99%. Mp 184 °C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.89$ (s, Me), 2.20 (s, Me), 2.37 (s, Me), 4.4 (m, 1H, OH), 5.1 (m, 1H, OH), 6.83 (s, 1H), 7.2–7.4 (4H), 7.8 (1H), 7.88 (d, $J = 9.1$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 15.4$ (Me), 17.0 (Me), 21.0 (Me), 113.4 ($C_{ortho\text{-}O}$), 114.8 ($CH_{ortho\text{-}O}$), 115.6 ($C_{ortho\text{-}O}$), 117.4 ($CH_{ortho\text{-}O}$), 123.8, 124.0, 127.2, 128.0 (C), 128.3, 129.2 (C), 130.7, 133.1 (C), 137.6 (C), 139.1 (C), 151.8 (C–O), 152.0 (C–O) ppm. MS (DCI/NH_3) m/z (%): 286 (M + NH_4, 100%), 279 (M + H, 87%). Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 79.09; H, 6.64. $[\alpha]_D = +24$ (c 1, $CHCl_3$).

4.5. (*R*)-5,6-Benzo-2,2′-bis(diphenylphosphino)-4′,5′,6′-trimethylbiphenyl 5

The bis-triflate of **4** was prepared by adding slowly a solution of trifluoromethanesulfonic anhydride (9.75 mmol) in CH_2Cl_2 (65 mL) to a cooled solution containing diol **4** (0.90 g, 3.2 mmol) and pyridine (0.79 mL, 9.75 mmol) in CH_2Cl_2 (65 mL). After the addition was complete the reaction mixture was allowed to warm slowly to room temperature and stirred for 16 h. After evaporation of the solvent, the final product was purified by filtration on a short neutral alumina column with cyclohexane/ethyl acetate (90:10 mixture) as the eluent ($R_f = 0.7$). The bis-triflate of **4** was obtained in 95% yield as a white solid. Mp 135 °C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.97$ (s, Me), 2.31 (s, Me), 2.46 (s, Me), 7.19 (s, 1H), 7.4–7.6 (4H), 7.97 (dd, $J = 8$ Hz, $J = 1$Hz, 1H), 8.04 (d, $J = 9.3$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 15.8$ (Me), 18.1 (Me), 20.9 (Me), 119.0, 119.6, 123.4 (C), 125.7 (C), 126.3, 127.0, 127.8, 128.3, 131.2, 132.3 (C), 132.7 (C), 136.2 (C), 139.2 (C), 139.4 (C), 144.8 (C–O), 145.1 (C–O) ppm. MS (EI) m/z (%): 542 (M, 20%), 276 (40%), 260 (50%), 69 (100%).

A solution of $NiCl_2$ (dppe) (160 mg, 0.3 mmol) in anhydrous DMF (5 mL) was degassed. $HPPh_2$ (150 μL, 0.87 mmol) was added and the mixture was heated at 100 °C for 45 min. A degassed solution containing the bis-triflate of **4** (0.82 g, 1.5 mmol) and DABCO (0.68 g, 6.0 mmol) in DMF (10 mL) was added to the nickel solution. The mixture was heated at 100 °C and further portions of $HPPh_2$ (150 μL for each portion; total amount of $HPPh_2 = 3.5$ mmol) were added after 1, 3, and 8 h. Heating was maintained for further 3 days. After evaporation of the solvent, the final product was purified by flash chromatography on silica gel with a cyclohexane/ethyl acetate gradient (from 95:5 to 80:20 mixtures) as eluent. The diphosphine **5** and the corresponding monoxides **6** and **7** were obtained in a total 72% yield.

4.5.1. Diphosphine 5. White solid. Mp 85–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.34$ (s, Me), 2.12 (s, Me), 2.29 (s, Me), 6.89–7.32 (m, 22H), 7.74 (d, $J = 8.8$ Hz, 1H), 7.77 (d, $J = 8.8$ Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$) (selected data): $\delta = 17.6$ (Me), 21.2 (Me), 27.0 (Me), 143.0 (C, dd, $J = 28.8$, Hz, $J = 10.5$ Hz), 147.0 (C, dd, $J = 30.7$ Hz, $J = 9.7$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = -14.0$ and -13.8 ($J_{AB} = 19.6$ Hz); MS (DCI/NH_3) m/z (%): 615 ($[M + H]^+$, 100%); HRMS-DCI/NH_3: $[M + H]^+$ calcd for $C_{43}H_{36}P_2$: 615.2371; found: 615.2363; $[\alpha]_D = +43$ (c 1, $CHCl_3$).

4.5.2. Diphosphine oxide 6 or 7. White solid. Mp 102–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.01$ (s, Me), 2.09 (s, Me), 2.32 (s, Me), 6.90–7.69 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) (selected data): $\delta = 16.2$ (Me), 16.7 (Me), 21.1 (Me); ^{31}P NMR (121 MHz, $CDCl_3$): $\delta = -15.0$ and 26.9.

4.5.3. Diphosphine oxide 6 or 7. White solid. Mp 108–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.47$ (s, Me), 1.98 (s, Me), 2.19 (s, Me), 6.70–7.80 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) (selected data): $\delta = 15.8$ (Me), 17.9 (Me), 30.2 (Me); ^{31}P NMR (121 MHz, $CDCl_3$): $\delta = -15.4$ and 27.9.

4.6. Reduction of the phosphine oxides 6 and 7

To a solution of the two phosphine oxides **6** and **7** (642 mg, 1.018 mmol) in dry xylene (7 mL) were added *n*-tributylamine (2.91 mL, 12.22 mmol) and trichlorosilane (1.03 mL, 10.18 mmol). The resulting mixture was heated at 140 °C overnight. After cooling to room temperature, 10 mL of degassed 1 N aqueous HCl were added dropwise and the mixture was stirred for 30 min. Dry CH_2Cl_2 (30 mL) was then added, the organic layer was washed with degassed 4 N aqueous NaOH (10 mL), degassed distilled water (10 mL), degassed brine (10 mL) and concentrated under vacuum. The crude product was purified by column chromatography with degassed cyclohexane/ethyl acetate (70:30) mixture as eluent to afford **5** in 97% yield (610 mg) as a white solid.

4.7. Diphosphine selenides

To a mixture of a diphosphine (0.03 mmol) and selenium powder (50 mg, excess) was added degassed chloroform (2 mL). The mixture was stirred and heated at reflux for 5 h and then cooled to room temperature. After filtration on Celite eluting with chloroform, the solvents were removed under reduced pressure and a yellow pale solid was obtained.

TriMe–NAPhePHOS selenide: ^{31}P NMR ($CDCl_3$) $\delta = 33.7$ and 37.3 ppm

MeO–NAPhePHOS selenide: ^{31}P NMR ($CDCl_3$) $\delta = 33.6$ and 34.7 ppm

4.8. RhCl(CO)(P*P)] complexes

To a mixture of $[ClRh(CO)_2]_2$ (0.03 mmol) and a diphosphine ligand (0.06 mmol) was added degassed CH_2Cl_2 (1.5 mL). The mixture was stirred at room temperature for 1 h. The solvents were removed under reduced pressure and an orange crystalline solid was obtained.

TriMe–NAPhePHOS gave a 1:1 mixture of two isomeric complexes. Complex A (tentative assignment): ^{31}P NMR ($CDCl_3$) at $\delta = 23.2$ ($J_{P-Rh} = 128$ Hz, $J_{P-P} = 45$ Hz), 45.0 ($J_{P-Rh} = 162$ Hz). Complex B (tentative assignment): ^{31}P NMR ($CDCl_3$) at $\delta = 24.4$ ($J_{P-Rh} = 129$ Hz, $J_{P-P} = 45$ Hz), 46.1 ($J_{P-Rh} = 164$ Hz).

The ^{31}P NMR spectrum of the MeO–NAPhePHOS-rhodium complex showed broad signals at about 24 and 44 ppm.

4.9. Computational methods

The molecular geometries of ruthenium complexes incorporating diphosphine ligands were optimized with the molecular mechanics program CAChe (Computer Aided Chemistry), using the force field parameters MM2. Calculation type: structure optimization, optimization method: conjugate gradient for no more than 3000 updates or until convergence to 10^{-4} kcal mol^{-1}.

4.10. Asymmetric hydrogenation. Typical procedure

Hydrogenation experiments were performed in a glass tube, under magnetic stirring. All reactions have been made at a 1 mmol scale, with 1% ruthenium catalyst, which was prepared from (COD)Ru(2-methylallyl)$_2$ (3.2 mg) and the chiral diphosphine **5** (7.4 mg, 1.2 equiv), by addition of 2.2 equiv of aqueous HBr (0.16–0.18 M) in acetone. After evaporation of the solvent, the crude residue was taken up in degassed MeOH (2 mL) or EtOH (2 mL), substrate was added and the glass tube was placed in a stainless steel autoclave, under H_2 at a given pressure and temperature (see Table 1). In parallel experiments several glass tubes were introduced in the same autoclave. Conversions were determined by ^1H NMR. Enantiomeric excesses and absolute configurations were determined by GC or HPLC, by comparison with known samples.

Methyl 3-hydroxybutyrate. *GC analysis*: Lipodex A column, flow 1 mL/min, initial temperature 35 °C (30 min), rate 1 °C/min, final temperature 100 °C. Retention times 45.3 (*S*), 48.0 (*R*).

Ethyl 3-hydroxy-3-phenylpropionate. *GC analysis*: Lipodex A column, flow 1 mL/min, temperature 110 °C. Retention times 74.0 (*S*), 75.4 (*R*).

Ethyl 3-hydroxy-4-methylvalerate. GC analysis: Lipodex A column, flow 0.5 mL/min, initial temperature 40 °C (15 min), rate 0.5 °C/min, final temperature 70 °C. Retention times 93.4 (*S*), 94.9 (*R*).

Ethyl 4-chloro-3-hydroxybutyrate. *GC analysis*: Lipodex A column, flow 0.5 mL/min, temperature 70 °C. Retention times 74.5 (*S*), 77.8 (*R*).

Ethyl 4,4,4-trifluoro-3-hydroxypropionate. *GC analysis*: Lipodex A column, flow 1 mL/min, initial temperature 50 °C (15 min), rate 2 °C/min, final temperature 100 °C. Retention times 30.8 (*S*), 31.1 (*R*).

Ethyl 4,4,5,5,5-pentafluoro-3-hydroxypropionate. *GC analysis*: Lipodex A column, flow: 0.5 mL/min, initial temperature 40 °C (45 min), rate 0.5 °C/min, final temperature 90 °C. Retention times 82.3 (*R*), 83.4 (*S*).

Diethyl 2-hydroxypropylphosphonate. *GC analysis*: Chiralsil-L-Val column, flow 1.4 mL/min, temperature 110 °C. Retention times 56.2 (*R*), 58.8 (*S*).

Ethyl 2-hydroxy-3-méthylbutyrate. *GC analysis*: Lipodex A column, flow 1 mL/min, temperature 45 °C. retention times 39.3 (*S*), 40.2 (*R*).

Methyl mandelate. *GC analysis*: Lipodex A column, flow 1 mL/min, temperature 100 °C. retention times 31.2 (*S*), 33.3 (*R*).

Dimethyl succinate. *HPLC analysis*: Chiralcel OD-H column, eluent hexane/propan-2-ol (98:2), flow 0.8 mL/min, $\lambda = 215$ nm. Retention times 10.5 (*S*), 20.8 (*R*).

N-Acetamidophenylalanine methyl ester. *HPLC analysis*: Chiralcel OD-H column, eluent hexane/propan-2-ol (90:10), flow 1 mL/min, $\lambda = 254$ nm. Retention times 10.8 (*S*), 13.4 (*R*).

4.11. Rhodium promoted 1,4-additions of boronic acids to unsaturated ketones: typical procedure

To a mixture of degassed Rh(acac)$(C_2H_4)_2$ (3 mol %), a diphosphine ligand (3.3 mol %) and arylboronic acid (5 equiv) at room temperature were successively added

dioxane (1 mL), water (0.1 mL) and the enone substrate (0.4 mmol). The homogeneous mixture was heated at 100 °C for 5 h and then cooled to room temperature. After filtration on Celite (ethyl acetate), the organic layer was washed with saturated aqueous $NaHCO_3$ and brine. It was dried then over $MgSO_4$ and evaporated under reduced pressure. Chromatography over silica gel (cyclohexane/AcOEt = 90:10) afforded the corresponding 1,4-addition product. Enantiomeric excesses were determined by HPLC analysis.

3-Phenylcyclohexanone. HPLC analysis: Chiralpak AS-H column, eluent hexane/propan-2-ol (98:2), flow 1.0 mL/min, $\lambda = 215$ nm. Retention times 18.6 (*R*), 20.8 (*S*).

4-Phenylnonan-2-one. *HPLC analysis*: Chiralcel OJ column, eluent hexane/propan-2-ol (99:1), flow 1.0 mL/min, $\lambda = 215$ nm. Retention times 8.1 and 8.7.

3-(3-Methoxyphenyl)cyclohexanone. *HPLC analysis*: Chiralcel OJ column, eluent hexane/propan-2-ol (90:10), flow 1.0 mL/min, $\lambda = 215$ nm. Retention times 13.7 and 15.6.

3-(1-Naphtyl)cyclohexanone. *HPLC analysis*: Chiralpak AD column, eluent hexane/propan-2-ol (95/5), flow 1.0 mL/min, $\lambda = 215$ nm. Retention times 10.7 and 13.8.

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