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Construction of *P*-stereogenic center by selective ligation of N–P–N type ligands and application to asymmetric allylic substitution reactions

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Abstract—Chiral bisoxazolylphosphine ligands **1** [(*S*,*S*)-PhP(Ox-R)$_2$: R = Me, ^{i}Pr, ^{t}Bu] with an N–P–N backbone were prepared from chiral 4-alkyl-2-phenyl-4,5-dihydrooxazole compounds. These ligands coordinated to Pd(II) ion as bidentate ligands selectively to give a stereogenic phosphorus atom. The Pd-(*S*,*S*)-PhP(Ox-^{t}Bu)$_2$ **1c** catalyst evoked high enantioselectivity in asymmetric allylic substitutions of acyclic substrates using dimethyl sodiomalonate as nucleophile. In the reaction of 3-penten-2-yl acetate, which affords a π-allyl intermediate with a small steric factor, the Pd-**1c** catalyst successfully induced very high enantioselectivity (94% ee) indicating the effectiveness of the *P*-stereogenic center formed by selective ligation of ligand **1**. In the reaction of cyclic substrates, moderate to high enantioselectivity was obtained by Pd-**1** catalyst using the sodium salt of dimethyl methylmalonate.

In catalytic asymmetric reactions, many chiral phosphine ligands have been reported[1] to induce high enantioselectivity, e.g. in asymmetric hydrogenation, allylic substitution, hydrosilylation, etc. Among them, phosphine ligands, which have stereogenic phosphorus atom(s) induce extremely high enantioselectivity in asymmetric hydrogenation.[1d,2] These *P*-stereogenic ligands, however, involve some synthetic difficulties including resolution and can suffer from racemization at higher temperatures.

We have reported chiral phosphinediamine ligands having an N–P–N backbone, which would enable the construction of a stereogenic phosphorus center by selective ligation of the ligand to metal with their central phosphine unit and one of amine units. These chiral phosphinediamine ligands afforded high enantioselectivities up to 95% ee in the Rh(I)-catalyzed asymmetric hydrogenation of acrylic acid derivatives.[3] In this reaction, the presence of stereogenic phosphorus atoms formed by the ligation and utilization of electrostatic interactions between the substrate and the free amino unit of the ligand enabled effective chiral induction.[3] We have designed other N–P–N type ligands [(*S*,*S*)-PhP(Ox-R)$_2$)] **1a**–**c** having a phosphine unit and two homochiral dihydrooxazolyl units[4] to examine the possibility of the formation of *P*-stereogenic centre by the ligation to metal and their application in asymmetric allylic substitution reactions (Scheme 1).

Bis[((*S*)-4-alkyl-4,5-dihydrooxazol-2-yl)phenyl]phenylphosphine (*S*,*S*)-bisoxazolylphosphine: (*S*,*S*)-PhP(Ox-R)$_2$] ligands **1a**–**c** were prepared by lithiation of 4-alkyl-2-phenyl-4,5-dihydrooxazole followed by the reaction with dichlorophenylphosphine and were purified by column chromatography using an eluent of either hexane–ethyl acetate or of hexane–diethyl ether mixture.[5] ^{31}P and ^{1}H NMR analyses indicated that ligands **1a**–**c** coordinated to various metal ions, such as Pd(II), Pt(II), Ni(II), or Rh(I), as a bidentate ligands.[6] As for $PdCl_2$ and $PtCl_2$ complexes bearing **1a**–**c** ligands, only one complex was observed by ^{31}P NMR analysis in the temperature range of 25 to −40°C which implies a highly selective ligation of these ligands to metal. In the case of π-C_3H_5 palladium complexes bearing ligand **1**, the complex forms a mixture of *exo*- and *endo*-iso-

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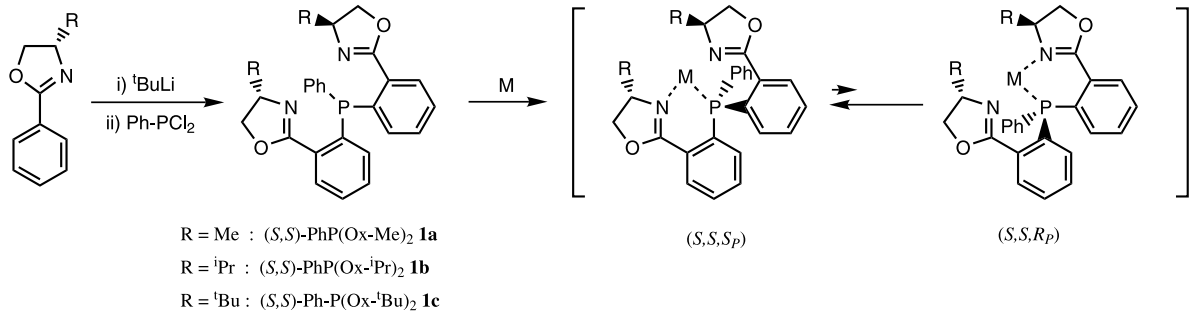
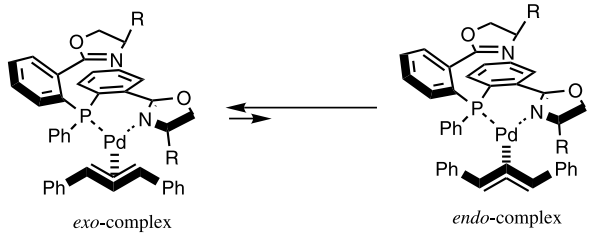


Scheme 1.

mers in solution and the equilibrium favoured largely one isomer for the complexes bearing the **1b** or **1c** ligand. X-Ray crystal analysis of the single crystals obtained from $[PdCl_2((S,S)\text{-PhP(Ox-}^tBu)_2)]$ or $[Pd(\eta^3\text{-}MeC_3H_3Me)((S,S)\text{-PhP(Ox-}^tBu)_2)]PF_6$ indicated that the selective bidentate ligation of the ligand and the phosphorus atom in the complexes had an (*S*)-configuration[7] (Fig. 1). Thus the bisoxazolylphosphine ligands **1** could afford a stereogenic phosphorus atom by the selective ligation to metals which form a square-planar complex. In the case of the 1,3-dimethyl-π-allyl complex, the π-allyl unit coordinated to the palladium in an *exo*-manner in the crystal. As to the equilibrium of *exo*- and *endo*-species in solution, [Pd(1,3-diphenyl-π-allyl)(**1c**)]$^+$ and [Pd(1,3-diphenyl-π-allyl)(**1b**)]$^+$ complexes were examined by ^1H and ^{31}P NMR and showed that the equilibrium between two diastereomeric complexes favoured to the *exo*-species (Scheme 2).[8] The diastereomeric ratios (*exo* to *endo* ratio) in [Pd(1,3-diphenyl-π-allyl)(**1c**)]$^+$ and [Pd(1,3-diphenyl-π-allyl)-(**1b**)]$^+$ were 81:19 and 69:31, respectively, at ambient temperature. In the case of the 1,3-dimethyl-π-allyl complexes, the *exo*-species was also dominant.

In the asymmetric allylic alkylation of 1,3-diphenyl-propenyl acetate with dimethyl sodiomalonate, the ligand **1c** having *tert*-butyl substituents afforded high enantioselection of 94% ee in acetonitrile, while the ligand **1a** with methyl units evoked lower chiral induction of 75% ee (Table 1). Thus the bulkiness of the alkyl substituent on the oxazoline ring affected the chiral induction in this asymmetric alkylation reaction. For 3-penten-2-yl acetate **2b**, which affords 1,3-dimethyl-π-allyl intermediate, high stereoinduction has been seldom reported. The non *P*-stereogenic phosphinooxazoline ligands[9,10] by Pfaltz, Helmchen or Williams, phosphine imine ligand by Morimoto[11] or pyridinophosphine ligand by Ito[12] caused moderate chiral induction between 60 and 80% ee in the alkylation of this 3-penten-2-yl acetate. High enantioselectivities about 90% ee have been achieved with the chiral diphosphine ligand developed by Trost[13] or with the phosphinooxazoline ligand bearing tricyclic oxazoline moiety by Helmchen.[14] The present N–P–N type ligand **1c** afforded very high ee (94%) at room temperature,



Scheme 2.

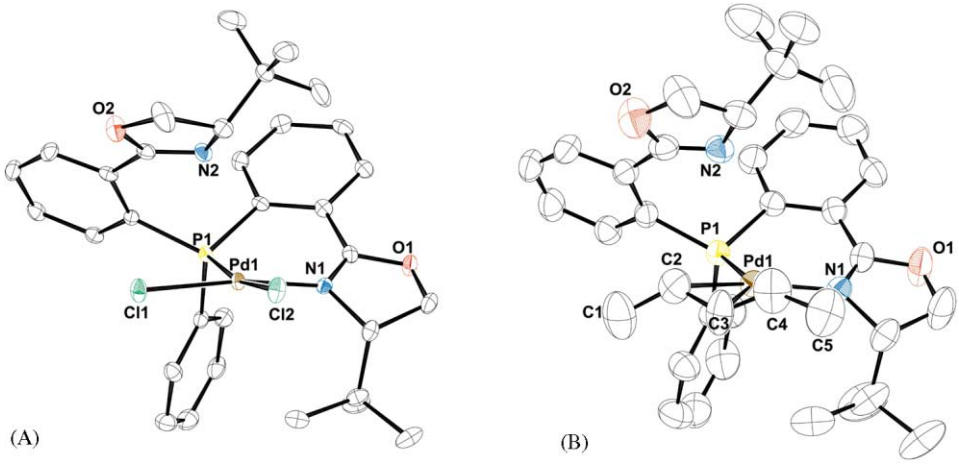
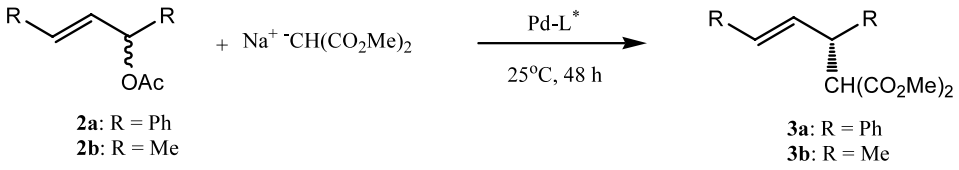


Figure 1. Crystal structure of Pd-(*S*,*S*)-**1** complexes. **A**: $[PdCl_2((S,S)\text{-PhP(Ox-}^tBu)_2)]$. **B**: $[Pd(\eta^3\text{-}MeC_3H_3Me)((S,S)\text{-PhP(Ox-}^tBu)_2)]^+$.

Table 1. Asymmetric allylic alkylation of racemic-**2** by Pd(C_3H_5)(bisoxazolylphosphine) catalysts[a]



2a: R = Ph
2b: R = Me

3a: R = Ph
3b: R = Me

Entry	R of **2**	Pd-L*	Solvent	Yield (%)[b]	% ee (Confign.)[c]
1	Ph	Pd-**1a**	THF	62	75 (*S*)
2		Pd-**1b**	THF	74	92 (*S*)
3		Pd-**1c**	THF	38	70 (*S*)
4		Pd-**1a**	CH_3CN	49	75 (*S*)
5		Pd-**1b**	CH_3CN	52	94 (*S*)
6		Pd-**1c**	CH_3CN	33	94 (*S*)
7	Me	Pd-**1a**	THF	92	64 (*S*)
8		Pd-**1b**	THF	99	85 (*S*)
9		Pd-**1c**	THF	98	94 (*S*)
10		Pd-**1a**	CH_3CN	46	50 (*S*)
11		Pd-**1b**	CH_3CN	46	75 (*S*)
12		Pd-**1c**	CH_3CN	26	84 (*S*)

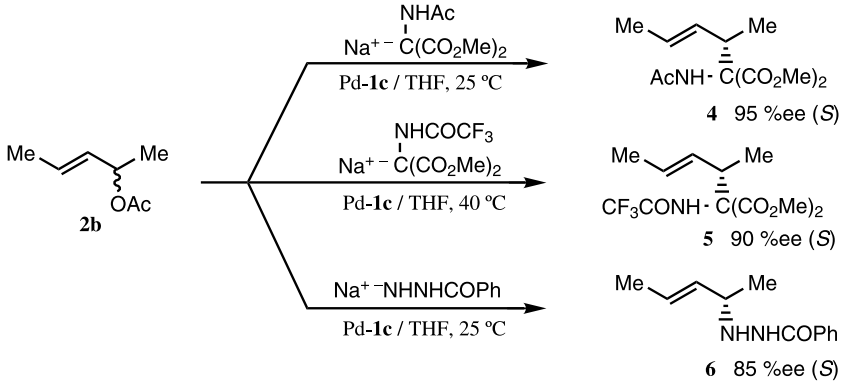
[a] Conducted at 25°C with **2** (1 mmol), dimethyl malonate (1 mmol), NaH (1 mmol), and [Pd(η^3-C_3H_5)(bisoxazolylphosphine **1**)]PF_6 (0.01 mmol) in 10 ml of THF or acetonitrile.

[b] Isolated yield.

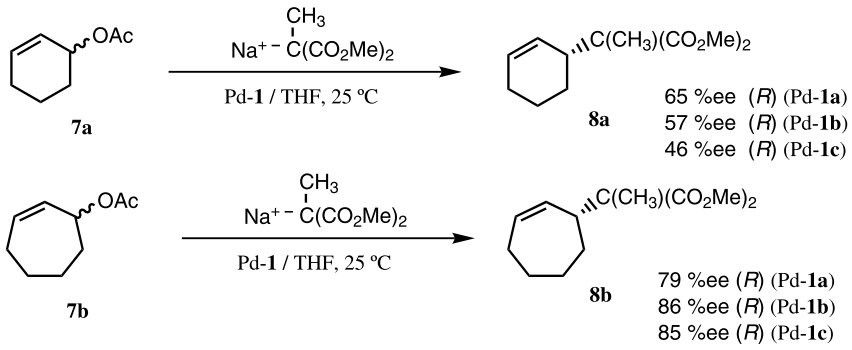
[c] Determined by HPLC (Chiralcel OD) for the product from 1,3-diphenylpropenyl acetate. Determined by ^{1}H NMR analysis in C_6D_6 using shift reagent (Eu(hfc)$_3$) for the product from pentenyl acetate.

which is the highest value so far reported in the alkylation of 3-penten-2-yl acetate, while with the non *P*-stereogenic phosphineoxazoline (Ph_2P(Ox-R)) catalyst only moderate ee's (56–71%) were reported.[9a,10] Various nucleophiles were also examined in the reaction of **2b**. With sodium salt of dimethyl acetamidomalonate as nucleophile, the Pd-**1c** complex afforded very high enantioselectivity of 95% ee in the reaction in THF at 25°C. With dimethyl sodiotrifluoroacetamidomalonate, the Pd-**1c** catalyst induced 90% ee at 40°C. The asymmetric allylic amination of the pentenyl acetate with the ligand **1c** also afforded high ee (85%) using sodiobenzoylhydrazine as nucleophile (Scheme 3). These results would indicate the effectiveness of the chiral field of the *P*-stereogenic center formed through the selective ligation of the ligand to palladium(II) species.

It is well accepted that, in the allylic alkylation reaction by Pd catalyst bearing a P–N type ligand, the nucleophile attacks the π-allyl carbon *trans* to the phosphine unit,[9c,10,15] and that the stereoselection strongly depends on the ratio of the *exo*- and *endo*-species in solution. In the reaction of 3-penten-2-yl acetate or 1,3-diphenylpropenyl acetate using bisoxazolylphosphine ligand **1c**, the observed enantioselectivities can not be explained only by the ratio of the *exo*- and *endo*-species in solution. The stoichiometric reaction of [Pd(1,3-diphenyl-π-allyl)((*S*,*S*)-PhP(Ox-^{t}Bu)$_2$)]$^+$ species with dimethyl sodiomalonate was monitored by ^{31}P NMR analysis at low temperature under the conditions of a slow equilibrium between the *exo*- and *endo*-species; it was seen that the dominant *exo*-species had a much higher reactivity toward the enolate anion than the



Scheme 3.



Scheme 4.

endo-species did. This reactivity difference between the *exo*- and *endo*-complexes would also explain the high stereoselection by Pd-**1c** catalyst in the acyclic substrates.

In the alkylation of cyclic substrates, the asymmetric induction was dependent on the size of substrate and the ligand used: In the reaction of cyclohexenyl acetate **7a** with the sodium salt of dimethyl methylmalonate, the Pd-**1** catalysts afforded a moderate ee, though the Pd-**1a** catalyst afforded a higher ee than Pd-**1b** or **1c** (Scheme 4). Similar results were also obtained in the case of cyclopentenyl acetate. In the reaction of cycloheptenyl acetate **7b**, the ligands with a bulky substituent, **1b** and **1c** afforded high ee (85–86%). The stereoselection was also dependent on the nature of nucleophile which suggests a change in reactivity difference between the *exo*- and *endo*-species towards the nucleophiles; with dimethyl sodiomalonate, the cyclohexenyl acetate afforded a lower ee (ca. 30%), while the Pd-phosphinooxazoline complex without a *P*-stereogenic center afforded a nearly racemic product in the case of cyclohexenyl acetate.[16] Thus, the present *P*-stereogenic Pd-bisoxazolylphosphine catalysts[17] proved to be effective at inducing a high enantioselectivity in the allylic substitution of acyclic and cyclic substrates.[18] We are currently applying these chiral N–P–N type ligands to other asymmetric reactions.

Acknowledgements

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5. **1a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (3H, d, 8.8 Hz, C*H*$_3$), 1.09 (3H, d, 8.8 Hz, C*H*$_3$), 3.65 (1H, dd, 7.8, 7.8 Hz, C*H*$_2$), 3.70 (1H, dd, 7.8, 7.8 Hz, C*H*$_2$), 4.13 (2H, m, C**H*), 4.24 (1H, dd, 7.8, 9.3 Hz, C*H*$_2$), 4.28 (1H, dd, 7.8, 9.3 Hz, C*H*$_2$), 6.94–6.99 (2H, m, Ph), 7.27–7.37 (9H, m, Ph), 7.81–7.84 (2H, m, Ph). ^{31}P NMR (162 MHz, $CDCl_3$): δ −7.33. FAB-MS: 429 $[M+1]^+$. $[\alpha]_D^{25} = -56.7$ (*c* 1.27, CH_2Cl_2).
1b: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.65 (6H, dd, 6.4, 6.4 Hz, C*H*$_3$), 0.72 (6H, dd, 6.8, 6.8 Hz, C*H*$_3$), 1.43–1.54 (2H, m, C*H*(CH$_3$)$_2$), 3.79–3.85 (4H, m, C*H*$_2$), 4.04–4.09 (2H, m, C**H*), 6.83–6.89 (2H, m, Ph), 7.16–7.29 (9H, m, Ph), 7.77–7.79 (2H, m, Ph). ^{31}P NMR (162 MHz, $CDCl_3$): δ −7.52. FAB-MS: 485 $[M+1]^+$. $[\alpha]_D^{25} = -50.9$ (*c* 1.66, CH_2Cl_2).
1c: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.67 (9H, s, C*H*$_3$), 0.71 (9H, s, C*H*$_3$), 3.86 (1H, dd, J = 7.8, 10.3 Hz, C*H*$_2$), 3.88 (1H, dd, J = 8.8, 10.3 Hz, C*H*$_2$), 3.97–4.03 (3H, m, 2C**H*+C*H*$_2$), 4.10 (1H, dd, 8.8, 10.3 Hz, C*H*$_2$), 6.90 (2H, m, Ph), 7.22–7.33 (13H, m, Ph). ^{31}P NMR (162 MHz, $CDCl_3$): δ −7.19. FAB-MS: 513 $[M+1]^+$. $[\alpha]_D^{25} = -39.5$ (*c* 1.97, CH_2Cl_2).
6. *^{1}H NMR of [Pd(C_3H_5)(**1b**)]PF_6 in $CDCl_3$*: Oxazoline unit of [Pd(C_3H_5)(**1b**)]PF_6: δ 3.97 (1H, CHC*H*$_2$), 4.05 (1H, C*H*CH$_2$), 4.24 (1H, CHC*H*$_2$) for free oxazoline unit and δ 4.32 (1H, CHC*H*$_2$), 4.55 (1H, C*H*CH$_2$), 4.64 (1H, CHC*H*$_2$) for oxazoline unit coordinated to Pd The protons of the oxazoline ring coordinating to the palladium

shifted to lower magnetic field by 0.4–0.5 ppm indicating the bidentate ligation of the ligand to palladium in solution. Similar lower field shifts of one oxazoline unit were observed with other N–P–N ligands on π-allyl palladium and dichloropalladium complexes.

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17. *Preparation of* $[Pd(C_3H_5)((S,S)\text{-}PhP(Ox\text{-}R)_2)]PF_6$ *complex*: Di-μ-chlorobis(π-C_3H_5)dipalladium complex was stirred with 2 equiv. of bisoxazolylphosphine ligand [(*S*,*S*)-PhP(Ox-R)$_2$] **1a**–**c** in chloroform overnight and after the addition of NH_4PF_6 methanol solution, the mixture was stirred for 2 h. The mixture was washed with water and the organic layer was evaporated to dryness. After repeated precipitation with chloroform–diethyl ether, the complex was recrystallized from chloroform–hexane to afford white crystals. ^1H and ^{31}P NMR in $CDCl_3$ indicated the presence of an equilibrium mixture of diastereomeric *exo*- and *endo*-complexes. FAB-MS: $[Pd(C_3H_5)((S,S)\text{-}\mathbf{1a})]PF_6$ $m/z = 575$ $[M-PF_6]^+$; $[Pd(C_3H_5)((S,S)\text{-}\mathbf{1b})]PF_6$ $m/z = 631$ $[M-PF_6]^+$; $[Pd(C_3H_5)((S,S)\text{-}\mathbf{1c})]PF_6$ $m/z = 659$ $[M-PF_6]^+$.
18. *Typical allylic alkylation procedure*: In a Schlenk tube was placed $[Pd(C_3H_5)(PhP(Ox\text{-}R)_2)]PF_6$ (0.01 mmol), 1,3-diphenyl-2-propenyl acetate (1 mmol) and a solvent (THF, 5 ml). The resulting solution was stirred under nitrogen at 25°C. To this mixture was added dimethyl sodiomalonate (1 mmol) solution in THF (5 ml), which had been prepared in another Schlenk tube, via a stainless cannula. The solution was stirred at 25°C for 48 h and water then added. The mixture was extracted with ethyl acetate, the organic layer dried over $MgSO_4$ and evaporated in vacuo. The residue was subjected to chromatographic separation (short silica gel column, ethyl acetate/hexane (1/5) eluent) to give a viscous oil. The enantioselectivity was determined by HPLC using a chiral column (Chiralcel OD-H) with hexane/2-propanol (99/1) eluent. The asymmetric alkylation of 3-penten-2-yl acetate or cycloalkenyl acetate was conducted similarly and the product was purified by column chromatography. The enantioselectivity was determined by ^1H NMR analysis using the chiral shift reagent (Eu(hfc)$_3$) in benzene-d_6.