1-(1-Naphthyl)ethylamine and Derivatives thereof as Chiral Modifiers in the Enantioselective Hydrogenation of Ethyl Pyruvate over Pt–Alumina

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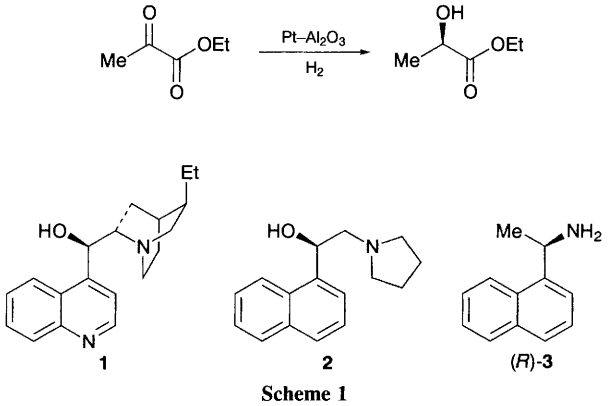
Catalytic quantities of (*R*)- or (*S*)-1-(1-naphthyl)ethylamine induce up to 82% e.e. in the hydrogenation of ethyl pyruvate over Pt–alumina, the actual modifier responsible for enantioselection being the secondary amine resulting from imine formation with ethyl pyruvate and subsequent reduction of the C=N bond; a series of related derivatives has been prepared by reductive amination and tested as chiral modifiers.

Catalytic amounts of cinchona alkaloids or related derivatives such as dihydrocinchonidine **1** have a dramatic effect on the hydrogenation of α-keto esters over platinum catalysts: the reaction becomes enantioselective with a significant rate increase.[1–5] Although excellent enantiomeric excesses (up to 95%) have been obtained in the reduction of ethyl pyruvate, the application range and the mechanistic understanding of this catalyst system are still very limited. We have recently found that substantial enantioselectivities can also be induced by much simpler amino alcohols such as **2**.[6] At low H_2 pressure in AcOH, **1** and **2** give very similar results (68–75% e.e. at 1–10 bar) whereas at high pressures, **1** becomes more effective (87–92% e.e. with **1**,[2,6] 46% e.e. with **2**[6] at 75–100 bar). The two modifiers **1** and **2** possess analogous 2-aminoethanol side chains and, not surprisingly, molecular modelling studies suggest that their preferred conformations are similar.[6b] However, screening of various chiral nitrogen compounds revealed that this structural analogy to the cinchona alkaloids is not a prerequisite for achieving significant e.e.'s.[7] Here, we report our studies of 1-(1-naphthyl)ethylamine **3** which was found to be an even more effective modifier than **2**.[7]†

Comparison of commercially available (*R*)- and (*S*)-**3** with **1** and **2** as modifiers in the hydrogenation of ethyl pyruvate in acetic acid (Scheme 1) showed that at low pressures between 1 and 10 bar, naphthylethylamine affords better enantioselectivities than **1** and **2** (under optimised conditions: 82% e.e.; **1** and **2**: 73–75% e.e.;[6] see Table 1). Modifiers **2** and **3** both become less effective at higher pressures due to partial hydrogenation of the naphthalene system.[6] This contrasts with the behaviour of **1** which requires high pressure for optimum performance (87–92% e.e. at 75–100 bar).[2b] As observed with modifiers **1** and **2**, naphthylethylamine **3** effects a significant increase of the initial rate of pyruvate hydrogenation by a factor of up to 6. The e.e. and initial rate show a similar dependence on the modifier concentration as found for **1**[2] and **2**.[6]

NMR analysis of the reaction mixture revealed that naphthylethylamine (*S*)-**3** is quantitatively consumed during the hydrogenation reaction and converted to the secondary amine **5a** (Scheme 2) and minor amounts of unidentified products (presumably di- or tetra-hydronaphthalene derivatives). This transformation, which proceeds by imine formation and subsequent reduction of the C=N bond, is highly diastereoselective. According to HPLC analysis, the ratio between (*S*,*S*)-**5a** and the corresponding (*S*,*R*)-isomer **5b** exceeds 97:3.† Although diastereoselective reductive aminations of this type are known,[8] the selectivities reported in the literature are distinctly lower than in our case. The configuration of the major isomer **5a** was determined by transformation to the (*S*)-alanine derivative **6**. When analytically pure **5a** was employed as modifier in the hydrogenation of ethyl pyruvate, the same results within

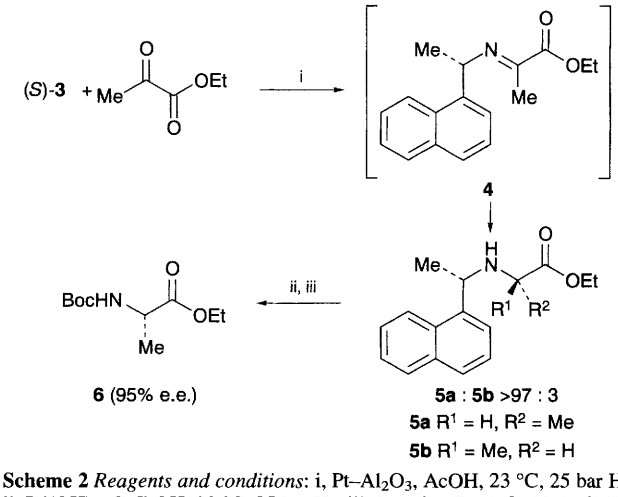


Scheme 1

Table 1 Enantioselective hydrogenation of ethyl pyruvate (Scheme 1)[a]

Modifier	H_2 pressure/ bar	*t*/h	Conversion (%)[b]	Enantiomeric excess (%)[c]
3	8	1.0	100	82[c]
	25	1.0	60	58
	75	1.0	50	53
5a	25	1.0	70	58
	75	1.0	70	54
5b	25	1.0	80	58
	75	1.0	60	51
7	25	1.0	60	40
8	25	1.0	40	36
9	25	1.0	50	45
10a	25	1.0	40	37
10b	25	1.0	50	49
11	25	3.0	50	9

[a] Reactions were performed on a 10 mmol scale in 2 ml of AcOH at 23 °C. Hydrogenations at 25 and 75 bar: 10 mg of 5 mass% Pt–Al_2O_3, [substrate]/[modifier] = 1500. [b] Determined by GC analysis (permethylated β-cyclodextrin). [c] 20 ml AcOH, 400 mg 5 mass% Pt–Al_2O_3, [substrate]/[modifier] = 74000, 10 ml ethyl pyruvate, 9 °C and 8 bar.



Scheme 2 *Reagents and conditions*: i, Pt–Al_2O_3, AcOH, 23 °C, 25 bar H_2; ii, $Pd(OH)_2$–C, EtOH, 23 °C, 25 bar H_2; iii, 2 equiv. $(Boc)_2O$, 10% of NEt_3 in EtOH, 23 °C

experimental error as with naphthylethylamine (*S*)-**3** were obtained (Table 1). From this we conclude that the secondary amine **5a**, which is rapidly formed under the reaction conditions specified in Table 1, functions as the actual modifier in the enantioselective reduction of ethyl pyruvate.

Use of $Ti(OEt)_4$–$Na[BH_3(CN)]$[9] for reductive alkylation of (*S*)-**3** with ethyl pyruvate allowed the preparation of both diastereoisomers **5a** and **5b**. The two diastereoisomers, which were formed in a *ca.* 1 : 1 ratio, were separated by column chromatography. Unexpectedly, both (*S,S*)-**5a** and (*S,R*)-**5b** were found to induce the same enantioselectivity in the hydrogenation of ethyl pyruvate (Table 1). A control experiment showed that less than 3% isomerisation of **5b** to **5a** takes place during the reaction. This implies that the results obtained with **5b** are significant and that the configuration at the stereogenic centre α to the ester group has no influence on the enantioselection of modifiers **5a** and **5b**.

Reductive alkylation of **3** with different aldehydes or ketones provides easy access to a variety of related modifiers such as **7**–**10**. The pyrrolidine derivative **11** was prepared by alkylation with butane-1,4-diol ditosylate. None of these modifiers can compete with **5a** or **5b**. Nevertheless, the substantial enantiomeric excess obtained with **9** shows that an oxygen function, as present in **2** and **5** and the cinchona alkaloids, is not an indispensable structural element for achieving significant enantioselection. This supports the conclusions previously reached[6,7] that there are only two structural elements which are essential for the function of the modifier, an extended aromatic π-system which anchors the modifier to the catalyst surface, and a chiral amino side chain which in the protonated form interacts with the substrate, presumably by a hydrogen bond to the keto group of ethyl pyruvate.

Not so long ago, the general opinion was that high enantioselectivity can only be achieved with structurally unique complex modifiers as the cinchona alkaloids. However, our results obtained with simple chiral amines demonstrate the contrary. With enantiomeric excesses exceeding 80%, commercially available naphthylethylamine **3** is the most effective chiral modifier for low pressure hydrogenation of ethyl pyruvate reported to date. Thus we are confident that further research will lead to other more effective modifiers extending the scope of enantioselective heterogeneous hydrogenation.

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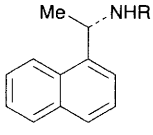
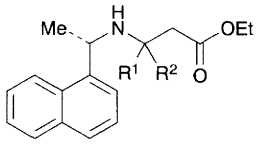
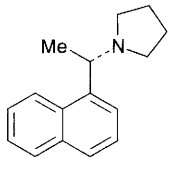


7 R = Me
8 R = Pr^i
9 R = CH_2Ph



10a R^1 = H, R^2 = Me
10b R^1 = Me, R^2 = H



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Footnote

† All compounds gave correct elemental analyses. Selected for **5a**: pale yellow oil; $[\alpha]_D^{23}$ −109 (*c* 0.9, $CHCl_3$); 98.8% d.e. (HPLC analysis on a Daicel-Chiralcel OJ column, hexane–Pr^{i}OH 95 : 5); ^{1}H NMR ($CDCl_3$; *J*/Hz) δ 8.22–8.15 (m, 1H), 7.90–7.87 (m, 1H), 7.78–7.75 (m, 2H), 7.52–7.47 (m, 3H), 4.63 (q, 1H, *J* 6.6), 4.16 (q, 2H, *J* 7.2), 3.19 (q, 1H, *J* 7.1), 1.95 (bs, 1H, NH), 1.51 (d, 3H, *J* 6.6), 1.30 (d, 3H, *J* 7.1), 1.21 (t, 3H, *J* 7.2); ^{13}C NMR ($CDCl_3$): δ 176.7 (C), 140.5 (C), 134.0 (C), 131.4 (C), 128.9 (CH), 127.2 (CH), 125.7 (CH), 125.6 (CH), 125.2 (CH), 123.2 (CH), 123.0 (CH), 60.5 (CH_2), 54.3 (CH), 52.4 (CH), 24.5 (CH_3), 19.9 (CH_3), 14.2 (CH_3). IR ν/cm^{-1}: 3339w, 1724s, 1452m, 1375m. MS (CI): 272 (100, M$^+$+H), 155 (83), 118 (32). TLC (hexane–EtOAc 5 : 1): R_f = 0.29. For **5b**: yellow oil; $[\alpha]_D^{23}$ +10 (*c* 1.0, $CHCl_3$); 98.1% d.e. (HPLC); ^{1}H NMR: δ 8.26 (d, 1H, *J* 8.3), 7.90–7.87 (m, 1H), 7.77 (d, 1H, *J* 8.0), 7.67 (d, 1H, *J* 7.1), 7.57–7.46 (m, 3H), 4.73 (q, 1H, *J* 6.6), 4.19–4.11 (m, 2H), 3.52 (q, 1H, *J* 6.9), 2.13 (bs, 1H, NH), 1.54 (d, 3H, *J* 6.6), 1.34 (d, 3H, *J* 6.9), 1.24 (t, 3H, *J* 7.1); ^{13}C NMR: δ 175.5 (C), 140.9 (C), 133.9 (C), 131.1 (C), 128.9 (CH), 127.4 (CH), 125.9 (CH), 125.6 (CH), 125.3 (CH), 123.0 (CH), 122.9 (CH), 60.6 (CH_2), 53.9 (CH), 50.5 (CH), 22.6 (CH_3), 19.0 (CH_3), 14.1 (CH_3). IR ν/cm^{-1}: 3331w, 1726s, 1475m, 1375m. MS (CI): 272 (100, M$^+$ + H), 155 (61), 118 (43). TLC (hexane–EtOAc 5 : 1): R_f = 0.20.

References

1 Y. Orito, S. Imai and S. Niwa, *J. Chem. Soc. Jpn.*, 1979, 1118; S. Niwa, S. Imai and Y. Orito, *J. Chem. Soc. Jpn.*, 1982, 137.
2 (*a*) H. U. Blaser, H. P. Jalett, D. M. Monti, J. F. Reber and J. T. Wehrli, *Stud. Surf. Sci. Catal.*, 1988, **41**, 153; (*b*) M. Garland and H. U. Blaser, *J. Am. Chem. Soc.*, 1990, **112**, 7048; (*c*) H. U. Blaser, *Tetrahedron Asymmetry*, 1991, **2**, 843; (*d*) H. U. Blaser, M. Garland and H. P. Jalett, *J. Catal.*, 1993, **144**, 569.
3 J. L. Margitfalvi, P. Marti, A. Baiker, L. Botz and O. Sticher, *Catal. Lett.*, 1990, **6**, 281; A. Baiker, *DGMK Tagungsber.*, 1992, **9305**, 119; O. Schwalm, B. Minder, J. Weber and A. Baiker, *Catal. Lett.*, 1994, **23**, 271.
4 I. M. Sutherland, A. Ibbotson, R. B. Moyes and P. B. Wells, *J. Catal.*, 1990, **125**, 77; G. Bond, P. A. Meheux, A. Ibbotson and P. B. Wells, *Catal. Today*, 1991, **10**, 371; S. P. Griffiths, P. Johnston, W. A. N. Vermeer and P. B. Wells, *J. Chem. Soc., Chem. Commun.*, 1994, 2431.
5 R. L. Augustine, S. K. Tanielyan and L. K. Doyle, *Tetrahedron Asymmetry*, 1993, **4**, 1803.
6 (*a*) G. Wang, T. Heinz, A. Pfaltz, B. Minder, T. Mallat and A. Baiker, *J. Chem. Soc., Chem. Commun.*, 1994, 2047; (*b*) K. E. Simons, G. Wang, T. Heinz, T. Giger, T. Mallat, A. Pfaltz and A. Baiker, *Tetrahedron Asymmetry*, 1995, **6**, 505.
7 B. Minder, M. Schürch, T. Mallat and A. Baiker, *Catal. Lett.*, 1995, **31**, 143.
8 K. Harada, *Asymmetric Heterogeneous Catalytic Hydrogenation*, in *Asymmetric Synthesis*, vol. 5, *Chiral Catalysis*, Academic, New York, 1985; M. Tamura, S. Shiono and K. Harada, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 3838.
9 R. J. Mattson, K. M. Pham, D. J. Leuck and K. A. Cowen, *J. Org. Chem.*, 1990, **55**, 2552.