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Synthesis of Chiral Biphenol-Based Diphosphonite Ligands and Their Application in Palladium-Catalyzed Intermolecular Asymmetric Allylic Amination Reactions

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Dedicated to Professor Eiichi Nakamura on the occasion of his 60th birthday

Abstract: A library of new 2,2′-bis(diphenylphosphinoyloxy)-1,1′-binaphthyl (binapo)-type chiral diphosphonite ligands was designed and synthesized based on chiral 3,3′,5,5′,6,6′-hexasubstituted biphenols. These bop ligands have exhibited excellent efficiency in a palladium-catalyzed intermolecular allylic amination reaction, which provides a key intermediate for the total synthesis of *Strychnos* indole alkaloids with enantiopurities of up to 96% *ee*.

Keywords: amination · biphenols · chirality · ligands · palladium

Introduction

Metal-catalyzed asymmetric reactions have been playing an important role in the synthesis of biologically active substances.[1] Among various transformations, transition-metal-catalyzed allylic substitution reactions provide unique and powerful methods for the regio- and stereocontrolled formation of carbon–carbon bonds and carbon–heteroatom bonds.[2] Whilst most enantioselective versions of these reactions are using palladium complexes as the metal catalysts,[3] the use of molybdenum,[4] tungsten,[5] ruthenium,[6] rhodium,[7] and iridium catalysts[8] has been steadily increasing, albeit their efficiencies are not as high as that of palladium catalysts. Thus, chiral palladium catalysts have been used almost exclusively for applications of asymmetric allylic substitutions in the total synthesis of complex natural products and their congeners.[2,9]

Extensive efforts have been made for the development of efficient chiral ligands for palladium-catalyzed asymmetric allylic substitution reactions.[2] Among the most successful ligands, "modular" diphosphine ligands developed by Trost et al.[2,9] and a series of P–N ligands developed by Pfaltz, Helmchen, and Williams independently[10] have been widely used. However, these chiral ligands do not always achieve high enantioselectivity and catalyst efficiency in different reaction systems.[11] Thus, there is a continuous need for new and efficacious chiral ligands for asymmetric allylic substitution reactions. A diphosphonite ligand 2,2′-bis(diphenylphosphinoyloxy)-1,1′-binaphthyl (binapo), originally developed by Grubbs and DeVries for asymmetric hydrogenation,[12] was found to be effective and better than 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (binap) in palladium-catalyzed allylic substitution reactions.[13] The efficacy of binapo has been demonstrated in several total syntheses of natural products by Mori and co-workers[14] However, the highest enantioselectivity reported for the palladium/(*S*)-binapo catalyst is 84% *ee* and no systematic modifications of binapo had been reported. Thus, the usage of binapo and chiral diphosphonite ligands has been limited.

We have designed and synthesized a series of new chiral biphenol compounds (**1**) that contain various substituents at the 3,3′-positions,[15] and used them to create the libraries of novel monodentate phosphite and phosphoramidite ligands with fine-tuning capabilities.[15–16] These novel monodentate phosphorus ligands have demonstrated excellent efficiency in various transition-metal-catalyzed asymmetric transformations.[15–16] We recognized that the enantiopure C_2-symmetric biphenols **1** would also serve as the axial chirality component of binapo-type novel diphosphonite (bop) ligands with wide bite angles (Scheme 1). We hypothesized

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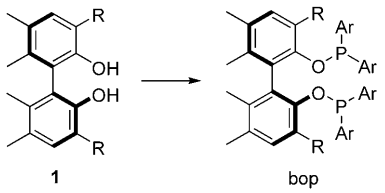
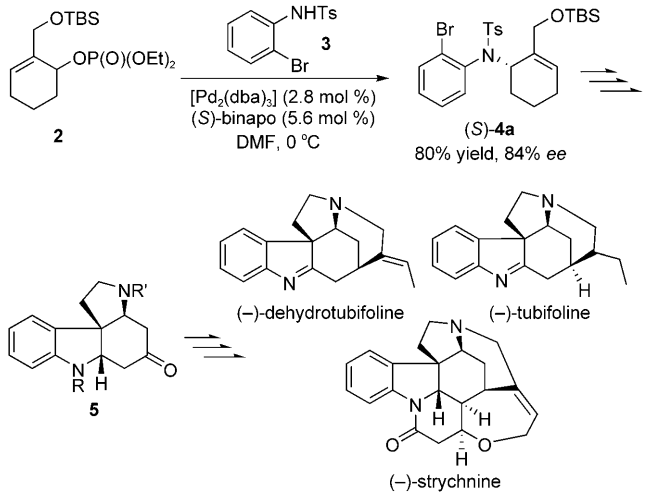


Scheme 1. Biphenol-based diphosphonite ligands (bops).

that a judicious choice of substituents at the 3,3′-positions of the bop ligand would influence the conformational rigidity of the bop/metal complex by controlling the orientation of the aryl groups on the phosphorus atoms. The development of chiral ligands bearing fine-tuning capability based on easily modifiable core structures is crucial for a practical combinatorial approach to the selection of the most-suitable ligand for a specific catalytic asymmetric process. Thus, we set out to develop a series of novel bop ligands with a variety of substituents at the 3,3′-positions.

In 2003, Mori and co-workers reported the total synthesis of *Strychnos* indole alkaloids using a palladium/binapo complex to catalyze the key intermolecular allylic amination reaction to construct the critical chiral center (Scheme 2).[14c]



Scheme 2. Mori's total synthesis of *Strychnos* indole alkaloids via key intermediate **4a** obtained from Pd/binapo-catalyzed asymmetric allylic amination.

The product (*S*)-**4a** from this key reaction was converted into versatile key intermediate **5** through several steps, which was used as a common intermediate in the total syntheses of (−)-tubifoline, (−)-dehydrotubifoline, and (−)-strychnine (Scheme 2).[14c]

As shown in Scheme 2, the best result for the key step, that is, the intermolecular asymmetric allylic amination, was 84% *ee* and 80% yield, when the reaction was performed at 0°C. Recrystalization was required in the subsequent steps to obtain enantiomerically pure key intermediate **5**.[14c] Accordingly, this very useful process still needs substantial improvement in its enantioselectivity and chemical yield. Thus, we selected this process as a showcase to examine the validity of our combinatorial approach to the optimization of the process through fine-tuning of the novel bop ligands. Herein, we report the design and synthesis of a series of enantiopure BOP ligands and their application to the intermolecular asymmetric allylic amination process.

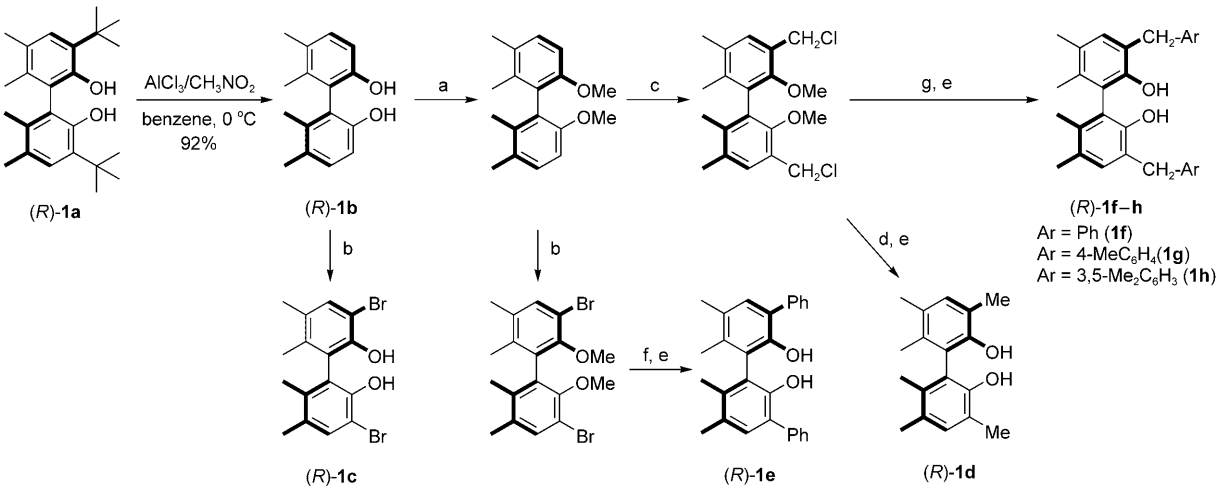
Results and Discussion

Enantiopure biphenol (*R*)-**1a** was prepared by following our previously reported procedure.[17] The *tert*-butyl groups at the 3,3′-positions of (*R*)-**1** were removed by treating with $AlCl_3$ in nitromethane/toluene in a transfer Friedel–Crafts reaction to give biphenol (*R*)-**1b** without any loss of enantiopurity.[15,18] The biphenols (*R*)-**1c–e** (R = Br, Me and Ph, respectively) were prepared from (*R*)-**1b** by using our previously reported procedures.[15] Biphenols (*R*)-**1f–h** bearing benzyl or substituted benzyl groups (Ar = Ph, 4-MeC_6H_4, and 3,5-$Me_2C_6H_3$, respectively) were synthesized through a copper(I)-mediated cross-coupling reaction[19] from (*R*)-3,3′-bis(chloromethyl)biphenol, followed by removal of the methyl groups in excellent overall yields (Scheme 3).

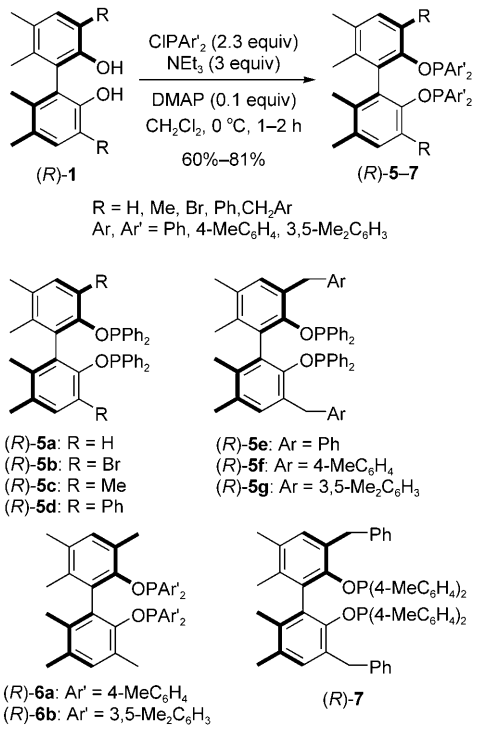
The 3,3′-disubstituted-biphenol-based diphosphonite bop ligands were synthesized according to the synthetic protocol described for the binapo ligand (Scheme 4).[20] The coupling reaction between biphenols (*R*)-**1b–h** and chlorodiarylphosphines ($ClPAr_2$) proceeded smoothly, affording the corresponding diphosphonites in good to excellent yields. By using this protocol, we created a small bop ligand library, (*R*)-**5a–g**, (*R*)-**6a**,**b**, and (*R*)-**7**, shown in Scheme 4 (only the *R* series is shown for simplicity).

For initial bop-ligand screening, we employed only slightly modified conditions for the palladium/binapo catalyst system reported by Mori et al (Scheme 5).[14c] 2-TBSO-methylcyclohex-2-en-1-yl vinylcarbonate (**8a**; TBS = *tert*-butyldimethylsilyl) was used as the allylic component as it was the best substrate in Mori's reactions with a palladium/binapo catalyst, and *N*-tosyl-2-bromoaniline (**3**) as the amine component. As solvent, tetrahydrofuran and *N*,*N*-dimethylformamide were used with the concentration of **8a** at 0.05 M and a palladium/ligand ratio of 1:1.5. Ligands (*R*)-**5a–d** were screened first under these conditions (Table 1).

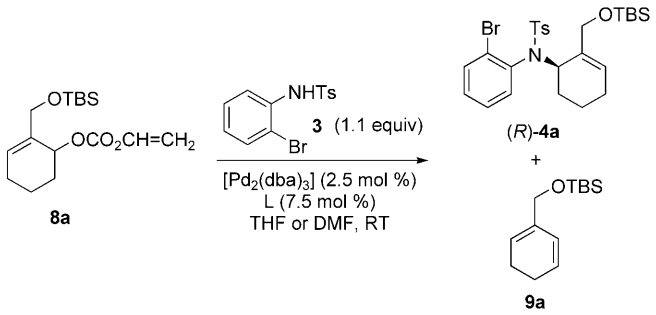
All reactions gave the desired product (*R*)-**4a**, but with different conversion and enantioselectivities as the substituents at the 3,3′-positions of the biphenol moieties of bop ligands varied. We also observed the formation of **9a**, which was not reported previously.[14c] It is highly likely that the ceiling of the chemical yield (64–80%) reported for the formation of **4a** by Mori et al. is attributed to the considerable formation of **9a**. The ratio of **4a** to **9a** was determined by ^1H NMR spectroscopic analysis. Results from the reactions in tetrahydrofuran indicate that the reaction slows down as the size of the 3,3′-substituents increases (Table 1, entries 1–4). When **5a** (R = H) and **5c** (R = Me) were used, the reactions were complete in 48 hours (Table 1, entry 1) and 60 hours (Table 1, entry 3), respectively. However, when



Scheme 3. Synthesis of enantiopure biphenols (**1b–h**; only the *R* series is shown for simplicity). a) Me_2SO_4, nBu_4NI, KOH, CH_2Cl_2; b) Br_2, $CHCl_3$; c) H_3PO_4, HCl, AcOH, $(CH_2O)_n$; d) $LiAlH_4$, THF; e) BBr_3, CH_2Cl_2; f) $[Pd(PPh_3)_4]$, $PhB(OH)_2$, $NaHCO_3$, DME/H_2O 1.5:1, reflux; g) CuI (cat.), ArMgBr, THF, 0–50 °C. THF = tetrahydrofuran, DME = 1,2-dimethoxyethane.



Scheme 4. Synthesis of novel diphosphonite bop ligands (only the *R* series is shown for simplicity).



Scheme 5. Asymmetric allylic amination of **8a** (initial screening of chiral ligands).

bulkier ligands, **5b** (R = Br; Table 1, entry 2) and **5d** (R = Ph; Table 1, entry 4), were employed, the reactions gave little or low conversion after 72 hours. When the 3,3′-substituents were changed from H to Me, the enantioselectivities increases from 65 to 89 % *ee* (Table 1, entries 1 and 3). The use of larger 3,3′-substituents led to a decrease in the enantioselectivity and poor catalytic activity (Table 1, entries 2 and 4). When *N*,*N*-dimethylformamide was used as the solvent, a clear acceleration of reaction rate as well as a substantial increase in the **4a**/**9a** ratio (up to 95:5) was observed (Table 1, entries 5 and 6). Accordingly, the combina-

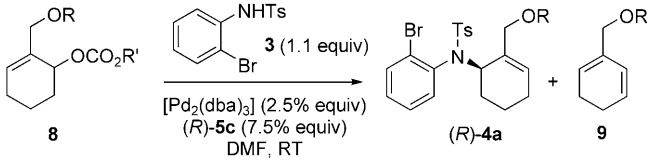
Table 1. Initial screening of chiral ligands.

Entry	Ligand (*R*)-**5**	Solvent	*t* [h]	Conv. [%][a,b]	*ee* **4a** [%] (**4a**/**9a**)[a,b]
1	**5a**	THF	48	100	65 (70:30)
2	**5b**	THF	72	~30	74 (50:50)
3	**5c**	THF	60	100	89 (65:35)
4	**5d**	THF	72	<5	n.d.
5	**5a**	DMF	12	100	67 (95:5)
6	**5c**	DMF	20	100	88 (95:5)

[a] Product ratio was determined by ^1H NMR spectroscopy. [b] The enantiopurity of **4a** was determined by HPLC by using Chiralpak AD-RH, CH_3CN/H_2O (80:20).

tion of **5c** (R = Me) as the chiral ligand and *N*,*N*-dimethylformamide as the solvent afforded the best result in this first screening.

Next, we screened the allylic substrates (**8a–e**) by using the optimized conditions: (*R*)-**5c** as the chiral ligand in *N*,*N*-dimethylformamide (Scheme 6). The use of TBS or triisopropylsilyl (TIPS) groups as the bulky silicon protecting group for the allylic alcohol moiety did not make large differences in the reaction rate, enantioselectivity, or product selectivity (Table 2). There were recognizable differences in the enantioselectivity when vinyl, trichloroethyl, and diethylphosphonyl groups were used as the substituents of the carbonate moiety (Table 2, entries 1–3). Thus, **8d** (R = TIPS; R′ = vinyl) appears to be the best allylic substrate of the ones examined, and the reaction of **8d** achieved 91% *ee* at room temperature (25°C).



Scheme 6. Screening for allylic substrates **8** for the asymmetric allylic amination.

We then carried out the optimization of the bop ligands for the reaction of **8d** (R = TIPS; R′ = vinyl) under the standard conditions by using our library of bop ligands (see Scheme 4). Excellently, ligand (*R*)-**5e** (Ar = Ar′ = Ph) achieved 96% *ee* (**4b**/**9b** = 93:7) with complete conversion in 24 hours (Table 3). The introduction of substituted phenyl groups at the 3,3′-position, that is, (*R*)-**5f** (Ar = 4-MeC_6H_4; Ar′ = Ph) and (*R*)-**5g** (Ar = 3,5-$Me_2C_6H_3$; Ar′ = Ph), did not improve the enantioselectivity or product selectivity (Table 3, entries 2 and 3 versus Table 3, entry 1). The introduction of substituted phenyls to the diarylphosphorus moieties, that is, (*R*)-**6a** (R = Me; Ar′ = 4-MeC_6H_4), (*R*)-**6b** (R = Me; Ar′ = 4-MeC_6H_4), and (*R*)-**7** (R = $PhCH_2$; Ar′ = 4-MeC_6H_4), slowed down the reaction, and also lowered the enantioselectivity as well as the product selectivity (Table 3, entries 4–6), especially when (*R*)-**7** was used (Table 3, entry 6).

In addition, the effects of reaction temperature and additives were examined, by using the optimal chiral ligand (*R*)-**5e** and allylic substrate **8d** (Table 4).

Although it was reported that the best results (84% *ee*, 64% yield or 84% *ee*, 80% yield) with the use of binapo were obtained at 0°C,[14c] no advantage was observed in our reaction (Table 4). The addition of acetic acid to the system was detrimental to the reaction (Table 4, entry 3). The addition of triethylamine to the system accelerated the reaction, but the enantioselectivity decreased (Table 4, entry 4). A

Table 2. Screening of allylic substrates by using (*R*)-**5c** ligand at room temperature.

Entry	Allylic substrate	*t* [h]	Conv. [%][a,b]	*ee* **4a**,**b** [%] (**4**/**9**)[a,b,c]
1	**8a** R = TBS R′ = vinyl	20	100	89 (95:5)
2	**8b** R = TBS R′ = CH_2CCl_3	24	100	85 (90:10)
3	**8c** R = TBS R′ = P(O)$(OEt)_2$	16	100	83 (97:3)
4	**8d** R = TIPS R′ = vinyl	24	100	91 (95:5)
5	**8e** R = TIPS R′ = CH_2CCl_3	30	100	88 (90:10)

[a] Products of entries 1–3 are **4a** and **9a** and those of entries 4 and 5 are **4b** and **9b**. [b] Product ratio was determined by ^{1}H NMR spectroscopy. [c] Enantiopurity was determined by HPLC by using Chiralpak AD-RH with CH_3CN/H_2O (80:20) for *O*-TBS product **4a** and Chiralcel OD-H with hexanes/*i*PrOH (98:2) for *O*-TIPS product **4b** after desilylation with 4 M HCl.

Table 3. Optimization of chiral ligands for the reaction of **8d** at room temperature.

Entry	Ligand	*t* [h]	Conv. [%][a,b]	*ee* **4b** [%] (**4b**/**9b**)[a,b]
1	(*R*)-**5e**	24	100	96 (93:7)
2	(*R*)-**5f**	24	100	94 (89:11)
3	(*R*)-**5g**	24	100	91 (90:10)
4	(*R*)-**6a**	50	100	89 (85:15)
5	(*R*)-**6b**	50	100	89 (80:20)
6	(*R*)-**7**	50	100	43 (65:35)

[a] Product ratio was determined by ^{1}H NMR spectroscopy. [b] Enantiopurity of **4b** was determined by HPLC by using a Chiralcel OD-H column with hexanes/*i*PrOH (98:2) after desilylation with 4 M HCl.

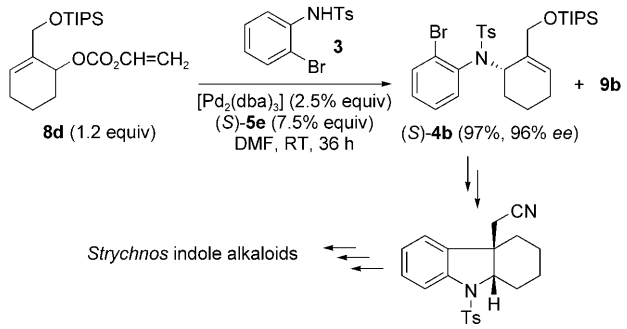
Table 4. Effects of temperature and additive.

Entry	Additive	T [°C]	t [h]	Conv. [%][a,b]	*ee* **4b** [%] (**4b**/**9b**)[a,b]
1	–	25	24	100	96 (93:7)
2	–	0	48	100	96 (90:10)
3	AcOH (1 equiv)	25	24	<5	–
4	NEt_3 (1.1 equiv)	25	8	100	88 (92:8)
5	NEt_3 (1.1 equiv)	0	17	100	91 (80:20)
6	NEt_3 (1.1 equiv)	−25	48	~80	77 (80:20)

[a] Product ratio was determined by ^{1}H NMR spectroscopy. [b] Enantiopurity of **4b** was determined by HPLC by using Chiralcel OD-H column with hexanes/*i*PrOH (98:2) after desilylation with 4 M HCl.

modest increase in enantioselectivity (88 to 91% *ee*) was observed for the reaction at 0°C, but the enantioselectivity substantially dropped (to 77% *ee*) at −25°C (Table 4, entries 5 and 6). The product selectivity was low at 0°C and −25°C, compared to that at room temperature (25°C). Accordingly, the reaction was found to be optimal at room temperature.

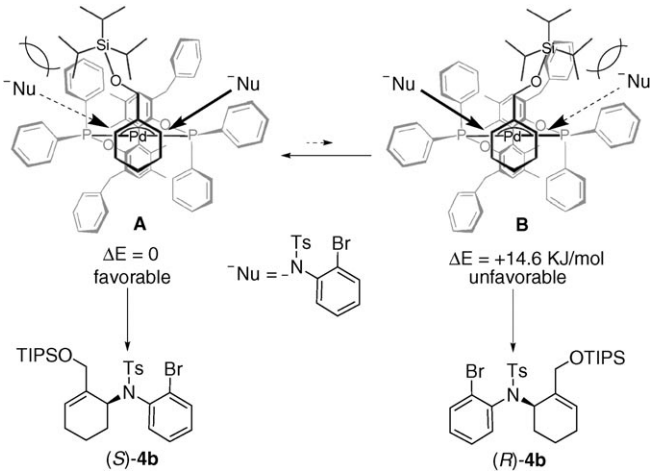
Furthermore, we carried out the synthesis of (*S*)-**4b**, which is the correct enantiomer for the naturally occurring *Strychnos* indole alkaloids, by using the (*S*)-**5e** ligand under the optimized reaction conditions mentioned above, except for 36 hours reaction time (Scheme 7). The reaction of **8d** with **3** (1.0 mmol) was run by using a slight excess of **8d** (1.2 equiv) to maximize the product yield. Then, (*S*)-**4b** with 96% *ee* was isolated in 97% yield.



Scheme 7. Synthesis of (*S*)-**4b**, a key intermediate for *Synchonus* indole alkaloids.

It is reasonable to assume that the palladium/bop ratio is 1:1 in the active catalyst species. Thus, we carried out the molecular modeling of a simplified active catalyst species $[Pd^{II}L^*(\pi\text{-allyl})]^+$ (L* = (*R*)-**5e**) by using the Spartan program (MM2/PM3 for energy minimization). The result after energy minimization clearly indicated a pseudo C_2-symmetrical structure, in which the Ph groups on the PPh_2 moieties formed a C_2-symmetric environment surrounding the allyl moiety. As anticipated, this complex had a large bite angle (P*-Pd-P*) of 125°, which should be beneficial in achieving high enantioselectivity in the asymmetric allylic amination reaction.

Next, we constructed a cationic palladium/(*S*)-**5e** complex with the π-allylic 2-TIPS-*O*-methylcyclohexenyl group, which was the most likely intermediate in the first step of the asymmetric allylic amination process when using **8d** or **8e** as the substrate, that is, formation of the π-allylic Pd^{II}/L* species. A molecular modeling study of the complex revealed that there were two possible conformational isomers, arising from two possible orientations of the bulky TIPS-*O*-methyl group. Both orientations led to the local-energy-minimized structures **A** and **B** (Scheme 8). The energy difference between **A** and **B** was calculated to be 14.6 kJ mol^{-1}, with **A** being the favorable conformer. The observed energy



Scheme 8. Proposed mechanism for enantioselection by a Pd/(*S*)-**5e** catalyst, leading to the highly selective formation of (*S*)-**4b**.

difference can be attributed to the steric repulsion between the TIPS group and one of the phenyl moieties of the benzyl group at the 3,3′-positions of the backbone chiral biphenyl (Scheme 8). Accordingly, the predominant pathway for the nucleophilic attack of the anion of TsNH(bromophenyl) (**3**) should be through the **A** complex. In the **A** complex, the nucleophilic attack from the left side obviously suffered from the steric hindrance of the bulky TIPS group. Thus, the reaction should proceed through attack from the right side, leading to the formation of (*S*)-**4b**.

Conclusions

A highly efficient palladium/bop catalyst system has been developed for the intermolecular asymmetric allylic amination reaction of **8** and **3**, giving the desired product **4** with up to 96% *ee*, through systematic optimization of the chiral

ligand, allylic substrate, and reaction variables. The results clearly show the highly beneficial feature of bop ligands bearing fine-tuning capability with various substituents on the chiral biphenyl core, especially those at the 3,3′-positions. Further study on the development of bop ligands and their applications to various catalytic asymmetric reactions are actively underway in our laboratory.

Experimental Section

Materials

Enantiopure biphenols (*R*)-**1b–e** were synthesized according to our previously reported procedures.[15] *N*-(4-methyl-benzenesulfonyl)-2-bromoaniline (**3**),[21] 2-(hydroxymethyl)cyclohex-2-en-1-ol, 2-*tert*-butyldimethylsiloxymethyl-2-cyclohexenol,[14c] 2-(1-*tert*-butyldimethylsiloxymethyl)cyclohex-2-en-1-yl ethenyl carbonate (**8a**),[14c] and 2-(*tert*-butyldimethylsiloxymethyl)cyclohex-2-en-1-yl diethylphosphinate (**8c**)[14c] were prepared according to the literature procedures.

(*R*)-3,3′-Dibenzyl-2,2′-dimethoxy-5,5′,6,6′-tetramethyl-1,1′-biphenyl ((*R*)-1f): A solution of phenylmagnesium bromide in THF (1 M, 1.5 mL, 3 equiv) was added at 0 °C to a solution of 3,3′-bis(chloromethyl)biphenyl (183 mg, 0.5 mmol, 1 equiv) in THF (5 mL) containing CuI (24 mg, 0.125 mmol, 0.25 equiv) under nitrogen over 30 min. The mixture was warmed up to room temperature and stirred for an additional 30 min and then at 50 °C for 10 h. The reaction was quenched with aqueous NH_4Cl solution (10 mL) and the reaction mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was washed with water (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc = 30:1 to 10:1) to afford (*R*)-3,3′-dibenzyl-2,2′-dimethoxy-5,5′,6,6′-tetramethyl-1,1′-biphenyl (209 mg, 93 %) as a colorless oil. $[\alpha]_D^{20} = +14.0$ ($c = 0.8$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.95$ (s, 6H), 2.27 (s, 6H), 3.27 (s, 6H), 4.08 (q, $J = 6.8$ Hz, 4H), 7.23 (s, 2H), 7.30–7.35 (m, 2H), 7.41–7.45 (m, 4H), 7.58–7.61 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.4$, 19.8, 121.6, 125.6, 127.1, 128.4, 129.2, 129.3, 132.1, 136.4, 137.9, 148.4 ppm; HRMS (EI): *m*/*z*: calcd for $C_{32}H_{34}O_2$ 450.2559 $[M]^+$; found: 450.2560 ($\Delta = +0.1$ ppm); (*S*)-3,3′-dibenzyl-2,2′-dimethoxy-5,5′,6,6′-tetramethyl-1,1′-biphenyl was prepared in the same manner: yield: 92 %; $[\alpha]_D^{22} = -14.0$ ($c = 0.9$ in CH_2Cl_2,).

BBr_3 (1.1 mL, 1.0 M solution in CH_2Cl_2) was added dropwise over 20 min to a stirred solution of (*R*)-3,3′-dibenzyl-2,2′-dimethoxy-5,5′,6,6′-tetramethyl-1,1′-biphenyl (225 mg, 0.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The mixture was stirred at 0 °C for 1.5 h. The reaction was quenched by the slow addition of water. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc = 15:1 to 5:1) to give (*R*)-**1f** (186 mg, 88 %) as a colorless oil. $[\alpha]_D^{22} = +9.0$ ($c = 0.75$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.92$ (s, 6H), 2.26 (s, 6H), 4.04 (q, $J =$ 6.8 Hz, 4H), 4.69 (s, 2H), 7.00 (s, 2H), 7.24 (m, 4H), 7.33 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.1$, 19.7, 35.8, 120.3, 124.7, 125.8, 128.3, 128.7, 128.8, 132.4, 134.7, 141.0, 149.5 ppm; HRMS (EI): *m*/*z*: calcd for $C_{30}H_{30}O_2$: 422.2246 $[M]^+$; found: 422.2248 ($\Delta = +0.2$ ppm); (*S*)-**1f** was synthesized in the same manner from (*S*)-3,3′-dibenzyl-2,2′-dimethoxy-5,5′,6,6′-tetramethyl-1,1′-biphenyl: yield: 87 %; $[\alpha]_D^{20} = -8.9$ ($c = 1.1$ inCH_2Cl_2).

In the same manner, chiral biphenols, (*R*)-**1g** and (*R*)-**1h** were synthesized. The characterization data for these biphenols are shown in the Supporting Information.

General Procedure for the Preparation of the Diphosphonite Ligands

A solution of chlorodiarylphosphine (2.5 mmol) in CH_2Cl_2 (5 mL) was added slowly over 20 min to a solution of an enantiopure biphenol **1** (1 mmol), 4-*N*,*N*-dimethylaminopyridine (DMAP) (10 mol %), and triethylamine (0.8 mL, 6 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at the same temperature for an additional 2 h. The reaction mixture was then concentrated in vacuo. The residue was redissolved in toluene (10 mL) and filtered through a pad of Celite. The filtrate was concentrated again and the crude product was purified on a silica gel column pretreated with NEt_3 by using hexanes/NEt_3 (100:1) as the eluent to give the corresponding diphosphnite ligand (BOP), **5**, **6**, and **7**. The characterization data for (*R*)-**5e** and (*S*)-**5e** are shown below, and those for all other BOP ligands are summarized in the Supporting Information.

(*R*)-2,2′-Bis(diphenylphosphinyloxy)-3,3′-dibenzyl-5,5′,6,6′-tetramethyl-1,1′-biphenyl ((*R*)-5e): White foam; yield: 74 %; m.p. 75–77 °C; $[\alpha]_D^{25} = -101$ ($c = 2.2$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.81$ (s, 6H), 1.90 (s, 6H), 3.54 (d, $J = 16$ Hz, 2H), 3.70 (d, $J = 16$ Hz, 2H), 6.45 (s, 2H), 7.23 ppm (m, 30H); ^{31}P NMR (162 Hz, $CDCl_3$): $\delta = 110.9$ ppm; HRMS (EI): *m*/*z*: calcd for $C_{54}H_{48}O_2P_2$: 790.3130 $[M]^+$; found: 790.3136 ($\Delta = +0.8$ ppm); (*S*)-**5e** was synthesized in the same manner from (*S*)-**1f**; yield: 73 %; $[\alpha]_D^{20} = +101$ ($c = 1.0$ in $CHCl_3$).

General procedure for the preparation of 2-(siloxymethyl)cyclohex-2-en-1-ols

A solution of 2-hydroxymethyl-2-cyclohexenol[14c] (60 mmol), *tert*-butyldimethylsilylchloride (TBSCl) or triisopropylchlorosilane (TIPSCl) (60 mmol), and imidazole (182 mmol) in THF (100 mL) was stirred at 0 °C for 1.5 h. Then, EtOAc was added and the organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexanes/EtOAc 6:1) to give the corresponding 2-(siloxymethyl)cyclohexenol in high yield as a colorless oil.

Triisopropylsiloxymethyl-2-cyclohexenol (10): Colorless oil; yield: 83 %; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.03$ (m, 21H), 1.53 (m, 1H), 1.80 (m, 3H), 1.95 (m, 1H), 2.01 (m, 1H), 2.92 (br s, 1H), 4.25 (m, 3H), 5.72 ppm (br t, $J = 4.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 11.8$, 17.9, 25.1, 30.9, 66.3, 68.2, 126.5, 137.5 ppm; HRMS (EI): *m*/*z*: calcd for $C_{13}H_{25}O_2Si$: 241.1624 $[M-i\mathrm{Pr}]^+$; found: 241.1622 ($\Delta = +0.2$ ppm).

General procedure for the preparation of allylic substrates, 2-(siloxymethyl)cyclohex-2-en-1-yl carbonates

Chloroformate (3.41 mmol) was added to a solution of **10** (3.39 mmol) and pyridine (3 mL) in CH_2Cl_2 (10 mL) at 0 °C. The resulting solution was stirred at 0 °C for 1 h. After removal of the solvent, the residue was subjected to column chromatography on silica gel by using hexane as the eluent to give **8** as a colorless oil. The characterization data for **8d** is shown below, and those for all other allylic substrates are summarized in the Supporting Information.

2-(Triisopropylsiloxy)methylcyclohex-2-en-1-yl ethenyl carbonate (8d): Colorless oil; yield: 87 %; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.06$ (m, 21H), 1.69 (m, 3H), 2.04 (m, 3H), 4.12 (d, $J = 12.6$ Hz, 1H), 4.23 (d, $J =$ 12.6 Hz, 1H), 4.53 (dd, $J = 2$, 6.4 Hz, 1H), 4.88 (dd, $J = 2$, 14 Hz, 1H), 5.29 (br s, 1H), 6.01 (br s, 1H), 7.09 ppm (dd, $J = 6.4$, 14 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.9$, 17.9, 24.7, 28.3, 64.4, 71.9, 97.3, 128.5, 134.2, 142.7, 152.4 ppm; HRMS (EI): *m*/*z*: calcd for $C_{16}H_{27}O_4Si$: 311.1679 $[M-i\mathrm{Pr}]^+$; found: 311.1675 ($\Delta = -1.3$ ppm).

General Procedure for the Asymmetric Allylic Substitution Reaction

A solution of a subtrate **8** (0.1 mmol) in THF or DMF (1.0 mL) was added to a solution of $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) (2.5 μmol) and (*R*)-**5** or (*S*)-**5** (7.5 μmol) in THF or DMF (0.5 mL), which was preincubated for 15 min before the addition. Sulfonamide **3** (0.11 mmol) in THF or DMF (0.5 mL) was added to this solution and the mixture was stirred at an appropriate temperature. Then, EtOAc was added to quench the reaction. The reaction mixture was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was passed through a short pad of silica gel by using hexanes/EtOAc (5:1) as the eluent to remove the catalyst and ligand. The filtrate was concentrated and subjected to HPLC analysis. The corresponding product *N*-(2-*b*romophenyl)-*N*-(2-siloxymethyl-cyclohex-2-en-1-yl)(4-methylbenzene)sulfonamide (**4**) was isolated by flash chromatography on silica gel by using hexanes/EtOAc (20:1–5:1) as the

eluent by combining crude products from a couple of runs. A small amount of 2-siloxymethylcyclo-hexa-1,3-diene (**9**)[22] was also isolated as the sole byproduct.

***N*-(2-Bromophenyl)-*N*-(2-(triisopropylsilyloxy)methylcyclohex-2-en-1-yl)-(4-methylbenzene)sulfonamide (4b)**: Colorless oil; 96% *ee* (HPLC); $[\alpha]_D^{23} = -2.4$ for *R* and +2.4 for *S* ($c = 0.05$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.71$ (m, 0.2H), 1.11 (m, 21H), 1.72 (m, 4.3H), 2.22 (m, 1.5H), 3.12 (s, 0.75H), 3.21 (s, 2.25H), 4.62 (m, 2H), 5.92 (brs, 0.2H), 6.07 (brs, 0.8H), 7.17 (m, 4H), 7.64 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$; a mixture of two rotational isomers): $\delta = 12.0$ (major), 12.6 (minor), 18.0 (major), 18.8 (minor), 24.3, 28.6 (minor), 29.4 (major), 41.1 (major), 41.9 (minor), 55.2 (major), 57.1 (minor), 65.1 (major), 65.7 (minor), 127.8 (m), 129.7 (m), 134.3 (m), 135.6 (minor), 136.9 ppm (major); HRMS (EI): *m*/*z*: calcd for $C_{26}H_{35}O_3NBrSSi$: 548.1290 $[M-i\mathrm{Pr}]^+$; found: 548.1288 ($\Delta = -0.2$ ppm); isolated yield from the 0.1 mmol reactions for (*R*)-**4b** was 79–88% and that for (*S*)-**4b** from the 1.0 mmol reaction by using 1.2 equiv of **8d** to **3** was 97%.

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[1] a) M. Schlosser, *Organometallics in Synthesis*, VCH, New York, **1994**; b) I. Ojima, *Catalytic Asymmetric Synthesis*, *2nd ed.*, VCH, New York, **1999**.
[2] B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921.
[3] E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis I–III*, Springer, Berlin, Germany, **1999**.
[4] a) A. V. Malkov, I. R. Baxendale, D. Dvorak, D. J. Mansfield, P. Kocovsky, *J. Org. Chem.* **1999**, *64*, 2737; b) F. Glorius, A. Pfaltz, *Org. Lett.* **1999**, *1*, 141; c) B. M. Trost, I. Hachiya, *J. Am. Chem. Soc.* **1998**, *120*, 1104; d) F. Glorius, M. Neuburger, A. Pfaltz, *Helv. Chim. Acta* **2001**, *84*, 3178.
[5] G. C. Lloyd-Jones, A. Pfaltz, *Angew. Chem.* **1995**, *107*, 534; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 462.
[6] a) S. Cenini, F. Ragaini, S. Tollari, D. Paone, *J. Am. Chem. Soc.* **1996**, *118*, 11964; b) Y. Matsushima, K. Onitsuka, T. Kondo, T.-A. Mitsudo, S. Takahashi, *J. Am. Chem. Soc.* **2001**, *123*, 10405; c) J. L. Renaud, C. Bruneau, B. Demerseman, *Synlett* **2003**, 0408; d) B. M. Trost, P. L. Fraisse, Z. T. Ball, *Angew. Chem.* **2002**, *114*, 1101; *Angew. Chem. Int. Ed.* **2002**, *41*, 1059; e) S.-W. Zhang, T.-A. Mitsudo, T. Kondo, Y. Watanabe, *J. Organomet. Chem.* **1993**, *450*, 197.
[7] a) P. A. Evans, J. E. Robinson, J. D. Nelson, *J. Am. Chem. Soc.* **1999**, *121*, 6761; b) P. A. Evans, D. K. Leahy, *J. Am. Chem. Soc.* **2000**, *122*, 5012; c) P. A. Evans, J. E. Robinson, K. K. Moffett, *Org. Lett.* **2001**, *3*, 3269; d) P. A. Evans, D. K. Leahy, *J. Am. Chem. Soc.* **2002**, *124*, 7882.
[8] a) J. P. Janssen, G. Helmchen, *Tetrahedron Lett.* **1997**, *38*, 8025; b) B. Bartels, G. Helmchen, *Chem. Commun.* **1999**, 741; c) T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 15164; d) F. López, T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 3426.
[9] B. M. Trost, *Chem. Pharm. Bull.* **2002**, *50*, 1.
[10] a) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336; b) A. Pfaltz, *Acta Chem. Scand. B* **1996**, *50*, 189; c) G. Helmchen, S. Kudis, P. Sennhenn, H. Steinhagen, *Pure Appl. Chem.* **1997**, *69*, 513; d) J. M. J. Williams, *Synlett* **1996**, 705.
[11] a) B. M. Trost, C. Lee in *Catalytic Asymmetric Synthesis*, *2nd ed.* (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, pp. 593; b) G. Helmchen, U. Kazmater, S. Förster in *Catalytic Asymmetric Synthesis*, *3rd ed.* (Ed.: I. Ojima), Wiley, Hoboken, **2010**, pp. 497.
[12] R. H. Grubbs, R. A. DeVries, *Tetrahedron Lett.* **1977**, *18*, 1879.
[13] B. M. Trost, D. J. Murphy, *Organometallics* **1985**, *4*, 1143.
[14] a) H. Yoshizaki, H. Satoh, Y. Sato, S. Nukui, M. Shibasaki, M. Mori, *J. Org. Chem.* **1995**, *60*, 2016; b) M. Mori, S. Kuroda, C. Zhang, Y. Sato, *J. Org. Chem.* **1997**, *62*, 3263; c) M. Mori, M. Nakanishi, D. Kajishima, Y. Sato, *J. Am. Chem. Soc.* **2003**, *125*, 9801.
[15] Z. Hua, V. C. Vassar, I. Ojima, *Org. Lett.* **2003**, *5*, 3831.
[16] a) Z. Hua, V. C. Vassar, H. Choi, I. Ojima, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5411; b) H. Choi, Z. Hua, I. Ojima, *Org. Lett.* **2004**, *6*, 2689; c) B. D. Chapsal, I. Ojima, *Org. Lett.* **2006**, *8*, 1395; d) B. D. Chapsal, Z. Hua, I. Ojima, *Tetrahedron: Asymmetry* **2006**, *17*, 642; e) C. Shi, I. Ojima, *Tetrahedron* **2007**, *63*, 8563.
[17] J. B. Alexander, R. R. Schrock, W. M. Davis, K. C. Hultzsch, A. H. Hoveyda, J. H. Houser, *Organometallics* **2000**, *19*, 3700.
[18] T. Yamato, K. Hasegawa, Y. Saruwatari, L. K. Doamekpor, *Chem. Ber.* **1993**, *126*, 1435.
[19] W. Lee, C. Park, E. Kim, *J. Org. Chem.* **1994**, *59*, 4495.
[20] a) Y. Zhou, W. Tang, W. Wang, W. Li, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 4952; b) Y. Zhou, X. Zhang, *Chem. Commun.* **2002**, 1124.
[21] B. M. Trost, W. Tang, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 14785.
[22] D. L. Boger, M. Patel, F. Takusagawa, *J. Org. Chem.* **1985**, *50*, 1911.

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