

Novel 1,4-Diphosphanes with Imidazolidin-2-one Backbones as Chiral Ligands: Highly Enantioselective Rh-Catalyzed Hydrogenation of Enamides**

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Transition metal catalyzed asymmetric hydrogenation is one of the most powerful methods for the synthesis of optically active compounds, and the development of new chiral phosphanes plays a crucial role in this area.^[1, 2] Since Kagan and Dang developed the first C_2 -symmetric 1,4-diphosphane ligand (diop) in the early 1970s,^[3] many diop analogues (**A** and **B** in Figure 1) have been synthesized and

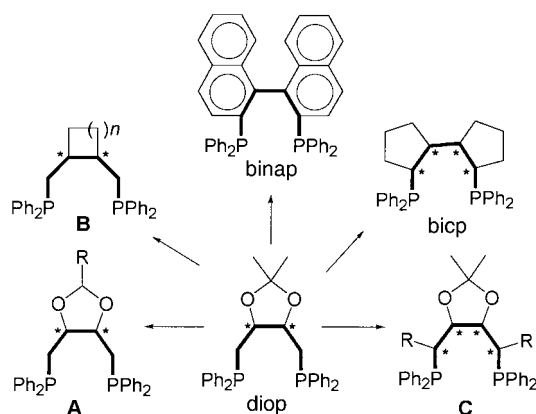


Figure 1. Various types of 1,4-diphosphanes forming seven-membered metal chelate rings.

applied in various asymmetric catalytic reactions.^[4] However, the enantioselectivities obtained with these diop-type 1,4-diphosphane ligands are not always sufficiently high. It is generally believed that the low enantioselectivities with diop-type 1,4-diphosphanes are largely due to the formation of conformationally flexible seven-membered metal-chelate rings. Thus, transfer of backbone chirality through a methylene group to the phenyl group on the phosphane may not be efficient.^[5] Only a few diphosphane ligands forming seven-membered metal chelates (e.g., axially chiral binap^[6] and bicp^[7]) achieved high enantioselectivities. More recently, ligands **C** have been introduced in which the configurations of the stereogenic centers are crucial to obtain high enantio-

selectivity.^[8] Here we report a new type of 1,4-diphosphane ligands with an imidazolidin-2-one backbone, namely, (4*S*,5*S*)-4,5-bis(diphenylphosphanylmethyl)imidazolidin-2-ones **1** (bdpmi, Figure 2), which showed excellent enantioselectivities in Rh-catalyzed hydrogenation of α -arylenamides, a reaction that has attracted considerable attention recently.^[9]

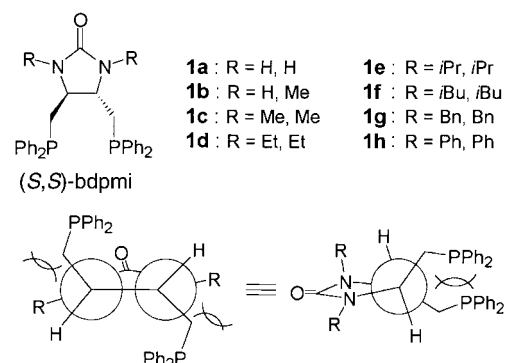
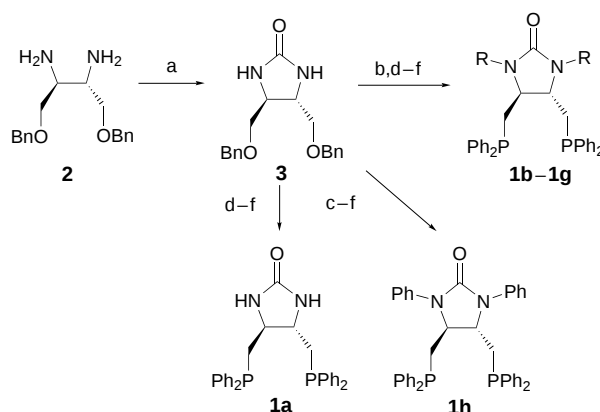


Figure 2. (*S,S*)-bdpmi ligands **1** and the Newman projection showing possible *gauche* interactions.

The design of the bdpmi ligands **1** was based on the following hypothesis: the consecutive *gauche* steric interactions between the N-substituents and phosphanylmethyl groups, as revealed in Newman projections (Figure 2), may influence the conformational flexibility of the seven-membered metal-chelate ring, and the enantioselectivity could therefore be strongly dependent on the steric nature of the R groups.

To test this hypothesis, a number of substituents R with different bulkiness were introduced on the nitrogen atom of imidazolidin-2-one (Scheme 1). Straightforward conversion of L-tartaric acid to the C_2 -symmetric vicinal diamine **2**^[10] and subsequent reaction of **2** with carbonyldiimidazole (CDI) led to the key intermediate **3** in 40% overall yield. Deprotection



Scheme 1. a) CDI (1.2 equiv), CH_2Cl_2 , reflux, 4 h, 94%; b) NaH, RBr, THF, reflux; R = H, Me: 35%; Me, Me: 89%; Et, Et: 91%; *i*Pr, *i*Pr: 16%; *i*Bu, *i*Bu: 43%; Bn, Bn: 90%; c) PhBr, *t*BuONa, Pd-dppf, toluene, 96%; d) $\text{H}_2/\text{Pd}-\text{C}$, MeOH, RT, 82–99% or for R = Bn, Pd(OH)₂/C, cyclohexene, MeOH/EtOAc (1:1), reflux, 81%; e) TsCl (2.2 equiv), pyridine, 71–86% or for R = Bn: MsCl (2.2 equiv), Et₃N, CH_2Cl_2 , 74%; f) KPPH₂, CH_2Cl_2 , RT, R = H, H: 76%; H, Me: 73%; Me, Me: 70%; Et, Et: 67%; *i*Pr, *i*Pr: 74%; *i*Bu, *i*Bu: 77%; Bn, Bn: 74%; Ph, Ph: 70%. dppf = 1,1'-bis(diphenylphosphino)ferrocene.

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of the *O*-benzyl groups (after *N*-alkylation for **1b–1g**) and tosylation (mesylation for **1g**) followed by reaction with potassium diphenylphosphide afforded ligands **1a–1g**. The *N*-phenyl group of **1h** was introduced by using the Hartwig–Buchwald arylamination method.^[11]

N-Acetylphenylethanamine (**4a**) was used as model substrate for hydrogenation. All reactions were carried out at 20 °C under 1 atm of H₂ and with an Rh:ligand ratio of 1:1.2 (Table 1).^[12] Although a standard reaction time of 12 h was

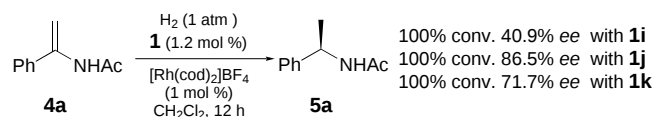
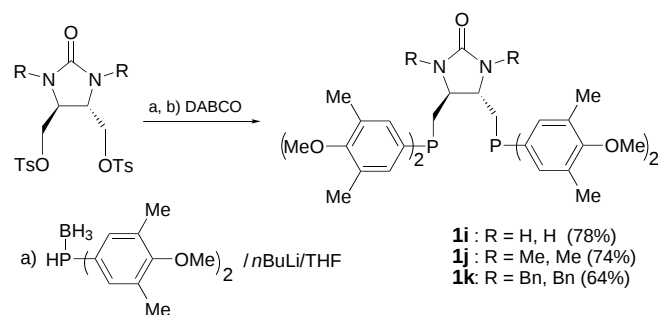
Tabelle 1. Rh-catalyzed asymmetric hydrogenation of *N*-acetyl phenylethanamine **4a** with **1a–1h** as chiral ligands.^[a]

Entry	Ligand	Conv. [%] ^[b]	<i>ee</i> [%] ^[c]	Config. ^[d]
1	(<i>S,S</i>)-diop	100	60.2	<i>R</i>
2	1a	100	86.4	<i>R</i>
3	1b	100	94.0	<i>R</i>
4	1c	100	98.5	<i>R</i>
5	1d	100	97.3	<i>R</i>
6	1e	100	95.7	<i>R</i>
7	1f	100	97.2	<i>R</i>
8	1g	100	96.2	<i>R</i>
9	1h	100	94.6	<i>R</i>

[a] The reaction conditions were [Rh(cod)₂]BF₄:ligand:substrate 0.01:0.012:1, H₂ pressure 1 atm, reaction time 12 h, solvent CH₂Cl₂, room temperature. [b] Determined by ¹H NMR and GC analysis. [c] Determined by chiral GC on a CP-Chirasil-Dex CB column. [d] Determined by comparing the sign of the optical rotation with that reported in ref. [9b].

chosen, most reactions were complete within 4 h. With **1a**, which does not have *N*-substituents, **4a** was hydrogenated to **5a** with 86.4% *ee* (entry 2). Under the same conditions, 60.2% *ee* was obtained with diop (entry 1). Introducing one *N*-methyl group (**1b**) increased the enantioselectivity to 94.0% *ee* (entry 3). The enantioselectivity was further increased with *N,N*-dimethylated ligand **1c** to 98.5% *ee* (entry 4). Comparison of the sense of asymmetric induction imparted by diop, **1a**, **1b**, and **1c** suggested that the steric interactions between the *N*-substituents and the phosphanyl-methyl group is one of the key elements that controls enantioselectivity. However, *N*-substituents larger than methyl resulted in slightly lower enantioselectivities (entries 5–9), that is the *ee* values decreased with increasing *A* values of the *N*-substituents.^[13]

Significantly lower *ee* values were obtained with **1i–1k**, synthesized by reaction of the tosylated intermediates for ligands **1a** and **1c** (mesylated for **1g**) with lithium bis(3,5-dimethyl-4-methoxyphenyl)phosphide–borane complex.^[14] The NH ligand **1i** hydrogenated **4a** with only 40.9% *ee*, whereas the enantioselectivity with the *N,N'*-dimethylated ligand **1j** increased to 86.5% *ee* (Scheme 2). The ligands **1i–1k** possessing electron richer and bulkier phosphane groups uniformly give lower *ee* values than the corresponding **1a**, **1c**, and **1g**, and this indicates that steric effects alone may not be responsible for controlling enantioselectivity. However, the reason for the striking deterioration in enantioselectivity with **1i–1k** is not clear at present.



Scheme 2. Synthesis of ligands **1i–k** and Rh-catalyzed hydrogenation of enamide **4a** with **1i–1k** as ligands. DABCO = 1,4-diaza[2.2.2]bicyclooctane.

The catalytic hydrogenation can be applied successfully to a series of α -arylenamides **4b–4g** to give chiral amine derivatives **5b–5g** with Me₂bdpmi **1c** (Table 2). In all cases, the *N,N*-dimethylated ligand **1c** exhibited excellent enantioselectivity. The electronic nature of the *para* substituents in α -phenylenamides has an effect on the enantioselectivity. Enamides with electron-donating substituents (**4b** and **4e**, entries 1 and 4 in Table 2) give higher enantioselectivity than those with electron-withdrawing substituents (**4c** and **4d**, entries 2 and 3). Remarkably, the mixtures of *E*- and *Z*-enamides **4g–4k** (*E/Z* = 1:2.0–2.5) were also reduced with very high enantioselectivities (>99.0% *ee*, entries 6–10). It is noteworthy that the *ee* values of 97.8–99.0% obtained with bdpmi ligand **1c** are higher than or comparable to those obtained with other families of efficient chiral diphosphane ligands.^[8, 9]

Tabelle 2. Rh-catalyzed asymmetric hydrogenation of various *N*-acetyl α -arylenamides with **1c** as chiral ligand.^[a]

Entry	4	Ar, R ¹	Conv. [%] ^[b]	<i>ee</i> [%] ^[c]	Config. ^[d]
1	4b	<i>p</i> -MeC ₆ H ₄ , H	100	98.6	<i>R</i>
2	4c	<i>p</i> -FC ₆ H ₄ , H	100	97.9	<i>R</i>
3	4d	<i>p</i> -ClC ₆ H ₄ , H	100	97.8	<i>R</i>
4	4e	<i>p</i> -MeOC ₆ H ₄ , H	100	99.0	<i>R</i>
5	4f	2-naphthyl, H	100	> 99.0 ^[e]	<i>R</i>
6	4g	C ₆ H ₅ , Me	100	> 99.0	<i>R</i>
7	4h	C ₆ H ₅ , Et	100	> 99.0	<i>R</i>
8	4i	<i>p</i> -MeOC ₆ H ₄ , Me	100	> 99.0	<i>R</i>
9	4j	<i>p</i> -ClC ₆ H ₄ , Me	100	> 99.0	<i>R</i>
10	4k	<i>p</i> -MeC ₆ H ₄ , Me	100	99.0	<i>R</i>

[a] The reaction conditions were [Rh(cod)₂]BF₄:**1c**:substrate 0.01:0.012:1, H₂ pressure 1 atm, reaction time 12 h, solvent CH₂Cl₂, room temperature. [b] Determined by ¹H NMR and GC analysis. [c] Determined by chiral GC on a CP-Chirasil-Dex CB column. [d] Absolute configurations were ascertained by comparison of the sign of optical rotation with that reported in ref. [9b]. [e] Determined by HPLC on a Chiralcel OD column.

In summary, we have developed a new family of 1,4-diphosphanes **1** with an imidazolidin-2-one backbone as chiral ligands and showed their utility in the hydrogenation of α -enamides. The modular construction of this ligand class allows for wide structural diversity. Studies of this kind and mechanistic investigations are underway.

Experimental Section

For details on the synthesis of **1a–1k** and their precursors, see Supporting Information.

General procedure for the asymmetric hydrogenation of enamide **4**: **1** (0.0074 mmol) was added to a solution of [Rh(cod)₂]BF₄ (2.5 mg, 0.0062 mmol; cod = 1,5-cyclooctadiene) in CH₂Cl₂ (2 mL). After the reaction mixture had been stirred at 20 °C for 20 min, enamide **4** (0.62 mmol) was added. The hydrogenation was performed at 20 °C under 1 atm of hydrogen for 12 h. The reaction mixture was passed through a short silica gel column to remove the catalyst. The enantiomeric excess and the reaction conversion were measured by chiral GC or HPLC without any further purification.

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Mimicking Metallophosphatases: Revealing a Role for an OH Group with No Libido**

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Typically, descriptions of enzyme catalysis use multiple simultaneous interactions between the substrate and the active site to explain the remarkable efficiency which is normally observed.^[1] This poses the intriguing question—do the different interactions operate cooperatively? That is, can a catalytic interaction have a bigger impact when it acts in concert with other complementary interactions than when it is used alone. This is difficult to mimic with simple compounds; usually when multiple interactions are introduced into a model system, it is found that they act independently rather than simultaneously, and such models generally do not rival enzyme efficiency.^[2] Here we report how catalysis of phosphate monoester hydrolysis by an intramolecular OH group becomes much more effective when combined with catalysis by a dinuclear metal ion complex.

We have incorporated phosphate monoesters **1a–c** into dinuclear Co^{III} complexes **2a–c**. We have previously studied this type of complex as a structural and functional model for dinuclear metallophosphatases.^[3] We wanted to investigate the effect of combining intramolecular general acid catalysis with this highly reactive core, as X-ray crystallography has revealed that as well as the metal ions in the active sites of metallophosphatase such as protein phosphatase-1 (PP-1) and kidney bean purple acid phosphatase (KBAP), potential

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