Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1025–1028

TETRAHEDRON: *ASYMMETRY*

A new C_2-symmetric chiral diphosphine ligand: palladium-catalyzed enantioselective allylic alkylation of cycloalkenyl substrate

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Received 23 February 1999; accepted 15 March 1999

Abstract

A novel C_2-symmetric chiral diphosphine ligand **1** was developed using (2*S*)-2-amino-1-(diphenylphosphino)-3-methylbutane **2** which was derived from L-valine as in the previous work for the chiral amidine ligand, VALAP. Ligand **1** demonstrated extremely high levels of asymmetric induction, over 99% ee in palladium-catalyzed allylic alkylations of 2-cyclohexen-1-yl pivalate **5**.

Palladium-mediated allylic reactions have been attracting much attention as an efficient synthetic tool for C–C bond formation that can be applied to intramolecular cyclization reactions and the production of various kinds of natural products.[1] The great demand for stereoselective transformations in the applied science led to the development of chiral auxiliaries which could create a chiral environment for asymmetric induction along with efficient transformations of substrates.[2] In this field, we have been developing the new chiral amidine ligand **3**, VALAP[3] derived from L-valine in which a variety of modifications and further extensions of the ligand system[4] are envisioned.

Based on our point of view to overcome the limitation with respect to reaction types,[3a] we have been investigating palladium-catalyzed asymmetric allylic transformation of sterically less demanding substrates. Among the various kinds of enantioselective allylic reactions, the asymmetric induction of cyclic allyl compounds has proven to be the most difficult so that only a few examples concerning high enantioselective induction beyond 90% ee have been reported.[5] Chiral phosphanyldihydrooxazoles, P–N hybrid ligands which are being investigated by numerous research groups, are effective for asymmetric allylations of acyclic substrates, however the use of cyclic allyl substrates leads to low enantioselectivities except for phosphanyldihydrooxazoles with fine tuning by a cymantrene unit.[5c,6] On the other hand, chiral diphosphine ligands with a large bite angle induced remarkably high enantioselectivities for cycloalkenyl substrates.[5a,d] Optically active diphosphine ligands with C_2-symmetry have been found to possess effective chiral environments for substrates and nucleophiles.[7] All assignable to this class

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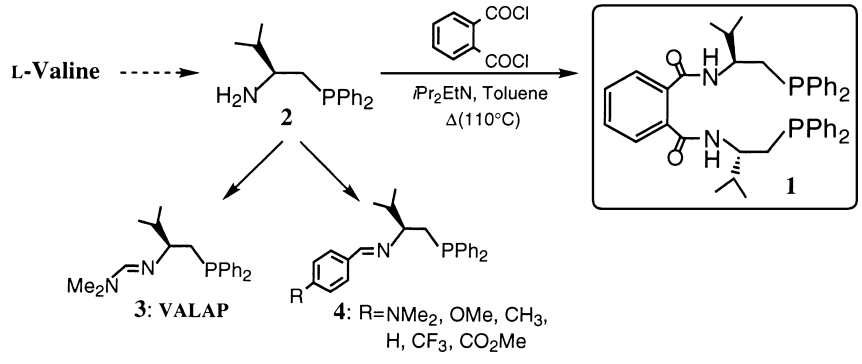
0957-4166/99/$ - see front matter
PII: S0957-4166(99)00100-7

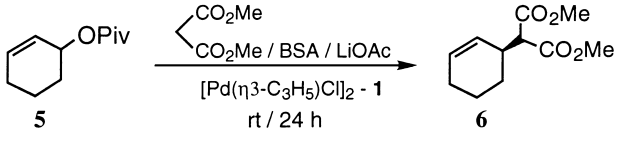
of ligands have been used for a variety of transition metal-catalyzed reactions. Hence we designed a new C_2-symmetric diphosphine ligand **1** as an extension of our concept for VALAP. Herein we wish to demonstrate the development of the chiral diphosphine ligand **1** on the basis of α-amino acid and remarkable levels of asymmetric induction in palladium-catalyzed allylic alkylations of 2-cyclohexen-1-yl pivalate **5**.

The new ligand **1** was prepared in one step from the precursor of VALAP **2**[3a] which was easily accessible from L-valine. Two equivalents of **2** were treated with phthaloyl chloride in the presence of diisopropylethylamine in toluene at reflux. The desirable product was isolated by silica gel column chromatography as a white solid in 53% yield (Scheme 1).[8]



Scheme 1.

The new ligand thus prepared was subjected to palladium-catalyzed allylic alkylations of 2-cyclohexen-1-yl pivalate **5** with an anionic soft nucleophile derived from dimethyl malonate/BSA/AcOLi (Scheme 2).[9] As listed in Table 1, the present ligand demonstrated remarkably high asymmetric induction, giving (*S*)-**6**[10] in over 99% ee. The use of halogenated hydrocarbon solvents appeared to be appropriate for the reactivity (entries 1 and 3) so that switching to THF resulted in a decrease of catalytic activity (entry 4). However, no influence of solvent was observed in terms of enantioselectivity. The reduction of the catalyst amount resulted in somewhat lower asymmetric induction (entry 2). In the current chiral auxiliary, the combination of C_2-symmetry, rigidity of the amide skeleton to fix the two arms extending from the benzene ring, and the influence of the isopropyl groups on the stereogenic carbons on the conformation of the phenyl rings on the phosphorus atoms would serve as a favorable chiral binding site. All the present observations of this remarkable asymmetric induction suggest an appropriate chelate coordination of diphosphine **1** to the metal, thus providing the effective chiral environment.[11]



Scheme 2.

In summary, we extended our ligand concept for VALAP to the development of new C_2-symmetric chiral diphosphine ligand **1** which possessed remarkably high enantioselectivities in the palladium-catalyzed allylic reactions of a cyclohexenyl substrate. The present ligand system will be extended by employing other acid chlorides in which different chiral environments can be constructed by various bite angles of ligands around the palladium atom. Further efforts including the optimization of ligand

Table 1
Asymmetric allylic alkylations of **5** catalyzed by a palladium–**1** complex[a]

Entry	Solvent	Mol equiv. of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	0.025	64	≥ 99(*S*)[d]
2	CH_2Cl_2	0.015	46	91(*S*)
3	$ClCH_2CH_2Cl$	0.025	54	≥ 99(*S*)
4	THF	0.025	11	≥ 99(*S*)

a. Molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/**5**/dimethyl malonate/BSA/AcOLi =1.5-2.5/3.6-6/100/300/300/5. b. Isolated yield. c. Enantiometric excess for **6** was determined by gas chromatography with a CP-Chirasil-DEX CB column [25 m x 0.25 mm(ID), 0.25 μm film thickness]. As a reference sample, rac-**6** was prepared using a Pd-dppp catalyst. d. $[\alpha]_D^{23}$ -43.2 (*c* 1.75, $CHCl_3$); Specific rotation value of (*R*)-**6** extrapolated to 100% ee: $[\alpha]_D$ +46.1 (*c* 2.86, $CHCl_3$).[6a]

synthesis, application to other asymmetric reactions, and mechanistic considerations[12,13] are being currently pursued.

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4. As one of the strategies, we derived chiral P–N hybrid ligands **4** consisting of imino groups with diverse phenyl substituents from the precursor of VALAP, (2*S*)-2-amino-1-(diphenylphosphino)-3-methylbutane **2**,[3a] in which the drastic improvement of catalytic performance by electronic tuning for the ligands was demonstrated in palladium-catalyzed asymmetric allylations. Saitoh, A.; Misawa, M.; Morimoto, T. *Synlett*, in press.
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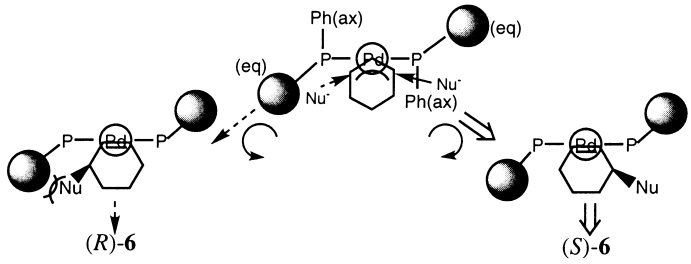
8. Analytical data for the ligand **1** isolated as a white solid: mp=57–59°C; $[\alpha]_D^{24}$ +21.3 (*c* 0.5, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ: 0.90 (d, 6H, *J*=6.6 Hz), 0.92 (d, 6H, *J*=6.6 Hz), 2.00–2.12 (m, 2H), 2.26–2.41 (m, 4H), 4.03–4.17 (m, 2H), 6.78 (d, 2H, *J*=8.9 Hz), 7.26–7.47 (m, 24H); $^{31}P\{^1H\}$ NMR (161.7 MHz, $CDCl_3$, H_3PO_4) δ: −22.74; FAB-MS: *m/z* 673 (MH^+); IR (KBr): 1643 cm^{-1} (C=O), 3256 cm^{-1} (NH).
9. Typical procedure for asymmetric reactions (entry 1): A solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (4 mg, 0.0109 mmol) and **1** (17.6 mg, 0.0262 mmol) in 1 ml of CH_2Cl_2 (dry and oxygen free) was stirred at room temperature under Ar, followed by adding compound **5** (79.4 mg, 0.436 mmol) in 1 ml of CH_2Cl_2. To the mixture was added a nucleophile solution prepared in another flask by mixing dimethyl malonate (173 mg, 1.31 mmol) and BSA (266 mg, 1.31 mmol) in the presence of lithium acetate (1.4 mg, 0.0218 mmol) in 2 ml of the solvent. After stirring at room temperature for 24 h and checking the reaction by gas chromatography, the volatiles were removed in vacuo. The residue was purified by preparative TLC (toluene:AcOEt=20:1). (*S*)-Dimethyl cyclohex-2-enylmalonate **6**: ^1H NMR (270 MHz, $CDCl_3$) δ: 1.31–1.81 (m, 4H),

1.96–2.06 (m, 2H), 2.86–2.95 (m, 1H), 3.29 (d, 1H, *J*=9.2 Hz), 3.74 (s, 3H), 3.75 (s, 3H), 5.52 (dd, 1H, *J*=2.3, 10.2 Hz), 5.74–5.82 (m, 1H).

10. The absolute configuration was determined on the basis of specific rotation.[6a]
11. A ^{31}P NMR spectrum of the catalyst solution which was prepared by mixing $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and **1** in $CDCl_3$ was measured as a preliminary study for the conformation of the Pd–**1** complex. Two doublet peaks with the same coupling constant were observed, suggesting a bidentate P–Pd–P bond and incompletely symmetrical chelation. $^{31}P\{^1H\}$ NMR (161.7 MHz, $CDCl_3$, H_3PO_4) δ: 6.43 (d, $^2J_{P,P}$=34.8 Hz), 9.46 (d, $^2J_{P,P}$=34.8 Hz).
12. In recent work Osborn et al.[5d] proposed a concept that nucleophilic attack on a π-allyl complex and the subsequent rotation to a Pd–olefin complex are controlled by chiral ligands where it is essential for the π-allyl complex to avoid steric repulsion in the late transition state (product-like). We have been considering the rotational mechanism concerning the stereo-determining step by the combination with the *P/M* chirality concept[13] in which the positioning array of the four phenyl rings of diphosphine ligands established by X-ray analysis data closely correlates with the absolute configuration of asymmetric hydrogenation products. In the asymmetric allylic alkylation of **5** using (*S*)-BINAP with *M*-chirality[13] as a representative diphosphine ligand, (*S*)-**6** was produced in 34% ee under the same condition as that of entry 1. The predominant *S*-selectivity was speculated upon by correlating the rotational concept with the *M*-chirality as depicted in Scheme 3. According to the absolute configuration of the products, a similar path may be considered in the present reactions using **1**. Studies regarding the correlation of enantioselectivity with the *P/M* chirality are in progress.



Gray circles : Sterically hindered area assignable to pseudo-equatorial phenyl groups

Scheme 3.

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