The Remarkable Effect of *E*/*Z* Isomers on the Catalytic Asymmetric Hydrogenation of Oximes

Albert S. C. Chan,*[a,b] Chih-Chiang Chen,[a] Ching-Wen Lin,[b] Ying-Chih Lin,[c] Ming-Chu Cheng[c] and Shie-Ming Peng[c]

[a] *Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong*
[b] *Department of Chemistry, National Chung Hsing University, Taichung, Taiwan*
[c] *Department of Chemistry, National Taiwan University, Taipei, Taiwan, ROC*

The *E* and *Z* isomers of 1-acetonaphthone oxime are isolated, characterized, and subjected to catalytic asymmetric hydrogenation; the chiral products from the asymmetric hydrogenation reflect the effect of the *E* and *Z* isomers on the enantioselectivity of the reaction.

The homogeneous asymmetric catalytic hydrogenation of prochiral C=N bonds has been an interesting subject for over a decade.[1] Unlike the highly successful asymmetric hydrogenation of prochiral C=C and C=O bonds,[2] the asymmetric hydrogenation of C=N bonds is usually less successful and substantially less well understood.[3] Most of the past studies on this subject focused on the asymmetric hydrogenation of imines, unfortunately, the effect of *E*/*Z* isomerism on the enantioselectivity of the reaction was not addressed clearly, owing to the rapid interconversion of the *E* and the *Z* isomers of the imines studied.

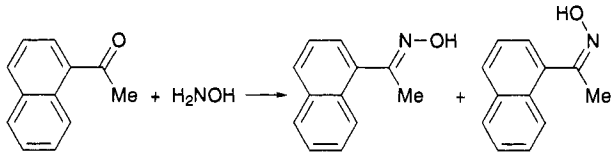
In the study of the asymmetric hydrogenation of prochiral imines by Kang *et al.*, the investigators found the *E*/*Z* ratio of the starting materials to be essentially constant during the course of the reaction.[4] This observation was explained in terms of two possibilities: (*i*) the rates of hydrogenation of the two isomers were identical; or more likely, (*ii*) the rate of the interconversion of the two isomers was much faster than the rates of hydrogenation. Therefore, a rapid equilibrium of the two isomers was maintained throughout the course of the hydrogenation.

Oppolzer *et al.* found that cyclic sulfonimide (in which the C=N bond was fixed in a ring system) was hydrogenated with a Ru(BINAP) catalyst to give essentially quantitative optical yields.[5] Similar success was achieved by Willoughby and Buchwald in the asymmetric hydrogenation of C=N bonds in heterocyclic compounds.[6] Burk and Feaster achieved high optical yields in the Rh(DuPhos)-catalysed asymmetric hydrogenation of *N*-aroylhydrozones,[7] probably due to the preferred coordination of one isomer forced by the bidentate chelation of the hydrazones.

Because of the difficulty in isolating the *E* and *Z* isomers of most regular prochiral imines and studying their corresponding asymmetric hydrogenation, no information on the effect of *E*/*Z* isomerism on the asymmetric hydrogenation of imine was obtained.

In contrast to the rapid *E*/*Z* isomerization of imines, the *E* and *Z* isomers of oximes and oxime ethers are much more stable and in many cases both the *E* and *Z* isomers can be isolated as discrete species. Therefore the study of the asymmetric hydrogenation the *E* and the *Z* isomers of oximes and oxime ethers will offer a great opportunity to probe the effect of *E*/*Z* isomerism on the asymmetric hydrogenation of prochiral C=N bonds.In this paper we report the first example of such a study which gives a clear picture of the effect of the *E*/*Z* isomers.

Our criteria for choosing a suitable oxime for a definitive hydrogenation study were: (*i*) the *E* and *Z* isomers of the oxime could be isolated separately and unambiguously characterized; (*ii*) both isomers could be hydrogenated under reasonably mild conditions. After much screening we found 1-acetonaphthone oxime to be an excellent choice for this study. This oxime was easily prepared by the condensation of hydroxylamine with 1-acetonaphthone. The *E* and *Z* isomers were separated by column chromatography with silica gel. The two isomers were easily distinguishable by the different chemical shifts of the corresponding methyl groups in ^{1}H NMR [^{1}H NMR ($CDCl_3$) *E* isomer: δ(Me) 2.43; *Z* isomer: δ(Me) 2.31]. The unambiguous characterization of the *E*-isomer was achieved by single crystal X-ray diffraction.



Both the *E* and the *Z* isomers of 1-acetonaphthone oxime were found to be hydrogenated smoothly under 1000 psig at 100 °C with rhodium chiral phosphine catalysts. The optical yields of the hydrogenation products from these two isomers were found to be significantly different. In the cases of using Rh(DIOP), Rh(skewphos) and Rh(prophos) catalysts, the optical rotations of the reaction products from the *E* and the *Z* isomers were even found to be in opposite directions. A more detailed comparison of the product enantiomeric excess (e.e.) for the asymmetric hydrogenation is summarized in Table. 1.

Although the reactions have not been optimized and the e.e.s listed in Table 1 are not very high, the data have important implications, in that in the asymmetric hydrogenation of imines and other C=N groups, one must consider the isomerization of the *E*/*Z* isomers and their effect on optical yields.

We thank the Hong Kong Research Grant Council and the National Science Council of ROC for financial support of this study.

Table 1. A comparison of the asymmetric catalytic hydrogenation of *E*- and *Z*-1-acetonaphthone oxime[a]

Catalyst	Optical yields[b] for the products from *E*-isomer	*Z*-isomer
[Rh(NBD)(*S*-BINAP)]BF_4	30 (*S*)	66 (*S*)
[Rh(COD)(*R*,*R*-DIOP)]BF_4	14 (*R*)	26 (*S*)
[Rh(NBD)(*R*,*R*-DIPAMP)]BF_4	8 (*R*)	15 (*R*)
[Rh(NBD)(*R*,*R*-Skewphos)]BF_4	12 (*S*)	35 (*R*)
[Rh(NBD)(*R*-Prophos)]BF_4	11 (*S*)	25 (*R*)

[a] Substrate/Catalyst (mol/mol) = 250; solvent = methanol–benzene (*v* : *v* = 10 : 1); P_{H_2} = 1000 psig; reaction temp. = 100 °C; reaction time = 5 days.
[b] Optical yields were determined using Mosher's reagent.[3]

Received, 15th May 1995; Com. 5/03046C

References

1 For recent reviews, see for example, R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994, pp. 82–86 and references therein.

2 See for example K. E. Koenig, in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic, New York, 1985, vol. 5, ch. 3; H. Brunner, *Top. Stereochem.*, 1988, **18**, 129; R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994, pp. 16–94.

3 H. Alper and P. Krasik, *Tetrahedron Asymmetry*, 1992, **3**, 1283.

4 G.-J. Kang, W. R. Cullen, M. D. Fryzuk, B. R. James and J. P. Kutney, *J. Chem. Soc., Chem. Commun.*, 1988, 1466.

5 W. Oppolzer, M. Wills, C. Starkemann and G. Bernadinelli, *Tetrahedron Lett.*, 1990, **31**, 4117.

6 C. A. Willoughby and S. L. Buchwald, *J. Am. Chem. Soc.*, 1992, **114**, 7562.

7 M. J. Burk and J. E. Feaster, *J. Am. Chem. Soc.*, 1992, **114**, 6266.