Ligand Design

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Chiral Mixed Secondary Phosphine-Oxide–Phosphines: High-Performing and Easily Accessible Ligands for Asymmetric Hydrogenation**

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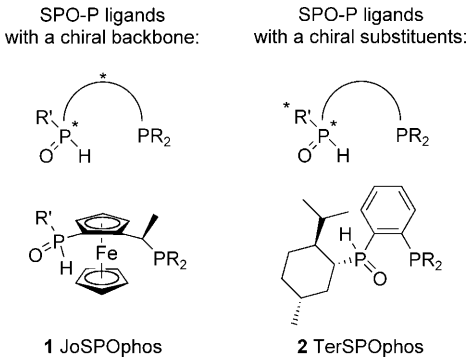
Dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday

Chiral diphosphines are the most frequently used ligands in asymmetric catalysis.[1] In contrast, chiral secondary phosphine oxides (SPOs) are little explored as ligands. While their chemical and physical properties are well known, their use in asymmetric catalysis is still in its infancy.[2]

SPOs are stable molecules which exist in equilibrium between two tautomeric forms:[3] the preferred pentavalent phosphine oxide and the trivalent phosphinous acid. When two different substituents are attached to the phosphorus atom, a configurationally stable, P-chiral group results which can coordinate to metals either through the phosphorus atom or through the oxygen atom.

To date, only a few examples of asymmetric catalytic reactions with chiral SPOs have been described.[2] Ph-(*t*Bu)P(O)H, a monodentate P-chiral SPO gave approximately 80% *ee* in the palladium-catalyzed allylic alkylation,[4] while over 90% *ee* was obtained with P-chiral diamino phosphine oxides.[5] In asymmetric hydrogenation, Rh and Ir complexes of monodentate chiral SPO ligands gave only moderately active and selective catalysts (*ee* values up to 85%).[2c,6]

We thought that these somewhat disappointing results might be due to an insufficient affinity of SPOs for Rh, Ir, or Ru centers, the typical metals used in asymmetric catalytic hydrogenations. Our idea was therefore to combine an SPO with a PR_2 substituent which should not only lead to stronger coordination to the metal center but also should give better defined complexes. To avoid cumbersome resolution procedures[2c,6,7] we used either a chiral backbone or a chiral substituent, so that the chiral SPO unit could be built up in diastereoselective reactions (Scheme 1).



Scheme 1. Concept and generic structures of SPO–P ligands.

Herein we present results for selected members of two SPO–P ligand families based on a chiral ferrocenyl backbone and a menthyl substituent, respectively (Scheme 1). The first approach leads to ligands structurally similar to the well known Josiphos[8] (therefore called JoSPOphos) while the second gives menthyl derivatives (called TerSPOphos since other terpene moieties are feasible). Both ligand families are modular, allowing the ligand properties to be tuned by the choice of the R and R′ groups. First tests showed that these novel ligands give excellent enantioselectivities and high turnover numbers for the hydrogenation of a variety of functionalized alkenes.

Two routes were developed for the preparation of the JoSPOphos ligands (Scheme 2). In route 1 the phosphine group was introduced before the SPO group, starting from (*R*)-*N*,*N*-dimethyl-1-[(*S*)-2-bromoferrocenyl]ethylamine (**3**), obtained by lithiation/bromination of the (*R*)-Ugi amine.[9] The dimethylamino group was exchanged for the desired PR_2 group to give ferrocenyl phosphine bromides **4** with retention of configuration. JoSPOphos ligands **1a–d** were obtained by treating **4a** or **4b** with BuLi at low temperature, subsequent addition of the chosen dichlorophosphine, and finally hydrolysis with water. Since surprisingly the SPO moiety withstood

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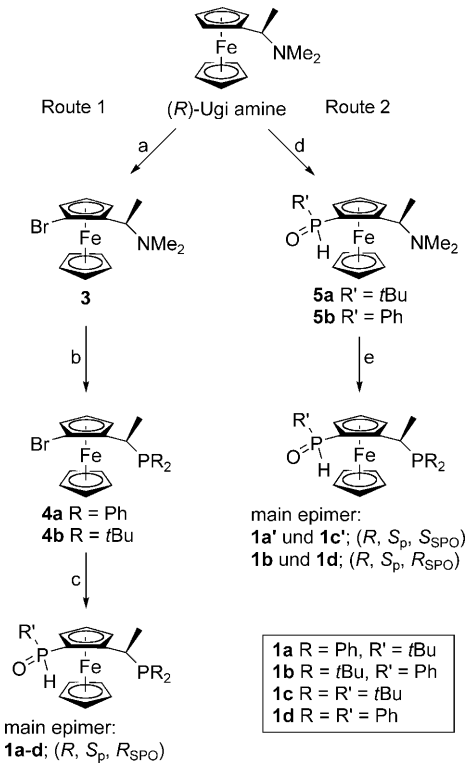
Supporting information for this article (detailed procedures for the ligand syntheses and for the hydrogenation experiments) is available on the WWW under http://dx.doi.org/10.1002/anie.201002225.

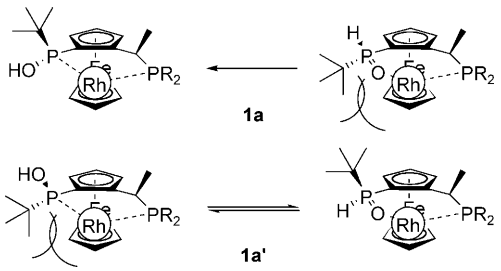


Scheme 2. Synthesis and absolute configuration of the JoSPOphos ligands **1a–d**. Reagents and conditions: a) 1. *s*BuLi, Et_2O, 2. $(BrF_2C)_2$ or $(BrCl_2C)_2$; b) HPR_2, AcOH; c) 1. *n*BuLi, TBME; 2. Cl_2PR'; 3. hydrolysis; d) 1. *s*BuLi, Et_2O; 2. Cl_2PR'; 3. hydrolysis; e) HPR_2, AcOH. TBME = *tert*-butyl methyl ether.

heating in acetic acid, the "reverse" procedure, that is, first the introduction of the SPO group to give **5**, and subsequent exchange of the NMe_2 moiety, was another option (route 2). In this way the lithiation/bromination step and the isolation of **3** could be avoided.

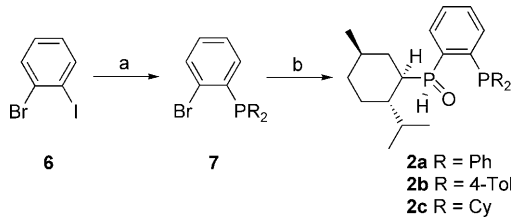
In both variants, the JoSPOphos ligands **1** were obtained in good yields with a diastereomeric ratio of typically around 10:1 and purified either by crystallization or by chromatography on silica gel. While the stereogenic carbon atom (*R*-configuration) and the ferrocene ring (S_p-configuration) had the same absolute configuration in both routes (controlled by the absolute configuration of the Ugi amine), the configuration of the SPO group depended on the nature of R′. With R′ = Ph (**1b** and **1d**), both routes yielded preferentially R_{SPO}. In contrast, for R′ = *t*Bu (**1a** and **1c**), route 1 gave R_{SPO} whereas route 2 gave mainly S_{SPO} isomers allowing the controlled preparation of either epimer. Variation of the hydrolysis conditions[10] in route 2 also gave access to a small sample of the S_{SPO} ligand **1b′**.

The absolute configuration of all the JoSPOphos ligands, as well as the coordination mode (P versus O coordination) were determined by single-crystal X-ray analysis of a rhodium norbornadiene (nbd) tetrafluoroborate complex of ligand (S_{SPO})-**1a′** and of a $ZnBr_2$ complex of ligand (R_{SPO})-**1b**.[11] As expected, the oxophilic zinc ion is coordinated to the oxygen atom in the phosphine oxide but the coordination behavior of rhodium is more subtle. Of particular interest was the comparison of ligands **1a** and **1a′** which differ only in the absolute configuration of the SPO moiety. The Rh complex of **1a** (prepared with $[Rh(nbd)_2]BF_4$) gave a ^{31}P NMR spectrum with two doublets of doublets at $\delta = 113.1$ ppm and $\delta = 58.4$ ppm (both $J_{RhP} = 165$ Hz, $J_{PP} = 35$ Hz), showing that the Rh center is coordinated to both phosphorus atoms. With ligand **1a′** a P,P complex giving rise to two doublets of doublets at $\delta = 132.3$ ppm and $\delta = 57.9$ ppm (both $J_{RhP} = 168$ Hz, $J_{PP} = 39$ Hz) as well as a P,O complex (PR_2: doublet of doublet at $\delta = 40.5$ ppm; $J_{RhP} = 174$ Hz, $J_{PP} = 2$ Hz; SPO: doublet at $\delta = 66.2$ ppm; $J_{PP} = 2$ Hz) was detected. We assume that the different behavior of **1a** and **1a′** is due to the steric interactions of the *tert*-butyl group of the SPO moiety and the ferrocenyl backbone (see Scheme 3).



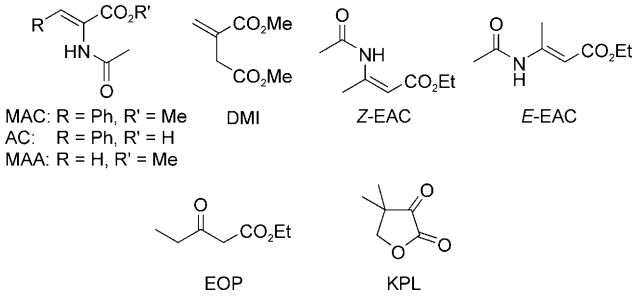
Scheme 3. Coordination modes of ligands **1a** and **1a′** with Rh.

The TerSPOphos ligands **2a–c** were prepared starting from 2-bromoiodobenzene (**6**) which was metallated and then treated with a chlorophosphine to give **7** (Scheme 4). Lithiation of **7** and reaction with dichloro[(−)-menthyl]phosphine[12] yielded the chlorophosphine intermediates which were hydrolyzed with 0.1 M NaOH to give the SPO–P ligands in good yields and with diastereomeric ratios of around 10:1. The pure ligands **2a–c** were obtained by recrystallization or column chromatography. A single-crystal X-ray analysis of a $ZnBr_2$ complex of ligand **2b** allowed the absolute configuration of the major epimer of **2a–c** to be assigned as (S_{SPO}).[11] Also in this case, the zinc ion coordinates to the oxygen atom.



Scheme 4. Synthesis of the TerSPOphos ligands **2a–c**. Reagents and conditions: a) 1. *i*PrMgCl, THF; 2. $ClPR_2$; b) 1. *n*BuLi, THF; 2. (L-menthyl)PCl_2; 3. hydrolysis.

The ligands were tested in hydrogenation experiments, using standard substrates (Scheme 5) to show the scope and limitations for their synthetic applications. Most tests were carried out with a Symyx HTS robot which uses plates with



Scheme 5. Test substrates for hydrogenation.

96 vials (for reaction conditions see Table 1). Selected hydrogenations at higher substrate to catalyst ratios (s/c) were carried out in 10–50 mL reactors.

Table 1: Enantioselectivities obtained with JoSPOphos and TerSPOphos in rhodium-catalyzed hydrogenations of six functionalized alkenes (see Scheme 5).[a]

Entry	Ligand	R (P)	R′ (SPO)	Config. SPO	MAC	AC	MAA	DMI	*Z*-EAC	*E*-EAC
1	**1a**	Ph	*t*Bu	*R*	+38[b]	**+98**[b]	+71[c]	**+95**[c,f]	+25[c,f]	**−96**[b,f])
2	**1a′**	Ph	*t*Bu	*S*	**−97**[b]	**−99**[b]	**−97**[b]	**−98**[b]	+61[c]	**+94**[c]
3	**1b**	*t*Bu	Ph	*R*	**+90**[b]	**+98**[b]	**+99**[d]	**+94**[c]	**−98**[c]	**−99**[c]
4	**1b′**	*t*Bu	Ph	*S*	–	–	–	−84[c]	−1[c]	+70[c]
5	**1c**	*t*Bu	*t*Bu	*R*	+75[b]	−11[b]	**+94**[c]	+19[c]	−51[c]	−58[b]
6	**1c′**	*t*Bu	*t*Bu	*S*	**−99**[b]	**−99**[b]	**−98**[b]	**−93**[c]	+76[b]	+76[b]
7	**1d**	Ph	Ph	*R*	+85[b]	**+98**[b]	**+93**[c]	**+99**[b]	−72[b]	**−90**[b]
8	**2a**	L-Men	Ph	*S*	–	–	**−95**[e]	–	–	–
9	**2b**	L-Men	4-Tol	*S*	**−96**[b]	**−99**[b]	**−98**[b]	**−98**[b]	+68[b]	**+94**[c]
10	**2c**	L-Men	Cy	*S*	**−94**[b]	**−98**[b]	**−96**[b]	–	–	–

[a] *ee* values ≥90% are in bold. The reactions were performed at room temperature, 1 bar H_2 pressure, with a s/c of 100 giving complete conversions in less than 2 h. The catalysts were prepared in situ by mixing 1.1 equivalent ligand with 1 equivalent of a rhodiumprecursor. [b] Rh precursor = $[Rh(nbd)_2]BF_4$; solvent = EtOH. [c] Rh precursor = $[Rh(nbd)_2]BF_4$; solvent = THF. [d] Rh precursor = $[Rh(cod)Cl]_2$; solvent = 1,2-dichloroethane. [e] As [b] but s/c 200. [f] Reaction time 14 h. nbd = norbornadiene, cod = 1,5-cyclooctadiene.

Most experiments were performed with six functionalized alkenes and selected results are shown in Table 1 for rhodium JoSPOphos (entries 1–7) and rhodium TerSPOphos complexes (entries 8–10). Both ligand families show excellent catalytic performance and many catalysts gave high enantioselectivities with several substrates. Notably, ligand **1b** gave *ee* values in the range of 90% to over 99% with all substrates, which is quite exceptional. Of special interest is the fact that *E*- and *Z*-EAC afford products with the same absolute configuration, allowing the use of *E*/*Z*-mixtures.[13] Ligand **1b** with a phenyl group on the SPO moiety and *t*Bu groups on the phosphine outperforms ligand **1a** where the phenyl and *t*Bu groups are transposed. Ligand **1b** also outperforms, ligands **1c** and **1d** which have only *t*Bu or Ph groups, respectively. The absolute configuration of the phosphorous center seems to dominate the sense of induction: in almost all cases tested to date, the product absolute configuration changes when going from R_{SPO} to S_{SPO} ligands. The influence of the other stereogenic units is less predictable, but it appears that for R′ = *t*Bu the (R,S_p,S_{SPO}) isomer (e.g. **1c′**) is superior to the R_{SPO} isomer (e.g. **1c**) whereas for R′ = Ph, the reverse behavior is observed

Similar results were obtained for the TerSPOphos ligands. Also in these cases most substrates are hydrogenated with *ee* values in the range of 94% to over 99%. The fact that ligands **2a** and **2b** with PAr_2 groups give similar enantioselectivities to **2c** (R = Cy) indicates that the electronic nature of the phosphine group hardly affects the *ee* value.

A few reactions with MAA and DMI were carried out in 50 mL reactors with s/c = 200–1000 at a hydrogen pressure of 1 bar. For all the ligands, the reactions were usually complete within 5 min (implying turnover frequencies (TOF) in the range of 2000–20000 h^{-1}), showing that both types of ligands yield very active catalysts for disubstituted alkenes.

Ligand families **1** and **2** were also tested for the ruthenium- and rhodium-catalyzed hydrogenation of a series of α-and β-ketoesters. The results indicate that the hydrogenation of such substrates with SPO–P ligands is not straightforward and that the structure/selectivity match is quite narrow. The best results were obtained with JoSPOphos ligand **1a** (R′ = *t*Bu), for the ruthenium-catalyzed hydrogenation of EOP (92% *ee*) and the rhodium-catalyzed hydrogenation of KPL (89% *ee*). On the positive side, a catalyst formed in situ from **1a** and $[\{RuCl_2(p\text{-cymene})\}_2]$ was highly active and productive, giving complete conversion within less than 17 h for the hydrogenation of EOP at a s/c of 5000.

In conclusion, the combination of an SPO and a phosphine group leads to ligands which form highly effective hydrogenation catalysts. The use of a chiral backbone or a chiral substituent at the SPO center allows easy access to this modular class of ligands. We have found that SPO–P ligands can coordinate to metal centers either through both phosphorus atoms or through one phosphorus and an oxygen atom. Although at present we do not have any experimental evidence, we assume that the P,P complex rather than the P,O complex is the active catalyst. Our results show that the corresponding Rh and Ru complexes exhibit excellent activities and enantioselectivities in the hydrogenation of functionalized alkenes and moderate enantioselectivity for ketoesters. Thus the combination of a SPO and a phosphine unit in a chelating ligand appears to be a promising approach to generate high-performing ligands. Preliminary work has shown that this concept can be extended to analogues of **1** with other chiral backbones, such as biaryls, or analogues of **2** with different aryl systems or other terpenes as the chiral moiety.

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[10] Hydrolysis was initially performed by adding water to the monochlorophosphine intermediates. We then realized that whereas hydrolysis conditions have little influence in route 1, they can strongly affect the diastereomeric ratio of the SPOs in route 2. Best results were obtained when the reaction mixture was poured onto a stirred mixture of NEt_3/water 1:10.

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