Asymmetric Catalysis

Binol-Derived Monodentate Phosphites and Phosphoramidites with Phosphorus Stereogenic Centers: Novel Ligands for Transition-Metal Catalysis**

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Recently three groups independently reported that binol-derived monodentate phosphites **1a**,[1] phosphonites **1b**,[2] and phosphoramidites **1c**[3] are efficient ligands in rhodium-catalyzed asymmetric olefin hydrogenation (*ee* values = 90–99%; binol = 2,2′-dihydroxy-1,1′-binaphthyl). A preliminary

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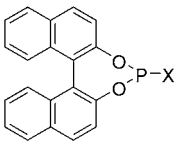
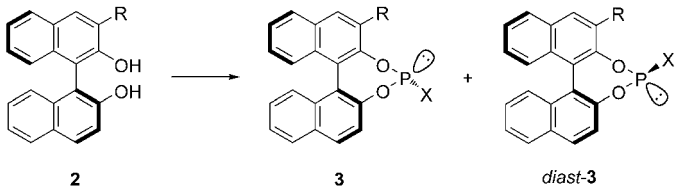


1 a X = OR
b X = alkyl, aryl
c X = NR_2

mechanistic study by our group shows that two monodentate phosphorus compounds are bonded to rhodium in the hydrogenation transition state. In an extension of this work we demonstrated that mixtures of two different monodentate phosphorus ligands can be used in a combinatorial approach.[4] Since binol is one of the cheapest chiral auxiliaries currently available, chemical modification resulting in the formation of new modular ligands appears attractive.

We wondered whether binol derivatives bearing a single *ortho*-substituent as in (*S*)-**2** (Scheme 1) can serve as starting materials for structurally unusual monodentate phosphorus ligands. This modification would not only reduce C_2 to C_1 symmetry, it would also lead to the creation of a stereogenic center at phosphorus (R_P and S_P in diastereomers **3**; Scheme 1).[5] Herein we report the synthesis of this novel class of phosphorus ligands and their use in rhodium-catalyzed olefin hydrogenation.

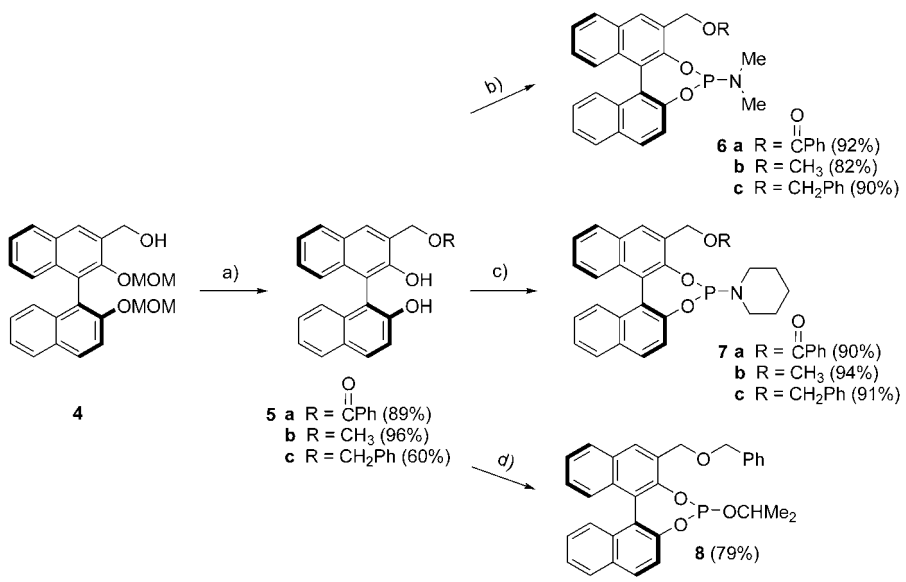


2 **3** *diast*-**3**

Scheme 1. Formation of diastereomeric ligands with stereogenic phosphorus centers.

Starting from the known methoxymethyl (MOM) protected (*S*)-binol-derivative **4**,[6] compounds **5a–c** were readily prepared which were then treated with $P(NMe_2)_3$ in boiling toluene. This reaction resulted in excellent yields of the phosphoramidites as diastereomeric mixtures or as pure compounds: **6a** (S,S_P:S,R_P = 2:1), **6b** (S,S_P pure), and **6c** (S,S_P:S,R_P = 10:1; Scheme 2). Reaction of **5a–c** with PCl_3/NEt_3 at −78 °C followed by treatment with piperidine provided phosphoramidites **7** (Scheme 2), the S,R_P compounds being the major diastereomers in these cases. The formation of the major diastereomers appears to be kinetically controlled under these conditions, because heating compound **7a** at 110 °C for 48 h changed the diastereomeric ratio S,R_P:S,S_P from 3:1 to 2.3:1. Treatment of compounds **5** with PCl_3/NEt_3 followed by reaction with an alcohol in the presence of NEt_3 provides the analogous phosphites, for example phosphite **8** (S,R_P:S,S_P = 3.8:1; Scheme 2).

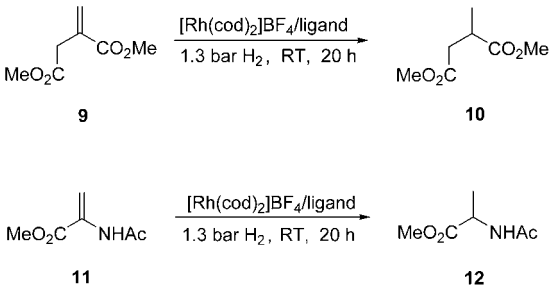
Some of the diastereomers were separated by crystallization, others by HPLC. The configuration assignments were



4
5 a R = CPh (89%)
b R = CH_3 (96%)
c R = CH_2Ph (60%)
6 a R = CPh (92%)
b R = CH_3 (82%)
c R = CH_2Ph (90%)
7 a R = CPh (90%)
b R = CH_3 (94%)
c R = CH_2Ph (91%)
8 (79%)

Scheme 2. Synthesis of phosphoramidites **6** and **7** and phosphite **8**. a) 1. RX/base, 2. CH_3OH/HCl; b) $P(NMe_2)_3$/toluene, 110 °C, 1–2 h; c) 1. PCl_3/Et_3N, Et_2O, −78→0 °C, 2. piperidine/Et_3N, Et_2O, RT, 24 h; d) 1. PCl_3/Et_3N, Et_2O, −78→0 °C, 2. *i*PrOH/Et_3N, Et_2O, RT, 24 h.

then made on the basis of an X-ray structural analysis of the major diastereomer of **6a**, which has the S,S_P configuration,[7] and in other cases by comparison of ^{31}P NMR spectroscopy data. In the ^{31}P NMR spectrum the signal of the S,S_P ligands appears at higher δ values than that of the S,R_P diastereomers, a conclusion that was corroborated by the X-ray data of another derivative (see below). Subsequently, the first rhodium-catalyzed hydrogenations were performed with olefins **9** and **11** (Scheme 3).



9 **10**
11 **12**

Scheme 3. Rhodium-catalyzed hydrogenation of olefins **9** and **11**; cod = cyclooctadiene.

Table 1 reveals that excellent enantioselectivities were achieved in some but not all cases and that the absolute configuration of the binol ligand dictates the direction of enantioselectivity. In the case of the hydrogenation of itaconic acid dimethyl ester (**9**) using ligand **6a** the configuration at the phosphorus center also plays a significant role. The pure S,S_P ligand leads to an *ee* value of 96.3 % (*S*; Table 1, entry 1), whereas the pure S,R_P diastereomer is less efficient (*ee* = 72.5 % *S*, entry 4). Thus, the S,S_P diastereomer represents the matched case. The mixtures of diastereomeric ligands give rise to intermediate *ee* values (entries 2 and 3). These

Table 1: Rhodium-catalyzed hydrogenation of olefins **9** and **11** by using ligands **6**, **7**, and **8**.[a]

Entry	Olefin	Ligand	Major enantiomer of **10** or **12**	*ee* [%]
1	**9**	**6a** (S,S_P pure)	*S*	96.3
2	**9**	**6a** (S,S_P:S,R_P = 2:1)	*S*	93.0
3	**9**	**6a** (S,S_P:S,R_P = 1:2.3)	*S*	90.5
4	**9**	**6a** (S,R_P pure)	*S*	72.5
5	**9**	**6b** (S,S_P pure)	*S*	95.4
6	**9**	**6c** (S,S_P:S,R_P = 10:1)	*S*	96.1
7	**9**	**7a** (S,S_P:S,R_P = 1:3)	*S*	96.0
8	**9**	**7b** (S,S_P:S,R_P = 1:1.4)	*S*	96.3
9	**9**	**7c** (S,S_P:S,R_P = 1:2.2)	*S*	96.8
10	**9**	**8** (S,S_P:S,R_P = 1:3.8)	*S*	91.3
11	**11**	**6a** (S,S_P pure)	*R*	99.0
12	**11**	**6a** (S,S_P:S,R_P = 2:1)	*R*	98.7
13	**11**	**6a** (S,S_P:S,R_P = 1:2.3)	*R*	98.7
14	**11**	**6a** (S,R_P pure)	*R*	97.8
15	**11**	**6b** (S,S_P pure)	*R*	98.3
16	**11**	**6c** (S,S_P:S,R_P = 10:1)	*R*	98.4
17	**11**	**7a** (S,S_P:S,R_P = 1:3)	*R*	> 99.0
18	**11**	**7b** (S,S_P:S,R_P = 1:1.4)	*R*	93.8
19	**11**	**7c** (S,S_P:S,R_P = 1:2.2)	*R*	98.8
20	**11**	**8** (S,S_P:S,R_P = 1:3.8)	*R*	97.0

[a] All reactions in CH_2Cl_2; Rh:L = 1:2; Rh:olefin = 1:200; 1.3 bar; 20 h; 100% conversion in all cases.

mixtures constitute a more complex case because, as the rhodium center is coordinated by two binol ligands, three catalysts are actually involved, namely Rh(S,S_P/S,S_P), Rh(S,R_P/S,R_P), and Rh(S,S_P/S,R_P), each is present in a different amount and reacts with a different rate. Table 1 shows that with **9**, in five cases the *ee* values exceed 96%, which is distinctly better than the 87% *ee* resulting from the use of the parent C_2-symmetric phosphoramidite **1c** (R = CH_3).[3a] The mixture of diastereomeric phosphites **8** leads to a respectable 91.3% *ee* (entry 10), but at present we do not know how the pure diastereomers perform. In the hydrogenation of olefin **11**, ligand **6a** (S,S_P pure) also constitutes the matched case, but the cooperative effect is not as pronounced (entry 11 versus 14).

We phosphorylated the known (*S*)-binol derivatives **13**[8] which resulted in formation of phosphoramidites **14a–e**, and in two cases proceeded with complete diastereoselectivity (Scheme 4).

The X-ray structural analysis of the triphenylsilyl-derivative **14e** shows the free ligand to have the S,S_P configuration.[7] The precatalyst [Rh(**14e**)$_2$(cod)]BF_4 was also characterized by X-ray crystallography (Figure 1).[9] The metal cation has an almost ideal twofold axis of symmetry despite a highly unsymmetrical crystal environment caused by the

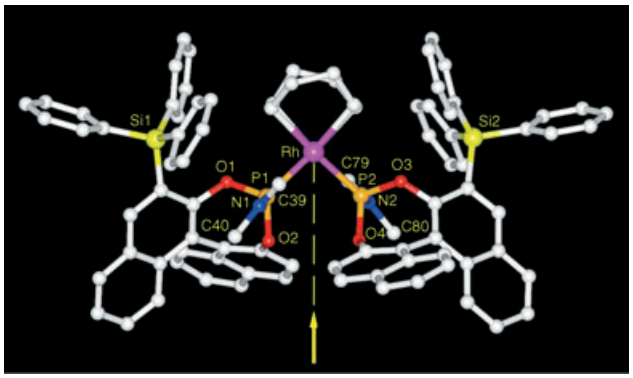
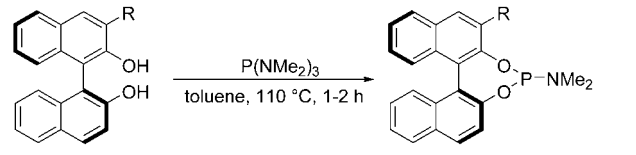


Figure 1. Structure of the cation of [Rh{(S,S_P)-**14e**}$_2$(cod)]BF_4 showing the almost exact twofold axis of symmetry passing through the Rh atom (arrow). Selected interatomic distances [Å], angles, and torsion angles [°]: Rh-P1 2.277(1), Rh-P2 2.275(1), P1-N1 1.640(2), P2-N2 1.633(3), C39···Rh 3.381(3), C79···Rh 3.377(3), P1-Rh-P2 94.89(2), C39-N1-P1-Rh 5(1), C79-N2-P2-Rh 3(1).[9]

$[BF_4]^-$ ion and CH_2Cl_2 solute of crystallization. This situation suggests that crystal-packing effects are not the cause of the high symmetry. An electron-donating effect of nitrogen onto phosphorus which is passed onto the positively charged rhodium center seems to be operating. Another feature is a weak C–H···Rh$^+$ interaction between one of the H atoms of a methyl group in the planar $N(CH_3)_2$ moiety and the metal.[10] Although the rhodium complexes of the other ligands which have less-bulky *ortho*-substituents could not be crystallized to date, they may have similar structures.

Upon employing the ligands **14** in the rhodium-catalyzed hydrogenation of olefins **9** and **11**, some remarkable observations were made (Table 2). The methyl derivative **14a** behaves much like the ligands **6**, **7**, and **8**, affecting *S* selectivity (91% *ee*, entry 1). In contrast, upon using the phenyl derivative **14b**, we were surprised to observe *R* selectivity (entries 2–5). This effect is opposite to what occurs when using the C_2-symmetric parent compounds (*S*)-**1** which also originates from (*S*)-binol; all of the parent ligands are known to be *S*-selective in the hydrogenation of **9** (**1a** (R = *i*Pr): 89.2% *ee*;[1] **1b** (X = CH_3): 90% *ee*;[2] **1c** (R = CH_3): 87% *ee*).[3a] Reversal of enantioselectivity on using ligand **14b** occurs both in the matched case S,R_P with 70% *ee* (entry 5) and in the non-cooperative combination S,S_P (20.6% *ee*, entry 2). This result means that breaking the symmetry of the ligands from C_2 to C_1 by introduction of an *ortho*-phenyl group induces a reversal of enantioselectivity which is independent of the configuration at the stereogenic phosphorus center. We also note that mixtures of diastereomers **14b** result in distinctly higher enantioselectivities than the use of the respective pure ligands themselves, *ee* values up to 90.3% being achieved (entries 3 and 4). The use of two diastereomers constitutes a novel extension of our concept of employing mixtures of two different monodentate ligands[4]



13 **a** R = CH_3
b R = Ph
c R = SPh
d R = $SiMe_3$
e R = $Si(Ph)_3$

14 **a** R = CH_3 [92%, (S,S_P):(S,R_P) = 7.8:1]
b R = Ph [85%, (S,S_P):(S,R_P) = 1:6]
c R = SPh [89%, (S,S_P):(S,R_P) = 1:1]
d R = $SiMe_3$ [97%, (S,S_P) pure]
e R = $Si(Ph)_3$ [96%, (S,S_P) pure]

Scheme 4. Synthesis of phosphoramidites **14**.

Table 2: Rhodium-catalyzed hydrogenation of olefins **9** and **11** using ligands **14**.[a]

Entry	Olefin	Ligand	Major enantiomer of **10** or **12**	*ee* [%]
1	**9**	**14a** (S,S_P:S,R_P = 7.8:1)	*S*	91.0
2	**9**	**14b** (S,S_P pure)	*R*	20.6
3	**9**	**14b** (S,S_P:S,R_P = 1:1)	*R*	90.3
4	**9**	**14b** (S,S_P:S,R_P = 1:6)	*R*	79.6
5	**9**	**14b** (S,R_P pure)	*R*	70.0
6	**9**	**14c** (S,S_P:S,R_P = 1:1)	*S*	23.0
7	**9**	**14d** (S,S_P pure)	*rac*	0
8	**9**	**14d** (S,S_P pure)[b]	*R*	31.6
9	**9**	**14e** (S,S_P pure)	*R*	3.4
10	**9**	**14e** (S,S_P pure)[b]	*R*	17.0
11	**11**	**14a** (S,S_P:S,R_P = 7.8:1)	*R*	98.0
12	**11**	**14b** (S,S_P pure)	*S*	33.6
13	**11**	**14b** (S,R_P pure)	*R*	50.6
14	**11**	**14c** (S,S_P:S,R_P = 1:1)	*R*	97.2
15	**11**	**14d** (S,S_P pure)	*R*	87.2
16	**11**	**14e** (S,S_P pure)	*R*	34.0

[a] Same conditions as in Table 1; 100% conversion. [b] In this case a ligand:Rh ratio of 1:1 was chosen.

and raises fundamental theoretical questions. The fact that the triphenylsilyl-derivative **14e** is a poor ligand for catalysis can be rationalized on the basis of the crystal structure of [Rh{(S,S_P)-**14e**}$_2$(cod)]BF_4 (Figure 1). The silyl groups are so bulky that hydrogenation may actually be inhibited; the rhodium complex with only one phosphoramide ligand may function as the actual (pre)catalyst.

In summary, we have prepared and characterized a new class of binol-derived monodentate phosphorus ligands bearing phosphorus stereogenic centers. They are excellent ligands in rhodium-catalyzed olefin hydrogenation, a result which raises important mechanistic questions. On the practical side, this new class of modular phosphorus compounds enlarges the structural diversity of binol-derived monodentate phosphorus ligands, which means that they are also candidates for our combinatorial approach using mixtures[4] of chiral monodentate phosphorus ligands in hydrogenation and in other transition-metal-catalyzed reactions.

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