Organic Syntheses

Discussion Addendum for:

Preparation of the COP Catalysts: [(*S*)-COP-OAc]$_2$, [(*S*)-COP-Cl]$_2$, and (*S*)-COP-hfacac

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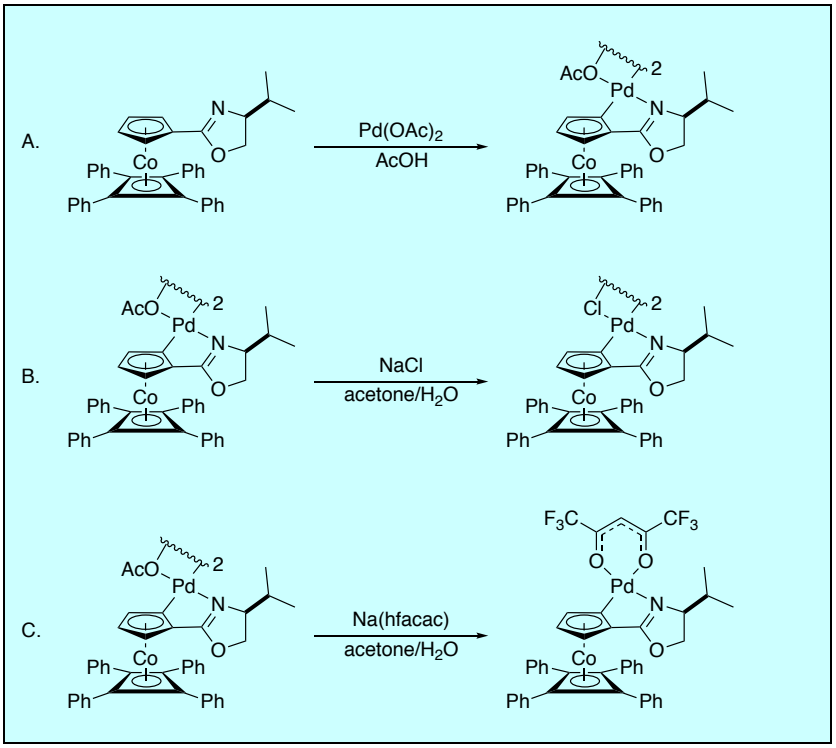

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Alkenes harboring allylic heteroatoms are a ubiquitous functional arrangement in organic molecules.[2,3,4] Their enantioselective synthesis under mild conditions is of broad utility for the preparation of many biologically active and complex organic structures. One opportunity for such enantioselective syntheses is the use of nucleophilic heteroatom species in allylic substitution reactions of prochiral alkenes containing allylic leaving groups. Palladium(II) catalysts are ideal reagents for these transformations because of their chemoselectivity as π-acids,[5] with catalyst complexes having planar chirality proven to be particularly effective for achieving antarafacial nucleopalladation of C–C double bonds.[6] Our group has utilized a family of chiral cobalt oxazoline palladacycle (COP) catalysts (Figure 1), originally discovered by Richards,[6a] for the activation of alkenes for enantioselective nucleopalladation/deoxypalladation rearrangement and allylic substitution reactions.[7,8] In 2007, we reported scalable syntheses of the three COP complexes depicted in Figure 1,[9] as they had proven to be excellent catalysts for the transformation of prochiral allylic trichloroacetimidates to either branched allylic trichloroacetamides or branched allylic esters in good yields and enantioselectivities (Scheme 1).[10] Although some attempts have been made to replicate the effectiveness of the COP catalysts with less elaborate ligand scaffolds, the COP complexes remain the most selective catalysts for these transformations.[6c,11] High enantioselectivities, essentially complete selectivity for formation of the branched allylic product, and mild reaction conditions that tolerate most functional groups—notably those that are base labile—are typical of COP-catalyzed allylic substitution reactions.[10,12] These features provide the COP family of catalysts with complementary reactivity to many catalytic enantioselective allylic functionalizations that proceed via π-allyl intermediates.[13]

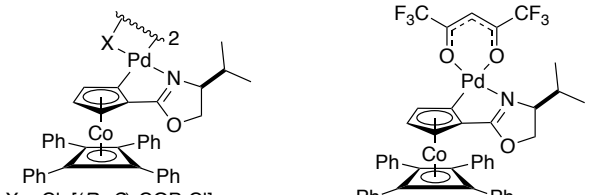
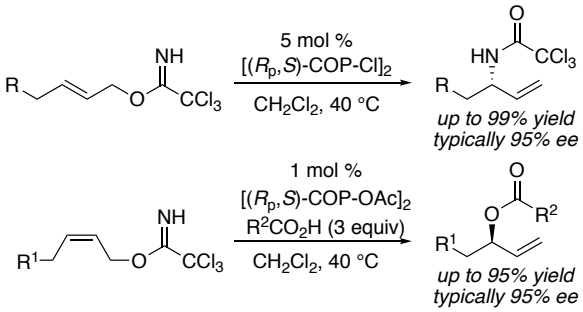


Figure 1. The COP family of catalysts

At the time of our report of the syntheses of the COP complexes, only the enantioselective trichloroacetimidate rearrangement and allylic substitution with carboxylic acid nucleophiles had been described (Scheme 1). In the following years, a number of new COP-catalyzed transformations and synthetic applications of the allylic products have been reported. These advances will be the focus of this Addendum.[14]

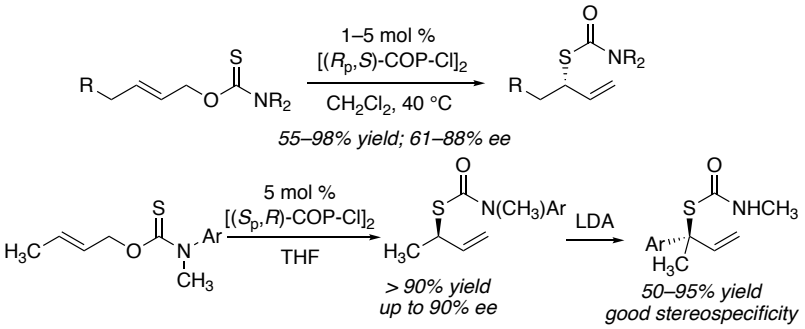


Scheme 1. Applications of COP catalysts in allylic trichloroacetimidate rearrangement and allylic ester synthesis

(I) Rearrangements

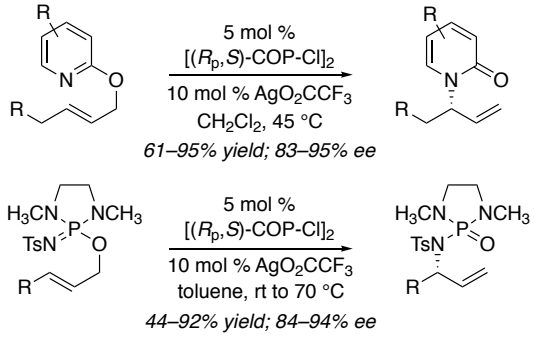
Additional transformations involving formal [3,3]-sigmatropic rearrangements of 1,3-dihetero-1,5-hexadienes catalyzed by COP catalysts have been reported. It has been found that the complex $[COP\text{-}Cl]_2$, having bridging chloride ligands, is generally the optimal catalyst for these applications.

The enantioselective synthesis of allylic thiocarbamates by the palladium-catalyzed rearrangement of carbamothioates has been described by our and the Clayden research groups (Scheme 2).[15,16] Typical of this family of palladium-catalyzed rearrangements, the substrate scope was fairly broad and included unprotected alcohols and secondary carbamates. Clayden extended this chemistry by utilizing a subsequent lithiation/Smiles-type rearrangement to enable the synthesis of fully-substituted sulfur stereocenters. This tactic overcame the inability of the COP complexes to catalyze rearrangements of allylic precursors having two substituents at the site of C–S bond formation. The stereoselectivity of this two-step sequence was generally high, with the configuration of the newly formed stereocenter being determined by the enantioselectivity of the COP-catalyzed rearrangement.[15]



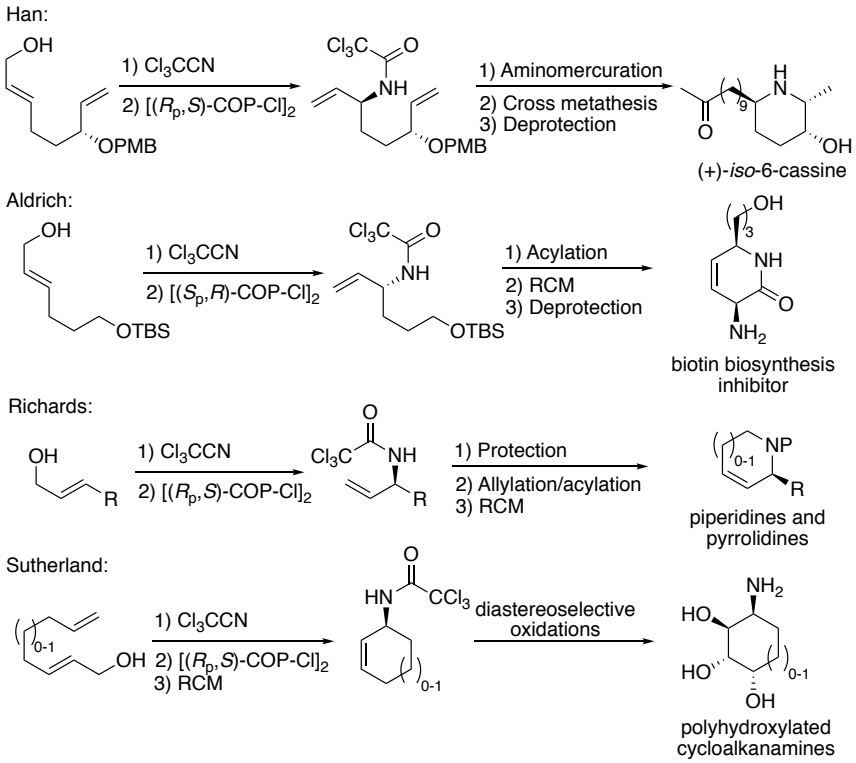
Scheme 2. Enantioselective rearrangements of allylic carbamothioates

The enantioselective introduction of nitrogen-containing stereocenters by COP-catalyzed allylic rearrangements has been extended to allylic alcohol precursors other than trichloroacetimidates. Batey recognized the opportunity to utilize 2-allyloxypyridines as imidate surrogates in palladium-catalyzed rearrangements using COP complexes (Scheme 3).[17] These transformations provide *N*-allylpyridones in good yields and enantioselectivities using $[COP\text{-}Cl]_2$. It was found that generation of a cationic complex by removal of the chloride ligands with silver trifluoroacetate significantly enhanced the rate of the rearrangement without reduction in enantioselectivity. Batey also demonstrated that other allyloxy-substituted nitrogen heterocycles, including quinolines and benzothiazoles, could be transformed in a similar fashion to *N*-allylated products in good yields and enantioselectivities. In addition, Batey reported the COP-catalyzed rearrangement of iminodiazaphospholidines to provide chiral allylic phosphoramides, which upon reaction with 1 M HCl gave the corresponding allylic tosylamide.[18] In the presence of silver trifluoroacetate and $[COP\text{-}Cl]_2$, this rearrangement proceeded in moderate to good yields and modest to high enantioselectivities. As a method for enantioselective synthesis of chiral amines, the COP-catalyzed allylic trichloroacetimidate rearrangement has a broader scope and provides products readily converted to the corresponding primary amine.



Scheme 3. Enantioselective rearrangements to generate C-N bonds: allyloxypyridines and iminodiazapholidines

The typically broad scope, mild conditions, and high enantioselectivity of COP-catalyzed allylic trichloroacetimidate rearrangements has led to this reaction being employed as a key step in the enantioselective construction of various nitrogen-containing molecules (Scheme 4). A common tactic is to strategically combine this reaction with ruthenium-catalyzed alkene cross-metathesis or ring-forming metathesis. For example, Han followed the COP-catalyzed enantioselective rearrangement of an allylic alcohol with an aminomercuration/demercuration reaction to construct 2,6-disubstituted piperidines.[19] Cross metathesis was then employed to append a 2-octanone side chain to yield, after alkene hydrogenation, the CNS-active piperidine alkaloid (+)-*iso*-6-cassine. Combining COP-catalyzed allylic trichloroacetimidate rearrangements with ring-closing metathesis (RCM) to construct nitrogen heterocycles was reported by Aldrich and Richards.[20,21] After palladium-catalyzed rearrangement, both strategies appended an allyl or homoallyl group to the resulting nitrogen. Ruthenium-catalyzed RCM of the resulting dienes provided the targeted heterocycles. Aldrich utilized this strategy to construct a piperidinone inhibitor of biotin synthesis. Richards was able to synthesize a number of functionalized enantioenriched piperidines, pyrrolidines, quinolizidines, and indolizidines, including the natural products anisomycin and coniine. Sutherland also employed a palladium-catalyzed rearrangement/RCM strategy on dienol starting materials to construct amine-substituted carbocycles that were then elaborated to polyhydroxylated aminocarbocycles.[22]



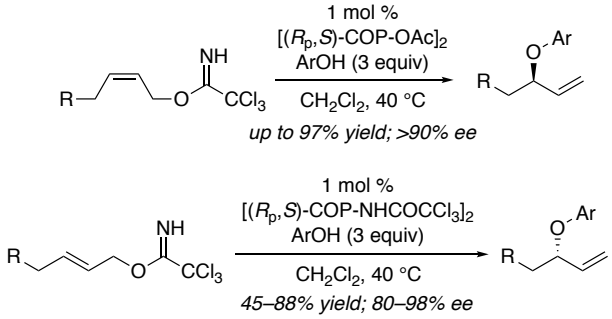
Scheme 4. Applications of [COP-Cl]$_2$-catalyzed rearrangements in synthesis

(II) Allylic Substitution Reactions

One other important use of the COP family of catalysts is to promote enantioselective S_N2'-type reactions of prochiral allylic imidates. Our original report of the intermolecular allylic esterification motivated us and others to pursue the utility of other nucleophiles in the enantioselective synthesis of branched allylic substitution products.[9c,d] In general, successful nucleophiles needed to be relatively acidic (pK_a <12) in order to participate in the S_N2' reactions. This requirement is particularly important for intermolecular reactivity and presumably results from the need to eventually protonate the imidate leaving group. Furthermore, intermolecular substitutions catalyzed by the COP family of catalysts require the use of the *Z*-allylic imidate in order to suppress competing [3,3]-

sigmatropic rearrangement by increasing the steric demand of the intramolecular iminopalladation step.

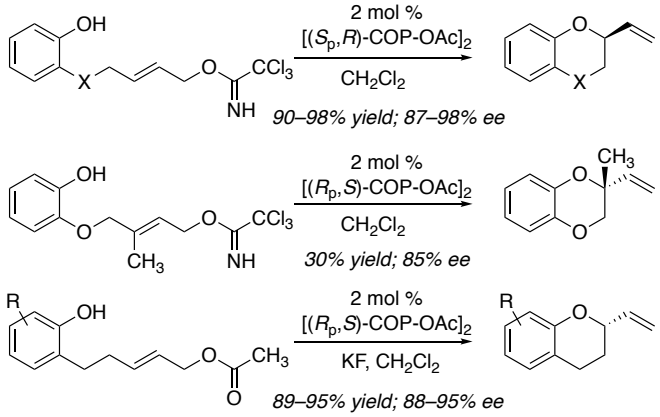
Phenols were quickly found to be particularly useful nucleophiles for the generation of allyl aryl ethers (Scheme 5).[23] S_N2' substitution onto prochiral *Z*-allylic imidates provided the corresponding allyl aryl ethers in good yields and consistently high enantioselectivities. As in the synthesis of allylic esters, the palladacyclic complex $[COP\text{-}OAc]_2$ was ideal for this transformation of the *Z*-allylic imidates. In the course of these studies, a new complex, $[COP\text{-}NHCOCCl_3]_2$, was discovered in which the bridging acetate ligands were replaced by bridging trichloroacetamidates.[24] This complex was the first catalyst capable of promoting the intermolecular S_N2' substitutions of *E*-allylic imidates. For reasons still not well understood, $[COP\text{-}NHCOCCl_3]_2$ is a comparatively poor catalyst for the allylic trichloroacetimidate rearrangement, allowing useful yields of allyl aryl ethers to be produced without the formation of significant amounts of allyl amide byproducts. Unfortunately, this reactivity could not be translated to the allylic esterification, as $[COP\text{-}NHCOCCl_3]_2$ readily converts to a carboxylate-ligated species in the presence of carboxylic acids.[12] These carboxylate complexes, like $[COP\text{-}OAc]_2$, are also competent catalysts for the competing allylic trichloroacetimidate rearrangement.



Scheme 5. Enantioselective intermolecular S_N2' reactions with phenol nucleophiles

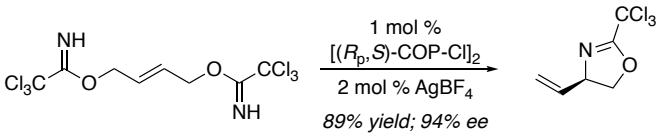
Catalytic, enantioselective, intramolecular substitution reactions with phenol nucleophiles were also realized with $[COP\text{-}OAc]_2$ (Scheme 6).[25] Vinylchromans and other oxygen heterocycles were synthesized in good yields and enantioselectivities. In particular, *E*-alkenes were found to be the ideal substrates, as the corresponding *Z* isomers provided products having

significantly reduced enantioselectivities. This intramolecular reactivity allowed two firsts for the COP family of complexes: (1) the stereoselective synthesis of fully-substituted stereocenters in good enantioselectivity, albeit in low yield; and (2) the use of allylic acetates as effective and more atom-economical leaving groups giving allylic substitution products in comparable yields and enantioselectivities. In this latter case, basic potassium fluoride was required to promote the reaction.



Scheme 6. Enantioselective synthesis of 2-vinyl substituted oxygen heterocycles

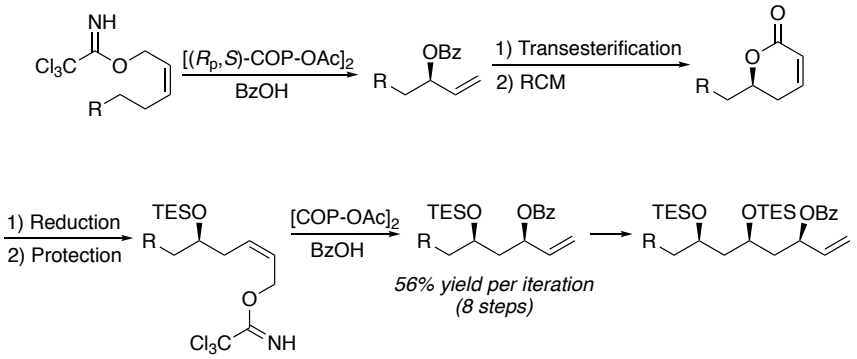
Jirgensons also reported a COP-catalyzed intramolecular substitution of allylic bis-trichloroacetamidates (Scheme 7).[26] In this case, the *E*-alkene stereoisomer of the bisimidate was required to achieve high yield and diastereoselectivity.



Scheme 7. Synthesis of a vinyloxazoline by a [COP-Cl]$_2$-catalyzed substitution reaction

The allylic substitution reaction has found some use in total synthesis efforts. For instance, Kirsch demonstrated an iterative approach for the synthesis of 1,3-polyols.[27] This strategy utilizes a ring-closing metathesis to generate a 5,6-dihydro-α-pyrone intermediate. Conversion of this lactone to

the *Z*-allylic imidate allowed for a subsequent COP-catalyzed S_N2' reaction to establish the next stereocenter. Kirsch demonstrated that this method could be used to construct all of the possible stereoisomers of 1,3-polyols with high levels of catalyst control, providing programmed access to polyketide scaffolds. Kirsch employed this iterative approach to synthesize polyrhacitides A and B.[28] Kirsch also utilized the $[COP\text{-}OAc]_2$-catalyzed allylic ester synthesis in his syntheses of rugulactone and chloriolide.[27b]



Scheme 8. Iterative strategy for 1,3-polyols utilizing COP-catalyzed S_N2' reactions

Conclusion

Several advances in the utility of the COP family of palladacyclic catalysts have been realized in recent years. These catalysts have proven to be relatively general enantioselective catalysts for both bimolecular and intramolecular allylic substitution reactions involving heteropalladation/deoxypalladation steps. We anticipate that these complexes will continue to find use in similar reactions where mild conditions and high selectivity for forming the branched product are paramount.

References

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Jeff Cannon obtained his B.A. in Chemistry from Occidental College in Los Angeles. He obtained his Ph.D. from University of California, Irvine working with Prof. Larry Overman. After an NIH postdoctoral fellowship with Prof. Robert Grubbs at Caltech, Jeff returned to Occidental as an assistant professor in 2014. Jeff's current research interests are focused on the development of new stereoselective carbon-carbon bond forming reactions inspired by synthetic needs in natural product synthesis.