Transition Metal Complexes with C-Stereogenic Alkyl Ligands and P-Stereogenic Analogues: Synthesis, Configurational Stability, Stereochemistry of Fundamental Transformations, and Intermediacy in Catalysis

David S. Glueck*

6128 Burke Laboratory

Department of Chemistry

Dartmouth College

Hanover, New Hampshire, 03755, United States

*glueck@dartmouth.edu

Contents

Keywords C-stereogenic, P-stereogenic, metal alkyl, stereochemistry, configurational stability, asymmetric catalysis

Word count: 13,156 words

Abstract

Enantiomerically or diastereomerically enriched transition metal complexes bearing formally anionic, sp^3-hybridized, C-stereogenic alkyl ligands ([M]-R*) are historically important for applications in determining the stereochemistry of fundamental steps in organometallic chemistry; isoelectronic P-stereogenic analogues ([M]-P*) have been studied more recently. These complexes are key intermediates in asymmetric catalysis, and the stereochemistry of their formation and reactions controls stereoselectivity. Understanding these processes with chiral catalysts may enable rational design of asymmetric transformations. This review covers their chemistry, including preparation by resolution or asymmetric synthesis (controlled by chiral substrates or chiral ligands), configurational stability, the stereochemistry of fundamental transformations, and their role in catalysis.

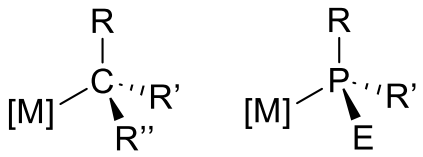
1. Introduction

1.1 Why?

This review covers enantiomerically or diastereomerically enriched transition metal complexes bearing formally anionic, sp^3-hybridized, C-stereogenic alkyl ligands, abbreviated here as [M]-R* (Scheme 1, left). This class of compounds is historically important for its applications in determining the stereochemistry of fundamental steps in organometallic chemistry, such as oxidative addition/reductive elimination and migratory insertion. As noted by Whitesides, "The most valuable single type of information to have in characterizing the mechanism of a reaction that makes or breaks bonds at a tetrahedral carbon atom is the stereochemistry of the transformation at that carbon."[1] The S_N1 and S_N2 substitutions are classic examples in organic chemistry; progress in this area for organometallics was reviewed by Flood[2] in 1981 and, in part,

by Malinakova[3] in 2004; this manuscript includes more recent examples. In asymmetric catalysis, [M]-R* complexes are key intermediates and the stereochemistry of their formation and reactions controls stereoselectivity. Understanding these processes with chiral catalysts may enable rational design of asymmetric transformations.

Scheme 1. Transition Metal Complexes with C-Stereogenic Alkyl Ligands and Their P-Stereogenic Analogues



To complement study in these well-established areas, more recent work has investigated P-stereogenic analogues (Scheme 1, right). In addition to two anionic substituents (R,R' = H, alkyl/aryl, halide, alkoxide, etc.) these "carbon copies"[4] also include a group (E = O, S, BH_3) which gives them a formal negative charge and distinguishes their chemistry from the more common phosphine ligands, PR_3.

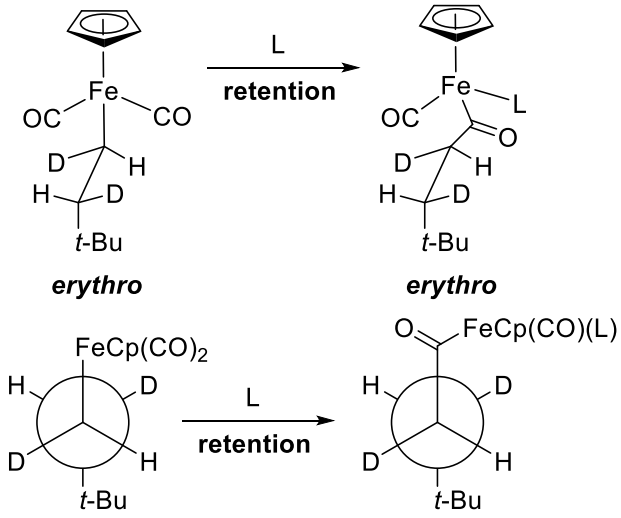
1.2 Scope of this review

This review focuses on transition metal complexes which have been isolated or observed spectroscopically, omitting studies where the stereochemistry of catalytic or stoichiometric transformations of a chiral substrate is used to infer details about the process.[5] Main group [M]-R* complexes, for example of Mg or Li, appear only when used for transmetalation to transition metals. These extensively studied organometallics, however, are useful in asymmetric synthesis and stereochemical studies, as described in multiple reviews.[6] Although complexes with other chiral hydrocarbyl ligands are known, the focus here is on simple alkyls, leaving out π-allyl,[7] atropisomeric,[8] and planar-chiral examples.[9] In most cases, the R* group is enantiomerically

enriched, but diastereomeric mixtures sometimes also provide valuable information, as described below.

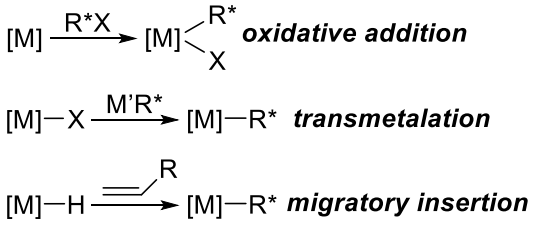
Although not covered here, one such approach deserves special mention. Whitesides developed an NMR method to determine the stereochemistry of reactions which formed or destroyed [M]-R* bonds.[1] It relies on the magnitude of H-H coupling in *threo* and *erythro* isomers of specifically deuterium-labeled organometallics. Scheme 2 shows an example, where migratory insertion was shown to proceed with retention of configuration at carbon, since the *erythro* starting material was converted to an *erythro* product, in which H and D remained *syn* to each other. Newman projections are often used to illustrate these processes. Since its introduction in 1974, this approach has been applied in more than 100 papers, which are accessible from citations of reference 1.

Scheme 2. Example of the Whitesides NMR Method for Determining the Stereochemistry of Reactions at Metal-Carbon Bonds



2. Synthesis [M]-R* complexes may be prepared by the standard methods used for other organometallics. Scheme 3 shows some of the most common approaches. Oxidative addition of an enantiomerically enriched chiral substrate R*X gives a C-stereogenic ligand. X is commonly a halide or related leaving group, but examples of C-H, C-C, or C-P oxidative addition are also known. Transmetalation, often from a main group organometallic [M']-R*, may transfer enantiomerically enriched R* with complete retention or inversion of configuration. However, configurational instability of the main group and/or transition metal alkyls (see section 3 below) provides the opportunity for asymmetric induction in this step. Finally, migratory insertion of an alkene into a M-H bond, with appropriate regiochemistry, may also yield [M]-R* groups in a process often seen in asymmetric catalysis.

Scheme 3. Synthesis of Transition Metal Complexes with C-Stereogenic Alkyl Ligands

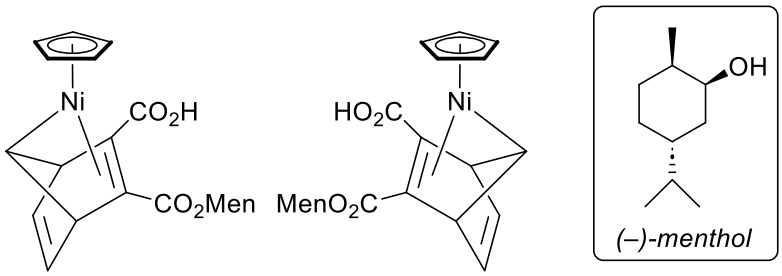


2.1 Resolution

Instead of starting with an enantiomerically enriched substrate, a more general approach to [M]-R* complexes is resolution, often using reagents derived from the chiral pool. Ideally, separation of the resulting diastereomers gives them both in high yield and purity, and the resolving agent can be removed from the products without erosion of enantiopurity and recovered. In practice, resolution often requires trial and error, and it is often challenging to accomplish all these goals.[10]

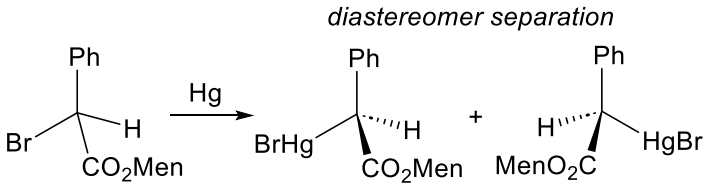
Scheme 4 shows an early example, in which diastereomeric Ni-alkyls were partially separated by recrystallization of their menthyl esters.[11]

Scheme 4. Diastereomeric Chiral Nickel Alkyls Bearing a Pendant Menthyl Ester



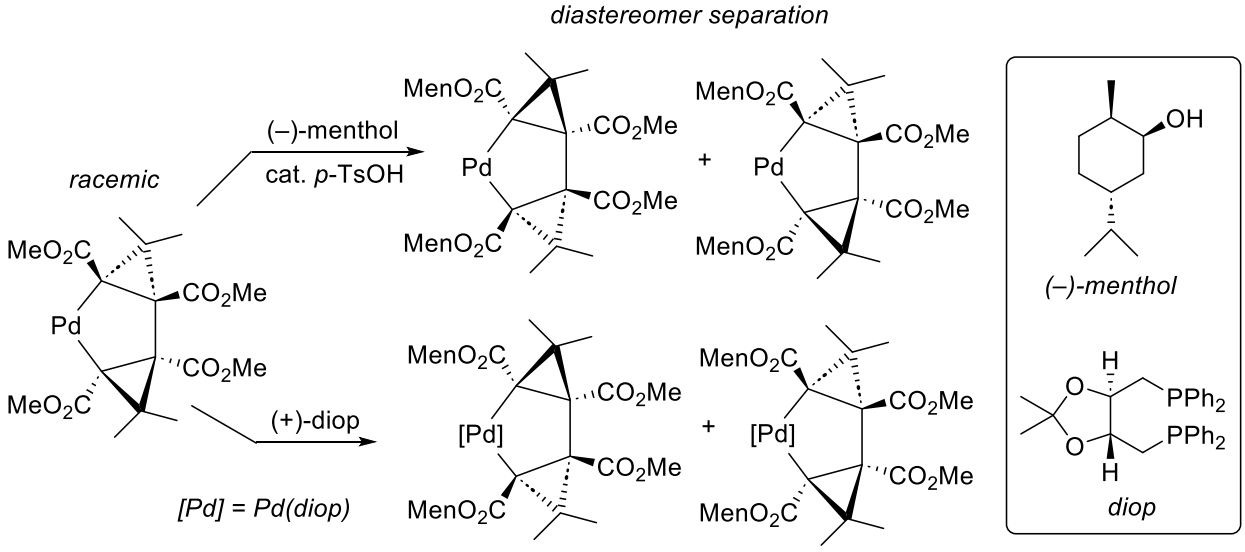
Similarly, oxidative addition of a diastereomeric mixture of alkyl bromides bearing a menthyl ester substituent to mercury metal gave separable [Hg]-R* diastereomers (Scheme 5).[12]

Scheme 5. Synthesis and Diastereomer Separation of Chiral Organomercury Complexes Bearing a Pendant Menthyl Ester



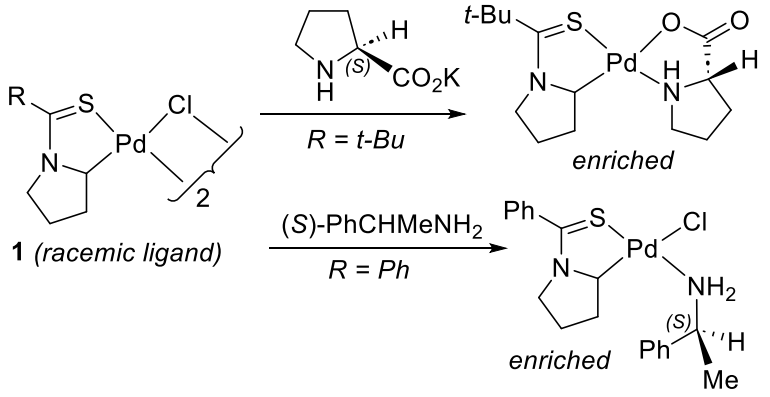
The tricyclic palladacycles in Scheme 6 formed polymeric aggregates but are shown as monomers for simplicity. As in Schemes 4-5, preparation of menthyl esters, here by transesterification, gave separable diastereomers.[13] A similar resolution was accomplished using the chiral bis(phosphine) diop.[14]

Scheme 6. Resolution of Chiral Palladacycles Using Menthol or Bis(phosphine) Chiral Auxiliaries



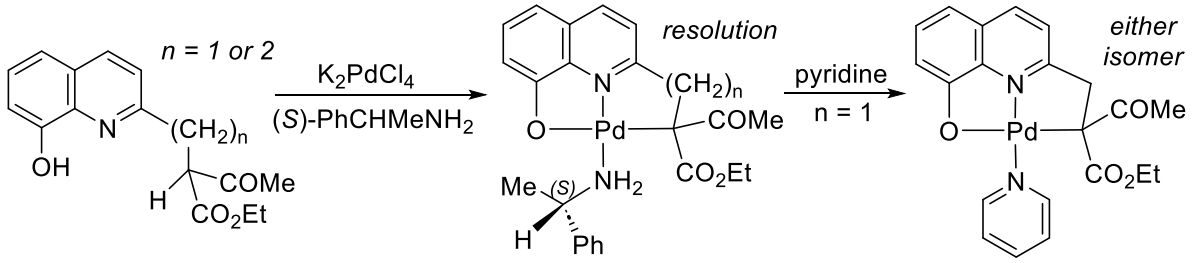
Chiral amines and amino acids are often used as resolving agents for [M]-R* complexes because of their low cost, structural diversity, and ready removal with acid. For example, Scheme 7 shows resolution of palladacycles with the readily available $PhCHMeNH_2$ or a proline derivative.[15,16] Note: depending on the relative orientation of the bidentate ligands, dinuclear Cl-bridged palladacycles like **1** can exist as *cis* or *trans* isomers, which may interconvert in solution,[17] and their structures have not been determined in some cases. To reflect this ambiguity, this common motif (see also Schemes 9-12 and 16 below) is drawn in this review as a generic dimer, except in cases where the geometry is known.

Scheme 7. Resolution of Palladacycles Using a Chiral Amine or Amino Acid



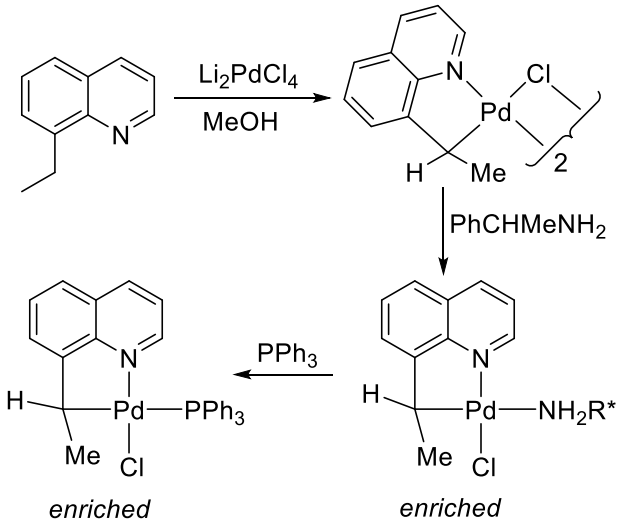
Similarly, cyclopalladation of a quinoline-phenol gave chiral amine adducts (Scheme 8).[18] For n = 1, after separation of the diastereomers, the chiral amine could be replaced with pyridine.

Scheme 8. Resolution of a Quinoline-Derived Palladacycle with a Chiral Amine



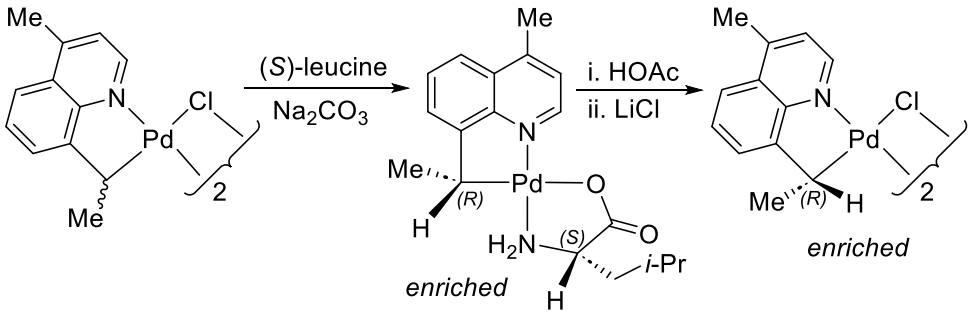
A 1972 report of direct cyclopalladation of ethylquinoline with Li_2PdCl_4 (Scheme 9) was later claimed to be irreproducible.[19] Nevertheless, resolution of the resulting Cl-bridged dimer with $PhCHMeNH_2$ enabled isolation of enantioenriched adducts. Replacement of the chiral amine with PPh_3 gave another optically active derivative.[20]

Scheme 9. Resolution of an Ethylquinoline-Derived Palladacycle with a Chiral Amine



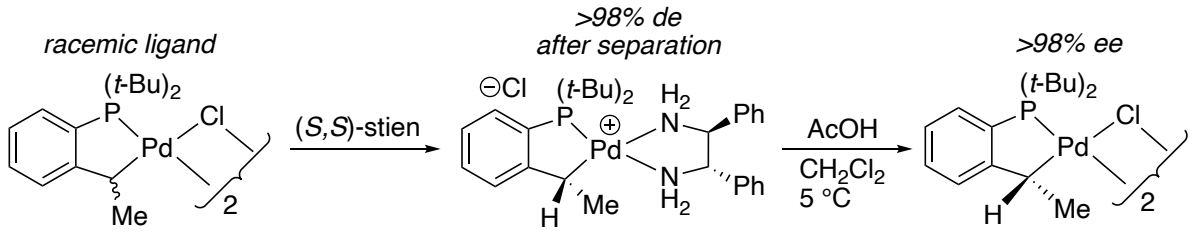
Related palladacycles formed from ethylquinoline were resolved using the amino acid *S*-leucine to give both diastereomers in about 90% de. Scheme 10 shows an example where the resolving agent could be removed with acetic acid.[21]

Scheme 10. Resolution of a Chiral Ethylquinoline-Derived Palladacycle Using an Amino Acid



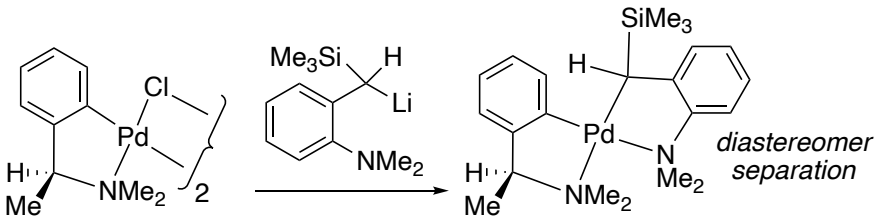
Scheme 11 shows a related resolution with a chiral diamine. The product was thermally stable (110 °C, 3 h, no epimerization), but attempted amine removal with HCl caused some loss of enantiopurity. However, using acetic acid at lower temperature avoided this problem.[22]

Scheme 11. Resolution of a Chiral Palladacycle Using a Chiral Diamine



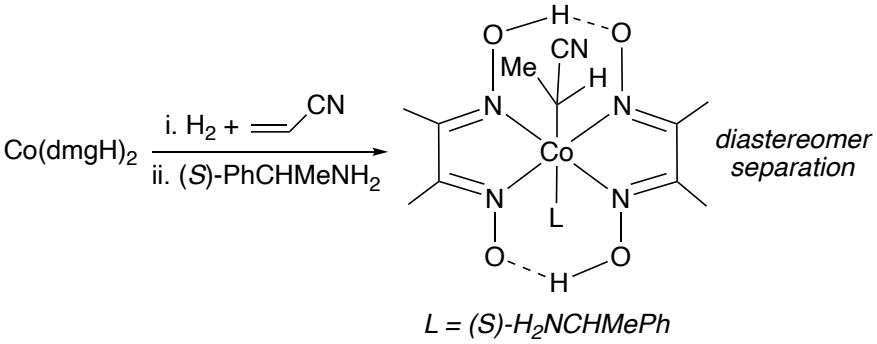
In a variation of this approach, transmetalation of a chiral (racemic) organolithium to a chiral amine-palladacycle gave diastereomers which were separated by recrystallization (Scheme 12).[19]

Scheme 12. Formation of Diastereomeric Palladacycles by Transmetalation from Lithium



Resolutions with chiral amines are not restricted to [Pd]-R* complexes. Scheme 13 shows a related process in cobaloxime complexes, where a chiral Co-alkyl group was generated from hydrogen and an alkene.[23]

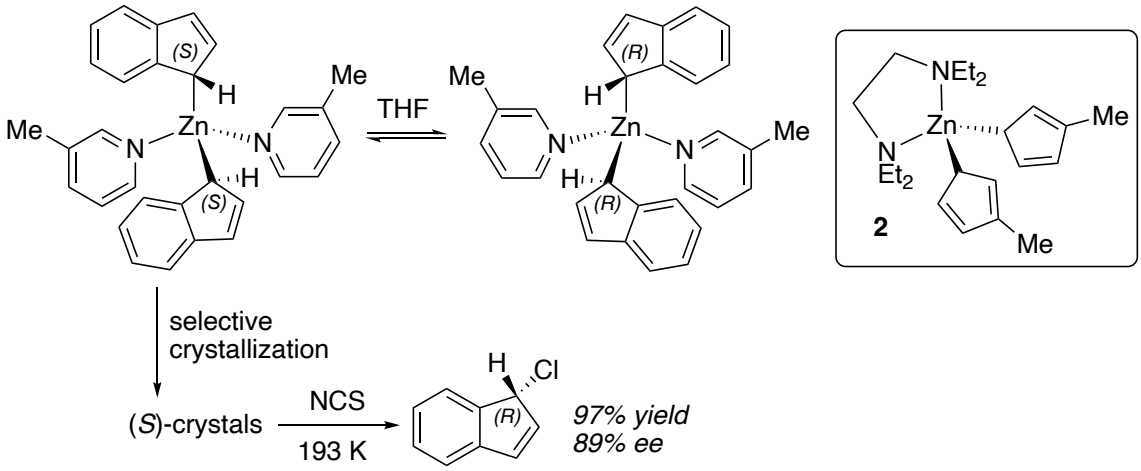
Scheme 13. Synthesis of Chiral Cobalt Alkyls from Hydrogen and Acrylonitrile and Their Resolution Using a Chiral Amine



2.2 Absolute asymmetric synthesis

Resolution provides at most a 50% yield of one enantiomer. In an unusual but attractive approach, some racemic compounds which crystallize in a chiral space group form enantiomerically pure crystals. This "absolute asymmetric synthesis" has been discovered only by trial and error, but when successful it provides [M]-R* complexes without requiring any chiral material. For example (Scheme 14), the bis-picoline adduct of bis-indenyl zinc crystallized in high enantiomeric excess and could then be halogenated with high ee.[24] Similarly, spontaneous resolution of bis-MeCp complex **2** also occurred, giving enantiomerically pure crystals.[25]

Scheme 14. Absolute Asymmetric Synthesis of a Chiral Organozinc Reagent and its Stereoselective Halogenation



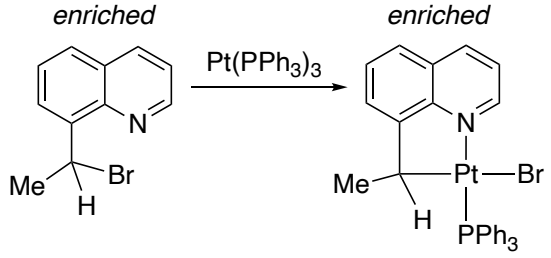
2.3 Chiral substrates

[M]-R* groups may be prepared directly from chiral substrates by oxidative addition of enantiomerically enriched R*X, where X = halide or H, by selective activation of one hydrogen in a CH_2 group, or by other methods.

2.3.1 Oxidative addition

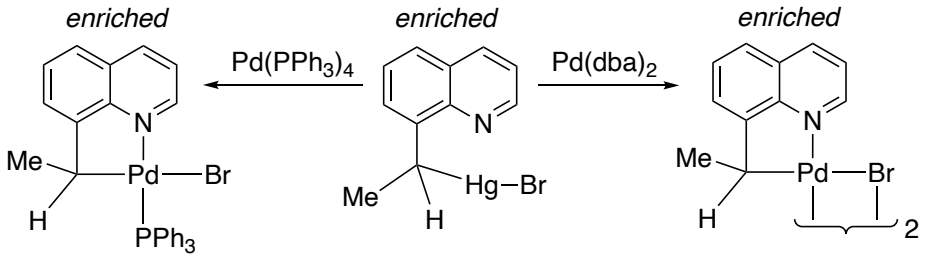
Oxidative addition of an enantiomerically enriched quinoline derivative to Pt(0) gave a platinacycle whose regiochemistry was not reported; Scheme 15 shows one possible regioisomer. On the basis of optical activity measurements, inversion of configuration at carbon was claimed. However, as acknowledged in the paper, the authors were not able to gauge the extent of stereoselection or the absolute configurations of the reactants and products.[26]

Scheme 15. Synthesis of a Chiral Platinacycle by Oxidative Addition of a Chiral Quinoline Alkyl Bromide Derivative



Related palladacycles were prepared from an enantiomerically enriched organomercury complex, which was resolved using camphorsulfonic acid. After Hg-Br oxidative addition to Pd(0), yielding a Pd-Hg bond, "redox transmetalation" gave Pd(II) complexes (Scheme 16). The enantiopurity of the reagents and products, studied by optical rotation measurements, was not quantified.[27]

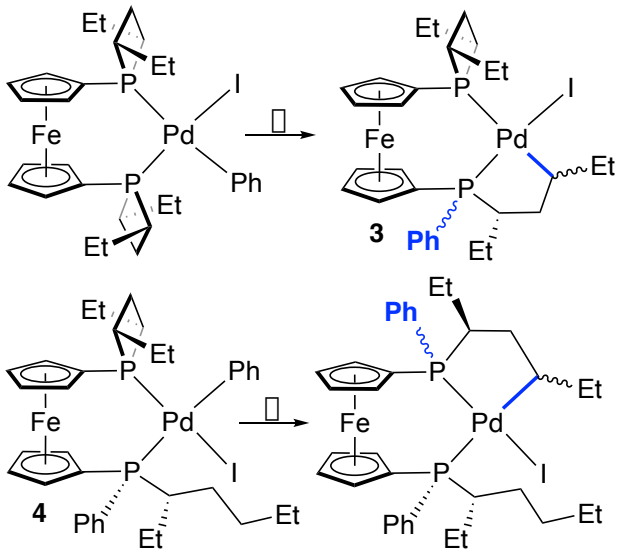
Scheme 16. Synthesis of Chiral Ethylquinoline-Derived Palladacycles by Redox Transmetalation from Mercury to Palladium



Analogous chiral palladacycles were formed by P-C cleavage of chiral phosphine ligands, in which the C-stereogenic center was transferred to Pd with or without stereocontrol. In Scheme 17, heating a Pd((*S,S*)-Et-FerroTANE) complex gave palladacycle **3** as a mixture of diastereomers, presumably via P-C reductive elimination to yield a phosphetanium cation, followed by P-C oxidative addition.

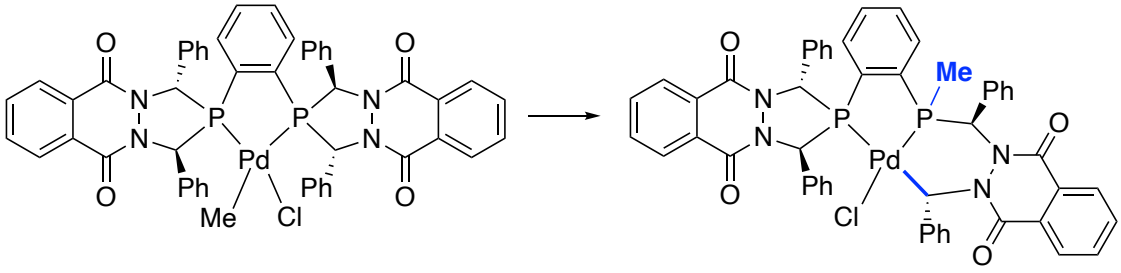
The kinetic stereochemistry of this process could not be determined, because the isomers of **3** interconverted in solution, presumably via reversible β-hydride elimination/reinsertion. A similar process in **4** opened the second phosphetane ring, again yielding a mixture of stereoisomers.[28] The newly formed Pd-C and P-Ph bonds are shown in blue.

Scheme 17. Synthesis and Epimerization of Chiral Palladium Alkyls by Ring Opening of a Chiral Bis(phosphetane) Ligand



In contrast, similar chemistry in a chiral Pd-diazaphospholane complex gave only one isomer, with stereospecific methyl transfer from palladium to phosphorus and ring opening to yield a new [Pd]-R* stereogenic center (Scheme 18, with the new Pd-C and P-C bonds in blue).[29]

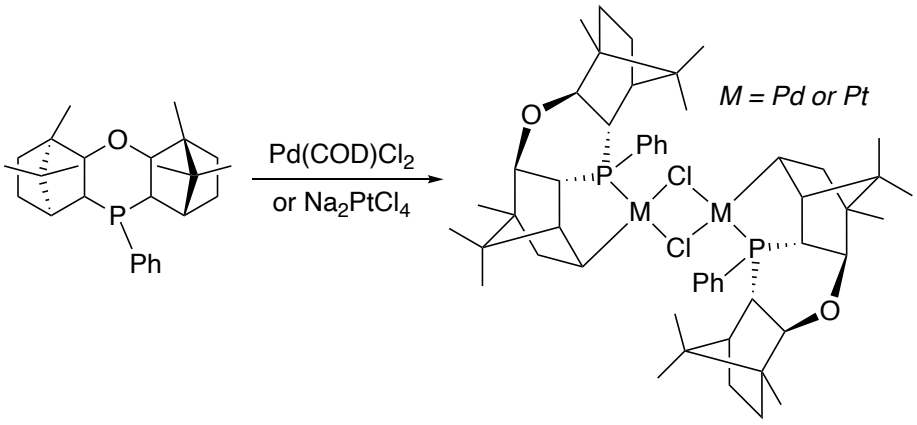
Scheme 18. Stereospecific Synthesis of a Chiral Palladium Alkyl by Ring Opening of a Chiral Bis(phospholane) Ligand



2.3.2 Diastereoselective cyclometalation of CH_2 groups

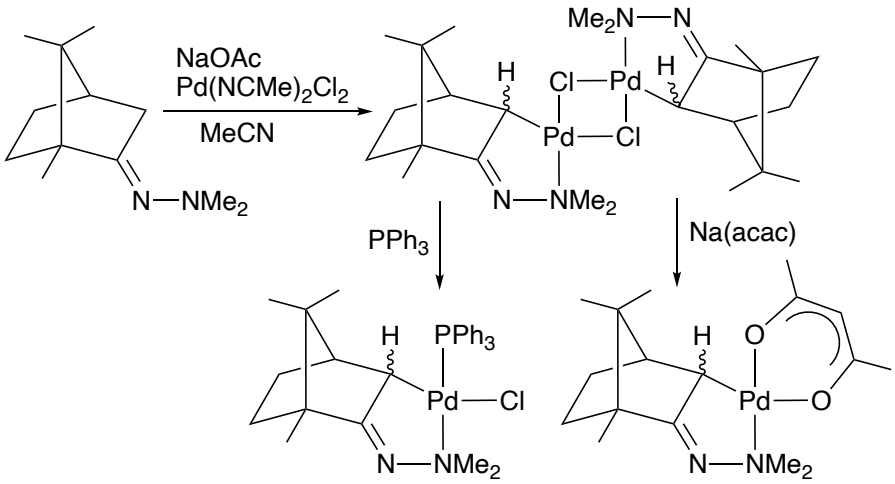
In these reactions, anchoring a chiral substrate to a metal with a donor group enables selective activation of a neighboring CH_2 group to yield a [M]-R* complex. For example, cyclometalation of the camphor-derived phosphine phenop at Pd or Pt generated several new chiral centers, including one at the metal-bound carbon (Scheme 19).[30]

Scheme 19. Synthesis of Chiral Metallacycles by Cyclometalation of a Camphor-Derived Phosphine



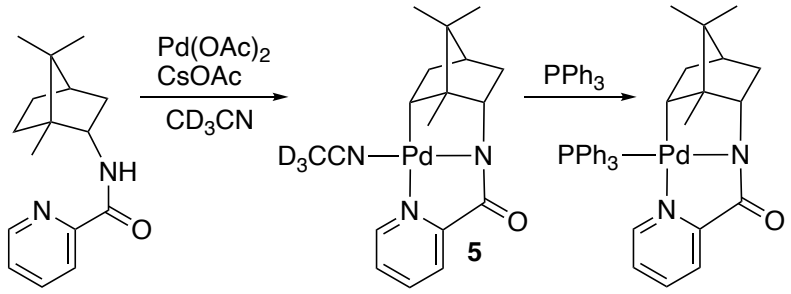
In a less selective example, cyclopalladation of a related camphor hydrazine derivative gave an inseparable *cis*-*trans* mixture of Cl-bridged dimers without stereocontrol at the Pd-bound carbon; Scheme 20 shows a *trans* isomer which was crystallographically characterized. Treatment with Na(acac) or PPh_3 gave monomeric complexes which could be partially separated by chromatography to give diastereoenriched mixtures which slowly epimerized in solution.[31]

Scheme 20. Synthesis of Chiral Palladacycles from a Camphor-Derived Hydrazone



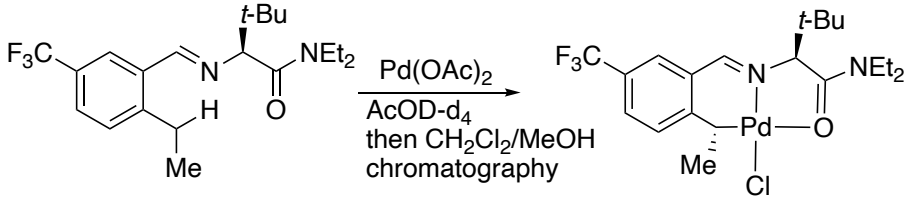
With a similar chiral substrate, coordination of both pyridine and amide nitrogens resulted in selective formation of palladacycle **5**, in which coordinated acetonitrile could be replaced with PPh_3 (Scheme 21).[32] See Scheme 114 below for application of this process in catalytic asymmetric C-H functionalization.

Scheme 21. Synthesis of a Chiral Palladacycle from a Bornylamine Derivative



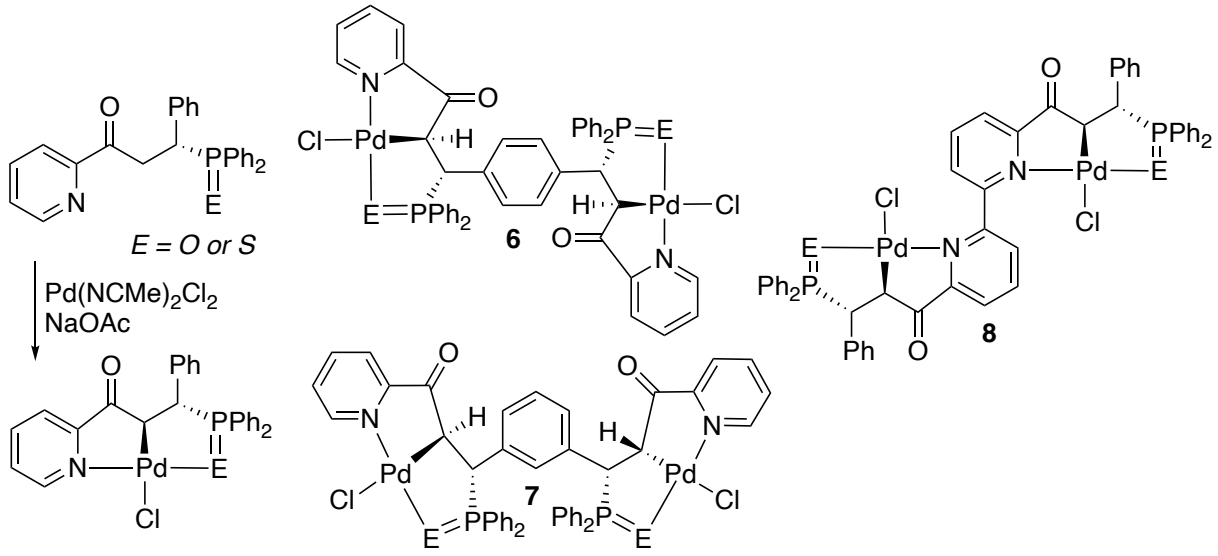
Related bidentate coordination of a chiral imine-amide resulted in selective C-H activation of an ethyl CH_2 group to yield a palladacycle with an NOC pincer ligand (Scheme 22).[33] See Scheme 75 below for additional stereochemical studies of this [Pd]-R* group.

Scheme 22. Synthesis of a Chiral Palladacycle via C-H Activation of a Chiral Bifunctional Imine-Amide



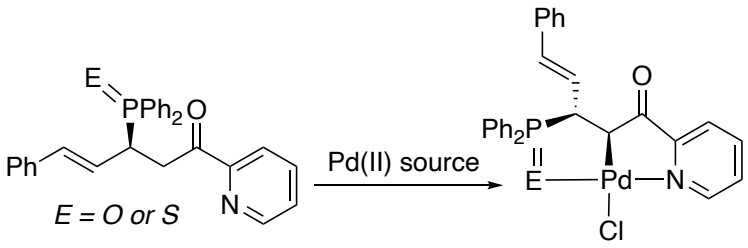
Similarly, bidentate coordination of an enantiomerically enriched pyridine-phosphine chalcogenide to palladium resulted in stereospecific activation of a ketone CH_2 group to yield chiral Pd-alkyl pincer complexes (Scheme 23).[34] This reaction was extended from the parent pyridine derivative to dinuclear ones featuring *meta*- or *para*-arene cores, or a bipyridine, yielding [Pd]-R* complexes **6**-**8**.

Scheme 23. Synthesis of Chiral Palladacycles from Enantiomerically Enriched Phosphine Chalcogenide-Pyridine Substrates



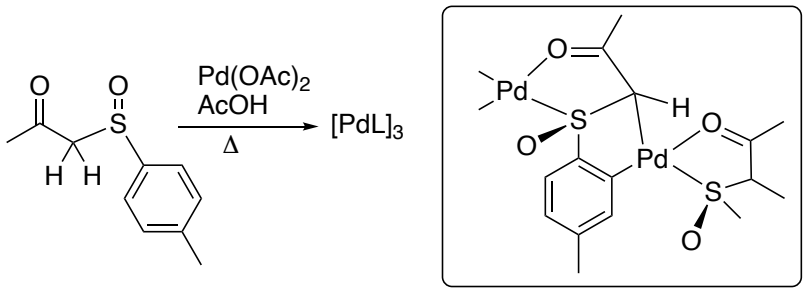
Similar chemistry occurred with a substrate bearing a vinyl substituent at the C-stereocenter, with a variety of Pd(II) sources (Scheme 24).[35]

Scheme 24. Cyclopalladation of an Enantiomerically Enriched Pyridine-Phosphine Chalcogenide



Cyclopalladation of a chiral sulfoxide caused formation of two Pd-C bonds, with stereocontrol at the Pd-bound alkyl group. Bidentate S/O coordination led to a trimeric palladacycle, with distorted square planar Pd(II) centers (Scheme 25 shows the local environment at Pd).[36]

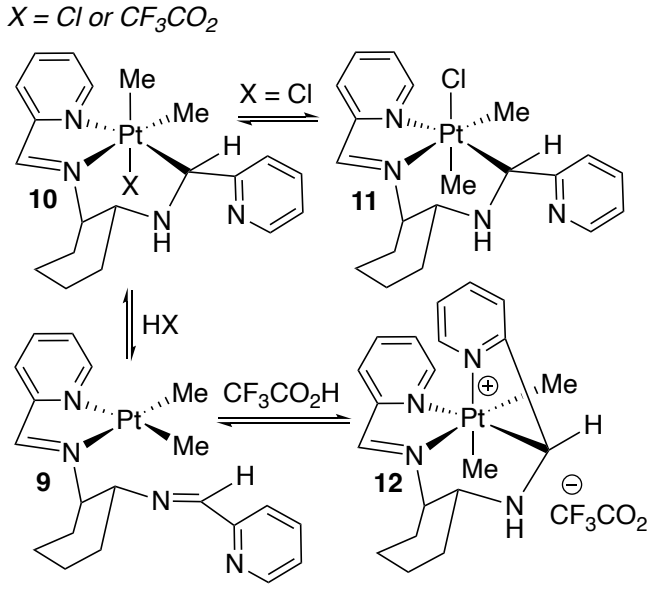
Scheme 25. Synthesis of a Trimeric Chiral Palladacycle from C-H Activation of an Enantiomerically Enriched Sulfoxide



2.3.3 Other methods

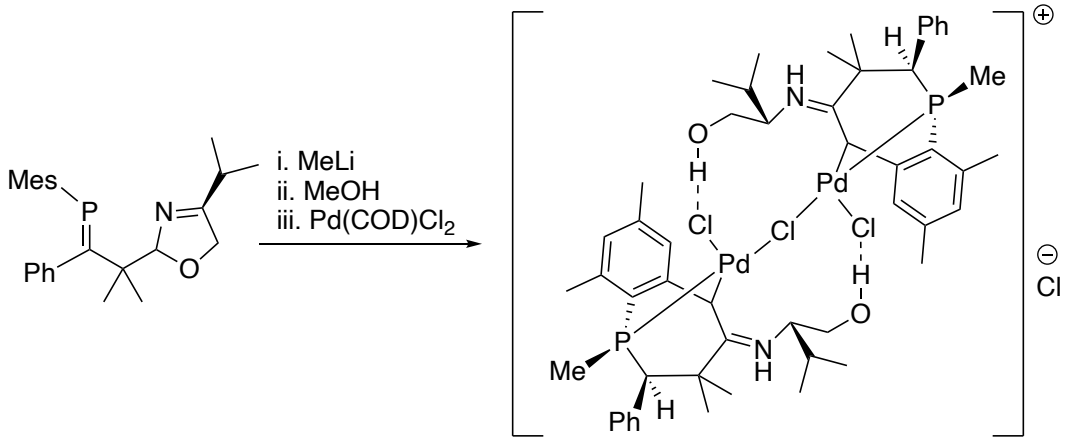
Protonation of square planar **9** gave octahedral Pt complexes with high stereoselectivity controlled by a potentially tetradentate chiral bis(imine)-bis(pyridine) ligand derived from *cis*-cyclohexanediamine (Scheme 26). In the proposed mechanism, after imine N-protonation in **9**, attack of Pt at carbon yields **10** or **12**, whose structure depended on the anion.[37] With chloride coordination, the ligand was tridentate, and kinetic product **10** was converted to thermodynamically favored **11**. With the more weakly coordinating trifluoroacetate anion, pyridine coordination to give **12** required the opposite configuration at the Pt-bound carbon.

Scheme 26. Stereoselective Formation of Chiral Platinum Alkyls by Protonation of a Cyclohexanediamine-Derived Ligand



In a complicated process whose mechanism is unclear, a chiral oxazoline-phosphaalkene ligand was converted to a chiral dinuclear complex, in which the [Pd]-R* ligand was formed from an *ortho* methyl in a P-mesityl group (Scheme 27).[38]

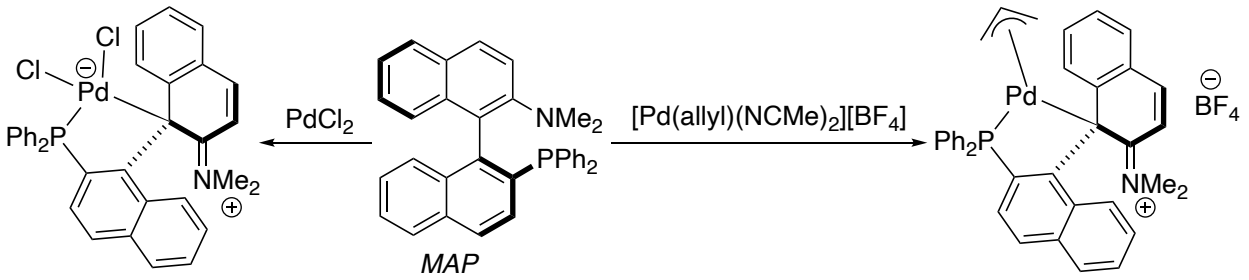
Scheme 27. Synthesis of a Dinuclear Palladium Chiral Alkyl Complex After Selective Ring Opening of an Enantiomerically Enriched Phosphaalkene-Oxazoline



2.3.4 Ligand Isomerization

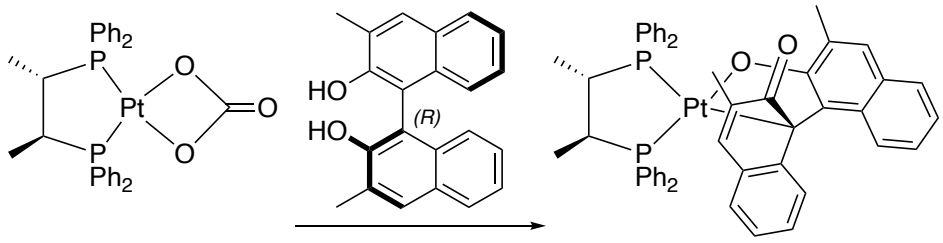
Unexpected isomerization of chiral binaphthyl-based bidentate ligands is another route to [M]-R* complexes. For example, isomerization of the P~N BINAP analogue MAP gave a P~C-chelate with a Pd-bound C-stereogenic center.[39] A related process yielded a π-allyl complex (Scheme 28).

Scheme 28. Formation of Chiral Palladacycles via Isomerization of the Binaphthylphosphine-amine MAP



This P~C-bonding mode also occurred in Pt-Binolate complexes, like the enantiopure one in Scheme 29; [40] similar coordination was originally discovered with a racemic ligand.[41]

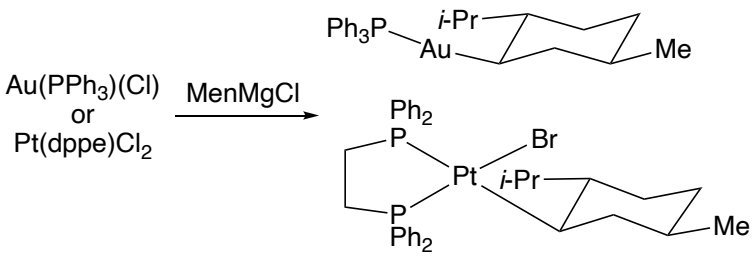
Scheme 29. Formation of a Cyclic [Pt]-R* Complex via Isomerization of a Chiral Binaphtholate Ligand



2.3.5 Transmetalation

The configurational instability of main group organometallics [M']-R* makes selective synthesis of [M]-R* complexes by transmetalation challenging. However, this process can be highly diastereoselective when R* contains more than one chiral center. For example, treatment of menthyl chloride with Mg gives an interconverting mixture of the expected MenMgCl and its C-epimeric neomenthyl isomer NeoMenMgCl. Because the menthyl reagent reacts more quickly with electrophiles, this cocktail often preferentially yields menthyl products with main group reagents such as phosphorus and tin derivatives.[42] Extending this approach to transition metal halides gave gold and platinum menthyl complexes; the Pt-Br came from dibromoethane used to generate the Grignard reagent (Scheme 30).[43]

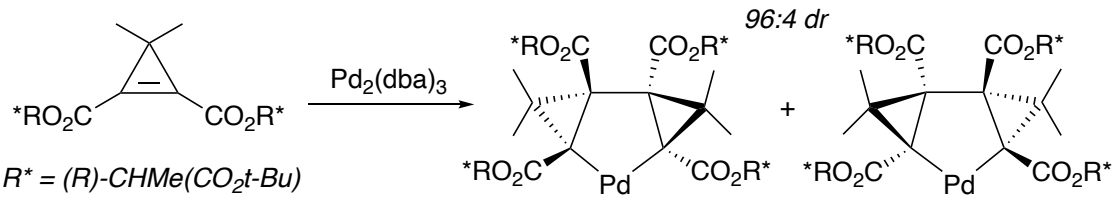
Scheme 30. Synthesis of Chiral Gold and Platinum-Menthyl Complexes by Transmetalation from Magnesium



2.3.6 Oxidative Cyclization

The palladacycles whose resolution was shown in Scheme 6 were prepared as racemates by oxidative cyclization of cyclopropenes. Using C_2-symmetric cyclopropenes with enantiomerically enriched lactic acid ester substituents resulted in asymmetric synthesis of enantiomerically enriched [Pd]-R* complexes (Scheme 31 shows an example).[44]

Scheme 31. Synthesis of Chiral Palladacycles via Oxidative Cyclization of C_2-Symmetric Chiral Cyclopropenes

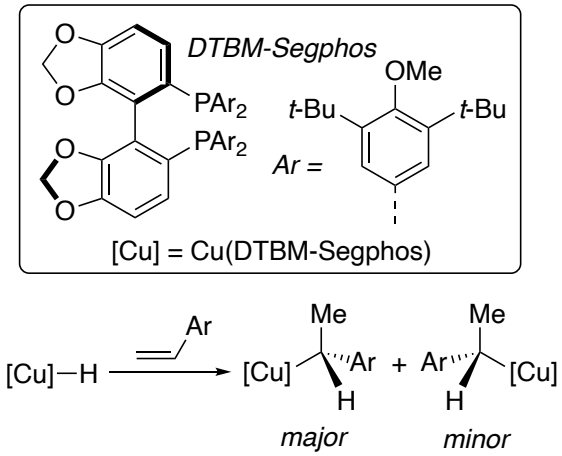


2.4 Stereocontrol by chiral ligands Synthesis of [M]-R* complexes does not require preformed R* groups for oxidative addition or transmetalation. Instead, they may be formed from achiral substrates, for example by 2,1-insertion of α-olefins like styrene into metal-hydride bonds.

2.4.1 Migratory insertion

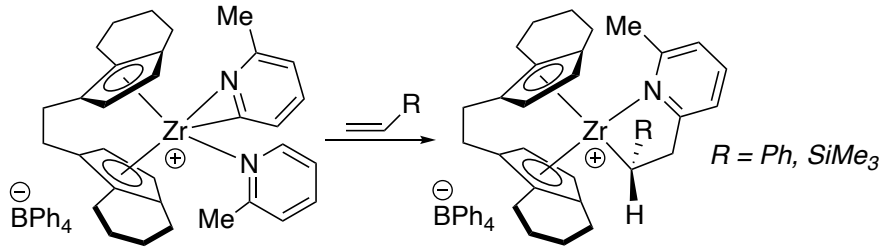
Generation of a chiral bis(phosphine) copper hydride complex in the presence of styrenes resulted in formation of [Cu]-R* complexes with high diastereoselectivity arising from relative insertion rates (Scheme 32). As shown in more detail in Scheme 109 below, this process is important in catalytic asymmetric hydroboration of alkenes.[45]

Scheme 32. Diastereoselective Synthesis of Chiral Copper Alkyls by Reaction of Styrenes with a Bis(phosphine) Copper Hydride Complex



Similarly, regio- and stereospecific 2,1-insertion of styrene or vinyltrimethysilane into a Zr-C bond gave metallacycles in which the α-substituent pointed away from the chiral ligand (Scheme 33); related insertions of *cis*- or *trans*-2-butene were also stereospecific.[46]

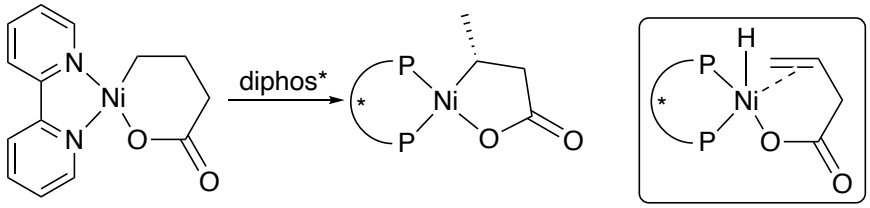
Scheme 33. Regio- and Stereospecific 2,1-Insertion of Styrene into a Zr-C Bond Yielded a Chiral Alkyl Complex



Replacing bipyridine with a chiral bis(phosphine) diphos*, such as Chiraphos, caused a β-hydride elimination-reinsertion sequence which resulted in ring contraction and formation of a [Ni]-R*

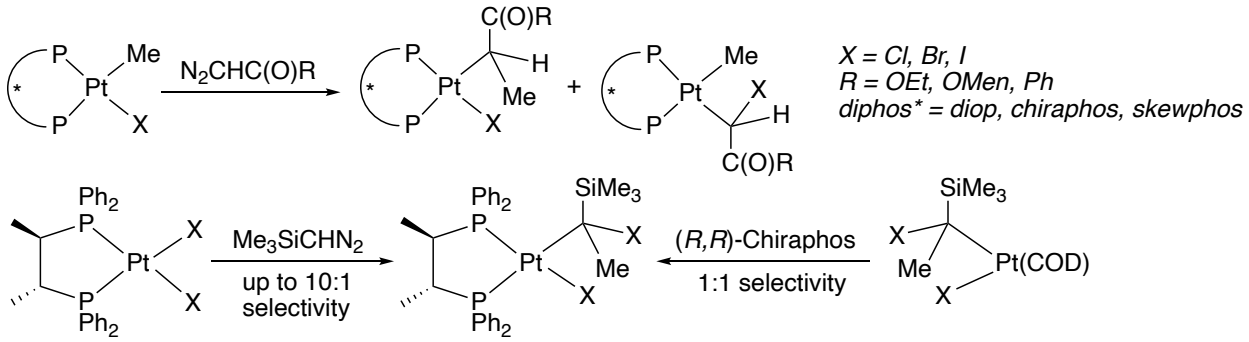
metallacycle, in which the C-stereocenter could epimerize via the Ni-hydride intermediates shown in the box (Scheme 34).[47]

Scheme 34. Formation of Chiral Nickel Metallacycles by Ring Contraction and Their Isomerization via Reversible β-Hydride Elimination and Reinsertion



Related [Pt]-R* complexes were prepared by carbene insertion into Pt-halide (X) or Pt-Me bonds; separation of diastereomers bearing chiral bis(phosphine) ligands enabled isolation of enantiomerically pure complexes (Scheme 35). As might be expected, starting with a chiral complex gave higher stereoselectivity than replacing COD with a chiral bis(phosphine).[48] These diastereoselective reactions were carried out with a variety of diazo precursors and diphos* ligands.[49]

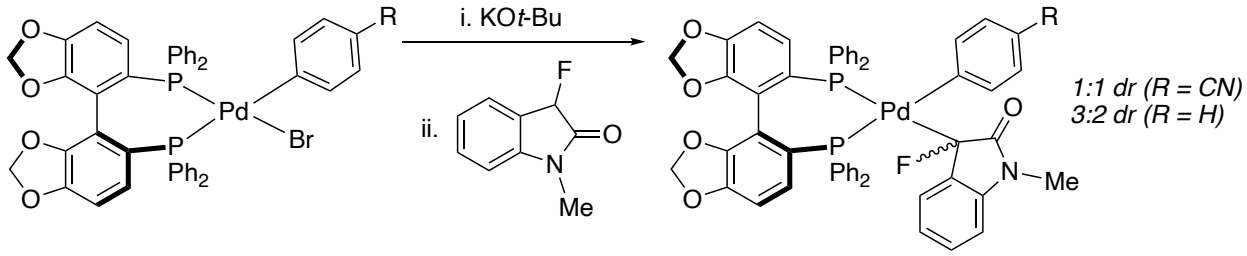
Scheme 35. Synthesis of Chiral Pt-Alkyl Complexes by Insertion of Carbenes into Pt-X or Pt-C Bonds



2.4.2 Enolate formation

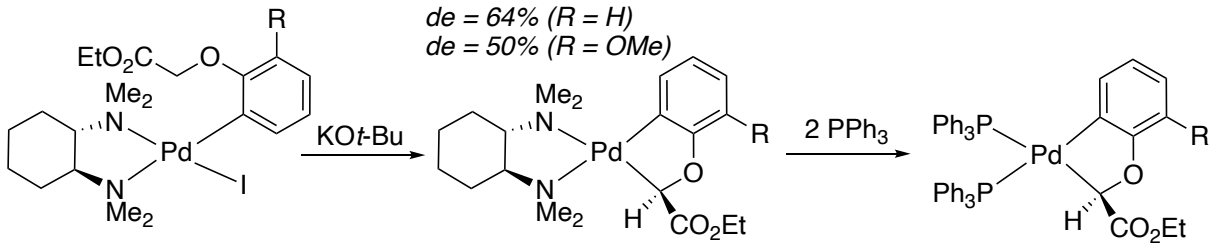
Keto-enol tautomerization provides the opportunity for kinetic and/or thermodynamic control of diastereoselectivity in formation of [M]-R* enolate complexes, which often undergo epimerization at the C-stereogenic carbon. For example, treatment of a cyclic amide with base in the presence of a chiral palladium aryl bromide complex gave mixtures of enolate complexes, in which the diastereoselectivity depended on the aryl substituents (Scheme 36).[50] See Scheme 111 below for their role in Pd-catalyzed cross-coupling, where C-C reductive elimination formed the products.

Scheme 36. Diastereoselective Synthesis of Palladium-Segphos Enolate Complexes



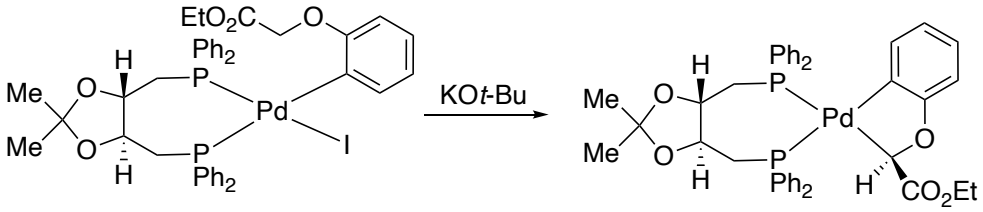
Similarly, a chiral cyclohexanediamine ligand controlled diastereoselectivity in formation of cyclic palladium enolates and could later be replaced by phosphines (Scheme 37).[51]

Scheme 37. Diastereoselective Synthesis of Chiral Palladium Enolate Complexes



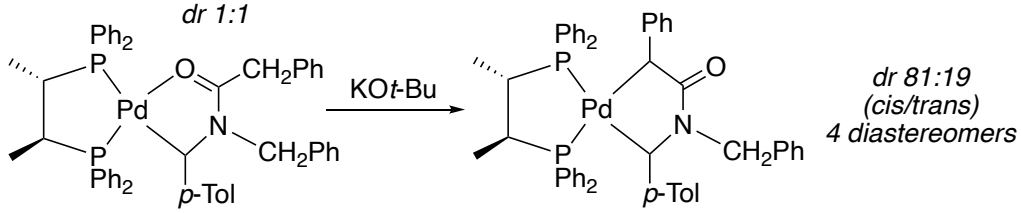
In related reactions with chiral bis(phosphines), diastereoselectivity depended on the ligand and the base, with kinetic or thermodynamic control observed (Scheme 38).[52] Related chemistry with a chiral diamine ligand gave aza- or oxapalladacycles, and addition of more base resulted in either enrichment or erosion of diastereomeric excess.[53]

Scheme 38. Diastereoselective Synthesis of Carbon-Bound Palladium Enolate Complexes



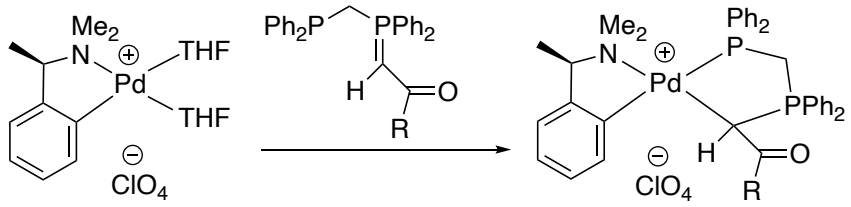
Extending this approach gave palladacycles with two [Pd]-R* groups as mixtures of diastereomers, with some control over the relative conformations of the Pd-C substituents (*cis*-*trans* ratio, Scheme 39).[54]

Scheme 39. Diastereoselective Synthesis of Palladacycle Enolate Complexes Containing Two Pd-Bound C-Stereogenic Centers



In a similar asymmetric synthesis of a thermodynamically controlled mixture of palladacycles, the ylide configuration was controlled by the chiral C~N chelate (Scheme 40).[55] Scheme 56 below shows interconversion of these diastereomers on warming.

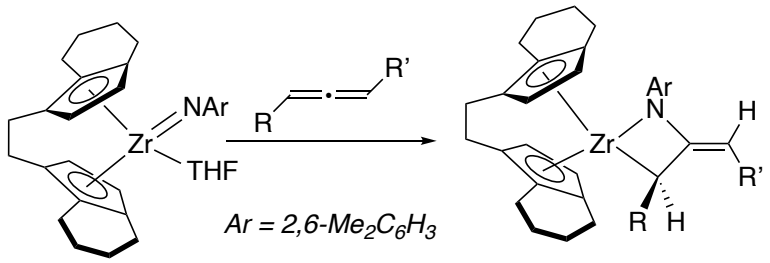
Scheme 40. Synthesis of Chiral Palladacycles Featuring a Pd-Bound Ylide Carbon



2.4.3 Cycloaddition

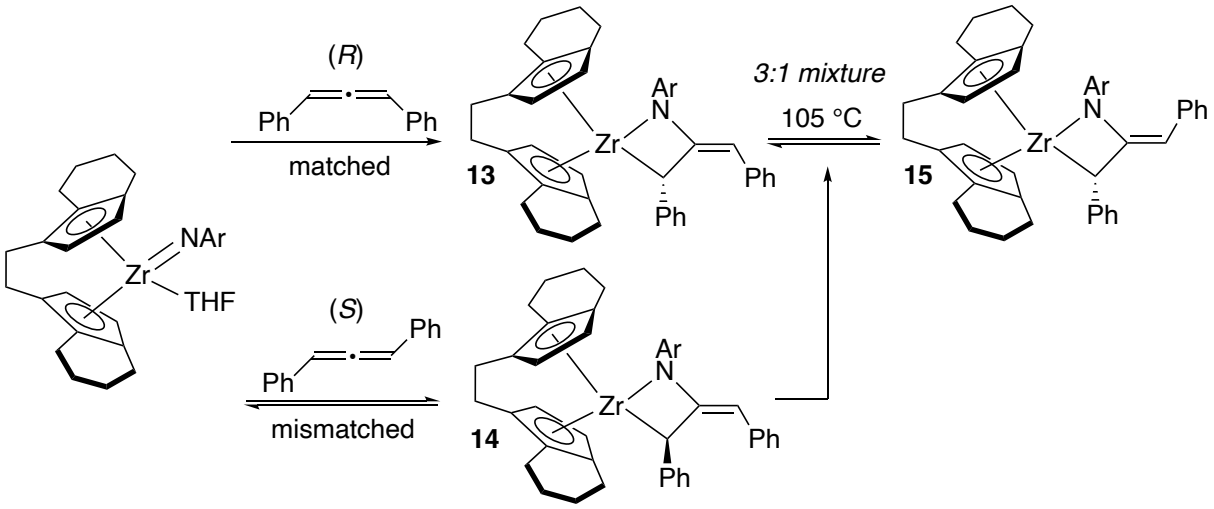
[Zr]-R* complexes were formed by highly selective [2+2] cycloaddition of a chiral zirconocene imido complex with a racemic allene to give one diastereomer of a chiral metal alkyl (Scheme 41). Using 2 equiv of racemic allene enabled stoichiometric kinetic resolution.[56]

Scheme 41. Synthesis of Chiral Metallacycles from a Zirconium-Imido Complex and Allenes



This system showed match-mismatch behavior, in which the matched allene enantiomer reacted quickly to make only **13**, while its enantiomer yielded an equilibrium mixture with mis-matched **14**. Heating **13** or **14** caused isomerization to a 3:1 mixture of **13** and **15** (Scheme 42). At lower temperature, mis-matched **14** formed a mixture of all four possible isomers; the mechanism of these isomerizations is discussed in Scheme 50 below.[57]

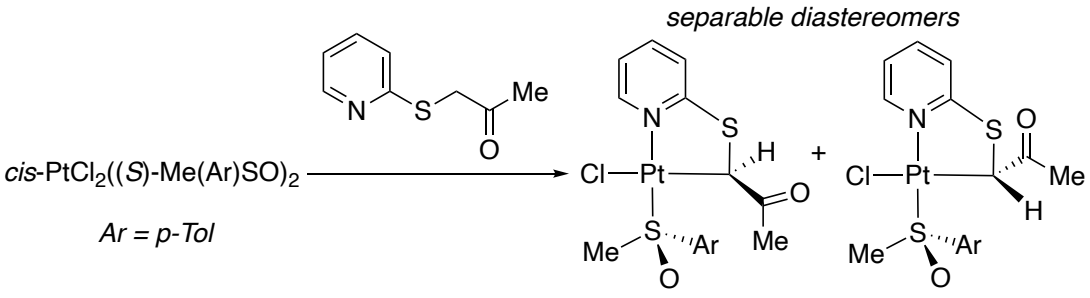
Scheme 42. Match-Mismatch Effects in Formation and Isomerization of Chiral Zirconacycles



2.4.4 Miscellaneous synthetic methods

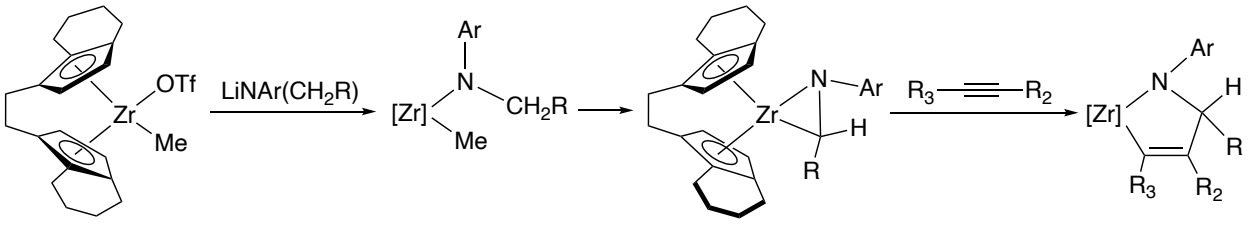
Section 2.3.2 above showed examples in which coordination of a chiral substrate led to selective intramolecular activation of a CH_2 group, yielding a [M]-R* center. Such processes may also occur with an achiral substrate, mediated by a separate chiral ligand. Thus, in Scheme 43, the chiral sulfoxide ligands promoted asymmetric cycloplatination to give a separable mixture of diastereomers of chiral Pt alkyls, obtained in 45% de.[58]

Scheme 43. Diastereoselective Synthesis of Chiral Pt-Alkyl Complexes via Asymmetric Cycloplatination



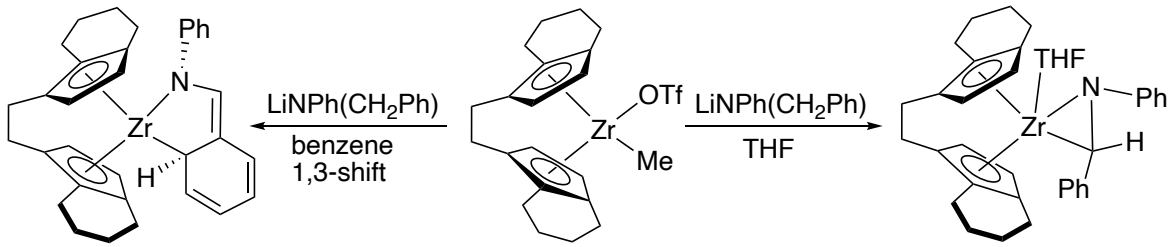
Similarly, a chiral ebthi ligand in an *ansa*-metallocene controlled the selectivity of β-CH_2 deprotonation to generate proposed zircona-aziridine intermediates in which the N-Ar and R groups were expected to be *trans* (Scheme 44). Insertion of an alkyne into the Zr-C bond, proposed to go with retention of configuration at carbon, gave metallacycles with high regioselectivity and diastereoselectivity.[59]

Scheme 44. Generation of Chiral Zircona-Aziridine Complexes and Selectivity of their Reaction with Alkynes



Switching the solvent to THF enabled isolation of a closely related zircona-aziridine (Scheme 45). When generated in benzene instead, it isomerized to form a bicyclic [Zr]-R* complex.[60]

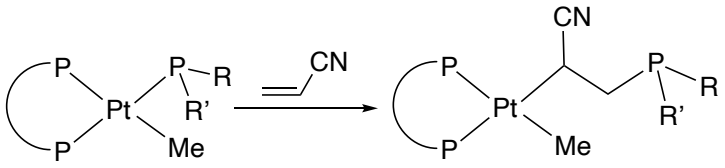
Scheme 45. Synthesis of a Chiral Zircona-aziridine and Its Solvent-Mediated Isomerization



Finally, diastereoselectivity of nucleophilic attack by a P-stereogenic Pt-phosphido group on acrylonitrile was controlled either by a chiral bis(phosphine) diphos* or by chiral phosphido

substituents (Scheme 46).[61] See Scheme 113 below for the importance of such processes in catalytic asymmetric hydrophosphination of Michael acceptor alkenes.

Scheme 46. Diastereoselective Formation of Chiral Pt Alkyl Complexes by Attack of a Phosphido Ligand on Acrylonitrile



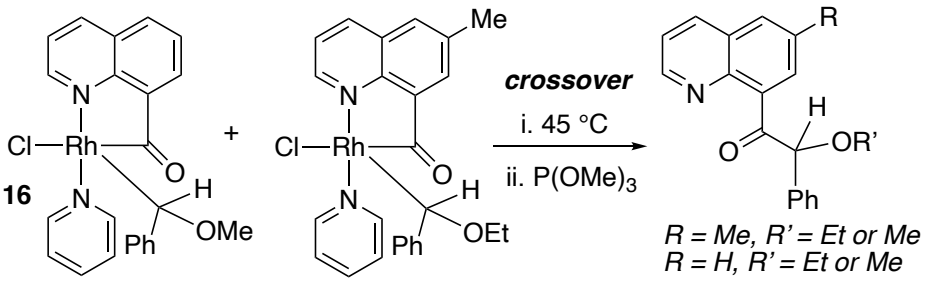
3. Configurational stability

The configurational stability, or instability, of [M]-R* complexes is important in their synthesis and applications. Epimerization of the C-stereocenter may occur by M-C homolysis, yielding radicals, by reversible reductive elimination/oxidative addition, by reversible β-hydride elimination/migratory insertion, or by other less common processes.

3.1 M-C bond homolysis

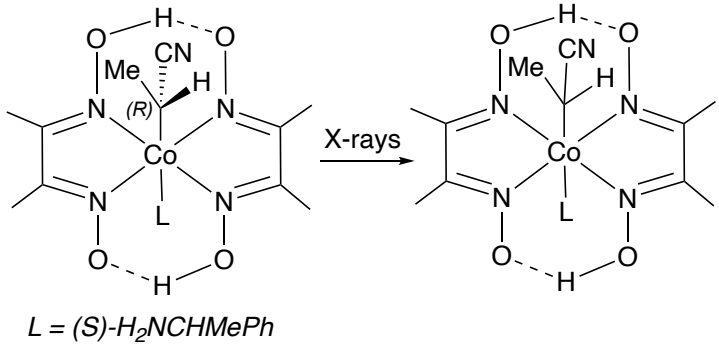
The enantiomerically enriched Rh-alkyl **16**, whose synthesis is described below in Scheme 62, racemized on heating via Rh-C homolysis, yielding radicals which either recombined or escaped the solvent cage, yielding observable fragmentation products. From the activation parameters of this first-order process, a Rh-C bond strength of 31 kcal/mol was estimated. In a crossover experiment using OMe and OEt-labeled substrates, after phosphite-induced C-C reductive elimination (see Scheme 73 below), the expected mixtures of quinolines were observed (Scheme 47).[62]

Scheme 47. Evidence for Rh-C Bond Homolysis in Racemization of Chiral Rhodacycle **16**



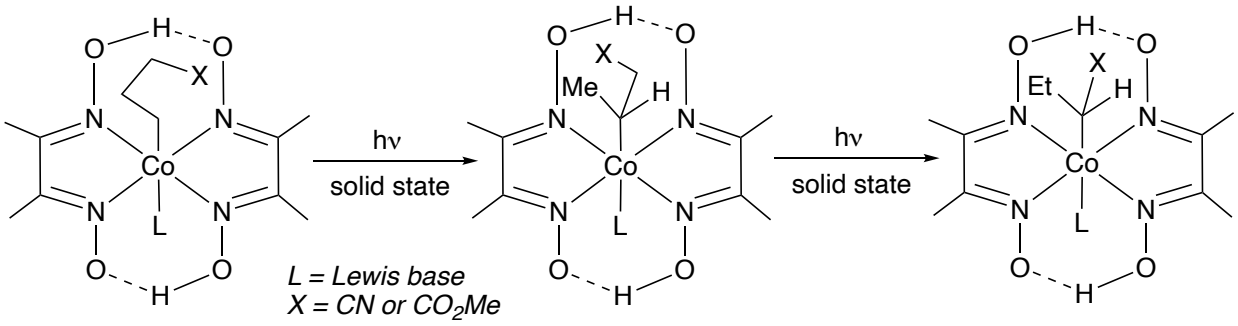
Another example of [M]-R* epimerization ascribed to M-C homolysis to give radicals, followed by their recombination, occurred in a single crystal to single crystal transformation observed upon exposing the chiral cobalt alkyl complex from Scheme 13 to X-rays (Scheme 48). Following the slow process by X-ray crystallography showed that the *R*-cyanoethyl complex was gradually converted to the disordered "racemate" (mixture of diastereomers).[63] Similar solid-state photoracemizations were observed in related $Co(dmgH)_2$ complexes, again attributed to radical formation and recombination, and analogous thermal reactions enabled estimation of the Co-C bond energy, about 28-29 kcal/mol.[64]

Scheme 48. X-Ray Induced Racemization of a Chiral Cobalt Alkyl Complex



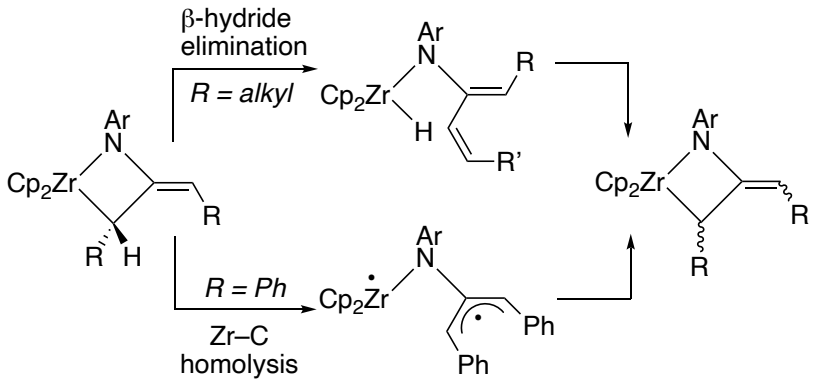
Related complexes were prepared in surprising consecutive photochemical solid-state transformations, which could be observed in single crystals by X-ray crystallography. For example, a 3-cyanopropyl group was converted first to 2-cyanopropyl, then to 1-cyanopropyl, with asymmetric induction controlled by the nature of the cobalt alkyl and the axial chiral Lewis base (Scheme 49).[65]

Scheme 49. Formation of Chiral Cobalt Alkyls by Solid-State Photoisomerization



C-epimerization of the chiral zirconacycles in Scheme 42 (R = Ph) was proposed to occur by a similar Zr-C homolysis-recombination pathway (Scheme 50).[57] However, for metallacycles derived from dialkylallenes, reversible β-hydride elimination caused both racemization and E-Z isomerization.

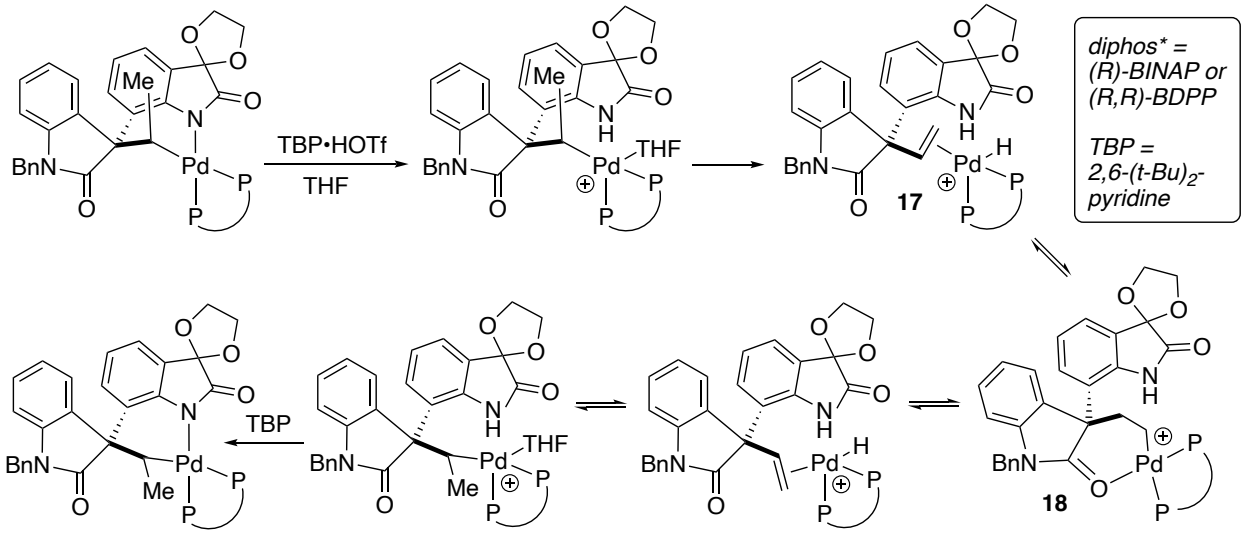
Scheme 50. Epimerization of Zirconium Metallacycles by Zr-C Bond Homolysis or β-Hydride Elimination



3.2 Reversible β-hydride elimination/migratory insertion

Chiral palladacycles, intermediates in asymmetric Heck catalysis (see Scheme 112 below), epimerized in the presence of acid via a proposed β-hydride elimination/reinsertion sequence in which several intermediates were observed (Scheme 51). After protonation at the amido nitrogen and ligand dissociation, β-hydride elimination gave Pd alkene hydride complex **17**, which can interconvert with linear Pd-alkyl **18**, or re-insert to make the other epimer of the Pd-CHMe group, followed by proton transfer and N-Pd coordination to complete the isomerization.[66]

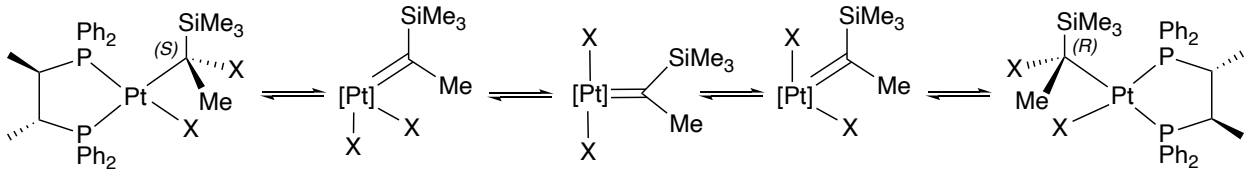
Scheme 51. Proposed Mechanism of Epimerization of a Chiral Palladacycle via Reversible β-Hydride Elimination/Insertion



3.3 Reversible α-elimination

α-Elimination, although less common than β-elimination, can also result in [M]-R* epimerization. For example, in Scheme 52, thermal epimerization of a Pt complex from Scheme 35 was faster with X = Br or I than for X = Cl and followed first-order kinetics. Rates were little affected by solvent polarity or addition of halide, suggesting an anchimeric assistance mechanism for epimerization, with neighboring group participation. Reversible α-elimination (C-X oxidative addition to Pt) to give a Pt-carbene intermediate was proposed to cause epimerization.[48]

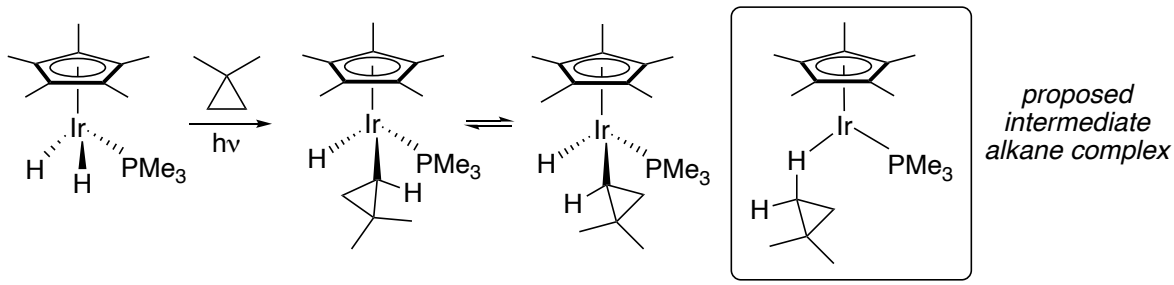
Scheme 52. Epimerization of a [Pt]-R* Complex Via Reversible α-Halide Elimination ([Pt] = Pt(Chiraphos), X = Halide)



3.4 Reversible reductive elimination/oxidative addition

C-H activation of a cyclopropane gave separable diastereomers of an [Ir]-R* complex, which upon heating interconverted faster than reductive elimination occurred (Scheme 53).[67] This C-epimerization was proposed to proceed by reversible reductive elimination/oxidative addition via an intermediate alkane complex.

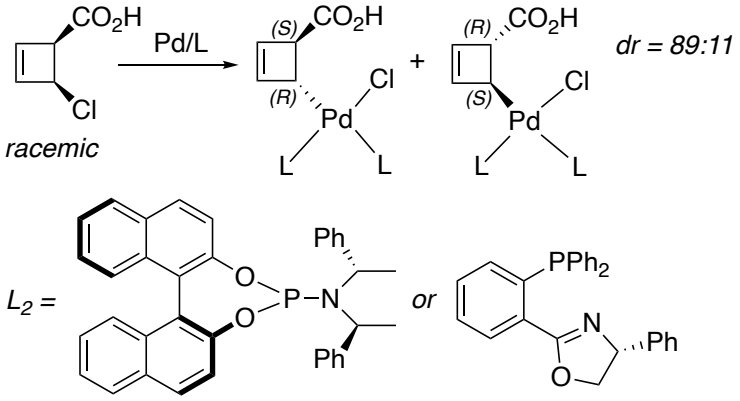
Scheme 53. Proposed Mechanism of Interconversion of Diastereomers of Iridium-Cyclopropyl Complexes via Reversible Reductive Elimination/Oxidative Addition



3.5 σ-π interconversions

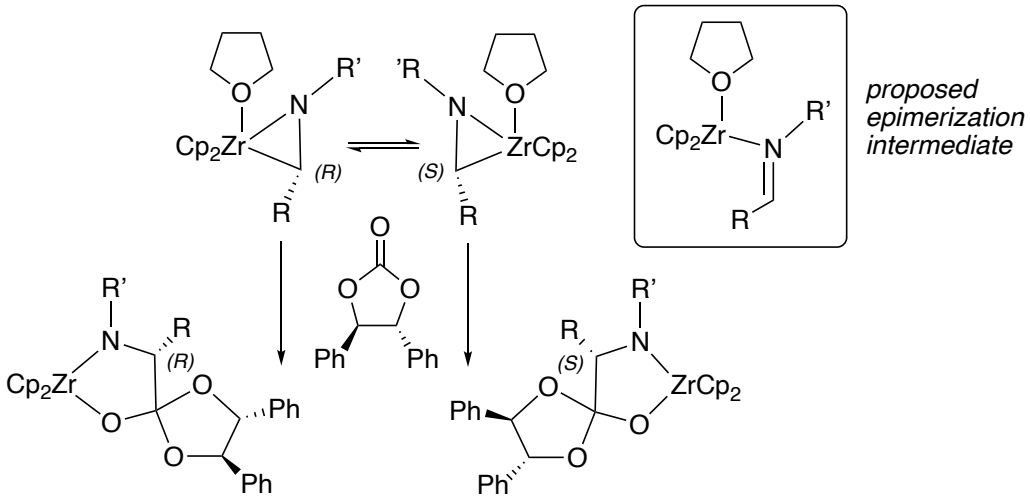
The C-epimeric Pd-alkyl complexes in Scheme 54 were initially formed with inversion of configuration at carbon in oxidative addition, then equilibrated, presumably via η^1-η^3-η^1 σ-π interconversions common in Pd-allyls.[68]

Scheme 54. Formation and Epimerization of Diastereomeric Pd-Cyclobutenyl Complexes



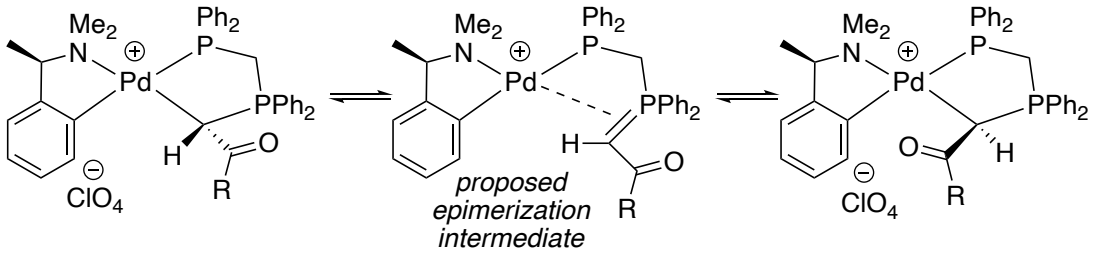
In a similar process, C-epimerization in zirconaaziridines like those in Schemes 44-45 was proposed to occur via interconversion of π- and N-bound imine complexes (Scheme 55). Because one enantiomer reacted faster than the other with a chiral carbonate, tuning the rate of the insertion by modifying the conditions resulted in high selectivity.[69]

Scheme 55. Role of Zirconaaziridine Epimerization in Diastereoselective Reaction with a Chiral Carbonate



In a similar σ-π process, the chiral Pd-ylide complexes from Scheme 40 were proposed to undergo C-epimerization via reversible formation of a π-bound intermediate (Scheme 56).[55]

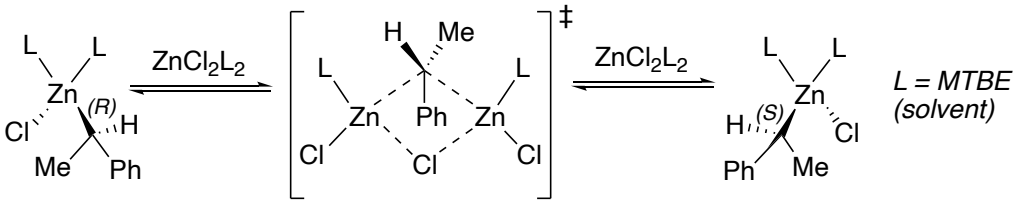
Scheme 56. Proposed Mechanism of C-Epimerization of [Pd]-R* Ylide Complexes



3.6 Transmetalation

Transmetalation of chiral main group alkyls [M']-R* to transition metal complexes is important in cross-coupling catalysis, so their mechanism of C-epimerization is of interest.[70] In a recent example, a computational study found that isomerization of a [Zn]-R* complex occurred via a concerted dinuclear mechanism promoted by addition of $ZnCl_2$, with the chiral alkyl group bridging two Zn atoms in the transition state (Scheme 57). [71]

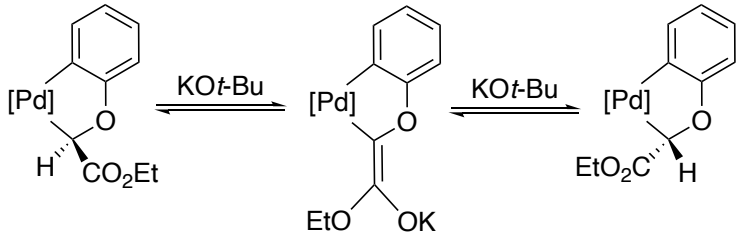
Scheme 57. Proposed Dinuclear Mechanism of Racemization of a Chiral Zn-Alkyl Complex



3.7 Via enolates

The base-mediated epimerization of chiral metal enolate complexes mentioned in Schemes 36-39 above may occur via reversible deprotonation of the metal-bound stereocenter, as proposed in Scheme 58.[52]

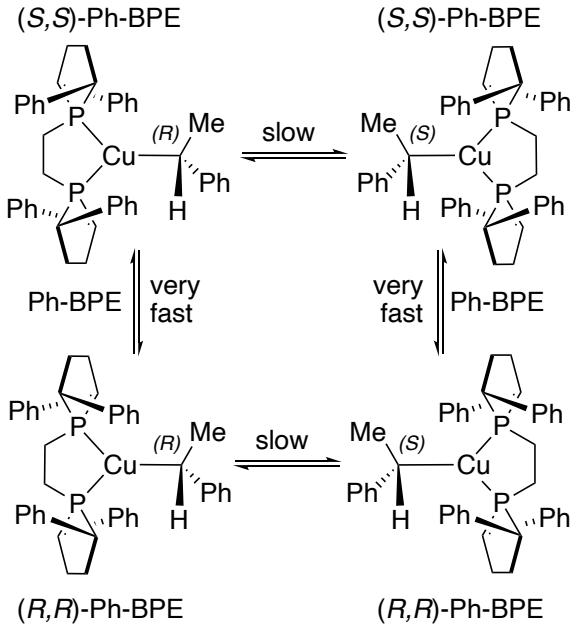
Scheme 58. Proposed Mechanism of Base-Mediated Epimerization of a Chiral Pd-Enolate Complex ([Pd] = Pd(diphos*))



3.8 Probing configurational stability via ligand exchange

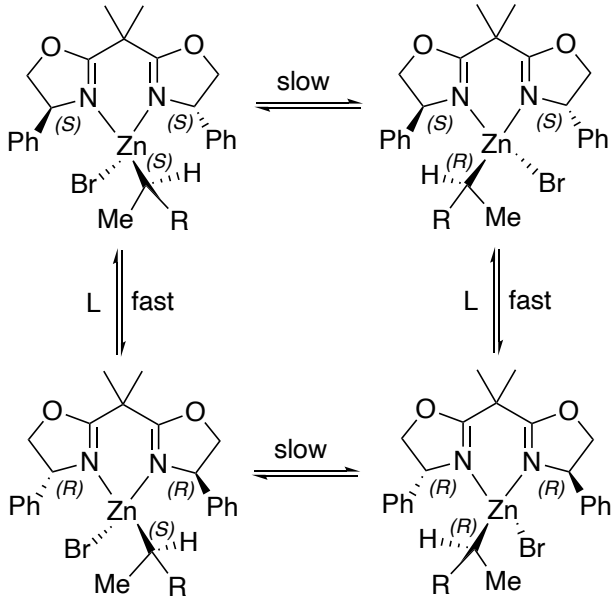
In some [M]-R* complexes, C-epimerization is too slow to be observed directly. However, if exchange of the enantiomers of an ancillary ligand is fast, the [M]-R* diastereomers will interconvert, enabling study of the thermodynamics and kinetics of C-epimerization. For example, in Scheme 59, C-epimerization, presumably via reversible β-hydride elimination/insertion was slow, but adding racemic Ph-BPE caused exchange on the NMR time scale, interconverting the diastereomers.[72] Please see Scheme 109 below for the importance of related processes in Cu-catalyzed asymmetric alkene hydroboration.

Scheme 59. Determining the Rate and Thermodynamics of Epimerization of a Chiral Copper Alkyl Complex by Ligand Substitution



Scheme 60 shows a similar approach to study of a configurationally stable [Zn]-R* bis(oxazoline) complex.[73] With R = Et or CH_2Ph, the two diastereomers interconverted slowly, with a free energy of activation of 27.2 kcal/mol at 25 °C. However, with added racemic ligand, Zn-L exchange was rapid on the NMR time scale, enabling determination of the relative thermodynamic stability of the diastereomers.

Scheme 60. Ligand Substitution in a Configurationally Stable Chiral Bis(Oxazoline)-Zinc Alkyl Complex



4. Stereochemistry of fundamental transformations

As mentioned in the introduction, study of [M]-R* complexes has been important in the development of mechanistic understanding in organometallic chemistry. This section describes recent examples, as an extension of Flood's original 1981 review.[2]

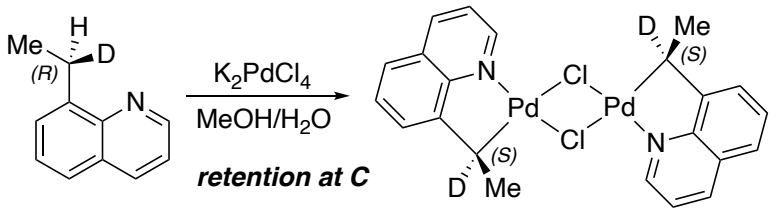
4.1 Oxidative addition

Oxidative addition may occur via a concerted mechanism, with retention at carbon, by an S_N2-type process, with inversion at carbon, or via radicals, leading to scrambling of stereochemistry. Experimental observation of the stereochemistry thus provides mechanistic information.

4.1.1 Retention at carbon (concerted)

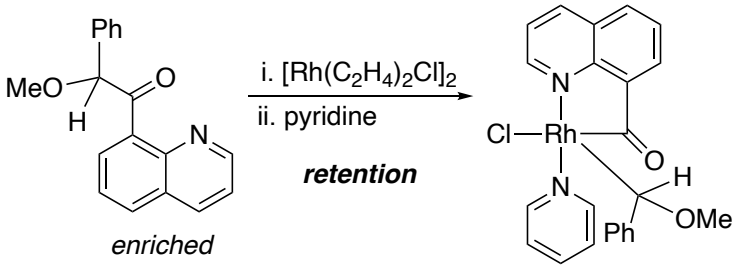
Cyclopalladation of a chiral deuterium-labelled ethylquinoline at palladium proceeded with retention of configuration and a large kinetic isotope effect, consistent with concerted oxidative addition (Scheme 61).[74]

Scheme 61. A Large Kinetic Isotope Effect in Selective Cyclopalladation of a Deuterium-Labeled Chiral Ethylquinoline



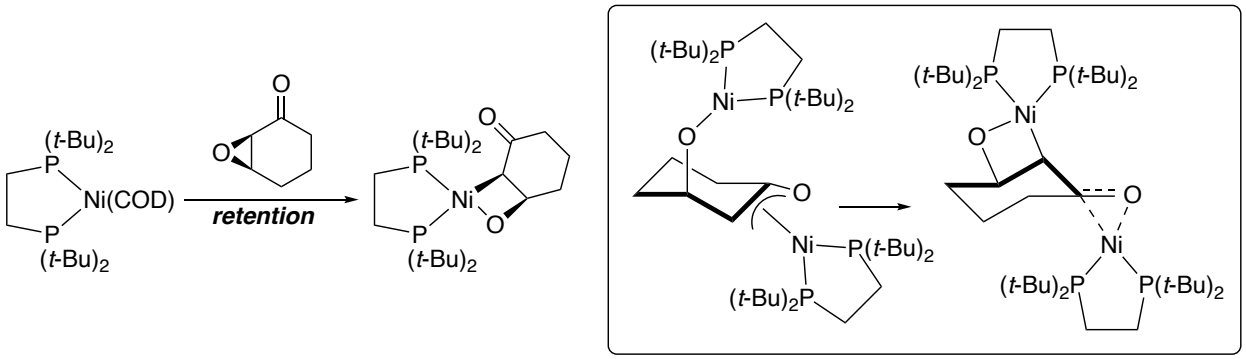
C-C oxidative addition of an enantiomerically enriched quinoline to Rh occurred with retention of configuration at carbon to give a chiral Rh alkyl (Scheme 62), whose configurational stability was discussed in Scheme 47.[62] See Scheme 73 for the reverse process, phosphite-induced C-C reductive elimination with retention of configuration at carbon, and additional comments.

Scheme 62. Retention of Configuration at Carbon in C-C Oxidative Addition of a Quinoline Derivative to Rhodium



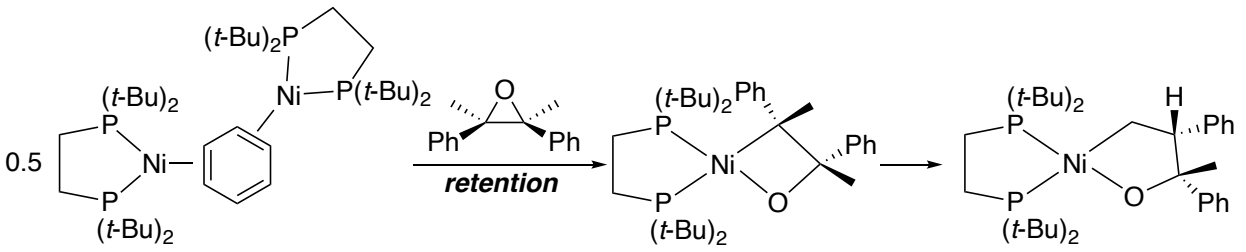
Similar retention of configuration in C-O oxidative addition of epoxides to Ni(0) was observed in two related studies. In Scheme 63, this observation was ascribed to a bimetallic pathway with stepwise epoxide ring opening and reclosing, via the intermediates in the box.[75]

Scheme 63. Retention of Configuration at Carbon in Oxidative Addition of a Racemic Epoxide to Ni(0)



With a more substituted *cis*-epoxide, oxidative addition was proposed to go with retention of configuration to form an observable nickelaoxetane intermediate, before β-hydride elimination and reinsertion gave the isolated ring-expanded product (Scheme 64).[76]

Scheme 64. Oxidative Addition of an Epoxide to Nickel Gave a Nickelaoxetane Intermediate with Retention of Configuration at Carbon

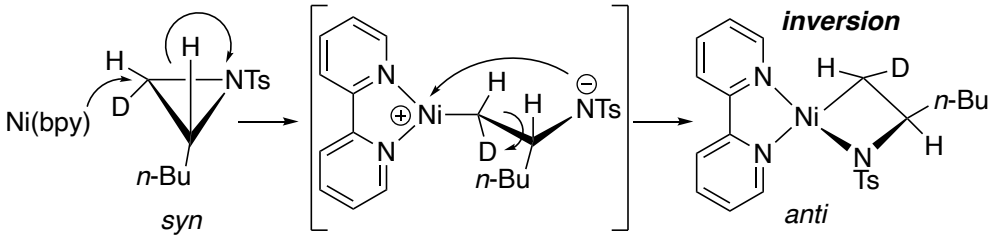


4.1.2 Inversion at carbon (S_N2-type)

In contrast to these epoxide examples, oxidative addition of a deuterium-labelled *syn*-aziridine to Ni(0) gave an *anti*-nickelacycle, with inversion at the C-stereocenter. This process was proposed

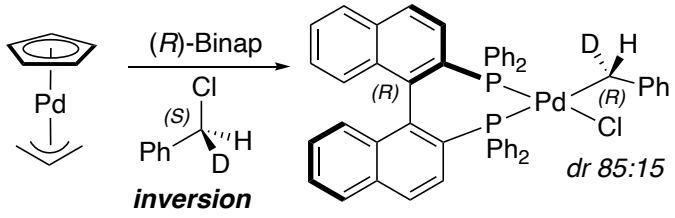
to occur via nucleophilic ring opening, followed by rotation about a C-C bond and ring closure by attack of the amido anion at nickel (Scheme 65).[77]

Scheme 65. Formation of a Nickela-azetidine by Ring Opening of a D-Labelled Aziridine with Inversion at Carbon



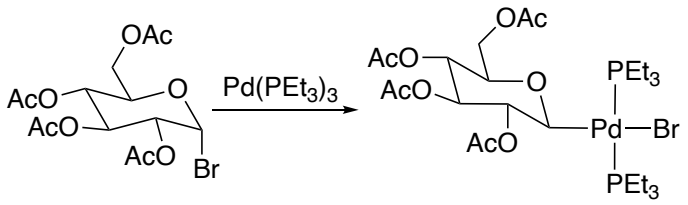
As in previous work establishing enantiomerically enriched D-labelled benzyl chlorides as useful stereochemical probe substrates, despite their limited configurational stability,[78] oxidative addition to Pd(0) gave a mixture of diastereomers of the [Pd]-R* product with predominant inversion of configuration (Scheme 66).[79]

Scheme 66. Inversion of Configuration at Carbon in Oxidative Addition of a Deuterium-Labelled Benzyl Chloride to Pd(0)



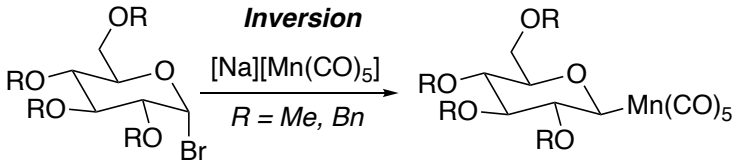
Oxidative addition of a sugar alkyl bromide derivative to Pd(0) occurred with inversion of configuration at carbon (Scheme 67).[80]

Scheme 67. Inversion of Configuration at Carbon in Oxidative Addition of a Sugar Alkyl Bromide to Palladium(0)



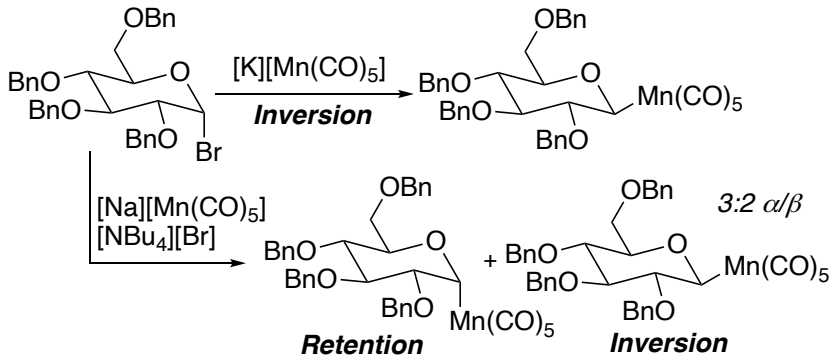
In a similar process with a manganese nucleophile, some sugars reacted with high stereoselectivity with inversion at carbon (Scheme 68). Oxidative addition was less selective in other cases, depending on the substrate substituents.[81]

Scheme 68. Stereochemistry of Nucleophilic Attack on Chiral Sugar Alkyl Bromide Derivatives



Changing reaction conditions also affected stereoselectivity of these oxidative additions (Scheme 69), which again proceeded with inversion using $KMn(CO)_5$ to give the β-isomer. However, in the presence of $[NBu_4][Br]$, which promotes anomerization, $NaMn(CO)_5$ formed a 3:2 mixture of isomers. Several related Mn-sugar complexes were formed in similar reactions.[82]

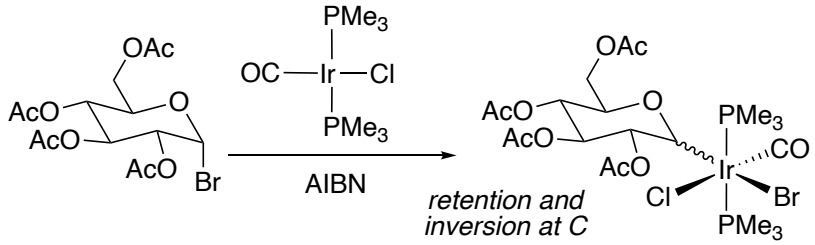
Scheme 69. Controlling Selectivity of Mn-C Bond Formation in the Reactions of $[Mn(CO)_5]^-$ with Chiral Sugar-Derived Alkyl Bromides



4.1.3 Scrambling (radical)

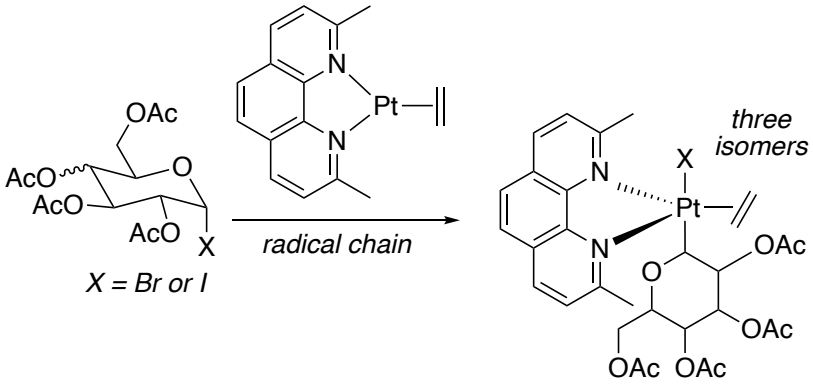
Oxidative addition of a related sugar alkyl bromide to iridium gave a mixture of inversion and retention products, consistent with a radical process, as expected for this AIBN-promoted reaction (Scheme 70).[83]

Scheme 70. Stereochemistry of Radical-Mediated Oxidative Addition of a Sugar Alkyl Bromide to Iridium



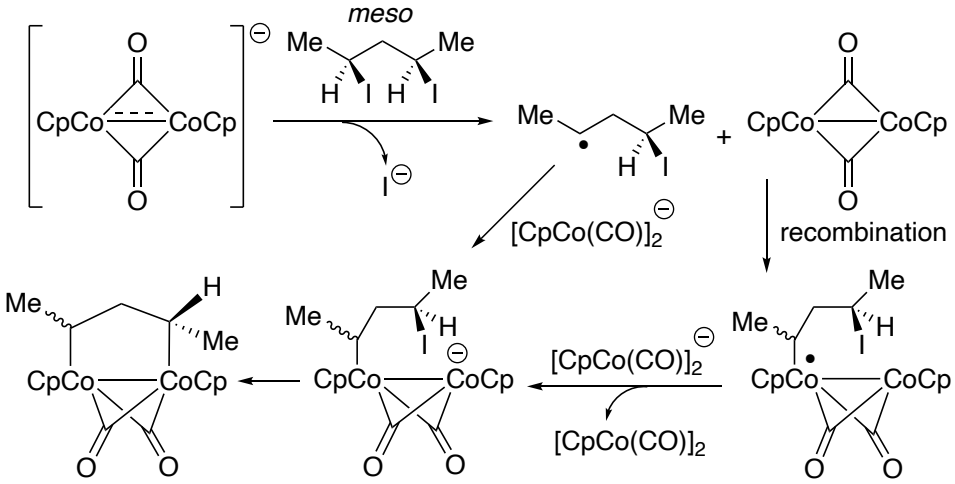
Similar reactions with Pt(0) gave a mixture of isomers, in which the α-sugar was favored (Scheme 71). A radical chain mechanism was proposed.[84]

Scheme 71. Stereochemistry of Oxidative Addition of Sugar-Derived Alkyl Halides to Platinum(0)



In a more complicated process, the stereochemistry of nucleophilic attack of a dinuclear metal carbonyl anion on an alkyl dihalide was investigated (Scheme 72). In the proposed mechanism, electron transfer gives a carbon radical, which inverts rapidly, destroying the stereochemical information at that center, then combines with cobalt to make one [Co]-R* bond unselectively. The second Co-C bond formation was suggested to proceed with higher selectivity, probably with inversion of configuration at carbon, to yield a dinuclear metallacycle.[85]

Scheme 72. Stereochemistry of Nucleophilic Attack of a Metal Carbonyl Anion on a Diiodoalkane

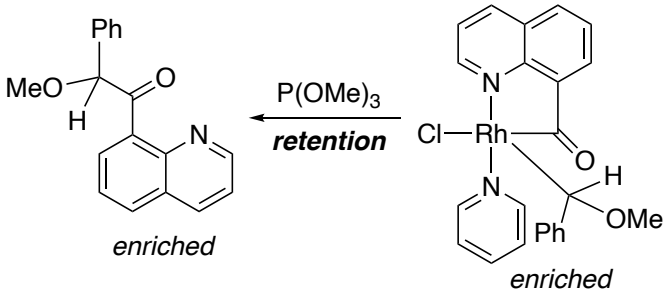


4.2 Reductive elimination

4.2.1 Retention at carbon (concerted)

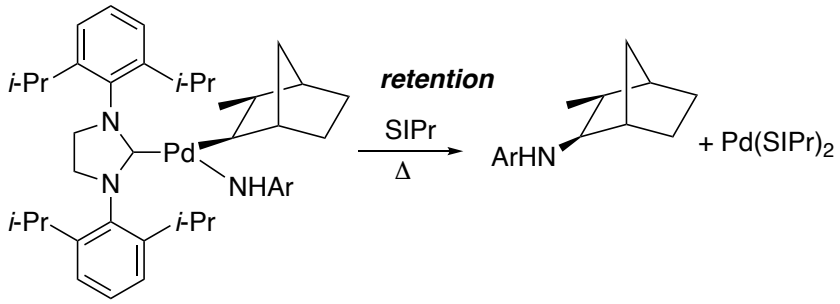
Treating a [Rh]-R* complex with $P(OMe)_3$ promoted C-C reductive elimination (Scheme 73), yielding the same enantioenriched quinoline derivative used to make the chiral Rh-alkyl by oxidative addition (Scheme 62 above).[62] Therefore, both oxidative addition and reductive elimination must have occurred with the same stereochemistry, either with double inversion or double retention. Since analogous reductive eliminations were known to proceed with retention, the authors concluded that both steps went with retention of configuration at carbon.

Scheme 73. Retention of Configuration at Carbon in C-C Reductive Elimination from a Quinoline-Derived Rhodacycle



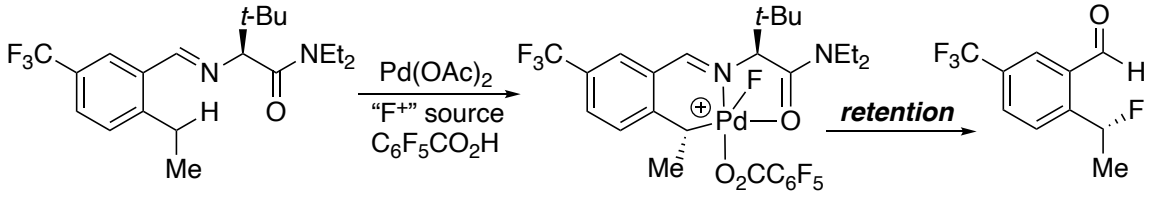
In Scheme 74, the relative configuration of the Pd and methyl norbornyl substituents provided a probe of the stereochemistry of C-N reductive elimination, which occurred for several different N-Ar groups on heating in the presence of the N-heterocyclic carbene SIPr. Since retention was observed, the authors proposed a concerted process.[86]

Scheme 74. C-N Reductive Elimination from Palladium with Retention of Configuration at Carbon



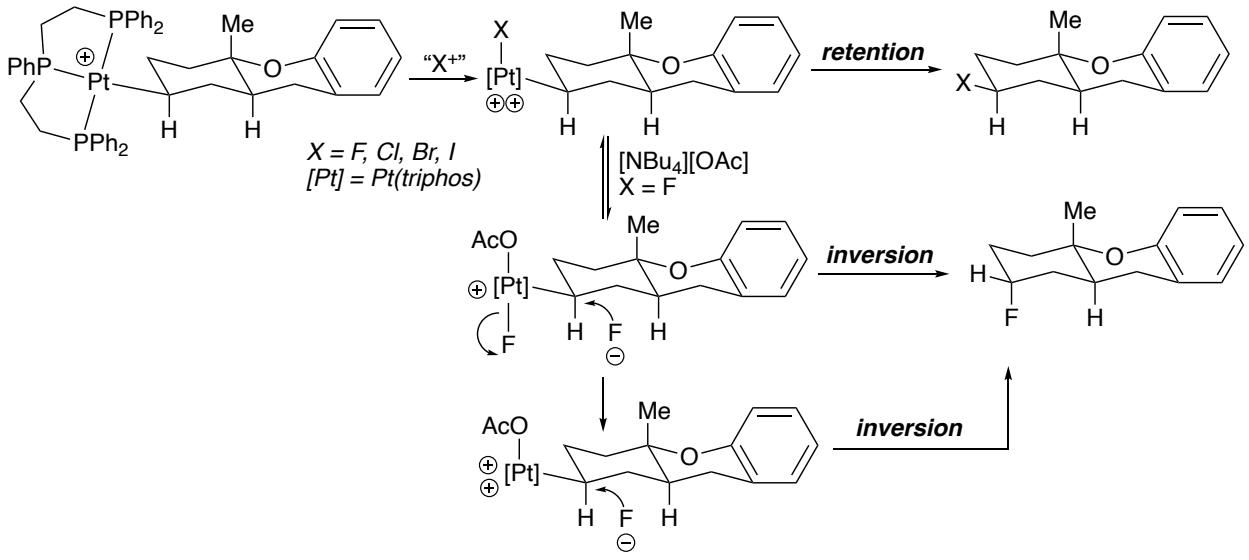
Similarly, because C-F reductive elimination from a chiral Pd alkyl occurred with retention of configuration, a concerted mechanism was proposed (Scheme 75, see Scheme 22 for generation of this [Pd]-R* group under related conditions).[33]

Scheme 75. Proposed Mechanism of Palladium-Catalyzed Oxidative C-F Bond Formation with Retention of Configuration at Carbon via Chiral Palladacycle Intermediates



In related C-F reductive eliminations from Pt(IV) (Scheme 76), oxidation with XeF_2 or related reagents gave dications, which formed products with retention of configuration at carbon, most easily explained by concerted reductive elimination. However, addition of anionic nucleophiles, such as [NBu_4][OAc], gave mixtures of retention and inversion products, which was rationalized by attack of acetate at platinum to form a six-coordinate complex, followed by displacement of fluoride anion, whose S_N2 attack at carbon causes inversion.[87]

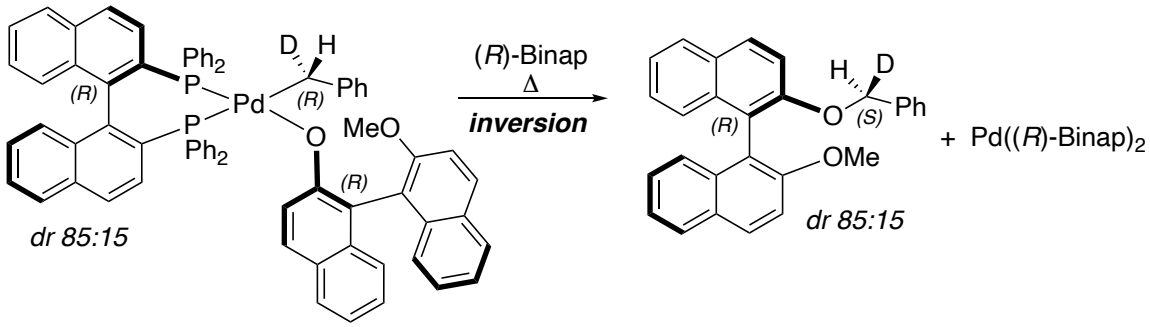
Scheme 76. Oxidatively Induced C-Halogen Bond Formation in Platinum Alkyls with Retention or Inversion of Configuration at Carbon Influenced by an Added Nucleophile



4.2.2 Inversion at carbon (S_N2-type)

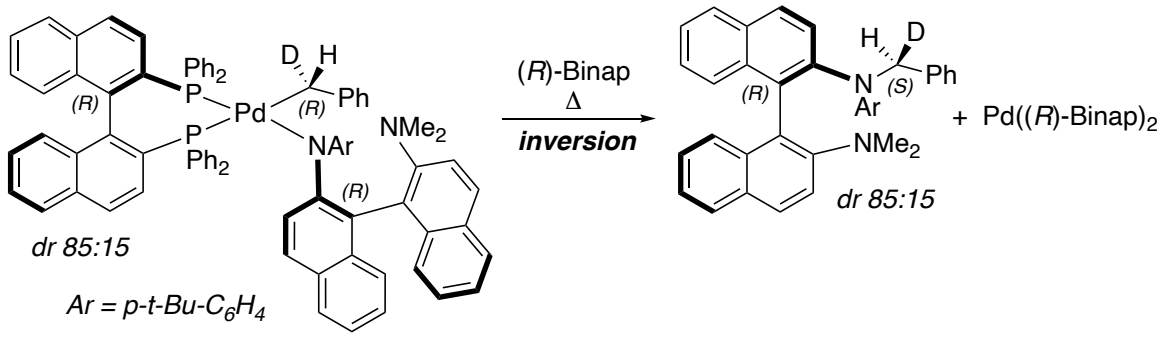
Similar invertive reductive elimination pathways are common when an anionic ligand dissociates from the metal, followed by attack on a coordinated alkyl group. For example, C-O reductive elimination of a diastereomerically enriched mixture of D-labelled Pd-benzyl complexes occurred with inversion at carbon, suggesting dissociation of the aryloxide anion, perhaps promoted by η^3-benzyl coordination, followed by nucleophilic attack (Scheme 77).[88]

Scheme 77. C-O Reductive Elimination from Palladium with Inversion of Configuration at Carbon



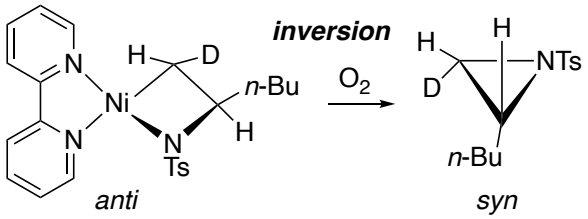
With the same D-labelled probe, inversion of configuration at carbon was also observed in C-N reductive elimination, with the same interpretation (Scheme 78).[7979]

Scheme 78. C-N Reductive Elimination from Palladium with Inversion of Configuration at Carbon



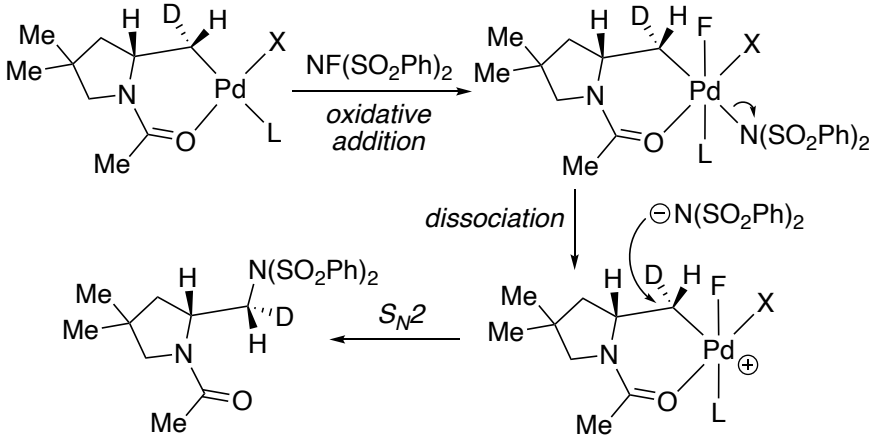
Inversion at carbon also occurred in oxidatively induced C-N reductive elimination from nickel (Scheme 79). By analogy to the proposed mechanism of formation of the D-labeled nickelacycle (Scheme 65), this process could occur by Ni-N heterolysis to yield an N-anion, which attacks at carbon in an S_N2 process. However, the involvement of oxygen suggested that a homolytic S_H1 pathway was also possible.[7777]

Scheme 79. Oxidatively Induced C-N Reductive Elimination of an Aziridine from Nickel



Treatment of a D-labelled [Pd]-R* palladacycle with $NF(SO_2Ph)_2$ resulted in C-N bond formation with inversion of configuration at carbon, consistent with the mechanism shown in Scheme 80. After N-F oxidative addition to yield Pd(IV), dissociation of the amido anion, followed by S_N2 attack at the Pd-bound carbon was proposed.[89]

Scheme 80. Proposed Mechanism Leading to Inversion of Configuration at Carbon in Reaction of a D-Labelled Palladacycle with $NF(SO_2Ph)_2$

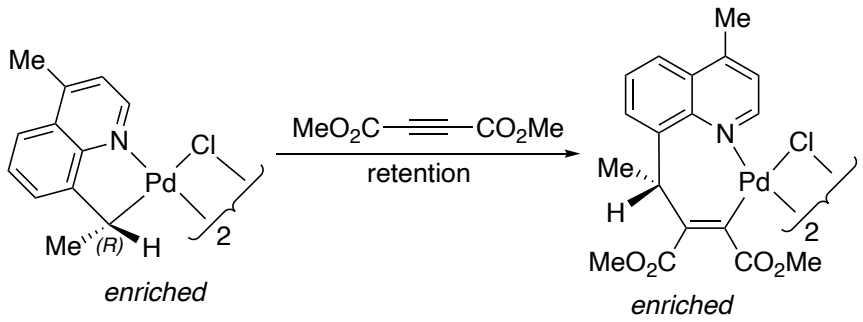


4.3 Migratory Insertion

On the precedent of observations like those in Scheme 2, migratory insertion is often assumed to proceed with retention of configuration at the migrating carbon. In Scheme 81, reaction of the

enantiomerically enriched palladacycle from Scheme 10 with an activated alkyne gave a new optically active palladacycle. Although the absolute configuration was not determined, the authors proposed that insertion proceeded with retention.[90]

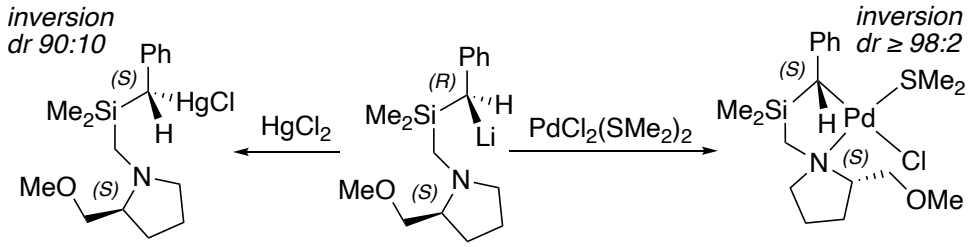
Scheme 81. Insertion of an Activated Alkyne into the Pd-C Bond of a Chiral Ethylquinoline-Derived Palladacycle



4.4 Transmetalation

Transmetalation of chiral alkyl groups from main group metals to transition metals, important in cross-coupling catalysis, may proceed with inversion or retention of configuration, which is commonly assessed using chiral probe molecules without isolation or observation of intermediates.[91] In Scheme 82, a configurationally stable chelated organolithium underwent transmetalation to Hg and Pd with predominant inversion of configuration, rationalized by the greater steric accessibility of the site opposite lithium to electrophiles.[92]

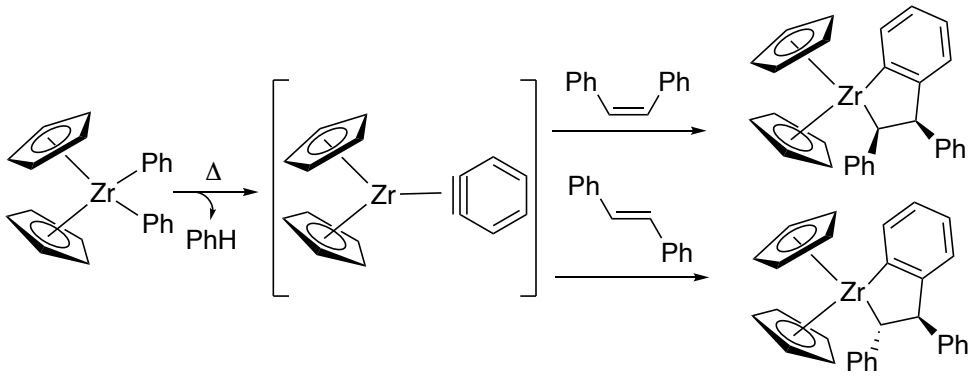
Scheme 82. Inversion of Configuration at Carbon in Transmetalation from a Chiral Lithium Alkyl to Mercury or Palladium



4.5 Cycloaddition

The structure of the products in [2+2] cycloadditions of *cis*- and *trans*-stilbene with a zirconocene-benzyne complex provided evidence for a concerted process with retention of stereochemistry (Scheme 83).[93]

Scheme 83. Retention of Stereochemistry in Cycloadditions of Stilbenes with a Zirconocene-Benzyne Complex

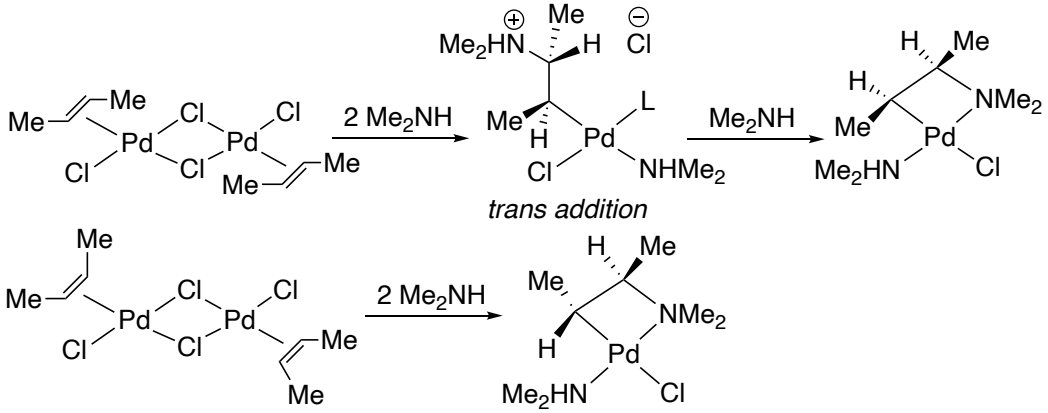


4.6 Nucleophilic attack on coordinated ligands

The stereochemistry of nucleophilic attack on coordinated alkenes provides mechanistic information. Trans attack occurs with an external nucleophile, while cis attack suggests an internal

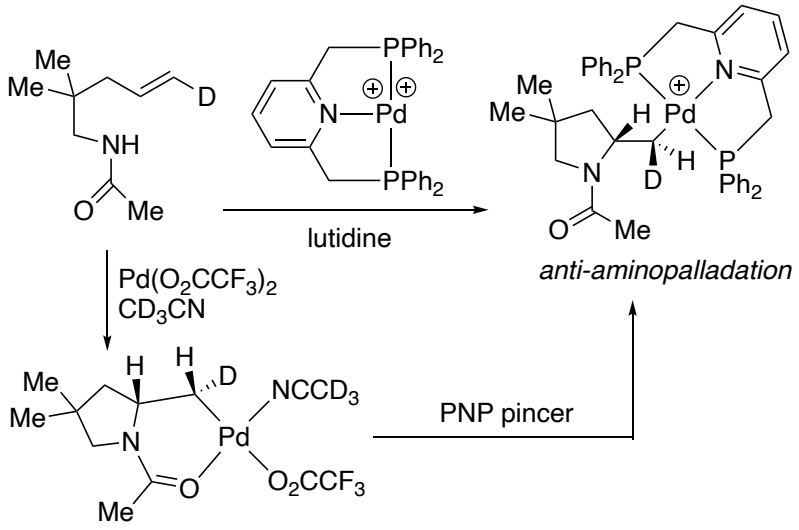
nucleophile, as in migratory insertion.[94] For example, the stereochemistry of the four-membered rings in Scheme 84 was direct evidence for trans attack of amines on Pd-bound E- or Z-butene.[95]

Scheme 84. Evidence for Trans Attack of an Amine on Coordinated Alkenes in Synthesis of a Palladacycloaminobutane



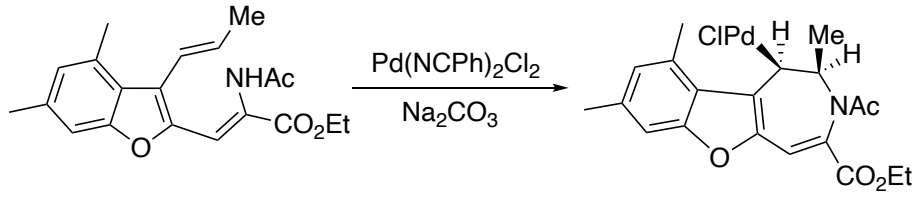
In a related example, treatment of a D-labeled alkene with a Pd(PNP) pincer dication must result in *anti*-aminopalladation by attack of the amine on coordinated alkene (Scheme 85, top). Instead, reaction with palladium trifluoroacetate, followed by the PNP ligand gave the same product, showing that amino-palladation occurred in both pathways, not alkene insertion into the Pd-N bond, which would give the *syn*-product (Scheme 85).[89]

Scheme 85. Evidence for *anti*-Aminopalladation in Pd-Mediated Intramolecular Hydroamination of a D-Labelled Substrate



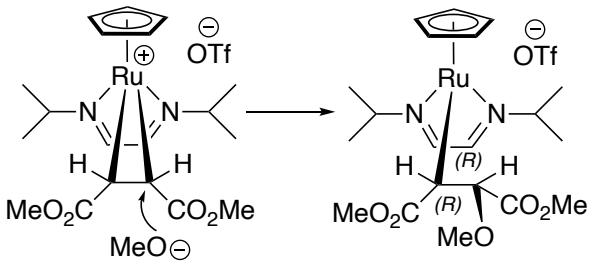
In contrast, *cis*-aminopalladation occurred in palladacycle formation in Scheme 86. The structure shown fits the reported empirical formula, but presumably this complex forms aggregates or coordinates additional ligands, with four-coordinate palladium.[96]

Scheme 86. *Cis*-Aminopalladation in Formation of a Palladacycle



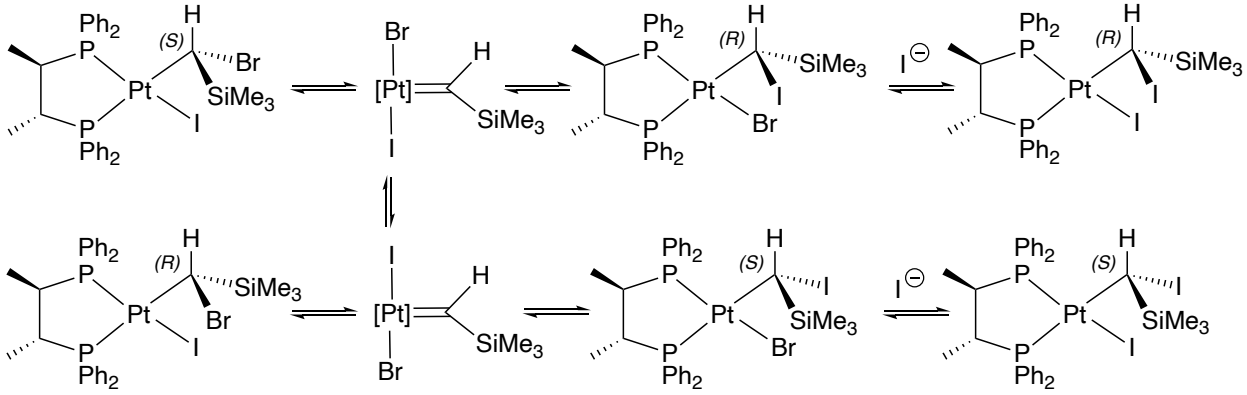
Nucleophilic attack on a coordinated alkene in Scheme 87 gave a 97:3 mixture of diastereomers which both contained two chiral centers, proposed to form from sterically preferred *anti* attack vs the less favored *syn* attack.[97]

Scheme 87. Anti Attack of Methoxide on a Ru-Bound Alkene Preferentially Gave the *RR* and *SS* Diastereomers of the Ru-Alkyl Product, Only One of Which is Shown



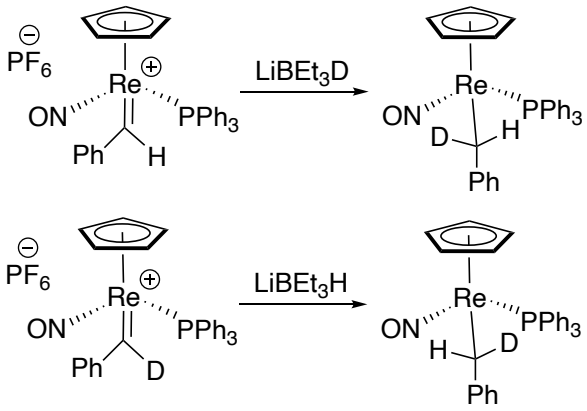
In an unusual process, halide ions attacked the chiral alkyl group in [Pt]-R* complexes (Scheme 88, see Schemes 35 and 52 for related transformations in this system). Displacement of bromide from carbon by iodide occurred with inversion of configuration in a proposed S_N1 process. This apparent contradiction was explained by anchimeric assistance by platinum via a proposed carbene intermediate.[48] After C-Br oxidative addition to Pt gives a five-coordinate carbene complex, migration of iodide to the carbene is faster than rotation about the Pt=C bond, resulting in inversion of configuration at C. Then halide exchange at platinum yields the product. Alternatively, a related mechanism with cationic intermediates formed by loss of bromide anion was possible.

Scheme 88. Anchimeric Assistance in Attack of Halides at Pt-C Bonds ([Pt] = Pt(Chiraphos))



Stereospecific nucleophilic attack of a borohydride reagent on a Re-carbene gave deuterium-labeled [Re]-R* benzyl complexes (Scheme 89).[98]

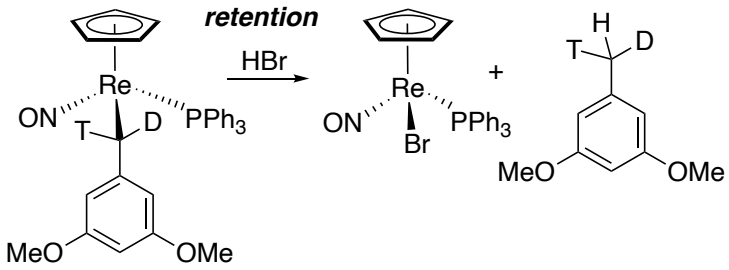
Scheme 89. Stereospecific Nucleophilic Attack on a Re-Carbene Gave Chiral Re-Benzyl Complexes



4.7 Electrophilic attack on coordinated ligands

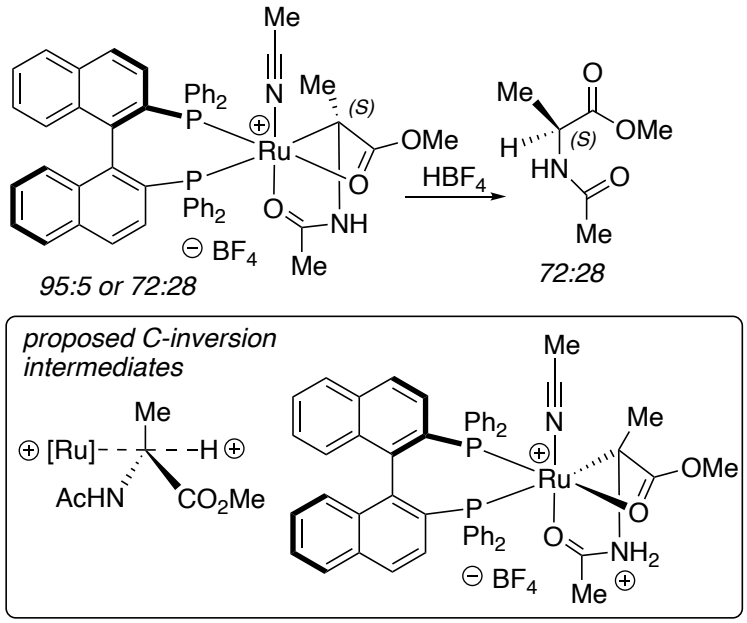
These processes usually occur with retention of configuration at carbon, but exceptions are known. Reactions may occur via addition to the metal, followed by reductive elimination, by direct attack at carbon, or via four-centered transition states. In Scheme 90, which involves Re-benzyl complexes like those in Scheme 89, protonolysis of a [Re]-R* group proceeded with retention at both Re and C.[99]

Scheme 90. Protonolysis of a C-Stereogenic Re-Bound Alkyl Ligand Resulted in Retention of Configuration at Both Carbon and Rhenium



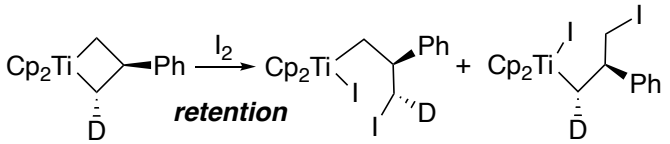
In Scheme 91, protonolysis of a diastereomeric mixture of [Ru]-R* complexes which differed only in the configuration of the metal-bound carbon was expected to proceed with retention of configuration via protonation at Ru, followed by reductive elimination. However, the process was not stereospecific, resulting in the same enantiomeric enrichment of the product for different mixtures of the metal complex, either 95:5 or 72:28 dr. Therefore, two parallel protonolysis pathways were proposed, with retention or inversion at C. To explain the latter, either protonation at the back side of the Ru-C bond or at N, followed by intramolecular proton transfer, were invoked (box, Scheme 91).[100]

Scheme 91. Non-Stereospecific Protonolysis of Chiral Ruthenium Alkyls and Proposed Mechanisms Leading to Inversion at Carbon



Treatment of a D-labelled titanocene with iodine resulted in retention of configuration at carbon (Scheme 92).[101]

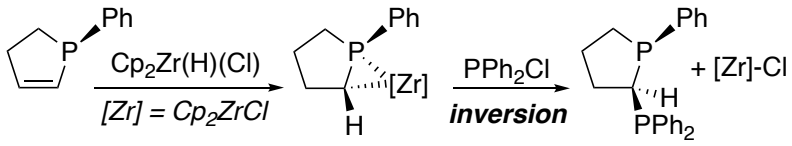
Scheme 92. Retention of Configuration at Carbon in Iodination of Ti-C Bonds



In related metallocene chemistry, however, hydrozirconation of a phospholene gave a [Zr]-R* C,P-chelated complex with *syn* Ph and H groups. Reaction with diphenylchlorophosphine resulted in P-C bond formation with inversion of configuration at carbon (Scheme 93). The authors suggested that the expected four-center retentive transition state was not accessible because the bidentate

ligand occupied a coordination site, necessitating an open transition state. However, with a closely related derivative, retention at carbon occurred, showing that these reactions are still not well understood.[102]

Scheme 93. Inversion of Configuration at Carbon in Electrophilic Cleavage of a Zr-C Bond



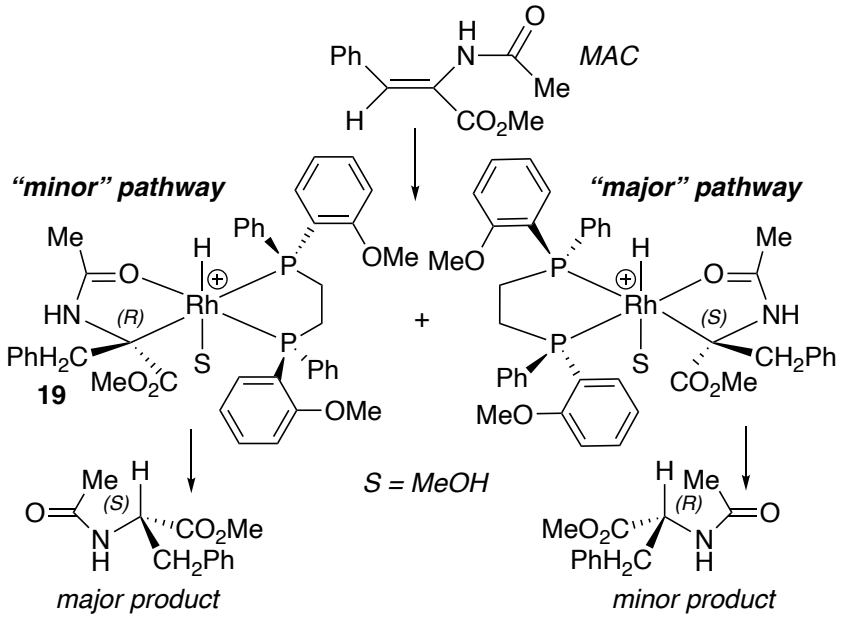
5. Catalysis

[M]-R* complexes are commonly invoked as intermediates in asymmetric catalysis, and in some cases they have been directly observed or even isolated. Their structural characterization in solution or the solid state provides information on the catalytic mechanism and the origin of asymmetric induction.

5.1 Asymmetric hydrogenation

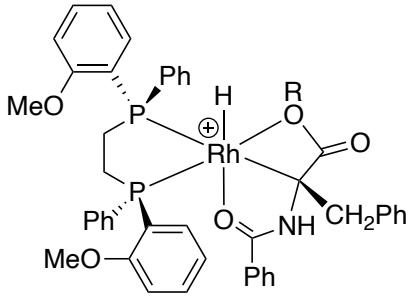
A key step in the most successful application of asymmetric catalysis, hydrogenation, involves selective insertion of an alkene into a metal-hydride bond to give a chiral metal alkyl, whose subsequent C-H reductive elimination, if another metal hydride is present, or protonolysis yields the enantiomerically enriched hydrogenation product. For example, in Landis and Halpern's impactful mechanistic studies of Rh-catalyzed asymmetric hydrogenation, the disfavored alkene adduct ("minor" pathway) led to the major hydrogenation product and [Rh]-R* intermediate **19** was observed by low-temperature ^{31}P NMR spectroscopy (Scheme 94).[103]

Scheme 94. Diastereomeric [Rh]-R* Alkyl Hydride Intermediates in Rh(Dipamp)-Catalyzed Asymmetric Hydrogenation of Methyl-(Z)-α-acetamidocinnamate (MAC)



With the same Rh(Dipamp) catalyst and a similar substrate, related chiral alkyl hydrides, featuring characteristic tridentate coordination of the [Rh]-R* group, were characterized by NMR spectroscopy.[104] In more recent studies (see below), however, the proposed Rh-O ester coordination in such complexes is considered to involve the carbonyl oxygen.

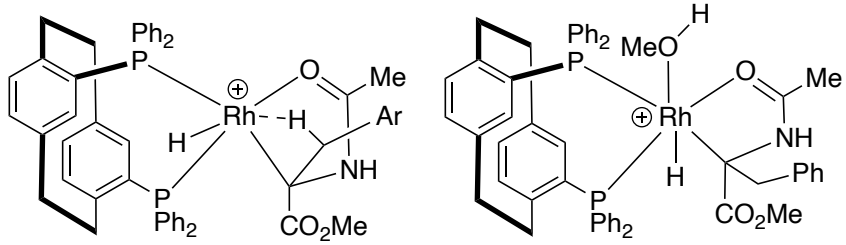
Scheme 95. Chiral Rhodium Alkyl Hydrides Observed as Intermediates in Rh-Catalyzed Asymmetric Hydrogenation



R = H, Me

Similar NMR observations have been made for a variety of chiral bis(phosphines) and functionalized alkene substrates. In Scheme 96, an alkyl hydride complex included an agostic C-H bond, while a classical [Rh]-R* isomer with solvent coordination was not seen.[105]

Scheme 96. Generation of a Rh(PhanePhos) Agostic Alkyl Complex Formed by Alkene Insertion

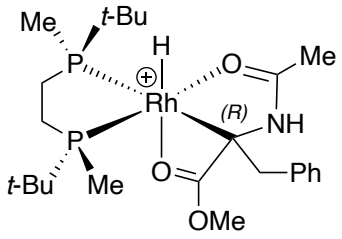


agostic alkyl
Ar = Ph or p-$CF_3C_6H_4$

not observed

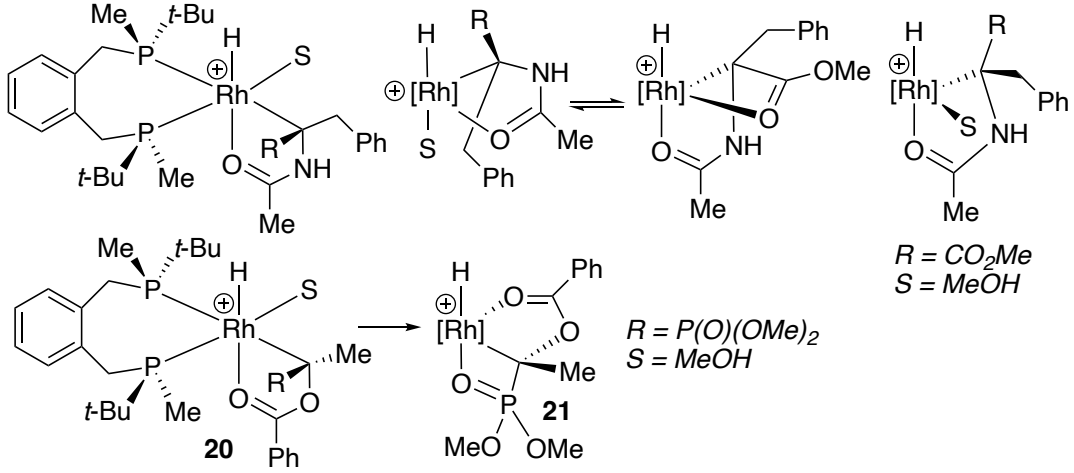
Similarly, with a more electron-rich chiral alkylphosphine, a rhodium alkyl hydride intermediate formed by enantiodetermining migratory insertion was observed by NMR spectroscopy (Scheme 97).[106]

Scheme 97. Observation of a Rhodium Alkyl Hydride Complex, an Intermediate in Rh-Catalyzed Asymmetric Hydrogenation



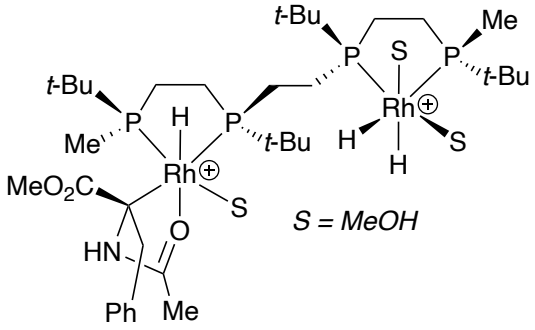
With a related ligand having a larger bite angle, a whole series of four isomeric alkyl hydrides was observed (Scheme 98, top). Replacing the usual amide substituent with a phosphonate gave chelate **20**, which underwent ligand substitution to yield the more stable **21**, with a tridentate ligand.[107]

Scheme 98. Observation of Four Isomeric Rhodium Alkyl Hydride Complexes and Phosphonate Analogues **20**-**21**



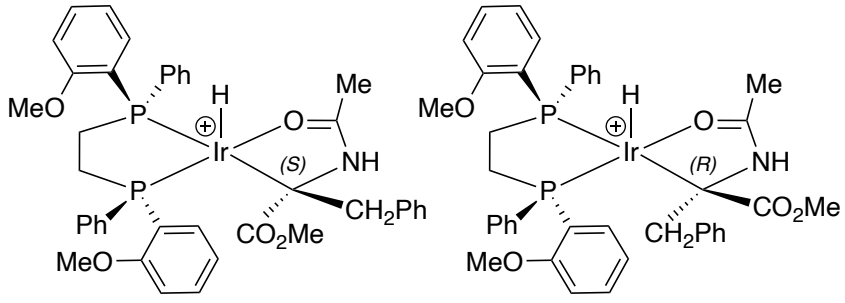
With an exotic tetraphosphine ligand designed to support dinuclear rhodium complexes, a trihydride intermediate, which is an analogue of the usual monohydrides, was observed (Scheme 99).[108]

Scheme 99. Observation of a Dinuclear Rhodium Alkyl Hydride Complex, an Intermediate in Rh-Catalyzed Asymmetric Hydrogenation



Analogous iridium complexes serve as models for the more active Rh catalysts, or as selective catalysts in their own right. With Dipamp (compare Rh complexes in Schemes 94-95), both C-epimers of stable [Ir]-R* cationic alkyl hydrides were formed by alkene insertion (Scheme 100). They did not interconvert under the reaction conditions, so that both isomers could be observed, in contrast to the Rh case, where only one was seen.[109]

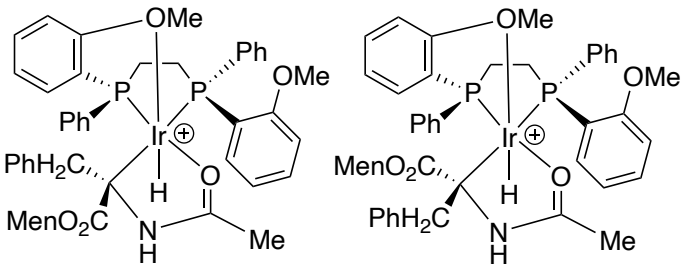
Scheme 100. Diastereomeric Cationic Ir(Dipamp) Alkyl Hydrides



In a follow-up paper from the same group, the absolute configurations of the chiral alkyl centers were determined by NOE studies of related C-epimeric diastereomers with menthyl ester

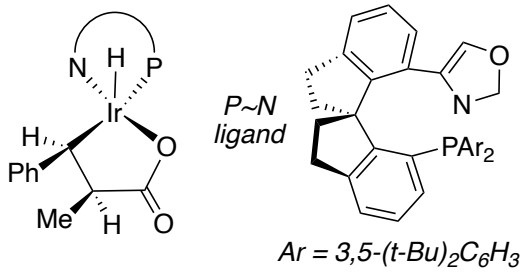
substituents, with coordination of the Dipamp MeO group (Scheme 101). Presumably similar binding occurred in Scheme 100, although those complexes were drawn as five-coordinate.[110]

Scheme 101. Diastereomeric Cationic Ir(Dipamp) Alkyl Hydrides with Menthyl Ester Substituents



With a P~N phosphine-oxazoline ligand, a five-coordinate Ir alkyl hydride complex was observed (Scheme 101).[111,112]

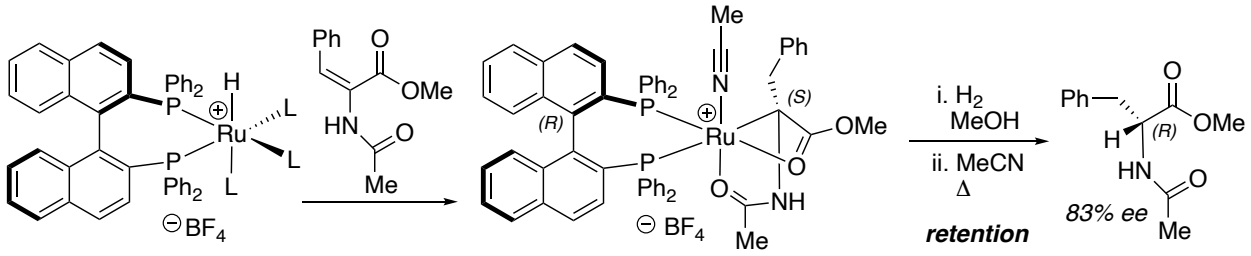
Scheme 102. Observation of an Iridium Alkyl Hydride Complex, an Intermediate in Ir-Catalyzed Asymmetric Hydrogenation



Rhodium and iridium dihydride intermediates react with alkenes to yield chiral alkyl hydrides, as in Schemes 94-102 above. In contrast, ruthenium-catalyzed asymmetric hydrogenation often involves monohydrides, in which alkene insertion again yields [Ru]-R* intermediates. Without a remaining hydride, C-H reductive elimination is not possible, so reaction with H_2, either by

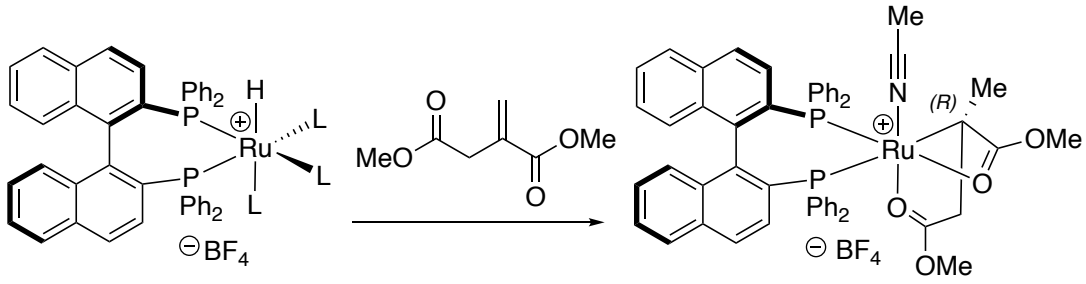
protonolysis or oxidative addition/reductive elimination, is required to complete the catalytic cycle. This sequence was observed with a Ru(Binap) catalyst in Scheme 103,[113] where β-hydride elimination was fast and reversible prior to irreversible hydrogenolysis of the Ru-C bond, which was assumed to proceed with retention of configuration at carbon.[114]

Scheme 103. Synthesis of a Chiral Ruthenium Alkyl via Insertion of a Functionalized Alkene into a Ru-H Bond, followed by Hydrogenolysis with Retention of Configuration (L = Acetone or Acetonitrile)



Similarly, the related substrate dimethyl itaconate gave an isolable chiral Ru alkyl as a mixture of diastereomers (only the major one is shown in Scheme 104).

Scheme 104. Synthesis of a Chiral Ruthenium Alkyl via Insertion of a Functionalized Alkene into a Ru-H Bond

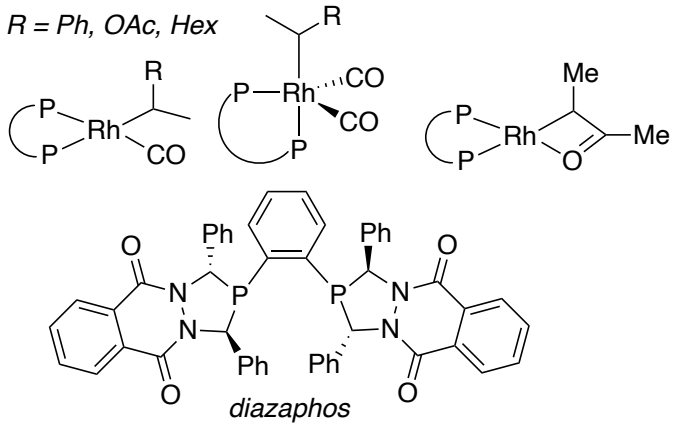


5.2 Asymmetric hydroformylation

As in asymmetric hydrogenation, [M]-R* intermediates are formed in asymmetric hydroformylation by alkene insertion into M-H bonds, but 2,1-insertion is required to yield the desired branched products instead of the linear ones normally formed in commercial hydroformylation of α-olefins.

Scheme 105 shows examples of such intermediates observed by NMR spectroscopy with a Rh(diazaphospholane) catalyst and the substrates styrene, vinyl acetate, and 1-octene. The kinetically favored branched alkyls were not configurationally stable, undergoing reversible β-H elimination to interconvert with the linear isomer, and acyl complexes were also observed.[115,116]

Scheme 105. Chiral Rhodium Branched Alkyls: Intermediates in Rh-Catalyzed Asymmetric Hydroformylation

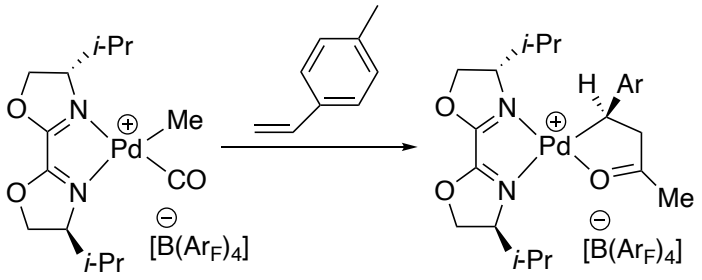


5.3 Asymmetric copolymerization

Related 2,1-insertions of alkenes into M-C bonds to give chiral alkyl intermediates are important steps in metal-catalyzed alkene-CO copolymerization. For example, reaction of a styrene with a

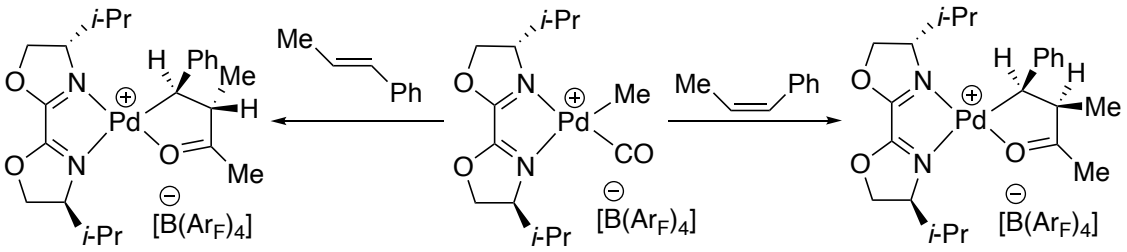
Pd(bis-oxazoline) cation gave only one diastereomeric metallacycle (Scheme 106), which underwent further alternating insertions of CO and styrene to form the polymer.[117]

Scheme 106. Diastereospecific Formation of a Chiral Palladacycle, an Intermediate in CO-Styrene Copolymerization



Similar processes occurred with isomeric propenylbenzenes (Scheme 107). These [Pd]-R* complexes were intermediates in catalytic alkoxy-carbonylation of styrenes.[118]

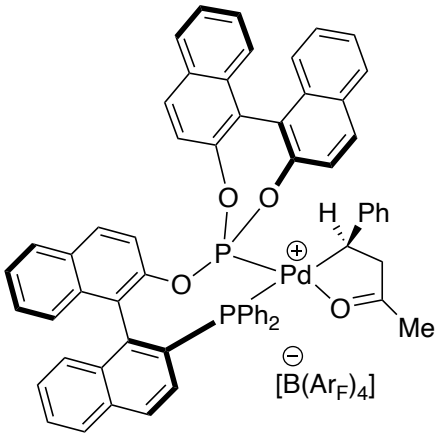
Scheme 107. Chiral Palladacycles as Intermediates in Catalytic Alkoxycarbonylation of Styrenes



Similarly, in Pd(BINAPHOS)-catalyzed copolymerization of styrene with CO, insertion of styrene to make linear or branched metallacycles was observed. Scheme 108 shows only the branched isomer, which was proposed to undergo β-H elimination, while the linear one was responsible for productive copolymerization.[119] Further NMR study using a high-pressure flow cell showed that

the branched isomer was inactive to further insertion but underwent β-H elimination more slowly under these conditions than previously expected.[120]

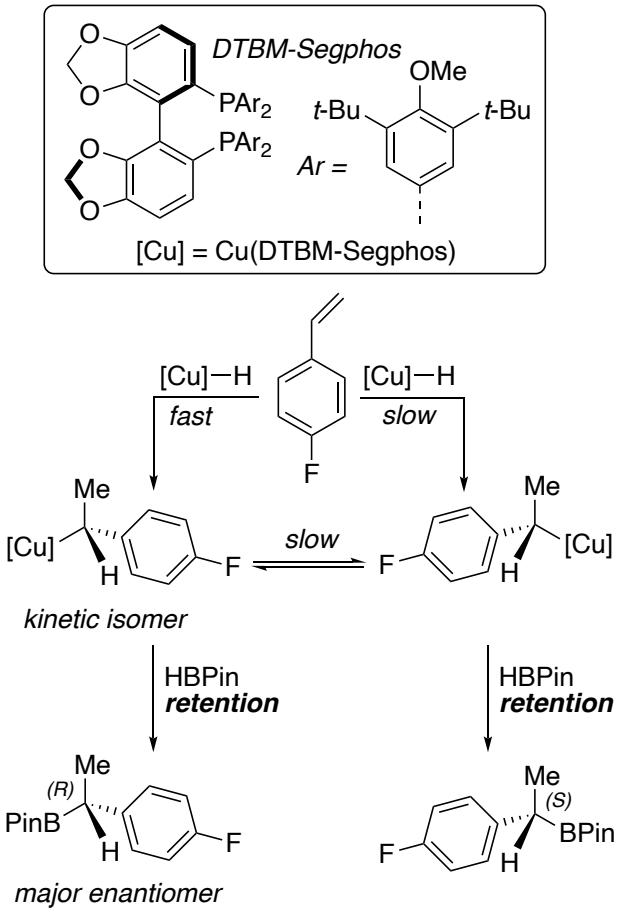
Scheme 108. Chiral Palladacycles as Intermediates in Pd-Catalyzed CO-Styrene Copolymerization



5.4 Asymmetric hydroboration

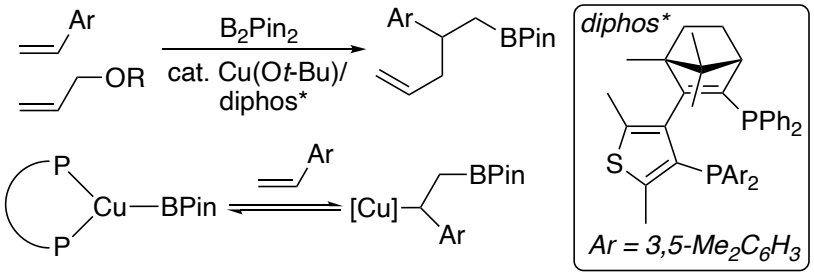
The chiral copper alkyls in Scheme 32 were key intermediates in catalytic asymmetric hydroboration (Scheme 109). In the proposed mechanism, kinetic selectivity in styrene insertion gave an initial 19:1 mixture of [Cu]-R* intermediates. Interconversion of these complexes by β-hydride elimination/reinsertion was slow compared to productive σ-bond metathesis with the borane, so enantioselectivity from the insertion step was retained. Comparing the configuration of the product with that of the Cu-alkyl intermediates showed that σ-bond metathesis went with retention of configuration at carbon.[45]

Scheme 109. Role of [Cu]-R* Intermediates in Catalytic Asymmetric Hydroboration of Styrenes



In a related copper-catalyzed reaction of styrenes, both B-C and C-C bonds were formed using B_2Pin_2 and a second olefin, with enantioselectivity controlled by a chiral bis(phosphine) (Scheme 110). A key step, diastereoselective insertion of a styrene into a Cu-B bond to form [Cu]-R* complexes, was observed by low-temperature NMR spectroscopy.[121]

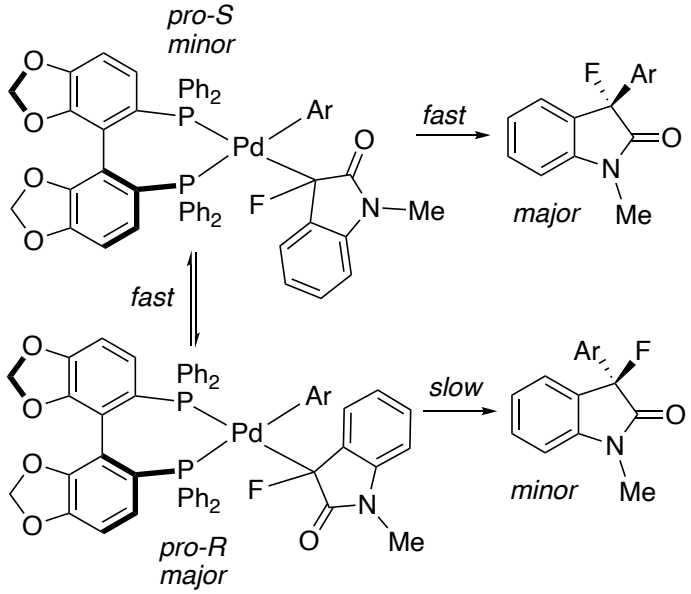
Scheme 110. Enantioselective Copper-Catalyzed Styrene/Alkene Coupling-Borylation and Formation of a [Cu]-R* Intermediate



5.5 Other asymmetric reactions

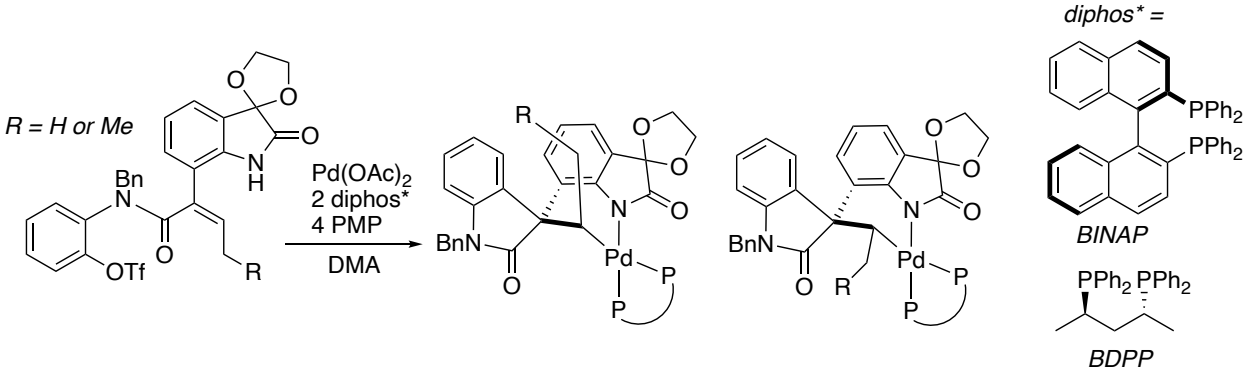
The chiral Pd enolates in Scheme 36 were intermediates in Pd-catalyzed cross-coupling with aryl halides (Scheme 111). Although the equilibrium between the C-epimeric [Pd]-R* diastereomers was only modestly selective, the minor isomer underwent C-C reductive elimination almost 100 times faster than the other, and Pd-enolate interconversion was faster to, or comparable in rate to reductive elimination, which proceeded with retention of configuration at carbon.[50]

Scheme 111. Origin of Enantioselectivity in Palladium(Segphos)-Catalyzed Cross-Couplings via Intermediate Chiral Enolate Complexes: Faster Reductive Elimination for One Diastereomer



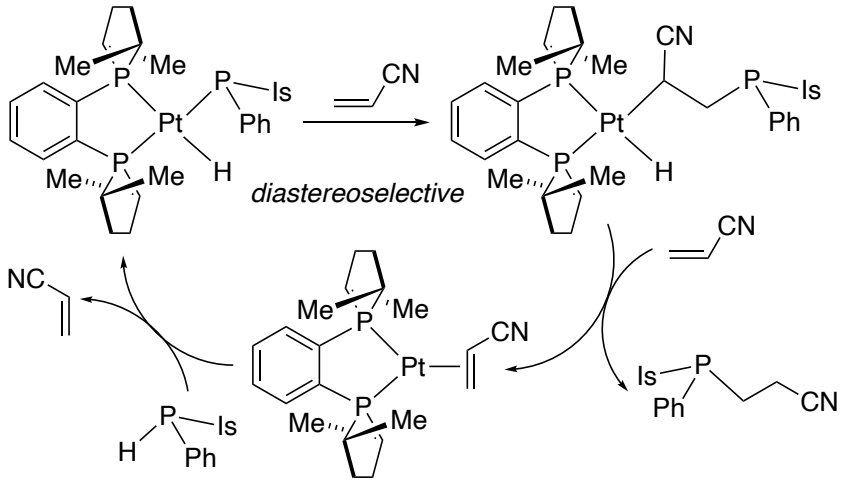
The chiral palladacycles whose C-epimerization was described in Scheme 51 were intermediates in asymmetric intramolecular Heck reactions (Scheme 112).[66]

Scheme 112. Chiral Palladacycles Observed in Studies of the Asymmetric Heck Reaction (PMP = 1,2,2,6,6-pentamethylpiperidine*)*



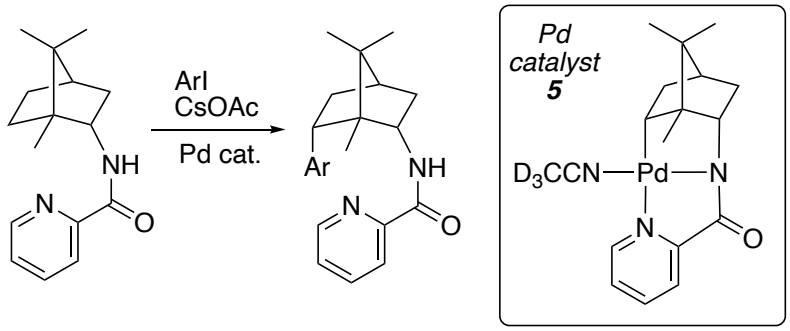
Diastereoselective formation of [Pt]-R* complexes by nucleophilic attack of a P-stereogenic phosphido ligand on a Michael acceptor alkene (Scheme 46) was the enantioselective step in asymmetric hydrophosphination catalysis, where it was observed directly (Scheme 113, Is = 2,4,6-(i-Pr)$_3$C$_6$H$_2$).[122] Although the C-stereocenter was destroyed by C-H reductive elimination, diastereoselective attack on the alkene controlled the configuration of the P-stereocenter.

Scheme 113. Diastereoselective Formation of Chiral Pt-Alkyl Intermediates in Catalytic Asymmetric Hydrophosphination of Acrylonitrile



Scheme 21 showed asymmetric cyclopalladation of a chiral bornylamine derivative. The resulting [Pd]-R* complex was a competent intermediate for Pd-catalyzed arylation of this substrate (Scheme 114), for which a mechanism involving oxidative addition to yield Pd(IV), followed by C-C reductive elimination, was proposed.[32]

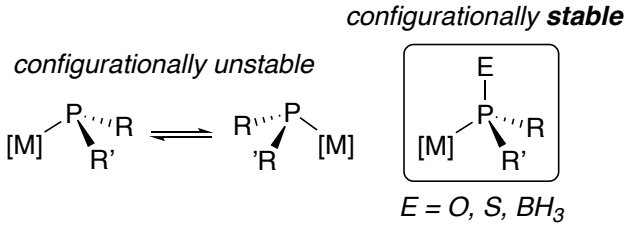
Scheme 114. A Chiral Bornylamine-Derived Palladacycle as Catalyst Precursor for Selective Cross-Coupling via C-H Activation



6. Analogous Chemistry with P-Stereogenic Anionic Ligands

Metal phosphido complexes M-PR_2 are isoelectronic analogues of metal alkyls M-CR_3, where the phosphorus lone pair takes the place of a carbon substituent. Although phosphines PR_3 are configurationally stable,[123] M-PR_2 complexes undergo rapid pyramidal inversion,[124] which makes it difficult to prepare P-stereogenic derivatives [M]-PRR' in enantiomerically or diastereomerically pure form for investigation of the stereochemistry of their reactions.[125] This configurational instability has been exploited in asymmetric catalysis to prepare P-stereogenic phosphines,[126] but does not enable direct comparison to the [M]-R* complexes which are the main subject of this review. However, replacing the P lone pair in [M]-PR_2 with an oxide, sulfide, or borane yields configurationally stable species whose stereochemical behavior and role in catalysis has been investigated (Scheme 115).

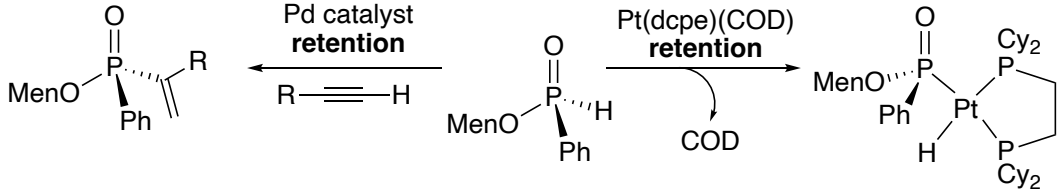
Scheme 115. Pyramidal Inversion in P-Stereogenic Metal Phosphido Complexes and Configurationally Stable Analogues



In contrast to the results with the more commonly studied [M]-R* complexes (section 4 above), fundamental transformations of [M]-P* analogues, including oxidative addition, reductive elimination, migratory insertion, and transmetalation have all been observed to proceed with retention of configuration. It is not clear if this reflects a fundamental difference between the chemistry of phosphorus and carbon, or simply the limited number of studies on P to date.

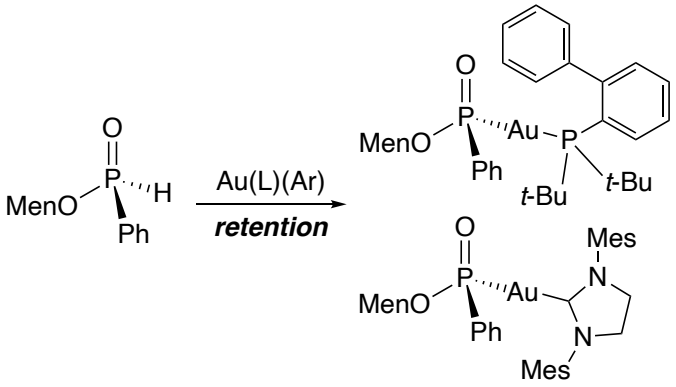
P-H oxidative addition of an enantiomerically pure menthoxy-phosphine oxide to Pt(0) occurred with retention of configuration, as did Pd-catalyzed hydrophosphinylation of alkynes with this substrate using the precursor $Pd(PPhMe_2)_2Me_2/Ph_2P(O)OH$ (Scheme 116).[127]

Scheme 116. Retention of Configuration at Phosphorus in P-H Oxidative Addition to Pt(0) and in Pd-Catalyzed Hydrophosphinylation of Alkynes



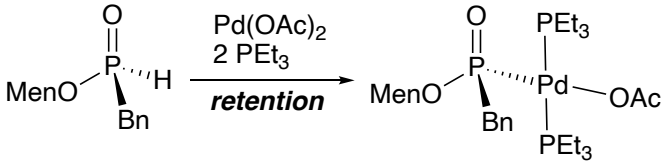
In analogous gold chemistry with the same substrate, Au-P bond formation proceeded with retention of configuration at P (Scheme 117).[128,129]

Scheme 117. Retention of Configuration at Phosphorus in Au-P Bond Formation



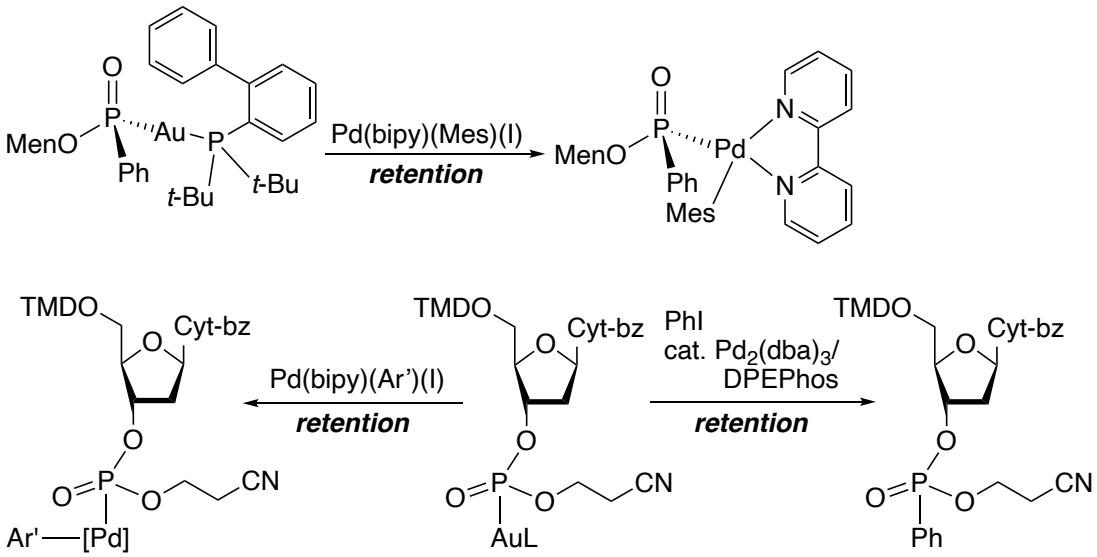
A similar P-H→P-M process on palladium, with a closely related menthol-derived substrate, also went with retention (Scheme 118).[130]

Scheme 118. Retention of Configuration at Phosphorus in Pd-P Bond Formation



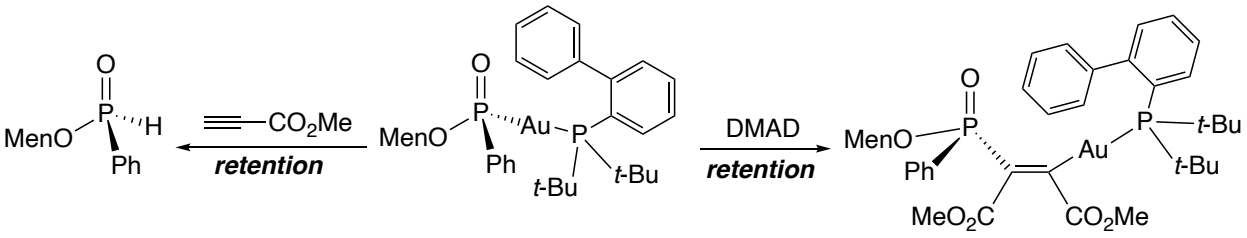
Transmetalation from gold to palladium transferred phosphido-oxide groups with retention of configuration at P, which was exploited in a stereospecific Pd-catalyzed P-C cross-coupling (Scheme 119).[128]

Scheme 119. Transmetalation of a Phosphido Oxide Group from Au to Pd with Retention of Configuration at Phosphorus, and Its Application in Cross-Coupling Catalysis



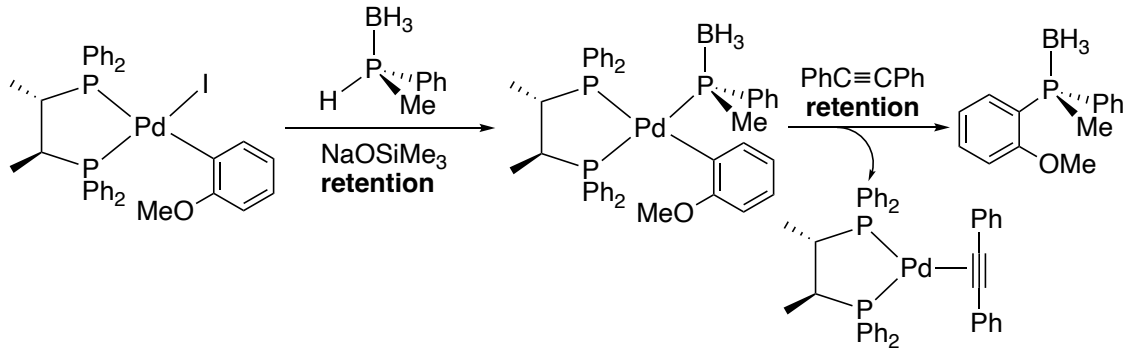
The reaction of a gold phosphido-oxide complex with a terminal alkyne resulted in protodemetalation, yielding the secondary phosphine oxide with retention of configuration at phosphorus. With an activated alkyne, DMAD, migratory insertion gave a gold-vinyl complex with retention of configuration at P (Scheme 120).[129]

Scheme 120. Retention of Configuration in Formation of Au-P Bonds from a P-Stereogenic Secondary Phosphine Oxide, and in Insertion of an Alkyne into an Au-P Bond



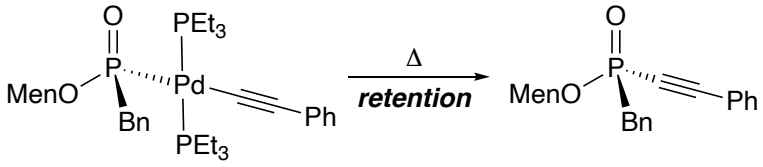
Pd-P bond formation involving an enantioenriched secondary phosphine-borane ("transmetalation") proceeded with retention at P, at low temperature (Scheme 121). However, on warming the stereospecificity was reduced, presumably because of the configurational instability of the phosphido-borane anion. This effect could be exploited by starting with racemic phosphine-borane at room temperature, which resulted in dynamic kinetic resolution with modest selectivity. P-C reductive elimination of a phosphido-borane Pd-aryl complex also went with retention at P.[131]

Scheme 121. Retention of Configuration at Phosphorus in Pd-P Bond Formation and P-C Reductive Elimination Involving a Phosphine-Borane



Scheme 122 shows an analogous P-C reductive elimination of a phosphido-oxide group, also with retention of configuration at P.[130]

Scheme 122. Retention of Configuration at Phosphorus In P-C Reductive Elimination from Pd



7. Conclusions

This survey has demonstrated the continued importance of [M]-R* and analogous [M]-P* complexes in determining the stereochemistry of fundamental transformations involving M-C and M-P bonds, such as oxidative addition, reductive elimination, transmetalation, and migratory insertion, and the use of these observations to provide mechanistic information. Synthesis or generation of these compounds exploits classical approaches in organometallic chemistry, applied to chiral substrates or controlled by chiral ligands. [M]-R* groups are often configurationally stable, but C-epimerization by processes such as β-hydride elimination or M-C homolysis is mechanistically significant and may be valuable or undesired in catalysis. Because the fundamentals appear relatively well established, further study of this subject will probably be focused on applications to asymmetric catalysis, where more mechanistic knowledge should prove useful in rational design.

Acknowledgement I thank the U. S. National Science Foundation for support of our work in this area (current grant CHE-2350114).

References

[1] Bock PL, Boschetto DJ, Rasmussen JR, Demers JP, Whitesides GM. Stereochemistry of Reactions at Carbon-Transition Metal σ Bonds. $(CH_3)_3CCHDCHDFe(CO)_2C_5H_5$. *J Am Chem Soc*. 1974;96(9):2814-2825.

[2] Flood TC. Stereochemistry of Reactions of Transition Metal-Carbon Sigma Bonds. In: Geoffroy GL, ed. *Topics in Stereochemistry*. Wiley; 1981:37-117.

[3] Malinakova HC. Chiral Nonracemic Late-Transition-Metal Organometallics with a Metal-Bonded Stereogenic Carbon Atom: Development of New Tools for Asymmetric Organic Synthesis. *Chem Eur J*. 2004;10(11):2636-2646.

[4] Dillon KB, Mathey F, Nixon JF. *Phosphorus: the Carbon Copy. From Organophosphorus to Phospha-organic Chemistry*. John Wiley and Sons; 1998.

[5] For examples of this approach applied to transmetalation in cross-coupling catalysis, see for example: (a) Matos K, Soderquist JA. Alkylboranes in the Suzuki-Miyaura Coupling: Stereochemical and Mechanistic Studies. *J Org Chem*. 1998;63(3):461-470. (b) Ridgway BH, Woerpel KA. Transmetalation of Alkylboranes to Palladium in the Suzuki Coupling Reaction Proceeds with Retention of Stereochemistry. *J Org Chem*. 1998;63(3):458-460. (c) Taylor BLH, Jarvo ER. Stereochemistry of Transmetalation of Alkylboranes in Nickel-Catalyzed Alkyl–Alkyl Cross-Coupling Reactions. *J Org Chem*. 2011;76:7573–7576.

[6] (a) Hoffmann RW. Test on the Configurational Stability/Lability of Organolithium Compounds. *Top Stereochem*. 2010;26:165-188. (b) Hoffmann RW. The Quest for Chiral Grignard Reagents. *Chem Soc Rev*. 2003;32:225-230. (c) Beak P, Basu A, Gallagher DJ, Park YS, Thayumanavan S. Regioselective, Diastereoselective, and Enantioselective Lithiation-Substitution Sequences: Reaction Pathways and Synthetic Applications. *Acc Chem Res*. 1996;29:552-560. (d) Hoppe D, Hense T. Enantioselective Synthesis with Lithium/(–)-Sparteine Carbanion Pairs. *Angew Chem, Int Ed Engl*. 1997;36:2282-2316. (e) Gawley RE. Overview of Carbanion Dynamics and

Electrophilic Substitutions in Chiral Organolithium Compounds. *Top Stereochem*. 2010;26:93-133.

[7] Hayashi T, Hagihara T, Konishi M, Kumada M. Stereochemistry of Oxidative Addition of an Optically Active Allyl Acetate to a Palladium(0) Complex. *J Am Chem Soc*. 1983;105:7767-7768.

[8] Zhang X, Zhao K, Gu Z. Transition Metal-Catalyzed Biaryl Atropisomer Synthesis via a Torsional Strain Promoted Ring-Opening Reaction. *Acc Chem Res*. 2022;55(12):1620-1633.

[9] López R, Palomo C. Planar Chirality: A Mine for Catalysis and Structure Discovery. *Angew Chem Int Ed*. 2022;61(13):e202113504.

[10] Eliel EL, Wilen SH, Mander LN. *Stereochemistry of Organic Compounds*. Wiley-Interscience; 1994.

[11] Brunner H, Pieronczyk W. Optically Active Transition Metal Complexes, LIII. Optically Active Ni-Complexes Obtained from the Reaction of Nickelocene With Unsymmetrically Substituted Acetylenes. *Bull Soc Chim Belg*. 1977;86(9):725-733.

[12] Sokolov VI, Reutov OA, Suleimanov GZ, et al. L-menthyl esters of α-bromomercuryphenylacetic acid: diastereoisomeric purity, symmetrization and reverse reaction. A stereochemical reinvestigation. *J Organomet Chem*. 1980;201(1):29-38.

[13] Hashmi ASK, Grundl MA, Riedel D, Rudolph M, Bats JW. A Highly Diastereoselective Recognition Process as the Basis for the Resolution of Palladatricyclo[4.1.0.02,4]heptanes. *Organometallics*. 2012;31(2):523-526.

[14] Hashmi ASK, Naumann F, Probst R, Bats JW. Preparation of Enantiomerically Pure 5-Palladatricyclo[4.1.0.02, 4]heptanes and Conversion into Enantiomerically Pure Complexes with Helical Chirality at Palladium. *Angew Chem Int Ed Engl*. 1997;36(1-2):104-106.

[15] (a) Dunina VV, Zalevskaya OA, Smolyakova IP, Potapov VM. Complete splitting into optical antipodes of a cyclopalladized complex based on N-thiobenzoylpyrrolidine. *Zhurnal Obshchei Khimii*. 1984;54(10):2290-2298. (b) Dunina VV, Zalevskaya OA, Smolyakova IP, Potapov VM. Optical splitting of an N-thiobenzoylpyrrolidine-based cyclopalladated complex. *Doklady Akademii Nauk SSSR*. 1984;278(3):628-630.

[16] Dunina VV, Golovan EB, Kazakova EI, Potapov GP, Beletskaya IP. Synthesis and resolution of a cyclopalladated complex with asymmetric carbon atom directly bonded by the metal. *Metalloorg Khim*. 1991;4:1391.

[17] Hockless DCR, Gugger PA, Leung P-H, Mayadunne RC, Pabel M, Wild SB. Facile Interconversions Between Diastereomers of Chloro-bridged Palladium(II) Dimers of Orthometallated (±)-Dimethyl[1-(1-naphthyl)ethyl]amine. *Tetrahedron*. 1997;53(11):4083-4094.

[18] Yoneda A, Hakushi T, Newkome GR, Fronczek FR. Synthesis and Characterization of Chiral Palladium(II) Complexes Containing a Pd-C*(sp3) .sigma.-Bond. *Organometallics*. 1994;13(12):4912-4918.

[19] Maassarani F, Pfeffer M, Le Borgne G, Jastrzebski JTBH, Van Koten G. Organopalladium compounds with a chiral palladated carbon atom. Facile isolation of optically active cyclopalladated complexes containing the (S)- or (R)-[2-$Me_2NC_6H_4CH(SiMe_3)$] monoanion. Molecular structure of [2-[1-(S)-(dimethylamino)ethyl]phenyl][2-(dimethylamino)-.alpha.-(trimethylsilyl)benzyl]palladium(II). *Organometallics*. 1987;6(5):1111-1118.

[20] Sokolov VI, Sorokina TA, Troitskaya LL, Solovieva LI, Reutov OA. Formation of a chiral carbon centre by direct metallation into a methylene group. *J Organomet Chem*. 1972;36(2):389-390.

[21] Spencer J, Maassarani F, Pfeffer M, DeCian A, Fischer J. Resolution of a cyclopalladated complex containing an asymmetric metallated carbon atom. *Tetrahedron: Asymmetry*. 1994;5(3):321-324.

[22] Dunina VV, Gorunova ON, Livantsov MV, et al. First enantiopure phosphapalladacycle with a palladium bonded stereogenic carbon as the sole chirality source. *Polyhedron*. 2011;30(1):27-32.

[23] Ohgo Y, Takeuchi S, Natori Y, Yoshimura J, Ohashi Y, Sasada Y. Preparations and Properties of Optically Active (Alkyl)bis(dimethylglyoximato)cobalt(III) Complexes. *Bull Chem Soc Jpn*. 1981;54(10):3095-3099.

[24] Lennartson A, Olsson S, Sundberg J, HÂkansson M. A Different Approach to Enantioselective Organic Synthesis: Absolute Asymmetric Synthesis of Organometallic Reagents. *Angew Chem Int Ed*. 2009;48(17):3137-3140.

[25] Olsson S, Lennartson A. Spontaneous resolution of a bis(η^1-methylcyclopentadienyl)zinc complex. *Inorg Chim Acta*. 2011;377(1):181-184.

[26] Sokolov VI. Stereochemistry of the oxidative addition of optically active 8-(α-bromoethyl)quinoline to tris (triphenylphosphine)platinum. *Inorg Chim Acta*. 1976;18:L9.

[27] Sokolov VI, Bashilov VV, Musaev AA, Reutov OA. Stereochemistry of redox-demercuration of an optically active 8-(α-bromomercuriethyl)quinoline with zerovalent palladium complexes. *J Organomet Chem*. 1982;225(1):57-61.

[28] Brunker TJ, Moncarz JR, Glueck DS, Golen JA, Rheingold AL. Diastereoselective Palladium-Mediated Phosphetane Ring Opening and Pd-to-P Phenyl Migration. Synthesis of a New P-Stereogenic C_2-Symmetric Diphosphine Ligand. *Organometallics*. 2004;23(10):2228-2230.

[29] Landis CR, Nelson RC, Jin W, Bowman AC. Synthesis, Characterization, and Transition-Metal Complexes of 3,4-Diazaphospholanes. *Organometallics*. 2006;25(6):1377-1391.

[30] Abdul Malik KM, Newman PD. Ligand Ambivalence in Pallada(platina)cyclic Complexes of a Rigid Phosphine. *Dalton Trans*. 2003;(18):3516-3525.

[31]Vasireddy PCR, Dickmu GC, Ugrinov A, Smoliakova IP. New optically active camphor-derived cyclopalladated complexes with an asymmetric carbon bonded to the metal. *J Organomet Chem*. 2019:120917.

[32] Coomber CE, Benhamou L, Bučar D-K, Smith PD, Porter MJ, Sheppard TD. Silver-Free Palladium-Catalyzed C(sp3)–H Arylation of Saturated Bicyclic Amine Scaffolds. *J Org Chem*. 2018;83(5):2495-2503.

[33] Park H, Verma P, Hong K, Yu J-Q. Controlling Pd(IV) reductive elimination pathways enables Pd(II)-catalysed enantioselective C(sp^3)−H fluorination. *Nature Chem*. 2018;10(7):755-762.

[34] Tay WS, Yang X-Y, Li Y, Pullarkat SA, Leung P-H. Efficient and stereoselective synthesis of monomeric and bimetallic pincer complexes containing Pd-bonded stereogenic carbons. *RSC Adv*. 2016;6(79):75951-75959.

[35] Yang X-Y, Tay WS, Li Y, Pullarkat SA, Leung P-H. The synthesis and efficient one-pot catalytic "self-breeding" of asymmetrical NC(sp^3)E-hybridised pincer complexes. *Chem Commun*. 2016;52(22):4211-4214.

[36] (a) García-Ruano JL, González AM, López-Solera I, et al. Enantiomerically Pure Palladacycles Derived from β-Ketosulfoxides. *Angew Chem Int Ed Engl*. 1995;34(12):1351-1353. (b) García-Ruano JL, González AM, Bárcena AI, Camazón MJ, Navarro-Ranninger C. Enantiomerically pure palladacycles with one stereogenic Csp^3 center directly bonded to the metal. *Tetrahedron: Asymmetry*. 1996;7(1):139-148.

[37] Baar CR, Carbray LP, Jennings MC, Puddephatt RJ, Vittal JJ. Stereoselective Formation of (Aminoalkyl)platinum Complexes from Imines. *Organometallics*. 2001;20(3):408-417.

[38] Serin SC, Patrick BO, Dake GR, Gates DP. Reaction of an Enantiomerically Pure Phosphaalkene-Oxazoline with MeM Nucleophiles (M = Li and MgBr): Stereoselectivity and Noninnocence of the P-Mesityl Substituent. *Organometallics*. 2014;33(24):7215-7222.

[39] (a) Kocovsky P, Vyskocil S, Cisarova I, et al. Palladium(II) Complexes of 2-Dimethylamino-2'-diphenylphosphino-1,1'-binaphthyl (MAP) with Unique P,C_σ-Coordination and Their Catalytic Activity in Allylic Substitution, Hartwig-Buchwald Amination, and Suzuki Coupling. *J Am Chem Soc*. 1999;121:7714-7715. (b) Lloyd-Jones GC, Stephen SC, Murray M, Butts CP, Vyskočil Ŝ, Kočovský P. Diastereoisomeric Cationic π-Allylpalladium-(P,C)-MAP and MOP Complexes and

Their Relationship to Stereochemical Memory Effects in Allylic Alkylation. *Chem – Eur J*. 2000;6(23):4348-4357.

[40] Brunkan NM, White PS, Gagne MR. Unorthodox C,O Binding Mode of Me_2BINOL in Pt(II) Complexes. *J Am Chem Soc*. 1998;120(42):11002-11003.

[41] Bergens SH, Leung PH, Bosnich B, Rheingold AL. Synthesis and structure of a biphenanthrol-palladium complex displaying an unusual bonding mode. *Organometallics*. 1990;9(8):2406-2408.

[42] (a) Beckmann J, Dakternieks D, Drager M, Duthie A. New Insights into the Classic Chiral Grignard Reagent (1R,2S,5R)-Menthylmagnesium Chloride. *Angew Chem Int Ed*. 2006;45(39):6509-6512. (b) Koller S, Gatzka J, Wong KM, Altmann PJ, Pöthig A, Hintermann L. Stereochemistry of the Menthyl Grignard Reagent: Generation, Composition, Dynamics, and Reactions with Electrophiles. *J Org Chem*. 2018;83(24):15009–15028.

[43] Zuzek AA, Reynolds SC, Glueck DS, Golen JA, Rheingold AL. Synthesis and Structure of Gold and Platinum Menthyl Complexes. *Organometallics*. 2011;30(7):1812-1817.

[44] Hashmi ASK, Naumann F, Bolte M. Asymmetric Synthesis of Palladacycles by Regioselective Oxidative Cyclization of C_2-Symmetrical, Chiral Alkenes and Determination of the Configuration of All Stereocenters. *Organometallics*. 1998;17(12):2385-2387.

[45] Xi Y, Hartwig JF. Mechanistic Studies of Copper-Catalyzed Asymmetric Hydroboration of Alkenes. *J Am Chem Soc*. 2017;139(36):12758–12772.

[46] Rodewald S, Jordan RF. Stereoselective Olefin Insertion Reactions of Chiral (EBI)Zr(.eta.2-pyrid-2-yl)+ and (EBTHI)Zr(.eta.2-pyrid-2-yl)+ Complexes. *J Am Chem Soc*. 1994;116(10):4491-4492.

[47] Yamamoto T, Sano K, Yamamoto A. Effect of ligand on ring contraction of six-membered nickel-containing cyclic esters, $L_nNiCH_2CH_2CH_2COO$, to their five-membered-ring isomers, $L_nNiCH(CH_3)CH_2COO$. Kinetic and thermodynamic control of asymmetric induction by chiral diphosphines in the ring contraction. *J Am Chem Soc*. 1987;109(4):1092-1100.

[48] Argazzi R, Bergamini P, Costa E, et al. Anchimeric Assistance by Platinum(II) in the Epimerizations of [$PtX(CHXSiMe_3)$(R,R-chiraphos)]. *Organometallics*. 1996;15(26):5591-5597.

[49] (a) Bergamini P, Costa E, Orpen AG, Pringle PG, Smith MB. Reactions of Diazo Carbonyls with [$PtX(CH_3)$(chiral diphosphine)] (X = Cl, Br, I): Chemoselectivity and Diastereoselectivity of Pt-C and Pt-X Carbene Insertion. *Organometallics*. 1995;14(7):3178-3187. For related chemistry, see: (b) McCrindle R, McAlees AJ. Mechanism and stereochemistry of the reaction of dichloroplatinum(II) complexes with diazo compounds. Mono versus bis insertion and competition between capture of chloride and capture of an internal nucleophile by carbenoid intermediates in the second insertion step. *Organometallics*. 1993;12(7):2445-2461.

[50] Kalkman ED, Hartwig JF. Direct Observation of Diastereomeric α-C-Bound Enolates during Enantioselective α-Arylations: Synthesis, Characterization, and Reactivity of Arylpalladium Fluorooxindole Complexes. *J Am Chem Soc*. 2021;143(30):11741–11750.

[51] Lu G, Malinakova HC. Regio- and Diastereoselective Insertion of Allenes into Stable Oxapalladacycles with a Metal-Bonded Stereogenic Carbon. Preparation of Contiguously Substituted 3,4-Dihydro-2H-1-Benzopyrans. *J Org Chem*. 2004;69(24):8266-8279.

[52] Portscheller JL, Lilley SE, Malinakova HC. Ligand-Controlled Asymmetric Induction at a Transition Metal-Bonded α-Carbon in Ester and Amide Enolates. Diastereoselective Formation of Oxapalladacycles Applied to the Synthesis of a Chiral Nonracemic 2H-1-Benzopyran. *Organometallics*. 2003;22(14):2961-2971.

[53] Lu G, Malinakova HC. Mechanism of Stereoinduction in Asymmetric Synthesis of Highly Functionalized 1,2-Dihydroquinolines and 2H-1-Benzopyrans via Nonracemic Palladacycles with a Metal-Bonded Stereogenic Carbon. *J Org Chem*. 2004;69(14):4701-4715.

[54] Hershberger JC, Day VW, Malinakova HC. Diastereoinduction in the Synthesis of Pallada(II)pyrrolidinones: Palladacycles with Two Pd-bonded Stereogenic Carbons. *Organometallics*. 2009;28(3):810-818.

[55] Falvello LR, Fernandez S, Navarro R, Urriolabeitia EP. Stereoselective induction in the synthesis of [Pd((*R,S*)-dmphea)((*R,S*)-dppmY$_{cor}$)](ClO$_4$) derivatives. X-ray crystal structure of [Pd((*R*)-dmphea)((*R*)-dppmY$_{CO2Me}$)](ClO$_4$)·CHCl$_3$. *New J Chem*. 1997;21(8):909-917.

[56] Sweeney ZK, Salsman JL, Andersen RA, Bergman RG. Synthesis of Chiral, Enantiopure Zirconocene Imido Complexes: Highly Selective Kinetic Resolution and Stereoinversion of Allenes, and Evidence for a Stepwise Cycloaddition/Retrocycloaddition Reaction Mechanism. *Angew Chem Int Ed*. 2000;39(13):2339-2343.

[57] Michael FE, Duncan AP, Sweeney ZK, Bergman RG. Rearrangements and Stereomutations of Metallacycles Derived from Allenes and Imidozirconium Complexes. *J Am Chem Soc*. 2005;127(6):1752-1764.

[58] Ryabov AD, Panyashkina IM, Polyakov VA, Fischer A. Access to Central Carbon Chirality through Cycloplatination of 1-(2-Pyridinylthio)propanone by cis-[PtCl$_2$(S-SOMe(*p*-tolyl))]. The Crystal Structure of (S_sS_c)-[Pt{py{SCHC(O)Me}-2}Cl(SOMe(p-tolyl))]. *Organometallics*. 2002;21(8):1633-1636.

[59] Grossman RB, Davis WM, Buchwald SL. Enantioselective, zirconium-mediated synthesis of allylic amines. *J Am Chem Soc*. 1991;113(6):2321-2322.

[60] Gately DA, Norton JR. Origin of Stereochemistry in the α-Amino Acid Esters and Amides Generated from Optically Active Zirconaaziridine Complexes. *J Am Chem Soc*. 1996;118(14):3479-3489.

[61] (a) Wicht DK, Kovacik I, Glueck DS, Liable-Sands LM, Incarvito CD, Rheingold AL. Chiral Terminal Platinum(II) Phosphido Complexes: Synthesis, Phosphorus Inversion, and Acrylonitrile Insertion. *Organometallics*. 1999;18:5141-5151. For related compounds, see: (b) Scriban C, Glueck DS, Zakharov LN, et al. P-C and C-C Bond Formation by Michael Addition in Platinum-Catalyzed Hydrophosphination and in the Stoichiometric Reactions of Platinum Phosphido Complexes with Activated Alkenes. *Organometallics*. 2006;25(24):5757-5767.

[62] Suggs JW, Jun CH. Synthesis of a chiral rhodium alkyl via metal insertion into an unstrained C-C bond and use of the rate of racemization at carbon to obtain rhodium-carbon bond dissociation energy. *J Am Chem Soc*. 1986;108(15):4679-4681.

[63] Ohashi Y, Yanagi K, Kurihara T, Sasada Y, Ohgo Y. Crystalline state reaction of cobaloxime complexes by x-ray exposure. 1. Direct observation of cobalt-carbon bond cleavage in [(R)-1-cyanoethyl][(S)-(-)-.alpha.-methylbenzylamine]bis(dimethylglyoximato)cobalt(III). *J Am Chem Soc*. 1981;103(19):5805-5812.

[64] (a) Arai Y, Ohgo Y. Reactions in Solid and Constrained State. IV. Preparation and Solid-State Photoracemization of Optically Active Alkyl Cobaloxime Complexes. *Bull Chem Soc Jpn*. 1998;71(8):1871-1886. (b) Ohgo Y, Arai Y, Takeuchi S. Solid-state Photoracemization of Optically Active Alkyl Cobaloxime Complexes. Solid-state Specific Effect of Axial Ligand. *Chem Lett*. 1991;20(3):455-458. (c) Ohgo Y, Orisaku K, Hasegawa E, Takeuchi S. Thermal Racemization of Chiral Alkyl Cobalt Complexes and Estimation of Co-C Bond Dissociation Energy. *Chem Lett*. 1986;15(1):27-30.

[65] Ohgo Y, Ishida K, Hiraga Y, Arai Y, Takeuchi S. Solid state-specific and chiral lattice-controlled asymmetric photoisomerization of 3-substituted propyl cobalt complexes, and direct observation of the intermediate complex. *J Organomet Chem*. 2006;691(10):2319-2326.

[66] (a) Burke BJ, Overman LE. Enantioselective Synthesis of Six-Membered Palladacycles Having Metal-Bound Stereogenic Carbons: Isolation and Reactivity of Palladacycles Containing Readily Accessible b-Hydrogens. *J Am Chem Soc*. 2004;126(51):16820-16833. (b) Oestreich M, Dennison PR, Kodanko JJ, Overman LE. Thwarting β-Hydride Elimination: Capture of the Alkylpalladium Intermediate of an Asymmetric Intramolecular Heck Reaction. *Angew Chem Int Ed*. 2001;40(8):1439-1442.

[67] Mobley TA, Schade C, Bergman RG. Diastereomeric and Isotopic Scrambling in (Hydrido)alkyliridium Complexes. Evidence for the Presence of a Common "Alkane Complex" Intermediate. *J Am Chem Soc*. 1995;117(29):7822-7823.

[68] Primozic JJ, Ilgen J, Maibach P, Brauser M, Kind J, Thiele CM. Pd-Catalyzed Asymmetric Allylic Alkylation of Cyclobutenes: From Double Inversion to Double Retention. *J Am Chem Soc*. 2023;145(29):15912–15923.

[69] Cummings SA, Tunge JA, Norton JR. Direct Measurement of the Rate of Interconversion of Zirconaaziridine Enantiomers. *J Am Chem Soc*. 2008;130(14):4669-4679.

[70] Hayashi T, Konishi M, Fukushima M, et al. Asymmetric Synthesis Catalyzed by Chiral Ferrocenylphosphine-Transition Metal Complexes. 2. Nickel- and Palladium-Catalyzed Asymmetric Grignard Cross-Coupling. *J Am Chem Soc*. 1982;104:180-186.

[71] Preinfalk A, Oost R, Menger MFSJ, et al. Enantioconvergent Negishi Cross-Couplings of Racemic Secondary Organozinc Reagents to Access Privileged Scaffolds: A Combined Experimental and Theoretical Study. *Angew Chem Int Ed*. 2024;63(50):e202414868.

[72] Gribble MW, Liu RY, Buchwald SL. Evidence for Simultaneous Dearomatization of Two Aromatic Rings under Mild Conditions in Cu(I)-Catalyzed Direct Asymmetric Dearomatization of Pyridine. *J Am Chem Soc*. 2020;142(25):11252–11269.

[73] Guijarro A, Rieke RD. Study of the Configuration Stability of the Carbon-Zinc Bond, Direct Measurement of Enantiomeric Ratios, and Tentative Assignment of the Absolute Configuration in Secondary Organozinc Halides. *Angew Chem Int Ed*. 2000;39(8):1475-1479.

[74] Holcomb HL, Nakanishi S, Flood TC. Stereochemistry at Carbon of the Cyclometalation of 8-(α-Deuterioethyl)quinoline by Palladium(II) Salts. *Organometallics*. 1996;15(20):4228-4234.

[75] Desnoyer AN, Bowes EG, Patrick BO, Love JA. Synthesis of 2-Nickela(II)oxetanes from Nickel(0) and Epoxides: Structure, Reactivity, and a New Mechanism of Formation. *J Am Chem Soc*. 2015;137(40):12748–12751.

[76] Desnoyer AN, Geng J, Drover MW, Patrick BO, Love JA. Catalytic Functionalization of Styrenyl Epoxides via 2-Nickela(II)oxetanes. *Chem Eur J*. 2017;23(48):11509-11512.

[77] Lin BL, Clough CR, Hillhouse GL. Interactions of Aziridines with Nickel Complexes: Oxidative-Addition and Reductive-Elimination Reactions that Break and Make C-N Bonds. *J Am Chem Soc*. 2002;124(12):2890-2891.

[78] Becker Y, Stille JK. Stereochemistry of Oxidative Addition of Benzyl-a-d Chloride and Bromide to Tris(triethylphosphine)palladium(0). Direct Observation of Optical Activity in a Carbon-Palladium σ-Bonded Complex. *J Am Chem Soc*. 1978;100(3):838-844.

[79] Marquard SL, Rosenfeld DC, Hartwig JF. C(sp^3)-N Bond-Forming Reductive Elimination of Amines: Reactions of Bisphosphine-Ligated Benzylpalladium(II) Diarylamido Complexes. *Angew Chem Int Ed*. 2010;49(4):793-796.

[80] Munro-Leighton C, Adduci LL, Becker JJ, Gagné MR. Oxidative Addition of Secondary C–X Bonds to Palladium(0): A Beneficial Anomeric Acceleration. *Organometallics*. 2011;30(10):2646-2649.

[81] DeShong P, Slough GA, Elango V, Trainor GL. Organo-transition-metal based approach to the synthesis of C-glycosides. *J Am Chem Soc*. 1985;107(25):7788-7790.

[82] DeShong P, Soli ED, Slough GA, et al. Glycosylmanganese pentacarbonyl complexes: an organomanganese-based approach to the synthesis of C-glycosyl derivatives. *J Organomet Chem*. 2000;593-594:49-62.

[83] Pelczar EM, Munro-Leighton C, Gagne MR. Oxidative Addition of Glycosylbromides to trans-$Ir(PMe_3)_2(CO)Cl$. *Organometallics*. 2009;28(3):663-665.

[84] Annunziata A, Cucciolito ME, Esposito R, et al. Oxidative Addition of α-Glycosyl Halides to a Platinum(0) Olefin Complex: Stereochemistry of Pt−C Bond Formation. *Eur J Inorg Chem*. 2021;2021(6):534-539.

[85] Yang GK, Bergman RG. Stereochemistry of metallacycle formation in the double alkylation of bis(triphenylphosphine)nitrogen(1+) bis(η^5-cyclopentadienyl)-bis(μ-carbonyl)dicobaltate with α,γ-diiodoalkanes. *J Am Chem Soc*. 1983;105(19):6045-6052.

[86] Hanley PS, Marquard SL, Cundari TR, Hartwig JF. Reductive Elimination of Alkylamines from Low-Valent, Alkylpalladium(II) Amido Complexes. *J Am Chem Soc*. 2012;134(37):15281–15284.

[87] Geier MJ, Dadkhah Aseman M, Gagné MR. Anion-Dependent Switch in C–X Reductive Elimination Diastereoselectivity. *Organometallics*. 2014;33(17):4353–4356.

[88] Marquard SL, Hartwig JF. C(sp^3)–O Bond-Forming Reductive Elimination of Ethers from Bisphosphine-Ligated Benzylpalladium(II) Aryloxide Complexes. *Angew Chem Int Ed*. 2011;50:7119-7123.

[89] Sibbald PA, Rosewall CF, Swartz RD, Michael FE. Mechanism of N-Fluorobenzenesulfonimide Promoted Diamination and Carboamination Reactions: Divergent Reactivity of a Pd(IV) Species. *J Am Chem Soc*. 2009;131(43):15945-15951.

[90] Spencer J, Pfeffer M. The Fate of the Stereogenic Centre Linked to Palladium Upon Reaction with an Alkyne. *Tetrahedron: Asymmetry*. 1995;6(2):419-426.

[91] (a) Hoffmann RW, Hölzer B. Stereochemistry of the Transmetalation of Grignard Reagents to Copper (I) and Manganese (II). *J Am Chem Soc*. 2002;124(16):4204-4205. (b) Hölzer B, Hoffmann RW. Kumada-Corriu Coupling of Grignard Reagents, Probed with a Chiral Grignard Reagent. *Chem Commun*. 2003:732-733.

[92] Strohmann C, Abele BC, Lehmen K, et al. Enantiomerically enriched 'carbanions': Studies on the stereochemical course of selective transformations of metal alkyls. *J Organomet Chem*. 2002;661(1):149-158.

[93] Kropp K, Erker G. Stereospecific formation of five-membered metallacycles. Zirconaindans from thermally generated (η^2-dehydrobenzene)dicyclopentadienylzirconium(II) and cis- and trans-stilbene. *Organometallics*. 1982;1(9):1246-1247.

[94] McDonald RI, Liu G, Stahl SS. Palladium(II)-Catalyzed Alkene Functionalization via Nucleopalladation: Stereochemical Pathways and Enantioselective Catalytic Applications. *Chem Rev*. 2011;111(4):2981-3019.

[95] Åkermark B, Zetterberg K. Palladium-promoted amination of olefins. Direct proof for the trans stereochemistry. *J Am Chem Soc*. 1984;106(19):5560-5561.

[96] Isomura K, Okada N, Saruwatari M, Yamasaki H, Taniguchi H. Firm Evidence for Cis-Aminopalladation in the Reaction of 1-Aminohexatrienes with Palladium Dichloride. *Chem Lett*. 1985;14(3):385-388.

[97] de Klerk-Engels B, Delis JGP, Vrieze K, Goubitz K, Fraanje J. Synthesis of Cyclopentadienyl(1,4-diisopropyl-1,3-diazabutadiene)(L)ruthenium Trifluoromethanesulfonate (L = Alkene, Alkyne, CO, Pyridine, PPh_3). X-ray Structure of [(η^5-C_5H_5)Ru(iPr-DAB)(η^2-propene)][CF_3SO_3]. *Organometallics*. 1994;13(8):3269-3278.

[98] Kiel WA, Lin GY, Constable AG, et al. Synthesis and properties of [(η-C_5H_5)Re(NO)(PPh_3)(=CHC_6H_5)]$^+PF_6^-$: a benzylidene complex that is formed by a stereospecific α-hydride abstraction, exists as two geometric isomers, and undergoes stereospecific nucleophilic attack. *J Am Chem Soc*. 1982;104(18):4865-4878.

[99] O'Connor EJ, Kobayashi M, Floss HG, Gladysz JA. A versatile new synthesis of organic compounds with chiral methyl groups: stereochemistry of protolytic rhenium-carbon bond cleavage in chiral alkyl complexes (η^5-C_5H_5)Re(NO)(PPh_3)(R). *J Am Chem Soc*. 1987;109(16):4837-4844.

[100] Wiles JA, Bergens SH, Young VG, Jr. Stereochemistry at Carbon upon Protonolysis of a Late Transition Metal-Alkyl Bond: a Reaction of Relevance to Catalytic Enantioselective Hydrogenation of Olefins. Article. *Can J Chem*. 2001;79(5/6):1019-1025.

[101] Ho SCH, Straus DA, Grubbs RH. An alternate path to reductive elimination for Group IVB metals: mechanism of cyclopropane formation from titanacyclobutanes. *J Am Chem Soc*. 1984;106(5):1533-1534.

[102] Zablocka M, Igau A, Cenac N, et al. Unprecedented Inversion of Configuration at Carbon in the Electrophilic Cleavage of the Carbon-Zirconium(IV) Bond. *J Am Chem Soc*. 1995;117:8083-8089.

[103] Landis CR, Halpern J. Asymmetric Hydrogenation of Methyl-(Z)-α-acetamidocinnamate Catalyzed by {1,2-Bis(phenyl-*o*-anisoyl)phosphino)ethane}rhodium(I): Kinetics, Mechanism, and Origin of Enantioselection. *J Am Chem Soc*. 1987;109(6):1746-1754.

[104] Brown JM, Chaloner PA. Structural Characterisation of a Transient Intermediate in Rhodium-catalysed Asymmetric Homogeneous Hydrogenation. *J Chem Soc, Chem Commun*. 1980:344-346.

[105] (a) Giernoth R, Heinrich H, Adams NJ, Deeth RJ, Bargon J, Brown JM. PHIP Detection of a Transient Rhodium Dihydride Intermediate in the Homogeneous Hydrogenation of Dehydroamino Acids. *J Am Chem Soc*. 2000;122(49):12381-12382. (b) Heinrich H, Giernoth R, Bargon J, Brown JM. Observation of a stable cis-diphosphine solvate rhodium dihydride derived from PHANEPHOS. *Chem Commun*. 2001;(14):1296-1297.

[106] Gridnev ID, Higashi N, Asakura K, Imamoto T. Mechanism of Asymmetric Hydrogenation Catalyzed by a Rhodium Complex of (S,S)-1,2-Bis(tert-butylmethylphosphino)ethane. Dihydride Mechanism of Asymmetric Hydrogenation. *J Am Chem Soc*. 2000;122(30):7183-7194.

[107] Gridnev ID, Higashi N, Imamoto T. Formation of a Stable Rhodium Dihydride Complex and Its Reactions with Prochiral Substrates of Asymmetric Hydrogenation. *Organometallics*. 2001;20:4542-4553.

[108] Imamoto T, Yashio K, Crepy KVL, et al. *P*-Chiral Tetraphosphine Dirhodium Complex as a Catalyst for Asymmetric Hydrogenation: Synthesis, Structure, Enantioselectivity, and Mechanism. Stereoselective Formation of a Dirhodium Tetrahydride Complex and Its Reaction with Methyl (*Z*)-α-Acetamidocinnamate. *Organometallics*. 2006;25(4):908-914.

[109] Alcock NW, Brown JM, Derome AE, Lucy AR. Iridium analogues of catalytic intermediates in asymmetric hydrogenation. *J Chem Soc, Chem Commun*. 1985;(9):575-578.

[110] Brown JM, Maddox PJ. Solution structures of iridium alkyl hydrides pertaining to asymmetric hydrogenation. *J Chem Soc, Chem Commun*. 1987;(17):1276-1278.

[111] Li M-L, Yang S, Su X-C, et al. Mechanism Studies of Ir-Catalyzed Asymmetric Hydrogenation of Unsaturated Carboxylic Acids. *J Am Chem Soc*. 2017;139(1):541-547.

[112] Zhu S-F, Zhou Q-L. Iridium-Catalyzed Asymmetric Hydrogenation of Unsaturated Carboxylic Acids. *Acc Chem Res*. 2017;50(4):988-1001.

[113] Wiles JA, Bergens SH, Young VG. The First Structure Determination of a Possible Intermediate in Ruthenium 2,2‘-Bis(diphenylphosphino)-1,1‘-binaphthyl Catalyzed Hydrogenation with a Prochiral Group Bound to Ruthenium. Stoichiometric Reaction of a Chiral Ruthenium−Carbon Bond with Dihydrogen Gas. *J Am Chem Soc*. 1997;119(12):2940-2941.

[114] (a) Wiles JA, Bergens SH. Mechanistic Investigations of an Enantioselective Hydrogenation Catalyzed by a Ruthenium−BINAP Complex. 1. Stoichiometric and Catalytic Labeling Studies. *Organometallics*. 1998;17(11):2228-2240. (b) Wiles JA, Bergens SH. The First Structure Determination of a Diastereomeric Hydrido−Olefin Putative Intermediate in Catalytic Enantioselective Hydrogenation. *Organometallics*. 1999;18(18):3709-3714.

[115] Nelsen ER, Landis CR. Interception and Characterization of Alkyl and Acyl Complexes in Rhodium-Catalyzed Hydroformylation of Styrene. *J Am Chem Soc*. 2013;135 (26):9636–9639.

[116] Nelsen ER, Brezny AC, Landis CR. Interception and Characterization of Catalyst Species in Rhodium Bis(diazaphospholane)-Catalyzed Hydroformylation of Octene, Vinyl Acetate, Allyl Cyanide, and 1-Phenyl-1,3-butadiene. *J Am Chem Soc*. 2015;137:14208-14219.

[117] Binotti B, Carfagna C, Gatti G, Martini D, Mosca L, Pettinari C. Mechanistic Aspects of Isotactic CO/Styrene Copolymerization Catalyzed by Oxazoline Palladium(II) Complexes. *Organometallics*. 2003;22(5):1115-1123.

[118] Carfagna C, Gatti G, Mosca L, et al. Carbonylation of styrenes catalyzed by bioxazoline Pd(II) complexes: mechanism of enantioselectivity. *Dalton Trans*. 2011;40(25):6792-6801.

[119] Nozaki K, Komaki H, Kawashima Y, Hiyama T, Matsubara T. Predominant 1,2-Insertion of Styrene in the Pd-Catalyzed Alternating Copolymerization with Carbon Monoxide. *J Am Chem Soc*. 2001;123(4):534-544.

[120] Iggo JA, Kawashima Y, Liu J, Hiyama T, Nozaki K. High-Pressure NMR Studies on the Alternating Copolymerization of Styrene with Carbon Monoxide Catalyzed by a Palladium(II)−(R,S)-BINAPHOS Complex. *Organometallics*. 2003;22(26):5418-5422.

[121]Lee J, Radomkit S, Torker S, del Pozo J, Hoveyda AH. Mechanism-based enhancement of scope and enantioselectivity for reactions involving a copper-substituted stereogenic carbon centre. Article. *Nature Chem*. 2018;10:99–108.

[122] Kovacik I, Wicht DK, Grewal NS, et al. Pt(Me-Duphos)-Catalyzed Asymmetric Hydrophosphination of Activated Olefins: Enantioselective Synthesis of Chiral Phosphines. *Organometallics*. 2000;19:950-953.

[123] Baechler RD, Mislow K. The Effect of Structure on the Rate of Pyramidal Inversion of Acyclic Phosphines. *J Am Chem Soc*. 1970;92:3090-3093.

[124] (a) Geer AM, Tejel C. Organo-phosphanide and -phosphinidene complexes of Groups 8–11. *Adv Organomet Chem*. 2022;77:243-330. (b) Rogers JR, Wagner TPS, Marynick DS. Metal-Assisted Pyramidal Inversion in Metal-Phosphido Complexes. *Inorg Chem*. 1994;33:3104-3110.

[125] For recent computational predictions of stereochemistry in Rh-mediated P-H oxidative addition of a secondary phosphine and P-C reductive elimination of a tertiary phosphine, see: Chachula ST, Hughes RP, Glueck DS. Rhodium-Catalyzed Asymmetric Dehydrocoupling-Cyclophosphination of Supermesitylphosphines: Enantioselective Synthesis of a P-Stereogenic Benzophospholane via C–H Activation–Functionalization. *Organometallics*. 2024;43(21):2797–2811.

[126] (a) Rojo P, Riera A, Verdaguer X. Bulky P-stereogenic ligands. A success story in asymmetric catalysis. *Coord Chem Rev*. 2023;489:215192. (b) Glueck DS. Metal-Catalyzed Asymmetric Synthesis of P-Stereogenic Phosphines. *Synlett*. 2007:2627-2634. (c) Glueck DS. Catalytic

Asymmetric Synthesis of P-Stereogenic Phosphines: Beyond Precious Metals. *Synlett*. 2021;32(9):875-884.

[127] Han L-B, Zhao C-Q, Onozawa S, Goto M, Tanaka M. Retention of Configuration on the Oxidative Addition of P-H Bond to Platinum (0) Complexes: The First Straightforward Synthesis of Enantiomerically Pure P-Chiral Alkenylphosphinates via Palladium-Catalyzed Stereospecific Hydrophosphinylation of Alkynes. *J Am Chem Soc*. 2002;124(15):3842-3843.

[128] Richard ME, Ciccarelli RM, Garcia KJ, et al. Stereospecific Protodeauration/Transmetalation Generating Configurationally Stable P-Metalated Nucleoside Derivatives. *Eur J Org Chem*. 2018:2167–2170.

[129] Masonheimer CL, Atwood MG, Hartzell SE, Reph EA, Pike RD, Stockland RA. Syn-Insertion of Alkynes into Gold–Phosphito Bonds: Stereoselectivity and Reversible Protodeauration. *Organometallics*. 2021;40:2546-2556.

[130] Yang J, Chen T, Zhou Y, Yin S-F, Han L-B. Mechanistic Studies on the Palladium-Catalyzed Cross Dehydrogenative Coupling of P(O)–H Compounds with Terminal Alkynes: Stereochemistry and Reactive Intermediates. *Organometallics*. 2015;34(20):5095–5098.

[131] (a) Moncarz JR, Brunker TJ, Glueck DS, Sommer RD, Rheingold AL. Stereochemistry of Palladium-Mediated Synthesis of PAMP-BH_3: Retention of Configuration at P in Formation of Pd-P and P-C Bonds. *J Am Chem Soc*. 2003;125(5):1180-1181. (b) Moncarz JR, Brunker TJ, Jewett JC, et al. Palladium-Catalyzed Asymmetric Phosphination. Enantioselective Synthesis of PAMP-

BH_3, Ligand Effects on Catalysis, and Direct Observation of the Stereochemistry of Transmetalation and Reductive Elimination. *Organometallics*. 2003;22(16):3205-3221.