Pergamon

Tetrahedron Letters 42 (2001) 7481–7483

TETRAHEDRON LETTERS

# On the economic application of DuPHOS rhodium(I) catalysts: a comparison of COD versus NBD precatalysts

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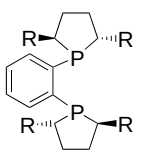
Received 27 June 2001; revised 6 August 2001; accepted 23 August 2001

**Abstract**—The effectiveness of cyclooctadiene and norbornadiene precatalysts of the type [Rh(DuPHOS)(diolefin)]$BF_4$ in catalytic asymmetric hydrogenation of various prochiral olefins has been examined. In some of the systems studied, the NBD complex gave rise to the catalytically active species more rapidly than the corresponding COD complex, as expected. However, as catalyst loadings were reduced to levels more conducive to economic manufacture, the difference between the use of COD and NBD precatalysts became increasingly insignificant. This was conveniently highlighted by the formation of low enantiomeric excess products upon using an equimolar mixture of (*S*,*S*) and (*R*,*R*) precatalysts, bearing COD and NBD respectively. With other substrates, the system displayed no induction time for either precatalyst and identical reaction profiles were observed. 

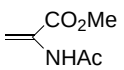
Cationic complexes of rhodium bearing the chiral diphosphine ligand DuPHOS **1** are industrially important for the asymmetric hydrogenation of many prochiral olefins.[1] The precatalysts are typically of the composition [Rh(DuPHOS)(diolefin)]$BF_4$, the active catalysts being generated by the removal of the diene ligand (e.g. cyclooctadiene or norbornadiene) via hydrogenation. It has recently been reported by Heller et al.[2,3] that the removal of cyclooctadiene (COD) takes considerably longer than norbornadiene (NBD). Furthermore, at a molar substrate to catalyst ratio (S/C) of 100, a significant amount of the expensive COD precatalyst remained unreacted at the end of the reaction. It was consequently suggested that the use of COD complexes cannot be regarded as economical.[3]

Owing to the ready availability of the COD complexes and our use of such precatalysts in industrial applications, for example towards the synthesis of Candoxatril,[4] we undertook a comparison of COD and NBD precatalysts under conditions more representative of industrial hydrogenations. In particular, we sought to investigate the use of lower catalyst loadings, since with expensive catalysts this is a critical parameter for process economy.

Four substrates were chosen for our study, methyl acetamidoacrylate **2**, methyl acetamidocinnamate **3**, dimethyl itaconate **4** and the Candoxatril precursor **5**. The precatalysts [(*R*,*R*)-Me-DuPHOS Rh (NBD)]$BF_4$,




**1**

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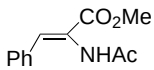


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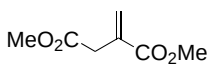


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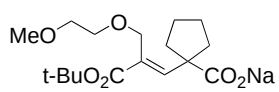


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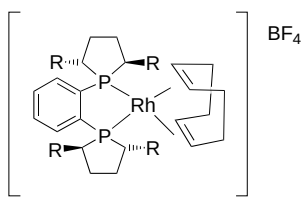
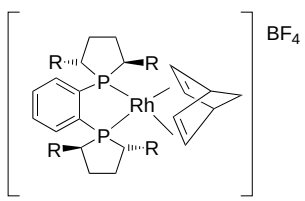



(*R*,*R*)-**6a** R=Me
(*R*,*R*)-**6b** R=Et




(*R*,*R*)-**7a** R=Me
(*R*,*R*)-**7b** R=Et

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0040-4039/01/$ - see front matter 
PII: S0040-4039(01)01552-0

(*R*,*R*)-**7a**, and [(*S*,*S*)-Et-DuPHOS Rh (NBD)]$BF_4$, (*S*,*S*)-**7b**, were prepared according to literature procedures.[2]

Hydrogenation of methyl acetamidoacrylate **2** with (*R*,*R*)-**7a**, at 1000/1 molar substrate/catalyst (S/C) ratio was very fast and reactions were complete in less than 10 minutes giving (*R*)-methyl *N*-acetylalanine in >99% e.e. (3 bar $H_2$ pressure, room temperature).[5] Under the same conditions, (*S*,*S*)-**6a**, gave (*S*)-methyl *N*-acetylalanine in >99% e.e. Competition reactions were carried out in order to gain a measure of the relative productivity of the two precatalysts. These experiments involved using an equimolar mixture of (*S*,*S*)-**6a** and (*R*,*R*)-**7a** in the same reaction. Since the precatalysts have opposite enantiomers of ligand, then the closer the overall productivity given by the NBD and COD precatalysts, the closer the product will be to racemic. At a total S/C of 1000, the (*R*)-isomer of product was obtained with 46% e.e., reflecting a faster activation of the NBD precatalyst. However, at S/C = 10,000 the reaction was >95% complete after 60 min and the product was obtained in only 15% e.e. (*R*).

Methyl acetamidocinnamate **3** was used in a more detailed study[6] and allowed direct comparison with earlier reported work.[2,3] The hydrogenation reactions were performed with a S/C = 2000 of the Rh-Et-DuPHOS catalyst in methanol at 26°C and 3 bar $H_2$ pressure.[7] In the case of (*R*,*R*)-**6b**, we observed an induction period qualitatively consistent with Heller's data (Fig. 1). Thereafter, both reactions proceeded at the same rate giving products of >99% e.e. The difference in the overall reactions times (~15 min for (*S*,*S*)-**7b** and ~20 min for (*R*,*R*)-**6b**) is due to the induction time observed for the COD precatalyst. In a competition experiment with a 1:1 mixture of (*R*,*R*)-**6b** and (*S*,*S*)-**7b**, the product was obtained in 23% e.e. (*S*)-isomer, which is produced by the catalyst generated from the NBD complex, (*S*,*S*)-**7b**. When the same experiment was repeated at S/C = 5000, the product was obtained after 50 min in 7% e.e. (*S*), indicating that at lower catalyst loadings the two precatalysts tend towards equal effectiveness.

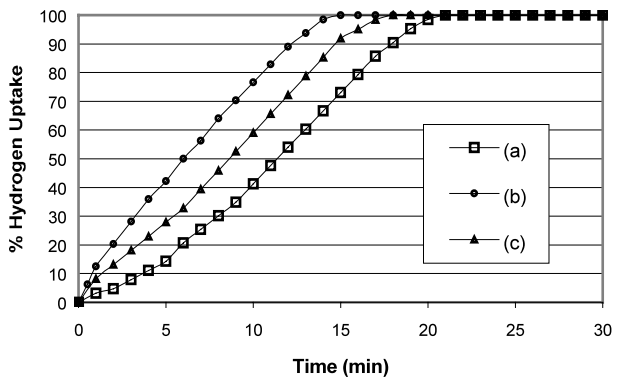


**Figure 1.** Hydrogenation of **3** comparing (a) (*R*,*R*)-**6b**, (b) (*S*,*S*)-**7b** and (c) 1:1 mixture of (*R*,*R*)-**6b**, and (*S*,*S*)-**7b**.

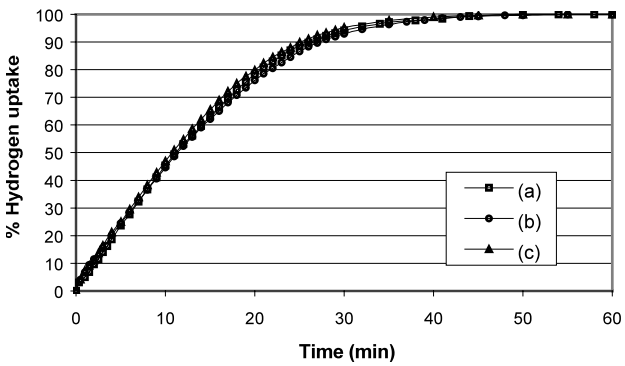


**Figure 2.** Hydrogenation of **4** comparing (a) (*S*,*S*)-**6a**, (b) (*R*,*R*)-**7a** and (c) 1:1 mixture of (*S*,*S*)-**6a**, and (*R*,*R*)-**7a**.

Dimethyl itaconate **4** is a very reactive substrate towards hydrogenation and complete conversion is achievable at low catalyst loadings. With a Rh-MeDuPHOS precatalyst at S/C = 10,000 in methanol at 25°C and 5 bar $H_2$ pressure, we observed no significant difference in the rates over the course of reaction between COD and NBD precatalysts (Fig. 2).[8] In both cases the reactions were complete in 50 min with enantiomeric excesses in the range 97.4–98.0%. Moreover, there was no evidence of any induction period and competition experiments with 1:1 (*S*,*S*)-**6a** and (*R*,*R*)-**7a** gave essentially racemic product (<3% e.e). It would appear that, under these conditions, the active catalyst is formed with equal facility from either the COD or NBD pre-catalyst.[9]

The Candoxatril precursor **5** was chosen as a substrate for which we had already developed a multi-kilogram hydrogenation process.[4] As for dimethyl itaconate, no induction time was seen and both precatalysts, (*S*,*S*)-**6a** and (*R*,*R*)-**7a**, gave practically identical reaction profiles (S/C = 4200, 5 bar $H_2$ pressure, MeOH, 26°C) (Fig. 3).[10] The reactions were complete in 20 min. It is worth noting that under less efficient stirring conditions, the reaction took 90 min to go to completion.[11] This implies that for this type of hydrogenation, the reaction rate is dependent on the hydrogen mass transfer into solution.[12]

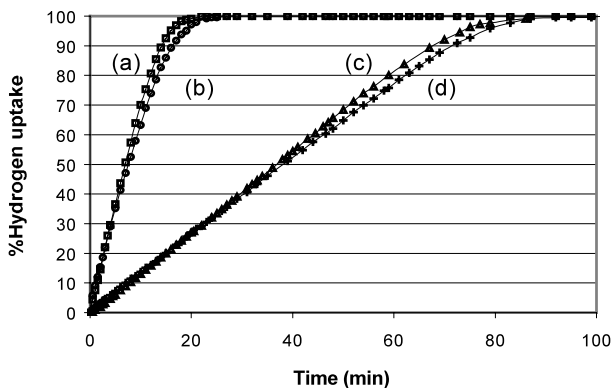


**Figure 3.** Hydrogenation of **5** comparing (a) (*S*,*S*)-**6a**, (b) (*R*,*R*)-**7a**, (c) (*S*,*S*)-**6a** with less efficient stirring and (d) (*R*,*R*)-**7a** with less efficient stirring.

In conclusion, we have confirmed that NBD precatalysts can give faster initial reaction rates than the corresponding COD precatalysts. However, as catalyst loadings are reduced to levels more conducive to economic manufacture, the difference between the use of COD and NBD precatalysts becomes increasingly insignificant. Furthermore, with certain substrates and conditions we see no induction period with the COD precatalyst. We suggest that generally the more readily available COD precatalysts are appropriate for use under industrial conditions, at least in the case of rhodium-DuPHOS catalysts. For other rhodium–bisphosphine–diolefin precatalysts, it is possible that an unacceptable induction period could occur with the COD precatalyst[3] such that appropriate comparative characterisation is recommended. The absence or presence of any induction period depending on the substrate or conditions may be associated with effects of hydrogen availability at the catalyst and in particular by the rate of uptake of hydrogen by the COD pre-catalyst relative to that of the substrate–catalyst complex. This aspect is currently being explored further.

## Acknowledgements

We are grateful to Dr. Steve Challenger and Pfizer Ltd for supporting this work through their supply of the Candoxatril precursor and useful discussion. We also thank Natasha Cheeseman of the *Chiro*Tech analytical team for her skilled technical assistance.

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5. The hydrogenations of methyl acetamidoacrylate **2** were performed in a 50 mL Parr hydrogenation vessel using the same procedure as outlined in Ref. 6. Methyl acetamidoacrylate **2** (0.7–2.9 g, 5–20 mmol) in MeOH (5–10 mL), precatalyst (0.0016–0.0053 mmol), 3 bar $H_2$, room temperature; GC analysis: DEX-CB column, 60°C for 5 min, then 5°C/min to 150°C, 17.0 min (*S*), 17.2 min (*R*).
6. In a typical experiment a 600 mL Parr hydrogenation vessel is charged with a MeOH solution of the substrate and pressurised with nitrogen to 10 bar under vigorous stirring. The system is allowed to equilibrate over 20 min before releasing the pressure. This procedure is repeated three times with nitrogen and three times with hydrogen. A solution of the catalyst in deoxygenated MeOH is introduced via syringe. The vessel is quickly purged a further three times with hydrogen (less than 20 s required) and pressurised to the required reaction pressure (gauge reading). The amount of hydrogen uptake is monitored at standard intervals and the pressure constantly maintained within 0.5 bar of the initial pressure reading. When no further hydrogen consumption is detected the pressure is released and samples taken for conversion and selectivity analysis. The curves of hydrogen uptake versus time are normalised to 100% uptake.
7. Methyl acetamidocinnamate **3** (10.0 g, 27 mL, 45.6 mmol) in MeOH (200 mL), precatalyst (0.023 mmol) in MeOH (2 mL), 3 bar $H_2$, 26°C; GC analysis: DEX-CB column, 150°C for 25 min, then 5.0°C/min to 200°C, 20.3 min (*R*), 21.0 min (*S*).
8. Dimethyl itaconate **4** (30.0 g, 190 mmol) in MeOH (250 mL), precatalyst (0.019 mmol) in MeOH (3 mL+20 mL, total reaction volume: 300 mL), 5 bar $H_2$, 23°C; GC analysis: G-TA column, 40–130°C at 5°C/min, then to 170°C at 15°C/min, 21.8 min (*S*), 22.05 min (*R*).
9. $^{31}P\{^1H\}$ and $^1H$ NMR experiments indicated that no reaction occurred between dimethyl itaconate and (*R*,*R*)-**6b** or (*S*,*S*)-**7b** in MeOH-$d_4$. This demonstrates that no significant displacement of COD or NBD occurs in the absence of hydrogen gas.
10. Candoxatril precursor **5** (29.5 g, 84.3 mmol) in MeOH (350 mL), precatalyst (0.020 mmol) in MeOH (2 mL), 5 bar $H_2$, 26°C; work up and analysis as reported in Ref. 4.
11. The 600 mL Parr hydrogenation vessel is configured with two impellers. When the upper impeller is positioned just below the surface of the reaction solution, a more efficient transfer of hydrogen into solution is achieved (Fig. 3, curves a and b) than when the impeller is placed deep within the bulk of the solution (Fig. 3, curves c and d).
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