Title
Palladium(II)-Catalyzed Enantioselective Reactions Using COP Catalysts.

Permalink
https://escholarship.org/uc/item/3jn7b64r

Journal
Accounts of chemical research, 49(10)

ISSN
0001-4842

Authors
Cannon, Jeffrey S
Overman, Larry E

Publication Date
2016-10-01

DOI
10.1021/acs.accounts.6b00398

Peer reviewed
Palladium(II)-Catalyzed Enantioselective Reactions Using COP Catalysts

Jeffrey S. Cannon*† and Larry E. Overman*

Department of Chemistry, University of California, 1102 Natural Sciences II, Irvine, California 92697-2025, United States

CONSPECTUS: Allylic amides, amines, and esters are key synthetic building blocks. Their enantioselective syntheses under mild conditions is a continuing pursuit of organic synthesis methods development. One opportunity for the synthesis of these building blocks is by functionalization of prochiral double bonds using palladium(II) catalysis. In these reactions, nucleopalladation mediated by a chiral palladium(II) catalyst generates a new heteroatom-substituted chiral center. However, reactions where nucleopalladation occurs with antarafacial stereoselectivity are difficult to render enantioselective because of the challenge of transferring chiral ligand information across the square-planar palladium complex to the incoming nucleophile.

In this Account, we describe the development and use of enantiopure palladium(II) catalysts of the COP (chiral cobalt oxazoline palladacyclic) family for the synthesis of enantioenriched products from starting materials derived from prochiral allylic alcohols. We begin with initial studies aimed at rendering catalyzed [3,3]-sigmatropic rearrangements of allylic imidates enantioselective, which ultimately led to the identification of the significant utility of the COP family of Pd(II) catalysts. The first use of an enantioselective COP catalyst was reported by Richards’ and our laboratories in 2003 for the enantioselective rearrangement of allylic N-arylimidates. Shortly thereafter, we discovered that the chloride-bridged COP dimer, [COP-Cl]$_2$, was an excellent enantioselective catalyst for the rearrangement of (E)-allylic trichloroacetimidates to enantioenriched allylic trichloroacetamides, this conversion being the most widely used of the allylic imidate rearrangements. We then turn to discuss $S_N2'$ reactions catalyzed by the acetate-bridged COP dimer, [COP-OAc]$_2$, which proceed by a unique mechanism to provide branched allylic esters and allylic phenyl ethers in high enantioselectivity. Furthermore, because of the unique nucleopalladation/deoxypalladation mechanism of these $S_N2'$ reactions, they provide exclusively the branched allylic product. Importantly, both enantiomers of the [COP-Cl]$_2$ and [COP-OAc]$_2$ catalysts are commercially available. We also briefly consider several other enantioselective reactions catalyzed by COP complexes.

The mechanism of enantioselective COP-catalyzed allylic rearrangements and allylic substitutions is discussed in some detail. In both reactions, nucleopalladation is found to be the enantiodetermining step. The cyclobutadienyl “floor” of the COP catalyst is critical for transmitting chiral information across the palladium square plane in these reactions. This structural feature enables high enantioselection to be realized in spite of the nearly 180° angle between the catalyst, electrophile and nucleophile in the enantiodetermining step. Our discussion concludes by considering several uses of the COP family of catalysts by other researchers for the enantioselective synthesis of biologically active chiral molecules. We anticipate that additional uses for COP catalysts will emerge in the future. In addition, the structural features of these catalysts that we have identified as important for achieving high enantioselection should be useful in the future development of improved enantioselective Pd(II) catalysts.

INTRODUCTION

Over 40 years ago, one of us first reported the rearrangement of allylic trichloroacetimidates to transposed allylic trichloroacetamides (eq 1).$^1$ The broad scope, high yields, and excellent suprafacial stereospecificity of this reaction led to it being widely used for the synthesis of allylic amides and amines, particularly of enantioenriched chiral allylic amides from chiral enantioenriched allylic alcohol precursors.$^1$ The discovery that this transposition could be catalyzed by α-acidic mercury(II) or palladium(II) complexes inspired our investigations into a catalytic, enantioselective version of this sigmatropic rearrangement.

The transition metal-catalyzed variants of allylic imidate rearrangements are considered to occur by a cyclization-induced rearrangement mechanism involving antarafacial alkene reactivity (Scheme 1).$^{1-3}$ In the palladium(II) catalyzed variant, coordination with the double bond is followed by anti attack by the imidate nitrogen on alkene complex 3 to generate cyclopalladate intermediate 8. Anti-deoxypalladation of complex...
leads to the observed allylic amide product 5. The pathway leading to major product 5 is favored over the 2 → 6 → 7 sequence because cyclopalladate intermediate 8 has all substituents positioned pseudoequatorially. When the cyclization-induced rearrangement was first proposed for the Hg(II)- and Pd(II)-catalyzed rearrangements, the antarafacial nature of nucleomercuration and nucleopalladation reactions was widely established; however, syn-nucleopalladation is now known to be quite common. A mechanism involving syn-iminopalladation followed by syn-deoxypalladation would also give rise to products 5 and 7 and would be consistent with the suprafacial chirality transfer that is a hallmark these rearrangements. However, syn-iminopalladation of alkene complexes such as 2 and 3 would deliver a cyclopalladate intermediate having the bulky palladium substituent axial (e.g., 4 and 9). Moreover, a syn-iminopalladation/syn-deoxypalladation sequence would not readily rationalize the preferential formation of stereoisomeric product 5.

This Account summarizes the development of planar-chiral palladium(II) catalysts for enantioselective [3,3]-sigmatropic rearrangements of allylic imidates with a special focus on the state-of-the-art cobalt oxazoline palladacyclic (COP) family of catalysts. In addition, the discovery and development of several additional enantioselective reactions catalyzed by COP catalysts is discussed, as is our current understanding of the mechanisms of these transformations. Key features of these mechanisms and the catalyst structure, as determined by experimental and computational studies, should aid in the design of new enantioselective Pd(II) catalysts and reactions.

DISCOVERY OF PLANAR-CHIRAL PALLADIUM(II) CATALYSTS OF THE COP FAMILY AND THEIR USE TO PROMOTE ALLYLIC REARRANGEMENTS

It was easy to envision that chiral, nonracemic palladium(II) catalysts could lead to the formation of enantioenriched chiral allylic amides from prochiral allylic alcohols. Our early studies of chiral palladium(II) complexes focused on cationic complexes having L2-type ligands and achieved modest reactivities and enantioselectivities (Figure 1). However, the scope and general utility of these catalysts was limited. In the search for more effective catalysts, we noted that ligand substitution at palladium(II) complexes had been shown in almost all cases to occur by an associative mechanism. Although not ultimately a correct mechanistic analysis, we speculated that projecting steric bulk both above and below the palladium square plane might bias stereoselection toward reaction from a single enantiotopic face of a square-pyramidal intermediate complex 15 (Scheme 2).

With this ligand design in mind, the first highly enantioselective palladium(II) catalysts were discovered (Figure 2). The best of these early precatalysts was the iodide-bridged ferrocene oxazoline palladacyclic (FOP) complex 17, which required activation with 4 equiv of silver trifluoroacetate to form the active cationic catalyst. This complex catalyzed the rearrangement of (Z)-allylic N-arylbenzimidates such as 10a with good rates, yields and enantioselectivities (Table 1, entry 1). However, lower enantioselectivities were observed for (E)-allylic substrates such as 10b (entry 2).
The FOP catalysts, while effective, presented significant drawbacks in practicality. The most useful of the family, iodide-bridged dimer catalyst 17, required activation immediately prior to its use, as the active trifluoroacetate catalyst is not stable for prolonged periods of time. This instability likely arises in part from oxidation of the ferrocene group to the ferrocenium10 or of the palladium(II) center to palladium-(III)11 upon exposure to silver salts. Additionally, FOP catalysts required high catalytic loadings (e.g., 5 mol % of 17 = 10 mol % palladium catalyst). Later, the planar-chiral ferrocene catalyst motif was investigated further by Moyano et al. (18)12 and Peters et al. (19),10 resulting in significant improvements in turnover.13

Shortly after we reported the use of FOP catalysts for the rearrangement of allylic imidates, the Richards laboratory described the synthesis of the dimeric cobalt oxazoline palladacyclic (COP) complex 22 ([COP-Cl]2, Figure 3).14 This complex possesses significant structural similarity to the FOP catalysts and conserves the key design element of projecting steric bulk both above and below the palladium square plane. Notably, the size of the tetraphenylcyclobutadienyl moiety is significantly larger than the Cp fragment of the FOP catalysts. As a result, it was logical for us to collaborate with the Richards group to examine the catalytic reactivity of COP complex 22.15

The discovery of the catalytic activity of [COP-Cl]2 (22) was a major breakthrough in the development of synthetically useful enantioselective catalysts for the rearrangement of allylic imidates. These palladium(II) complexes presented a number of notable improvements over catalysts of the FOP family. The bench-stable chloride-bridged dimer 22 was a viable catalyst for the rearrangement of allylic imidates without the need for preactivation with silver salts (Table 1, entries 5 and 6).15 Moreover, this enhanced reactivity extended for the first time to the conversion of N-unsubstituted allylic trihaloacetimidates (21) to allylic trihaloacetamides (26) in high yields and enantioselectivities (entry 6 vs entry 4).16 This success in the rearrangement of N-unsubstituted allylic trihaloacetimidates was notably important, as the conversion of allylic N-aryl amides (e.g., products of Table 1, entries 1–3 and 5) to the corresponding allylic amines cannot be accomplished in one step and is often plagued by modest chemical yields. In

![Figure 2. Ferrocene-derived planar-chiral palladium(II) complexes and their representative performance in the enantioselective rearrangement of imidates 10 to amides 11 [precatalysts 16, 17, and 19 were preactivated by reaction with 4 equiv of Ag(OCOCF3)].](image)

**Table 1. Comparison of the Reactivity of FOP Precatalyst 17 and COP Catalyst 22**

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>imidate</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>E/Z yield/ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17b</td>
<td>10a</td>
<td>4-MeOC6H4</td>
<td>Ph</td>
<td>Z</td>
<td>83/91 (R)</td>
</tr>
<tr>
<td>2</td>
<td>17b</td>
<td>10b</td>
<td>4-MeOC6H4</td>
<td>Ph</td>
<td>E</td>
<td>93/83 (S)</td>
</tr>
<tr>
<td>3</td>
<td>17b</td>
<td>20</td>
<td>4-MeOC6H4</td>
<td>CF3</td>
<td>E</td>
<td>88/76 (S)</td>
</tr>
<tr>
<td>4</td>
<td>17b</td>
<td>21a</td>
<td>H</td>
<td>CCl3</td>
<td>E</td>
<td>50/43 (S)</td>
</tr>
<tr>
<td>5</td>
<td>22c</td>
<td>20</td>
<td>4-MeOC6H4</td>
<td>CF3</td>
<td>E</td>
<td>92/99 (S)</td>
</tr>
<tr>
<td>6</td>
<td>22c</td>
<td>21a</td>
<td>H</td>
<td>CCl3</td>
<td>E</td>
<td>99/95 (S)</td>
</tr>
<tr>
<td>7</td>
<td>22d</td>
<td>21a</td>
<td>H</td>
<td>CCl3</td>
<td>E</td>
<td>85/92 (S)</td>
</tr>
</tbody>
</table>

*Absolute configuration in parentheses. *5 mol %, preactivated with 4 equiv Ag(OCOCF3), CH2Cl2, 40 °C. *5 mol %, CH2Cl2, 40 °C. *0.25 mol %, MeCN, 80 °C, 48 h.

![Figure 3. Cobalt oxazoline palladacycle (COP) family of catalysts.](image)
contrast, allylic trichloroacetamides are readily transformed to the corresponding amine without erosion of enantiopurity under mildly basic or more forcing acidic conditions. Additional optimization of the rearrangement of allylic trichloroacetimides was carried out by Richards and co-workers who showed that the catalyst loadings of [COP-Cl]2 could be reduced to 0.25 mol % in reactions carried out at 80 °C in acetonitrile (entry 7). The improved reactivity of [COP-Cl]2 (22) versus neutral [FOP-Cl]2 catalysts can be attributed to the increased electron-deficiency of the cyclopentadienyl ligand when part of a cobalt sandwich complex rather than a ferrocene complex.

The increased reactivity and substrate compatibility of [COP-Cl]2 allowed for significant broadening of the scope of enantioselective allylic trichloroacetimidate rearrangements (Figure 4). Free alcohols (26c), basic amines (26g), and acid sensitive functionalities such as dioxolanes (26f) and tert-butyl carbamates (26d) were tolerated. As always, some limitations were observed. For instance, cinnamyl derived (e.g., R = Ph) and sterically hindered (R = t-Bu) trichloroacetimidates rearranged slowly, and provided only low yields of the allylic amide product. Selection of the desired enantiomer of the allylic amide product must be done by choice of the proper enantiomer of the COP catalyst, as (Z)-allylic trichloroacetimides are poor substrates for enantioselective [COP-Cl]2-catalyzed allylic imidate rearrangements. Fortunately, both enantiomers of [COP-Cl]2 and [COP-OAc]2 are commercially available, and the synthesis of these catalysts on scale has been documented in Organic Syntheses.

Allylic rearrangements catalyzed by [COP-Cl]2 (22) are not limited to allylic imidates. For example, enantioselective C=S bond formation was realized by catalytic rearrangements of E-allylic xanthates and carbamothioates, with greater enantioselectivities being observed with carbamothioates (27, Figure 5). This [COP-Cl]2-catalyzed allylic rearrangement exhibits many of the same features as the allylic trichloroacetimidate rearrangement, including compatibility with free alcohols (28c), and carbamate-protected amines (28e). Of note is the complete regioselectivity for the branched product, as achieving high branched-selectivity is often a challenge for other methods of catalytic enantioselective allylic C=S bond formation.

In an attempt to extend this cyclization to the formation of enantioenriched 4-vinylazolidinones, a new transformation, bimolecular enantioselective S_N2′ reactions of allylic trichloroacetamides, was discovered. When acetoxybutenyl trichloroacetimide 31a was exposed to a catalytic amount of 24 at 40 °C, a ∼ 1:1 mixture of the expected 4-vinylazolidin-2-ones 30 in high yield and enantioselectivities (Figure 6).23

![Figure 5. Enantioselective rearrangements of carbamothioates.](image)

![Figure 6. Enantioselective synthesis of 4-vinylazolidinones.](image)
reactivity and enantioselection. The premier complex for allylic imidate [3,3]-sigmatropic rearrangements, [COP-Cl]$_2$ (22), displayed poor catalytic rates, as well as monomeric hexafluoroacetacetionate complex 23. Exchanging the bridging chloride ligands of 22 for acetate or trichloroacetamidate (catalysts 24 or 25) resulted in significantly increased catalytic rates and high levels of enantioselectivity. At the time of the discovery of this transformation, catalyst 25 was still unknown, and therefore [COP-OAc]$_2$ (24) was chosen as the preferred catalyst. Catalyst 24 remains the best catalyst for this reaction, because it is commercially available and trichloroacetimidate-bridged catalyst 25 is rapidly converted to di-μ-carboxylate complexes under the reaction conditions.

These early studies showed that the COP-catalyzed enantioselective S$_{N}2'$ allylic esterification reaction would require a (Z)-allylic formimidate precursor, as (E)-allylic trichloroacetimidates underwent competitive allylic rearrangement under these conditions (e.g., eq 2). Furthermore, the enantioselectivity of the allylic ester product ent-33b was diminished. (Z)-Allylic imidates have significantly reduced rates for sigmatropic rearrangement, and therefore the bimolecular displacement outcompetes rearrangement for these substrates.

The scope of this enantioselective allylic esterification reaction of trichloroacetimdate derivatives of (Z)-allylic alcohols was found to be fairly broad (Figure 8). A variety of aliphatic carboxylic acids can be successfully employed in this enantioselective construction of 3-acyloxy-1-alkenes, including bulky acids such as pivalic acid (33e). The synthesis of esters of indole-3-acetic acid (33f) suggests the potential application of this method to more complex systems. A one-pot procedure for the direct synthesis of allylic esters from starting prochiral allylic alcohols was also developed (e.g., 34 to 33g). This streamlined process produced allylic ester products in useful yields with only slightly diminished enantioselectivities. Exceptionally high branched-to-linear ratios, some measured to be greater than 800:1, are characteristics of this reaction.

Several limitations were observed while investigating carboxylic acid nucleophiles. In general, the carboxylic acid must be soluble in dichloromethane in order to achieve acceptable catalytic rates, leading to the failure of nucleophiles such as unprotected amino acids. Pyridine-containing nucleophiles competitively coordinate to the palladium complex, inhibiting reactivity. Of most significance, allylic imidates with substituents at C-2 or C-3 were found to be poor substrates. Substitution at C-2 presumably hinders coordination of the catalyst to the double bond, whereas introduction of a substituent at C-3 provided low yields of a mixture of linear and branched products suggesting competitive formation of allylic cations that are stabilized by the additional C-3 substituent.

It seemed likely that other acidic nucleophiles would be suitable nucleophiles for this palladium(II)-catalyzed S$_{N}2'$ reaction. In fact, phenols were found to be competent nucleophiles under similar conditions (Figure 9). The reaction of a wide range of phenols and allylic imidate substrates exemplify the utility of this allyl aryl ether synthesis. In contrast to enantioselective allylic substitutions that proceed via η$^3$-allyl intermediates, neutral phenol nucleophiles are used in the COP-catalyzed reaction, allowing the presence of

![Figure 7. Discovery and optimization of palladium-catalyzed 3-acyloxy-1-alkene synthesis.](image)

![Figure 8. Representative scope of carboxylic acid nucleophiles.](image)

![Figure 9. Enantioselective synthesis of allylic phenols.](image)
base-sensitive functionality such as a phenyl acetate (35d). As in the COP-catalyzed allylic esterification reaction, uncommonly high branched-to-linear ratios are distinctive features of this allylic substitution reaction.26

In some cases, the nature of the bridging ligand of a COP complex can influence the partitioning between the Sn2′ and [3,3]-sigmatropic rearrangement pathways. During the course of our studies of this Sn2′ reaction, careful analysis of the reaction mixtures revealed that di-μ-amidate dipalladium complex [COP-NHCOCl], (25) was formed by complexation of the trichloroacetamide byproduct. As 25 is a poor catalyst for allylic trichloroacetimidate rearrangements, prochiral (E)-allylic trichloroacetimidates can be employed in this enantioselective construction of chiral allylic phenols (eq 3).28

However, catalyst 25 is not useful for promoting enantioselective Sn2′ allylic esterifications, because rapid exchange of the amidate ligand for the carboxylate nucleophile effectively regenerates a competent allylic rearrangement catalyst.

Enantioselective intramolecular Sn2′ allylic substitution reactions have also been employed to construct heterocycles.29 For example, [COP-OAc]2-catalyzed cyclization of (E)-allylic trichloroacetimidates 36 harboring pendant phenol substituents delivered chromanes (37a–c), benzoazaine (37d), and benzodioxanes (37e–f) in high yields and enantioselectivities (Figure 10). In this study, the first example of COP-catalyzed allylic substitution to form a fully substituted stereocenter (37f) was described, albeit in modest yield. The (E)-alkenes are suitable substrates in this case because the intramolecular Sn2′ reaction outcompetes the catalyzed [3,3]-sigmatropic rearrangement in most cases. With catalysts less competent for the Sn2′ reaction, such as 22 and 23, imidate rearrangement was competitive. Cyclizations of (Z)-allylic imidates also could be accomplished in high yield, but enantioselection was low.

Allylic acetates were also found to be competent leaving groups for the intramolecular Sn2′ reaction of phenols (Figure 10, 38 → 37). With potassium fluoride as an added base, 2-vinylnorbornanes 37a–c were synthesized in high yield and enantioselectivity using 2 mol % of [COP-OAc]2 (24) as the catalyst. Again, the (E)-allylic precursor was required, as the products resulting from reaction of (Z)-allylic acetates were found to be of low enantiomeric purity.

To date we have been unable to find other suitable nucleophiles for the palladium(II)-catalyzed enantioselective bimolecular displacement of allylic imidates. Of particular interest would be carbon nucleophiles. However, all attempts at utilizing acidic carbon nucleophiles (e.g., β-dicarbonyl, nitroalkyl, sulfonfyl) have been unsatisfactory, providing substitution products in low yields or poor enantiopurity.

### MECHANISTIC DETAILS OF COP-CATALYZED ENANTIOSELECTIVE REACTIONS

#### General Catalyst Considerations

The resting state for many of the palladacyclic complexes of the COP family is as an X-type ligand-bridged homodimer. However, experimental evidence suggests that the active catalyst is a monomeric species presumably produced upon substrate complexation.29 Independent studies conducted by Richards found a small, positive nonlinear effect for the allylic trichloroacetimidate rearrangement catalyzed by [COP-OAc]2 suggesting either a (ML)2 system or a reservoir effect. Although direct participation of a (ML)2 complex in the catalytic cycle is inconsistent with our own studies,30 a small reservoir effect could be operative by sequestering of the minor enantiomer as the meso dimer in solution. We did not find nonlinear effects in the [COP-OAc]2-catalyzed Sn2′ reaction.

#### Allylic Imidate Rearrangement

The first reaction investigated in some mechanistic detail was the COP-catalyzed [3,3]-sigmatropic rearrangement of (E)-allylic trichloroacetimidates.30 On the basis of the larger binding equilibrium of [COP-Cl]2 to methyl trichloroacetimidate (Kq ≈ 2.2 \times 10^4) than to 2-pentene (Kq ≈ 5.4 \times 10^3), nitrogen-bound complex 39 is presumed to lie on the catalytic cycle (Scheme 3). Rearrangement of 39 to the η2-alkene complex 40 activates the double-bond for rate-limiting iminopalladation, which generates charge-separated cyclopalladate complex 41. Deoxypalladation generates the η2-alkene complex 42. Exchange of amide 26 for imidate 21 closes the catalytic cycle. This mechanism was the best fit to computational simulations of the kinetic results, DFT predictions, and the observation that a non-hydrogen substituent at the internal alkene carbon prevented the catalyzed rearrangement. The antarafacial iminopalladation step (40 → 41) is the rate- and enantiodetermining step, as supported by the kinetic simulations and computational studies.

Computational modeling of the full ligand scaffold for the iminopalladation step identified the key features of the COP catalyst that are important for enantioselection (Figure 11). Initial modeling indicated that the preferred coordination site of the alkene was trans to the less electron-donating oxazoline ligand, placing the substrate in the more open quadrant of the chiral catalyst. The calculated low-energy transition-state structure 43 correctly predicted attack of the imidate nitrogen.
onto the Si face of the (E)-allylic formimidate precursor (Figure 12). This transition-state structure has minimal steric interactions between the ligand and the forming cyclopalladate intermediate, and points the R substituent into a vacant quadrant. Rotation around the forming C−Pd σ-bond leads to higher-energy transition structure 44, which incurs steric repulsion between the C-1 methylene hydrogens and the proximal hydrogen of the cyclopentadienyl ring. A similar H−H interaction is present in transition-state structure 45 resulting from Re-face attack that would lead to the minor R enantiomer of the product 26. This destabilizing interaction is presumably responsible for the ∼3 kcal/mol energy difference between transition-state structures 44 and 45 and the favored structure 43. The second-lowest energy transition state was calculated to be structure 46, which would lead to the minor R enantiomer of 26. The key destabilizing interaction in this transition-state structure is between the R substituent and the tetraphenylcyclobutadienyl floor of the COP catalyst. In accordance with these findings, allylic trichloroacetimidates 21 with bulkier side chain groups rearrange with higher enantioselectivity, underscoring the importance of the bulky tetraphenylcyclobutadienyl moiety for enantioselection.

Studies conducted by Richards found that the nature of the X-type ligand had little effect on the enantioselectivity, but had a large effect on catalysis rate. This observation is consistent with the model for stereoinduction advanced in Figure 11, as the chloride plays little role in the steric environment of the palladium catalyst, but would be expected to effect the reactivity of the palladium center toward both alkene coordination and iminopalladation.

**Allylic Substitution Reactions**

Following the success of experimental and computational studies on COP-catalyzed imidate rearrangements, we turned to apply these methods toward an understanding of the mechanism of the COP-catalyzed SN2′-allylic substitution reactions. Of fundamental importance in constructing a mechanistic model for these reactions were labeling experiments that established that [COP-OAc]2-catalyzed allylic esterification and etherification reactions take place with complete antarafacial chirality transfer (47, Figure 13). Assuming that catalysis occurs by an oxypalladation/deoxypalladation mechanism analogous to the well-studied rearrange-
ment reaction, this result requires that these two steps take place by opposite stereochemical pathways.

The mechanism outlined in Scheme 4, in which allylic substitution occurs by an anti-oxypalladation/syn-deoxypalladation mechanism, is favored for a number of reasons. The intermediacy of complex 48 is consistent with the high reactivity of substrates harboring the trichloroacetimidate leaving group, which would coordinate strongly to Pd(II).30 Furthermore, the high catalytic efficiency of [COP-OAc]₂ compared to [COP-Cl]₂ would be consistent with more facile dissociation of the weaker X-type acetate ligand to generate cationic bidentate intermediate 48. Computational studies supported this conclusion, finding that transition-state structures in which the imidate nitrogen and the alkene form a chelate with the palladium(II) are most energetically accessible. Mechanistic pathways involving syn-oxypalladation/anti-deoxypalladation were calculated to require significantly more energy overall, as these required coordination to palladium of a weakly binding acetate in place of the imidate nitrogen.

Our computational investigations also allowed for a model for stereoinduction to be developed (Figure 14).30 The lowest energy transition state structure 51 for the stereochemistry-determining anti-oxypalladation step is consistent with formation of the observed enantiomer of the allylic acetate product (Figure 15). As in transition structures for the allylic imidate rearrangement,30 destabilizing interactions between the substrate and the tetraphenylcyclobutadienyl moiety of the COP catalyst are present in transition structure 52 leading to the enantiomeric allylic ester product. Additionally, the isopropyl group plays a key role in orienting the alkene for stereoselective attack (51 vs 52 or 54). As in the imidate rearrangement, the electronic trans-effect of square planar palladium(II) is also important for dictating the placement of the olefin trans to the oxazoline ligand and into the more open quadrant of the chiral catalyst.

As noted earlier, the [COP-OAc]₂-catalyzed enantioselective synthesis of 2-vinyl heterocycles, was limited to (E)-allylic trichloroacetimidate precursors, as low stereoinduction was observed for the (Z)-allylic trichloroacetimidate precursors. After confirming that these reactions also occur with antarafacial stereospecificity, modeling of the enantiodetermining oxypalladation step found that the ΔG‡ was larger for (E)-imidates because of enhanced steric interactions between the substrate and the tetraphenylcyclobutadienyl fragment of the catalyst.29

Some common mechanistic aspects of COP-catalyzed reactions are apparent from the reactions studied. The intermediacy of the N-bound imidate complex is persistent,
and the nature of the X-type ligand appears to partition reactivity between rearrangement and $S_N2'$-substitution. Additionally, in all three studies the enantioselectivity is largely governed by the tetraphenylcyclobutadienyl catalyst “floor”, which is able to transmit chiral information across the palladium(II) square plane.

### SOME APPLICATIONS OF COP-CATALYZED CATALYTIC ENANTIOSELECTIVE REACTIONS

Many applications of the COP family of catalysts have been reported by other research groups. Enantioselective allylic trichloroacetimidate rearrangements have become a reliable method for the construction of secondary allylic amines, especially in the construction of heterocycles (Figure 16). For instance, Han used a $[\text{COP-Cl}]_2$ rearrangement to establish the amine stereocenter in his synthesis of (+)-iso-cassine.32 In this sequence, the amine stereocenter subsequently controlled diastereoselection in the formation of the piperidine ring. The COP-catalyzed synthesis of enantioenriched allylic amines has been combined with ruthenium-catalyzed olefin metathesis in the synthesis of several alkaloids. For example, Aldrich et al. prepared lactam inhibitors of biotin biosynthesis in this way.33 Sutherland and Swift generalized and streamlined the combined use of the $[\text{COP-Cl}]_2$-catalyzed allylic trichloroacetimidate rearrangements and ring-closing metathesis.34 Their one-pot method provided rapid access to enantiopure aminocycloalkenes from linear dienyl alcohol substrates. Sutherland and co-workers have further applied this strategy to the enantioselective synthesis of polyhydroxylated aminocycloalkane glycosidase inhibitors35 and bicyclic $\gamma$-lactams.36 The COP family of catalysts has also been used in other constructions of allylic carbon-heteroatom bonds (Figure 17).

![Figure 15. Calculated geometry of transition state 51.](image)

Figure 15. Calculated geometry of transition state 51.

![Figure 16. Applications of COP-catalyzed imidate rearrangements.](image)

Figure 16. Applications of COP-catalyzed imidate rearrangements.

![Figure 17. Applications of COP catalysts in nonimidate rearrangements.](image)

Figure 17. Applications of COP catalysts in nonimidate rearrangements.

For example, Clayden found that enantiopure thiocarbamates produced from the COP-catalyzed rearrangement of carbamothioates could undergo lithiation/Smiles-type rearrangement to provide tertiary thiol derivatives.37 In this case, the aryl migration occurred with high stereospecificity in some cases to provide tertiary thiocarbamates in good overall yields and enantipurity. In another application of $[\text{COP-Cl}]_2$, Batey et al. reported the catalytic enantioselective rearrangement of 2-allyloxypyridines to $N$-allyl pyridones.38 COP-catalyzed $S_N2'$ displacement reactions have also found applications outside of our research group (Figure 18). Jirgensons et al. reported that allylic bisimides were suitable substrates for the synthesis of vinyl oxazolines using a cationic COP/BF$_4$ complex.39 Kirsch and co-workers developed the application of COP-catalyzed allylic esterifications to build 1,3-polyol scaffolds with high stereoselectivity.40 Their iterative approach converted a terminal alkene product of COP-catalyzed $S_N2'$ esterification, such as 33i, to a new Z-allylic alcohol (55) in six steps by hydroboration/oxidation followed by Ando homologation. The trichloroacetimide derivative of alcohol 55 was then allowed to react with benzoic acid in the presence of either enantiomer of $[\text{COP-OAc}]_2$ (24) to provide a 1,3-diol, with syn or anti diastereoselectivity determined by catalyst control (33j or 33k). This eight-step process averaged 93% for each step, and provided complete stereocontrol of the 1,3-polyol products. Kirsch and co-workers have utilized the COP-catalyzed $S_N2'$ reaction to construct several natural products, three of which are depicted in Figure 18.40b
Sigmatropic Rearrangements of Allylic Trichloroacetimidates. The 1,3-
\[\text{SN}_2\] anti-sandwich complex, which projects steric in
architecture of the COP catalysts. Foremost is the cobalt
processes have revealed important facets of the planar-chiral
heteropalladation step is central. In addition, the knowledge
future use in enantioselective catalysis of reactions in which a
branched allylic product.

Mechanistic and computational investigations of both
processes have revealed important facets of the planar-chiral
architecture of the COP catalysts. Foremost is the cobalt
sandwich complex, which projects steric above and
below the square plane of these palladium(II) center. The large
tetraphenylcyclobutadienyl floor of these catalysts is responsible
for much of the enantioselectivity of the key heteropalladation
step in both the rearrangement and allylic substitution catalytic
cycles.

One can anticipate that the COP family of catalysts will find
future use in enantioselective catalysis of reactions in which a
heteropalladation step is central. In addition, the knowledge
gained about the origin of enantioselectivity in the COP-
catalyzed reactions discussed in this review will assist in future
optimization of the COP-catalyst architecture and potentially
defining other, perhaps structurally simpler, Pd(II) complex
motifs having improved performance.41

■ CONCLUSION AND OUTLOOK

The utility of the COP family of palladium(II) complexes for
catalyzing the enantioselective introduction of heteroatom
functionality (N, O, S) into C–C double bonds is now well
established. The chloride-bridged dimer, [COP-Cl]₂, is the best
enantioselective catalyst reported to date for the widely utilized
allylic trichloroacetimidates to allylic
enantioselective catalyst reported to date for the widely utilized
SN\[\text{2}\] and allylic pyridones. In addition, enantioselective bimolecular
SN\[\text{2}\]′-allylic substitutions by carboxylic acid and phenol
nucleophiles are catalyzed by [COP-OAc]₂. These reactions
proceed by a novel \textit{anti}-oxypalladation/syn-deoxypalladation
mechanism, which leads to the exclusive formation of the
branched allylic product.

Mechanistic and computational investigations of both
processes have revealed important facets of the planar-chiral
architecture of the COP catalysts. Foremost is the cobalt
sandwich complex, which projects steric above and
below the square plane of these palladium(II) center. The large
tetraphenylcyclobutadienyl floor of these catalysts is responsible
for much of the enantioselectivity of the key heteropalladation
step in both the rearrangement and allylic substitution catalytic
cycles.

One can anticipate that the COP family of catalysts will find
future use in enantioselective catalysis of reactions in which a
heteropalladation step is central. In addition, the knowledge
gained about the origin of enantioselectivity in the COP-
catalyzed reactions discussed in this review will assist in future
optimization of the COP-catalyst architecture and potentially
defining other, perhaps structurally simpler, Pd(II) complex
motifs having improved performance.41

■ ACKNOWLEDGMENTS

We thank the NSF (CHE-9726471 and CHE-1265964) for
financial support of our research in this area. Additional
unrestricted support from Amgen, Merck, and Pfizer is
gratefully acknowledged.

■ REFERENCES

(1) Overman, L. E. Thermal- and Mercuric Ion-Catalyzed [3,3]-
Sigmatropic Rearrangements of Allylic Trichloroacetimidates. The 1,3-
Transposition of Alcohol and Amine Functions. \textit{J. Am. Chem. Soc.}

(2) For a comprehensive review, see Overman, L. E.; Carpenter, N.

(3) Overman, L. E. Mercury(II)- and Palladium(II)-Catalyzed [3,3]-
Sigmatropic Rearrangements. \textit{Angew. Chem., Int. Ed. Engl.}

(4) McDonald, R. I.; Liu, G.; Stahl, S. S. Palladium(II)-Catalyzed
Alkene Functionalization via Nucleopalladation: Stereochemical Pathways
and Enantioselective Catalytic Applications. \textit{Chem. Rev.}
2011, 111, 2981–3019.


