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A novel optically active bisphosphine ligand CDP, derived from an anti head-to-head coumarin dimer: synthesis and application to the rhodium-catalyzed asymmetric hydrogenation of arylenamides

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Abstract

A novel optically active bisphosphine ligand CDP containing a C_2-symmetric cyclobutane ring was prepared from an enantiopure anti head-to-head coumarin dimer. CDP was successfully applied to the rhodium-catalyzed asymmetric hydrogenation of arylenamides, affording the corresponding amides up to 93% e.e.

Development of chiral ligands is one of the most fascinating methods to achieve high enantioselectivity of a given catalytic asymmetric reaction.[1] Chiral ligands derived from an artificial chiral source play an important role in catalytic asymmetric synthesis, although the resolution of the chiral ligands themselves or their precursors is required in the preparation step. We have already reported a convenient procedure for the resolution of anti head-to-head coumarin dimer **1**,[2] which is easily prepared by the [2+2] photodimerization of coumarin.[3] On the basis of the fact that some C_2-symmetrical bisphosphine ligands give excellent results for many kinds of reactions[1] and that the structural characteristics of **1** would allow its transformation to a C_2-symmetrical bisphosphine related to C4DIOP,[4] (Fig. 1) the dimer **1** was converted into 1,2-bis(diphenylphosphinomethyl)-3,4-bis(2-methoxyphenyl)cyclobutane (CDP, **2**). Herein we report the synthesis of CDP and its application to the rhodium-catalyzed asymmetric hydrogenation of arylenamides.

CDP **2** was prepared from enantiopure anti head-to-head coumarin dimer (−)-**1**[2] by following the procedure described in Scheme 1. Treatment of (−)-**1** with dimethyl sulfate in aqueous acetone in the presence of NaOH gave dimethyl ester **3**, which was reduced with $LiAlH_4$ to give the corresponding diol

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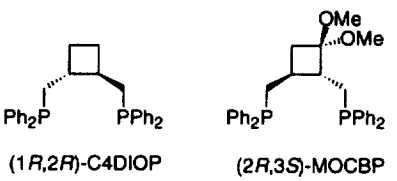
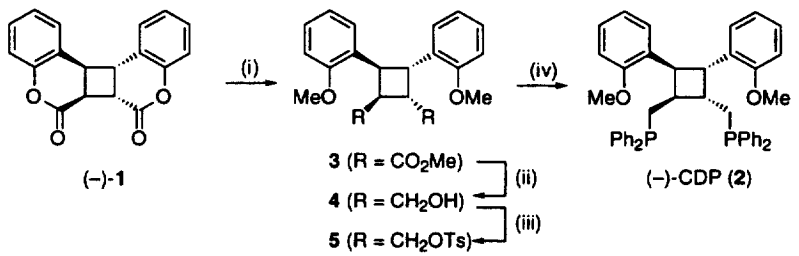


Fig. 1.

4. Tosylation of the hydroxyl groups of **4**, followed by nucleophilic substitution with $NaPPh_2$ generated in situ, afforded bisphosphine CDP **2** in 55% total yield.[5]



Scheme 1. Synthesis of (−)-CDP (**2**) from (−)-**1**

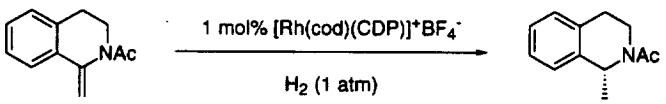
CDP was first applied as a ligand in the rhodium-catalyzed asymmetric hydrogenation of arylenamide **6**,[6–8] where structurally-related bisphosphine ligand MOCBP (Fig. 1) having a cyclobutane ring is reported to be effective.[6] A cationic rhodium catalyst $[Rh(cod)(CDP)]^+BF_4^-$ (cod=1,5-cyclooctadiene) was prepared in 98% yield by the reaction of CDP with $[Rh(cod)_2]^+BF_4^-$ in THF. The reaction of **6** proceeded smoothly at 50°C using the CDP–Rh complex as a catalyst, and the corresponding amide **7** was obtained in quantitative yield with 76% e.e. after reacting for 1 hour (Table 1, entry 1). The reaction was also complete within 1 hour at 20°C with improvement of the enantioselectivity to 86% e.e. (Table 1, entry 2), while lowering the reaction temperature to 0°C resulted in no reaction (Table 1, entry 3). Ethanol is the solvent of choice due to the high reactivity of the catalyst in this solvent. In contrast, the reactions in other solvents gave lower chemical yields and much longer reaction times, although similar enantioselectivities were maintained (Table 1, entries 4–6).

The CDP–Rh catalyst was then applied to the hydrogenation of acyclic arylenamides. In all cases shown in Table 2, the hydrogenation of enamides **8** proceeded smoothly to afford amides **9** in good to excellent yields with good enantioselectivity. These results show that CDP has potent asymmetric induction ability similar to known ligands.[9] Worth noting is that enimide **8b** gave a superior result in both the reactivity and the selectivity, compared with the corresponding enamide **8a**. Since enimides were reported to be intermediates in the synthesis of the corresponding enamides[10] and gave the same amines after hydrogenation followed by hydrolysis, the enimides would be alternative substrates of enamides in asymmetric hydrogenation.

The torsional angle of the cyclobutane framework of C4DIOP has been demonstrated to be suitable in the rhodium-catalyzed hydrogenation of *N*-acyldehydroamino acids.[4b] However, troublesome resolution is required as a key step for the synthesis of C4DIOP. An analogous ligand, MOCBP, has been prepared to solve the resolution problem to show good enantioselectivity in the rhodium-catalyzed hydrogenation of enamides.[6] The present ligand, CDP, which could be easily prepared, has not only a cyclobutane framework, but also aromatic substituents on the cyclobutane ring in a *cis* relationship to each of the diphenylphosphinomethyl groups; the aromatic substituents might push out the phenyl groups on the phosphorus atoms to the central metal to realize high enantioselectivity in the present reaction.

In conclusion, we synthesized a new chiral bisphosphine ligand CDP and applied it as a chiral ligand

Table 1
Asymmetric hydrogenation of **6** by Rh–CDP catalyst[a]



6 **7**

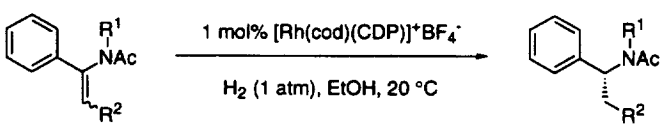
Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	%e.e (Abs. Config.)[c]
1	EtOH	50	1	quant.	70 (*R*)
2	EtOH	20	1	96	83 (*R*)
3	EtOH	0	24	0	–
4	MeOH	20	24	35	85 (*R*)
5	Benzene	20	24	38	78 (*R*)
6	CH_2Cl_2	20	24	99	76 (*R*)

a) All hydrogenations were carried out in a 0.5 mmol-scale.

b) Isolated yields.

c) The enantiomeric excesses were determined by HPLC (Daicel Chiralcel OD, hexane/2-propanol = 11/1). Absolute configurations were determined by comparison of their signs of optical rotation with those given in the literature.[7]

Table 2
Rh–CDP catalyzed asymmetric hydrogenation of enamides **8**[a]



8a–d **9a–d**

Entry	Substrate	R^1	R^2	Time (h)	Yield (%)[b]	%e.e (Abs. Config.)[c]
1	**8a**	H	H	1	93	76 (*R*)
2	**8b**	Ac	H	2	98	93 (*R*)
3	**8c**	Bn	H	24	64	93 (*R*)
4	**8d**[d]	H	Me	1	99	92 (*R*)

a) All hydrogenations were carried out in a 0.5 mmol-scale ([Subst.] = 0.2M).

b) Isolated yields.

c) The enantiomeric excesses were determined by HPLC (Daicel Chiralcel OB, hexane/2-propanol = 9/1 for **9a**; Daicel Chiralcel OD, hexane/2-propanol = 15/1 for **9b**, **9c** and **9d**). Absolute configurations of **9a** and **9b** were determined by comparison of the chromatograms with those of authentic samples prepared from optically active amines. The others were speculated from the trends of the chromatograms.

d) A mixture of E/Z isomers (E/Z = 65/35) was used.

in the rhodium-catalyzed asymmetric hydrogenation of arylenamides. Further applications of this new chiral ligand in catalytic asymmetric synthesis are now under investigation.

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