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Induction of reversal chirality by C_2-symmetric diamide linked-diphosphine ligands in catalytic asymmetric allylations

Akihito Saitoh, Takashi Uda and Toshiaki Morimoto*

School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka-shi 422-8526, Japan

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Abstract

Bridging parts X between two amide skeletons of C_2-symmetric diphosphine ligands **1** were varied using various kinds of diacyl chlorides. The ligand **1c** derived from phthaloyl chloride, which was remarkably effective in the asymmetric induction on palladium-catalyzed asymmetric allylic substitutions of 2-cyclohexenyl pivalate or acetate, exhibited a moderate level of enantioselectivity, 72% ee, in the transformations of 1,3-diphenyl-2-propenyl pivalate. The newly developed ligands **1g–i** having one carbon spacers X demonstrated higher degrees of enantiomeric excess up to 93% ee. Interestingly, the present reactions catalyzed by Pd–**1c–e**,**g–j** complexes afforded the product **4** with the opposite absolute configuration *S* compared with the reactions using VALAP, which has the same chiral source as that of **1**. The ligands **1a**,**b**,**f** exhibited the induction of *R* configuration although the yields were very low. The production of *S*-**4** was discussed on the basis of the *Pr*/*Mr* chirality model.

Optically active diphosphines with C_2-symmetry[1] have been recognized as useful auxiliaries to create an effective chiral environment in metal-catalyzed asymmetric reactions. In our novel versatile ligand system,[2] diamide-linked diphosphine ligands, **1a**,**c**,**f**,[2d–f] consisting of 2-aminoethylphosphine as a chiral unit have been recently developed from the synthetic precursor of the phosphine–amidine hybrid ligand, VALAP.[2a] The versatile system consisting of the hetero-hybrid types or the diphosphines has actually played an important role in the variation of reaction types and substrates. Among our previous studies, high levels of asymmetric induction over 99% ee were achieved using **1c** in palladium-catalyzed asymmetric allylic transformations[3] of sterically less demanding 2-cyclohexenyl acetate or pivalate. In a further study using **1c**, the application to asymmetric allylic substitutions of 1,3-diphenyl-2-propenyl pivalate as a typical acyclic allyl substrate led to a moderate level of asymmetric induction, but

* Corresponding author. E-mail: morimtt@ys2.u-shizuoka-ken.ac.jp

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interestingly the opposite absolute configuration was observed compared with the *R* configuration in the products obtained using VALAP and its analogous ligands.[2a,c,f] However, the reactions using **1a**,**f** resulted in the production of *R*-**4**. Thus, we further prepared various diphosphine ligands in addition to **1a**,**c**,**f** and studied a ligand structure–enantioselectivity relationship, in which high levels of asymmetric induction were achieved for the acyclic allyl substrate using the further developed ligands. This paper reports induction of reversal chirality by the ligands **1** in palladium-mediated enantioselective allylic transformations of acyclic allyl substrate and a possible mechanistic consideration for the production of *S*-**4**.

Since the diphosphine ligand **1c** exhibited high levels of asymmetric induction over 99% ee in palladium-catalyzed enantioselective alkylations of cyclic allyl substrates, 2-cyclohexenyl pivalate or acetate,[2d–f] the catalytic behavior for 1,3-diphenyl-2-propenyl pivalate **3** as an acyclic allyl substrate was next examined. The reaction was conducted using dimethyl malonate/BSA/AcOLi as a nucleophile. The ligand **1c** was not so effective at inducing high enantioselectivity, giving an alkylated product **4** with 72% ee in 14% yield, but interestingly the product **4** exhibited the opposite absolute *S* configuration to *R* observed in the reactions using the chiral hybrid ligands represented by VALAP.[2a–c,f] The use of ligands **1a**,**f**, reported before, also gave no satisfactory catalytic activity and enantioselectivity. In the reactions using **1a**,**f**, however, the products with *R* configuration were obtained.

In the ligands **1**, it could be expected that the bridging parts X and the substituents R on the stereogenic carbons would affect the positioning array of the four phenyl rings on phosphorus atoms. In this way, further extension of the present ligand system was planned (Fig. 1). New diphosphine ligands **1b**,**d**,**e**,**g**,**j** with various bridging parts X were prepared by treatment of the synthetic precursor of VALAP, **2**, with the corresponding diacyl chlorides according to the preparation of **1a**,**c**,**f**.

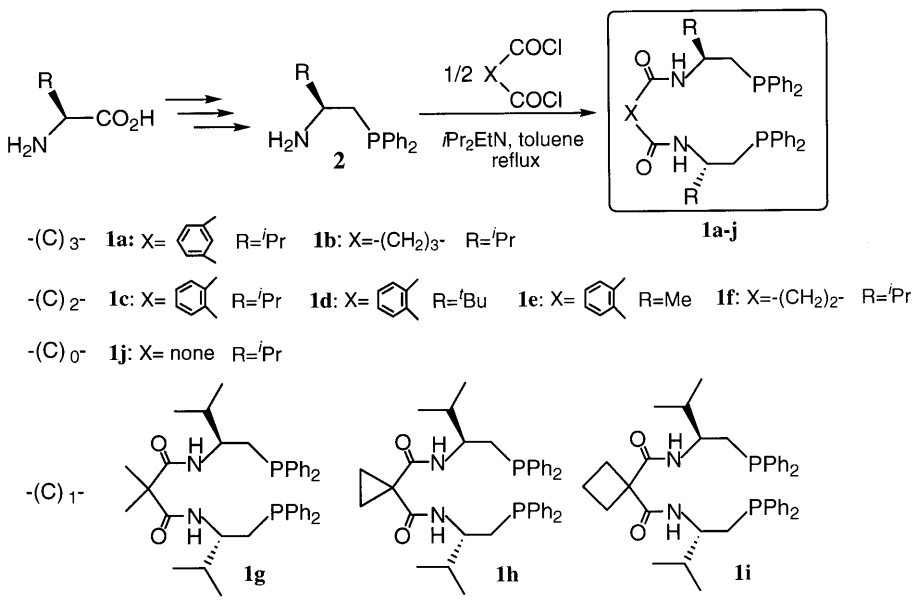
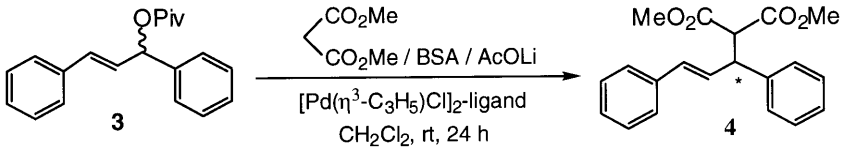


Figure 1. C_2-symmetric diphosphine ligands consisting of 2-aminoethylphosphine as a chiral unit

Effects of the R substituents were first evaluated using the ligands **1d** and **1e** derived from L-*tert*-leucine and L-alanine. The use of **1e** with methyl groups resulted in a decrease in the enantiomeric excess (Table 1, entry 5). However, the ligand **1d** bearing the bulky substituent worked for raising the enantioselectivity along with the catalytic activity (entry 4).

Table 1
Diverse catalytic behavior of ligands **1** in allylic reactions of **3**[a]



Entry	Ligand	Yield[b] (%)	Ee[c] (%)
1	**1a**	13	64 (*R*)
2	**1b**	5	83 (*R*)
3	**1c**	14	72 (*S*)
4	**1d**	52	81 (*S*)
5	**1e**	40	62 (*S*)
6	**1f**	4	47 (*R*)
7	**1g**	54	84 (*S*)
8	**1h**	45	87 (*S*)
9	**1i**	50	93 (*S*)[d]
10	**1j**	3	5 (*S*)

[a] Molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/**1**/**3**/dimethyl malonate/BSA/AcOLi = 2.5/6/100/300/300/5.
[b] Isolated yield by preparative TLC on silica gel.
[c] The enantiomeric excess was determined by HPLC with a chiral column, Daicel Chiralpack AD.
[d] $[\alpha]_D^{24} = -18.7$ (*c* 1, $CHCl_3$).

The ligand **1b** with a propylene unit as X gave the product with *R* configuration as expected from the result using **1f** (entry 2). The catalytic activity was low as well as that in the reaction using **1f**; however, an enantiomeric excess over 80% was achieved. The ligand **1j** with no bridging part X afforded only a small amount of the product with a much lower ee. The use of **1g** derived from dimethylmalonyl chloride demonstrated a significant improvement of the enantioselectivity to 84% ee. The absolute configuration of **4** in the run using **1g** was *S* in a similar manner to the reactions using **1c**–**e**.

In a study on asymmetric hydrogenations of *N*-acetyldehydroamino acids using DIOP and its related chiral diphosphine ligands, the ring size of cyclic parts between two diphenylphosphinomethyl groups gave a significant effect on the enantioselectivity.[4] Large torsional angles of the two diphenylphosphinomethyl groups induced by small rings led to the improvement of enantioselectivity. Such an obvious effect has not been demonstrated in palladium-catalyzed asymmetric allylic alkylations. In the present study, it was expected that the introduction of cyclic groups would change bond angles of two amide groups and give different chiral arrangements. Based on the reported result and the present finding with respect to the ligand **1g**, further preparation of diphosphine ligands **1h**,**i** having 1,1-disubstituted cyclopropane and cyclobutane bridging parts was carried out.[5] As expected, the use of **1h**,**i** resulted in the improvement of enantioselectivity up to 93% ee. The most effective ligand **1i** in the present

reaction was applied to the substitution of 2-cyclohexenyl pivalate, but the result more than that using **1c** was not obtained. Thus, it was found that the versatility of diphosphine ligands **1** worked well for the variation of substrate types in the allylic substitutions.

Recently, we proposed a *Pr*(plus region)/*Mr*(minus region) chirality model to visualize the bulky quadrant in chiral ligands (Fig. 2).[2f] A good correlation between the *Pr*/*Mr* chirality of ligands and the absolute configuration of asymmetric allylation products was found. The relationship was well explained by the mechanistic consideration that the direction of a nucleophilic attack could be controlled to avoid the steric repulsion in a palladium–olefin complex assignable to the late transition state. In the allylic transformations, chiral ligands with *Mr* chirality generally afford the *R* product from the diphenylallyl substrate and the *S* product from the cyclic allyl substrate.[2f] It is envisioned from the result of allylic transformations of 2-cyclohexenyl pivalate that the ligand **1c** has *Mr* chirality. Therefore, the present unexpected observation for the production of *S*-**4** in the reactions using **1c–e,g–j** may not be simply explained by the *Pr*/*Mr* chirality model.[6]

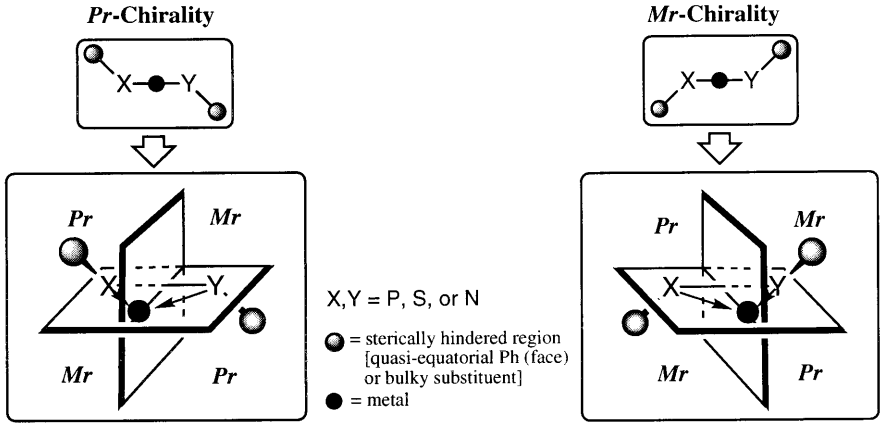


Figure 2. *Pr*/*Mr* chirality model

In the use of **1b,f** with the flexible bridging part, the yield of **4** was considerably low, which suggested the presence of only a small amount of active Pd complex catalysts. Since the *R* product was obtained in the reactions using **1b,f** as well as that using VALAP, a hybrid type complex such as intermediate species coordinated at the amide part and the phosphine in one side of the ligands, might be formed because of the flexible spacer which could detach both phosphorus atoms.

In summary, various types of diphosphine ligands **1** exhibited markedly different behavior and induction of reversal chirality in palladium-catalyzed allylic alkylations of the acyclic substrate **3**. The tendency of the effects was different in the reactions using acyclic and cyclic substrates. High level of asymmetric induction was achieved by the introduction of a 1,1-disubstituted cyclobutane part between two amide groups. Interestingly, the alkylated products **4** obtained using **1c–e,g–j** showed *S* absolute configuration, which is opposite to that obtained using VALAP.

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5. Analytical data for the representative ligand **1i**: yellowish solids; yield: 58%; $[\alpha]_D^{24}=+30.3$ (*c* 1.25, $CHCl_3$); mp 59–61°C; ^1H NMR (270 MHz, $CDCl_3$) δ 0.83 (d, 12H, $J=6.6$ Hz), 1.76–1.96 (m, 4H), 2.09–2.44 (m, 8H), 3.85–3.98 (m, 2H), 6.13 (d, 2H, $J=9.2$ Hz) and 7.26–7.39 (m, 20H); IR (KBr): 3314, 1642 and 1522 cm^{-1}; FAB-MS *m*/*z* 651 (MH^+).
6. As one of the possible mechanisms, the formation of a *syn–anti* π-allyl moiety may be considered. The subsequent nucleophilic attack could occur to avoid the steric repulsion in the *Mr* chirality model, yielding *S*-**4**. In palladium-catalyzed allylic amination using pyrazole–ferrocenyl phosphine ligands, Togni and his co-workers reported the similar drastic inversion of enantioselectivity, in which the presence of palladium complex having the bending allyl moiety as a major component was clearly demonstrated by X-ray diffraction in the solid state and 2D NMR spectroscopy in solution. See: Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031. The present ligands could form large membered cyclic complexes in such cyclic systems. As another possibility different types of chiral circumstances compared with the typical *Mr* chirality might be produced.