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Recent Applications of Chiral Phosphoric Acids in Palladium Catalysis

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Abstract

Through the combined action of palladium catalysts and chiral phosphoric acids (CPAs) a variety of catalytic asymmetric reactions have been realized during the past decade, including allylation, alkene functionalization, and C—H activation. This review surveys key examples across these various reaction types and examines the different mechanisms by which CPAs can affect stereoinduction in these reaction systems.

Introduction

During the past two decades, chiral Brønsted acids have enabled the development of a variety of efficient enantioselective organic reactions.^{1–6} Classically, these catalysts operate through non-covalent interactions such as protonation or hydrogen bonding activation of the electrophile (e.g., an imine), which creates a chiral pocket for the nucleophile (e.g., an enolate) to attack from *re/si* face. Several notable families of Brønsted acids have been reported, each with unique properties. Chiral thiourea and chiral diols, for example, are considered as weak acid catalysts with pK_a values in the range of 8–20. Chiral phosphoric acids (CPAs), as well as related catalysts, including *N*-triflyl phosphoramides, chiral disulfonimides, and chiral imidodiphosphates, are stronger acids with pK_a values in the 2–4 range and have been extensively developed during the past several years for a range of different transformations.

With CPAs quickly cementing themselves in asymmetric synthesis and catalysis during the 2000s, in more recent years their influence has also percolated into other fields, including organometallic chemistry and polymer chemistry.⁶ This emerging body of literature has revealed that CPAs have an ability to operate in synergy with transition metal catalysts, either as ligands that modulate the coordination sphere around the metal or as co-catalysts that participate in outer sphere substrate activation.^{7, 8} As such, the ever-growing CPA toolkit has revolutionized how researchers in homogeneous catalysis approach enantioselective methods development. More specifically, the past ten years have witnessed a vibrant proliferation of activity centered on merging palladium catalysis and chiral phosphoric acid/amide catalysis through a variety of proposed mechanisms and interactions

(Scheme 1). By combining the unique abilities of each of these catalytic modalities, unique reactivity and stereoselectivity has been achieved in a series of challenging transformations.

This review is intended to provide an overview of recent progress on this topic. Within a short amount of time, this co-catalysis approach has demonstrated a wide breadth of synthetic and mechanistic capability. The main areas of study thus far established are that of enantioselective allylation, alkene functionalization, and C—H activation. These major areas, as well as other miscellaneous reports, will be covered in this short review in hopes of aiding the development of future research on CPA and palladium co-catalysis. The reader should be aware that CPAs have also been actively studied in combination with other metal catalysts, a topic that has been reviewed elsewhere⁸⁻¹³ and is outside of the scope of the present article. Additionally, there exist separate reviews that recount work in merging transition metal catalysis with organocatalysis in general.¹⁴⁻²⁰

Background

The approach of utilizing chiral phosphates as counterions in palladium catalysis was first established in 1990 by Alper and coworkers in their seminal report on a highly regioselective and enantioselective hydrocarboxylation of styrenyl terminal alkenes catalyzed by palladium chloride and a simple BINAP-derived phosphoric acid (Scheme 2).²¹ Using this methodology, they were able to synthesize (*S*)-naproxen and (*S*)-ibuprofen under mild conditions with up to 91% and 84% ee, respectively. Other chiral ligand scaffolds such as menthol, BINOL, diethyl tartrate, and BINAP were explored, but none gave higher than 10% ee. Thus, although the exact mode of action of the CPA co-catalyst is currently unknown, this specific functionality is required for high enantioinduction.

Despite these promising seminal results, the field of CPA and palladium co-catalysis did not begin gaining traction until the mid 2000s, propelled by the pioneering discoveries by Akiyama²² and Terada²³ in 2004, who independently found that BINOL-derived CPAs bearing 3,3'-disubstitution were highly effective as Brønsted acid catalysts for an asymmetric Mannich reaction. This family of CPAs was then successfully employed in conjunction with late transition metal catalysis, including pioneering contributions by Krische in 2006 (ruthenium-catalyzed reductive coupling of 1,3-enynes and carbonyl compounds)²⁴, Toste in 2007 (intramolecular gold-catalyzed allene hydrofunctionalization)²⁵, and List in 2007 (palladium-catalyzed Tsuji–Trost allylic alkylation)²⁶.

(1) Allylation

(1A) Allylations employing allyl electrophiles

Enantioselective allylation constitutes one of the more actively studied reaction types in which CPAs and palladium catalysts have been employed. Efforts have been made to incorporate a variety of allyl electrophiles with and without a preinstalled desired oxidation state as well as to integrate a variety of nucleophilic coupling partners. As the leading pioneer in this area, the List group reported in 2007 their discovery of a palladium(0) and CPA co-catalytic system that enabled the enantioselective α -allylation of aldehydes with

allylamine electrophiles (Scheme 3).²⁶ They demonstrated the reaction's compatibility with a variety of substitutions on the α -position of the aldehyde and some substituents on the terminal position of the allyl electrophile. Moreover, the authors were able to apply their newly developed method toward the formal synthesis of (+)-cuparene in three steps. Mechanistically, they proposed condensation of the amine electrophile onto the aldehyde nucleophile to generate an activated allyl electrophile. Palladium(0) then undergoes oxidative addition into this *in situ* generated electrophile to give a cationic π -allyl complex and an enamine nucleophile. Nucleophilic attack as directed by a hydrogen-bonding complex with the CPA co-catalyst and the enamine N—H bond allows for enantioselective formation of the desired product upon hydrolysis of the imine precursor.

In later work, the List group also demonstrated enantioselective α -allylation of aldehydes using allyl alcohols in place of allyl amines as electrophiles (Scheme 4).²⁷ In this case, the allyl alcohol is activated for oxidative addition via hydrogen bonding to the CPA co-catalyst. The authors found that when a simple enol nucleophile undergoes the desired attack, the resulting product is generated with low enantioselectivity, likely due to a mixture of *E/Z*-enol nucleophiles in solution. Thus, a primary amine additive is necessary to ensure complete formation of *E*-enamine nucleophile by *in situ* condensation with the aldehyde substrate. Thus, desired reactivity and enantioselectivity arises from a subtle collaboration between three different catalysts: 1) palladium, 2) (*S*)-TRIP (3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diylhydrogenphosphate), and 3) benzhydrylamine. The major benefits of this method lie in the ability to use simple allyl alcohol starting materials and to enantioselectively generate all-carbon quaternary stereocenters. A follow up mechanistic study using DFT calculations was later published by the Sunoj group.²⁸ Recently, the Gong group reported a similar allylation transformation in which the aldehyde is generated *in situ* by rhodium-catalyzed hydroformylation of a terminal alkene substrate.²⁹ Although the enamines generated in the cases above are normally hydrolyzed, the Gong group has utilized a CPA-palladium co-catalysis strategy to synthesize cyclic imine products.³⁰ In this work, a gold(I) catalyst is necessary to generate the enamine nucleophile via hydroamination of a tethered alkyne.

Aside from aldehyde-derived nucleophiles, other types of nucleophiles can also be enantioselectively allylated at the α -position, as shown by the Gong group in a 2013 publication (Scheme 5).³¹ In this work, the combination of a palladium(0) catalyst, a chiral phosphoramidite ligand, and a simple BINOL-PA allows enantioselective α -allylation of pyrazol-5-ones using allylic alcohol electrophiles. Analogous to List's work, the allyl alcohol is again activated for oxidative addition by hydrogen bonding to the CPA, and key hydrogen bonding interactions between CPA and nucleophilic enol tautomer are also cited for the enantioselective attack of the cationic π -allyl palladium intermediate. In this case, no amine additive is necessary due to the cyclic nature of the pyrazol-5-one nucleophile, generating only one stereoisomer upon tautomerization. The authors also noted a synergistic relationship between the chiral phosphoramidite ligand and BINOL-PA, with (*R*)-BINOL-PA and (*R*)-phosphoramidite ligand giving higher enantioselectivity than (*S*)-BINOL-PA and (*R*)-phosphoramidite ligand.

In 2017, the Shi group presented a related α -functionalization of pyrazol-5-ones, also enabled by CPA-palladium cooperative catalysis. For this work, the alcohol electrophiles were 2-indolylmethanols, and allylation occurred at the 3-position of the indole ring. The resulting allylated product underwent rapid isomerization to regenerate aromaticity, giving a formal arylation product. The scope of this reaction encompassed various substitutions on the indole ring as well as the pyrazol-5-one nucleophile. However, diaryl substitution at the 2-position of 2-indolylmethanol electrophiles is required.³²

Another innovative approach towards CPA and palladium co-catalytic enantioselective allylation was taken by the Ooi group in the synthesis of α -allyl benzofuran-2(3*H*)-ones (Scheme 6).³³ Rather than relying on ionic interactions between an anionic chiral phosphate and a cationic palladium intermediate, the authors instead utilized a cationic ammonium-phosphine hybrid ligand to facilitate ligand-phosphate ion-pairing. This strategy allows for modularity in reaction optimization as the ligand and chiral anion can be individually varied to probe multiple ionic pairing combinations. The authors were able to demonstrate these facile optimization tactics for different classes of allyl electrophiles. In subsequent publications, the group was also able to extend this type of reactivity to benzothiophen-2(3*H*)-ones and allyl electrophiles with substitution at the 2-position.^{34, 35} With 2,3-disubstituted allyl electrophiles, they were able to maintain the stereochemistry of the alkene in the resulting product by using a new CPA.

In 2016, the List group reported a breakthrough discovery in which they achieved direct α -allylation of ketones with either allylic carbonate or alcohol electrophiles using cooperative CPA and palladium catalysis. Interestingly, use of carbon dioxide gas catalytically enabled the incorporation of allyl moieties from simple allyl alcohol starting materials. Under their conditions, the authors demonstrated allylation of cyclic 6- and 5-membered ketones to form a series of products containing quaternary α -stereocenters with up to 94% yield and up to 96% *ee*. Furthermore, the newfound methodology was applied toward the enantioselective synthesis of (+)-crinane.³⁶ In a subsequent total synthesis of Stephadiamine by the Trauner group, this method was utilized to access a key intermediate with good enantioselectivity.³⁷

In a 2014 publication, Beller and coworkers reported allylation using racemic allyl alcohol electrophiles with amine nucleophiles rather than carbon-based nucleophiles, generating a series of enantioenriched allylamine products.³⁸ The use of a phosphoramidite ligand in conjunction with BINOL-PA resulted in both high regioselectivity and compatibility with a broad range of allyl alcohol electrophiles. Despite having very similar substituents on the allyl alcohol component, the authors observed almost complete regioselectivity, which they postulate arises from a rapid nucleophilic attack and slow isomerization of the allyl palladium(II) intermediate. The nucleophile scope, on the other hand, was somewhat limited in that an aryl substituent on the amine nucleophile was necessary to diminish basicity of the nitrogen, which would otherwise prevent CPA-mediated activation of the allyl electrophile.

Outside of more classical palladium(0)-catalyzed allylation reactions, there exist some examples of allylation reactions in which the palladium catalyst does not undergo any redox events and instead plays a modest role as a Lewis acid or isomerization catalyst. For instance, the List group in 2011 demonstrated the synthesis of allyl amines from allyl

imidates using an intramolecular palladium(II)-catalyzed enantioselective Overman rearrangement approach, whereby palladium acts as a π -Lewis acid (Scheme 8).³⁹ Previous methods to achieve the same transformation had utilized planar chiral palladium complexes to induce enantioselectivity. However, these methods are limited in the difficult synthesis of these complexes. List alternatively exhibited that high yield and enantioselectivity can be attained by the combination of a commercially available aryl palladium chloride dimer and the silver salt of (*S*)-TRIP. Although the palladium catalyst contains a chiral ligand, the authors found that exclusion of the CPA component lead to completely racemic product. They also observed a mild synergistic effect between chiral palladium catalyst and CPA.

In the examples examined thus far, the palladium catalyst and CPA have both been simultaneously involved in key steps of the catalytic cycle. However, the Murakami group has reported an enantioselective method toward synthesizing (*E*)- δ -boryl-substituted *anti*-homoallylic alcohols in which the palladium catalyst and CPA act independently in separate steps (Scheme 9).⁴⁰ In this work, an *in situ* generated palladium hydride species catalytically isomerizes a 1,1-di(boryl)alk-3-ene to the corresponding 1,1-di(boryl)alk-2-ene. This resulting allylic di(boryl) intermediate then undergoes enantioselective nucleophilic allyl addition to an aldehyde substrate as catalyzed by (*R*)-TRIP through a six-membered chair-like transition state. Although formation of the (*Z*)-product over the (*E*)-product is favored by this transition state, the (*Z*)-product can then be transformed *in situ* to the (*E*)-product via palladium-catalyzed isomerization. The authors note that nucleophilic addition of the (*Z*)-1,1-di(boryl)alk-2-ene is significantly slower than that of the (*E*)-isomer, therefore keeping the diastereoselectivity high. However, the (*Z*)-allyl di(boryl) isomer did not isomerize to the (*E*)-isomer over time, thus innately limiting the maximum yield of the desired product. Murakami's work demonstrates that palladium and CPA co-catalysis can enable enantioselective synthesis of valuable products without necessitating direct collaborative interactions between these two components. Along similar lines, the Gong group published the enantioselective synthesis of substituted 3-buten-1-ol products through the intermediacy of allyl boronic esters, which were in turn generated via borylation of an allyl-palladium species.⁴¹⁻⁴³ Interestingly, the allyl-palladium species could be accessed by a 1,2-migratory insertion of an aryl⁴¹/alkynyl⁴² group into a 1,3-diene or by use of an allyl alcohol⁴³ electrophile.

Palladium(0) and CPA co-catalyzed enantioselective allylation methodology has been a prolific and varied domain of chemistry. Despite tremendous success in expanding the allyl electrophile scope in many of these cases, there remains fundamental limitations in which nucleophiles are compatible with the currently available methods. Often, nucleophiles are required to breach a certain level of innate reactivity, stereocontrol, and hydrogen-bonding ability while remaining innocuous to deleterious interactions with either catalyst. Creative approaches in the near future may expand the scope of nucleophilic components to readily available and immediately valuable moieties.

(1B) Allylation via allylic C—H activation

Examples of enantioselective allylation reactions discussed thus far largely utilize allyl electrophiles such as allyl alcohols, amines, and carbonates. A contrasting but powerful

approach derives the desired allyl electrophile from an allylic C—H activation using palladium(II) as active catalyst in combination with an external oxidant. The first example of such an approach was presented by the Rainey group in 2012 toward the synthesis of enantioenriched spirocyclic indenenes (Scheme 10).⁴⁴ Initial enantioselective C—H activation at an allylic and benzylic position, facilitated by (*S*)-TRIP as ligand, gives rise to an enantioenriched π -allyl palladium intermediate. This intermediate then undergoes a semipinacol rearrangement, cleaving the cyclobutanol ring and forging the spirocyclic C—C bond of the product. Oxidation by 1,4-benzoquinone regenerates the initial palladium(II) active catalyst. The reaction was found to be tolerant of a wide range of substitutions on the cyclobutanol ring, but only one example of substitution on the indenyl ring was demonstrated. Upon performing kinetic isotope experiments, the authors found a primary kinetic isotope effect suggesting that the C—H activation step is rate limiting. Subsequent DFT computational studies were generated from the Sunoj group suggesting a Wacker-type mechanism with a palladium-*bis*-phosphate active catalyst.^{45, 46}

Following this discovery from the Rainey group, Gong and coworkers reported an intermolecular “cross-dehydrogenative coupling,” in which they intercept similar π -allyl palladium intermediates with α -aryl enamine nucleophiles generated *in situ* from α -aryl aldehydes and an amine additive (Scheme 11).⁴⁷ Formation of the π -allyl palladium species was favored by aryl and alkenyl substituents on the electrophilic component, which activate the C—H bond of interest. The authors postulate that the enantiodetermining nucleophilic attack of the π -allyl intermediate is facilitated by hydrogen bonding interactions between the phosphate ligand on palladium and the enamine N—H bond.

The Gong group then published a subsequent analogous transformation in which pyrazol-5-one nucleophiles are utilized in place of *in situ* generated enamines (Scheme 12).⁴⁸ The mechanistic pathway remains similar with a π -allyl electrophile being generated through C—H activation and a proposed hydrogen-bonding interaction between the pyrazol-5-one nucleophile and the palladium-bound CPA. Despite these parallels, the authors found that a chiral phosphoramidite ligand, in addition to a CPA additive, is necessary for high yield, regioselectivity, and enantioselectivity. Interestingly, a synergistic effect on enantioselectivity was observed between the phosphoramidite ligand and the CPA co-catalyst, where (*R*)-CPA with (*S*)-phosphoramidite ligand gave significantly higher yield and enantioselectivity than (*S*)-CPA paired with (*S*)-phosphoramidite. In this report, the electrophile scope was expanded beyond allyl arenes to include a series of 1,4-pentadiene electrophiles. However, this electrophile class did not require the use of CPA co-catalysts. Instead, a simple benzoic acid co-catalyst was utilized, and enantioselectivity for 1,4-pentadiene electrophiles originated entirely from the phosphoramidite ligand.

The Gong group later expanded their approach on using 1,4-dienes as electrophilic allyl coupling partners through a C—H activation step. In this example, the authors were able to use CPA and palladium co-catalysis with an amine additive to allylate aldehydes with an aryl and a methyl substituent at the α -position. A wide scope of substituents on the aromatic ring of the aldehyde and various 1,4-dienes were shown to be compatible. However, the type of 1,4-diene used had a great effect on the regioselectivity of the reaction.⁴⁹

In a preliminary example, the Gong group was able to trap the allyl palladium following C—H activation with a diboron reagent to give an allyl boronic ester intermediate.⁵⁰ This intermediate was then coupled diastereoselectively with an aldehyde using phosphoric acid catalysis. In one case, significant but low ee was obtained with (*S*)-TRIP. Two years later, the group was able to significantly improve the ee of this reaction, showing that the combination of a chiral allyl pinanediol boronic ester and an anthracenyl-substituted BINOL-PA was key, giving up to 98% ee.⁵¹

In a uniquely related publication, the Gong group demonstrated the ability to generate allyl electrophiles from internal alkynes using CPA and palladium co-catalysis. With the help of an amine additive, the authors showed that these electrophilic intermediates could be used to allylate a variety of α -disubstituted aldehydes enantioselectively. The authors propose that the allyl electrophile is access starting from a palladium hydride via oxidative addition of palladium(0) into the O—H bond of the CPA. This palladium hydride undergoes 1,2-migratory insertion into the alkyne coupling partner, generating a vinyl palladium species that generates an allene following β -hydride elimination. Reinsertion gives the desired π -allyl palladium intermediate.⁵²

The use of CPA and palladium(II) co-catalysis in cross dehydrogenative coupling reactions provides a unique variation to traditional allylation chemistry where the oxidation state at the allylic position is installed beforehand. However, because of the increased difficulty of a C—H activation as opposed to an allylic oxidative addition, compatible electrophiles are limited to those with aryl and alkenyl substituents to activate the desired C—H bond and aid in regioselectivity. Furthermore, avoidance of a pre-installed oxidation state necessitates the use of a terminal oxidant such as BQ when using nucleophilic coupling partners. These limitations in substrate scope, regioselectivity, and terminal oxidants remain a challenge to be overcome in the near future.

(2) Alkene Functionalization

While the use of CPA co-catalysts with palladium(II) as active catalyst in alkene functionalization has been slow to start, the field of palladium(0)-catalyzed alkene functionalization using CPA's as chiral anion phase transfer catalysts has been prolific within the last few years. The groups of Toste, Sigman, and Sunoj have pioneered this mode of reactivity, showing that combination of an insoluble aryl diazonium electrophile with CPA's as phase transfer reagents under palladium catalysis can lead to development of a diverse array of synthetically enabling enantioselective transformations.⁵³⁻⁵⁷

Although previous approaches to induce enantioselectivity focused on use of chiral ligands directly bound to the palladium center, Toste and coworkers provided groundbreaking findings of enantioinduction via a chiral phosphate anion in a 2015 publication (Scheme 13).⁵³ This report describes an enantioselective 1,1-arylborylation of allyl methyl carbonate and ethyl acrylate using aryl diazonium electrophiles and $B_2(\text{pin})_2$ as nucleophile following the catalytic cycle as shown in Scheme 13. A palladium(0) active catalyst first performs oxidative addition into an aryl diazonium that is rendered soluble via ion pairing with a CPA additive. The resulting aryl-palladium(II) species then undergoes 1,2-migratory insertion

into the alkene substrate, β -hydride elimination, and reinsertion to generate a benzylic cationic palladium(II) intermediate. Ion pairing between the cationic palladium intermediates and the anionic chiral phosphate leads to enantioinduction during these steps. Transmetalation and reductive elimination generate the corresponding arylborylation product and palladium(0) active catalyst. In the case of allyl methyl carbonate as substrate, an additional exogenous *m*-CF₃-dibenzylidene acetone (*m*-CF₃-dba) ligand was required for higher yields. The authors demonstrated compatibility with a variety of substituted aryl diazonium electrophiles but did not show any examples of electron-withdrawing substituents.

Using aryl boronic acids rather than B₂(pin)₂ as nucleophile, Sigman and Toste soon after reported an enantioselective palladium(0)-catalyzed 1,1-diarylation of benzyl acrylates via a similar chiral anion phase transfer approach (Scheme 14).⁵⁴ The authors performed detailed analysis on the characteristics of the chiral anion that affect enantioinduction through the use of multidimensional modeling. While calculations focusing on the ligand parameters alone revealed some insight, a study of the relationship between the nature of the benzyl group on the acrylate substrate and the reaction enantioselectivity provided an interesting pattern suggesting important non-covalent interactions (such as π -stacking) between the substrate and the CPA in the enantiodetermining step. The authors published a more detailed mechanistic study soon after.⁵⁵

In the subsequent year, Toste and Sunoj developed an enantioselective palladium(0)-catalyzed Heck-Matsuda arylation of five-, six-, and seven-membered cyclic alkenes (Scheme 15).⁵⁶ The strategy of enantioinduction remained analogous to previous publications, using an insoluble aryl diazonium electrophile and a chiral phosphoric acid phase transfer catalyst. However, the authors noted that basicity of the phosphoric acid co-catalyst played an important role in preventing isomerization of some substrate classes. In cases where isomerization was problematic, a binaphthyl diamine (BINAM) phosphoric acid backbone was utilized to increase basicity of the chiral anion, thus promoting reductive elimination of any palladium(II)-hydride intermediates that may otherwise participate in isomerization of leftover starting material. The authors were able to perform density functional theory calculations to support this claim, showing that the reductive elimination transition state is indeed lower in energy with a BINAM-derived phosphoric acid than a BINOL-derived phosphoric acid. Further computational studies were performed and reported in late 2018 by Sunoj and Toste, specifically focusing on the effects of the BINAM-derived phosphoric acid co-catalyst on enantioinduction.⁵⁷ These experiments highlight key noncovalent interactions between the aryl substituents on the BINAM-CPA nitrogen atoms and the substrate during the enantiodetermining 1,2-migratory insertion. Using these calculated transition states, the authors demonstrated the ability to roughly predict the enantiomeric excess corresponding to different BINAM-CPA's with varying nitrogen aryl substituents.

The delicate interplay between palladium and CPA's through a solely ionic interaction to induce enantioselectivity has been a very recent and distinctively lucrative extension to the original field of palladium and CPA co-catalysis. One can imagine that such an approach would greatly multiply ligand combination parameters in high throughput experimentation

as well as enable enantioinduction in cases where the proposed ligand coordination or ligand type is not compatible with the desired transformation. There is no doubt that this specific area and the use of chiral counterions with transition metal catalysis in general will thrive in the near future.

Although a chiral anion phase transfer strategy has shown incredible progress in alkene functionalization, concurrent work from the Bäckvall group demonstrated the potential of palladium(II) active catalysts in intramolecular oxidative carbocyclization of enallenes. In their first report on enantioinduction in this area via CPA's, they achieved carboborylation of an allene-tethered alkene by using $B_2(\text{pin})_2$ and a biphenol-derived CPA (Scheme 16).⁵⁸ Mechanistically, a vinyl palladium species is first formed from nucleophilic attack by the disubstituted allene onto the palladium center. This vinyl palladium then undergoes an enantioselective 1,2-migratory insertion as controlled by the CPA ligand. Following migratory insertion, transmetalation with $B_2(\text{pin})_2$ and reductive elimination give the desired enantioenriched borylated carbocycle product. Oxidation of the resulting palladium(0) with 1,4-benzoquinone regenerates the active catalyst. Due to these oxidative conditions, CPA's stand out as a preferred ligand class due to their resilience toward decomposition by oxidative pathways. The authors demonstrated a wide scope of various substitutions on the enallene substrate, but noted that terminal disubstitution of the allene was necessary for good yields and enantioselectivity.

In later work from Bäckvall, a similar vinyl palladium species was intercepted instead with a 1,1-migratory insertion by CO to give an acyl palladium species (Scheme 17).⁵⁹ Using a VAPOL-derived CPA, the authors were able to induce enantioselectivity in the following 1,2-migratory insertion into the tethered alkene. The resulting alkyl palladium intermediate is then captured again by a 1,1-migratory insertion by CO, and the ensuing acyl palladium species then undergoes coupling with a terminal alkyne through coordination and reductive elimination. Again, oxidation by 1,4-benzoquinone regenerates active palladium(II) catalyst. As observed previously, a variety of substitutions were tolerated, but terminal disubstitution of the allene was required for good yield and enantioselectivity. This expansion of the group's previous chemistry allows rapid synthesis of a series of complex diones with enantioenriched α -stereocenters.

Another recent manner of alkene functionalization in which CPA and palladium co-catalysis has been shown to be promising is in Wacker-type reactivity. In this mode, binding of the alkene π -electrons to a palladium(II) center increases the electrophilic nature of a typically unreactive alkene, facilitating a nucleopalladation event to initiate functionalization of the substrate of interest. Although enantioselective variants of Wacker-like reactions have been developed,⁶⁰⁻⁶² only a handful of examples exist thus far using chiral phosphoric acid catalysis to beget enantioselectivity. One of the first instances of such a transformation originated from the Gong group, where (*S*)-TRIP and a Quinox ligand were used in an intramolecular aminopalladation followed by Heck reaction to give fused 6,5-bicyclic heterocycle products.⁶³ Another case of enantioselective intramolecular Wacker-type reactivity arose from the Zheng group soon after.⁶⁴ Using (*R*)-STRIP as the CPA, the authors demonstrated the synthesis of dihydrofurans via desymmetrization of allenic diols. One of the more recent examples of intramolecular Wacker comes from the Zhu group, in

which 1,4-cyclohexadiene substrates with tethered sulfonamides are desymmetrized via an aza-Wacker using a chiral pyrox ligand in conjunction with a biaryl CPA.⁶⁵ The authors apply their newly developed methodology to the enantioselective syntheses of (–)-mesembrane and (+)-crinane. In work from the Engle and Liu groups, prochiral carbon-based azlactone nucleophiles undergo intermolecular palladium(II)-catalyzed outer sphere nucleopalladation with unactivated alkene substrates to generate α -quaternary amino acid products as directed by a tethered 8-aminoquinoline (AQ) amide (Scheme 18).⁶⁶ Enantioselectivity arises from the use of a catalytic amount of a BINOL-derived phosphoric acid with sterically encumbering substituted aryl groups at the 3- and 3'-positions. The authors did not observe any nonlinear effects, supporting a 1:1 ratio of palladium to CPA in the enantiodetermining step. Further density functional theory calculations suggest the protodepalladation step to be rate limiting and enantiodetermining due to the reversible nature of the nucleopalladation step. The 8-aminoquinoline group allowed a series of diversifications based on previously established C—H activation chemistry and was easily deprotected to the corresponding methyl ester or free carboxylic acid.

c) C—H Activation

Due to the resemblance of chiral phosphoric acid and amide ligands to carboxylic acid ligands in terms of structure, binding, and acidity, the field of palladium-catalyzed C—H activation has successfully employed CPA's toward enantioselective C—H carbofunctionalization in a variety of systems. Although many of these examples utilized tethered directing groups to bring the active palladium(II)-catalyst into proximity of the C—H bond of interest, allowing a more facile CMD step, a few early examples in the realm of C—H activation instead solved the issue of proximity by tethering the electrophilic coupling partner and relying on the intramolecular nature of the subsequent C—H activation to favor formation of the desired product. For example, Duan and coworkers reported an enantioselective intramolecular C—H arylation of achiral ferrocenyl starting materials to generate planar chiral ferrocenyl products using an aryl bromide substituent off one of the cyclopentadienyl ligands as an intramolecular electrophile.⁶⁷ Previous approaches to the synthesis of this class of compounds employed a chiral BINAP ligand to induce enantioselectivity. However, Duan was able to achieve enantioinduction in his work via combination of an achiral monophosphine ligand and a simple BINOL-derived CPA. The authors were also able to demonstrate synthesis of substituted indoline products with moderate enantioselectivity under similar reaction conditions starting with protected *N*-alkyl ortho bromo aniline starting materials.

In the following year, the Baudoin group also reported a comparable method to enantioselectively synthesize indolines with tri- and tetra-substituted stereocenters using tricyclohexyl phosphine as achiral ligand and a BINOL-derived CPA with electron-poor aryl substituents at the 3- and 3'-positions (Scheme 20).⁶⁸ Again, a tethered aryl bromide electrophile enabled the intramolecular C—H activation of a methyl group on the *N*-alkyl substituent. The two examples described here represent, so far, the sparse nature of this approach toward CPA-palladium co-catalysis in C—H activation. Though this approach may be revisited in the future, inherent limitations lie in the difficulty of synthesis of such a class of substrates with tethered electrophiles.

A much more expansive scope of substrates and products can be accommodated using tethered directing groups with CPA's in enantioselective palladium(II)-catalyzed C—H activation chemistry. Seminal work from the Duan group showcases the ability to perform enantioselective C(sp³)—H arylation of aliphatic amides as directed by 8-aminoquinoline with simple BINOL-derived phosphoric acid and amide co-catalysts (Scheme 21).⁶⁹ The reaction can achieve up to 82% ee and is most compatible with substrates containing an aryl group at the β-position, which is the site of the C—H activation. The authors found that the rate of the reaction is increased the most with the phosphoric amide additive and is significantly increased with the phosphoric acid additive. The observation of a kinetic isotope effect of 3.9 suggests the C—H activation step to be rate-limiting. The authors propose that the phosphoric amide/acid is bound to palladium prior to the C—H activation step and imparts enantioselectivity via a concerted metalation-deprotonation (CMD) mechanism.

Soon after publication of Duan's original work, the Chen group reported an enantioselective palladium(II)-catalyzed γ-arylation of benzylic C(sp³)—H bonds in aliphatic tertiary amine substrates with a bidentate picolinamide (PA) directing group (Scheme 22).⁷⁰ Using the same simple BINOL-PA catalyst, they were able to achieve up to 97% ee, but observed high sensitivity to steric encumbrance from the aryl iodide component. Interestingly, nonlinear effects were observed in this case, suggesting that more than one CPA participates in the enantioselective C—H activation step. From this information and the observed dependence of reaction yield and enantioselectivity on the cesium cation in their cesium carbonate base, the authors surmised that a cesium phosphate complex may play an important role in C—H activation under these conditions.

In the year following Chen's publication, the Yu group demonstrated that an oxidative enantioselective α-arylation of saturated aza-heterocycles with a monodentate thioamide directing group is also possible (Scheme 23).⁷¹ Aryl and methyl boronic acid coupling partners were employed with 1,4-benzoquinone as the terminal oxidant to regenerate palladium(II) for the desired C—H activation. The ideal CPA was found to be BINOL-derived with anthracenyl substituents at the 3- and 3'-positions, giving up to 98% ee. The method was shown to be extremely versatile, tolerating a variety of aza-heterocycles such as pyrrolidine, piperidine, azepane, azetidine, indoline, and tetrahydroisoquinoline derivatives. Furthermore, dialkyl acyclic amine substrates were also compatible with good to high enantioselectivities and moderate yields. Notably, the aryl boronic acid scope was equally varied in terms of steric and electronic characteristics.

Directly following this series of publications, Gaunt and coworkers reported an enantioselective intramolecular oxidative C—H amination of morpholinones (X = O) and piperazinones (X = NR²) to give the corresponding aziridine products using (*R*)-TRIP as CPA co-catalyst (Scheme 24).⁷² The authors observed that high concentrations of acetate lead to dramatically lower enantioselectivity, while excluding acetate lead to low yields. Based on this data, they hypothesized that the racemic background reaction requires two acetate ligands on palladium, while the desired enantioselective C—H activation occurs with one acetate and one chiral phosphate ligand. The proposed C—H activation pathway is closely modeled to their previous work on the racemic reaction, in which there exists a key

hydrogen-bonding interaction between the free N—H of the substrate and the carbonyl of either the chiral phosphate ligand or the acetate ligand. This interaction, along with binding of the nitrogen lone pair to palladium, brings the metal center into close proximity of the C—H bond of interest, facilitating the desired C—H cleavage. Interestingly, the authors also note a linear correlation between enantioselectivity, or log (e.r.), and the Hammett σ constant of the aryl substituent on the amide nitrogen of piperazinone substrates. When the aryl substituents were more electron-withdrawing, the corresponding products were formed with higher enantioselectivity. Although these results were intriguing, the authors did not provide a mechanistic explanation as to how these trends arose.

A follow-up mechanistic study via density functional theory calculations was published by Zhang, in which the acetate ligand was found to participate in the C—H activation in a CMD fashion while the chiral phosphate ligand took part in the key hydrogen-bonding interaction with the free N—H of the substrate.⁷³ This differentiation in ligand roles was explained by the difference in Brønsted basicity between the more basic acetate and the less basic phosphate.

Although the reports by Duan and Chen discussed above represented significant steps forward in achieving enantioselective arylation of benzylic C(sp³)—H bonds in acyclic substrates, the difficulty of the C—H activation step on completely unactivated methylene C(sp³)—H bonds lead to a significant decrease in enantioselectivity when applied toward substrates with simple alkyl rather than aryl substituents at the β -position. Previous pioneering studies in unactivated enantioselective methylene C—H activation have utilized acetyl-protected aminoethyl quinoline ligands and electron-deficient amide directing groups to enable enantioselective C—H arylation.⁷⁴ Interested in developing an enantioselective method toward arylating completely unbiased C(sp³)—H bonds, the Shi group discovered in 2018 that such a transformation could be achieved by use of a 2-pyridinylisopropyl (PIP) amide auxiliary in conjunction with a non-C₂-symmetric BINOL-derived CPA ligand.⁷⁵ Shi's group also performed kinetic isotope effect experiments and found a k_H/k_D value of 2.1, suggesting that the C—H activation may be rate-limiting. A lack of a nonlinear effect supports the presence of only one CPA ligand in the enantiodetermining step. A very recent report from Lan, Lin, and Shi demonstrates enantioselective aryl C—H olefination using biaryl quinoline substrates and an (*R*)-STRIP CPA.⁷⁶

The introduction of CPA's with palladium catalysis has provided a creative and prolific approach to the problem of enantioselective C—H activation, offering a valuable workaround especially in cases where an achiral bidentate directing group is required. Though the methods developed thus far are significantly enabling, future goals include access to different types of C—H bonds regio- and enantioselectively, the use of simpler or more versatile directing groups, and expansion of functionalization diversity.

3) Miscellaneous

Naturally, the broad applicability of palladium and CPA co-catalysis has led to the development of a handful of unique reactivity manifolds that cannot be securely classified under any of the traditional three categories of alkene functionalization, C—H activation, or

allylation. Thus, these innovative examples will be discussed in a broader miscellaneous section.

The first method, developed by the Yao group,⁷⁷ is most closely related to List's work with the enantioselective Overman rearrangement (Scheme 26). Here, palladium(II) is again used as a π -Lewis acid through a redox-neutral catalytic cycle to generate an isochromenylium intermediate via intramolecular nucleopalladation of *ortho*-alkynylbenzaldehydes and ketones. These reactive intermediates then undergo a hetero-Diels-Alder reaction where stereocontrol arises from proposed hydrogen bonding interactions with the CPA ligand and the *ortho*-vinyl phenol dienophile. Intramolecular displacement of the oxonium with the phenolic oxygen followed by protodepalladation gives a complex bridged bicyclic product with multiple contiguous stereocenters. The authors found that electron withdrawing substituents on the central aryl ring of the *ortho*-alkynylbenzaldehyde or ketone substrate lead to diminished enantioselectivity and that the (*Z*)-isomer of the dienophile was non-reactive, instead preferring to isomerize to the (*E*)-isomer before engaging in the hetero-Diels-Alder step.

In the same year, Hu and coworkers reported an enantioselective three component conjunctive coupling between a free pyrrole, aryl diazoesters, and aryl imines enabled by a palladium(II) catalyst and a CPA ligand (Scheme 27).⁷⁸ The reaction is initiated by the formation of a palladium carbene from the aryl diazoester component, which then undergoes nucleophilic attack by the free pyrrole. Trapping of the resulting palladium enolate with the electrophilic aryl imine yields a product with two highly substituted contiguous stereocenters. Stereochemical control of this step arises from various hydrogen bonding interactions between the CPA ligand and the pyrrole and/or imine. Although the authors initially used (*R*)-TRIP as CPA ligand, they found that the opposite diastereoselectivity could be achieved by employing a BINOL-derived phosphoric acid with triphenyl silyl substituents at the 3- and 3'-positions along with (+)-tartaric acid additive. Therefore, by varying the absolute stereochemistry and type of CPA used, one could access enantioenriched samples of all four possible stereoisomers of the pyrrole derivative products.

These outstanding examples may be few in number at the time of our survey, but they provide innovative platforms for expanding the synthetic capability of CPA and palladium co-catalysis. As the field of organic chemistry matures, we will no doubt encounter novel manifolds of reactivity that bring with them previously unfamiliar obstacles to achieving the desired reactivity, chemoselectivity, regioselectivity, and/or enantioselectivity. By keeping the unique benefits and mechanistic capabilities of CPA/palladium co-catalysis in mind, we will continue to apply this cooperative approach in maneuvering over present and future chemical hurdles.

Although the field of CPA and palladium co-catalysis has been proliferative, there remain some inherent difficulties in the application of this synthetic tactic. A major obstacle lies in the inconvenience of CPA synthesis and derivatization. Coupled with the fact that only a handful of CPAs are commercially available, this issue of co-catalyst accessibility currently hampers research toward synthetically useful methodology. Furthermore, despite efforts to further the understanding of the mechanisms of reactivity and enantioinduction, there

remains a lack of predictive power in selecting and synthesizing CPAs effectively for a given transformation. Lastly, the intricacies of CPA and palladium co-catalysis presently force restrictions on compatible reaction conditions (e.g. solvent polarity). Resolving any of these issues will significantly accelerate development of the field.

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Scheme 1.
Various roles of CPA with palladium catalysis.

Scheme 2.
Hydrocarboxylation of styrenes by Alper (1990)

Scheme 3.
 α -Allylation of aldehydes with allyl amines by List (2007)

Scheme 4.

α -Allylation of aldehydes with allyl alcohols by List (2011)

Scheme 5.

α -Allylation of pyrazol-5-ones with allyl alcohols by Gong (2013)

Scheme 6.

α-Allylation of benzofuran-2(3*H*)-ones with allyl carbonate esters by Ooi (2013)

Scheme 7.
Amination of racemic allyl alcohols by Beller (2014)

Scheme 8.
Palladium(II)-catalyzed Overman rearrangement by List (2011)

Scheme 9.

Synthesis of (*E*)- δ -boryl-substituted *anti*-homoallylic alcohols by Murakami (2017)

Scheme 10.
Synthesis of spirocyclic rings via C—H activation and semipinacol rearrangement by Rainey (2012)

Scheme 11.

Oxidative cross dehydrogenative coupling for α -allylation of aldehydes with alkenes by Gong (2014)

Scheme 12.

Oxidative cross dehydrogenative coupling for α -allylation of pyrazol-5-ones with alkenes by Gong (2016)

Scheme 13.
 1, 1-Arylborylation of alkenes by Toste (2015)

Scheme 14.

1, 1-Diarylation of acrylates by Sigman and Toste (2016)

Scheme 15.
Heck-Matsuda arylation of cyclic alkenes by Toste and Sunoj (2017)

Scheme 16.
Carbocyclization-borylation of enallenes by Bäckvall (2015)

Scheme 17.
Carbonylative carbocyclization and cross dehydrogenative coupling of enallenes by Bäckvall (2017)

Scheme 18.

Alkylation of azalactones with nonconjugated alkenes by Engle (2019)

Scheme 19.

Synthesis of planar chiral ferrocenes and indolines by Duan (2016)

Scheme 20.
Synthesis of indolines by Baudoin (2017)

Scheme 21. Arylation of C(sp³)—H bonds of aliphatic amides by Duan (2015)

Scheme 22. Arylation of $\text{C}(\text{sp}^3)\text{—H}$ bonds of aliphatic amines by Chen (2016)

Scheme 23. α -Arylation/methylation of thioamides by Yu (2017)

Scheme 24.

C—H activation and aziridination of aliphatic amines by Gaunt (2017)

Scheme 25. Arylation of unactivated C(sp³)–H bonds of aliphatic amides by Shi (2018)

Scheme 26.
Oxa-Diels-Alder of *in situ* generated isochromenyliums by Yao (2013)

Scheme 27.

Three-component reaction of pyrroles, diazoesters, and imines by Hu (2013)