Highly Enantioselective Cyclocarbonylation of Allylic Alcohols Catalyzed by Novel Pd-1,4-bisphosphine Complexes

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Transition metal-catalyzed carbonylation reactions are fundamentally important organic transformations.[1,3] Despite the great potential of asymmetric carbonylation reactions and the extensive effort devoted to this reaction during the last several decades,[4] only moderate success (<90% ee) has been achieved, and the development of efficient asymmetric carbonylations is still viewed as one of the most challenging problems in asymmetric catalysis. We have been interested in exploring the asymmetric cyclocarbonylation of allylic alcohols for the synthesis of chiral γ-butyrolactones, important functionalities in many natural products and biologically active molecules.[5] Alper et al. have extensively studied Pd-catalyzed cyclocarbonylation of allylic alcohols and developed the first enantioselective variant of this reaction using commercially available chiral bisphosphine ligands albeit with moderate ee's.[6] The asymmetric reaction is, however, restricted to β-substituted allylic alcohols with dialkyl substitution at the α position (geminal dialkyl effect) (**1** to **2**, Scheme 1). Herein we report the highly enantioselective cyclocarbonylation of allylic alcohols **1** catalyzed by Pd complexes with BICP and related ligands developed in our lab (Figure 1). Another major advance in this study is the development of the first highly enantioselective cyclocarbonylation of β,γ-substituted allylic alcohols **3** lacking geminal dialkyl substituents at the α position (**3** to **4**, Scheme 1),

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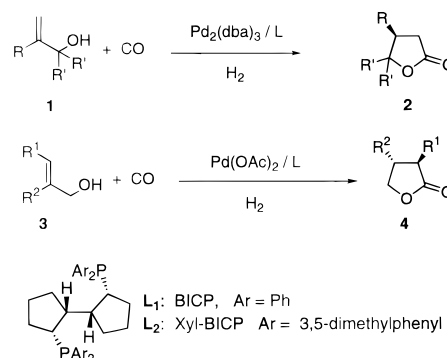
Scheme 1

Figure 1. BICP and Xyl-BICP ligands.

which significantly increases the scope and synthetic utility of the asymmetric carbonylation reaction.

Recently, we have achieved high enantioselectivity in a number of Rh−BICP and Ru−BICP catalyzed asymmetric hydrogenation reactions.[7] These results demonstrated that the BICP ligand is an excellent chiral motif for group VIII transition metal-catalyzed reactions. To optimize the steric and electronic properties of BICP, we have also synthesized a modified BICP ligand by substituting the phenyl groups by *m*-xylene [(2R, 2′R)-bis[bis-(3,5-dimethylphenyl)phosphino]-(1R,1′R)-dicyclopentane, Xyl-BICP, Figure 1].[8] Alper[6e] and van Leeuwen[9] have studied the rate of CO insertion into a Pd−alkyl bond and found that the rate decreases in the order: 1,4-bisphosphine > 1,3-bisphosphine ≫ 1,2-bisphosphine. The high catalytic reactivity the Pd-catalyzed carbonylation with a 1,4-bisphosphine ligand is associated with a relatively flexible ligand−metal seven-membered ring chelate. Since BICP is one of the most effective chiral 1,4-bisphosphines, we chose to evaluate this ligand as it might meet the two primary requirements for achieving high enantioselectivity and activity in Pd-catalyzed cyclocarbonylation reactions: (1) conformational rigidity of Pd−bisphosphine complexes conducive to chiral induction and (2) a relatively flexible seven-membered ligand−metal chelate favorable for rapid CO insertion.

We selected 3,3-dimethyl-2-phenyl propenol (**1a**) as the initial substrate for study. Several experiments have been conducted to identify CH$_2$Cl$_2$ under a CO/H$_2$ atmosphere (total pressure = 800 psi, ratio of CO/H$_2$ = 1:1) at 80 °C with 1 mol % of Pd-catalyst(Table 1). The Pd−BICP catalyst was prepared in situ from Pd$_2$(dba)$_3$ and (R,R)-BICP. Under these conditions, cyclocarbonylation of **1a** gave product **2a** in 95%ee (entry 1). When Xyl-BICP was examined under the same reaction conditions, lactone **2a** was generated in 95% ee and 87% yield (entry 2). To the best of our knowledge, this is the highest enantioselectivity reported to date for the cyclocarbonylation of 2-methyl-3-phenyl-3-buten-2-ol. In a related study, Alper et al.[6e] reported an 81% ee for cyclocarbonylation of **1a** using a Pd−BPPM catalyst, whereas 45% ee and 31% ee were obtained with Pd−DIOP and Pd−BINAP catalysts, respectively. No cyclocarbonylation of **1a** occurred when DuPhos and CHIRAPHOS were used as the chiral ligands. Slow CO insertion into a rigid five-membered ring Pd-ligand complex was proposed as a possible reason for this lack of reactivity.[6e,9]

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Table 1. Enantioselective Cyclocarbonylation of Geminally Disubstituted Allylic Alcohols[a]

entry	substrate		product		ligand	yield%	ee %[b]	conf.[c]
1		1a		2a	BICP	51	95	(-)R
2					Xyl-BICP	87	95	
3		1b		2b	BICP	91	94	(-)R
4					Xyl-BICP	91	96	
5		1c		2c	BICP	51	92	(-)R
6					Xyl-BICP	91	92	
7		1d		2d	BICP	90	91	(-)R
8					Xyl-BICP	61	97	
9		1e		2f	BICP	95	49	+[d]
10		1g		2g	Xyl-BICP	91	74	+[d]

[a] The reaction was carried out at 80 °C under an initial total pressure of 800 psi ($CO/H_2 = 1/1$) for 24 h in CH_2Cl_2 [substrate (1 mmol, 0.1 M)/$Pd_2(dba)_3$/ligand = 1:0.005:0.011]. [b] The ee's obtained were determined by chiral GC. [c] The absolute configuration was assigned by comparison of the optical rotation with reported data. [d] Sign of the optical rotation.

We have carried out cyclocarbonylation of various aliphatic and aromatic unsaturated allylic alcohols catalyzed by Pd−BICP and Pd−Xyl-BICP complexes under the optimal reaction conditions (Table 1). In general, enantioselectivity in the cyclocarbonylation of several of the allylic alcohols with the Pd−Xyl-BICP catalyst is slightly higher than those obtained with the Pd−BICP complex (entries 4 and 8). Overall, asymmetric cyclocarbonylation of allylic alcohols containing an aromatic subsitituent gave chiral γ-butyrolactones in high enantioselectivity and good yields (entries 1−8). However, cyclocarbonylation of allylic alcohols bearing aliphatic substituents at the α-position (**1e**, **1g**) provides γ-butyrolactones in only moderate to good enantiomeric excesses (entries 9 and 10). These results are consistent with Alper's observations with the Pd−BPPM catalyst.[7] Furthermore, we have confirmed Alper's experimental results that the cyclocarbonylation requires at least one substituent at the allylic position of the alcohols (the geminal dialkyl effect). Alcohols such as 2-phenyl-2-propen-1-ol, cinnamyl alcohol, and 2-pentene-1-ol do not give the desired lactone products under the carbonylation conditions.

In an effort to expand the substrate scope and increas synthetic utility of the carbonylation reaction, we explored asymmetric palladium-catalyzed cyclocarbonylation of β,γ-substituted allylic alcohols **3** without geminal dialkyl substituents at the α position (Scheme 1). Although Alper et al. have recently developed a new protocol for Pd-catalyzed cyclocarbonylation of β,γ-substituted allylic alcohols **3**,[6f] there is no report on asymmetric modification leading to products **4**, *trans* α,β-Disubstituted chiral lactones are key structural features of diverse lignans with cancer-protective properties.[10] Table 2 summarizes our experimental results of the first Pd-catalyzed enantioselective cyclocarbonylation of β,γ-substituted allylic alcohols **3**. We chose (*E*)-2-methyl-cinnamyl alcohol **3a** as the substrate for initial optimization studies. Cyclocarbonylation reactions performed at 80 °C in ClCH$_2$CH$_2$-Cl using a catalyst prepared from 4 mol % Pd(OAc)$_2$ and 4.4 mol % BICP gave the best enantioselectivity (entry 1, Table 2, 84% ee). Under these optimal reaction conditions for **3a** (entry

Table 2. Palladium-Catalyzed Enantioselective Cyclocarbonylation of Allylic Alcohols[a]

Entry	substrate		product		Ligand	yield%	ee %[b]	config. (optical rotation)
1		3a		4a	BICP	64	84	-
2					Xyl-BICP	87	76	
3		3b		4b	BICP	60	93	-
4					Xyl-BICP	80[c]	91	
5		3c		4c	BICP	39[c]	93	
6					Xyl-BICP	50[c]	92	
7		3d		4d	BICP	89	45	-
8		3e		4e	BICP	87	93	(R, R)
9					BICP	54[d]	98	
10		3f		4f	BICP	97	86	(R, R)

[a] The reaction was complete at 80 °C under an initial total hydrogen and carbon monoxide pressure of 800 psi ($CO/H_2 = 1/1$) for 24 h using ClCH$_2$CH$_2$Cl as solvent. Substrate (0.25 mmol, 0.05M/Pd(OAc)$_2$/Ligand = 1:0.04:0.044. [b] The ee was determined by GC. [c] The reaction was run under 60 °C.

1), cyclocarbonylation of an array of allylic substrates **3** gave chiral γ-butyrolactones **4** in good to excellent enantioselectivities (up to 98% ee) (Table 2).

In general, introduction of aromatic substituents at the β or γ position of allylic alcohols enhances the enantioselectivity (entries 1−6 vs entry 7). The lactonization of the allylic alcohols **3** likely proceeds through *cis* Pd−H migratory insertion to the allylic C═C bond followed by CO insertion into the transient Pd−C bond to give *trans* chiral γ-butyrolactones. This *trans* stereochemistry was confirmed by ^{1}H NMR and 2D NOESY spectroscopic studies. The observed stereospecificity probably results from *cis* addition of the palladium hydride to the allylic C═C bond as proposed by Alper. A notable advance emerging from these studies is the asymmetric cyclocarbonylation of the six-membered ring allylicalcohol **3e** using a Pd−BICP catalyst. At 80 °C, chiral γ-butyrolactone **4e** was formed in 93% ee and 87% yield (entry 8). Upon lowering the reaction temperature to 60 °C, up to 98% ee was achieved (entry 9). A derivative (**4f**) of chiral γ-butyrolactone **4e** can be made by incorporating functional groups to the six-membered ring of **3e** (entry 10). Therefore, this cyclocarbonylation method provides an efficient route to chiral six- and five-membered fused ring compounds, which themselves are useful building blocks for the synthesis of natural products and bioactive molecules. For example, Weinreb's recent synthesis of the antitumor reagent papuamine used the chiral γ-butyrolactone **4e** as the starting material.[11]

In summary, we have developed a highly enantioselective Pd-catalyzed asymmetric cyclocarbonylation of geminally disubstituted allylic alcohols and demonstrated the first highly enantioselective cyclocarbonylation of β,γ-substituted allylic alcohols lacking dialkyl substituents at the α position. These results demonstrate that BICP is a unique chiral ligand for Pd-catalyzed asymmetric carbonylation.

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