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Highly enantioselective hydrogenation of α-dehydroamino acids by rhodium complex with H_8-MonoPhos

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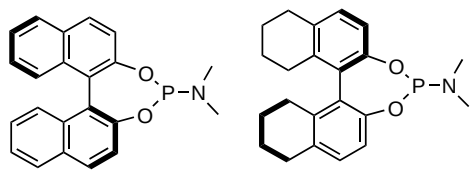
Abstract—H_8-MonoPhos, a new stable and easily prepared monodentate phosphoramidite ligand, has been synthesized from H_8-BINOL. The ligand showed extremely highly enantioselectivity of higher than 99.9% e.e. in the asymmetric Rh-catalyzed hydrogenation of α-dehydroamino acids. Our study further supports the new concept that there is no gap in efficiency and enantioselectivity between monodentate and chelating ligands for asymmetric catalysis.

An important recent breakthrough in asymmetric hydrogenation is the discovery that monodentate catalytic ligands may induce higher enantioselectivity than their bidentate analogues. Herein our study further demonstrates that monodentate ligands may provide excellent chiral induction, comparable to that of the best chelating ligands.

Amongst the monodentate phosphorous ligands,[1–3] Feringa's MonoPhos **1** (Fig. 1) derived from 1,1′-bi-2-naphthol (BINOL) gave the best results.[3] However, its solubility is low in some solvents, which resulted in decreased rate of hydrogenation.[3] We thought that if the BINOL backbone was replaced by H_8-BINOL, the resulting compound would have better solubility. Furthermore, H_8-BINOL is somewhat different from BINOL in conformation and electronic character. Some ligands based on H_8-BINOL show higher asymmetric induction than those based on BINOL in many asymmetric transformations such as hydrogenation,[4] alkylation of aldehydes[5] and hetero-Diels–Alder reaction.[6] Prompted by these results and the facile preparation of H_8-BINOL from BINOL, we synthesized the H_8-BINOL based monodentate phosphoramidite **2** (shorted as H_8-MonoPhos) and investigated its application in the enantioselective hydrogenation of α-dehydroamino acid derivatives. To our best knowledge, no H_8-BINOL backbone has been used as a monodentate phosphorous ligand until now.



(*S*)-MonoPhos **1** (*R*)-H_8-MonoPhos **2**

Figure 1. (*S*)-MonoPhos **1** and (*R*)-H_8-MonoPhos **2**.

H_8-BINOL was prepared by the reduction of BINOL with Ni–Al alloy under strongly basic conditions.[7] Treatment of (*R*)-H_8-BINOL with hexamethylphosphorous triamide gave (*R*)-H_8-MonoPhos **2**[8] in high yield. Its structure was fully characterized by ^1H, ^{13}C and ^{31}P NMR. Unlike MonoPhos **1**, H_8-MonoPhos **2** is soluble in most common organic solvents, which provides a wide scope of solvents for optimizing the reaction conditions for various substrates.

Initially, we screened solvents and hydrogen pressure in the hydrogenation of dehydro-*N*-acetylphenylalanine methyl ester **3a** (Table 1). All of the resulting e.e. values in the tested solvents are higher than or comparable to

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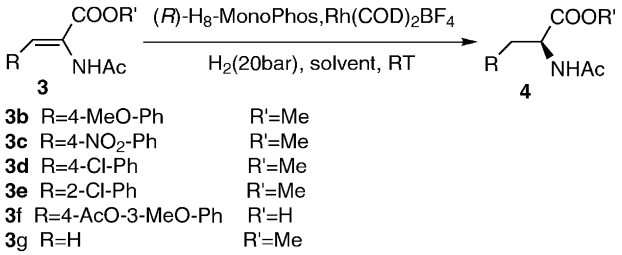
Table 1. Enantioselective hydrogenation of α-dehydroamino acid derivatives **3** by H_8-MonoPhos-Rh complex[a]



Entry	Substrates	*t* (h)	Solvents	E.e.[b] (%)	Conv.[b] (%)
1	**3a**	2	Toluene	94.9	99.1
2	**3a**	0.5	$ClCH_2CH_2Cl$	95.0	99.7
3	**3a**	0.5	CH_2Cl_2	94.4	99.3
4	**3a**	0.5	AcOEt	95.7	96.9
5	**3a**	0.5	THF	94.2	90.2
6	**3a**	1	Acetone	95.4	99.2
7	**3a**	0.5	*i*-PrOH	96.0	98.9
8[c]	**3a**	6	*i*-PrOH	94.8	99.7
9[d]	**3a**	1	*i*-PrOH	95.6	96.8
10[e]	**3a**	0.5	*i*-PrOH	95.6	99.6
11[f]	**3a**	8	Acetone	96.4	99.9
12	**3b**	0.5	Acetone	94.4	95.9
13[g]	**3c**	5	CH_2Cl_2	96.0	99.9
14[g]	**3d**	5	CH_2Cl_2	98.0	99.9
15	**3e**	0.5	Acetone	92.5	98.6
16	**3f**	2	Acetone	95.9	99.9
17	**3g**	0.5	Acetone	99.9	99.9
18[f]	**3g**	8	Acetone	99.9	99.9

[a] Reactions were performed with 0.1 M solutions of substrates at S/C = 100/1 at rt and 20 bar initial hydrogen pressure unless otherwise noted.
[b] E.e. and conversion were determined by GC on a CP-Chirasil-L-Val column. The configurations of all the predominant products were in *S* form.
[c] 1 bar of H_2.
[d] 10 bar of H_2.
[e] 40 bar of H_2.
[f] The substrate to catalyst mole ratio is 500.
[g] 100 psi of H_2.

those of MonoPhos. The effects of solvents on the chiral induction are minimal (entries 1–7); that is, H_8-MonoPhos is one of the rare ligands that have extensive adaptation to various solvents. Increased hydrogen pressure accelerated the reaction but played a minor role in enantioselectivity (entries 7–10). Interestingly, when the substrate to catalyst ratio was increased from 100 to 500, the reaction gave consistent e.e. value (entry 11). It is notable that the substrate could not be completely hydrogenated in toluene with 5 (mol)% rhodium–MonoPhos complex under ambient H_2 pressure for 20 h due to poor solubility of the catalyst;[3] but the reaction did reach completion with 1 mol% H_8-MonoPhos–rhodium complex under 20 bar of H_2 for 2 h (entry 1).

We next sought to investigate the hydrogenation of some other dehydroamino acid substrates. Excellent enantioselectivities were achieved for the dehydrophenylalanines **3b**, **3c** and **3d** with electron-donating and withdrawing *para*-substituents on the phenyl group, but for the *ortho*-substituted **3e** a slightly lower e.e. value was obtained (entries 12–15). The precursor of L-Dopa **3f** was reduced completely over 2 h with excellent e.e. (entry 16). In particular, methyl *N*-acetamidoacrylate **3g** was hydrogenated to give **4g** with higher than 99.9% e.e. (entries 17 and 18) and quantitative conversion even in the presence of 0.2 mol% catalyst, which is comparable to the results of the best chelating catalysts.

In summary, a new monodentate phosphoramidite H_8-MonoPhos **2** was designed and synthesized. Excellent e.e. values are obtained in the H_8-MonoPhos–rhodium-catalyzed hydrogenation of α-dehydroamino acid derivatives, which demonstrates that H_8-MonoPhos is comparable to the best mono- and bidentate phosphine ligands.

Acknowledgements

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References

1. Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun*. **2000**, 961.
2. (a) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3889; (b) Reetz, M. T.; Sell, T. *Tetrahedron Lett*. **2000**, *41*, 6333.
3. Van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; Van Esch, J.; De Vries, A. H. M.; De Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc*. **2000**, *122*, 11539.
4. (a) Zhang, X.; Uemura, T.; Matsumura, K.; Kumobayashi, H.; Sayo, N.; Takaya, H. *Synlett* **1994**, *7*, 501; (b) Uemura, T.; Zhang, X.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Org. Chem* **1996**, *61*, 5510; (c) Zhang, F. Y.; Pai, C. C.; Chan, A. S. C. *J. Am. Chem. Soc*. **1998**, *120*, 5808; (d) Zhang, F. Y.; Kwok, W. H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2337.
5. (a) Chan, A. S. C.; Zhang, F. Y.; Yip, C. W. *J. Am. Chem. Soc*. **1997**, *119*, 4080; (b) Zhang, F. Y.; Yip, C. W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585; (c) Zhang, F. Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651.
6. Wang, B.; Feng, X. M.; Cui, X.; Liu, H.; Jiang, Y. Z. *Chem. Commun*. **2000**, 1605.
7. Guo, H.; Ding, K. L. *Tetrahedron Lett*. **2000**, *41*, 10061.
8. (*R*)-H_8-MonoPhos **2**: $[\alpha]_D^{32}$−310 (*c* 0.610, THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52–1.62 (m, 2H), 1.74–1.81 (m, 6H), 2.18–2.36 (m, 2H), 2.486 (d, 6H, J=8.8 Hz), 2.56–2.71 (m, 2H), 2.74–2.87 (m, 4H), 6.836 (d, H, J=6.0 Hz), 6.990 (d, H, J=3.9 Hz), 7.010 (d, H, J=3.9 Hz), 7.068 (d, H, J=6.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.5, 22.7, 22.8, 27.6, 27.7, 22.7, 29.0, 29.1, 35.6, 35.9, 118.5, 118.6, 128.2, 128.3, 129.2, 132.9, 137.4, 137.8, 137.9, 148.2, 148.3, 148.6; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 143.4.