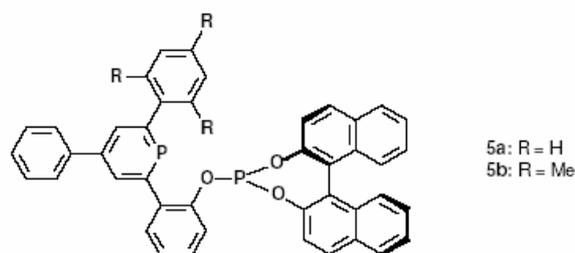


## SPR16 Application Note

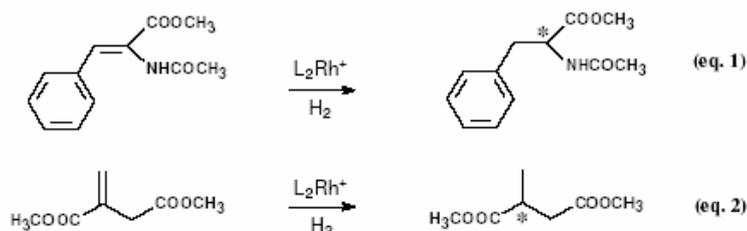
### Application of Chiral Bidentate Phosphabenzene Ligands in Rhodium Catalysed Asymmetric Hydrogenations

Adapted from: Müller et al, *Tetrahedron Letters*, 47, 2006, 2017-2020

Novel hydroxyl-functionalised phosphabenzenes were synthesised which act as bidentate ligands towards rhodium centres. The corresponding metal complexes were applied in the rhodium catalysed asymmetric hydrogenation of prochiral substrates using four SPR16 autoclaves.



The above complexes **5a**/Rh<sup>+</sup> and **5b**/Rh<sup>+</sup> were applied in the rhodium catalysed asymmetric hydrogenation of methyl 2-(N-acetylamino)cinnamate and dimethyl itaconate. The reactions were performed simultaneously in the SPR16 reactor system under different reaction conditions.



The general procedure for the experiments was as follows: Four stainless steel autoclaves of the SPR16 were heated to 90°C and flushed with argon four times. Subsequently the reactors were cooled to room temperature and again flushed four times with argon. The reactors were charged with 4 ml of a precatalyst solution and 4 ml of the substrate, dissolved in CH<sub>2</sub>Cl<sub>2</sub> under argon. The atmosphere in the reactors was exchanged with hydrogen and the reactors were pressurised with hydrogen to 3 bar. After heating to the final temperature the final pressure was adjusted. Hydrogen uptake was monitored and recorded automatically. At the end of the experiments the reactors were cooled to room temperature and the autoclave contents analysed using a GC.

At  $T = 25^\circ\text{C}$  and a hydrogen pressure of 5 bar, almost no conversion of the enamide to the hydrogenated product was observed. However, by increasing the temperature to  $40^\circ\text{C}$  and  $p(\text{H}_2)$  to 10 bar, a fast and quantitative hydrogenation with the system **5a**/ $\text{Rh}^+$  took place ( $\text{TOF} = 1030 \text{ h}^{-1}$  at 20% conversion). Analysis of the reaction product revealed an enantiomeric excess (*ee*) of 62% of the *R* product. Under the same reaction conditions the **5b**/ $\text{Rh}^+$  system showed a slightly reduced activity ( $\text{TOF} = 800 \text{ h}^{-1}$ ). However, the  $\text{CH}_3$  substituents on the phenyl ring showed a dramatic effect on the stereoselection process; an enantiomeric excess of only 19% (*R* product) was found.

At  $T = 25^\circ\text{C}$  and a hydrogen pressure of 10 bar, dimethyl itaconate was quantitatively hydrogenated with the system **5a**/ $\text{Rh}^+$  and a  $\text{TOF}$  of  $2500 \text{ h}^{-1}$ , see Figure 1 (a)

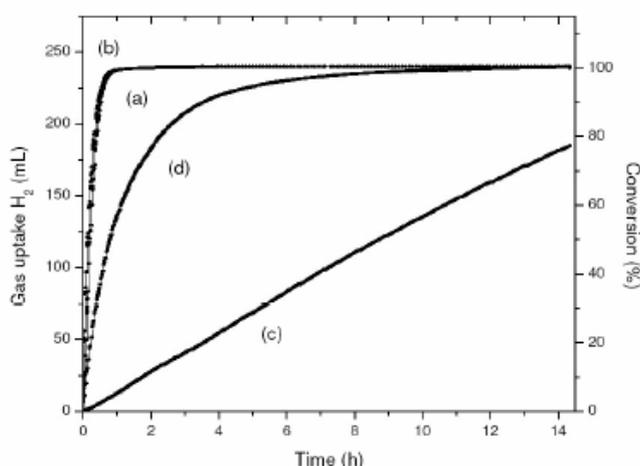


Figure 1: Gas uptake curves for the hydrogenation of dimethyl itaconate with **5a/b**/ $\text{Rh}^+$  ( $p(\text{H}_2) = 10 \text{ bar}$ ,  $\text{Rh}:\text{S} = 1:1000$ ,  $c_{\text{Rh}} = 1.25 \text{ mM}$ ) a) **5a**/ $\text{Rh}^+$ ,  $T = 25^\circ\text{C}$ , b) **5a**/ $\text{Rh}^+$ ,  $T = 40^\circ\text{C}$ , c) **5b**/ $\text{Rh}^+$ ,  $T = 25^\circ\text{C}$ , d) **5b**/ $\text{Rh}^+$ ,  $T = 40^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$

Interestingly an *ee* of 79% of the *S*-configured product was found. Increasing the reaction temperature to  $40^\circ\text{C}$  led to a very active hydrogenation catalyst with a  $\text{TOF}$  of  $5300 \text{ h}^{-1}$  along with a slight drop in *ee* to 68% (b). The system **5b**/ $\text{Rh}^+$  showed reduced activity, most likely due to the steric bulk of the substituted phenyl ring close to the metal centre: while a  $\text{TOF}$  of  $60 \text{ h}^{-1}$  was observed at  $25^\circ\text{C}$  (c), the activity of the catalyst increased at  $40^\circ\text{C}$  and a  $\text{TOF}$  of  $1050 \text{ h}^{-1}$  was found. A decrease in the enantioselectivity (*ee* = 14.0% at  $25^\circ\text{C}$ , *ee* = 9.2% at  $40^\circ\text{C}$ , *S*-product) was observed for this system.

Original Article:

Chiral Bidentate Phosphabenzene-based Ligands: Synthesis, Coordination Chemistry, and Application in Rh-catalyzed Asymmetric Hydrogenations

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