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P-stereogenic P/N hybrid ligands: a remarkable switch in enantioselectivity in palladium-catalyzed asymmetric allylation ☆

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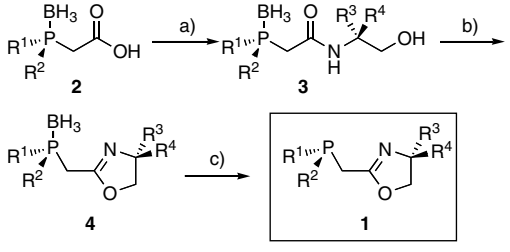
Abstract—Optically active P-stereogenic phosphine/oxazoline bidentate ligands (**1**) were prepared and applied to palladium-catalyzed allylic substitution of 1,3-diphenyl-1-acetoxy-2-propene with dimethyl malonate. The absolute configuration of the allylation product was remarkably switched by changing a palladium/ligand ratio between 1/1 and 1/2.

Many types of optically active ligand have been designed and prepared to develop efficient catalytic asymmetric transformation processes.[1] Among them, the bidentate ligands with two different donor atoms (the so-called 'hybrid ligands') are one of the most effective classes, and the catalytic ability of the metal complexes of these ligands has recently been well documented.[2] One advantage of this type of ligand lies in the difference in *trans* influence between two donor atoms.[3] Furthermore, the coordination ability of the donor atoms may affect reactivity and stereoselectivity in catalytic processes.

Previously, we demonstrated that P-stereogenic bis(trialkylphosphine) ligands (abbreviated to BisP* and MiniPHOS) were effective in rhodium-catalyzed asymmetric hydrogenation of various enamides.[4] The P-stereogenic trialkylphosphine unit constructs an asymmetric environment very close to the rhodium center, and consequently exhibits high enantioselectivity. Moreover, oxidative addition of the rhodium to hydrogen is accelerated due to high electron density at the donor atom.

To display the extended utility of these P-stereogenic phosphine ligands, we report herein the preparation of the phosphine/oxazolines with two chirogenic centers both at the phosphorus atom and the oxazoline ring as a new class of P/N hybrid ligands **1**, and their use in palladium-catalyzed asymmetric allylic substitution (Scheme 1). We anticipated that the cooperation of the two stereogenic centers would lead to characteristic reactivity and selectivity in catalytic asymmetric reactions.

Phosphine/oxazoline ligands **1** were prepared from P-stereogenic boranatophosphinoacetic acid **2** via intermediates **3** and **4** according to the reported procedure (Scheme 1).[5,6] Non-P-stereogenic phosphine/oxazoline ligand **1c** was prepared in a similar manner.[7]



	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
1a	*t*-Bu	Me	H	*i*Pr	**1e**	*t*-Bu	Me	H	*t*-Bu
1b	*t*-Bu	Me	*i*Pr	H	**1f**	1-Ad	Me	H	*t*-Bu
1c	*c*-Hex	*c*-Hex	H	*i*Pr	**1g**	Ph	Me	H	*t*-Bu
1d	*t*-Bu	Me	Me	Me	**1h**	Fc	Me	H	*t*-Bu

Scheme 1. Preparation of optically active P/N hybrid ligands **1**. Reagents and conditions: (a) amino alcohol, EDCI, HOBt, DMF, rt; (b) MsCl, Et_3N, CH_2Cl_2, rt; (c) 1: $HBF_4{\cdot}OMe_2$, −10 °C to rt, 2: aq $NaHCO_3$, rt. EDCI = *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole, MsCl = methanesulfonyl chloride, 1-Ad = 1-adamantyl, Fc = ferrocenyl.

Keywords: Palladium; Asymmetric allylic substitution; P-stereogenic phosphine; P/N hybrid ligand.

☆ Supplementary data associated with this article can be found at doi:10.1016/j.tetlet.2003.10.160

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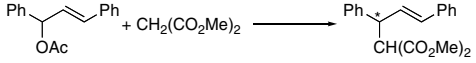
Deboranation of **4** was achieved by the reaction with tetrafluoroboric acid and subsequent treatment with degassed aqueous sodium bicarbonate without damage to the oxazoline ring.[8]

The enantioinduction ability of the P/N hybrid ligands thus obtained was evaluated in Pd-catalyzed asymmetric allylic substitution of allyl acetate. The results are summarized in Table 1. Ligand **1a**, derived from L-valinol and (*S*)-*tert*-butylmethylphosphinoacetic acid, gave a quantitative yield of methyl 2-methoxycarbonyl-3,5-diphenyl-4-pentenoate in 86% ee (*S*) (entry 1). Lower reactivity and selectivity were observed with ligand **1b**, diastereoisomer of **1a**, probably due to mismatched combination of the two stereogenic centers (entry 2). Non-P-stereogenic ligand **1c** furnished 62% of enantioselectivity, whereas ligand **1d**, having no stereogenic center at the oxazoline ring gave only 10% ee of the allylation product (entries 3 and 4). These results indicate that enantioinduction in this allylation reaction is mainly controlled by the chiral oxazoline moiety rather than the chiral phosphine group. By selecting *tert*-butyl group as a substituent at oxazoline, enantioselectivity was improved to 96% (entry 5). Similar results were obtained with ligands **1e** and **1f**, possessing *tert*-butyl and 1-adamantyl groups, respectively. Air-stable P-stereogenic monoarylphosphine/oxazoline ligands were also examined. Decreased reactivity and enantioselectivity were observed when **1g** bearing a phenyl group was employed (57% ee (*S*), entry 8), whereas the ferrocenyl version of P/N ligand **1h** regained high reactivity and enantioselectivity (95% ee, entry 9). These results imply that the steric factor is more important for the substituent on phosphorus than electronic features. In this case, ferrocenyl group are considered to be an electron-withdrawing group, which prevented rapid oxidation of the phosphorus center.

Table 1. Asymmetric allylation of 1,3-diphenyl-1-acetoxy-2-propene with dimethyl malonate catalyzed by Pd complexes of **1**[a]



Entry	Ligand	Yield (%)[b]	Ee (%) (config)[c]
1	**1a**	99	86 (*S*)
2[d]	**1b**	88	26 (*R*)
3[e]	**1c**	99	62 (*S*)
4[d]	**1d**	89	10 (*S*)
5	**1e**	99	96 (*S*)
6[f]	**1e**	99	95 (*S*)
7	**1f**	99	96 (*S*)
8[e]	**1g**	54	57 (*S*)
9	**1h**	99	95 (*S*)

[a] All reactions were carried out in dichloromethane with 3.0 equiv of dimethyl malonate, 3.0 equiv of BSA, and 0.12 equiv of K_2CO_3 in the presence of 5 mol% of $[(\pi\text{-}C_3H_5)PdCl]_2$ and 10–12 mol% of ligand **1** at room temperature for 16 h unless otherwise noted.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Daicel Chiralpak AD, hexane/2-propanol 9:1).
[d] Reaction time: 96 h.
[e] Reaction time: 72 h.
[f] 2.5 mol% of $[(\pi\text{-}C_3\ H_5)PdCl]_2$ and 6 mol% of **1e** were used.

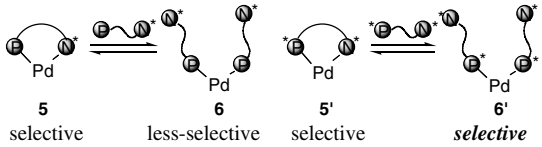


Figure 1. Hemilabile behavior of a P/N hybrid ligand in a metal complex.

Recently, hemilabile behavior of phosphine/oxazoline hybrid ligands in their palladium or platinum complexes was independently discussed by several groups (Fig. 1).[9] It was mentioned that the chelate structure of metal complex **5** is opened to give metal/bis(phosphine) complex **6** by the addition of more than 1 equiv of the P/N ligand (Fig. 1). Complex **6** was more reactive but less stereoselective catalyst species in palladium-catalyzed allylation. In this case, the chiral oxazoline moiety is oriented too far from the reaction center to induce high enantioselection. On the other hand, we recently reported that some P-stereogenic monodentate phosphine ligands were effective in palladium-catalyzed asymmetric allylic substitution.[10] In this system, a 1:2 molar ratio of palladium and the ligand is required for enantioinduction. This fact revealed us the possibility of realizing high enantioselectivity in both 1/1 and 1/2 molar-ratio conditions by using P-stereogenic P/N hybrid ligands (complexes **5′** and **6′**, respectively).

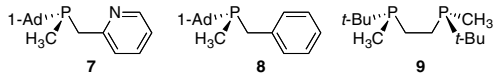
To observe the effect of hemilability on enantioselectivity in our catalyst system, the palladium-catalyzed allylic substitution was examined with several P-stereogenic phosphine ligands at different metal/ligand ratios. The results are listed in Table 2. When ligand **1e** was employed in 1/2.4 of a Pd/ligand ratio, the reaction was complete within 1 h to give a quantitative yield of the alkylation product in 59% ee, and enantioselectivity was increased to 88% at −20 °C (entries 2 and 3). The P-stereogenic P/N ligand exhibited high enantioselectivity both in the form of **5′** and **6′**. It should be noted that the absolute configuration of the product was determined to be *R*, opposed to that obtained by the 1/1 complex of Pd and **1e**. The addition of triphenylphosphine (1 equiv with respect to palladium) led to a racemic product, probably due to formation of a non-selective Pd/**1e**/PPh_3 complex (entry 4). A similar switch in enantioselectivity was observed in the case of ligand **7** bearing a 2-picolyl group. The reaction proceeded smoothly to afford a quantitative yield of the allylation product in 12% ee (*S*) and 44% ee (*R*), respectively (entries 5 and 6). Furthermore, P-stereogenic monodentate phosphine **8** also exhibited remarkable changes in enantioselectivity in both 1/1 and 1/2 molar-ratio conditions. Thus, ligand **8** in 1/1 molar-ratio conditions gave an almost racemic product, probably responsible for the flexible structure of the 1/1 complex of Pd and **8** (entry 7). On the other hand, the reaction in 1/2 molar-ratio conditions afforded an allylation product in 74% ee (*R*), implying formation of a Pd–diphosphine complex like **6′** (entry 8).

The relationship between a Pd/ligand ratio and enantioselectivity is shown in Figure 2. The ferrocenyl version

Table 2. Asymmetric allylic substitution of 1,3-diphenyl-1-acetoxy-2-propene with dimethyl malonate catalyzed by Pd complexes of various P-stereogenic phosphine ligands[a]

Entry	Ligand	Pd/L	Time (h)	Yield (%)[b]	Ee (%) (config)[c]
1	**1e**	1/1	2	94	95 (*S*)
2	**1e**	1/2	0.7	99	59 (*R*)
3[d]	**1e**	1/2	16	92	88 (*R*)
4[e]	**1e**	1/1	0.5	86	2 (*R*)
5	**7**	1/1	0.3	99	12 (*S*)
6	**7**	1/2	0.1	93	44 (*R*)
7	**8**	1/1	72	96	7 (*R*)
8	**8**	1/2	2.5	91	74 (*R*)
9	**9**	1/1	16	96	88 (*S*)

[a] All reactions were carried out in dichloromethane with 3.0 equiv of dimethyl malonate, 3.0 equiv of BSA, and 0.1 equiv of K_2CO_3 in the presence of 5 mol% of $[(\pi\text{-}C_3H_5)PdCl]_2$ and 10–12 mol% (for Pd/L = 1/1) or 24 mol% (for Pd/L = 1/2) of ligand at room temperature unless otherwise noted.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Daicel Chiralpak AD, hexane/2-propanol 9:1).
[d] At −20 °C.
[e] 12 mol% of triphenylphosphine was added.



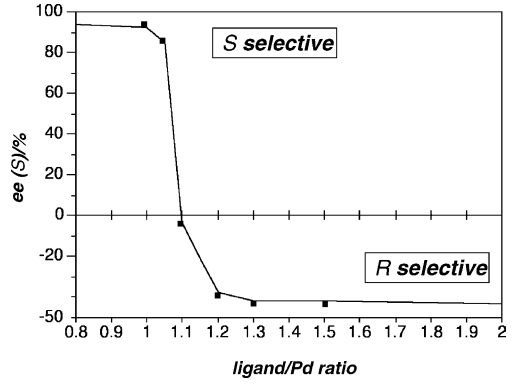


Figure 2. Plot of ee (*S*) versus ligand/Pd ratio for the allylic allylation of 1,3-diphenyl-1-acetoxy-2-propene and dimethyl malonate catalyzed by Pd/**1h** complex.

of P/N ligand **1h** was chosen because of its high enantioinduction ability and stability in air. Greater than 90% of *S* selectivity was maintained when the Pd/ligand ratio was below 1/1. As the ratio of **1h**/Pd increased, the selectivity dropped, and a complete racemic product was obtained at a ratio of 1/1.1. A further increase in the ratio inclined the reaction *R* selective. Enantiomeric excess reached 42% at a ratio of 1/1.3, and selectivity was maintained above this point. These results clearly indicate the existence of two different catalyst species, probably Pd/**1h** and more reactive Pd/2·**1h**. This is supported by the fact that [(1,3-diphenyl-η^3-allyl)Pd·**1e**]SbF_6 (**10**) afforded the *S* product in 87% ee, whereas the *R* product with 68% ee was obtained in the presence of 1.2 equiv of ligand **1e** (with respect to **10**). Ligand exchange between oxazoline nitrogen in **10** and phosphorus in **1e** partially occurred to form the Pd/2·**1e** complex. The formation of this complex was monitored by CSI-MS. The 1/1 mixture of **10** and **1e** in 0.9 mM of dichloromethane solution afforded a strong signal at m/z 542 assigned to $[Pd/\mathbf{1e}]^+$ (rel intensity: 100) and weak one at m/z 785 corresponding to $[Pd/2\cdot\mathbf{1e}]^+$ (rel intensity: 5). There would be a rapid equilibrium between Pd/**1e** and highly reactive Pd/2·**1e**.

To discuss structure–selectivity relationship, palladium-1,3-diphenyl-η^3-allyl complexes of **1e** and C_2 symmetric diphosphine ligand **9** ((*S*,*S*)-*t*-Bu-BisP*) were subjected to X-ray crystallographic analysis (Fig. 3).[11] The crystal structure of **10** revealed that the 1/1 complex of palladium and P/N ligand **1e** forms a five-membered chelate

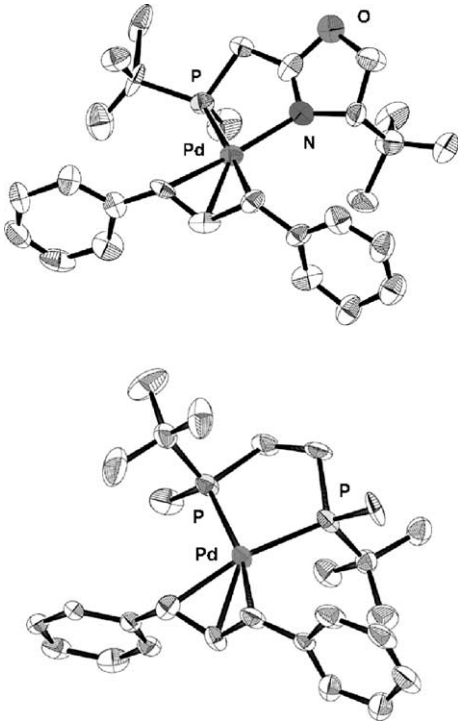


Figure 3. ORTEP drawings of **10** (top) and [(1,3-diphenyl-η^3-allyl)Pd·**9**]SbF_6 (bottom). Hydrogen atoms and counterions are omitted for clarity.

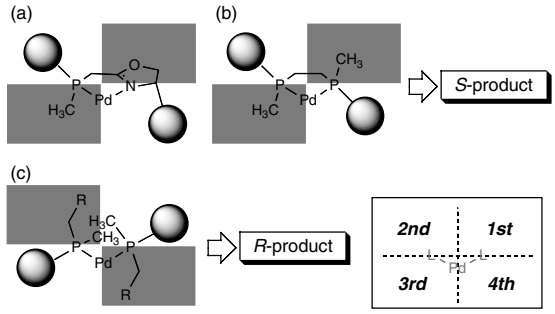


Figure 4. Quadrant diagrams for the palladium complexes of P-stereogenic bidentate ligands. The π-allyl ligand is omitted for clarity.

structure in which the substituents on the phosphorus and the oxazoline ring occupy the second and fourth quadrants of the space around the metal center as shown in Figure 4a. This configuration would tend to give an allylation product with *S* selectivity in the catalytic process.[2,12] This hypothesis is supported by the observation that *S* selectivity also occurred in the case of the palladium complex of ligand **9** whose crystal structure was determined as shown in Figure 4b (Table 2, entry 9). On the other hand, *R* selectivity was obtained by using the catalyst system consisting of palladium/**1e** in a 1/2 ratio. A reasonable interpretation of these results is that the catalyst species forms the structure shown in Figure 4c in which the two methyl groups on both the phosphorus atoms would face each other to minimize steric repulsion between the two ligands. As a result, the first and third quadrants are occupied by the bulky substituents, leading to *R* selectivity.

NMR studies provided some information about behavior of the Pd complexes in solution phase. Thus, ^{1}H NMR measurement of **10** in $CDCl_3$ gave two sets of signals that would correspond to a 5:1 mixture of diastereomers.[13] About the major isomer, NOE was found between the protons at *tert*-butyl group and allylic position, which is consistent with the structure as shown in Figure 3. ^{31}P NMR measurement of **10** provided narrow singlet at 36.98 ppm, which was broadened by the addition of excess of **1e**, indicating the existence of rapid equilibrium between Pd/**1e** and Pd/2·**1e**.

In conclusion, several types of P-stereogenic phosphine/oxazoline ligand were designed and prepared, and the enantioinduction ability was evaluated in palladium-catalyzed asymmetric allylic substitution of allyl acetate with a malonate ester. A remarkable switch in enantioselectivity was observed in this catalytic process when the palladium/ligand ratio was changed between 1/1 and 1/2.

Supplementary material

Experimental procedures and characterization data for new compounds are available online with this article on doi:10.1016/j.tetlet.2003.10.160.

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11. CCDC-218379 and 218380 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
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