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Chiral bidentate phosphabenzene-based ligands: synthesis, coordination chemistry, and application in Rh-catalyzed asymmetric hydrogenations

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Dedicated to Professor Arthur J. Ashe, III on the occasion of his 65th birthday

Abstract—Novel hydroxy-functionalized phosphabenzenes were synthesized, which provide the possibility to prepare chiral phosphabenzene–phosphites. These systems act as bidentate ligands toward rhodium centers and the corresponding metal complexes were applied in the rhodium-catalyzed asymmetric hydrogenation of prochiral substrates.

Phosphabenzenes (phosphinines, phosphorines), the higher homologues of pyridines, have been known for many decades, due to the pioneering work of Märkl and Ashe in the late 1960s.[1,2] These heterocycles are planar, aromatic systems in which one –CH– group of the aryl moiety is substituted by an isoelectronic phosphorus atom, thus exhibiting lone pair electrons suitable for σ-coordination to a metal center.[3] In comparison to aryl phosphines and aryl phosphites, which are frequently applied as ligands in metal-catalyzed reactions under homogeneous reaction conditions,[4] phosphabenzenes act qualitatively as σ-donor and π-acceptor ligands with electronic properties somewhat more similar to phosphites.[5] However, their application in homogeneous catalysis is still limited or even neglected,[5,6] despite the fact that very interesting results in terms of activity and selectivity were obtained in the hydroformylation of alkenes, as reported by Breit and co-workers.[6a,b] Even though a few examples of chiral bidentate ligands based on phosphabenzenes have been reported as well, no enantioselectivity in asymmetric catalytic reactions has been observed so far.[7]

We report here a synthetic route to novel hydroxy-functionalized phosphabenzenes, which can be easily converted into chiral, bidentate ligands. Results on their coordination chemistry and application in asymmetric hydrogenations are presented, and demonstrate a promising step forward in developing these truly unique phosphines to their full potential.

Reaction of the methoxy-functionalized pyrylium salts **1a/b**[8] with an excess of BBr_3 in CH_2Cl_2[9] gave, in a clean and quantitative reaction, the corresponding hydroxy-substituted compounds **2a/b** after aqueous work-up (Scheme 1).

The complete removal of the $-CH_3$ groups was confirmed by ^1H NMR spectroscopy. No resonances were observed by ^{19}F NMR spectroscopy, suggesting loss of the BF_4^- anion during aqueous work-up. In fact, the reaction with H_2O produced substantial amounts of HBr, which led to anion exchange of BF_4^- for Br^-, yielding quantitatively the pyrylium salts **2a/b** as red and yellow solids, respectively. Red crystals of **2a**, suitable for X-ray crystallography, were obtained by slow crystallization from methanol and the molecular structure is

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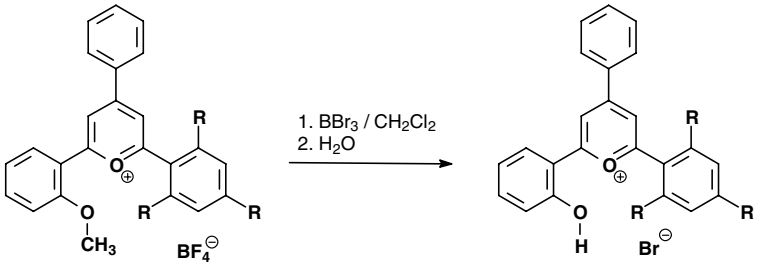


1a: R = H
1b: R = Me

2a: R = H
2b: R = Me

Scheme 1. Synthesis of hydroxy-functionalized pyrylium salts.

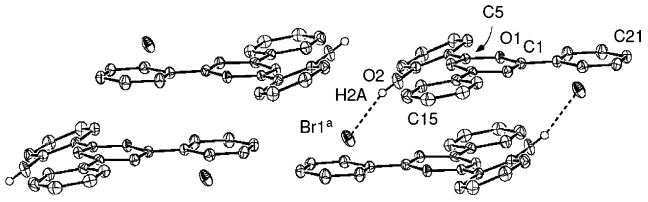


Figure 1. Crystal packing of **2a** (displacement ellipsoid plot[11] at 30% probability level, H atoms excluded with exception of those involved in hydrogen bonds). Superscript a denotes symmetry operation $1-x$, $1-y$, $-z$. Interatomic distances (Å) and angles (°): O2···Br1[a]: 3.1780(14), O1–C1: 1.349(2), O1–C5: 1.356(2), C1–O1–C5: 122.30(12); angles (°) between the central ring and the rings containing O2, C15, and C21 are 23.97(8), 9.98(8), and 1.32(8), respectively.

illustrated in Figure 1. It confirms not only the stability of the six-membered heterocycle under the applied harsh reaction conditions and the formation of the hydroxy-functionalized salt, but also the presence of a Br^-, rather than a BF_4^- anion. Salt **2a** crystallized in a layer-type structure with hydrogen bonds between the –OH functionalities and Br^- anions of different layers.[10]

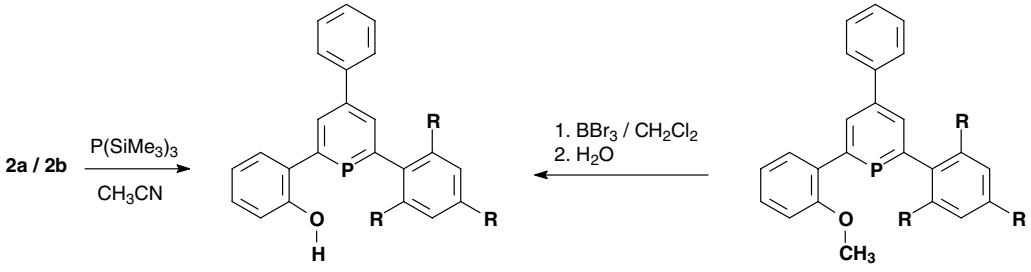
The pyrylium salts **2a** and **2b** were further reacted with $P(SiMe_3)_3$[12] and the corresponding hydroxy-functionalized phosphabenzenes **3a** and **3b** were obtained (Scheme 2).

Alternatively, **3a/b** were synthesized from the methoxy-functionalized phosphabenzenes **4a/b**, which were obtained from **1a/b** and $P(SiMe_3)_3$.[8] Cleavage of the –O–CH_3 group with BBr_3/CH_2Cl_2 followed by aqueous work-up gave the desired products **3a** and **3b** as yellow and red solids. In the ^{31}P NMR spectrum, compound **3a** showed a resonance at $\delta = 188.9$ ppm (C_6D_6), and a resonance at $\delta = 197.6$ ppm (C_6D_6) was observed for **3b**.

Due to their phenolic –OH group, compounds **3a/b** could easily be transformed into the corresponding chiral phosphabenzene–phosphites.[13] Thus, reaction of **3a/b** with (*S*)-BINOL-PCl[14] in the presence of NEt_3 gave the desired bidentate ligands **5a** and **5b**, respectively (Scheme 3).

Compounds **5a/b** were obtained in quantitative yields as yellow, air- and moisture-sensitive solids. Through-space coupling between the two different phosphorus nuclei was observed in the ^{31}P NMR spectrum of **5a**, as indicated by two doublets at $\delta = 190.3$ ppm (phosphabenzene-P) and $\delta = 145.4$ ppm (phosphite-P) and a coupling constant of $J_{P-P} = 5.9$ Hz (**5b**: $\delta = 197.6$ ppm, 145.0 ppm, $J_{P-P} = 10.4$ Hz).

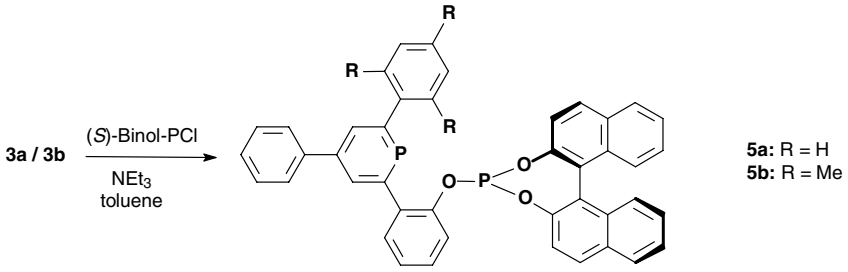
Upon addition of **5a** to 1 equiv of $Rh(cod)_2BF_4$, reaction under loss of COD took place and the corresponding rhodium complex $(P_1P_2)Rh(cod)BF_4$ (**5a**/Rh^+) was formed quantitatively. The ^{31}P NMR spectrum of **5a**/Rh^+ revealed that the phosphabenzene–phosphite ligand was indeed coordinated to the metal center in a bidentate fashion:[15] a doublet of doublets ($J_{Rh-P1} = 172.9$ Hz, $J_{P1-P2} = 68.8$ Hz) at $\delta = 160.5$ ppm was observed in the phosphabenzene region P_1 as well as



3a: R = H
3b: R = Me

4a: R = H
4b: R = Me

Scheme 2. Synthesis of hydroxy-functionalized phosphabenzenes.



Scheme 3. Synthesis of chiral, bidentate phosphabenzene–phosphites.

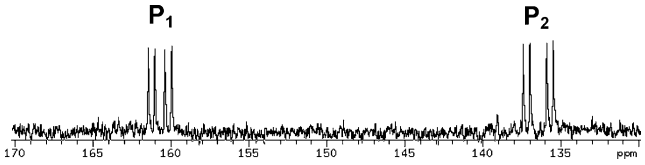
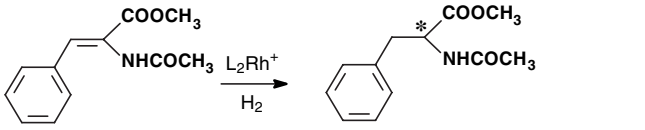


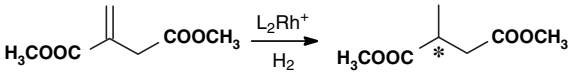
Figure 2. ^{31}P NMR spectrum of **5a**/Rh$^+$ (CD_2Cl_2, $T = 25$ °C).

in the phosphite region P_2 at $\delta = 136.5$ ppm ($J_{Rh-P2} = 243.2$ Hz, $J_{P2-P1} = 68.8$ Hz) (Fig. 2).

The complexes **5a**/Rh$^+$ and **5b**/Rh$^+$ were further applied in the rhodium-catalyzed asymmetric hydrogenation of methyl 2-(*N*-acetylamino)cinnamate as well as dimethyl itaconate[3,16] (Eq. 1 and 2); the reactions were performed simultaneously in a parallel reactor system (AMTEC SPR16) under different reaction conditions.



(1)



(2)

At $T = 25$ °C and a hydrogen pressure of 5 bar, almost no conversion of the enamide (100 equiv) to the hydrogenated product was observed. However, by increasing the temperature to $T = 40$ °C and $p(H_2)$ to 10 bar, a fast and quantitative hydrogenation reaction with the system **5a**/Rh$^+$ took place (TOF = 1030 h^{-1} at 20% conversion). Analysis of the reaction product by GC revealed an enantiomeric excess of 62% of the *R* product. Under the same reaction conditions, the system **5b**/Rh$^+$ showed a slightly reduced activity (TOF = 800 h^{-1}). However, the CH_3-substituents on the phenyl ring showed a dramatic effect on the stereoselection process: an ee of only 19% (*R* product) was found.

The bidentate system **5a**/Rh$^+$ was further compared with Rh-complexes based on the two monodentate ligands 2,4,6-triphenylphosphinine[1,6b] and (*S*)-BINOL-P-OPh.[17] Remarkably, the system **5a**/Rh$^+$ performed much better in the hydrogenation of methyl 2-(*N*-acetylamino)cinnamate in terms of activity, than any of the two other systems [2,4,6-triphenylphosphinine]$_2$Rh$^+$ (**6**/Rh$^+$) and [(*S*)-Binol-P-OPh]$_2$Rh$^+$ (**7**/Rh$^+$): a very low TOF of 55 h^{-1} was found for **6**/Rh$^+$, while a TOF of 530 h^{-1} was observed for **7**/Rh$^+$ ($T = 40$ °C, 10 bar H_2, 100 equiv substrate). Thus, the latter system showed only half of the activity compared to the system based on the bidentate ligand **5a**. Concerning the selectivity, the system **7**/Rh$^+$ showed only a slightly better performance in the stereoselection process compared to **5a**/Rh$^+$ under the applied reaction conditions (ee 70% vs 62%, *R*).

At $T = 25$ °C and a hydrogen pressure of 10 bar, dimethyl itaconate was quantitatively hydrogenated with the system **5a**/Rh$^+$ (0.1 mol %) and a TOF of 2500 h^{-1} (Fig. 3a).

Interestingly, an ee of 79% of the *S*-configured product was found. Increasing the reaction temperature to $T = 40$ °C led to a very active hydrogenation catalyst with a TOF of 5300 h^{-1}, along with a slight drop in ee to 68% (b). The system **5b**/Rh$^+$ showed reduced activity, most likely due to the steric bulk of the substituted phenyl ring close to the metal center: while a TOF of 60 h^{-1} was observed at $T = 25$ °C (c), the activity of the catalyst increased at $T = 40$ °C and a TOF of

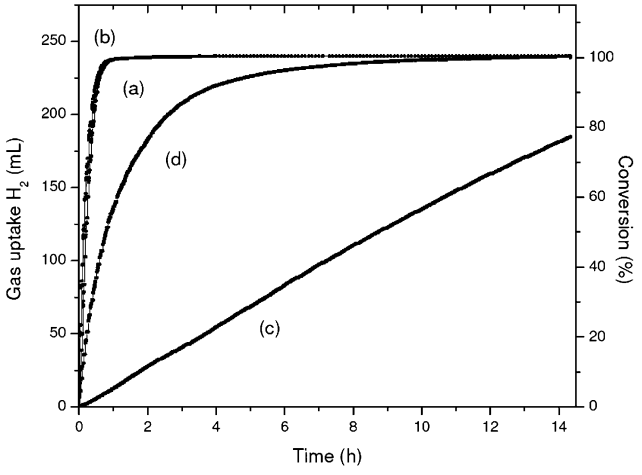


Figure 3. Gas uptake curves for the hydrogenation of dimethyl itaconate with **5a**/**b**/Rh$^+$ ($p(H_2) = 10$ bar, Rh/S = 1:1000, $c_{Rh} = 1.25$ mM). (a) **5a**/Rh$^+$, $T = 25$ °C; (b) **5a**/Rh$^+$, $T = 40$ °C; (c) **5b**/Rh$^+$, $T = 25$ °C; (d) **5b**/Rh$^+$, $T = 40$ °C, CH_2Cl_2.

1050 h^{-1} was found (d). Similar to the results mentioned above, a decrease in the enantioselectivity (ee = 14.0% at $T = 25$ °C; ee = 9.2% at $T = 40$ °C, *S*-product) was observed for this system.

In summary, phosphabenzenes should be regarded as far more than laboratory curiosities. Subsequent work to improve the activity and selectivity of chiral, bidentate phosphabenzenes-based ligands, as well as investigations on their scope and limitations in other asymmetric homogeneous catalytic reactions is currently being carried out in our laboratories.

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Supplementary data

Electronic supplementary information (ESI) available: A listing of experimental procedures and crystallographic data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.049.

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