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 carbocations is still viewed as one of the most challenging problems in asymmetric reactions. 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 (genuine dialkyl effect) (1 to 2, Scheme 1). Herein we report the highly enantioselective cyclocarbonylation of allylic alcohols 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 genuine dialkyl substituents at the α position (3 to 4, Scheme 1).

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[(3,5-dimethylphenyl)phosphino]-[1R,1′R]-dicyclopane, Xyl-BICP, Figure 1].8 Alper9 and van Leeuwen10 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 highly catalytic reactivity the Pd-catalyzed cyclocarbonylation 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-phenylpropanol (1a) as the initial substrate for study. Several experiments have been conducted to identify CH3Cl2 under a CO/H2 atmosphere (total pressure = 800 psi, ratio of CO/H2 = 1:1) at 80 °C with 1 mol % of Pd-catalyst (Table 1). The Pd–BICP catalyst was prepared in situ from Pd2dba 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.10b 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.6,9

Cl using a catalyst prepared from 4 mol % Pd(OAc)\textsubscript{2} and 4.4 mol % BICP gave the best enantioselectivity (entry 1, Table 2, palladium-catalyzed cyclocarbonylation of allylic alcohols). We chose (E)-2-methyl-cinnamyl alcohol as the substrate for initial optimization studies. Cyclocarbonylation reactions performed at 80 °C in CH\textsubscript{2}Cl\textsubscript{2} using a catalyst prepared from 4 mol % Pd(OAc)\textsubscript{2} and 4.4 mol % BICP gave the best enantioselectivity (entry 1, Table 2, 84% ee). Under these optimal reaction conditions for 3a (entry 9), 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 \textsuperscript{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 allylic alcohol 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.

In summary, we have developed a highly enantioselective Pd-catalyzed asymmetric cyclocarbonylation of geminally disubstituted allylic alcohols 3 with 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, 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. 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 CICCH\textsubscript{2}Cl\textsubscript{2} using a catalyst prepared from 4 mol % Pd(OAc)\textsubscript{2} and 4.4 mol % BICP gave the best enantioselectivity (entry 1, Table 2, 84% ee). Under these optimal reaction conditions for 3a (entry 9), cyclocarbonylation of an array of allylic substrates 3 gave chiral γ-butyrolactones 4 in good to excellent enantioselectivities (up to 98% ee) (Table 2).

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Supporting Information Available: Spectroscopic data and experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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