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Journal
Accounts of Chemical Research, 49(10)

ISSN
0001-4842

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Publication Date
2016-10-18

DOI
10.1021/acs.accounts.6b00398

Peer reviewed

ACCOUNTS of chemical research

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Palladium(II)-Catalyzed Enantioselective Reactions Using COP Catalysts

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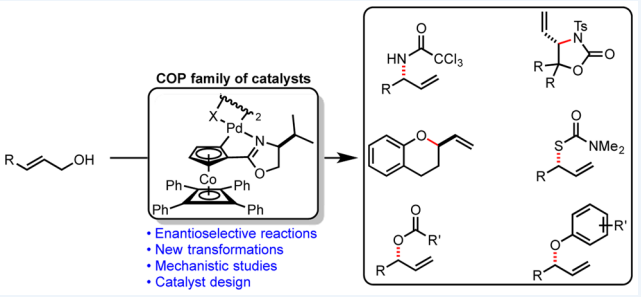
CONSPECTUS: Allylic amides, amines, and esters are key synthetic building blocks. Their enantioselective syntheses under mild conditions is a continuing pursuit of organic synthesis methods development. One opportunity for the synthesis of these building blocks is by functionalization of prochiral double 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.

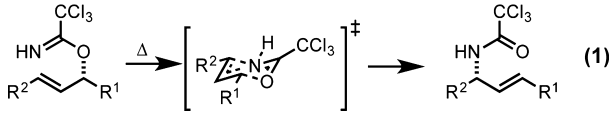


In this Account, we describe the development and use of enantiopure palladium(II) catalysts of the COP (chiral cobalt oxazoline palladacyclic) family for the synthesis of enantioenriched products from starting materials derived from prochiral allylic alcohols. We begin with initial studies aimed at rendering 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, $[COP\text{-}Cl]_2$, 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, $[COP\text{-}OAc]_2$, 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 $[COP\text{-}Cl]_2$ and $[COP\text{-}OAc]_2$ 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



(1)

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.[2] The discovery that this transposition could be catalyzed by π-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

Received: August 1, 2016
Published: September 30, 2016

DOI: 10.1021/acs.accounts.6b00398
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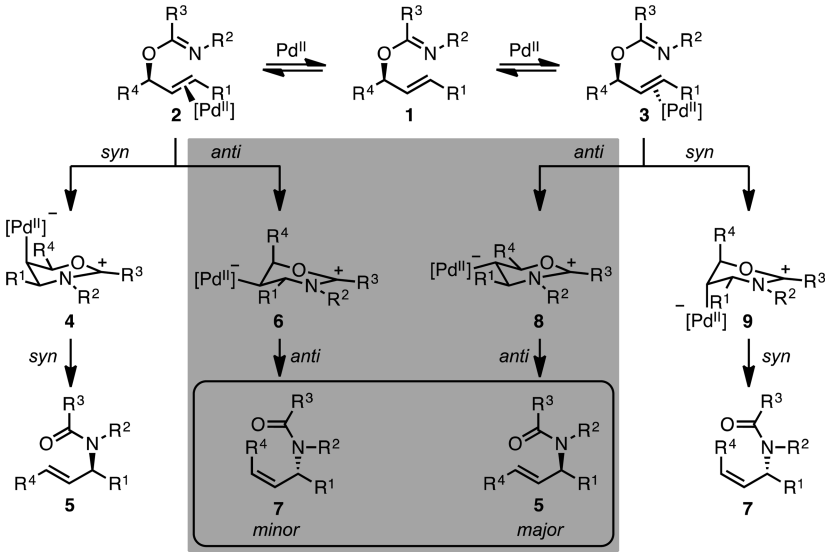
Scheme 1. Cyclization-Induced Rearrangement Mechanism



8 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;[1,3] however, *syn*-nucleopalladation is now known to be quite common.[4] 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.[2,5] 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.[6,7]

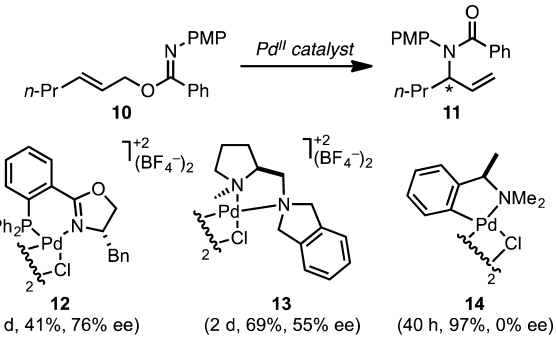
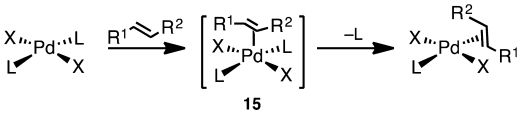


Figure 1. Reactivity of selected early enantioselective Pd(II) catalysts.

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.[8] 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).

Scheme 2. Associative Mechanism for Ligand Exchange at Square-Planar Palladium(II)



With this ligand design in mind, the first highly enantioselective palladium(II) catalysts were discovered (Figure 2).[9] 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).[9]

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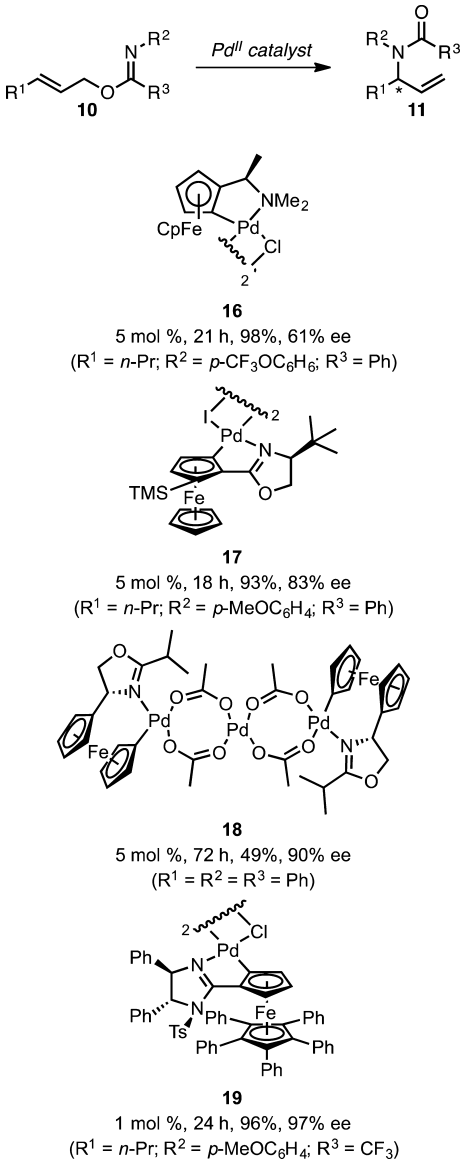
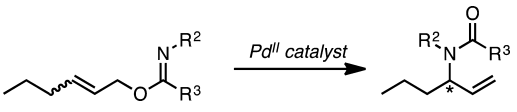


Figure 2. Ferrocene-derived planar-chiral palladium(II) complexes and their representative performance in the enantioselective rearrangement of imidates **10** to amides **11** [precatalysts **16**, **17**, and **19** were preactivated by reaction with 4 equiv of $Ag(OCOCF_3)$].

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



entry	cat.	imidate	R^2	R^3	*E*/*Z*	yield/ee (%)[a]
1	**17**[b]	**10a**	4-$MeOC_6H_4$	Ph	*Z*	83/91 (*R*)
2	**17**[b]	**10b**	4-$MeOC_6H_4$	Ph	*E*	93/83 (*S*)
3	**17**[b]	**20**	4-$MeOC_6H_4$	CF_3	*E*	88/76 (*S*)
4	**17**[b]	**21a**	H	CCl_3	*E*	50/43 (*S*)
5	**22**[c]	**20**	4-$MeOC_6H_4$	CF_3	*E*	92/99 (*S*)
6	**22**[c]	**21a**	H	CCl_3	*E*	99/95 (*S*)
7	**22**[d]	**21a**	H	CCl_3	*E*	85/92 (*S*)

[a]Absolute configuration in parentheses. [b]5 mol %, preactivated with 4 equiv $Ag(OCOCF_3)$, CH_2Cl_2, 40 °C. [c]5 mol %, CH_2Cl_2, 40 °C. [d]0.25 mol %, MeCN, 80 °C, 48 h.

The FOP catalysts, while effective, presented significant drawbacks in practicality. The most useful of the family, iodide-bridged dimer precatalyst **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 ferrocenium[10] 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** ($[COP\text{-}Cl]_2$, Figure 3).[14]

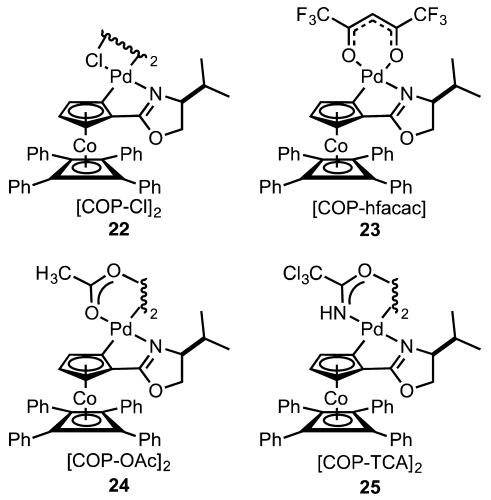


Figure 3. Cobalt oxazoline palladacycle (COP) family of catalysts.

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 a 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 $[COP\text{-}Cl]_2$ (**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*-arylamides (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

DOI: 10.1021/acs.accounts.6b00398
Acc. Chem. Res. 2016, 49, 2220−2231

contrast, allylic trichloroacetamides are readily transformed to the corresponding amine without erosion of enantiopurity under mildly basic or more forcing acidic conditions.[2] Additional optimization of the rearrangement of allylic trichloroacetimidates was carried out by Richards and co-workers who showed that the catalyst loadings of $[COP\text{-}Cl]_2$ could be reduced to 0.25 mol % in reactions carried out at 80 °C in acetonitrile (entry 7).[5,17] The improved reactivity of $[COP\text{-}Cl]_2$ (**22**) versus neutral $[FOP\text{-}Cl]_2$ 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.[18]

The increased reactivity and substrate compatibility of $[COP\text{-}Cl]_2$ allowed for significant broadening of the scope of enantioselective allylic trichloroacetimidate rearrangements (Figure 4). Free alcohols (**26c**), basic amines (**26g**), and acid

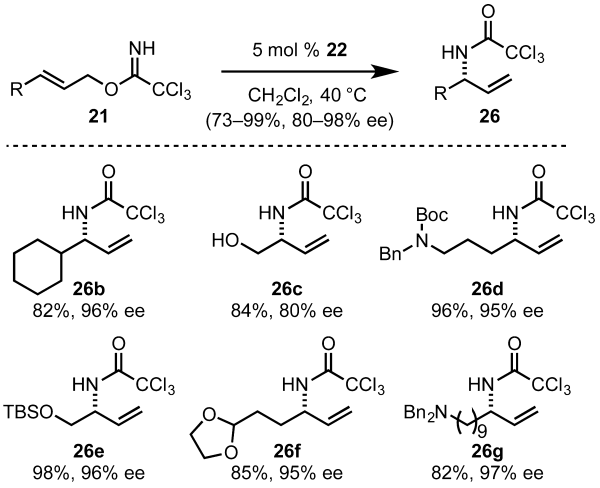


Figure 4. Enantioselective rearrangements of trichloroacetimidates.

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 trichloroacetimidates are poor substrates for enantioselective $[COP\text{-}Cl]_2$-catalyzed allylic imidate rearrangements. Fortunately, both enantiomers of $[COP\text{-}Cl]_2$ and $[COP\text{-}OAc]_2$ are commercially available, and the synthesis of these catalysts on scale has been documented in *Organic Syntheses*.[19]

Allylic rearrangements catalyzed by $[COP\text{-}Cl]_2$ (**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).[20] This $[COP\text{-}Cl]_2$-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.[21]

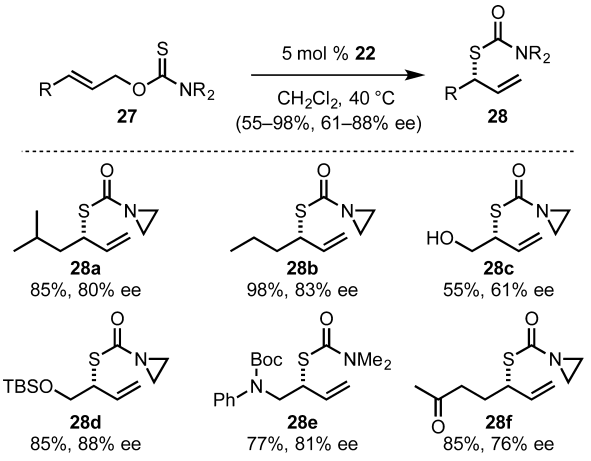


Figure 5. Enantioselective rearrangements of carbamothioates.

ENANTIOSELECTIVE S_N2' REACTIONS CATALYZED BY COP COMPLEXES

We anticipated that the COP family of catalysts would be useful for other enantioselective transformations in which aminopalladation/deoxypalladation was a central aspect. In an early study, we found that prochiral (*Z*)-2-acetoxy-4-(*N*-tosyl)-aminocarboxy-2-butenes **29** were transformed in the presence of 1 mol % of $[COP\text{-}OAc]_2$ (**24**) to 3-tosyl-4-vinyloxazolidin-2-ones **30** in high yield and enantioselectivities (Figure 6).[22]

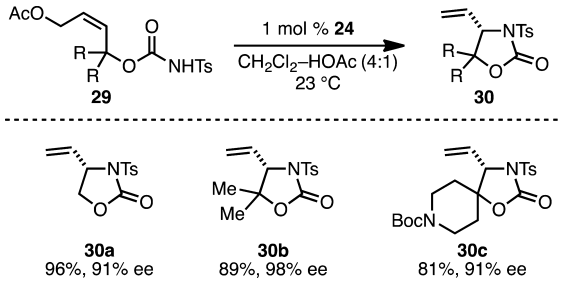


Figure 6. Enantioselective synthesis of 4-vinyloxazolidinones.

In an attempt to extend this cyclization to the formation of enantioenriched 4-vinyloxazolines, a new transformation, bimolecular enantioselective S_N2' reactions of allylic trichloroacetimidates, was discovered. When acetoxybutenyl trichloroacetimidate **31a** was exposed to a catalytic amount of **24** at 40 °C, a ~ 1:1 mixture of the expected 4-vinyloxazoline **32** and 1,2-diacetoxy-3-butene (**33a**) was formed (Figure 7).[23] As cyclopalladated catalysts such as **24** do not promote palladium π-allyl formation, the formation of **33a** suggested that S_N2' displacement of the imidate by acetic acid was occurring competitively with intramolecular cyclization. This hypothesis was confirmed when addition of excess acetic acid promoted exclusive bimolecular displacement to give butenyl diacetate **33a** in 98% yield. This discovery prompted the development of a new method for enantioselective allylic substitution.

Various enantiopure palladium(II) catalysts were examined for the synthesis of 3-acetoxy-1-hexene (**33b**) from (*Z*)-2-hexenyl imidate (**31b**) (Figure 7, bottom).[24] Ferrocene-containing complexes **16** and **17** provided **33b** in high yield after activation with silver trifluoroacetate; however, negligible levels of enantioselectivity were observed. Of the planar-chiral complexes investigated, only the COP family provided useful

DOI: 10.1021/acs.accounts.6b00398
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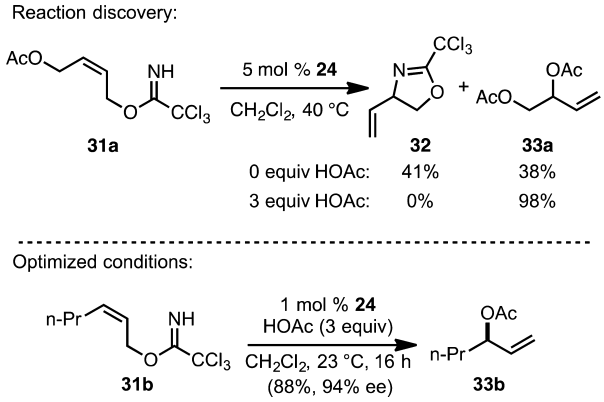
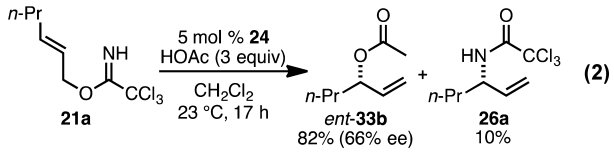


Figure 7. Discovery and optimization of palladium-catalyzed 3-acyloxy-1-alkene synthesis.

reactivity and enantioselection. The premier complex for allylic imidate [3,3]-sigmatropic rearrangements, $[COP\text{-}Cl]_2$ (**22**), displayed poor catalytic rates, as well as monomeric hexafluoroacetylacetonate complex **23**.[25] 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 $[COP\text{-}OAc]_2$ (**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_N2' 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).[24] Furthermore, the



enantioselectivity of the allylic ester product *ent*-**33b** was diminished. (*Z*)-Allylic imidates have significantly reduced rates for sigmatropic rearrangement,[16] and therefore the bimolecular displacement outcompetes rearrangement for these substrates.

The scope of this enantioselective allylic esterification reaction of trichloroacetimidate 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.[24]

Several limitations were observed while investigating carboxylic acid nucleophiles. In general, the carboxylic acid must be soluble in dichloromethane in order to achieve

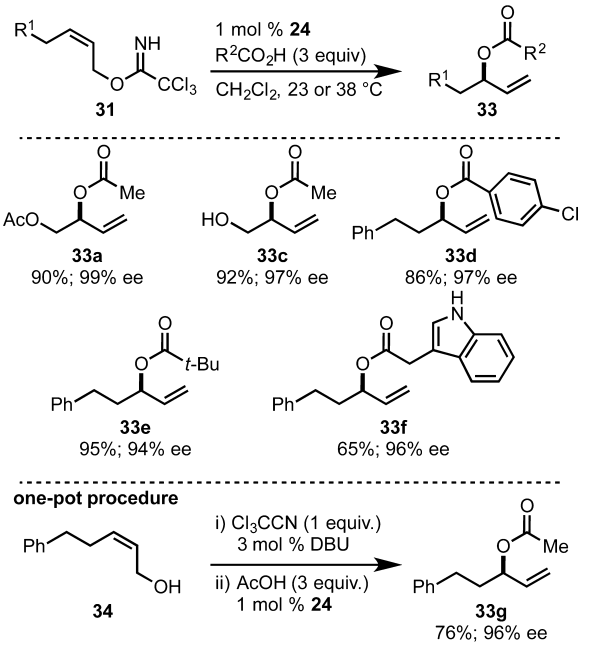


Figure 8. Representative scope of carboxylic acid nucleophiles.

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_N2' reaction. In fact, phenols were found to be competent nucleophiles under similar conditions (Figure 9).[26] 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,[27] neutral phenol nucleophiles are used in the COP-catalyzed reaction, allowing the presence of

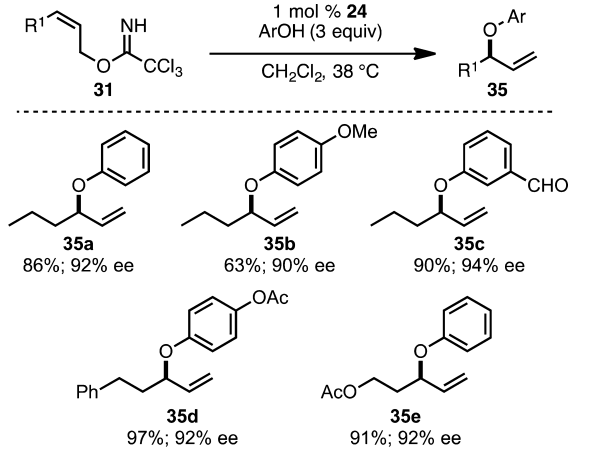
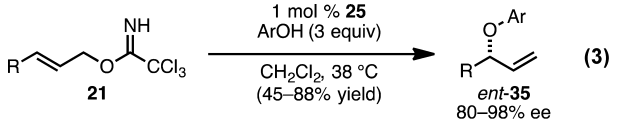


Figure 9. Enantioselective synthesis of allylic phenols.

DOI: 10.1021/acs.accounts.6b00398
Acc. Chem. Res. 2016, 49, 2220−2231

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 S_N2' and [3,3]-sigmatropic rearrangement pathways. During the course of our studies of this S_N2' reaction, careful analysis of the reaction mixtures revealed that di-μ-amidate dipalladium complex $[COP\text{-}NHCOCCl_3]_2$ (**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]



(3)

However, catalyst **25** is not useful for promoting enantioselective S_N2' allylic esterifications, because rapid exchange of the amidate ligand for the carboxylate nucleophile effectively regenerates a competent allylic rearrangement catalyst.

Enantioselective intramolecular S_N2' allylic substitution reactions have also been employed to construct heterocycles.[29] For example, $[COP\text{-}OAc]_2$-catalyzed cyclization of (*E*)-allylic trichloroacetimidates **36** harboring pendant phenol substituents delivered chromanes (**37a–c**), benzoxazine (**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 S_N2' reaction outcompetes the catalyzed [3,3]-sigmatropic rearrangement in most cases. With catalysts less competent for the S_N2' 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.

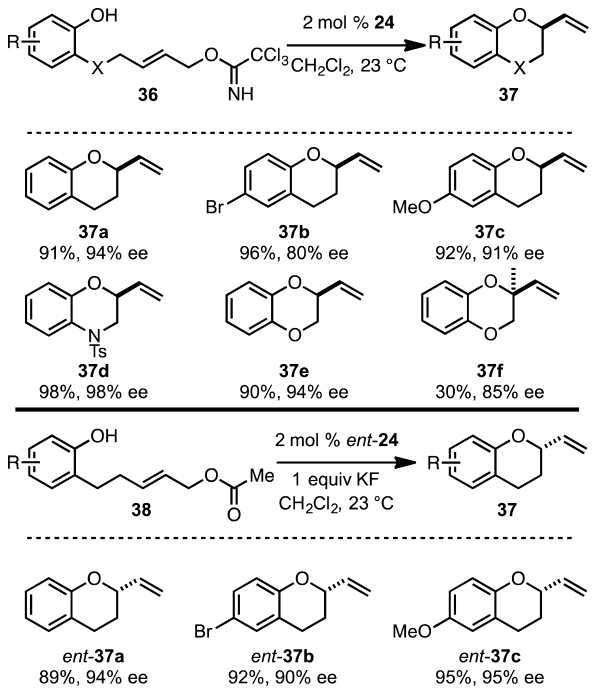


Figure 10. Enantioselective synthesis of oxygen heterocycles.

Allylic acetates were also found to be competent leaving groups for the intramolecular S_N2' reaction of phenols (Figure 10, **38** → **37**). With potassium fluoride as an added base, 2-vinylchromanes **37a–c** were synthesized in high yield and enantioselectivity using 2 mol % of $[COP\text{-}OAc]_2$ (**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, sulfonyl) 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 $[COP\text{-}OAc]_2$, suggesting either a $(ML)_2$ system or a reservoir effect.[5] 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 $[COP\text{-}OAc]_2$-catalyzed S_N2' reaction.[31]

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 $[COP\text{-}Cl]_2$ to methyl trichloroacetimidate ($K_{eq} \sim 2.2 \times 10^{-4}$) than to 2-pentene ($K_{eq} \sim 5.4 \times 10^{-8}$), nitrogen-bound complex **39** is presumed to lie on the catalytic cycle (Scheme 3). Rearrangement of **39** to the η^2-alkene complex **40** activates the double-bond for rate-limiting iminopalladation, which generates charge-separated cyclopalladate complex **41**. Deoxypalladation generates the η^2-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

DOI: 10.1021/acs.accounts.6b00398
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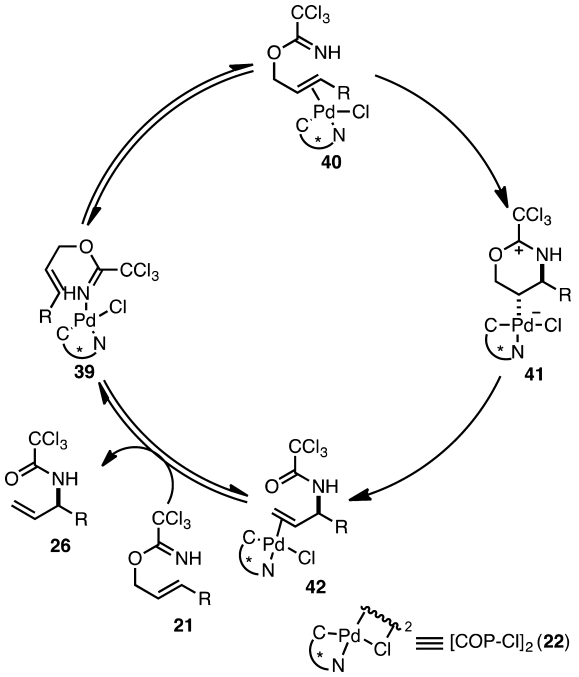
Scheme 3. Proposed Mechanism of the COP-Catalyzed [3,3]-Sigmatropic Rearrangement



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.

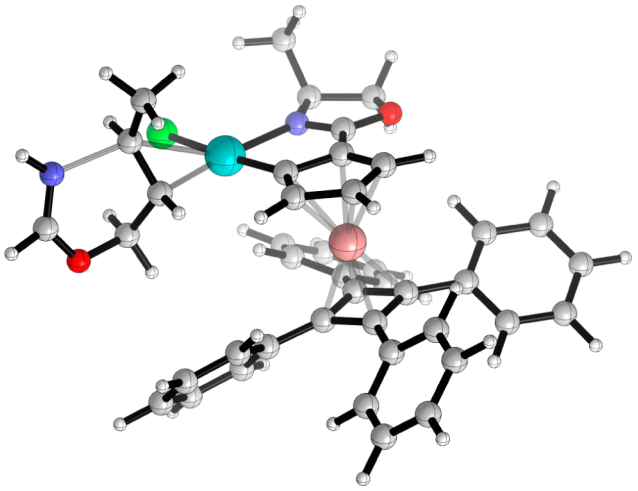


Figure 12. Calculated geometry of transition state **43**.

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.[5] 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 S_N2'-allylic substitution reactions.[31] Of fundamental importance in constructing a mechanistic model for these reactions were labeling experiments that established that $[COP\text{-}OAc]_2$-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-

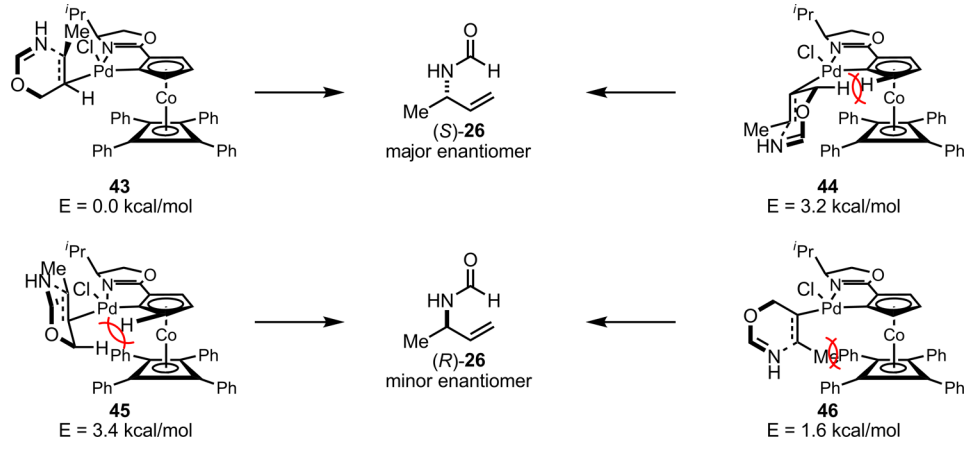


Figure 11. Model for enantioselection in the COP-catalyzed [3,3]-sigmatropic rearrangement.

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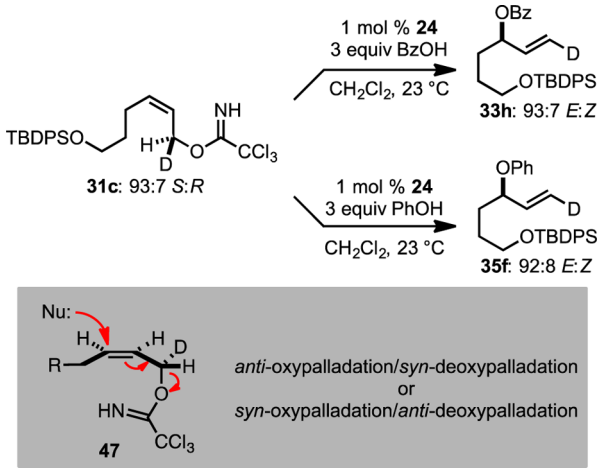
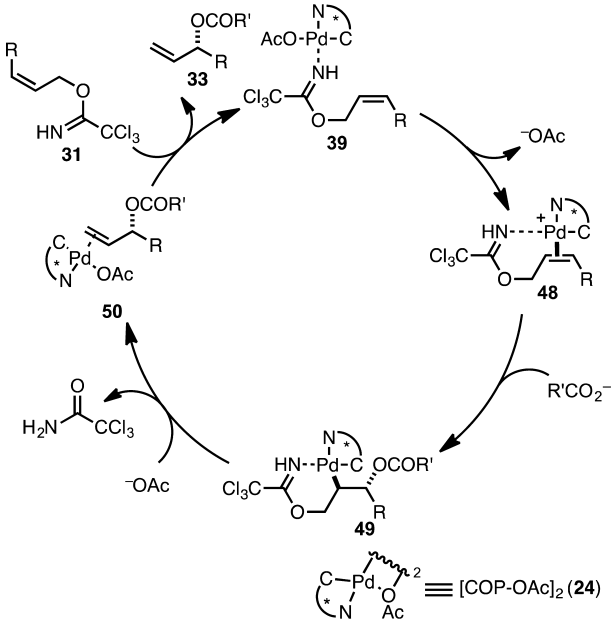


Figure 13. Stereochemical course of COP-catalyzed S_N2'-allylic substitution reactions.

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*-deoxypallada-

Scheme 4. Proposed Mechanism of COP-Catalyzed Bimolecular Allylic Substitution Reactions



tion 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 $[COP\text{-}OAc]_2$ compared to $[COP\text{-}Cl]_2$ 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

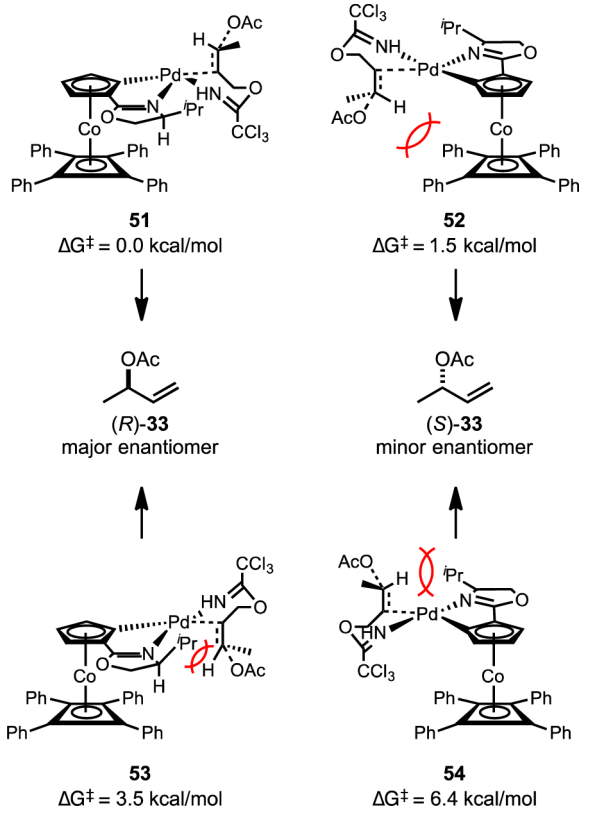


Figure 14. Model for enantioselection in the COP-catalyzed allylic esterification reaction.

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 $[COP\text{-}OAc]_2$-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 $\Delta G^{\ddagger}$ 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,

DOI: 10.1021/acs.accounts.6b00398
Acc. Chem. Res. 2016, 49, 2220−2231

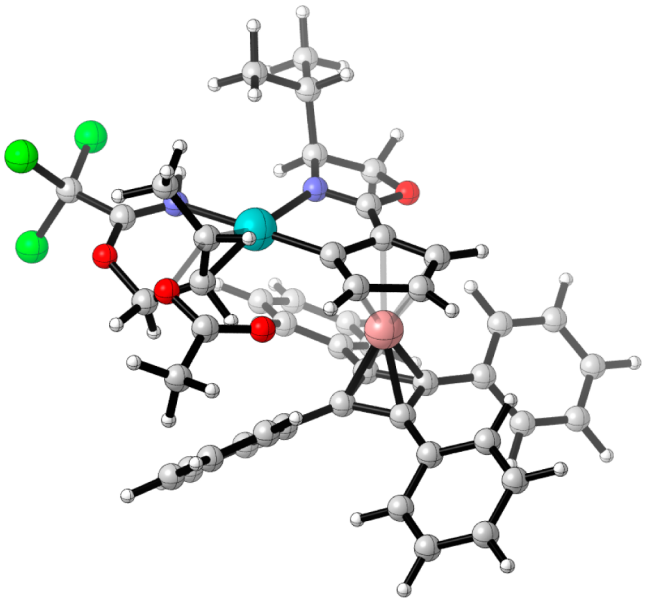


Figure 15. Calculated geometry of transition state **51**.

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 $[COP\text{-}Cl]_2$ (**22**) catalyzed rearrangement to establish the amine stereocenter in his synthesis of (+)-*iso*-cassine.[32] In this sequence, the amine stereocenter subsequently

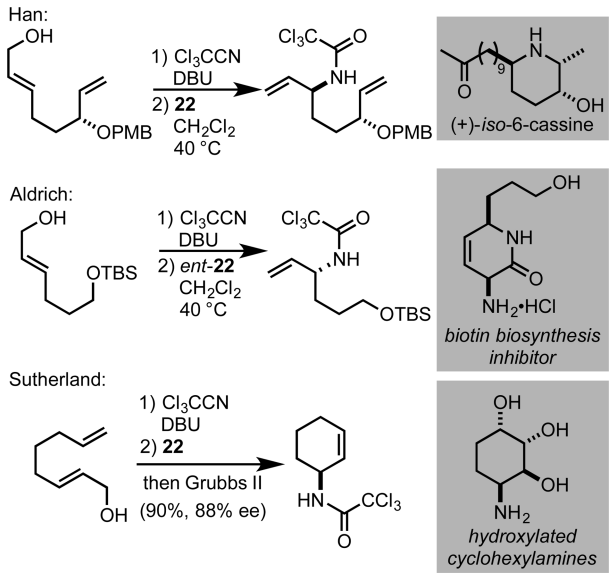


Figure 16. Applications of COP-catalyzed imidate rearrangements.

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 $[COP\text{-}Cl]_2$-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 inhibitors[35] and bicyclic γ-lactams.[36]

The COP family of catalysts has also been used in other constructions of allylic carbon-heteroatom bonds (Figure 17).

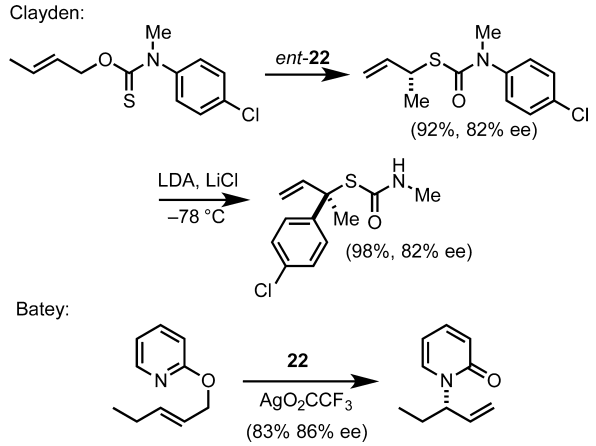


Figure 17. Applications of COP catalysts in nonimidate rearrangements.

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 enantiopurity. In another application of $[COP\text{-}Cl]_2$, 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 bisimidates 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 trichloroacetimate derivative of alcohol **55** was then allowed to react with benzoic acid in the presence of either enantiomer of $[COP\text{-}OAc]_2$ (**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] Of

DOI: 10.1021/acs.accounts.6b00398
Acc. Chem. Res. 2016, 49, 2220−2231

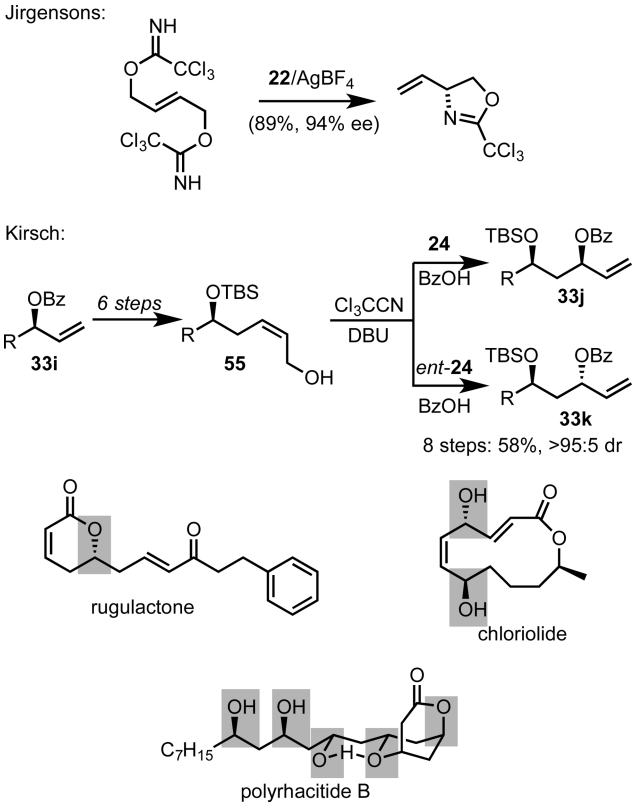


Figure 18. Applications of COP catalysts for S_N2' substitution, highlighted stereocenters established by COP-catalyzed S_N2' reactions.

particular note, they utilized the iterative strategy developed in his group to systematically assemble the five alcohol stereocenters of (+)-polyrhacitide B.[40b]

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, $[COP\text{-}Cl]_2$, is the best enantioselective catalyst reported to date for the widely utilized rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides (Overman rearrangement).[2,16] COP complexes are also excellent enantioselective catalysts for [3,3]-sigmatropic rearrangements that form chiral allylic thioesters and allylic pyridones. In addition, enantioselective bimolecular S_N2'-allylic substitutions by carboxylic acid and phenol nucleophiles are catalyzed by $[COP\text{-}OAc]_2$. These reactions proceed by a novel *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 influence 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]

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Notes

The authors declare no competing financial interest.

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Jeffrey S. Cannon studied at Occidental College in Los Angeles, CA, where he received his A.B. in chemistry. He earned his Ph.D. with Professor Larry Overman at the University of California, Irvine studying palladium catalysis and the asymmetric total synthesis of complex alkaloid natural products. After a NIH postdoctoral fellowship with Professor Robert Grubbs at the California Institute of Technology, he returned to Occidental College as an assistant professor. His current research interests focus on catalyst development for the enantioselective construction of complex natural products.

Larry E. Overman was born in Chicago, Illinois and raised in Hammond, Indiana. He obtained a B.A. degree from Earlham College and completed his doctoral dissertation with Professor Howard W. Whitlock, Jr. at the University of Wisconsin. After a NIH postdoctoral fellowship with Professor Ronald Breslow at Columbia University, he joined the faculty at the University of California, Irvine where he is now Distinguished Professor of Chemistry. Professor Overman's research interests center on the invention of new transformations and strategies in organic synthesis and the total synthesis of natural products and their congeners. Using synthesis strategies developed largely in his laboratory, Professor Overman's group has completed total syntheses of more than 90 structurally complex natural products.

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.

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