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Preparation of new C_2-symmetric tetraphosphine ligands for Rh-catalyzed asymmetric hydrogenation of arylenamides

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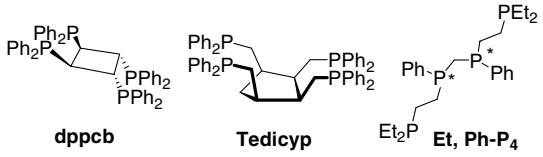
Abstract—A new type of chiral tetraphosphine ligands **1** were prepared from enantiopure anti-head-to-head coumarin dimer **5** and then utilized in Rh-catalyzed asymmetric hydrogenation reaction of arylenamides, affording the corresponding amides with up to 85% ee. Some chiral bisphosphine ligands derived from coumarin dimer **5** were also evaluated in the same reaction.

Asymmetric catalysis of organic reactions to provide enantio-enriched products is of central importance to modern synthetic and pharmaceutical chemistry.[1] Development of chiral ligands is one of the most fascinating methods to achieve high enantioselectivity for a given catalytic asymmetric reaction.[2] Phosphine ligands, especially monophosphines and chelating bisphosphines, have found widespread applications in various catalytic transformations. Although the idea to use polyphosphine[3] as ligands to stabilize transition metal catalysts has emerged early, the nondissociative nature of the chelating polyphosphines is often regarded as a disadvantage in catalytic processes, where unsaturated or labile sites at the metal center are often necessary for activity. This seems to be one of the reasons hindering the application of polyphosphines in catalysis. On the other hand, the excellent bonding ability and strong trans effect exhibited by polyphosphines may also confer themselves favorable catalytic properties over their monodentate phosphine counterparts, as demonstrated by several elegant examples including tetraphosphines such as dppcb,[4] Tedicyp,[5] Et, Ph–P_4,[6] etc.[7] The cofacial tetraphosphine Tedicyp has been demonstrated to be a versatile ligand for a broad range of palladium-catalyzed reactions with extremely high catalytic activities. This phenomenon is often ascribed to the strong coordination of the four phosphines close to the metal center, preventing the decomposition of the catalyst. The linear tetraphosphine Et, Ph–P_4 was mostly used as a bridging ligand to form a homobimetallic rhodium complex rac-$[Rh_2(nbd)_2L][BF_4]_2$ (nbd = norbornadiene, L = Et, Ph–P_4), which act as an active catalyst precursor for a highly regioselective hydroformylation of terminal alkenes.[6a–d] Furthermore, the bimetallic cooperativity of Et, Ph–P_4–Rh system uncovered by mechanistic studies provides inspiration for new catalyst design and development. Despite these efforts, however, successful catalytic applications of polyphosphines are still limited so far, and even rarer are in asymmetric catalysis.[6b] It would thus be highly desirable to explore the potential catalytic efficiency and asymmetric induction of enantiopure polyphosphines.



Previously we have reported a convenient procedure for inclusion resolution of racemic *anti-head-to-head* coumarin dimer **5**,[8b,c] which was demonstrated independently by Hayashi and us to be one type of privileged scaffold for the synthesis of chiral bisphosphine ligands bearing cyclobutane-backbone for catalytic asymmetric hydrogenation or allylic substitution reactions.[8a–c] We envisioned that the functionality of this coumarin dimer should facilitate its further derivation into a new type of chiral tetraphosphine ligands **1** (Scheme 1), allowing for

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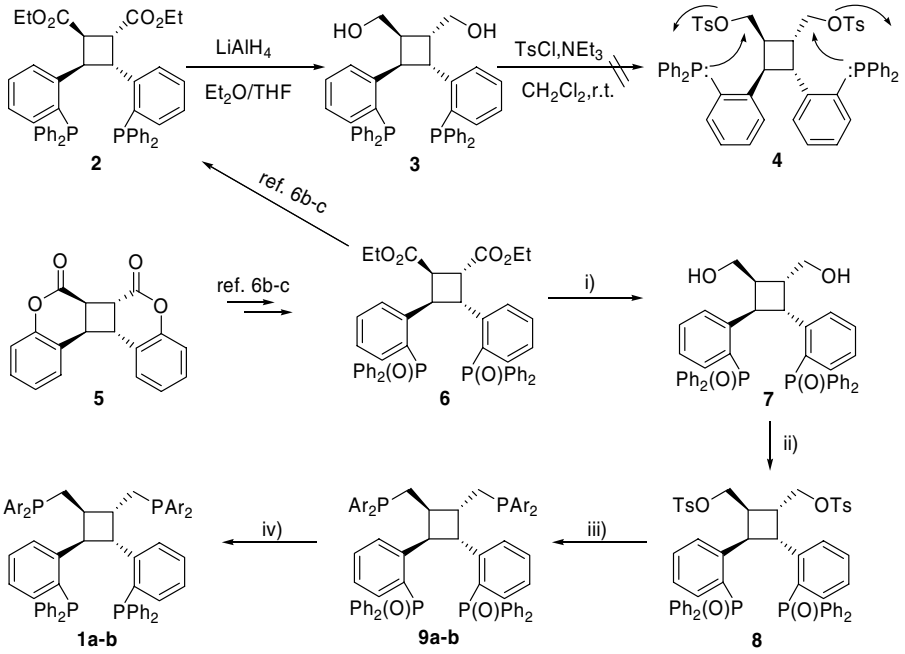


Scheme 1. Synthesis of tetraphosphine ligands **1**. Reagents and conditions: (i) $LiAlH_4$, Et_2O, rt, 90%; (ii) TsCl, NEt_3, DCM, rt, 12 h, **8**, 92%; (iii) $LiPAr_2$, THF, 0 °C, Ar = C_6H_5, **9a**, 56%; Ar = 3,5-$(Me)_2C_6H_3$, **9b**, 63%; (iv) $HSiCl_3$, $PhNMe_2$, PhMe, 100 °C, Ar = C_6H_5, **1a**, 62%; Ar = 3,5-$(Me)_2C_6H_3$, **1b**, 26%.

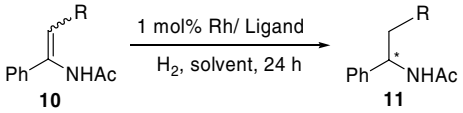
the examination of their catalytic behavior in asymmetric reactions. Herein, we report the synthesis of **1** and its use as the ligand in Rh-catalyzed asymmetric hydrogenation of arylenamides.

As shown in Scheme 1, we initially attempted to synthesize **1** via compound **3**, a known hydroxymethyl bisphosphine, easily derived from coumarin dimer **5**.[8c] Subsequent tosylation of dihydroxy groups of **3** followed by nucleophilic substitution of the tosylate with Ar_2PLi[9] was supposed to provide the desired tetraphosphine ligand **1**. However, the expected tosylate intermediate **4** could not be obtained from **3**, presumably due to a consequential intramolecular nucleophilic attack of the trivalent P atoms on the resulting tosylate groups.

We envisioned that the difficulty could be overcome by modulating the nucleophilicity of the PPh_2 moieties in the synthetic intermediates, either via its protection with BH_3 or by using its oxide form [$P(O)Ph_2$]. Compared with the former, the latter protocol seems to be more advantageous, since the relevant synthesis is more straightforward, and $P(O)Ph_2$ is more tolerant of either acidic or basic conditions than $PPh_2{\cdot}BH_3$.[10] Accordingly, our subsequent synthetic sequence employed hydroxymethyl bisphosphine oxide **7**, prepared in 90% yield by LAH reduction[11] of the ester groups of **6**. Treatment of **7** with tosyl chloride in the presence of triethylamine at room temperature led to the formation of tosylate **8** in high yield, which were smoothly phosphorylated with Ar_2PLi (Ar = C_6H_5 or 3,5-$(Me)_2C_6H_3$) to afford **9a** or **9b** in moderate yields. Subsequent reduction with $HSiCl_3$ afforded target tetraphosphine ligands **1a** and **1b** (Ar = C_6H_5, **1a**; Ar = 3,5-$(Me)_2C_6H_3$, **1b**), respectively (Scheme 1).

The stereocontrol capability of ligand **1a** was then examined in the rhodium-catalyzed asymmetric hydrogenation of arylenamides **10**, and the results are summarized in Table 1. Under 5 atm of hydrogen pressure at rt in ethanol, hydrogenation of **10a** proceeded smoothly in the presence of the 1 mol % of the in situ generated Rh(I)–**1a** complex, affording *N*-(1-phenylethyl)acetamide **11a** in 63% ee with quantitative conversion after 24 h (entry 1). As a comparison, several other coumarin-dimer-derived enantiopure polyphosphine ligands that potentially allow different chelating modes at the Rh center upon complex formation with $Rh(COD)_2BF_4$, including the synthetic intermediate **9a** and bisphosphine ligands **2** and **3**, were also tested in the same reaction under identical conditions (entries 2–4). Remarkably, the enantioselectivities of these bisphosphine ligands were consistently inferior to that of **1a**, even though the conversions were generally good to excellent (entries 2–4 vs 1).[12] Virtually racemic product was obtained in the case of ligand **9a** (entry 2), a structural analogue of tetraphosphine ligand **1a**, suggesting that the enantioselectivities of these catalytic systems are highly sensitive to the subtle modifications in the ligand structure. Although it is tempting to say that owing to the steric congestion it seems to be less likely that **1a** could act as a tetradentate ligand, the exact nature of the active species involved in the Rh(I)–**1a** catalyzed reaction still remains unknown. As a consequence of potentially multiple interacting factors on complex formation, such as the specific geometry of cyclobutane ring of the ligand backbone, the flexible methylene linkers, variable stoichiometry of the complex, as well as the potentially multiple chelating modes[13] at the metal center, a large variety of coordination

Table 1. Rh-catalyzed asymmetric hydrogenation of *N*-acetyl phenylethenamide **10** with phosphine ligands derived from coumarin dimer[a]



10 **11**

Entry	Ligand	R in **10**	Conditions	Conversion[b] (%)	ee[c] (%)
1	**1a**	H (**10a**)	Rh/**1a** molar ratio 1:1, 5 atm H_2, EtOH, 25 °C	>99	63
2	**9a**	H (**10a**)	Rh/**9a** molar ratio 1:1, 5 atm H_2, EtOH, 25 °C	>99	6
3	**2**	H (**10a**)	Rh/**2** molar ratio 1:1, 5 atm H_2, EtOH, 25 °C	60	23
4	**3**	H (**10a**)	Rh/**3** molar ratio 1:1, 5 atm H_2, EtOH, 25 °C	95	16
5	**1a**	H (**10a**)	Rh/**1a** molar ratio 1:1, 5 atm H_2, CH_2Cl_2, 25 °C	>99	61
6	**1a**	H (**10a**)	Rh/**1a** molar ratio 2:1, 5 atm H_2, CH_2Cl_2, 25 °C	>99	74
7	**1a**	H (**10a**)	Rh/**1a** molar ratio 2:1, 5 atm H_2, toluene, 25 °C	>99	69
8	**1a**	H (**10a**)	Rh/**1a** molar ratio 1.6:1, 5 atm H_2, CH_2Cl_2, 25 °C	>99	78
9	**1a**	H (**10a**)	Rh/**1a** molar ratio 1.8:1, 5 atm H_2, CH_2Cl_2, 25 °C	>99	78
10	**1a**	H (**10a**)	Rh/**1a** molar ratio 2.2:1, 5 atm H_2, CH_2Cl_2, 25 °C	>99	71
11	**1a**	H (**10a**)	Rh/**1a** molar ratio 1.8:1, 1 atm H_2, CH_2Cl_2, 25 °C	>99	71
12	**1a**	H (**10a**)	Rh/**1a** molar ratio 1.8:1, 1 atm H_2, CH_2Cl_2, 13 °C	>99	85
13	**1a**	H (**10a**)	Rh/**1a** molar ratio 1.8:1, 1 atm H_2, CH_2Cl_2, 0 °C	>85	75
14	**1b**	H (**10a**)	Rh/**1b** molar ratio 1.8:1, 1 atm H_2, CH_2Cl_2, 13 °C	>99	60
15	**1a**	CH_3 (**10b**)	Rh/**1a** molar ratio 1.8:1, 1 atm H_2, CH_2Cl_2, 13 °C	>99	84

[a] All reactions were performed in stainless steel autoclave at a 0.4 mmol (0.2 M) substrate scale in the presence of 1.0 mol % $Rh(COD)_2BF_4$ for 24 h.
[b] Determined by ^1H NMR analysis of the crude reaction mixture.
[c] The enantiomeric excess was determined by chiral HPLC on Chiralpak AD column. The configurations of all the products were found to be (*R*) by comparison of the signs of optical rotation to those reported in Refs. 6a and 11.

modes are conceivable for the resulting Rh(I)–**1a** system.

Subsequent screening of the solvent effect and the molar ratio of Rh precursor to ligand for **1a** mediated reaction led to further enhancement in the enantioselectivity (Table 1, entries 5–10), resulting in an optimal ee of 78% for the reaction in dichloromethane in the presence of 1.8:1 Rh/**1a** (entry 9). A preliminary ^{31}P NMR study for the Rh(I)–**1a** mixture in $CDCl_3$ (see Supplementary data) seems to be consistent with the aforementioned assumption, where the broad signals (and the absence of characteristic signal of free **1a**) suggest the co-existence of multiple rhodium-containing species, presumably involved in a succession of equilibria due to the coordination-dissociation processes of the four phosphines on the ligand.

We further proceeded to examine the ambient pressure hydrogenation of arylenamides **10a**,**b** using Rh(I) complexes of the coumarin dimer-derived *tetra*-phosphine ligands **1a**,**b** (Table 1, entries 11–15). For Rh(I)–**1a** catalyzed hydrogenation of **10a**, lowering the hydrogen pressure from 5 to 1 atm led to a slight decrease in the ee of the product under the otherwise identical conditions (entry 11 vs 9). A remarkable temperature dependence of the ee's was observed for the ambient pressure hydrogenation, where an optimal ee of 85% could be reached by carrying out the reaction at 13 °C (entries 11–13). Compared with **1a**, the reaction using tetraphosphine ligand **1b** afforded product **11a** in remarkably decreased ee (entry 14). Good ee was obtained for the ambient pressure hydrogenation of arylenamide **10b** using catalyst Rh–**1a** (entry 15).

In summary, a new type of chiral tetraphosphine ligands **1** were prepared from enantiopure *anti-head-to-head* coumarin dimer **5**, and then utilized in Rh-catalyzed asymmetric hydrogenation reaction of arylenamides, affording the corresponding amides with up to 85% ee. A preliminary ^{31}P NMR study revealed that multiple rhodium complex species are present in the Rh–**1a** system, where different types of reaction centers may be at work and the exact nature of the catalytically active one(s) remains unknown at the present stage.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.077.

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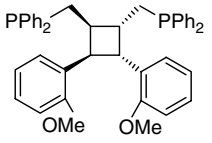

CDP

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