Rhodium(I)-catalysed Asymmetric Hydrogenation of Imines

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The imines ArC(Me)=NCH$_2$Ph (Ar = Ph, 2-MeO-C$_6$H$_4$, 4-MeO-C$_6$H$_4$) are hydrogenated to the corresponding secondary amines at 1000 psig H$_2$, in 1 : 1 C$_6$H$_6$/MeOH, using an *in situ* Rh^{I}/(*R*)-cycphos system (cycphos = Ph$_2$PCH(C$_6$H$_{11}$)CH$_2$PPh$_2$); a maximum of 91% enantiomeric excess (e.e.) is achieved at lower temperatures (−25 °C) in the presence of iodide cocatalyst.

The catalytic asymmetric hydrogenation of prochiral imines such as (**1**) has received relatively little attention,[1,2] and optical yields obtained are much lower than those reported for the hydrogenation of ketones[2,3] and olefins.[2,4] We now report a reliable procedure for the asymmetric hydrogenation, with high optical yield, of the imines (**1**), derived from benzylamine, by using an *in situ* catalyst based on rhodium(I).

For example the norbornadiene dimer [Rh(NBD)Cl]$_2$ (0.025 mmol) was dissolved in 10 ml of dry, degassed, benzene/methanol (1 : 1) in a Schlenk tube, under an argon atmosphere. (*R*)-(+)-Cycphos[5] (0.05 mmol) was added, followed by (**1a**) (5 mmol). The solution was transferred to a steel autoclave under argon. The reaction vessel was then flushed with hydrogen, pressurised to 1000 psig with the same gas, and the contents stirred for 18 h at 20 °C. The solvent was removed and the product, (**2a**), distilled at 88—90 °C (0.05 mm Hg), 100% yield, 67% enantiomeric excess (e.e.), Table 1.‡

The data of Table 1 show that the *in situ* catalyst is most effective for hydrogenation of (**1a**—**c**) when an equivalent of halide, preferably iodide, is added, and when the reaction is performed at lower temperatures. The high optical yields, maximum 91% e.e. for (**1c**), are remarkable because the

Table 1. The asymmetric hydrogenation of imines.[a]

Substrate	Halide added	Reaction time time (h)	Optical yield[b] e.e. (%)
(**1a**)	—	18	67
(**1b**)	—	90	60
(**1c**)	—	18	71
(**1a**)	KBr	144	72
(**1a**)	KI	90	79
(**1b**)	KI	120	71
(**1c**)	KI	72	84
(**1c**)[c]	KI	90	87
(**1c**)[d]	KI	144	91
(**1d**)	—	90	—

[a] Rh^{I} : (*R*)-cycphos: substrate = 1 : 1 : 100; added [halide] = [Rh^{I}]; at 20 °C unless stated otherwise. Chemical yield of amine is >99% in all cases, except for (**1b**) with KI (90%) and (**1d**) (0%). [b] Product configuration is (*S*) in all cases. [c] At 4 °C. [d] At −25 °C.

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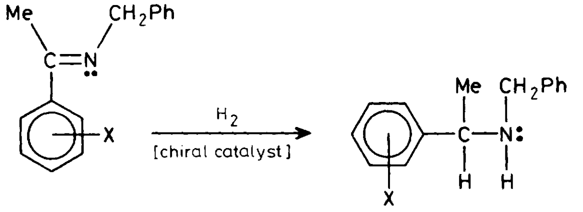
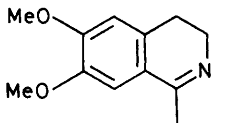
‡ The optical yield of (**2a**) was calculated by using the rotation of $[\alpha]_D^{20}$ = + 56.2° (*c* 1.07, EtOH) for (*R*)-(+)-(**2a**).[6] ^{1}H n.m.r. (400 MHz) spectroscopic data for the diastereoisomeric amides of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid were used to determine the optical yields of (**2b**) and (**2c**).[7]

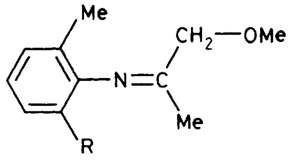


(1) (2)

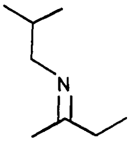
a X = H, b X = 2-OMe, c X = 4-OMe, d X = 2-OH



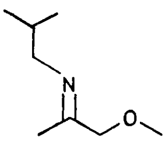
(3)



(4) a R = Me
b R = Et



(5)



(6)

substrate probably binds to the rhodium *via* only the imine functionality, although interaction with the benzyl phenyl group cannot be ruled out. When high optical yields are obtained from ketonic or olefinic substrates with closely related Rh catalysts, a secondary interaction by the substrate is invariably present;[2] further, these olefin systems commonly give an increase in optical yield with increasing temperature,[4] although exceptions are known.[8] It is likely that the imine (**1d**) forms a chelate *via* the OH group and blocks further reaction.

Vastag *et al.*[1] have reported that halide has a beneficial effect on the optical yield of (**2a**) when cationic [Rh(NBD)(Ph$_2$PCH(R)CH$_2$PPh$_2$)]ClO$_4$ catalysts are used (cycphos was not used); the highest optical yield obtained was 72% e.e. using an *in situ* [Rh(NBD)Cl]$_2$/valphos (R = CHMe$_2$) system, but the systems were reported to have poor reproducibility. We find that [Rh(NBD)(cycphos)]PF$_6$ catalyses the hydrogenation of (**1a**) under our conditions, but the optical yield is only 0—16% e.e. The effect of halide[9] is much more dramatic than that found by Vastag *et al.*, and, although its function has yet to be defined, the iodide must occupy a rhodium co-ordination site, perhaps limiting the number of bound substrates and therefore the number of diastereoisomers to be hydrogenated.

The use of methanol as a co-solvent is important; other alcohols slow the reactions, while the use of neat benzene completely inhibits the reaction. Wilkinson's group[10] reports that imines such as (**1a**) are hydrogenated at 1 atm H$_2$ in pure alcohols using RhCl(PPh$_3$)$_3$ or [Rh(PPh$_3$)$_2$(NBD)]PF$_6$ as catalysts, while addition of benzene (<5%) severely inhibits the reduction; these workers suggest that η^2-bonding of the C=N at a first-formed dihydridorhodium(III) centre is favoured in alcohols because of intramolecular hydrogen bonding between co-ordinated alcohol and the imine nitrogen. We favour the unsaturate route for our reductions, *i.e.*, imine co-ordination as the first step, because hydrides are not formed from the catalyst precursor plus H$_2$ (as usually found for such chelated diphosphine systems[2,5]), and because complexes of formula§ [Rh(diphos)(imine)$_2$]BF$_4$ can be isolated if the imine is reducible, *e.g.*, (**1b**), or non-reducible, *e.g.*, (**3**).

Imines such as (**4**), which are precursors to important herbicides, are hydrogenated by an *in situ* [Rh(NBD)Cl]$_2$/cyphos catalyst with >70% optical yield being achieved at low temperature.[11] Interestingly, iodide ion severely inhibits these reductions, and an isolated complex with these substrates is now of the type [Rh(diphos)(imine)]BF$_4$ with the ether oxygen presumably binding in addition to the nitrogen lone pair.

Finally, our catalyst system is not effective for asymmetric hydrogenation of aliphatic imines. For example, (**5**) is 100% reduced under the standard conditions, but with *ca.* 2% e.e., and (**6**) is not reduced.

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§ Diphos = 1,2-bis(diphenylphosphino)ethane. Treatment of a hydrogenated solution of [Rh(NBD)(diphos)]BF$_4$ with imine under Ar readily yields crystals of the complexes, which give the correct analytical data. N.m.r. studies in progress on the complexes are complicated by the presence of geometrical isomers; data for the complex with (**3**) (no coupling to Rh in the $^{13}C\{^1H\}$ n.m.r.) suggest the presence of η^1-imines (co-ordinated to rhodium *via* nitrogen).

References

1 S. Vastag, J. Bakos, S. Toros, N. E. Takach, R. B. King, B. Heil, and L. Marko, *J. Mol. Catal.*, 1984, **22**, 283.

2 For leading references see: H. B. Kagan, in 'Comprehensive Organometallic Chemistry,' eds. G. Wilkinson, F. G. A. Stone, and E. W. Abel, Pergamon Press, Oxford, 1982, vol. 8, p. 463; 'Asymmetric Catalysis,' ed. B. Bosnich, Martinus Nijhoff Publishers, Dordrecht, 1986; J. Halpern, in 'Asymmetric Synthesis,' ed. J. D. Morrison, Academic Press, New York, vol. 5, 1985; K. E. Koenig, in 'Asymmetric Synthesis,' ed. J. D. Morrison, Academic Press, New York, vol. 5, 1985; J. M. Brown, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 190; B. R. James, A. Joshi, P. Kvintovics, R. H. Morris, and I. S. Thorburn, in 'Catalysis of Organic Reaction,' ed. D. W. Blackburn, Marcel Dekker, New York, in the press.

3 M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, and R. Noyori, *J. Am. Chem. Soc.*, 1988, **110**, 629 and references therein.

4 C. R. Landis and J. Halpern, *J. Am. Chem. Soc.*, 1987, **109**, 1746 and references therein.

5 Cycphos = Ph$_2$PCH(C$_6$H$_{11}$)CH$_2$PPh$_2$, see D. P. Riley and R. E. Shumate, *J. Org. Chem.*, 1980, **45**, 5187.

6 K. Parek, *J. Prakt. Chem.*, 1912, **86**, 287.

7 J. A. Dale, D. L. Diell, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

8 W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, *Adv. Chem. Ser.* No. 132, 1974, 274; W. R. Cullen and Y. Sugi, *Tetrahedron Lett.*, 1978, **19**, 1635; I. Ojima, T. Kogure, and N. Yoda, *J. Org. Chem.*, 1980, **45**, 4728; D. Sinou, *Tetrahedron Lett.*, 1981, **22**, 2987.

9 The use of iodide to improve optical yields in the hydrogenation of the olefinic bond in prochiral imidazolinones has been described in U.S. patents 4,166,824 Sept. 4, 1979, and 4,168,381 Sept. 18, 1979.

10 C. J. Longley, T. J. Goodwin, and G. Wilkinson, *Polyhedron*, 1986, **5**, 1625.

11 W. R. Cullen, M. D. Fryzuk, B. R. James, G.-J. Kang, J. P. Kutney, R. Spogliarich, and I. S. Thorburn, U.S. Patent 079,625, filed July 30, 1987.