Asymmetric Hydrogenation

# Difluorphos, an Electron-Poor Diphosphane: A Good Match Between Electronic and Steric Features**

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The design and synthesis of new chiral ligands, which display high activity and enantioselectivity, is still a significant challenge in the development of transition-metal-catalyzed asymmetric reactions. In recent years, chelating diphosphanes supported by an atropisomeric scaffold, have proved to be among the most active, selective and versatile ligands in this area.[1] Leading diphosphanes such as binap[2] and more recently MeO-biphep[3] have shown excellent results, especially in the field of ruthenium-mediated asymmetric hydrogenation.[4] Many research groups have devoted their efforts toward the discovery of new efficient atropisomeric ligands[5] with unusual stereoelectronic profiles. Both the aryl phosphorus substituents and the biaryl backbone are tunable parts in this family of ligands (Figure 1). Replacing the phenyl

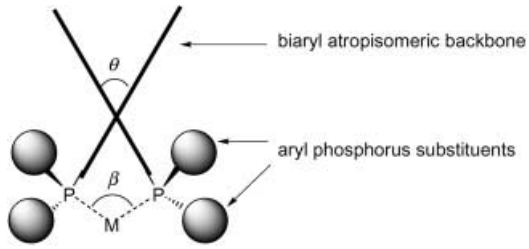


***Figure 1.*** General stereoelectronic tunable features of a $C_2$-symmetric atropisomeric diphosphane. M = transition metal center, $\beta$ = bite angle, $\theta$ = dihedral angle.

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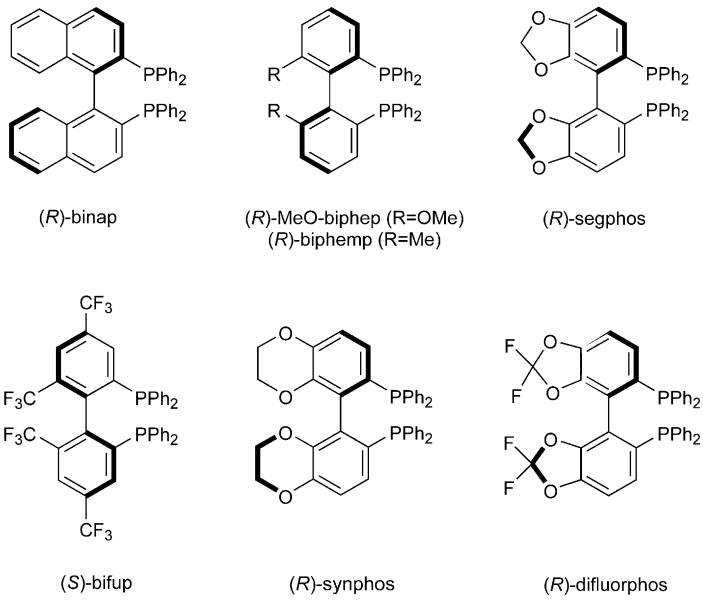
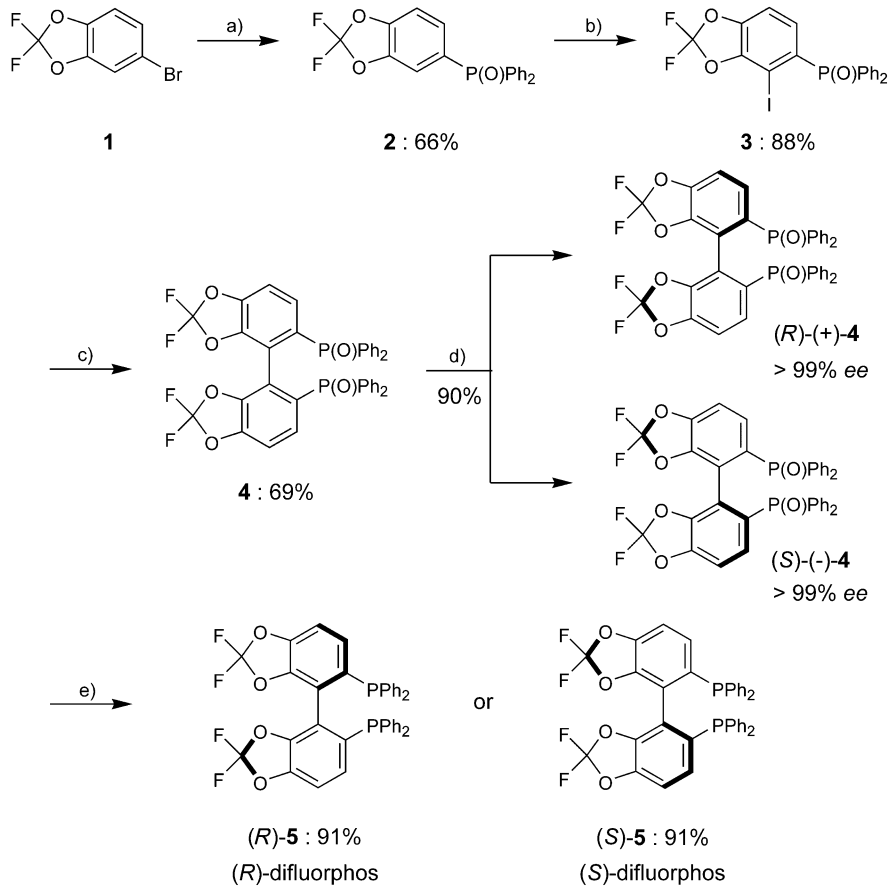
phosphorus substituents by bulkier aromatics (*p*-Tol- binap,[6] DTBM-segphos[7]), electronically modified substituents (*p*-F-binap, Cy-binap)[6] or heteroaromatics (α-furyl-MeO-biphep[3c]), can modify the steric hindrance around the metal and/or the electronic properties of the phosphorus centers and create more selective ligands. Structural variations of the biaryl backbone are at the origin of the wide diversity in the field of atropisomeric diphosphanes. The steric design of the biaryl core has been extensively explored: Cn-TunaPhos[8] by Zhang and co-workers, segphos[7] by Saito and co-workers, and recently synphos[9] by our group have been specially targeted because they displayed a (tunable or) narrow dihedral angle, a steric condition postulated as essential to obtain good enantioselectivities in asymmetric hydrogenation.[7b] However, the electronic design of atropisomeric diphosphanes has been less systematically studied: the more effective ligands designed to date bear an atropisomeric core, which is often electronically richer than that in binap[3,7–9] and there are only few examples of effective electrodeficient atropisomeric diphosphanes. Most of them are based on a biheteroaryl skeleton (binapFu,[10] tetraMe-bitianp[11]) and electron-poor biphenyl-based ligands have rarely displayed satisfactory enantioselectivities (bifup, fupmop).[12] Moreover, in the field of ruthenium-mediated enantioselective hydrogenation, electrodeficiency has sometimes been considered as a drawback for catalytic activity,[12,13] but its influence on enantioselectivity has rarely been underlined.

Following our interest in ligand design,[9a,14] we report herein the synthesis of a new atropisomeric diphosphane, based on a segphos-like backbone, which has a narrow dihedral angle and electron-withdrawing substituents, hereafter named difluorphos[9a] (Scheme 1). In addition, we describe studies regarding its steric and electronic features. Its performance in ruthenium-mediated asymmetric hydrogenation, compared to other electron-rich atropisomeric diphosphanes, has also been preliminary evaluated.

Our synthetic approach to enantiopure (*R*)- and (*S*)-[4,4′-bi(2,2-difluoro-1,3-benzodioxol)-5,5′-diyl]bis(diphenylphosphane) (**5**; difluorphos) is depicted in Scheme 2. Phosphorylation of commercially available **1** was through the organomagnesium formation, followed by the addition of chlorodiphenylphosphane oxide. Phosphane oxide **2** was obtained in 66% yield. *Ortho*-lithiation of **2** by LDA at −78°C and further iodination with $I_2$ furnished **3** in 88% yield. Iodide **3** was subjected to an Ullmann-type coupling[15] with copper in DMF at 130°C and afforded the bis(phosphane oxide) **4** in 69% yield. The optical resolution of (*RS*)-**4** was by chiral preparative HPLC using a Chirose C3 Column in 90% yield based on (*RS*)-**4**. (−)-**4** and (+)-**4** were enantiomerically pure (>99% *ee*) according to HPLC (Chiralpak AD column). Reduction of the resolved **4** was performed by heating with an excess of $HSiCl_3$ in xylene in the presence of tributylamine in 91% yields for (*R*)-**5** and (*S*)-**5** ((*R*)-difluorphos and (*S*)- difluorphos).[16] Subsequent oxidation of diphosphanes (*R*)-**5** and (*S*)-**5** with hydrogen




***Scheme 1.*** Typical diphosphane ligands




***Scheme 2.*** Reagents and conditions: a) Mg, THF, 60°C→RT; then $ClP(O)Ph_2$, 20°C; b) LDA, THF, −78°C, 2 h; then $I_2$, −78°C to RT; c) Cu, DMF, 130°C; d) Chiral preparative HPLC, Chirose C3 Column; e) $HSiCl_3$, $Bu_3N$, xylene, 140°C. LDA = lithium diisopropylamide.

peroxide showed that no racemization had occurred during the reduction process, in accord with the enantiomeric purities determined by HPLC. Therefore, both enantiomers of this new ligand were obtained on a multigram scale in five steps with an overall yield of 33%.

Having generated a new atropisomeric diphosphane, whose backbone was structurally close to existing electron-rich ligands (synphos or segphos), but with potentially different electronic properties, we performed a preliminary evaluation of its geometric and electronic profiles.

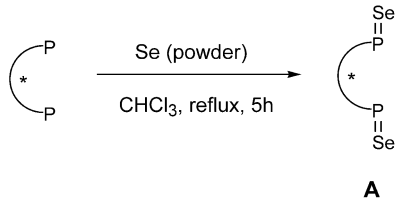
The quantification of steric properties of atropisomeric diphosphanes is conveniently achieved by measuring the dihedral angle ($\theta$) of the biaryl backbone. In transition-metal complexes, this parameter is geometrically related to the bite angle ($\beta$)[17] and controls directly the asymmetric spatial environment around the metal center (Figure 1). In asymmetric hydrogenation, the influence of $\theta$ on enantioselectivity has only recently been described by Zhang and co-workers,[8] Saito and co-workers[7b] and our group.[18] Based on steric considerations, but not on electronic properties, the narrowest dihedral angle seems to provide the highest selectivities. We used computer modeling to estimate the dihedral angle of difluorphos and five other atropisomeric diphosphanes, binap, biphemp, MeO-biphep, synphos and the closely related segphos (Scheme 1). We took particular care to model all ligands with the same Molecular Mechanics program[19] and parameter set,[20] so as to highlight a correct trend in dihedral angles. As expected, difluorphos and segphos have almost the same dihedral angle (67.6 and 67.2°, respectively), which is the narrowest of the series, followed by synphos (70.7°), MeO-biphep (72.3°), biphemp (74.5°), and then binap (86.2°). These results are in agreement with our previous results[18] and those obtained by Saito and co-workers on minimized structures of Ikariya-type ruthenium complexes.[7b] Therefore the original segphos-modified bi(difluorobenzodioxole) core gives difluorphos, a priori, ideal steric properties for asymmetric hydrogenation, but we expected its electronic profile to differ radically from usual diphosphanes.

A simple way of evaluating the σ-donor ability of a phosphane group is to measure the magnitude of $^1J_{P,Se}$ in the $^{77}Se$ isotopomer of the corresponding phosphane-selenide.[10,21] Allen and Taylor have reported[21a] that an increase in this coupling constant indicates an increase in the s character of the phosphorus lone-pair orbital (i.e., a less basic phosphane). To estimate the donor ability of phosphorus centers in difluorphos and compare it with other atropisomeric diphosphanes (Table 1), we prepared the corresponding diselenides **A** (Scheme 3) by simply treating

***Table 1:*** $^{31}P$–$^{77}Se$ coupling constants in compounds **A**.

| Entry | Diphosphane ligand | $^1J_{P,Se}$ in **A** [Hz] |
|---|---|---|
| 1 | binap | 738 |
| 2 | MeO-biphep | 742 |
| 3 | synphos | 740 |
| 4 | segphos[a] | 738 |
| 5 | difluorphos | 749 |
| 6 | $PPh_3$ | 732[21a] |

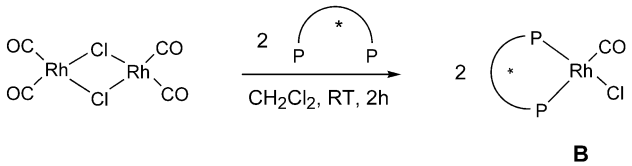
[a] (*R*)-segphos was prepared according to reported procedure.[7]




***Scheme 3.*** Synthesis of diphosphane selenides.

the diphosphanes with elemental selenium in refluxing chloroform. The value for binap (738 Hz, entry 1) is in good agreement with literature.[21a] Atropisomeric diphosphanes of entries 1–5 are less basic than triphenylphosphane (entry 6). Whereas binap, MeO-biphep, synphos, and segphos display equivalent σ-basicities ($^1J_{P,Se}$ around 740 Hz), difluorphos (749 Hz, entry 5) has a significantly lower σ-donor ability.

Electronic donor–acceptor properties of these diphosphanes have also been investigated by studying the carbonyl stretching frequencies of [RhCl(diphosphane)(CO)] complexes **B** which were prepared by the reaction of $[\{RhCl(CO)_2\}_2]$ with diphosphane ligands (Scheme 4).[22] The higher the carbonyl stretching frequency, the higher the π-acidic character of the diphosphane. Results are in Table 2.




***Scheme 4.*** Synthesis of [RhCl(diphosphane)(CO)] complexes **B**.

***Table 2:*** Carbonyl stretching frequencies of [RhCl(diphosphane)(CO)] complexes **B**.

| Diphosphane ligand | $\nu$(CO)[a] in **B** [$cm^{-1}$] |
|---|---|
| binap | 2017 |
| MeO-biphep | 2014 |
| synphos | 2012 |
| segphos[b] | 2016 |
| difluorphos | 2023 |

[a] in $CHCl_3$. [b] (*R*)-segphos was prepared according to the reported procedure.[7]

The five diphosphanes ordered by decreasing π acidity are as follows: difluorphos > binap and segphos > MeO-biphep > synphos. The electron-poor bi(difluorobenzodioxole) backbone of difluorphos is responsible for its higher π-back-donation ability, compared to nonfluorinated analogues, such as segphos or synphos.

Of the five ligands of this electronic comparative study, difluorphos is the poorest σ donor and the best π acceptor. Moreover, if we superimpose steric and electronic scales and line them up on binap (Figure 2), one can observe that oxygenated diphosphanes, such as MeO-biphep, segphos, or synphos, are systematically electron-richer than binap and

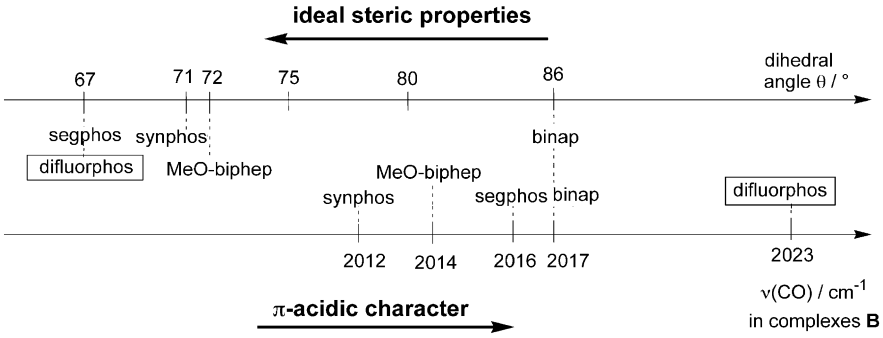
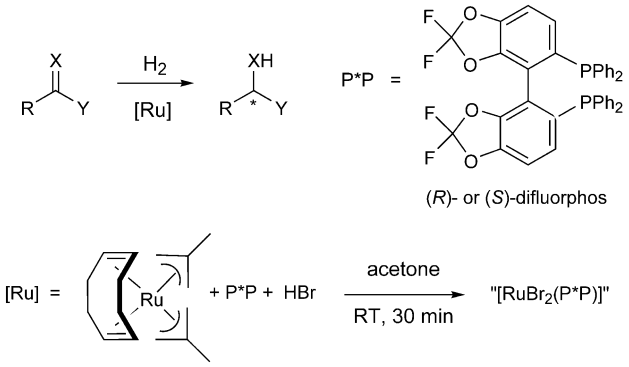



***Figure 2.*** Comparative steric and electronic scales of binap, MeO-biphep, synphos, segphos, and difluorphos.

have narrower dihedral angles. On the contrary, difluorphos does not follow the same trend and is placed at opposite ends of steric and electronic scales, with the narrowest dihedral angle and the most π-acidic character, which confers on it a totally unusual stereoelectronic profile.

To evaluate the performance of difluorphos in ruthenium-mediated asymmetric hydrogenation we followed our convenient procedure,[23] and prepared catalysts from $[(cod)Ru(\eta^3\text{-}(CH_2)_2CCH_3)_2]$ (cod = cyclooctadiene) and difluorphos by addition of a methanolic solution of HBr in acetone (Scheme 5). The hydrogenations were carried out on a 1 mmol scale using 1 mol% catalyst, in a stainless steel autoclave. The conversions were determined by $^1$H NMR spectroscopy and enantiomeric excesses of the products were determined by chiral GC (Table 3).

In all cases, complete conversion was obtained. The test substrate methyl acetoacetate was reduced in 99% *ee* using the [$RuBr_2$\{(*S*)-difluorphos\}] catalyst under 4 bar of hydrogen at 50°C (entry 1). We were pleased to notice that ethyl benzoylacetate and ethyl (4-fluoro)benzoylacetate were also reduced efficiently (10 bar, 80°C) to afford the corresponding β-hydroxy esters with 92 and 95% *ee*, respectively (entries 2 and 3). In our hands, using the same hydrogenation conditions, [$RuBr_2$\{(*R*)-binap\}] provided only 88% *ee* in the hydrogenation of ethyl benzoylacetate. Interestingly, the difluorphos ligand showed an unexpected efficiency in the Ru-catalyzed hydrogenation of ethyl 4-chloro-acetoacetate, a β-keto ester bearing a chelating substituent (entry 4). Under 10 bar hydrogen, at 110°C, ethyl (3*R*)-hydroxy-4-chloro-butyrate was obtained quantitatively in 97% *ee* using 1 mol% [$RuBr_2$\{(*S*)-difluorphos\}]. This result is in good agreement with work by the Noyori and Saito groups on other biphenyl

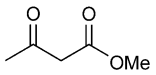
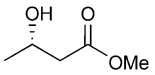
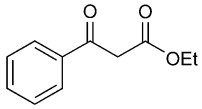
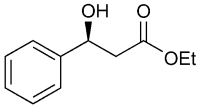
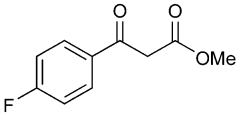
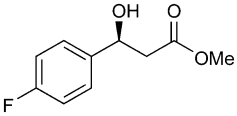
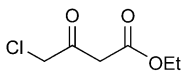
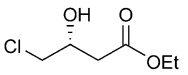



***Scheme 5.*** General procedure for ruthenium-mediated asymmetric hydrogenation reactions using difluorphos.

ligands, such as binap (97% *ee* using [$RuBr_2$\{(*S*)-binap\}] under 100 bar and 100°C)[24,4a] and segphos (98% *ee* using $[\{RuCl[(R)\text{-segphos}]\}_2(\mu\text{-}Cl)_3][NH_2Me_2]$ under 30 bar and 90°C).[7b]

These good results obtained with difluorphos in the hydrogenation of standard substrates encouraged us to investigate more carefully the hydrogenation of "tricky" substrates, especially fluorinated β-functionalized ketones.

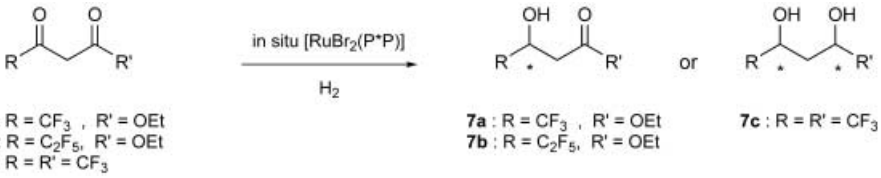
***Table 3:*** Hydrogenation results using the difluorphos ligand.

| Entry | Substrate[a] | Ligand[a] Config. | Solvent | $pH_2$ [bar] | *T* [°C] | *t* [h] | Product[b] | *ee*[c] [%] | Config. |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  | *S* | MeOH | 4 | 50 | 24 |  | 99 | *S* |
| 2 |  | *R* | EtOH | 10 | 80 | 24 |  | 92 | *S* |
| 3 |  | *R* | MeOH | 10 | 80 | 24 |  | 95 | *S* |
| 4 |  | *S* | EtOH | 10 | 110 | 3 |  | 97 | *R* |

[a] Reactions were conducted on a 1-mmol scale, using 1 mol% of in situ prepared[23] [$RuBr_2$\{(*R*)-or (*S*)-difluorphos\}] as catalyst. [b] All conversions were 100%, according to $^1$H NMR spectroscopy. [c] Enantiomeric excesses were determined by chiral gas chromatography (Lipodex A column).

We[25] and others[26] have already described low enantioselectivities in the ruthenium-mediated asymmetric hydrogenation of ethyl 4,4,4-trifluoroacetoacetate and ethyl pentafluoropropionylacetate using biphenyl atropisomeric diphosphanes, even at high temperature. Therefore we performed a comparative study between five diphosphanes in the asymmetric hydrogenation of substrates **6a–c** (Scheme 6). We conducted the hydrogenation reactions at least twice under strictly the same conditions for the five diphosphanes: hydrogen pressure, temperature, substrate concentration (0.5 M), substrate/catalyst ratio (S/C = 100; Table 4).




***Scheme 6.*** Asymmetric hydrogenation of fluorinated substrates. P*P = (*S*)-binap, (*S*)-MeO-biphep, (*S*)-synphos, (*R*)-segphos, or (*S*)-difluorphos.

***Table 4:*** Comparative study of difluorphos and other ligands in the ruthenium-catalyzed hydrogenation of fluorinated β-functionalized ketones.

| Substrate | Conditions[a] | *ee* [%][b] | | | | | Product Config. |
|---|---|---|---|---|---|---|---|
| | | binap | MeO-biphep | synphos | segphos[c] | difluorphos | |
| **6a** | 10 bar, 110 °C, 1 h, EtOH | 23 | 40 | 49 | 59 | 70 | *R* |
| **6b** | 10 bar, 110 °C, 1 h, EtOH | 44 | 57 | 63 | 76 | 81 | *R* |
| **6c** | 50 bar, 50 °C, 24 h, MeOH | 91 (*de* = 77 %) | 87 (*de* = 71 %) | 85 (*de* = 67 %) | 88 (*de* = 71 %) | 98 (*de* = 86 %) | *R*,*R* |

[a] Reactions were conducted on a 1-mmol scale, using 1 mol % of in situ prepared[23] [$RuBr_2${*S* ligand}] as catalyst. [b] All conversions were 100 %, according to $^1H$ and $^{19}F$ NMR spectroscopy. Enantiomeric and diastereomeric excesses were determined by chiral gas chromatography (Lipodex A column). [c] (*R*)-segphos was prepared according to the reported procedure.[7]

Note, for β-keto esters **6a** and **6b**, the enantiomeric excess is lineally related to the dihedral angle of the diphosphane: the narrower the dihedral angle ($\theta$(binap) > $\theta$(MeO-biphep) > $\theta$(synphos) > $\theta$(segphos) = $\theta$(difluorphos)), the better the enantioselectivities (*ee*(binap) < *ee*(MeO-biphep) < *ee*(synphos) < *ee*(segphos) < *ee*(difluorphos)). However, despite the geometric similarity between segphos and difluorphos, the latter provides the best enantiomeric excesses for the three substrates: β-hydroxy esters **7a** and **7b** were obtained in 70 and 81 % *ee*, respectively, and diol **7c** was obtained with very satisfactory diastereo- and enantioselectivity (86 % *de* and 98 % *ee* for the *R*,*R anti* diol). To our knowledge, this is the best reported *ee* values for the ruthenium-catalyzed hydrogenation of **6a**,[27] **6b** and **6c**[28] using biphenyl-based diphosphanes. In this particular case, the superiority of difluorphos over its nonfluorinated analogue segphos lies in the atypical combination of a narrow dihedral angle and a stronger electrodeficient character.

In summary, we have described an efficient synthesis of a new electrodeficient atropisomeric diphosphane, difluorphos. We have shown that its original stereoelectronic structure, based on a bi(difluorobenzodioxole) backbone, displayed a narrow dihedral angle combined with an unusual π-acidity. Comparison of difluorphos with other leading biphenyl-based ligands (binap, MeO-biphep, synphos and segphos) in ruthenium-mediated hydrogenation revealed that its electrodeficiency was crucial in obtaining high levels of enantioselection in the hydrogenation of challenging substrates. Theoretical and experimental studies are currently under investigation in order to rationalize the unusual behavior of difluorphos ligand in asymmetric catalysis.

## *Experimental Section*

Experimental procedures and characterization data for compounds **2**–**5**, **A**, and **B** are given in the Supporting Information.

Typical procedure for asymmetric hydrogenation: (*S*)-difluorphos (7.5 mg, 0.011 mmol) and [(cod)Ru($\eta^3$-$(CH_2)_2CCH_3)_2$] (3.2 mg, 0.01 mmol) were placed in a 10-mL flask, and degassed anhydrous acetone (1 mL) was added dropwise. A methanolic solution of HBr (122 μL, 0.18 M) was added dropwise to the suspension. The reaction mixture was stirred at room temperature for about 30 min and an orange suspension formed. The solvent was removed under vacuum. The orange solid residue was used without further purification as a catalyst for the hydrogenation reaction of the desired substrate (1 mmol) in MeOH or EtOH (2 mL). The reaction vessel was placed in a 500-mL stainless steel autoclave, which was adjusted at the desired pressure and warmed to the desired temperature for 24 h. The solvent was evaporated and the crude product was purified on a short pad of silica gel, eluting with cyclohexane:ethyl acetate (1:1). Conversion and enantiomeric excess were determined by $^1H$ NMR spectroscopy and chiral GC, respectively.

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**Keywords:** asymmetric catalysis · atropisomerism · fluorinated ligands · hydrogenation · ruthenium

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