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Palladium-Catalyzed Asymmetric Alkoxycarbonylation of Allyl Phosphates

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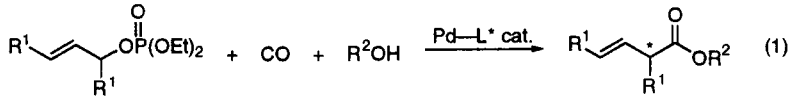
Abstract: Palladium-catalyzed alkoxycarbonylation of allyl phosphates proceeds with high efficiency affording the corresponding β,γ-unsaturated esters stereoselectively with inversion of configuration at the allylic carbon center. Palladium complexes bearing chiral monodentate phosphine ligands are effective catalysts for asymmetric allylic carbonylation of cyclohex-2-en-1-yl phosphates **1** to give optically active cyclohex-2-ene-1-carboxylates **2** in moderate enantiomeric excesses. © 1997 Elsevier Science Ltd.

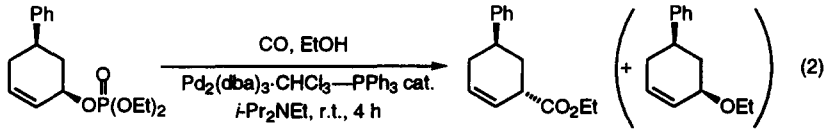
Exploitation of new methodology for utilization of carbon monoxide is one of the fundamental technologies for chemical feedstocks at present as well as in the future.[1] Alkoxycarbonylation of allylic compounds is one of the most attractive methods for the synthesis of β,γ-unsaturated carbonyl compounds. Recently, allylic carbonylation was found to take place under mild reaction conditions using allyl alcohol derivatives such as allyl carbonates,[2] phosphates,[3] acetates,[3] and formates.[4] However, asymmetric version of allylic carbonylation reactions have never been reported, although asymmetric allylic alkylations with stabilized carbanions have been demonstrated.[5] We wish to report here that the asymmetric alkoxycarbonylation of allyl phosphates occurs in the presence of a palladium complex bearing a chiral monodentate phosphine ligand as depicted by eq 1.



(1)

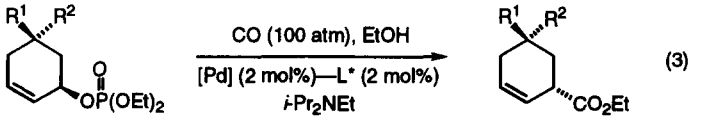
Alkoxycarbonylation of racemic *cis*-5-phenylcyclohex-2-en-1-yl diethyl phosphate (*cis*-**1a**) was examined to check the stereochemistry. Thus, alkoxycarbonylation of *cis*-**1a** (>99% cis) in the presence of $Pd_2(dba)_3$•$CHCl_3$ (1 mol%), PPh_3 (2 mol%), and *i*-Pr_2NEt (1 equiv) in EtOH under CO (100 atm) at room temperature for 4 h gave *trans*-ethyl 5-phenylcyclohex-2-ene-1-carboxylate (*trans*-**2a**) (>99% trans) in 73% isolated yield (eq 2). The stereoselectivity of overall inversion of configuration at the allylic carbon center is due to oxidative addition of palladium with inversion of configuration[6] followed by CO insertion with retention of configuration. The best results of carbonylation of *cis*-**1a** were obtained, when a 1:1 molar ratio of ligand/Pd was used. The addition of *i*-Pr_2NEt is essential to remove phosphoric acid, and **2a** could not be obtained without a base. Similar reaction under CO (60 atm) at 50 °C afforded **2a** (93% trans) in 90% isolated yield along with ethyl 5-phenylcyclohex-2-en-1-yl ether (**3**) (6% yield, 75% cis). Apparently, the formation of a

small amount of stereoisomeric ester *cis*-**2a** is due to *cis-trans* isomerization of intermediate π-allylpalladium complex catalyzed by palladium(0) complexes;[7] however, the isomerization was completely retarded at room temperature. Other allyl esters such as *cis*-5-phenylcyclohex-2-en-1-yl acetate, trifluoroacetate, and carbonate did not undergo carbonylation under similar reaction conditions.



cis-**1a** *trans*-**2a** *cis*-**3**

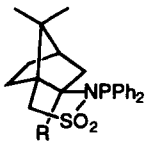
Asymmetric alkoxycarbonylation of *cis*-**1a** was examined under CO (100 atm) in the presence of *i*-Pr_2NEt (1 equiv) and 2 mol% of the palladium catalyst generated in situ from $Pd_2(dba)_3$•$CHCl_3$ and a chiral ligand (ligand/[Pd] = 1:1) in EtOH (eq 3). Alkoxycarbonylations are slow and not enantioselective with bisphosphines, such as (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), (*R,R*)-(-)-*O*-2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP), and (2*S*,3*S*)-(-)-bis(diphenylphosphino)butane (CHIRAPHOS), which are effective for asymmetric allylic alkylations with stabilized carbon nucleophiles.[8] In the allylic alkylation reactions, stabilized carbon nucleophiles attack externally to the π-allyl unit of π-allylpalladium(bisphosphine) complex. On the other hand, allylic carbonylation reactions proceed *via* CO coordination to palladium center and subsequent alkyl group migration to coordinated CO. Bidentate ligands are not suitable for allylic asymmetric alkoxycarbonylations, because there is no additional coordination site for CO on π-allylpalladium(bisphosphine) complex, and cleavage of a phosphine–palladium bond takes place to proceed CO coordination. Therefore, we used bulky chiral monodentate phosphine ligands for asymmetric allylic carbonylation reactions.



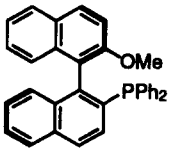
2a, b

cis-**1a**: R^1 = Ph, R^2 = H
trans-**1a**: R^1 = H, R^2 = Ph
1b: R^1 = R^2 = H

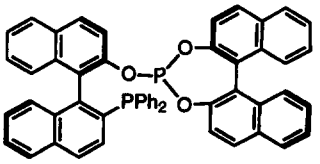
As bulky chiral monodentate aminophosphine ligands, we prepared (1*S*)-*N*-(diphenylphosphino)bornane-10,2-sultam ((1*S*,2*R*)-**4**)[9] and its 2-phenyl substituted analog (1*S*,2*S*)-**5**.[9] Alkoxycarbonylation of *cis*-**1a** with



R = H; (1*S*,2*R*)-**4**
R = Ph; (1*S*,2*S*)-**5**



(*R*)-**6**



(*R,S*)-**7**

(1*S*,2*R*)-**4** at 25 °C for 4 h gave *trans*-**2a** (>99% trans) in 83% yield ($[\alpha]_D^{21}$ –55.8 (*c* 1.30, $CHCl_3$)),[10] of which enantiomeric excess was determined to be 29% *ee* by an HPLC analysis (entry 1 in Table 1). It is noteworthy that the carbonylation using (1*S*,2*S*)-**5** afforded (+)-enantiomer of *trans*-**2a** ($[\alpha]_D^{24}$ +22.7 (*c* 1.06, $CHCl_3$), 11% *ee*) in 73% yield (entry 2). The reaction of *cis*-**1a** using commercially available chiral monodentate phosphine ligands, such as (+)-neomenthyldiphenylphosphine (NMDPP) and (*R*)-1-methoxy-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethane (PPFOMe), proceeded efficiently to give *trans*-**2a** stereoselectively in 92% and 74% yields, respectively; however, the enantiomeric excesses were low (3% *ee* and 7% *ee*).

Table 1. Asymmetric Alkoxycarbonylation of Allylic Phosphates Catalyzed by Palladium–Chiral Phosphine[a]

entry	allylic phosphate	ligand	conditions	product[b]	yield[c] (%)	% ee[d] (sign)[e]
1	*cis*-**1a**	(1*S*,2*R*)-**4**	25 °C, 4 h	*trans*-**2a**	83	29 (–)
2	*cis*-**1a**	(1*S*,2*S*)-**5**	25 °C, 4 h	*trans*-**2a**	72	11 (+)
3	*cis*-**1a**	(*R*)-**6**	25 °C, 4 h	*trans*-**2a**	84	31 (–)
4	*cis*-**1a**	(*R*)-**6**	0 °C, 4 h	*trans*-**2a**	70	46 (–)
5	*cis*-**1a**	(*S*)-**6**	0 °C, 4 h	*trans*-**2a**	66	48 (+)
6	*cis*-**1a**	(*R*),(*S*)-**7**	0 °C, 4 h	*trans*-**2a**	52	25 (–)
7	*trans*-**1a**	(*R*)-**6**	0 °C, 20 h	*cis*-**2a**	48[f]	2
8	**1b**	(*R*)-**6**	25 °C, 4 h	**2b**	49[g]	20 (–)

[a] The reaction was carried out under CO (100 atm) in EtOH in the presence of *i*-Pr_2NEt (1 equiv) and palladium catalyst prepared in situ by mixing $Pd_2(dba)_3$•$CHCl_3$ and a chiral ligand (1 equiv of Pd atom). [b] The stereoisomeric purity of **2a** was determined to be >99% by glc. [c] Determined by ^1H NMR. [d] Determined by HPLC equipped with CHIRALCEL® OJ (hexane/*i*-PrOH = 9/1) for **2a** and CHIRALCEL® OB-H (hexane/*i*-PrOH = 99.95/0.05) for **2b**. [e] $[\alpha]_D$ was measured in $CHCl_3$. [f] Ethyl ether **3** was obtained in 43% yield. [g] Isolated yield.

(*R*)-2-(Diphenylphosphino)-2'-methoxy-1,1'-binaphthyl (MOP, (*R*)-**6**)[11] can be used as an effective ligand for alkoxycarbonylation of *cis*-**1a** affording (–)-*trans*-**2a** with comparable enantiomeric excess (31% *ee*, entry 3). The carbonylation proceeded smoothly even at 0 °C to give (–)-*trans*-**2a** with higher enantioselectivity (46% *ee*, entry 4). It is noteworthy that the carbonylation using (*S*)-**6** as a ligand gave the opposite enantiomer, (+)-*trans*-**2a**, with essentially same enantiomeric purity (48% *ee*, entry 5). Alkoxycarbonylation using (*R*)-[2-(diphenylphosphino)-1,1'-binaphthylen-2'-yl]-[(*S*)-1,1'-binaphthylen-2,2'-yl]phosphite (BINAPHOS, (*R*,*S*)-**7**)[12] gave (–)-*trans*-**2a** (25% *ee*) in 52% yield (entry 6), which is the same enantiomer obtained using (*R*)-**6** as a ligand. These results indicate that the enantioselective course is depending on the binaphthylphosphine group not on the binaphthylphosphite group.

Alkoxycarbonylation of *trans*-**1a** under the same conditions gave racemic cis ester **2a** (>99% cis) in 48% yield along with ether **3** (87% trans) in 43% yield after 20 h reaction (entry 7). These two products, *cis*-**2a** and *trans*-**3**, were derived from a common π-allylpalladium complex. The low selectivity towards carbonylation is due to the steric interaction of a CO-coordinated π-allylpalladium intermediate. Cyclohex-2-en-1-yl diethyl phosphate (**1b**) also underwent smooth carbonylation to give the corresponding ester **2b** (20% *ee*) in 49% isolated yield (entry 8).

In summary, the asymmetric alkoxycarbonylation of allyl phosphates proceeds using monodentate chiral phosphines, such as **4** and **6**, to give the corresponding esters with moderate enantiomeric excesses. Further studies are underway to obtain an understanding of the mechanism of the enantioselection.

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9. Ligand (1*S*,2*R*)-**4** was prepared upon treatment of (1*S*)-bornane-10,2-sultam with NaH followed by $(C_6H_5)_2PCl$. (1*S*,2*R*)-**4**: mp 143.9–146.0 °C; $[\alpha]_D^{24}$ -81.7 (*c* 0.82, $CHCl_3$). (1*S*,2*S*)-**5**: mp 190.3–192.4 °C; $[\alpha]_D^{24}$ -93.5 (*c* 1.02, $CHCl_3$).
10. Optically pure *trans*-**2a** was obtained by optical resolution using a HPLC with CHIRALCEL OJ: $[\alpha]_D^{24}$ -192 (*c* 1.0, $CHCl_3$).
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