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Tetrahedron: *Asymmetry* 15 (2004) 2181–2184

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Tetrahedron: *Asymmetry*

Development of DIOP derivatives as efficient ligands for asymmetric hydrogenation: factors controlling the reactivities and enantioselectivities

Duan Liu, Wenge Li and Xumu Zhang*

Department of Chemistry, Pennsylvania State University, University Park, PA 16802, USA

Received 30 April 2004; accepted 19 May 2004

Abstract—Several DIOP derivatives have been developed as efficient ligands for Rh and Ir-catalyzed asymmetric hydrogenations. The conformational mobility of the backbone in this type of ligand plays an important role in governing both the reactivity and enantioselectivity. Isolation of pure pre-catalyst is another key factor to obtain high catalytic activity.

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1. Introduction

DIOP **1** (Fig. 1), developed by Kagan in the 1970's, is one of the earliest and most extensively explored chiral phosphine ligands in asymmetric hydrogenation, albeit with only moderate to good enantioselectivities.[1] It has shown synthetic chemists that the chirality does not have to be on the phosphorus centers for a phosphine compound to be a highly selective ligand for asymmetric catalysis, while the chiral backbone can play a significant role in the asymmetric induction. Based on Kagan's pioneering work, thousands of chiral phosphine compounds have been synthesized with diverse chiral backbones with many being proven to be efficient ligands for asymmetric catalysis.[2]

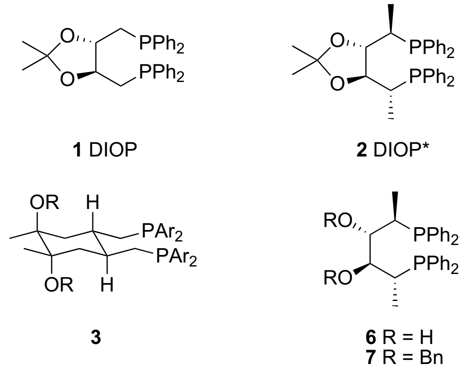

Figure 1. Structures of DIOP type ligands.

Recently, several modifications on the backbone of DIOP ligands have been reported leading to new 1,4-bisphosphine ligands with improved enantioselectivities in Rh-catalyzed asymmetric hydrogenations.[3] For example, we introduced (*R*,*S*,*S*,*R*)-DIOP* **2** (Fig. 1) with excellent results in the Rh-catalyzed hydrogenation of aryl-enamides.[4] Such high enantioselectivities were attributed to the increased conformational rigidity of the chiral backbone of the ligand.[4a] Based on a similar conformational analysis, we successfully applied another structurally related type of ligands **3**[5] (Fig. 1) with a 1,4-dioxane backbone, which showed comparable results to **2** in the Rh-catalyzed hydrogenation of aryl-enamides.[3j] Interestingly, we found that while Rh-**3** complex formed in situ catalyzed the hydrogenation of a more electron-rich substrate MOM-protected β-hydroxyl enamide **4a** to **5a** with full conversion and high enantioselectivity,[3j] Rh-**2** complex showed no reactivity under the same reaction conditions. These unexpected results prompted us to extend the conformational studies of this particularly important and interesting type of 1,4-bisphosphine. Herein, we report the extension of this ligand family, leading to the synthesis of two new ligands **6** and **7** (Fig. 1) with acyclic backbones, and the discussion of the influence of conformational

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* Corresponding author. Tel.: +1-814-865-4221; fax: +1-814-863-8403; e-mail: xumu@chem.psu.edu

0957-4166/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2004.05.042

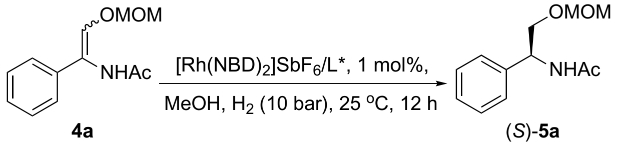
mobility of ligands on the reactivities and enantioselectivities based on the results of Rh-catalyzed asymmetric hydrogenation of MOM-protected β-hydroxyl enamides. Some preliminary results of Ir-catalyzed hydrogenation of a cyclic imine substrate with this type of ligands are reported as well.

2. Results and discussion

In general, increasing the conformational flexibility of ligand should enhance the reactivity of the metal catalyst. Ligand **2** was less reactive than **3** in Rh-catalyzed hydrogenation probably due to the two methyl groups at the α-position to the diphenylphosphine groups, which rigidified the seven membered metal–ligand chelate ring. One way to reduce the rigidity of this chelate ring is opening the five membered ketal ring on the backbone. The resulting ligands should be able to form reactive metal complexes easily. Thus, we envisioned that ligand **6** and **7** should form more reactive Rh catalysts than **2**. The syntheses of **6** and **7** are outlined in Scheme 1. Ligand **6** was prepared directly from the hydrolysis of DIOP*[6] with methanesulfonic acid, while ligand **7** was synthesized from the known epoxide **8**[7] via reduction, mesylation, and phosphination.

In order to verify our hypothesis, substrate **4a** was hydrogenated with Rh-complexes formed in situ with ligand **2** (DIOP*), **6**, and **7**, respectively, under the same reaction conditions. As we expected, while DIOP* showed no reactivity for this transformation (entry 1 in Table 1), both **6** and **7** provided full conversions of **4a** to **5a** with good enantioselectivities (entries 2 and 3 in Table 1). These results strongly supported our hypothesis that the conformational mobility of a ligand plays a significant role in governing the catalytic activity of its transition-metal complex. More flexible metal–ligand chelates, such as in Rh-**6** and Rh-**7**, provided higher reactivities than less flexible chelates, such as in Rh-**2**.

Table 1. Ligand comparison in asymmetric hydrogenation of an electron-rich substrate **4a** with in situ Rh complexes[a]

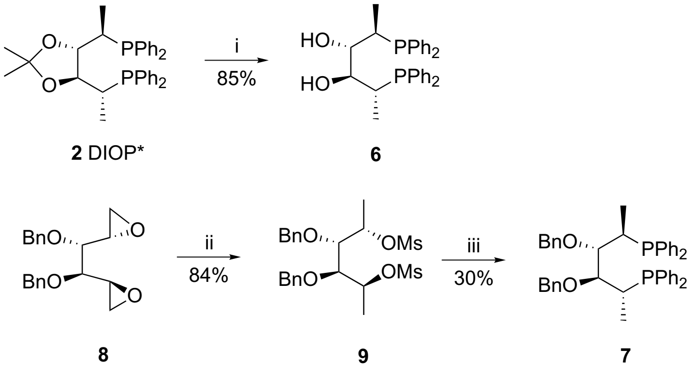


Entry	L*	Conversion (%)	Ee (%)[b]
1	**2**	0	—
2	**6**	100	80.2
3	**7**	100	84.6

[a] The reactions were carried out at rt under 10 bar of H_2 for 12 h. The catalyst was prepared in situ by mixing $[Rh(NBD)_2]SbF_6$ (1 mol%) and ligand (1.1 mol%) in MeOH.

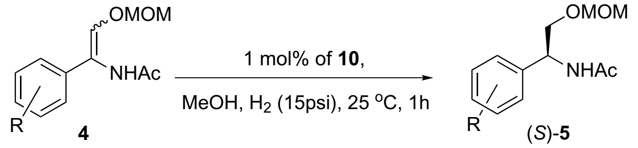
[b] The enantiomeric excesses were determined by chiral HPLC using a (*S*,*S*)-Whelk-01 column. The (*S*)-configurations of the products were determined by comparing the retention times of two enantiomers with reported data.

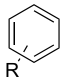
On the other hand, it was shown for different types of ligands that the isolated pure Rh-ligand complex performed with higher reactivity than the Rh complex generated in situ due to the existence of small amounts of less reactive metal species in the latter.[8] In order to verify if this principle applied to DIOP* and enhance the reactivity of its Rh catalyst, pure $[Rh(DIOP^*)(NBD)]SbF_6$ **10** was isolated and used as a catalyst precursor. It was found that complex **10** provided the best catalytic system of this ligand family for the hydrogenation of **4a**, affording **5a** quantitatively with 98.1% ee under very mild conditions within 1 h (entry 1 in Table 2). Such a dramatic increase in reactivity was apparently due to the isolation of pure Rh-DIOP* complex **10**. It is noteworthy that DIOP* provided higher enantioselectivity (98.1% ee) than ligand **6** and **7** (80.2% ee and 84.6% ee, respectively) in this reaction, which is actually quite reasonable. The conformational rigidity of a chiral ligand is an important factor governing not only the reactivity, but also the enantioselectivity in asymmetric catalysis.[9] Bidentate chiral ligands with a more rigid backbone between the two coordinating sites can form a more rigid metalocycle with fewer available conformations, and thus enhance the enantioface differentiation leading to chiral product with higher ee value. Although the Rh-DIOP* complex is less reactive than Rh complexes with **6** and **7**, it should be more enantioselective due to its more rigid backbone. Ligand **7** was slightly more enantioselective than **6**, which was in consistence with the trend of their



Scheme 1. Reagents and conditions: (i) MeOH, H_2O, $MeSO_3H$, refluxing; (ii) (a) $LiHB(Et)_3$, THF, 0 °C–rt; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C; (iii) $LiPPh_2$, THF, −78 °C–rt.

Table 2. Asymmetric hydrogenation of MOM-protected β-hydroxyl enamides with [Rh(DIOP*)(NBD)]SbF6 (**10**) as a catalyst precursor



Entry	Substrate	Conversion (%)	Ee (%)[a]
1	**4a** R = H	100	98.1
2	**4b** R = *o*,*p*-2F	100	95.8
3	**4c** R = *p*-F	100	99.4
4	**4d** R = *p*-Cl	100	95.7
5	**4e** R = CH_3	100	99.1
6	**4f** R = Ph	100	99.6
7	**4g** R = OMe	100	97.7
8	**4h**  = 2-Naphthyl	100	>99.9

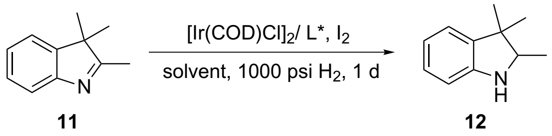
[a] The enantiomeric excesses were determined by chiral HPLC using an (*S*,*S*)-Whelk-01 column. The (*S*)-configurations of the products were determined by comparing the retention times of two enantiomers with reported data.

backbone rigidities. All these results clearly indicate that conformational analysis of the backbone rigidity could be an effective tool for designing good ligands in terms of both reactivity and enantioselectivity.

Chiral amino alcohols have been widely used as pharmaceutical components,[10] chiral ligands[11] and auxiliaries.[12] Although many synthetic methods have been well-documented,[13] developing new and practical catalysts for the preparation of such important chiral building blocks via simple asymmetric hydrogenation of **4** to **5** is still attractive. To further demonstrate its generality in high reactivity and enantioselectivity for this potentially useful transformation, Rh-DIOP* complex **10** was used to catalyze the hydrogenation of a series of MOM-protected β-hydroxyl enamides **4a–h** under very mild conditions. As shown in Table 2, all the reactions went to completion within 1 h with the enantioselectivities being excellent for all the substrates with different substituents on the phenyl ring (100% conversion, 96%–99% ee), providing a very selective and efficient catalytic system for the synthesis of nearly enantiomerically pure amino alcohol derivatives.

A number of 1,4-bisphosphine ligands were found to be effective for the Ir-catalyzed hydrogenation of imines.[2d,14] DIOP was among the earliest ligands explored for imine reduction, although only moderate ee values were obtained.[15] Thus, we were also interested in investigating imine reduction with those DIOP derivatives for comparison. Some of the preliminary results of Ir-catalyzed hydrogenation of a cyclic imine **11** with ligands **2**, **6**, and **7** are summarized in Table 3. With Ir-**7** complex generated in situ as a catalyst and 10 mol% I_2 as an additive, 85% ee was obtained at 0 °C in CH_2Cl_2 (entry 7 in Table 3), which is better than those previously reported with DIOP.[15]

Table 3. Ir-catalyzed asymmetric hydrogenation of a cyclic imine with DIOP derivatives as ligands[a]



Entry	L*	Solvent	Temp. (°C)	Conversion (%)	Ee (%)[b]
1	**2**	MeOH	25	20.0	6.0
2	**2**	Toluene	25	95.4	20.0
3	**2**	CH_2Cl_2	25	90.9	29.3
4	**6**	CH_2Cl_2	25	31.0	11.0
5	**7**	MeOH	25	13.0	6.4
6	**7**	Toluene	25	39.3	77.8
7[c]	**7**	CH_2Cl_2	0	96.6	85.0
8	**7**	CH_2Cl_2	25	96.4	81.6
9	**7**	CH_2Cl_2	60	98.4	41.1

[a] The reactions were carried out at the indicated temperature under 1000 psi of H_2 for 1 d. The catalyst was prepared in situ by mixing $[Ir(COD)Cl]_2$ (0.5 mol%) and ligand (1.1 mol%) in solvent followed by addition of I_2 (10 mol%).

[b] The enantiomeric excesses were determined by chiral GC using a chiral select 1000 column.

[c] The reaction time was 3 d.

3. Conclusion

In conclusion, several DIOP derivatives[16] have been developed as efficient ligands for Rh and Ir-catalyzed asymmetric hydrogenations. The results of the Rh-catalyzed hydrogenation of MOM-protected β-hydroxyl enamides strongly support our conformational analysis about the influence of the ligand backbone flexibility on the reactivities and enantioselectivities. Isolation of the pure catalyst precursor is also necessary to provide the most active catalytic species.

Acknowledgements

This work was supported by NIH. We gratefully acknowledge the generous loan of precious metals from Johnson Matthey Inc.

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16. Data for new ligands **6**, **7**, and Rh-complex **10**:

    3,4-Dihydroxy-2,5-bis(diphenylphosphanyl)hexane **6**: $[\alpha]_D^{20} = -15.2$ (*c* 0.40, $CHCl_3$); ^1H NMR (CD_2Cl_2, 360 MHz) δ 7.58–7.55 (m, 8H), 7.39–7.34 (m, 12H), 3.60–3.54 (m, 2H), 2.61–2.54 (m, 2H), 2.47 (br s, 2H), 0.84 (d, $J = 7.0$ Hz, 3H), 0.80 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.1 (dd, $J = 14,7$ Hz, $J = 51.7$ Hz), 134.3 (dd, $J = 8.0$ Hz, $J = 20.4$ Hz), 129.7 (d, $J = 28.2$ Hz), 129.0 (dd, $J = 7.2$ Hz, $J = 11.7$ Hz), 72.3 (dd, $J = 7.1$ Hz, $J = 11.4$ Hz), 33.9 (d, $J = 11.4$ Hz), 10.3 (d, $J = 17.4$ Hz); ^{31}P NMR ($CDCl_3$, 145 MHz) δ −7.68; HRMS (M^++1) *m*/*z* calcd for $C_{30}H_{33}O_2P_2$ 487.1950, found 487.1916.

    3,4-*O*-Dibenzyl-3,4-dihydroxy-2,5-bis(diphenylphosphanyl)hexane **7**: $[\alpha]_D^{20} = +74.6$ (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.48–7.07 (m, 30H), 4.54 (s, 4H), 3.49–3.43 (m, 2H), 2.44–2.37 (m, 2H), 0.89–0.83 (m, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 138.1, 136.4 (d, $J = 16.0$ Hz), 136.0 (d, $J = 15.8$ Hz), 133.5–132.4 (m), 128.3–126.8 (m), 79.0 (t, $J = 9.3$ Hz), 74.0 (d, $J = 4.0$ Hz), 33.4 (d, $J = 11.6$ Hz), 9.52 (d, $J = 17.9$ Hz); ^{31}P NMR ($CDCl_3$, 145 MHz) δ −8.24; HRMS (M^++1) *m*/*z* calcd for $C_{44}H_{45}O_2P_2$ 667.2889, found 667.2858.

    [Rh(DIOP*)(NBD)]SbF_6 **10**: ^1H NMR ($CDCl_3$, 360 MHz) δ 8.04–7.99 (m, 4H), 7.64–7.56 (m, 6H), 7.41–7.40 (m, 6H), 7.01–7.00 (m, 4H), 4.49 (br s, 2H), 4.15 (br s, 2H), 4.06 (m, 2H), 3.77 (br s, 2H), 2.60–2.57 (m, 2H), 1.39 (s, 2H), 1.20 (s, 6H), 1.10–1.04 (m, 6H); ^{31}P NMR ($CDCl_3$, 145 MHz) δ 32.89 (d, $J = 152.1$ Hz 6H); ^{31}P NMR ($CDCl_3$, 145 MHz) δ 32.89 (d, $J = 152.1$ Hz).