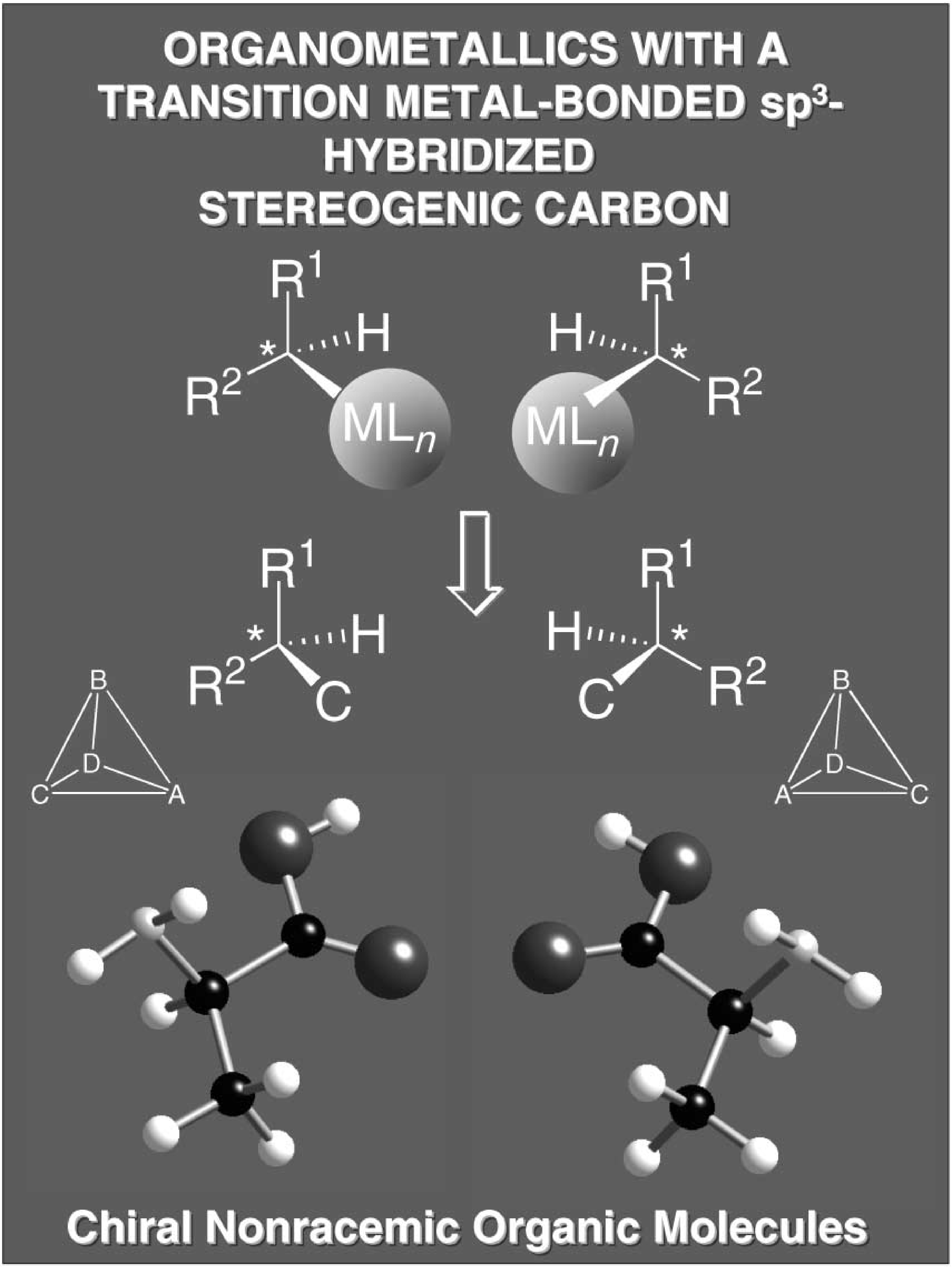

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Chiral Nonracemic Late-Transition-Metal Organometallics with a Metal-Bonded Stereogenic Carbon Atom: Development of New Tools for Asymmetric Organic Synthesis

Helena C. Malinakova*[a]

Abstract: Transition-metal-catalyzed cross-coupling reactions and the Heck reaction have evolved into powerful tools for the construction of carbon–carbon bonds. In most cases, the reactive organometallic intermediates feature a carbon–transition-metal σ bond between a sp^2-hybridized carbon atom and the transition metal (Csp^2–TM). New, and potentially more powerful approach to transition-metal-catalyzed asymmetric organic synthesis would arise if catalytic chiral nonracemic organometallic intermediates with a stereogenic sp^3-hybridized carbon atoms directly bonded to the transition metal (C^*sp^3–TM bond) could be formed from racemic or achiral organic substrates, and subsequently participate in the formation of a new carbon–carbon bond (C^*sp^3–C) with retention of the stereochemical information. To date, only a few catalytic processes that are based on this concept, have been developed. In this account, both "classical" and recent studies on preparation and reactivity of stable chiral nonracemic organometallics with a metal-bonded stereogenic carbon, which provide the foundation for the future design of new synthetic transformations exploiting the outlined concept, are discussed, along with examples of relevant catalytic processes.

Keywords: asymmetric synthesis · C–C coupling · C–H activation · metallacycles · transition metals

Introduction

Reactions catalyzed by late-transition-metal complexes have evolved into powerful tools for the creation of carbon–carbon bonds.[1] In particular, diverse variants of cross-coupling reactions, and the Heck reaction have been widely employed by the synthetic community.[2] For most practical purposes, these transformations directly connect sp- or sp^2-hybridized carbon atoms in organic electrophiles (e.g., organohalides) with sp-, sp^2-, or sp^3-hybridized carbon atoms in organic nucleophiles (RM, M = Mg, Zr, Zn, Al, B, Si, or Sn). The key reactive intermediates possess carbon–transition-metal (C–TM) σ bonds, and the new carbon–carbon bonds arise through carbometalation (Heck reaction) or by means of reductive elimination (cross-coupling).[3] Asymmetric Heck reactions,[4] in which enantioselection occurs through an enantioface selective carbometalation, represent the most successful application of this methodology to asymmetric synthesis of complex organic molecules. Atropisomer-selective aryl–aryl cross-coupling,[5] and desymmetrization through enantioposition-selective cross-coupling[6] and Heck reactions[7] have also been described. In all these processes the organic electrophiles give rise to organometallic intermediates with a sp^2-hybridized carbon bonded to the transition metal (Csp^2–TM bond) [reactions (1) and (2) in Figure 1].

A conceptually new and potentially more powerful approach to transition-metal-mediated asymmetric synthesis would arise if organic electrophiles could be converted into intermediates with a sp^3-hybridized, stereogenic carbon bonded to the transition metal (C^*sp^3–TM bond) [reactions (3) and (4) in Figure 1]. If such complexes could be generated in an enantiomerically pure form from either chiral nonracemic, racemic or achiral organic substrates, and subsequently participate in the "traditional" cross-coupling or Heck reactions, organic products with multiple adjacent stereogenic centers could be generated. When fully developed, this strategy holds the promise to allow for a direct coupling of two stereogenic carbon centers (R–M = C^*sp^3–M, Figure 1).

In numerous instances, synthetically powerful transition-metal-catalyzed reactions evolved from studies with stable isolated organometallic entities,[8a] although the outcome or the kinetic behavior of catalytic reactions may differ from the stoichiometric processes.[8b,c] Thus, to develop a new

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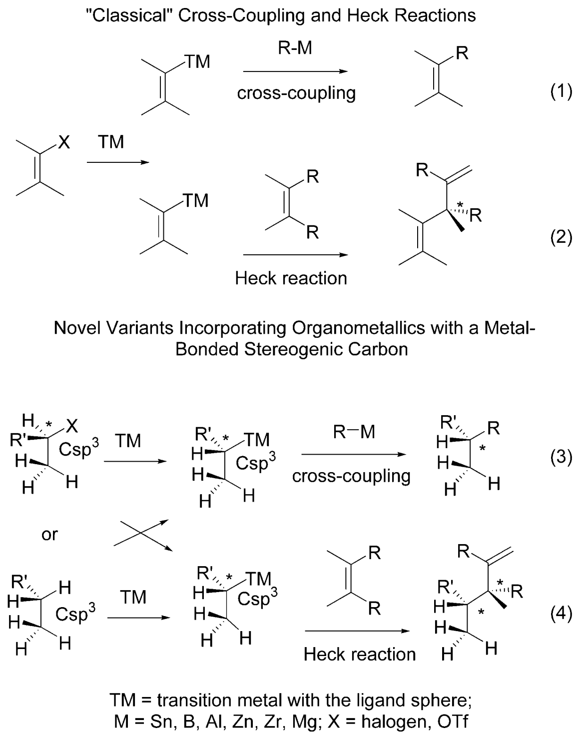


Figure 1. Comparison of classical and new strategies for transition-metal-mediated asymmetric synthesis.

technology that will realize the proposed approach to asymmetric functionalization of sp^3-hybridized carbon atoms [reactions (3) and (4) in Figure 1], systematic fundamental studies on the chemistry of stable chiral nonracemic transition metal complexes featuring a metal-bonded stereogenic sp^3-hybridized carbon atom must be performed (Figure 2).

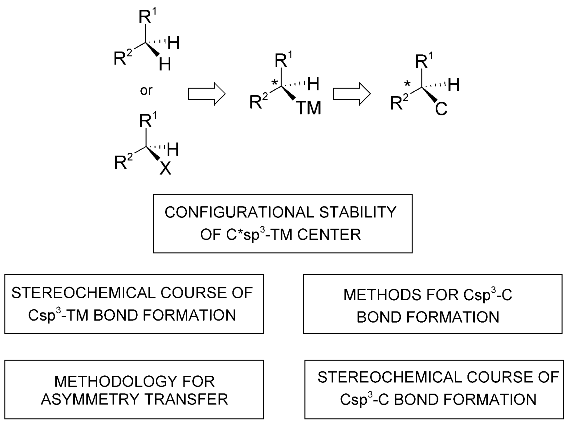


Figure 2. Key components of the research aimed at the design of new synthetic processes utilizing chiral nonracemic organometallics with a metal-bonded stereogenic sp^3-hybridized carbon atoms.

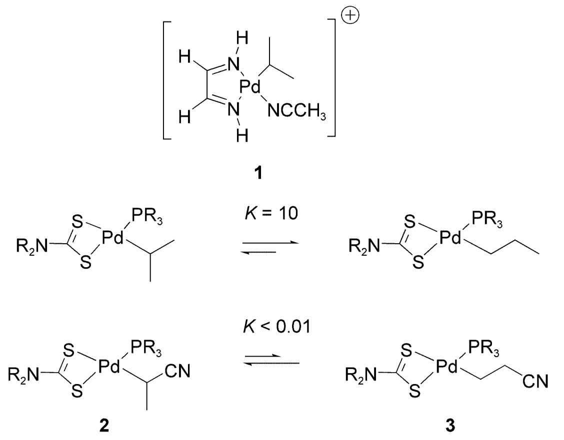
Specifically, new strategies for an enantioselective generation of complexes with a C^*sp^3−TM bond must be developed, in addition to efficient methods for asymmetry transfer into the metal-bonded stereocenter. Mechanistic studies clarifying the stereochemical course of the C^*sp^3−TM bond formation are needed along with precise understanding of the factors that control the configurational stability of the transition-metal-bonded stereocenters. Finally, stereochemical course of reactions that would incorporate the metal-bonded stereocenter into organic products must be studied, and new reaction pathways sought (Figure 2).

Herein, we aim to summarize and put into perspective both "classical" and recent studies with stable chiral nonracemic organometallics, and the relevant catalytic processes, that constitute the foundation for continued progress towards the design of a general methodology for an enantioselective transition-metal-catalyzed C−C bond formation to sp^3-hybridized carbon atoms.

Fundamental Chemistry of Complexes with the Csp^3−TM Bond

At the onset of the development of the chemistry of transition-metal–alkyl complexes the thermodynamic feasibility of a direct Csp^3−H activation was questioned owing to the presumed weakness of the Csp^3−M bond.[9] Since the energies of Csp^3−TM bonds were found to range from 40 to 80 kcal mol^{-1},[10] the difficulties associated with C−H activation of alkanes had to arise from kinetic factors, for example, decomposition through β-hydride elimination.[11] In general, β-hydride elimination could be limited by the lack of free coordination sites on the metal center, or if geometrical factors preclude a coplanar arrangement of M-C-C-H bonds.[11] Geometric rigidity around a transition-metal center has been found to contribute to an unexpectedly high thermal stability of complexes containing conformationally free β-hydrogen atoms.[12] Landmark mechanistic studies on hydrocarbon activation with homogenous rhodium complexes by Jones[13] established that relative strengths of C−TM bonds decrease in the order Csp^2(aryl)−M > Csp^2(vinyl)−M > CH_3−M > RCH_2−M > R_2CH−M > R_3C−M > $PhCH_2$−M. Steric hindrance between the metal with its coordination sphere and substituents on carbon was put forward to rationalize this trend. A recent theoretical study[14] examined differences between the strengths of various types of carbon–metal bonds for an entire series of second-row transition metals. Electronic factors correlating the increase of the bond strength to the increase of the ionic character of the $C^{\delta-}$−$M^{\delta+}$ bond when moving to the left of the periodic table, were suggested to play the most important role. In agreement with experimental work of Brookhart,[15] DFT calculations[16] on bisimino(propyl)palladium(II) complexes revealed that the branched isopropyl complex **1** (Scheme 1) was thermodynamically favored over the *n*-propyl isomer, as far as the palladium center remained electron deficient and sterically unhindered, resulting in a minimum negative charge at the metal-bonded stereogenic carbon atom. An experimental study revealed that the branched complex **2** was favored over the linear isomer **3** due to the stabilizing interaction between the cyano group and the partial negative charge on the neighboring carbon atom.[17]

These findings have opened up new avenues for overcoming unfavorable kinetic and thermodynamic characteristics

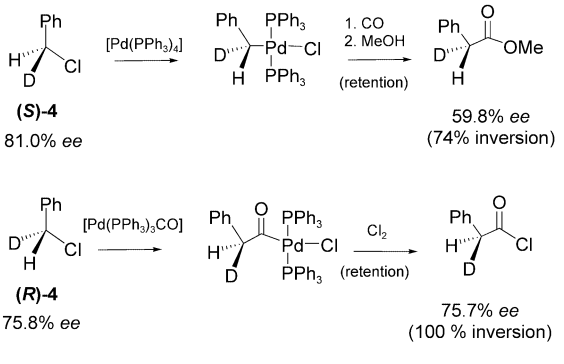


Scheme 1. Electronic effect of substituents (CN) on the relative stabilities of palladium–alkyl complexes with primary and secondary metal-bonded carbon atoms.

of transition-metal–alkyl complexes, thus significantly contributing to the evolution of new synthetic applications of organometallics with C*sp^3–TM bonds.

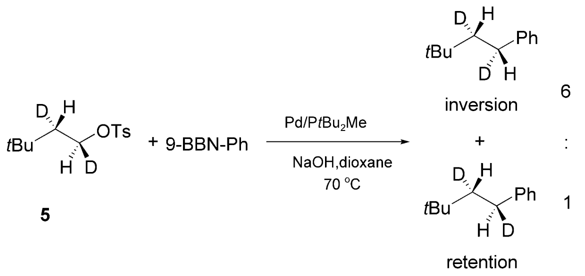
Stereochemical Course of the C*sp^3–TM Bond Formation—Mechanistic Studies

Oxidative addition: Oxidative addition is a common term for a class of reactions in which a metal is oxidized by the addition of a Y–X species.[18] Oxidative addition to chiral nonracemic organohalides with a halogen bonded to a stereogenic carbon atom would give rise to a metal-bonded stereogenic carbon atom, assuming that the reaction will proceed with either clean retention or inversion of the absolute configuration at the reaction center. Early exploratory studies on the stereochemical course of oxidative addition provided evidence for an S_N2-type displacement pathways operating with alkylhalide, or pseudohalide substrates.[18] The first unequivocal demonstration of the inversion of configuration at a stereogenic sp^3-hybridized carbon atom in oxidative addition of palladium(0) complexes to chiral nonracemic benzylic halides **4** was provided by Stille.[19a,b] These experiments are outlined in Scheme 2. Recently, C–Cl oxidative addition to Pd^0 involving retention of configuration at the metal-bonded carbon atom, was theoretically proposed to be feasible under certain conditions.[19c]



Scheme 2. Stille's experiments demonstrating the inversion of configuration at a stereogenic deuterated benzylic carbon atoms in oxidative addition with palladium(0) complexes.

Palladium-catalyzed Suzuki cross-coupling of diastereomerically pure deuterated alkyl tosylates **5** was realized[20] indicating about 6:1 selectivity for a pathway proceeding with an inversion of configuration at the stereogenic carbon (Scheme 3).[21]



Scheme 3. A catalytic Suzuki cross-coupling proceeding with predominant inversion of configuration at the stereogenic carbon.

C–H activation: The C–H activation corresponds to a direct replacement of a C–H bond in hydrocarbons with a C–TM bond. The general transformation can encompass an entire spectrum of mechanistic possibilities. The two most significant pathways (Figure 3) are: a) oxidative addition giving rise to a hydrido metal complex, and b) concerted activation by an electrophilic metal center.[22a–c] For the well-developed activation of C–H aromatic bonds by palladium complexes, a SEAr-type reaction seems to be ubiquitous.[22d]

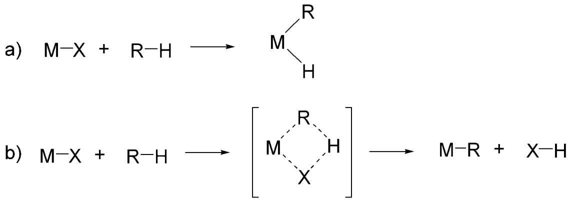
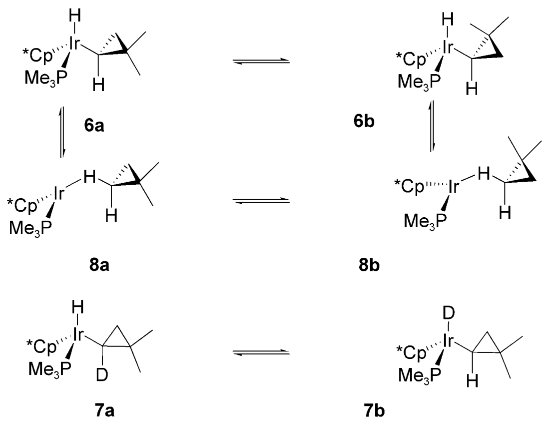


Figure 3. Alternative mechanistic pathways for transition-metal-mediated activation of C–H bonds.

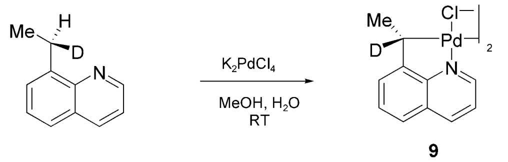
Early examples of a direct activation of Csp^3–H bonds by the action of a transition-metal complex exploited a photochemical removal of a coordinated ligand (L), or a reductive elimination of dihydrogen from stable complexes [MCp*(L)$_2$] or [MCp*(L)H$_2$] (Cp* = η^5-C$_5$Me$_5$; L = PMe$_3$, CO; M = Ir, Rh) yielding highly reactive 16-electron MCp*L fragments. These species induced thermal Csp^3–H activation in hydrocarbons to afford isolable [MCp*(L)(alkyl)(H)] complexes.[23] The C–H activation was found to be reversible, favoring the formation of primary RCH$_2$–TM bonds in reactions with acyclic aliphatic hydrocarbons.[24] The mechanism of similar reversible C–H activation was studied on diastereomerically pure iridium complexes **6a**,**b**, and their deuterated analogs **7a**,**b** (Scheme 4).[25] Upon thermolysis, diastereomerically pure complexes **6a** and **6b** underwent an inversion of configuration at the metal-bonded stereogenic



Scheme 4. Interconversion of diastereomeric (hydrido)alkyliridium complexes and the deuterium scrambling of their α-deuterio analogues.

carbon atom, and the deuterium-labeled complexes **7a–b** participated in isotope scrambling. Both processes occurred through the intermediate metal–alkyl complexes of the type **8a**,**b**, in which either of the two diastereotopic C−H bonds formed an agostic bond to the iridium center, and the C−H activation presumably proceeded with a retention of configuration and the sp^3-hybridized carbon.

The stereochemical course of an electrophilic cyclopalladation at a benzylic carbon was investigated (Scheme 5)[26] revealing a high (>11) kinetic isotope effect, and 94% stereospecifity for retention of configuration. Configurational stability of the metal-bonded stereogenic center was compromised under strongly acidic conditions (HCl), while a weak acid (HOAc) was tolerated without racemization of complex **9**.

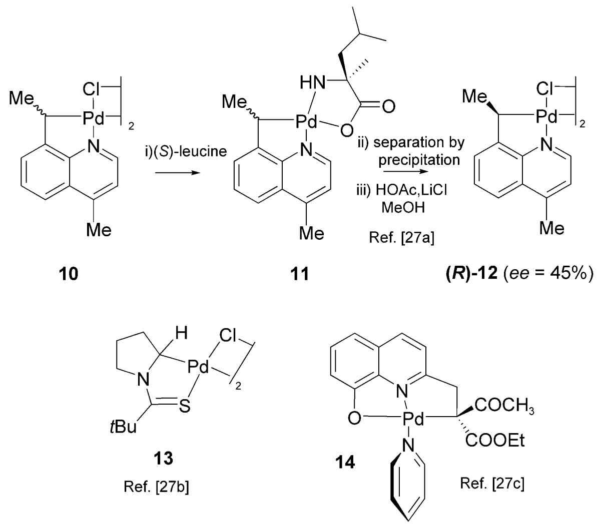


Scheme 5. The retention of configuration in an electrophilic cyclopalladation.

Sources of Stereochemical Information in Synthesis of Stable Chiral Nonracemic Organometallics with Transition-Metal-Bonded Csp^3-Hybridized Carbon Atoms

Application of the general principles of asymmetric synthesis to the preparation of enantiomerically enriched organometallic complexes opens up diverse pathways for the transfer of asymmetry to the metal-bonded stereogenic carbon.

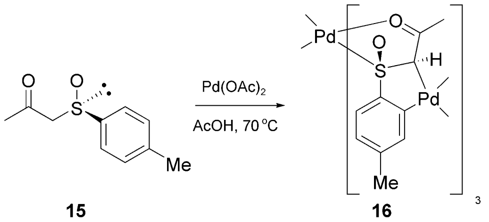
Classical resolution: The use of chiral nonracemic "spectator ligands" as "resolving agents" for separation of racemic transition-metal organometallics provided the first examples of chiral nonracemic complexes featuring a metal-bonded stereogenic sp^3-hybridized carbon atoms. By this method, enantiomerically enriched complexes **12**–**14** (Scheme 6) were obtained.[27]



Scheme 6. Preparation of enantiomerically enriched cyclopalladated complexes through classical resolution by using chiral auxiliary ligands as the resolving agents.

A bridge splitting reaction of racemic cyclopalladated dimer **10** with optically active (*S*)-leucine followed by a series of fractional precipitations yielded diastereomerically enriched cyclopalladated complex **11**, which upon the removal of the chiral resolving agent by the treatment with a mild acid (HOAc, racemization occured with HCl) generated dimeric complex **12** with *ee*'s up to 45%.[27a] Assumption that the carbon–metal bond remains intact during the ligand exchange process was supported by an excellent agreement between the *de* (33%) of the diastereomerically enriched complex **11**,[27d] and the *ee* (28%) measured for the final product **12**.

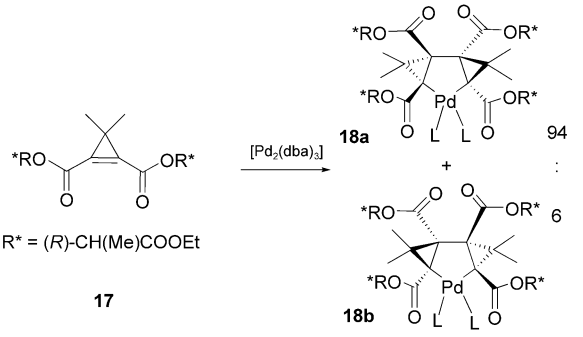
Substrate-directed asymmetry transfer: In an approach analogous to the "organic" substrate-induced stereocontrol, a chiral auxiliary group is covalently attached to the organic substrate, or the organic substrate incorporates a stereocontrolling element before its interaction with the metal center is initiated. This concept has been utilized for cyclopalladation of a chiral nonracemic β-ketosulfoxide **15** (Scheme 7)



Scheme 7. Synthesis of an enantiomerically pure cyclopalladated trimer by means of asymmetry transfer from a covalently bonded sulfoxide chiral auxiliary group.

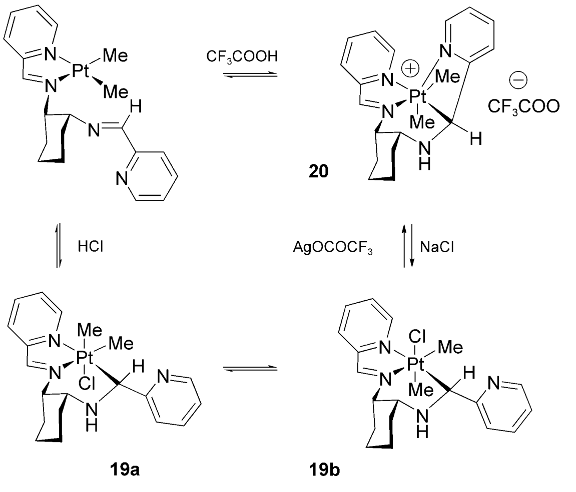
that afforded complex **16** with palladium in two distinct bonding modes and diastereoselectivity >98%.[28] The metal-bonded stereogenic center has been proposed to arise through a nucleophilic attack of an in situ generated palladium–enolate on an electrophilic palladium center to form a carbon–metal σ-bond stereoselectively, through the transfer of asymmetry from the sulfoxide stereocenter. *ortho*-Metalation of the aromatic ring completed the formation of complex **16**.

In an unusual variant of a palladium(0)-mediated oxidative cyclization, C_2-symmetrical cyclopropene **17**, bearing esters of the lactic acid as covalently bonded chiral auxiliaries, afforded selectively *trans*-palladacycle **18** (Scheme 8) as a 94:6 mixture of diastereomers **18a** and **18b**.[29] The asymmetry transfer was realized through a regioselective attachment of palladium and carbon to the two symmetry nonequivalent carbon atoms in the palladium π-complex with the cyclopropene. A preferential chelation of palladium to one of the two esters was proposed to direct the regiochemistry of the oxidative cyclization.



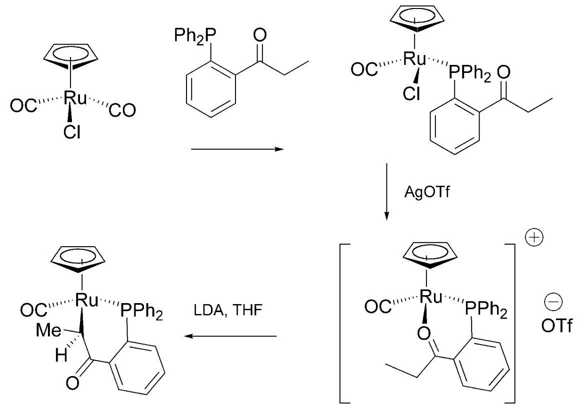
Scheme 8. Diastereoselective oxidative cyclization of chiral nonracemic C_2-symmetrical cyclopropenes yielding palladacycles with two metal-bonded stereogenic carbon atoms.

A formal diastereoselective hydridoplatination of a bis-imine ligand incorporating a chiral nonracemic 1,2-diaminocyclohexane backbone was achieved by means of a stepwise N-protonation/metalation sequence (Scheme 9).[30] The reaction proved highly diastereoselective giving rise to either the diastereomer **19a,b** or **20**, which differ in the configuration at the metal-bonded stereogenic carbon (Scheme 9). Reversible inversion of configuration at the metal-bonded stereocenter between complexes **19b** and **20** was achieved by the addition of NaCl and via halide abstraction with AgOTf.



Scheme 9. Stereodivergent, diastereoselective hydridoplatination of an imine yielding two chiral nonracemic (aminoalkyl)platinum complexes.

Stereocontrol by metal-centered chirality: It is conceivable that a stereogenic metal center could be employed as the stereocontrolling element for the creation of a metal-bonded stereogenic carbon. Racemic cationic ruthenium complex **21**, featuring a stereogenic ruthenium center, reacted with LDA to afford a cycloruthenated complex **22** as a 6:1 mixture of diastereomers (Scheme 10).[31]

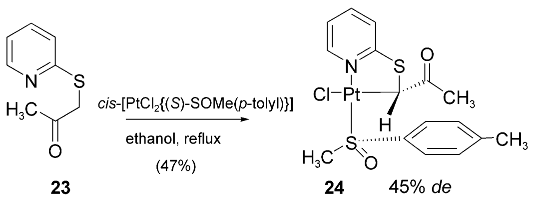


Scheme 10. Diastereoselective synthesis of a racemic carbon-bonded ruthenium enolate exploiting the transfer of stereochemical information from a stereogenic metal center.

Depending on the deprotonation conditions, different diastereomeric ratios of products were obtained, indicating that the main diastereomer **22** was the kinetic product with a relatively high barrier for epimerization of the metal-bonded stereogenic carbon.

Auxiliary ligand-controlled asymmetry transfer: The transfer of stereochemical information from chiral nonracemic "spectator" or "auxiliary" ligands into the transition-metal-bonded stereogenic carbon atom would constitute an attractive path for stereoinduction. Diverse reactions catalyzed by transition-metal complexes bearing chiral nonracemic ligands are in fact based on this premise.[32] However, transformations creating reactive intermediates with transition-metal-bonded stereogenic carbon atoms remain rare (vide infra). Furthermore, only a few studies on the efficiency and mechanism of the auxiliary ligand-induced asymmetry transfer were performed with stable isolated organometallic entities.[33,35]

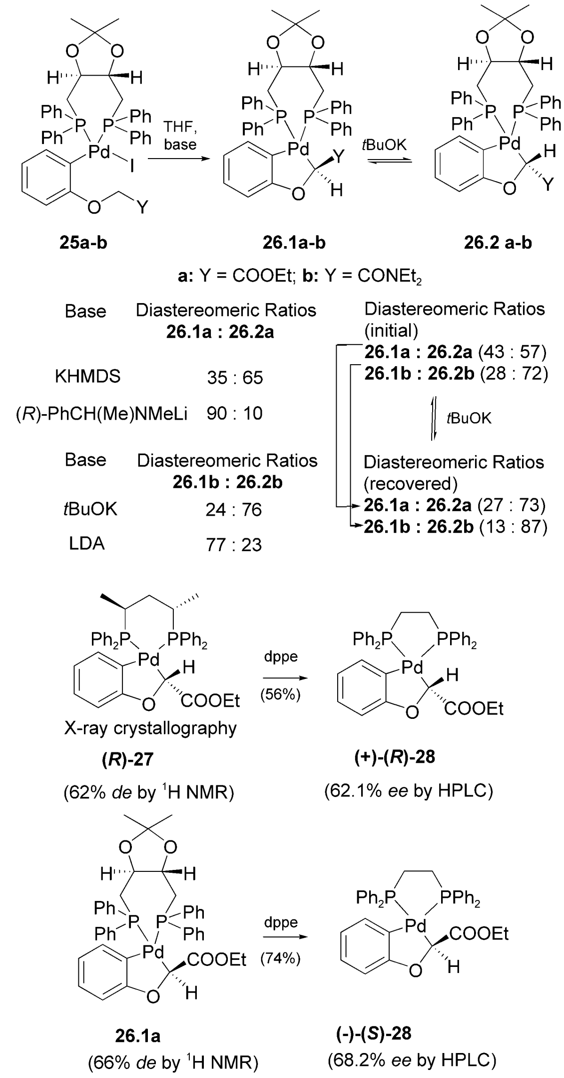
Asymmetric cycloplatination of a Csp^3–H bond yielding a diastereomerically enriched stable complex by the transfer of asymmetry from chiral nonracemic auxiliary sulfoxide ligands was demonstrated by Ryabov[33] (Scheme 11). Treatment of ketone **23** with a platinum complex armed with an enantiomerically pure sulfoxide ligand afforded a combined



Scheme 11. Asymmetric cycloplatination of a Csp^3–H bond with the transfer of asymmetry from a chiral nonracemic auxiliary sulfoxide ligand.

47 % yield of two separable diastereomeric cycloplatinated complexes **24** in 45 % diastereomeric excess.

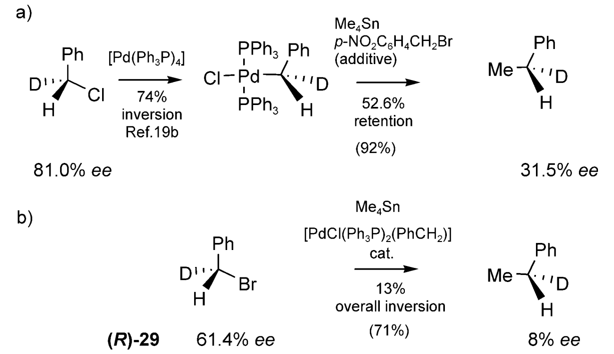
Our interest in this area relates to the chemistry of palladacycles.[34] Investigation of the transfer of asymmetry from chiral nonracemic bidentate phosphine ligands L ((*S*,*S*)-DIOP) in complexes **25** into the metal-bonded stereocenter in palladacycles **26 a**,**b** revealed that the absolute sense of stereoinduction could be controlled by the selection of the base (e.g., LDA or *t*BuOK) (Scheme 12),[35] yielding diastereomeric palladacycles (**26.1 a**,**b** and **26.2 a**,**b**) in 30–80 % *de*. Further enrichment in the content of the thermodynamic diastereomers **26.2 a** (from 14 % *de* to 46 % *de*) or **26.2 b** (from 44 % *de* to 74 % *de*) could be induced by the treatment with one equivalent of *t*BuOK. Absolute configurations of complexes **26.1 a** and **26.2 a** were assigned based on an X-ray crystallographic study on palladayacle **27** and correlations of the specific rotations for complexes **28** generated by ligand exchange (Scheme 12) assuming retention of configuration at the metal-bonded stereocenter. Enantiomerically enriched palladacycles **28** proved configurationally stable under standard workup and manipulations.



Scheme 12. Stereodivergent synthesis of enantiomerically enriched palladacycles featuring palladium-bonded ester and amide enolates.

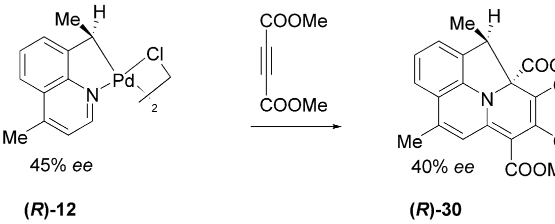
Stereochemical Course of Conversion of a C*sp^3–TM bond into a C*sp^3–C Bond

The "fate" of the metal-bonded stereocenters: To develop synthetically useful applications of chiral nonracemic transition-metal organometallics with a metal-bonded sp^3-hybridized stereogenic carbon atom, transfer of the metal-bonded stereocenter into a carbon framework of organic molecules must be explored. Mechanistically, the reactions could involve either migratory insertion of an unsaturated functionality into the C*sp^3–TM bond (C*sp^3–TM + C=C/C≡C→C*sp^3-C-C-TM/C*sp^3-C=C-TM), or a reductive elimination (C*sp^3-TM-C→C*sp^3-C + TM). Although it is generally accepted[36] that both migratory insertion and reductive elimination proceed with a retention of the absolute configuration at the migrating carbon atom, studies involving a step-by-step investigation of the stereochemical course of these pathways remain rare. Stille continued his seminal mechanistic work to elucidate the stereochemical course of reductive elimination.[37] Experiments outlined in Scheme 13 provided evidence indicating that the transmetalation/reductive-elimination sequence proceeded with 52.6 % retention of configuration in the stoichiometric transformation (Scheme 13a). In the catalytic reaction, 13 % overall inversion was observed (Scheme 13b). The poor stereoselectivity of the catalytic reaction was at least partially accounted for by the observed racemization of (*R*)-α-deuteriobenzylbromide **29** under the reaction conditions.



Scheme 13. Original Stille's studies on the stereochemical course of the reductive elimination indicating a partial retention of configuration at the metal-bonded stereogenic carbon atom.

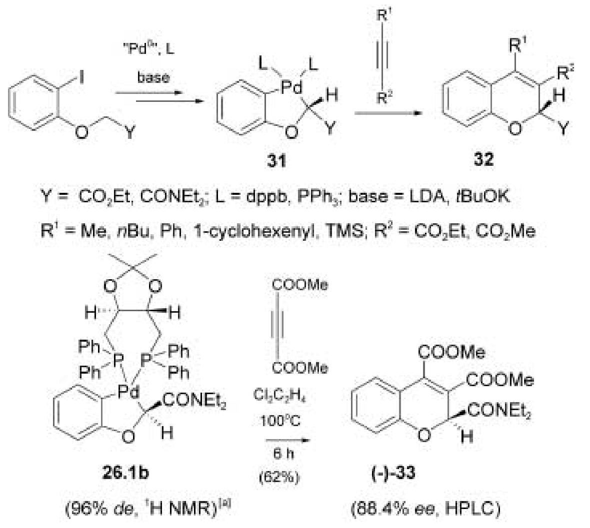
Migratory insertion of dimethyl acetylenedicarboxylate (dmad) into enantiomerically enriched cyclopalladated complex **12**, available by resolution (Scheme 6), was investigated with the aim to provide a relevant mechanistic insight, as well as a potential approach to enantiomerically enriched heterocycles.[27a] Reaction of complex (*R*)-**12** obtained in 45 % *ee*, with dimethyl acetylenedicarboxylate (dmad) afforded heterocycle **30** in 40 % *ee* (Scheme 14). By this process, the stereochemical information from complex **12** was transferred with 88 % efficiency into the heterocyclic product **30**, providing support for a concerted mechanism[36] of the migratory insertion process. In the absence of experimental evidence, the absolute configuration of the "originally" metal-bonded stereogenic carbon atom in the heterocycle **30** was assigned as *R*, assuming that the concerted migratory insertion proceeded with a retention of configuration. However, inversion of configuration at the metal-bonded stereocenter was not rigorously ruled out. The original evidence for a net retention (80 % efficiency) of absolute configuration at the migrating carbon atom was obtained in a study of insertion of dimethyl acetylenedicarboxylate into an iron–carbon bond in [CpFe(CO)$_2$CH(D)CH(D)*t*Bu].[38]



Scheme 14. "Fate" of the palladium-bonded stereogenic carbon atom during migratory insertion of dimethyl acetylenedicarboxylate. Preparation of an enantiomerically enriched heterocycle.

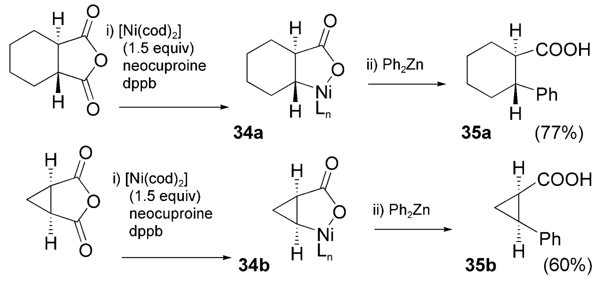
Following a precedent involving achiral palladacycles,[34d] preparation of racemic oxapalladacycles **31** and their conversion into highly substituted 2*H*-1-benzopyrans **32** through a regiocontrolled insertion of alkynes was demonstrated in our laboratories (Scheme 15).[39]

To approach the development of an asymmetric variant of this protocol, the insertion of dimethyl acetylenedicarboxylate into the chiral nonracemic palladacycle **26.1b**, generated in 54 % *de* by means of diastereoselective ring closure and further enriched up to 96 % *de* by flash column chromatography, was studied (Scheme 15).[35] Reaction proceeding for 6 h at 100 °C afforded the benzopyran (−)-**33** in 88.4 % *ee*, corresponding to 92 % efficiency in the transfer of the steAreochemical information embedded in complex **26.1b**. Since absolute configurations of both the complex **26.1b** and the benzopyran (−)-**33** could not be assigned, the retention of configuration at the metal-bonded stereogenic carbon atom as shown in Scheme 15, was assumed according to literature precedents;[36,38] however, the inversion could not be rigorously ruled out.



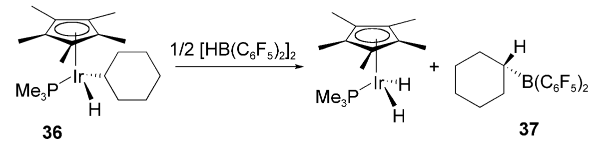
Scheme 15. Efficient transfer of the stereochemical information from a high-enantiopurity palladacycle with a palladium-bonded stereogenic carbon into a highly enantiopure 2*H*-1-benzopyran. [a] The assignment of the absolute configuration is arbitrary.

Recently, the first successful application of a stereoselective transmetalation/reductive-elimination sequence for cross-coupling of an sp^3-hybridized carbon atom in organic electrophiles to an sp^2-hybridized carbon atom in the nucleophile has been reported (Scheme 16).[40] Stoichiometric racemic nickelalactones **34a**,**b** featuring a metal-bonded stereogenic carbon atom, were generated in situ through the oxidative addition of the C(O)−O bond of an anhydride to a low-valent nickel complex followed by decarbonylation. Without isolation, the nickelalactones **34a**,**b** reacted with diphenylzinc to afford acids **35a**,**b** as single diastereomers with no loss of the stereochemical integrity at the metal-bonded sp^3-hybridized carbon.



Scheme 16. Decarbonylative nickel-mediated cross-coupling of cyclic anhydrides. Retention of the stereochemical integrity of nickel-bonded sp^3-hybridized carbon atoms during a reductive elimination event.

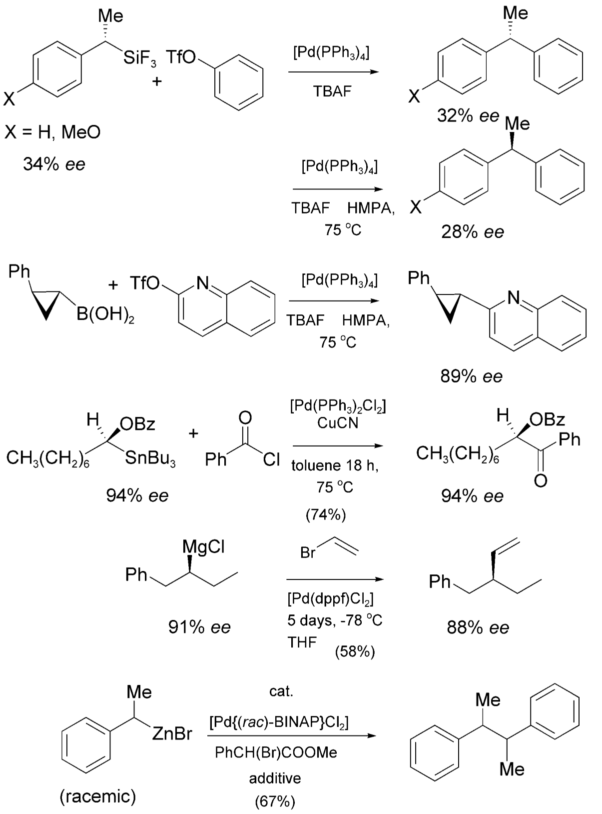
While the main focus of this review are methodologies directly leading to C*sp^3–C bond formation, reactions that convert complexes with C*sp^3–TM bond into activated organic compounds capable of subsequent carbon–carbon bond formation are also relevant. Most significant recent developments in this area are represented by both stoichiometric and catalytic borylation of hydrocarbons.[41] Racemic complex **36**,[41a] featuring a secondary (nonstereogenic) iridium-bonded sp^3-hybridized carbon, reacted with diarylborane to afford cyclohexylborane **37** (Scheme 17) in quantitative yields at ambient temperature.



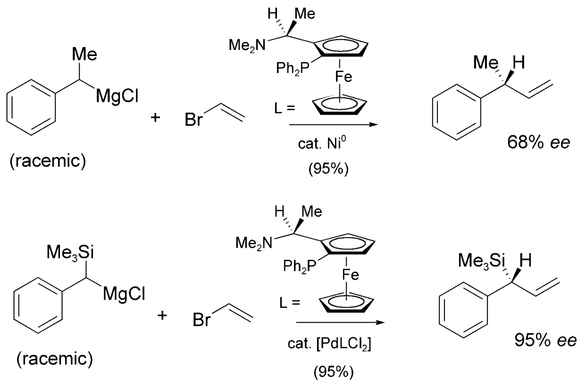
Scheme 17. Borylation of a racemic(hydrido)cyclohexyliridium complex yielding an achiral cyclohexane with a functionalized secondary carbon atom.

Catalytic Asymmetric Reactions Exploiting Intermediates with Stereogenic Metal-Bonded Csp^3-Hybridized Carbon Atoms

Transition-metal-catalyzed cross-coupling of chiral nonracemic main group metal reagents, featuring a metal-bonded stereogenic carbon to aryl or vinylic halides, mediated by catalytic organometallics of general formula Csp^2-TM-C*sp^3, was developed into a useful synthetic methodology (Scheme 18).[42] In several cases involving enantiomerically enriched silicon and tin reagents, the stereochemical course (inversion or retention) of the coupling reaction could be controlled by the choice of reaction conditions (solvent polarity).[43] However, for most practical purposes, absolute configurations of the cross-coupling products corresponded to overall retention of absolute configuration through the transmetalation/reductive-elimination events.[42]



Scheme 18. Representative examples of transition-metal-catalyzed cross-coupling reactions with chiral nonracemic main group metal reagents featuring a metal-bonded stereocenter.

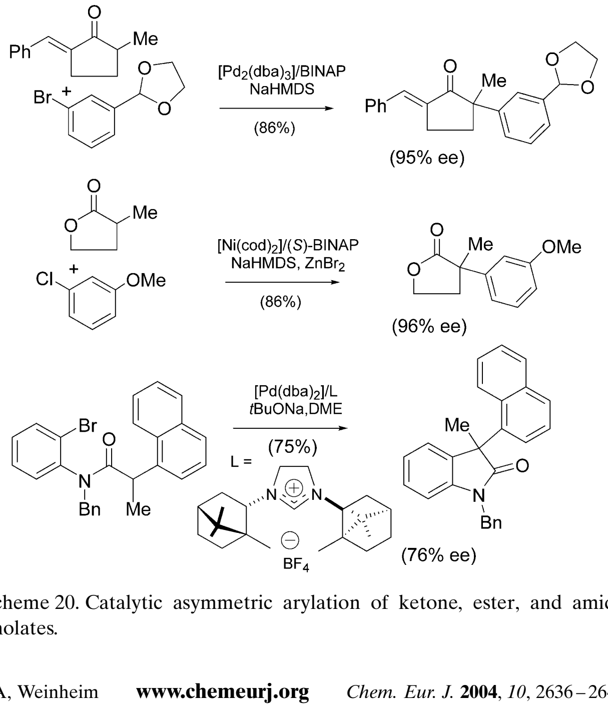


Scheme 19. Dynamic kinetic resolution of racemic organomagnesium reagents in cross-coupling reactions catalyzed by chiral-nonracemic nickel and palladium complexes.

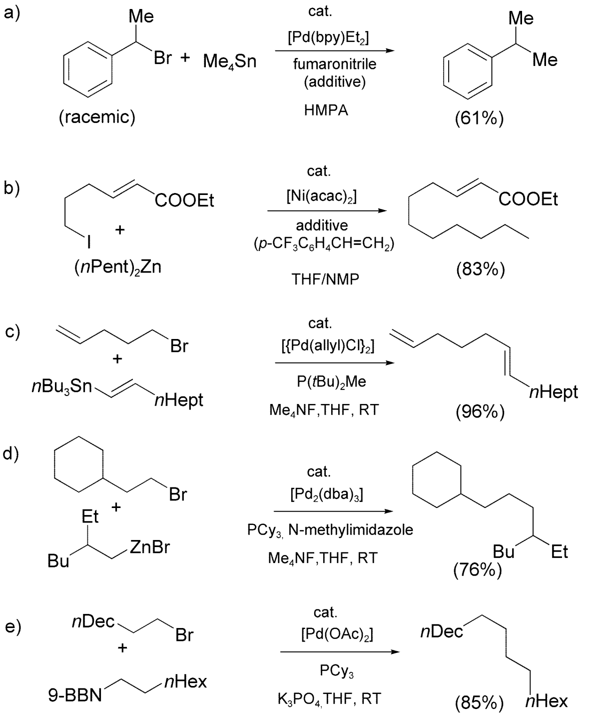
Methods described in Scheme 18 require an enantiomerically pure substrate to produce a chiral nonracemic cross-coupling product. Synthetically more attractive strategies would create the stereogenic carbon atom utilizing only catalytic quantities of a chiral material. A dynamic kinetic resolution of racemic organomagnesium and organozinc reagents during nickel- or palladium-catalyzed cross-coupling in the presence of chiral nonracemic phosphine ligands have met this challenge (Scheme 19).[44]

Arylation and vinylation of racemic or achiral ketone, ester, and amide enolates catalyzed by chiral nonracemic nickel and palladium(0) complexes[45] (Scheme 20) provided organic products in 70–98 % enantiomeric purities and already found applications to complex target synthesis.[45d]

Success of transformations described above, in which the nucleophilic component is the source of the stereogenic center, contrasts sharply with the paucity of complementary catalytic enantioselective methods involving electrophiles as the source of the stereogenic carbon atom. At present, research towards realizing such reactions evolves around the



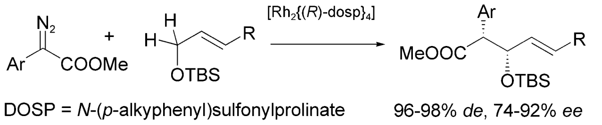
Scheme 20. Catalytic asymmetric arylation of ketone, ester, and amide enolates.



Scheme 21. Transition-metal-catalyzed cross-coupling to alkyl halides and pseudohalides.

development of methods for transition-metal-catalyzed cross-coupling to primary achiral alkylhalides (RCH_2X) (Scheme 21b–e).[46] Only rarely, cross-coupling to racemic stereogenic secondary carbon atoms in organic electrophiles was studied (Scheme 21a).[47]

Rhodium carbenoids generated by the action of chiral nonracemic rhodium complexes on α-diazoesters, participate in insertion into C–H bonds providing a process of extraordinary synthetic importance for the preparation of enantiomerically enriched organic products.[48] Although mechanistically distinct from processes discussed in this review, the net transformation allows for a metal-catalyzed conversion of a prochiral C–H bond into a C^*sp^3–C bond [reaction (4) in Figure 1]. The process shows preference for insertion into tertiary C–H bonds thus providing a pathway complementary to the "classical" C–H activation methods (Scheme 22).



Scheme 22. Catalytic enantioselective functionalization of prochiral Csp^3–H bonds through insertion of rhodium carbenoids arising from α-diazoesters.

Conclusion

In this account, studies on the preparation and reactivity of stable chiral nonracemic late-transition-metal organometallics with a metal-bonded sp^3-hybridized stereogenic carbon atom have been summarized, with the goal to define the foundations for the development of new catalytic asymmetric carbon–carbon bond-forming processes. Although late transition metals form relatively weak σ-bonds to sp^3-hybridized carbon atoms yielding complexes susceptible to β-hydride elimination, new avenues for fine-tuning of steric and electronic parameters of these organometallics that could facilitate the use of such entities as intermediates for asymmetric organic synthesis have been discovered. Especially the C–H activation appears a synthetically attractive avenue for stereoselective formation of a C^*sp^3–TM bond, as far as a sufficiently powerful stereocontrolling element could be designed. Studies exploring transfer of asymmetry either from covalently bonded chiral auxiliary, chiral nonracemic metal centers, or from chiral nonracemic "spectator ligands" demonstrated that stable organometallics featuring a metal-bonded stereogenic carbon centers could be generated in notable optical purities. This work provided useful data on configurational stabilities of the metal-bonded stereocenters. Only a few systematic studies investigating the conversion of stable nonracemic organometallics with a C^*sp^3–TM bond into nonracemic organic products are currently available. Migratory insertion of activated alkynes allowed for a highly efficient transfer of the stereochemical information into nonracemic heterocycles, and a recent report indicated that stereochemical integrity of a metal-bonded sp^3-hybridized carbon atom originating from an organic electrophile could also be retained during the transmetalation/reductive-elimination steps. It is our hope that this review will further stimulate research directed towards the design of new pathways for the incorporation of the transition-metal-bonded stereogenic carbon into high-enantiopurity organic molecules.[49] At present, asymmetric arylation of racemic ketone-, ester-, or amide enolates represents the only widely used methodology, catalytic in the source of asymmetry, that fulfills the concept outlined in this review.

Acknowledgement

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