Addition Reactions

Chiral Phosphine–Olefin Bidentate Ligands in Asymmetric Catalysis: Rhodium-Catalyzed Asymmetric 1,4-Addition of Aryl Boronic Acids to Maleimides**

*Ryo Shintani, Wei-Liang Duan, Takashi Nagano, Atsushi Okada, and Tamio Hayashi**

Transition-metal-catalyzed asymmetric transformations in the presence of chiral ligands have proved to be one of the most efficient methods for the construction of enantioenriched chiral compounds from achiral precursors.[1] The design and synthesis of novel chiral ligands have therefore been a topic of great interest in organic and organometallic chemistry in the past few decades. In late-transition-metal catalysis, the development of phosphorus- and/or nitrogen-based chiral ligands has been most extensively investigated. As conceptually novel chiral ligands, a series of chiral dienes were recently introduced, which opened up a new dimension in the field of asymmetric catalysis.[2,3] Herein we describe the development of chiral phosphine–olefin ligands **1** and their use in the rhodium-catalyzed asymmetric 1,4-addition of aryl boronic acids to maleimides with the highest enantioselectivity reported to date in this class of substrates.

Chiral diene ligands that we developed have been shown to be highly effective in various rhodium-catalyzed asymmetric processes[2] and are superior to conventional chiral bisphosphine ligands in some cases. There are, however, some drawbacks in the use of these chiral dienes: for example, diene ligands are generally weaker than phosphorus-based ligands in their coordination ability to transition metals.[4] To overcome this problem while still maintaining the advantages of chiral dienes, we decided to develop chiral phosphine–olefin ligands as a hybrid of bisphosphines and dienes which would incorporate positive features of both frameworks, namely, the high coordination ability of phosphines and the good chiral environment created around the olefins (Figure 1).

To realize the desired features of these phosphine–olefins, we chose compound **1** as the target. During the course of our study directed toward this goal, Grützmacher described the preparation of chiral phosphine–olefin **2** and utilized it as a

[*] Dr. R. Shintani, W.-L. Duan, Dr. T. Nagano, A. Okada, Prof. Dr. T. Hayashi
Department of Chemistry
Graduate School of Science, Kyoto University
Sakyo, Kyoto 606-8502 (Japan)
Fax: (+81) 75-753-3988
E-mail: thayashi@kuchem.kyoto-u.ac.jp

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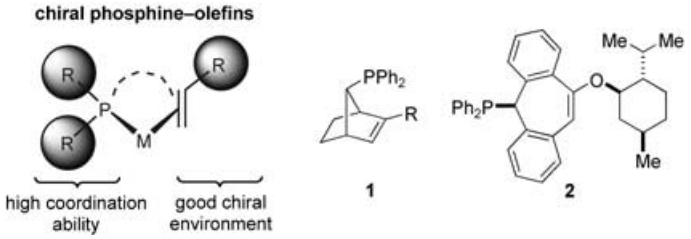
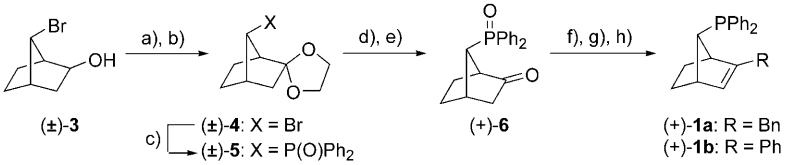


Figure 1. Chiral phosphine–olefin ligands designed to incorporate positive features of bisphosphine and diene ligands.

ligand for the iridium-catalyzed asymmetric hydrogenation of an imine with 86% *ee*.[5]

The synthesis of **1** began with known compound (±)-**3**[6] (Scheme 1). Swern oxidation of alcohol (±)-**3** followed by ketalization with ethylene glycol provided (±)-**4**, which was further converted into (±)-**5** by lithiation, phosphination, and then oxidation. Phosphine oxide (±)-**5** was resolved by chiral HPLC on a Chiralcel OD-H column to give each enantiomer



Scheme 1. a) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, 96%; b) cat. TsOH, ethylene glycol, C_6H_6, 94%; c) 1) *t*BuLi, THF; then $ClPPh_2$; 2) aqueous H_2O_2, acetone, 63% (over two steps); d) chiral HPLC resolution (OD-H column); e) aqueous HCl (1 N), THF, 99%; f) LDA, THF; then $PyNTf_2$, 89%; g) cat. [$NiCl_2$(dppp)], BnMgBr, Et_2O, 86% (for R = Bn); or cat. [$PdCl_2$(dppf)], PhMgBr, Et_2O, 86% (for R = Ph); h) $HSiCl_3$, Et_3N, C_6H_6, 90% for (+)-**1a** and 84% for (+)-**1b**. DMSO = dimethylsulfoxide; Ts = *p*-toluenesulfonyl; LDA = lithium diisopropylamide; Tf = trifluoromethanesulfonyl; dppp = propane-1,3-diylbis(diphenylphosphane); dppf = 1,1′-bis(diphenylphosphino)ferrocene.

of **5**, and then the ketal was cleaved to afford enantiopure ketone (+)-**6**. Conversion of (+)-**6** into its enol triflate, followed by Grignard cross-coupling and reduction with silane, completed the synthesis of (+)-**1a** (R = Bn, 39% overall yield) and (+)-**1b** (R = Ph, 36% overall yield).

We then carried out some complexation experiments with several transition metals to observe their mode of coordination. Thus, treatment of ligand (+)-**1b** (^{31}P NMR: $\delta = -17.1$ ppm; ^{1}H NMR: $\delta = 6.31$ ppm for the olefinic H atom) with 1 equivalent of [Rh(acac)$(C_2H_4)_2$] (acac = acetylacetonate) in dichloromethane at room temperature generated a new species, which showed a doublet at $\delta = 65.0$ ppm (J = 185 Hz) in the ^{31}P NMR spectrum and the signal for the olefinic H atom of (+)-**1b** was shifted upfield to $\delta = 3.82$ ppm in the ^{1}H NMR spectrum, thus indicating that both the phosphorus atom and the olefin were directly bound to rhodium. Similarly, a 1:1 mixture of (+)-**1b** and [$PdCl_2$-$(MeCN)_2$] in benzene led to the clean formation of [$PdCl_2$((+)-**1b**)]. Recrystallization of this complex from dichloromethane/benzene afforded single crystals suitable for X-ray crystallographic analysis.[7] As shown in Figure 2, (+)-**1b** does act as a phosphine–olefin bidentate ligand with

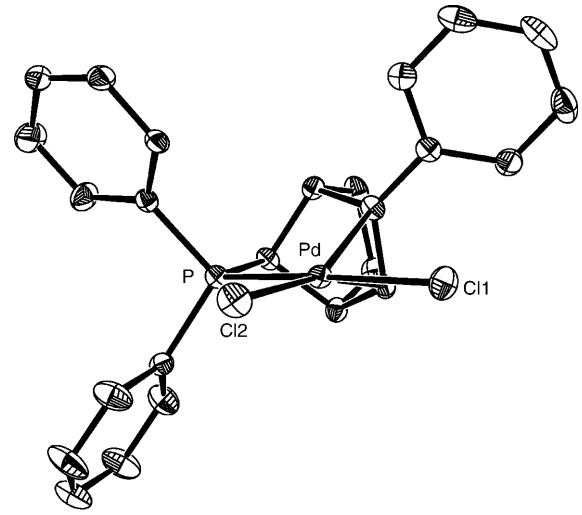
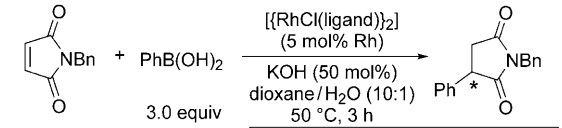


Figure 2. ORTEP illustration of [$PdCl_2$((+)-**1b**)] with thermal ellipsoids drawn at the 50% probability level (hydrogen atoms are omitted for clarity).

palladium, in accordance with the initial design of this novel hybrid ligand. The X-ray crystal structure also establishes the absolute configuration of (+)-**1b** as 1*R*,4*S*,7*R*.[8] Furthermore, it shows that the local structure around the phosphorus center is achiral and that the chirality mostly originates from the steric difference between the two substituents (Ph and H) on the olefin.

To investigate the potential of these ligands **1** in asymmetric catalysis, we chose to explore the rhodium-catalyzed 1,4-addition of aryl boronic acids to maleimides. As shown in Equation (1), the reaction of *N*-



(1)

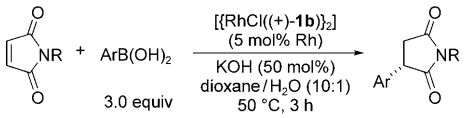
ligand	result
(*R*)-binap	70% yield, 58% *ee* (*R*)
(*R*,*R*)-**7**	88% yield, 69% *ee* (*R*)
(+)-**1a**	96% yield, 91% *ee* (*S*)
(+)-**1b**	98% yield, 93% *ee* (*S*)

benzylmaleimide with $PhB(OH)_2$ in the presence of (*R*)-binap, a typical chiral bisphosphine ligand for rhodium-catalyzed asymmetric 1,4-additions,[9] gave the 1,4-adduct with only 58% *ee*. The use of chiral norbornadiene (*R*,*R*)-**7**, which was reported by us as the benchmark ligand in the 1,4-addition to maleimides,[2b] led to the desired product with 69% *ee*. The use of benzyl-substituted phosphine–olefin (+)-**1a** significantly improved the enantioselectivity to 91% *ee*. By changing the substituent on the olefin from benzyl to phenyl ((+)-**1b**), the selectivity was improved further (93% *ee*).

Under these conditions with (+)-**1b** as the ligand, various *N*-substituted maleimides can be employed in the reaction

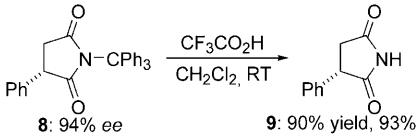
with $PhB(OH)_2$ to furnish the 1,4-adducts in uniformly high yield and enantioselectivity (Table 1, entries 1–5). With respect to the nucleophilic component, a variety of aryl boronic acids can be coupled with *N*-benzylmaleimide with high stereoselectivity as well (Table 1, entries 6–10).

Table 1: Rh–(+)-**1b**-catalyzed asymmetric 1,4-addition of aryl boronic acids to maleimides.



Entry	R	Ar	Yield [%]	*ee* [%]
1	Me	Ph	91	88
2	Cy	Ph	96	94
3	$CHPh_2$	Ph	95	94
4	CPh_3	Ph	95	94
5	Ph	Ph	88	90
6	Bn	Ph	98	93
7	Bn	4-$MeOC_6H_4$	98	93
8	Bn	4-FC_6H_4	90	89
9	Bn	3,5-$MeO_2C_6H_3$	90	92
10	Bn	2-MeC_6H_4	98	95

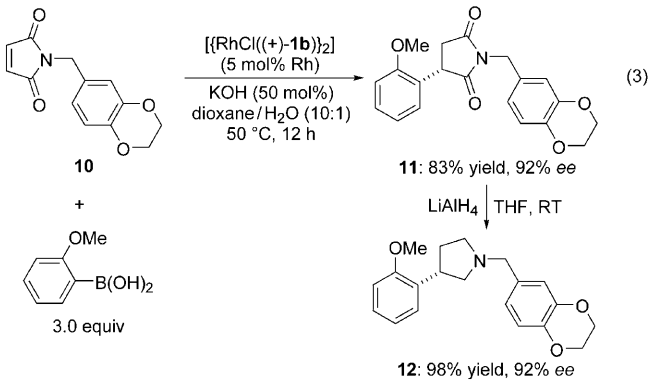
To show the utility of this highly enantioselective 1,4-addition to maleimides catalyzed by Rh–(+)-**1b**, we conducted a deprotection reaction of *N*-trityl 1,4-adduct **8** with 94% *ee* [Eq. (2)]. Thus, treatment of **8** with trifluoroacetic



(2)

acid in dichloromethane at room temperature furnished the desired product **9** in 90% yield with minimal erosion of the *ee* value.

The present asymmetric catalysis can also be applied to an enantioselective synthesis of biologically active compounds. Thus, addition of 2-$MeOC_6H_4B(OH)_2$ to maleimide **10** under Rh–(+)-**1b** catalysis led to 1,4-adduct **11** in 83% yield with 92% *ee* [Eq. (3)]. Reduction of the two carbonyl groups of **11**



(3)

with $LiAlH_4$ furnished pyrrolidine **12** in 98% yield, which is an enantiomer of the potent α-2-adrenoceptor antagonist developed by Novartis.[10]

The stereochemical outcome of these Rh–(+)-**1b**-catalyzed 1,4-additions can be rationalized as depicted in Figure 3,

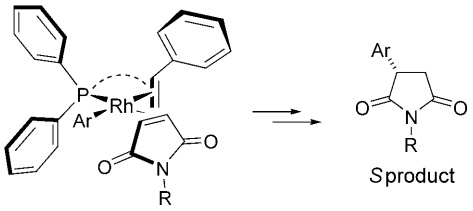
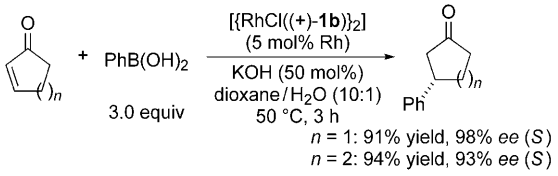


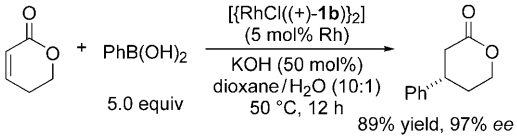
Figure 3. Proposed stereochemical pathway for the asymmetric 1,4-addition to a maleimide catalyzed by Rh–(+)-**1b**.

assuming that the maleimide approaches the aryl rhodium species bearing ligand (+)-**1b** *cis* to the olefin portion of the ligand. To avoid the steric repulsion between the imide moiety of maleimide and the phenyl group on the olefin, the product thus obtained should be an *S* isomer, which is consistent with the observed stereochemistry.

The Rh–(+)-**1b** catalyst is highly effective for asymmetric 1,4-addition to other α,β-unsaturated carbonyl compounds as well. For example, both cyclic enones and enoates[11] furnish the corresponding 1,4-adducts in high yield and enantioselectivity [Eq. (4) and Eq. (5)].



(4)



(5)

In summary, we have designed and synthesized novel chiral phosphine–olefin ligands. These ligands act as bidentate with some transition metals and have proved to be highly effective in the rhodium-catalyzed asymmetric 1,4-addition of aryl boronic acids to maleimides. Future studies will involve the exploration of further applications of these ligands to various transition-metal-catalyzed asymmetric processes.

Experimental Section

Procedure for Table 1: KOH (0.10 mL, 0.10 mmol; 1.0 M aqueous) was added to a solution of $[\{RhCl((+)\text{-}\mathbf{1b})\}_2]$ (4.9 mg, 10 μmol Rh) in 1,4-dioxane (0.50 mL), and the resulting solution was stirred for 5 min at room temperature. After addition of $ArB(OH)_2$ (0.60 mmol) and stirring for 5 min, this mixture was transferred to a vessel containing maleimide (0.20 mmol) with additional 1,4-dioxane (0.50 mL). The

resulting mixture was stirred for 3 h at 50 °C and was then passed through a pad of silica gel with EtOAc. The solvent was removed under vacuum, and the residue was purified by chromatography on silica gel with EtOAc/hexane to afford the 1,4-adduct.

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