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DOI: 10.1002/anie.201305972

Dearomatization by Coordination

Structure and Reactivity of Late Transition Metal η^3-Benzyl Complexes

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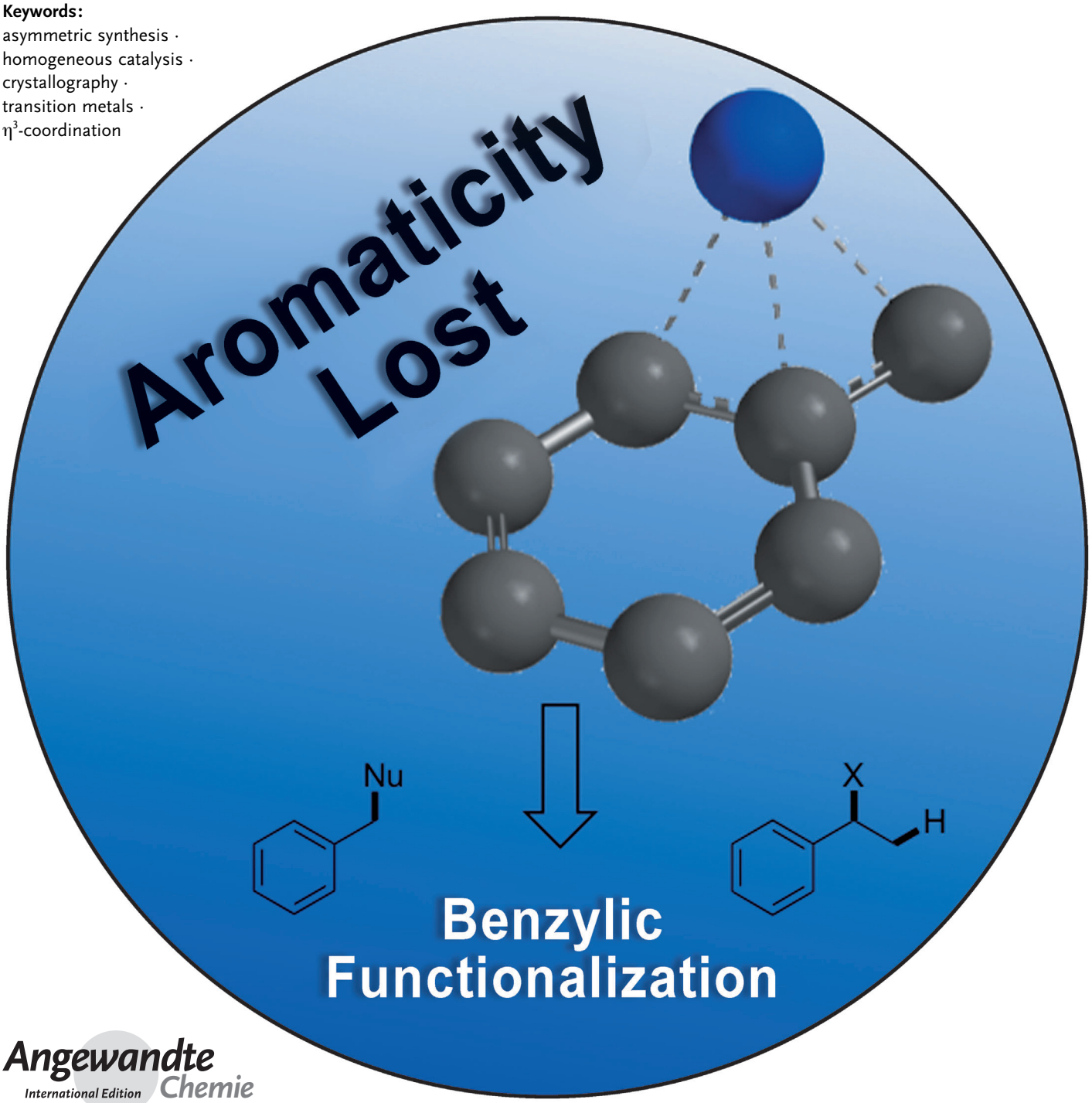
Keywords:
asymmetric synthesis · homogeneous catalysis · crystallography · transition metals · η^3-coordination



The coordination of transition metals to organic fragments can yield complexes with fascinating and unexpected binding patterns. The study of metal-benzyl complexes has demonstrated the feasibility of η^3-coordination, which results in a dearomatized ring. These complexes also offer insight into reaction mechanisms as proposed intermediates in catalytic cycles. In this Review we discuss the synthesis and characterization of these complexes with late transition metals and the subsequent development of catalytic benzylic functionalization methods, including asymmetric variants.

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1. Introduction

Transition metal catalysis has revolutionized organic chemistry, enabling transformations that would be either difficult or impossible by other means. Transition metals offer access to a variety of oxidation states and coordination spheres, the nature of which can be modified to induce chemo-, regio-, and stereoselectivity. The ability of transition metals to bind multiple atoms of a single ligand (hapticity) leads to interesting binding patterns in organometallic complexes.[1] Hapticity is studied by spectroscopy, wherein changes in IR stretching frequencies and NMR chemical shifts indicate metal-carbon bonds. X-ray crystallography is a very powerful tool for structure determination as it can unequivocally illustrate binding to a metal center.

Knowledge of the binding behavior of an organometallic fragment can guide the development and optimization of transition metal-catalyzed processes. Organometallic hapticity, driven by filling of metal valence shells, provides a view of the ligand environment at a metal center. Appropriate ligand design modulates the electron count or the steric environment at the metal, giving rise to haptomers. Electron pairs from carbon–carbon π-bonds frequently participate in such bonding, leading to organic fragments which are formally polydentate.

The allyl group is a well-studied example of multiple binding modes on an organometallic fragment. Metal allyls can exist as either the σ (η^1) complex, or the π (η^3) complex (Figure 1). The formation of the latter has been used to

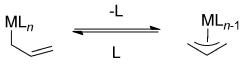


Figure 1. Metal-allyl binding modes.

explain the ease in which metals insert into the allylic position, in analogy to the increased acidity and leaving group ability at that site in classical reactions. In addition to stuctural studies, a wide variety of catalytic allylic functionalizations have been reported.[2]

A similar fragment that could stabilize a metal through η^3-binding is the benzyl group. However, the formation of the π-benzyl complex results in loss of aromaticity in the benzene ring, an energetic cost that is not present in the allyl system (Figure 2).

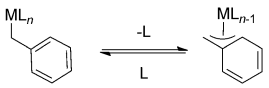
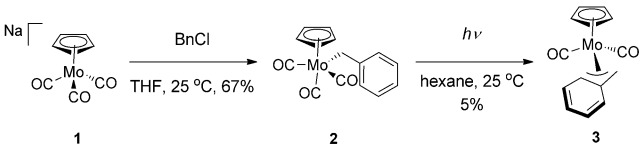


Figure 2. η^1 and η^3 Metal-benzyl binding modes.

Despite this energetic barrier, η^3-benzyl-metal complexes have been synthesized and characterized. The first evidence of such coordination to a metal center was reported by King and Fronzaglia in 1966.[3] Reaction of Na[Mo(CO)$_3$(Cp)] (**1**; Cp = cyclopentadienyl) with benzyl chloride furnished the neutral molybdenum complex **2**, which contained a σ-benzyl ligand (Scheme 1). Photolytic removal of a carbonyl ligand



Scheme 1. Molybdenum-benzyl complex reported by King.

provided **3** in low isolated yield. The isomerization of the benzyl group, presumably to achieve a d^{18} valency, was supported by NMR studies of **3**. At low temperature, all aromatic and both methylene protons were non-equivalent, as would be expected for a π-benzyl-metal complex.

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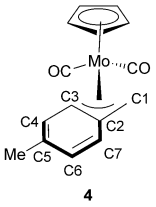

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Atoms	Distance
Mo-C1	2.269
Mo-C2	2.364
Mo-C3	2.480
C3-C4	1.419
C4-C5	1.361
C5-C6	1.426
C6-C7	1.328

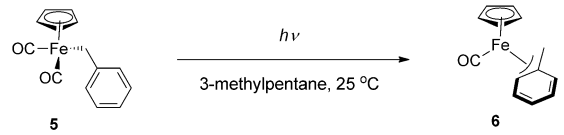
Figure 3. Structure of π-benzyl-molybdenum complex reported by Cotton with selected bond lengths.

King and Fronzaglia's findings were corroborated by results from X-ray crystallography by Cotton and LaPrade in 1968.[4] Bonding between Mo and C2 (2.364 Å) and C3 (2.480 Å) was observed in addition to benzylic carbon C1 (2.269 Å, Figure 3). The carbon–carbon bonds between C3–C6 resembled alternating single and double bonds, suggesting localization of the π-system on the ring. NMR studies of **4** were subsequently performed, and fluxional behavior of the complex was observed, leading to the conclusion that π–σ–π isomerization of the benzyl ligand was occurring.[5]

Following these initial studies, additional complexes have been synthesized with a number of transition metals. A variety of hapticities for metal–benzyl binding have been discovered as well, and have depended upon the conditions of generation as well as the electronic environment at the metal center. This Review will focus on η^3-benzyl complexes of late transition metals, both as characterized complexes and reactive intermediates.[6] Reaction development and understanding have been guided by initial studies on structure. The formation of a π-benzyl intermediate can be used to explain reaction regioslectivity or inform ligand design to facilitate formation. The Review is structured to move from left to right in the periodic table and will highlight both complex synthesis and characterization as well as catalytic benzylic functionalizations.

2. Iron

Spectroscopic evidence for an η^3-benzyl-iron complex was first disclosed in 1985 by Wrighton and Blaha.[7] Photolysis of $[CpFe(CO)_2Bn]$ (**5**) resulted in loss of one molecule of CO, and the isomerization of the benzyl group to η^3 coordination



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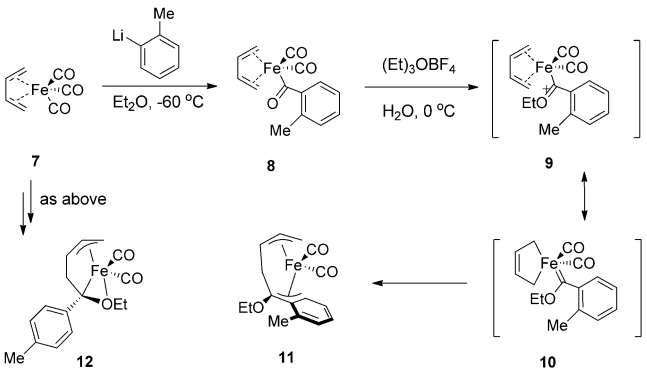
Scheme 2. Synthesis of η^3-benzyl-iron complex by photolysis of η^1-benzyl precursor.

accounted for UV/Vis activity consistent with 18-electron complex **6** (Scheme 2). A low-energy absorbance indicative of a 16-electron coordinatively unsaturated species was not observed. The authors noted that the analogous Fe-methyl complex was not observed upon photolysis, providing further support for a π-benzyl structure.

A second means to access complexes with η^3-benzyl-iron coordination was reported by Chen and co-workers in 1985.[8] Addition of an aryllithium to a carbonyl ligand of $[(C_4H_8)Fe(CO)_3]$ (**7**) followed by alkylation of **8** with Meerwein's salt yielded Fischer carbene **9**, which was not isolated (Scheme 3). Isomerization of the carbene through migration



Scheme 3. Synthesis of η^3-benzyl-iron complexes through Fischer carbene intermediate.

of a Fe–C bond in **10** resulted in **11**, the structure of which was determined by X-ray crystallography. Use of the isomeric aryllithium reagent provided complex **12**, wherein no binding between the benzyl group and Fe was observed. The steric demands of the aryl group dictate whether bonding occurs

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Barry M. Trost was born in Philadelphia, PA in 1941 and studied at the University of Pennsylvania (BA, 1962). He obtained his PhD in 1965 at MIT. He moved to the University of Wisconsin where he was made Professor in 1969 and subsequently Vilas Research Professor in 1982. He moved to Stanford University in 1987 and became Tamaki Professor of Humanities and Sciences in 1990. In addition to holding Visiting Professorships at several universities worldwide, he has been awarded numerous prizes. His interests span the entire field of organic synthesis, particularly in the development of methodology and strategy for total synthesis of bioactive complex molecules.

between iron and the benzylic oxygen atom or the benzyl group. A bond length of 2.253 Å between iron and the *ortho*-carbon indicated binding behavior and the alternation of single and double bond character on the phenyl ring was suggestive of localization of the π-system.

Chen and co-workers subsequently synthesized a number of iron complexes with η³-benzyl coordination in an identical fashion to that described above starting from cyclooctatetraene (**13**), limonene (**14**), and cyclohexadiene (**15**) iron tricarbonyls (Figure 4).[9] The formation of the π-benzyl

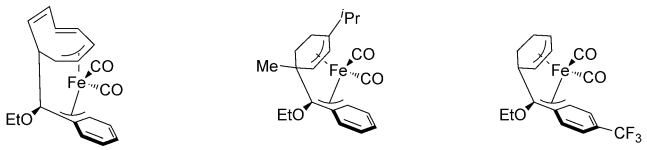
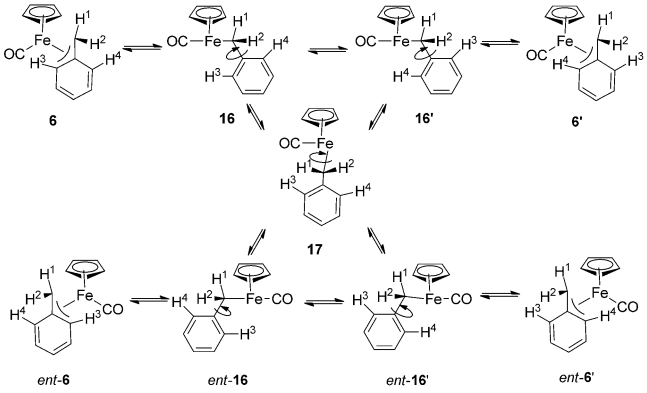


Figure 4. η³-benzyl-iron complexes synthesized by Chen.

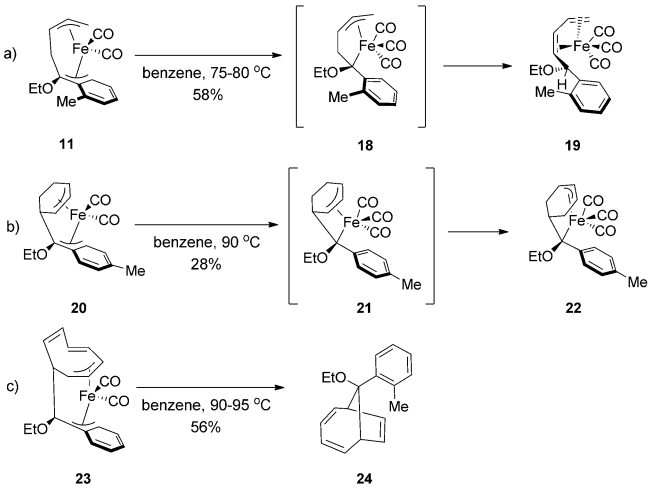
complex as opposed to coordination with the oxegen atom was again dependent on the steric environment at the aryl group.

The solution behavior of iron-π-benzyl complexes was studied via NMR spectroscopy by Brookhart and co-workers.[10] At −48 °C, two distinct doublets at 0.43 and 3.38 ppm with a 1.5 Hz coupling constant were observed for the benzylic protons of **6**, and the two *ortho*-protons were resolved. As the temperature was raised to 53 °C, broadening and eventual coalescence of the benzylic and *ortho*-proton chemical shifts was observed, an indication of dynamic behavior. The authors proposed isomerization from π-benzyl **6** to the σ-complex **16**, aryl rotation to **16′**, and relaxation back to π-complex **6′** as a pathway for scrambling of *ortho*-protons H^3 and H^4 (Scheme 4). Inversion at iron, proceeding through T-shaped intermediate **17**, would explain scrambling of benzylic protons H^1 and H^2.

More recently, the reactivity of Fischer carbene-derived iron-benzyl complexes was investigated. Heating **11** in benzene resulted in disproportionation. Tricarbonyl **18**, now with η¹ coordination from addition of a third carbonyl ligand,



Scheme 4. Proposed mechanism for dynamic behavior of iron-benzyl complex observed in ^{1}H NMR.



Scheme 5. Reactions of allyl-benzyl-iron complexes.

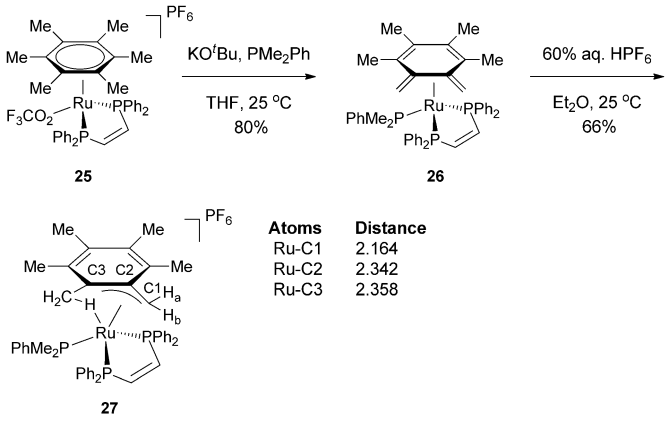
underwent a 1,2-hydride shift to yield **19** (Scheme 5a).[11] Under identical reaction conditions, **20** proceeded through **21** and after a 1,4 hydride shift, generated the observed product **22** (Scheme 5b).[12] When **23** was heated in benzene, bicycle **24** was observed (Scheme 5c). It was proposed that upon addition of a molecule of CO, reductive elimination from iron occurred to produce this interesting [4.2.1] system.

Iron-catalyzed benzylations of various nucleophiles have been reported using both benzyl halides and benzyl alcohols as electrophiles.[13] Iron salts are likely acting as Lewis acids to activate the leaving group; a benzyl cation would be invoked as the reactive intermediate in these reactions. Additionally, the ability for iron salts to catalyze the formation of benzylic radicals has been utilized in benzylation reactions.[14] An iron-catalyzed Negishi coupling with benzyl halides has been reported, but this process probably proceeds through a radical mechanism as well.[15] No catalytic processes likely to proceed through an iron-benzyl intermediate have been reported.

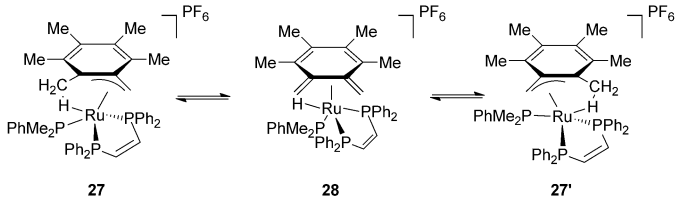
3. Ruthenium

As part of a study of ruthenium-xylyene complexes, Bennett and co-workers prepared a number of η³-benzyl-ruthenium complexes, including **27**.[16] Double deprotonation of ruthenium(II) salt **25** in the presence of phosphine ligand yielded **26**; coordination of ruthenium to the exocyclic olefins was confirmed by NMR spectroscopy and crystallography. Protonation of **26** with HPF_6 provided **27** in 66% yield (Scheme 6). The η³ hapticity was confirmed by X-ray crystallography.[17]

The solution-state behavior of **27** was probed using variable temperature NMR. At −80 °C, benzylic protons H_a and H_b were inequivalent, as were all the methyl protons. As the temperature was increased to 0 °C, coalescence of H_a and H_b as well as the *ortho* and *meta* methyl protons occurred. This behavior is suggestive of η³–η¹–η³ isomerization. At even higher temperature (60–80 °C), all the methyl groups became equivalent. This behavior is hypothesized to occur through



Scheme 6. Synthesis of an η^3-benzyl-ruthenium complex.



Scheme 7. Dynamic behavior of an η^3-benzyl-ruthenium complex.

formation of ruthenium hydride **28** and subsequent addition to an exocylic olefin (Scheme 7).

Catalytic N-benzylation using a ruthenium catalyst has been disclosed. The proposed mechanism invokes alcohol oxidation, imine formation, and reduction.[18] Decarboxylative benzylation of arenes with benzyl formate has also been disclosed under ruthenium catalysis, which likely proceeds through an electrophilic aromatic subsitution mechanism.[19]

4. Cobalt

The crystal structure of cobalt complex **29**, bearing a benzyl group and three phosphite ligands, was that of a distorted trigonal bipyramidal complex.[20] The benzyl group was coordinated in an η^3 fashion with the benzylic carbon occupying an axial site (Figure 5). The authors noted that relative to other metal-benzyl complexes, **29** had an elongated Co–C3 bond, which was 0.3 Å longer than the Co–C1 bond. Cobalt-benzyl complexes have also been generated through

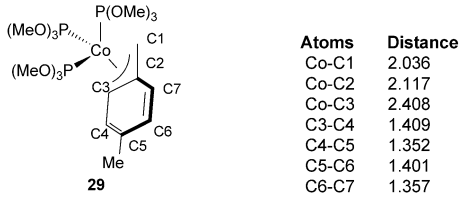
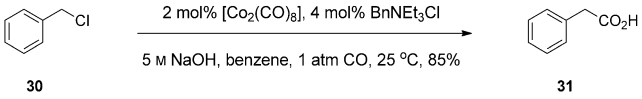


Figure 5. Crystal structure of a cobalt-benzyl complex with selected bond lengths.

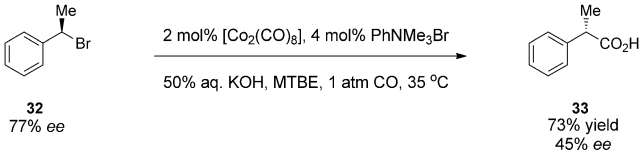
net substitution of a benzyl halide with Na[Co(CO)$_4$] as a mixture of η^1 and η^3 haptomers, the equilibrium of which was shifted towards the latter by bubbling argon through a solution of the mixture.[21] Under an atmosphere of carbon monoxide, migratory insertion to generate a cobalt acyl was observed.

The ability for anionic cobalt to form benzyl complexes has been applied to a catalytic process for carbonylation of benzyl halides such as benzyl chloride (**30**). Under phase transfer conditions with a tetraalkyl ammonium salt, attack by hydroxide generated an arylacetic acid anion, and the cobalt(I) anion was regenerated. Reported nearly simultaneously by Alper and Foa, these reactions proceeded using 2 mol% [Co$_2$(CO)$_8$] and could be performed at ambient temperature under atmospheric pressure of carbon monoxide to yield phenylacetic acid (**31**) in 85% yield (Scheme 8).[22]



Scheme 8. Cobalt-catalyzed carbonylation under phase transfer conditions to yield carboxylic acid.

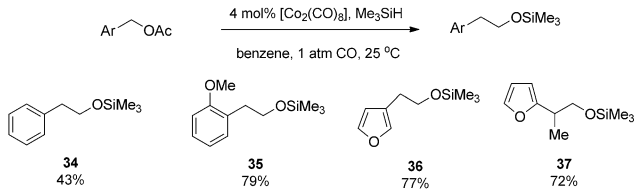
Subsequent studies indicated that secondary benzyl halides were competent substrates for formal carboxylation under phase transfer conditions.[23] Erosion of enantiomeric excess (*ee*) was observed in the carbonylation of an enantioenriched benzylic halide.[24] Reaction of **32**, prepared in 77% *ee*, led to carbonylated product **33** in 45% *ee* as the best result (Scheme 9). Racemization of the stereocenter may



Scheme 9. Racemization of secondary benzylic stereocenter under cobalt-catalyzed carbonylation. MTBE = methyl *tert*-butyl ether.

occur through β-hydride elimination, olefin rotation, and hydrometalation, the final process being precedented in stoichiometric studies. Alternatively, enolization of the cobalt acyl may account for the racemization. More recent studies of the carbonylation reaction have used polyethylene glycols as phase transfer catalysts as a more economic alternative to quaternary ammonium salts.[25]

Murai has reported cobalt-catalyzed homologation of benzylic acetates to yield β-phenethyl alcohols.[26] After carbonylation, the aldehyde was released in the presence of trimethylsilane (Scheme 10). Cobalt-catalyzed hydrosilylation of the aldehyde furnished a silylated alcohol, representing a 1-carbon homologation. Studies on benzene substitution indicated more efficient reactions with increased electron density, even with *ortho*-substitution (**34** vs **35**). Accordingly,

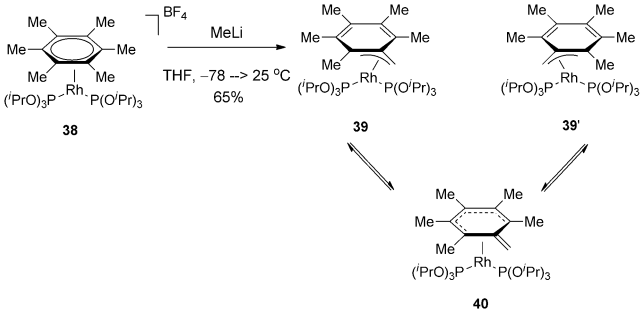


Scheme 10. Cobalt-catalyzed one-carbon homologation of benzyl acetates.

high yield was observed using a furan electrophile (**36**). It was also found that branching at the benzylic position was well-tolerated; furan **37** was isolated in 72% yield.

5. Rhodium

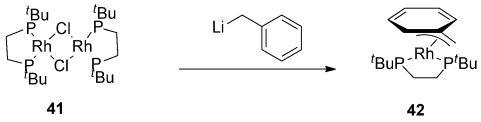
The synthesis and characterization of a rhodium-η^3-benzyl complex was first reported in 1982. While studying dehydrogenation pathways of Rh-cyclohexadienyl complexes, Day and co-workers attempted to synthesize an η^5-cyclohexadienyl-rhodium complex by organometallic addition to an arene.[27] Treatment of rhodium salt **38** with methyllithium did not yield the desired complex. Instead, **39** was isolated, the result of deprotonation and isomerization to the π-benzyl species (Scheme 11). The structure of **39** was determined by



Scheme 11. Synthesis of a Rh-benzyl complex by benzylic deprotonation of a half-sandwich complex.

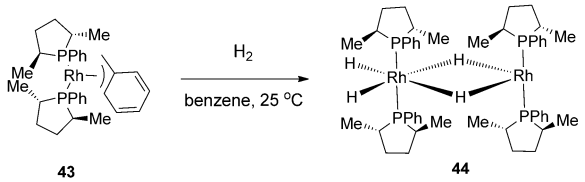
X-ray crystallography, and it was noted that the difference between bond lengths of Rh–C1 and Rh–C3 was 0.3 Å. This higher asymmetry of the bond may be attributed to anionic character of the benzyl ligand or steric repulsion with the *ortho*-methyl substituent. NMR studies were performed on **39**, and the presence of two distinct phosphorus signals over a wide temperature range led the authors to conclude a lack of π–σ–π dynamic behavior, which would require a 14-electron intermediate.[28] However, the *ortho*-carbons were equivalent, and the authors suggested dynamic behavior between η^3 and η^5 species **40**.

Rhodium-benzyl complexes have also been synthesized by addition of a benzyl organometallic to a Rh center. Ebbinghaus and Mattigan added benzyllithium to μ-chloride dimer **41**, synthesizing square-planar complex **42**, which contained a bulky bidentate phosphine ligand



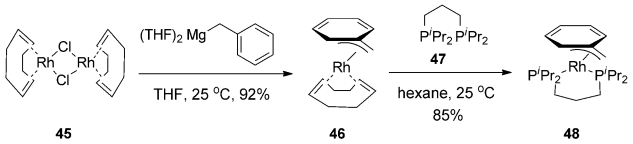
Scheme 12. Synthesis of a Rh-benzyl complex by addition of benzyllithium to a dimeric rhodium precursor.

(Scheme 12).[29] Bonding to the *ortho*-carbon as well as localization of the π-system was observed in crystallographic studies. Similar rhodium-benzyl bisphosphines were prepared through addition of benzyl Grignard reagents by Werner.[30] A bulky monodentate phosphine was utilized to synthesize **43**, and the authors described hydrogenolysis of the benzyl group to yield bisrhodium complex **44** (Scheme 13).



Scheme 13. Hydrogenolysis of Rh-benzyl complex.

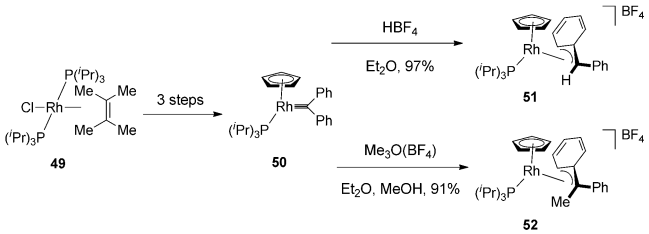
Fryzuk and co-workers approached the synthesis of benzyl-rhodium-complexes in a slightly different manner. The authors added either a benzyl Grignard THF complex or dibenzylzinc to the rhodium-cod complex **45** (Scheme 14;



Scheme 14. Synthesis of a Rh-benzyl complex by addition of an organometallic to a dimeric Rh-cod precursor.

cod = cyclooctadienyl).[31] Subsequent ligand exchange of **46** with bulky bidentate phosphine **47** yielded **48**.

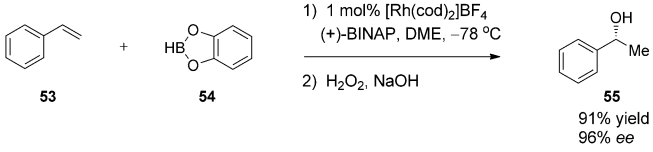
A third means to access rhodium-benzyl complexes is through electrophilic attack on a vinylidene, as has been demonstrated by Werner.[32] Rhodium diphenyl vinylidenes were accessed in three steps from **49** (Scheme 15),[33] and



Scheme 15. Synthesis of a Rh-benzyl complex by electrophilic attack on a vinylidene.

Werner demonstrated that half-sandwich complex **50** could be protonated with HBF_4 to form **51** in 97% yield. Additionally, treatment with Meerwein's salt afforded **52** in 91% yield as a single isomer. The geometric configuration of the benzyl unit was in part determined by the chemical shift of the benzylic proton of **51**. The NMR spectra of both compounds suggested rigid complexes that did not undergo π–σ–π equilibration. The steric bulk at the benzylic carbon may prevent isomerization to the σ-complex.

An η^3-benzyl-rhodium species has been proposed as an intermediate in catalytic hydroboration of styrenes.[34] Hayashi and co-workers reported asymmetric hydroboration of styrene (**53**) with catechol borane (**54**) with a cationic rhodium-BINAP complex generated in situ to form **55** upon oxidation (Scheme 16).[35] This regiochemistry is the opposite



Scheme 16. Asymmetric rhodium-catalyzed hydroboration of styrene reported by Hayashi. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

of that observed for uncatalyzed hydroborations with alkylboranes. Rhodium-catalyzed asymmetric hydroboration of styrene has been used as a test reaction for a variety of bidentate ligands.[36]

The proposed mechanism for Rh-catalyzed hydroboration begins with oxidative insertion of a cationic rhodium(I) complex into the B–H bond of the borane (Figure 6). Coordination of the olefin followed by hydrometalation furnishes a benzyl-rhodium(III) intermediate (path A). Though the terminal carbon is less sterically hindered, the stability gained from an η^3 intermediate leads to selective formation of the benzyl-rhodium species. Reductive elimination furnishes the secondary borane, which can be oxidized, or used as a Suzuki cross-coupling partner.[37] A second potential

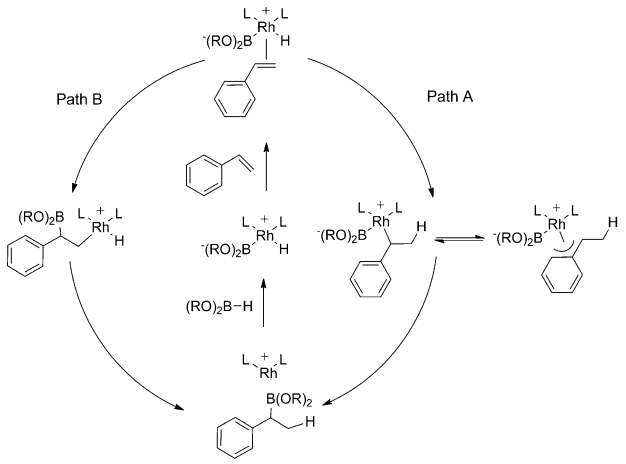
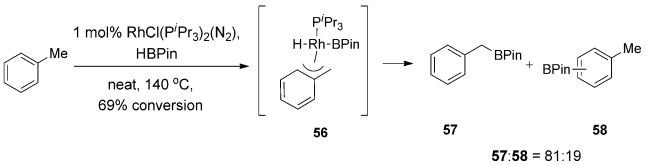


Figure 6. Proposed mechanistic pathways for rhodium-catalyzed hydroboration of styrene.

pathway invokes addition of the borane and rhodium across the olefin, followed by reductive elimination of the rhodium hydride (path B). Hammett studies of substituted styrenes and stilbenes were performed by Crudden and co-workers, and a break in the Hammett plot at $\sigma = 0$ was observed.[38] At negative σ values, a negative ρ value was observed, and at positive σ values, a positive ρ value was observed. This observed behavior indicates that the electronic nature of the benzene ring dictates the mechanistic pathway of the reaction.

Studies on rhodium-catalyzed C–H borylation with bis(pinacolato)diborane by Marder and co-workers yielded an interesting result using toluene, xylene, and mesitylene substrates.[39] Instead of arene C–H borylation observed for benzene, the authors observed benzylic borylation as the major isolated product (Scheme 17). The authors suggested



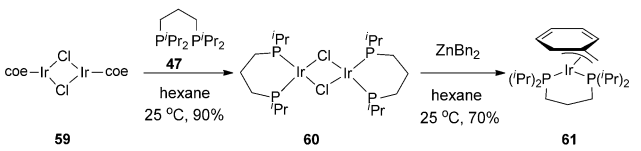
Scheme 17. Rhodium-catalyzed C–H borylation.

insertion of a Rh-BPin complex into the benzylic C–H bond or σ-bond metathesis of a rhodium hydride to generate the stabilized π-benzyl intermediate **56**. Use of toluene as a substrate yielded up to 56% yield of **57** determined by GC analysis at 69% conversion, with the remaining 13% of borylated products representing arene C–H borylation (**58**). DFT calculations support the proposed η^3-benzyl-rhodium intermediate.[40]

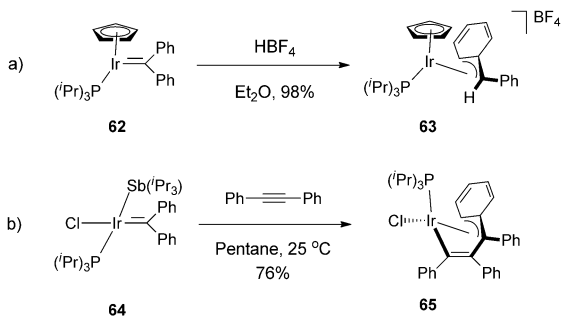
6. Iridium

Synthetic routes towards rhodium complexes have been applied to iridium analogues. Organometallic addition to an iridium center was used to synthesize **61**. Starting from dimer **59**, introduction of bisphosphine **47** followed by dibenzylzinc addition to dimer **60** yielded **61** (Scheme 18).[31] The NMR spectrum of this complex was similar to that obtained for **48**, suggesting that both adopt a similar η^3-benzyl coordination.

Protonation of benzylidene **62** with 54% HBF_4 in diethyl ether furnished ionic complex **63** (Scheme 19a). As with **61**, comparison of NMR spectra to the rhodium analogue supported the formation of the π-benzyl complex.[41] Reaction



Scheme 18. Synthesis of η^3-benzyl-iridium complex by benzyl organometallic addition. coe = cyclooctene.



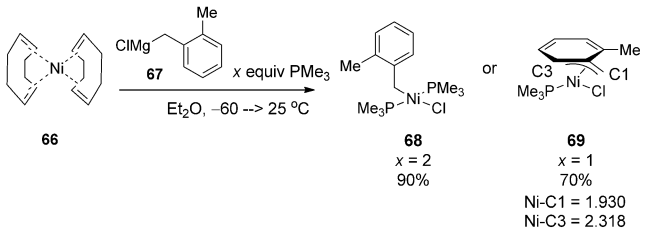
Scheme 19. Synthesis of η³-benzyl-iridium complex by a) benzylidene protonation and b) alkyne addition.

of diphenylacetylene with square planar iridium benzylidene **64** yielded addition product **65**, demonstrating yet another way to access an η³-benzyl-metal complex (Scheme 19b).

7. Nickel

7.1. Nickel-Benzyl Complexes

The formation of both η¹ and η³ *ortho*-methyl benzyl-nickel complexes was reported by Poveda and co-workers in 1987.[42] Addition of Grignard reagent **67** to **66** in the presence of either one or two equivalents of trimethylphosphine yielded η¹-coordinated **68** and η³-coordinated **69**, respectively (Scheme 20). Complex **69** was found to be square planar with Ni–C1 and Ni–C3 bond distances of 1.930 and 2.318 Å, respectively.



Scheme 20. Synthesis of η¹ and η³-*ortho*-methyl benzyl-nickel complexes by Poveda.

Poveda later synthesized binuclear nickel complexes by bis-oxidative addition to a dibromide.[43] As was seen before, formation of η³-benzyl complexes **70**, **71**, and **72** could be favored when one equivalent of trimethylphosphine per nickel atom was added to the reaction mixture (Figure 7).

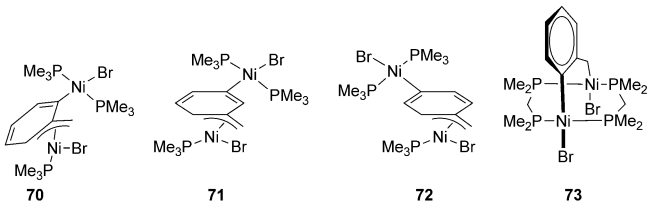


Figure 7. Bimetallic η³-benzyl-nickel complexes synthesized by Poveda.

Reaction of **70** with dimethylphosphino methane (dmpm) furnished the interesting complex **73**, which featured a bridging benzyl group.

7.2. Nickel-Benzyl Complexes as Polymerization Catalysts

Olefin oligomerization and polymerization are important processes for the synthesis of hydrocarbons. The development of homogeneous catalysts based upon late transition metals, including nickel, for these processes is an active area of research.[44] The mechanism for polymerization begins with ligand exchange to generate an olefin-coordinated complex (Figure 8). Migratory insertion into the olefin extends the

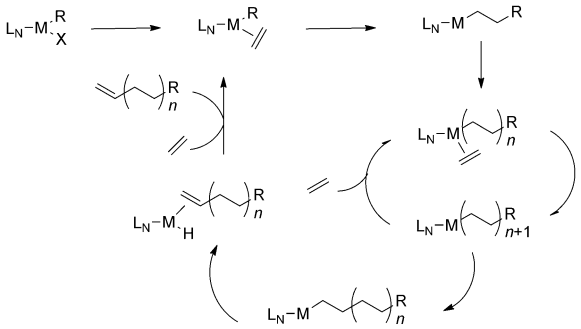


Figure 8. Catalytic cycle for metal-catalyzed olefin polymerization.

chain, which is propagated upon sequential olefin coordination and insertion. Oftentimes, an initiator is required to open the required coordination site on the metal center. A hemilabile bidentate ligand that can be readily displaced by monomer would remove the need for an added initiator and may improve the kinetic profile of the catalytic reaction.

The observation that nickel can bind a benzyl ligand in either η¹ or η³ fashion depending on the ligand environment at the metal center has been applied to the development of catalysts for olefin oligomerization and polymerization. The initial report of ethylene oligomerization was disclosed by Bazan and co-workers, in which complex **74** was found to consume ethylene more rapidly than the analogous methallyl complex (Figure 9).[45] This catalyst was less selective, however, with a lower linear α-olefin to branched olefin ratio observed. Addition of a triarylborane to the reaction mixture further increased reaction rate, presumably by decreasing electron density at the metal center. Bisphosphine complex **75**, developed by Campora, was demonstrated to selectively

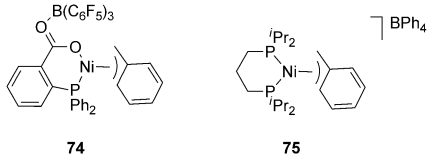


Figure 9. η³-Benzyl-nickel olefin oligomerization catalysts.

catalyze formation of oligomers, which was attributed to the larger bite angle of the ligand.[46]

Bazan applied the finding of increased activity with decrease of electron density to nickel-iminocarboxamidato complex **76**, which was found to be active for ethylene polymerization without the need for an activator such as MAO. Higher steric bulk led to higher branching in the polymer, and up to 850 kg/(mol Ni h) high-molecular weight polymer could be synthesized (Figure 10). Formation of low-

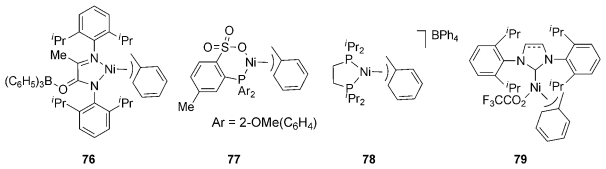


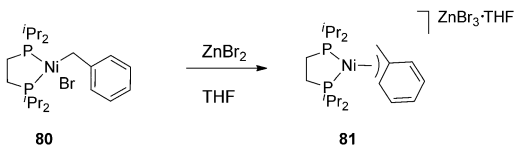
Figure 10. η^3-Benzyl-nickel olefin polymerization catalysts.

molecular weight polyethylene with low branching was observed in the polymerization of ethylene catalyzed by **77**, developed by Jordan.[47] Ethylene polymerization was observed in preference to oligomerization by Campora with bisphosphines containing smaller bite angles such as **78**, allowing for catalyst-controlled product distribution. Norbornene polymerization catalyzed by N-heterocyclic carbene (NHC)-ligated **79** was disclosed by Han in 2008, again without the requirement for an exogenous activator.[48]

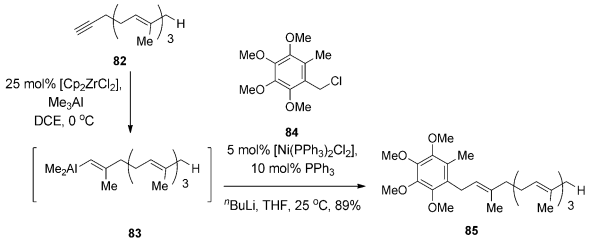
7.3. Nickel-Catalyzed Cross Coupling

Metal-catalyzed cross coupling is a powerful method for synthesizing carbon-carbon bonds. The process has been studied extensively with a wide variety of halide and pseudohalide electrophiles as well as organometallic nucleophiles.[49] Modulation of the various partners, catalytic metal, and reaction conditions has allowed for bond formation between carbons of all hybridization levels. If the accepted catalytic cycle is operative with a benzyl electrophile, a benzyl-metal species is generated upon oxidative addition. The knowledge of the different hapticities that the benzyl group may adopt can guide catalyst design and improve reaction conditions. Vicic and Anderson found that $ZnBr_2$, which would be generated as a transmetalation byproduct, was capable of abstracting a bromide atom from oxidative addition product **80** (Scheme 21).[50] The resulting cationic complex was determined to be the zinc tribromide salt **81** with a π-benzyl ligand. This non-innocent behavior of $ZnBr_2$ may facilitate transmetalation provided that isomerization to the σ-complex is more facile than transmetalation of four-coordinate complex **80**.

A protocol for nickel-catalyzed coupling of benzyl chlorides with vinylalanes was disclosed by Lipshutz in 1996. Trisubstituted vinylalanes were synthesized by zirconium-catalyzed methylalumination of alkynes such as **82**, a method precedented to provide regio- and stereo-defined vinylalanes.[51] Crude vinylalane **83** reacted with benzyl



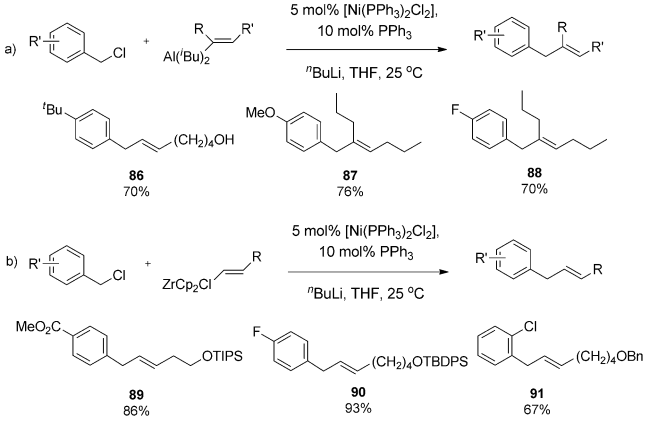
Scheme 21. Formation of an η^3-benzyl-nickel complex by halide abstraction by $ZnBr_2$.



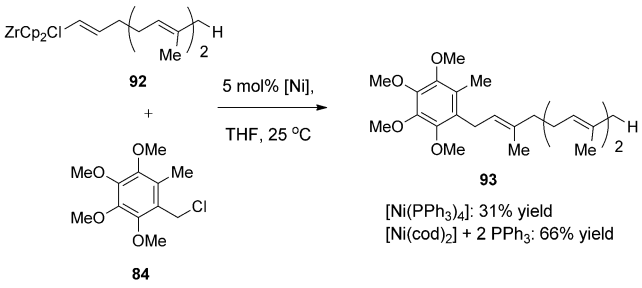
Scheme 22. Nickel-catalyzed coupling of benzyl chlorides and vinylalanes. DCE = 1,2-dichloroethane.

chloride **84** to furnish **85** in 89% yield (Scheme 22). This methodology was subsequently applied to the total synthesis of Coenzyme Q and other ubiquinone natural products. Chloromethyl heteroaromatics were also competent electrophiles, with the addition of LiCl necessary for supression of vinylalane dimerization.[52]

Lipshutz found that the conditions developed for benzylic vinylation with carboalumination products were generally applicable to the reaction with disubstituted vinylaluminum and vinylzirconium nucleophiles generated by hydrometalation of an alkyne.[53] Vinylaluminum nucleophiles generated from both terminal and internal alkynes reacted well with electron-rich and electron-poor benzylic chlorides (Scheme 23 a). Reactions of vinylzirconium nucleophiles demonstrated a similar electronic scope with respect to the benzyl chloride electrophile, and ester (**89**), fluorine (**90**), and *ortho*-substituents (**91**) were well-tolerated (Scheme 23 b).



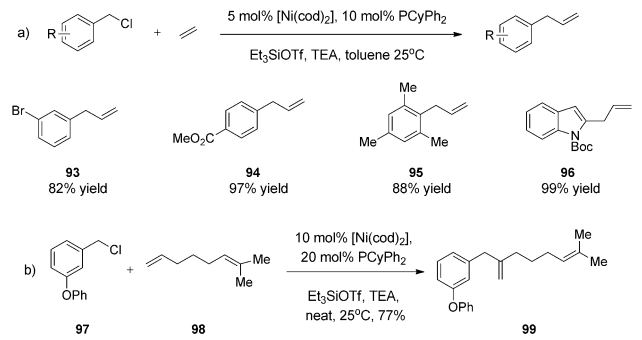
Scheme 23. Cross-coupling scope with vinyl a) aluminum and b) zirconium nucleophiles. TBDPS = *tert*-butyl diphenylsilyl.



Scheme 24. Nickel-catalyzed coupling of benzyl chlorides and vinylzirconocenes.

For highly electron-rich benzyl chlorides such as **84**, lower yields were observed with the standard $[Ni(PPh_3)_4]$ catalyst; homocoupled benzyl products were isolated in significant amounts (Scheme 24). Guided by the knowledge that ligand stoichiometry modulates the nickel-benzyl coordination, Lipshutz and co-workers used $[Ni(cod)_2]$ as a precatalyst and added only two equivalents of PPh_3 relative to nickel in the reaction between **92** and **84**, improving the yield of the cross-coupled product **93** from 31 to 66% yield. Diisobutylvinylaluminum diethyl ether complexes have also recently been demonstrated to act as nucleophiles in nickel-catalyzed vinylation of benzyl bromides and chlorides.[54]

A second method for generating allylaromatics is Heck-type coupling of a benzyl halide and an olefin, as reported by Jamison and co-workers in 2011.[55] The authors employed 5 mol% $[Ni(cod)_2]$ and 10 mol% $PCyPh_2$ to achieve coupling with ethylene at atmospheric pressure (Scheme 25a). The



Scheme 25. Nickel-catalyzed Heck-type coupling reported by Jamison. Cy = cyclohexyl, TEA = triethylamine.

reaction tolerated aryl halides (**93**), ester functionality (**94**), and could also be performed with *ortho*-substituted styrenes (**95**) and heterocycles (**96**). Reaction of **97** with an α-olefin such as **98** led to formation of 1,1-disubstituted product **99** with complete chemoselectivity for the terminal olefin (Scheme 25b). The formation of this olefin substitution pattern renders the process complementary to palladium-catalyzed processes, which typically lead to linear products. The authors postulated that the Et_3SiOTf additive abstracts chloride from the oxidative addition product, generating a π-benzyl cation that then undergoes migratory insertion.

7.4. Nickel-Catalyzed Addition across Vinylarenes

Nickel catalysis has been applied to a class of reactions in which net addition of a hydrogen atom and a second functional group (X) is performed. Addition to vinylarene substrates is typically regioselective for addition of the X group to the benzylic position, as is seen in rhodium-catalyzed hydroboration (vide supra). The observed regiochemistry can be rationalized from the proposed mechanism for the reaction (Figure 11). A nickel(0) precatalyst is oxidized to a nickel(II)

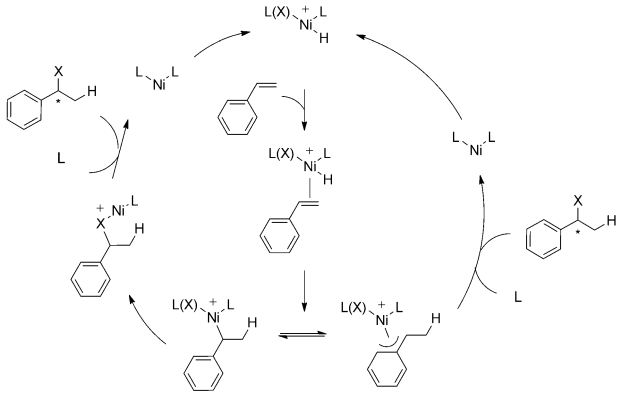
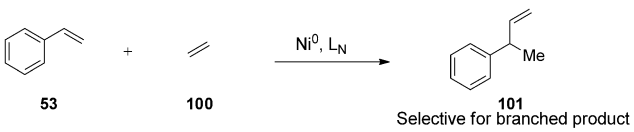


Figure 11. General mechanism for net H–X addition across styrene.

hydride, which undergoes hydrometalation after olefin coordination. Steric factors would favor placement of nickel on the less-substituted carbon, but the placement of nickel on the benzylic carbon offers access to the π-benzyl species. Addition of the X group to the benzylic position occurs through an inner sphere process. Release of the substrate and regeneration of the nickel(II)-hydride completes the catalytic cycle. The reaction forms a new stereocenter, and chiral ligands have been used to direct addition to the enantiotopic faces of the vinylarenes.

Hydrovinylation is mechanistically related to olefin oligomerization and polymerization, two processes run on large scale catalytically. A challenge to the process is controlling the number of migratory insertion steps to the alkyl-metal intermediate. Additionally, challenges arise in the formation of heterocoupled products and final olefin geometry.[56] Nickel complexes have emerged as highly reactive and enantioselective catalysts for the process (Scheme 26). Styrene (**53**) is typically used as a test substrate, and the reaction with ethylene yields methallylbenzene **101**. A diverse set of ligands have been developed for the process, and hemilabile ligands, which are hypothesized to stabilize the π-benzyl intermediate prior to olefin coordination, have found partic-



Scheme 26. Nickel-catalyzed hydrovinylation of styrene.

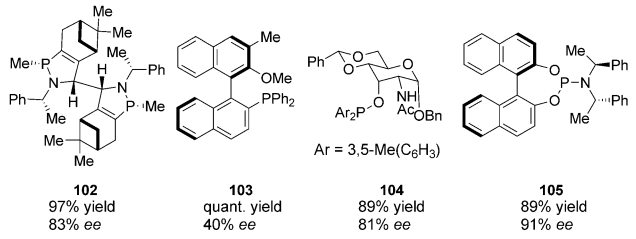
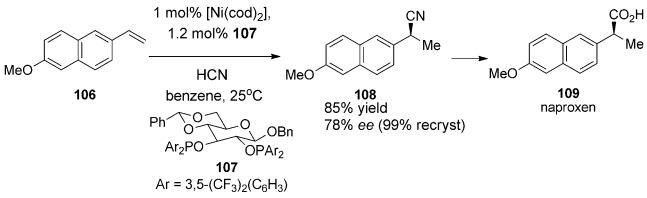


Figure 12. Selected ligands used in the asymmetric hydrovinylation of styrene.

ular success (Figure 12). Currently, the reaction scope is generally limited to reaction with ethylene as an olefin partner.

Asymmetric hydrocyanation of olefins has also been developed, the chiral nitriles representing useful precursors to carboxylic acid derivatives and amines. The first highly enantioselective nickel-catalyzed hydrocyanation of vinylarenes was reported by Rajanbabu in 1994.[57] The reaction of **106** proceeded with high enantioselectivity using carbohydrate-derived bis(alkoxydiphenyl)phosphine **107** (Scheme 27). Chiral nitrile **108** was obtained in 85% yield



Scheme 27. Asymmetric nickel-catalyzed hydrocyanation of vinylnaphthalene developed by Rajanbabu.

and 78% *ee*. Recrystallization afforded enantiomerically pure **108**, which could be further elaborated to the pharmaceutical naproxen (**109**). Additionally, Rajanbabu and co-workers demonstrated asymmetric hydrocyanation on a number of vinylnaphthalenes (**110**–**111**) and a substituted biphenylstyrene (**112**, Figure 13). Subsequent reports of nickel-cata-

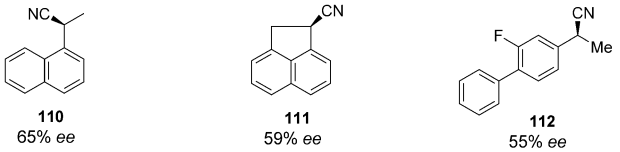
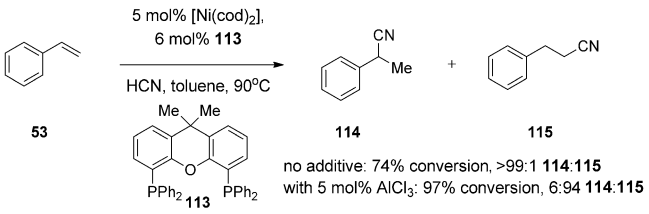


Figure 13. Vinylarene hydrocyanation scope.

lyzed asymmetric hydrocyanation have used BINOL-derived phosphites[58] as well as bisphosphines.[59]

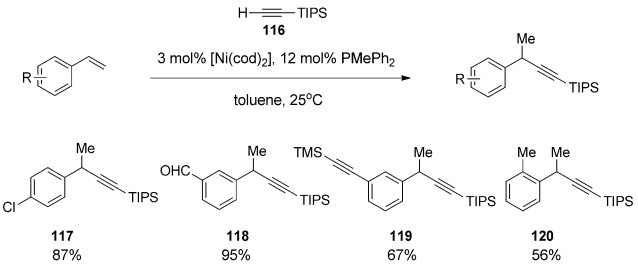
Regioselectivity for benzylic cyanation is typically observed, but it has been noted that the product ratio can be shifted through addition of Lewis acid.[60] Using HCN as a cyanide source, van Leeuwen and co-workers achieved complete selectivity for branched product **114** using Xantphos



Scheme 28. Lewis acid-controlled regioselectivity in catalytic hydrocyanation.

(**113**) as a ligand (Scheme 28). Upon addition of catalytic aluminum trichloride, regioselectivity was reversed, leading to a **114:115** ratio of 6:94.

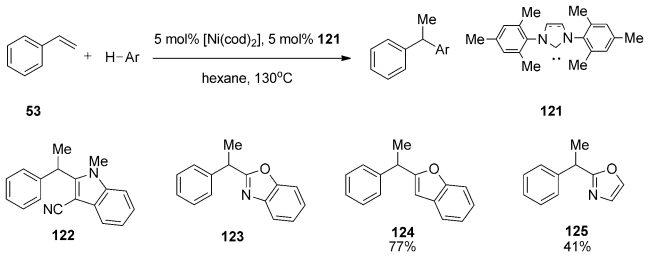
Shirakura and Suginome disclosed a method for nickel-catalyzed hydroalkynylation of styrenes in 2009.[61] Regioselective incorporation of tri(isopropyl)silyl acetylene (**116**) was achieved with a number of styrenes of varying electron density (Scheme 29). Monodentate phosphines were found to



Scheme 29. Nickel-catalyzed hydroalkynation of styrenes. TIPS = triisopropylsilyl.

be superior ligands for the reaction, as has been observed previously, supporting a similar mechanistic pathway. The substrate scope of this mild reaction included styrenes containing halogen (**117**), aldehyde (**118**), and alkyne (**119**) functionalities, as well as *ortho*-substituents (**120**).

Hydroheteroarylation of styrenes provides access to 1,1-diarylethanes, and a nickel-catalyzed process developed by Nakao and Hiyama offered access to this motif with substrates that are unable to undergo traditional Friedel–Crafts reactions (Scheme 30).[62] The authors propose that nickel(0) undergoes oxidative addition into the activated heteroarene–hydrogen bond, and this nickel(II)-hydride



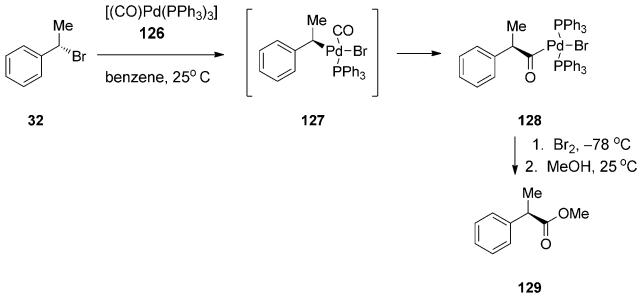
Scheme 30. Nickel-catalyzed hydroheteroarylation of styrenes.

participates in the catalytic cycle.[63] The IMes NHC ligand (**121**) was found to promote reactivity, and the reaction scope included both electron-rich and electron-poor styrene acceptors. A number of heteroarenes such as indole (**122**), benzoxazole (**123**), and benzofuran (**124**) were utilized. A monocyclic oxazole reacted moderately (**125**).

8. Palladium

8.1. Palladium-Benzyl Complexes

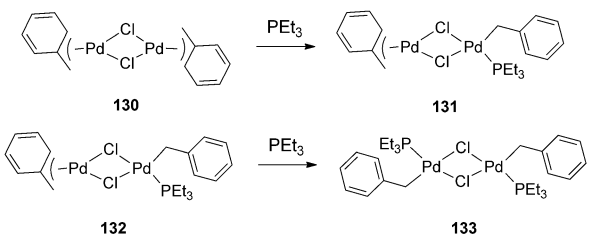
The most widespread studies of metal benzyl complexes and their reactivity have utilized palladium.[64] Early studies in the synthesis of palladium-benzyl complexes were performed with the intention of elucidating the stereochemistry of palladium(0) oxidative addition to an alkyl halide. An experiment designed by Stille probed the process through treatment of enantioenriched (*S*)-phenethyl bromide (**32**) with palladium carbonyl **126** (Scheme 31).[65] After oxidative



Scheme 31. Oxidative addition of palladium into a benzyl bromide proceeds with inversion.

addition, migratory insertion of the carbonyl ligand occurs more rapidly than β-hydride elimination. Acyl-palladium **128** was converted to methyl ester **129**. The optical rotation of **129** indicated that the (*R*)-enantiomer was formed. Because migratory insertion occurs with retention of stereochemistry, the inversion was concluded to occur at the oxidative addition step of the reaction, possibly through an S_N2-like mechanism. A similar inversion of stereochemistry was observed starting from optically enriched α-D-benzyl chloride. In each case, a small amount of racemization was observed, which could be attributed to palladium–palladium substitution.[66]

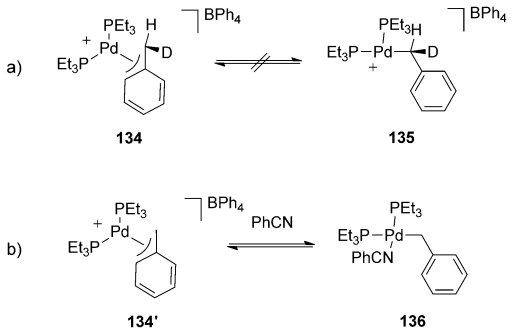
During the same time period, Roberts and Klabunde were investigating the thermal stability of coordinatively unsaturated RPdX species, and noted unusually high stability of the perfluorinated benzyl derivative relative to other fluorinated alkyls. This observation led them to synthesize palladium dimer **130** and perform an NMR study of the complex itself, as well as the products of sequential addition of triethylphosphine (Scheme 32).[67] The ^{1}H NMR spectrum of **130** showed equivalent benzylic protons as well as upfield, equivalent *ortho*-protons. The upfield position of the *ortho*-protons suggested non-aromatic character, and the equivalence suggests highly-fluxional solution behavior. Addition of a single



Scheme 32. Study of sequential addition of PEt_3 to a π-benzyl-Pd complex.

equivalent of PEt_3 led to the appearance of a second peak correlating to benzylic protons, as would be seen for a mixed η^3/η^1 system (**131**). The addition of a second equivalent of PEt_3 resulted in a return of benzylic proton equivalence, correlating to the structure of **133**. The downfield shift of the *ortho*-protons also corroborated a return to aromaticity upon addition of phosphine ligand. Going in the opposite direction, Stevens and Shier observed η^1 to η^3 isomerization upon abstraction of bromide from a tetracoordinated palladium-benzyl complex.[68]

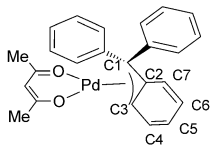
NMR studies probing the dynamic solution behavior of complex **134** were undertaken by Stille (Scheme 33).[69]



Scheme 33. Dynamic behavior of palladium-benzyl cations in solution.

Optically pure deuterated [D]-**134** did not undergo racemization at ambient temperature in noncoordinating solvents. No evidence of the σ-complex **135** was observed, suggesting that the π-benzyl isomer dominates under these conditions. Studies in coordinating benzonitrile show the existence of two discrete species, **134′** and **136**, at low temperature, with coalescence of the peaks as the temperature is raised. Together, these findings indicate that palladium-benzyl bisphosphine cations undergo π–σ–π equilibration, but only in the presence of an exogenous ligand to stabilize the 16-electron η^1 complex.

The first crystallographic evidence of η^3-benzyl coordination was disclosed in 1978. Oxidative addition into trityl chloride followed by ligand exchange furnished **137**, which was analyzed by X-ray crystallography.[70] Complex **137** was square planar and exhibited bonding between palladium and both the benzylic (C1) and *ortho*-carbon (C3, Figure 14). The η^3 coordination was quite symmetrical, with less than 0.1 Å difference in bond lengths to C1 and C3. Alternating single



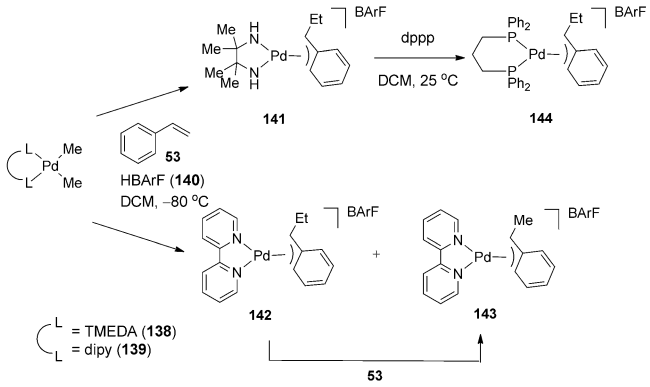
Atoms	Distance
Pd-C1	2.105
Pd-C2	2.154
Pd-C3	2.200
C3-C4	1.436
C4-C5	1.362
C5-C6	1.440
C6-C7	1.377

137

Figure 14. Structure of a palladium-η^3-trityl complex with selected bond lengths.

and double bonds in the disrupted phenyl ring were indicative of localization, in concert with findings for other transition metal-benzyl complexes. Trityl-coordinated palladium dimers have also been synthesized.[71]

In addition to oxidative addition to a benzyl halide, palladium-benzyl complexes can be prepared by migratory insertion of styrene into a palladium–alkyl bond. This method was utilized by Gatti starting from dimethyl palladium(II) complexes **138** and **139**.[72] These complexes were treated with styrene in the presence of borane **140**, yielding cationic benzyl complex **141** or a mixture of **142** and **143** (Scheme 34). The



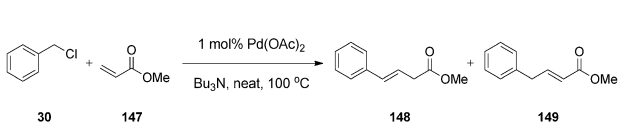
Scheme 34. Synthesis of π-benzyl complexes by migratory insertion into styrene. BArF = B[3,5-$(CF_3)_2C_6H_3]_4^-$, DCM = dichloromethane, TMEDA = *N,N,N′,N′*-tetramethylethylenediamine, bipy = bipyridine.

formation of **143** proceeds through β-hydride elimination from **142** followed by migratory insertion of styrene into the palladium hydride. X-ray analysis of **143** showed a *syn*-positioning of the benzylic methyl group. Ligand exchange of **141** with diphenylphosphino propane (dppp), provided **144**. Both 1D and 2D NMR studies of the π-benzyl complexes were performed, and evidence of π–σ–π isomerization as well as bond rotations in the σ-structure were observed. A Hammett study of this migratory insertion of a related palladium-methyl species, performed by Brookhart, yielded a ρ-value of −1.1.[73] The acceleration of insertion into electron-poor styrenes was rationalized on the basis that electron-rich styrenes stabilize the cationic palladium center in the palladium-styrene ground state.

The observation of aromaticity-disrupting η^3-binding to palladium(II) is not limited to benzyl ligands. Analogous complexes bearing a heteroaromatic moiety have also been synthesized and characterized (Figure 15). Takashi and co-workers synthesized indoylmethyl complex **145** through migratory insertion into a isocyanide followed by rearrangement.[74] Synthesis of furfuryl-containing complexes has been demonstrated through oxidative addition to furfuryl chloride. Spectroscopic studies were first performed by Onishi and Hiraki,[75] and later ester-substituted **146** was studied by Dewhurst and co-workers.[76] Complexes **145** and **146** were characterized by X-ray crystallography and NMR spectroscopy, the data from which confirmed η^3-binding.

8.2. Palladium-Catalyzed Cross-Coupling

The early studies on the generation and behavior of palladium-benzyl complexes, illustrating facile formation by oxidative addition, have led to use of benzyl halides and pseudohalides as electrophilic partners in catalytic cross-coupling methods. Predating the structural and mechanistic studies by Stille, Heck demonstrated that benzyl chloride (**30**) was a competent reaction partner with methyl acrylate (**147**) in the reaction that came to bear his name (Scheme 35).[77] A

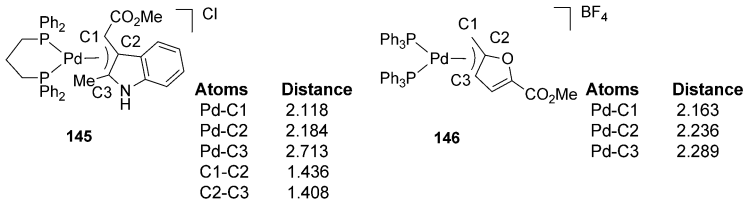


Scheme 35. Initial report of benzyl chloride electrophiles in Heck coupling.

mixture of olefin regioisomers (**148** and **149**) was observed. Of note is the faster reaction rate of **30** relative to β-bromostyrene.

An intramolecular Heck coupling of an unactivated olefin was disclosed by Negishi to form polycyclic products.[78] Benzylic chlorides bearing a tetherered olefin were cyclized with complementary regioselectivity to radical processes in the presence of catalytic $[Pd(PPh_3)_4]$. The reaction of **150** formed tricyclic spirocycles **151** and **152** (Scheme 36). Although β-hydride elimination led to olefin regioisomers, the moderate reactivity of a trisubstituted olefin is noteworthy. A later example utilized similar substrates under a CO atmosphere, giving rise to ketone and ester products.[79]

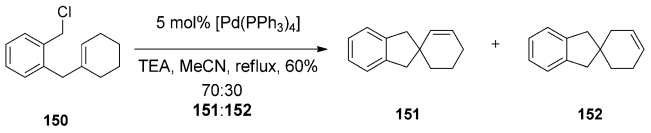
A cyclization variant in which the alkylpalladium intermediate is trapped with hydride or an organometallic was reported by Grigg.[80] Treatment of benzylic halide **153** with



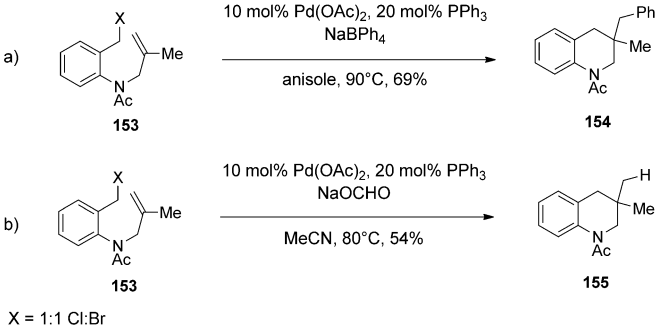
Atoms	Distance
Pd-C1	2.118
Pd-C2	2.184
Pd-C3	2.713
C1-C2	1.436
C2-C3	1.408

Atoms	Distance
Pd-C1	2.163
Pd-C2	2.236
Pd-C3	2.289

Figure 15. Palladium complexes with η^3-binding to a heteroaromatic.



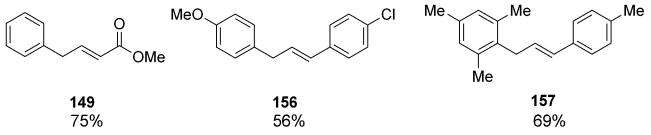
Scheme 36. Intramolecular Heck reaction of benzyl chlorides reported by Negishi.



Scheme 37. Intramolecular Heck reaction followed by trapping with a) organoboronate or b) hydride.

$NaBPh_4$ under palladium catalysis yielded bicycle **154** (Scheme 37a), while reaction with sodium formate furnished **155** (Scheme 37b).

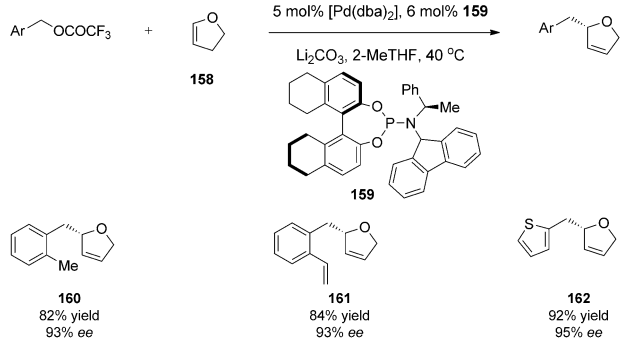
An update to Heck's procedure for benzylation of acrylates was developed by Shimizu, wherein benzyl trifluoroacetates were used as electrophiles.[81] Use of this electrophile obviated the need for exogenous base to neutralize a strong acid and enone **149** could be formed selectively (Scheme 38). The reaction was amenable to reaction with styrenes (**156**) and sterically-encumbered benzyl trifluoroacetates were able to react (**157**).



Scheme 38. Products of Heck reaction with benzyl trifluoroacetates.

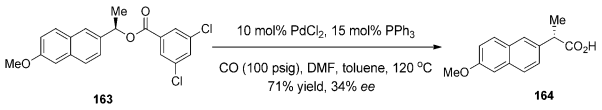
A recent example from Zhou reports an asymmetric Heck coupling of benzyl trifluoroacetates with dihydrofurans using a chiral phosphoramidite ligand.[82] Benzyl trifluoroacetates reacted with 2,3-dihydrofuran **158** in the presence of catalytic palladium(0) and ligand **159** to yield chiral 2-substituted dihydrofurans (Scheme 39). Both electron-rich and electron-poor electrophiles performed well, as did *ortho*-substituted substrates (**160**). The reaction was chemoselctive for addition across the dihydrofuran olefin, demonstrated by the high yield of **161**. Heterocycles such as thiophene were also well-tolerated (**162**).

The initial report of palladium-catalyzed carbonylation was reported by Heck in 1974, wherein butyl phenylacetate was formed in 45% yield.[83] The palladium-catalyzed transformation to yield phenylacetic acids has been studied



Scheme 39. Asymmetric Heck reaction between benzyl trifluoroacetates and dihydrofuran. dba = dibenzylideneacetone.

extensively; in analogy to cobalt catalysis, this reaction is often performed in biphasic medium to separate the product from the catalyst solution.[84] An alternative to use of toxic carbon monoxide for the carbonylation of benzyl halides is in situ generation from chloroform and hydroxide.[85] Lee and co-workers synthesized enantioenriched 2-arylpropanoic acids by palladium-catalyzed carbonylation of a chiral starting material (Scheme 40).[86] Arylethanes such as **163** reacted to

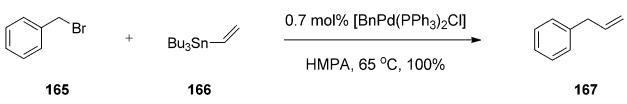


Scheme 40. Palladium-catalyzed carbonylation of benzyl acetate with moderate enantiospecificity.

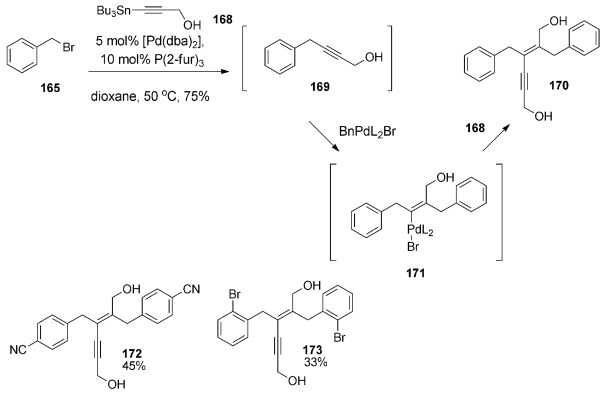
form **164** in up to 71% yield. The product was formed with inversion of stereochemistry, in analogy to the early work by Stille. Significant erosion of enantiomeric excess was observed, which was attributed to β-hydride elimination, olefin rotation, and reinsertion.

Stille and Milstein's initial report of palladium-catalyzed coupling between halides and organotin species included results obtained with benzyl bromide (**165**).[87] High yields were obtained at low catalyst loadings of 0.7 mol%. In the case of tributylvinyltin (**166**), preferential transmetalation of the vinyl group occured, providing **167** in quantitative yield (Scheme 41). Subsequent studies on Stille coupling with benzylic electrophiles have resulted in reports using benzylic carbonate electrophiles,[88] modified palladium precatalysts,[89] and monoorganostannane ($RSnX_3$) nucleophiles.[90]

Stille cross-coupling between **165** and propargyltins such as **168** did not yield the expected coupling product **169**; rather,



Scheme 41. Stille coupling with benzyl bromide and tributylvinyltin. HMPA = hexamethylphosphoric triamide.



Scheme 42. Formation of enyne products by sequential Stille coupling and carbopalladation.

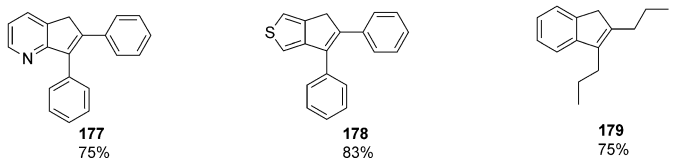
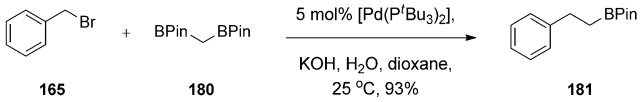


Figure 16. Annulation scope with bisvinylboranes.

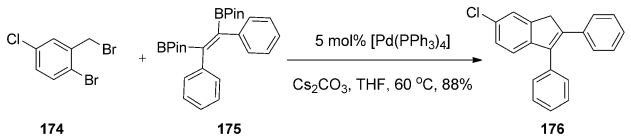


Scheme 44. sp^3–sp^3 Suzuki coupling of benzyl bromide and diborylmethane.

enyne **170** was observed.[91] The authors proposed that **169** underwent carbopalladation with catalytic palladium(II) to form **171**, which further reacted with further propargylstannane **168**, furnishing highly-substituted enyne products (Scheme 42). Investigation into the substrate scope indicated that the methodology was moderately tolerant of nitrile (**172**), and even *ortho*-aryl bromide (**173**) substituents.

Suzuki cross-coupling reactions of benzylic electrophiles and boron-containing organometallics have been widely studied. Early examples utilized benzyl halides with arylboroxines[92] and arylboronic acids.[93] Soon after, conditions for reactions of benzyl carbonates were developed by Kuwano for Suzuki coupling with aryl[94] and heteroaryl boronic acids.[95] Other benzylic leaving groups employed have been acetate[96] and phosphate.[97] Varying the organometallic, Molander and Elia have reported use of aryl trifluoroborates in the reaction with benzyl halides.[98]

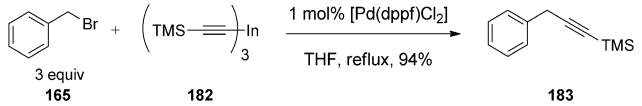
Recent examples of Suzuki coupling reactions highlight the use of boronic acid derivitives not bearing an aryl group. Shimizu and Hiyama reacted bisbromide **174** with a number of 1,2-vinyl diboranes to yield substituted indenes.[99] Reaction with **175**, the product of diboration of diphenylacetylene, yielded **176** in 88% yield (Scheme 43). Additionally, heterocyclic bisbromides were utilized to provide annulated products **177** and **178** (Figure 16). A 3-octyne-derived bisborane provided **179** in 75% yield.



Scheme 43. Synthesis of substituted indenes by bis-Suzuki coupling.

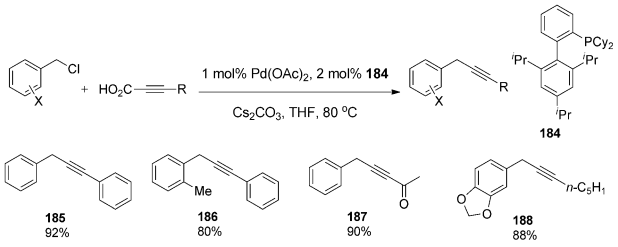
Extension of Suzuki coupling to sp^3–sp^3 coupling was realized in 2012 by Endo and Shibata.[100] Bisborylmethane **180** exhibited very high reactivity with **165**, the reaction between the two proceeding in two and half hours at ambient temperature (Scheme 44). The isolated yield was 93% using 5 mol% of a tri-*tert*-butylphosphine-ligated palladium catalyst. The steric bulk of the phosphine ligands may act to encourage reductive elimination to **181**, which contains an alkylborane available for further functionaliztion.

A number of alkynyl organometallic reagents have been employed to achieve sp–sp^3 coupling at a benzylic carbon. Sarandeses utilized a triorganoindium (**182**) reagent to affect alkynylation of benzyl bromide (Scheme 45). This organometallic is unique in that all three alkynyl groups are capable of transfer; thus only 0.34 equivalents were required for complete conversion of starting material to **183**.[101] Employment of alkynylzinc bromides was reported by Negishi in a catalytic system that was capable of over 70000 turnovers at an impressive 0.001 mol% catalyst loading.[102]



Scheme 45. Alkynylation of benzyl bromide with trialkynylindium reagent.

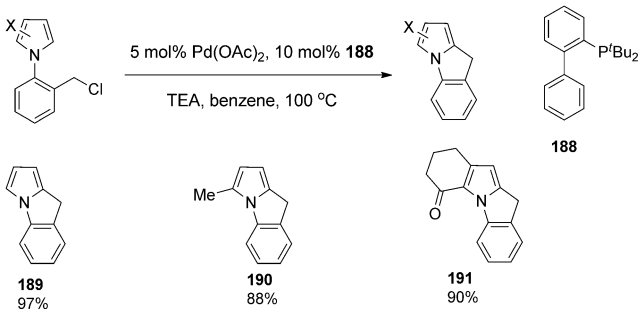
A system employing a metal-free alkyne coupling partner was reported by Li in 2010.[103] Alkynyl carboxylic acids were demonstrated to act as alkynylating agents of benzyl chlorides (Scheme 46). Presumably, ligation of the carboxylate to palladium(II) promotes decarboxylation to an alkynyl palla-



Scheme 46. Palladium-catalyzed decarboxylative alkynylation of benzyl chlorides.

dium species, replacing the transmetalation step of the catalytic cycle. Nineteen examples demonstrating substrate scope with respect to both coupling partners were disclosed.

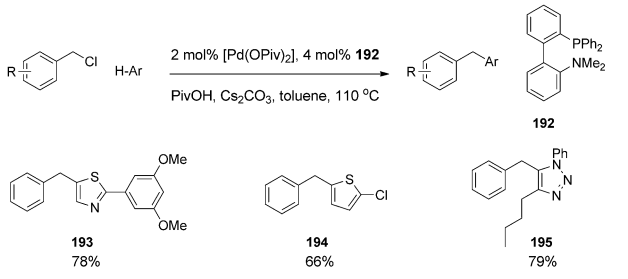
Another approach to cross-coupling is C–H functionalization.[104] Such methods eliminate metal wastes but reactivity and selectivity can be hard to control. With benzyl electrophiles, the first reports of arylation through C–H activation were intramolecular reactions. In 2008, Chang reported the synthesis of fused polycyclic aromatics through pyrrole benzylation using 5 mol% $Pd(OAc)_2$ and a bulky phosphine ligand (Scheme 47).[105] The authors suggested a directed C–H



Scheme 47. Palladium-catalyzed intramolecular cyclization by C–H activation.

activation pathway, ruling out a Friedel–Crafts process due to increased reactivity of electron-poor substrates. The methodology was extended to the formation of carbocycles soon after, the result of phenyl C–H activation.[106]

Intermolecular aryl C–H benzylation was first disclosed by Fagnou, who used benzyl chlorides to affect benzylation of a number of heterocycles with complete regioselectivity (Scheme 48).[107] Notable substrates included thiazole (**193**),



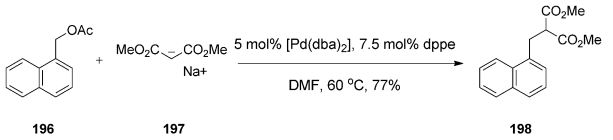
Scheme 48. Palladium-catalyzed intermolecular benzylation of heterocycles through C–H activation. Piv = pivaloyl.

thiophene (**194**), and triazole (**195**). Later studies used phosphate electrophiles for benzylation of benzoxazoles,[108] as well as methyl carbonates for sequential arene and benzylic C–H benzylation.[109] Intermolecular benzene C–H benzylation has been limited to highly activated polyfluorobenzenes, a method developed by Zhang in 2010.[110]

8.3. Palladium-Catalyzed Benzylic Alkylation

The η^3 coordination between palladium and a benzyl group draws analogies toward similar coordination with an allyl group. A π-allyl-palladium cation has been proposed as an intermediate in allylic alkylation reactions, wherein net allylic substitution is performed. Studies in allylic alkylation have investigated a number of catalytic transition metals, but palladium catalysis has found the broadest scope, especially in asymmetric processes.[111] In principle, an analogous catalytic cycle of ionization followed by nucleophilic attack could be realized with substrates containing a benzylic leaving group. Though the barrier to ionization would presumably be higher due to the energetic cost of dearomatization, early studies in palladium-benzyl complexes have shown that the energy requirement for this process is not prohibitively high.

The initial realization of this hypothesis was disclosed by Fiaud in 1992.[112] Naphthylmethyl esters such as **196** were subjected to $[Pd(dba)_2]$ and dppe with dimethyl sodiomalonate (**197**) acting as a nucleophile (Scheme 49). A 77% isolated yield of **198** was obtained, which formed only under catalytic conditions. The requirement of elevated temperatures as well as the observation that benzyl acetates were unreactive supported the hypothesis of a dearomatized intermediate, where the energetic cost is lower for a naphthalene system.



Scheme 49. Palladium-catalyzed benzylic alkylation with malonate nucleophile reported by Fiaud.

Alkylation with a malonate nucleophile was subsequently reported with quinoline-based electrophiles (**199**)[113] as well as benzofuran (**200**), indole (**201**), and benzothiophene (**202**) electrophiles bearing an acetate leaving group (Figure 17).[114]

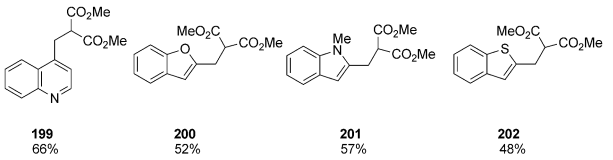
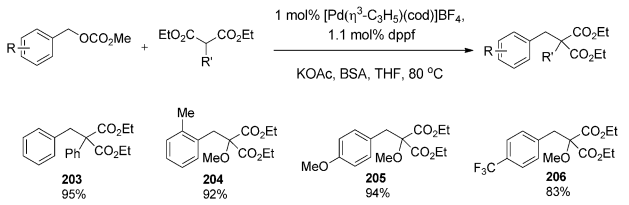


Figure 17. Heteroaromatic electrophiles used in benzylation by Fiaud.

Low reactivity and competitive substrate decomposition was observed when a monocyclic furfuryl electrophile was used.

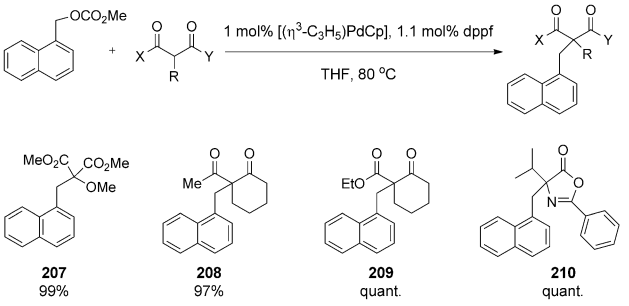
Extension of electrophile scope to monocyclic benzylic electrophiles was realized by Kuwano.[115] The authors used a more labile methyl carbonate leaving group, and found that reactivity was highly dependent upon the nature of the palladium precatalyst and the phosphine ligand. A cationic palladium precatalyst and dppf, which has a relatively large



Scheme 50. Palladium-catalyzed benzylic alkylation of benzyl carbonates with malonate nucleophiles. dppf = diphenylphosphinoferrocene, BSA = *N*,*O*-bis(trimethylsilyl)acetamide.

bite angle, were determined to be optimal. Palladium-catalyzed benzylation was performed with malonate nucleophiles to generate a new tetrasubstituted carbon (Scheme 50). High reactivity was observed at elevated temperature, even with bulky (**204**) and highly electron-deficient (**206**) electrophiles. Secondary amine nucleophiles were also demonstrated to undergo benzylation.

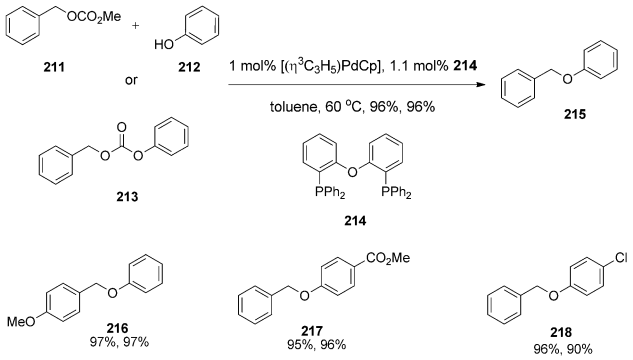
A modification to the procedure for benzylation of active methines utilized the highly active palladium(0) precursor [(η^3-C_3H_5)CpPd], and removed exogenous base, relying on the decarboxylated carbonate to deprotonate the nucleophile (Scheme 51).[116] In addition to malonates (**207**), 1,3-diketones



Scheme 51. Base-free palladium-catalyzed benzylation reported by Kuwano.

(**208**), β-ketoesters (**209**), and azlactones (**210**) were utilized as nucleophiles (Scheme 48). For monocyclic benzylic electrophiles, the addition of 10 mol% 1,4-cyclooctadiene was found to increase turnover numbers, presumably due to its ability to act as a stabilizing ligand.

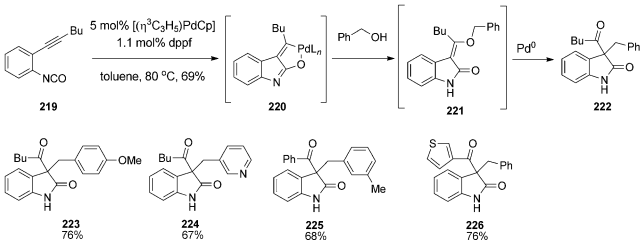
Studies on heteroatom nucleophiles were also performed by Kuwano. Sodium phenylsulfinate reacted to yield synthetically useful benzyl sulfone products.[117] Benzylation with phenolic nucleophiles was achieved by two different pathways.[118] Treatment of benzyl methyl carbonate (**211**) and phenol **212** with [(η^3-C_3H_5)CpPd] and DpePhos (**214**) yielded **215** in 96% yield (Scheme 52). An alternate method for access of **215** was the pseudo-intramolecular process starting from **213**, which generated the phenoxide **215** upon decarboxylation. Through this process, an identical yield could be obtained under the same reaction conditions, an observation observed for multiple substrates. Stoichiometric studies into benzylic etherification by Hartwig suggest that attack of the phenoxide occurs through an outer sphere process, as has



Scheme 52. Palladium-catalyzed benzylation of phenols by either intermolecular or intramolecular process.

been suggested for palladium-catalyzed allylic alkylations.[119] Extension of leaving group scope to acetate[120] and fluoride[121] electrophiles in the benzylation of both carbon and heteroatom nucleophiles has also been investigated. A second aryl group is tolerated at the benzyl position, alloweing for formation of diarylmethyl malonates.[122]

Recent work by Murakami reported a domino isocyanate cyclization/intramolecular benzylation protocol to synthesize 3,3-disubstituted oxindoles.[123] Oxidative cyclization of alkynyl isocyanate **219** to **220** followed by ligation of benzyl alcohol to **220** and reductive elimination yielded enol ether **221** (Scheme 53). Ionization of the benzyl group then

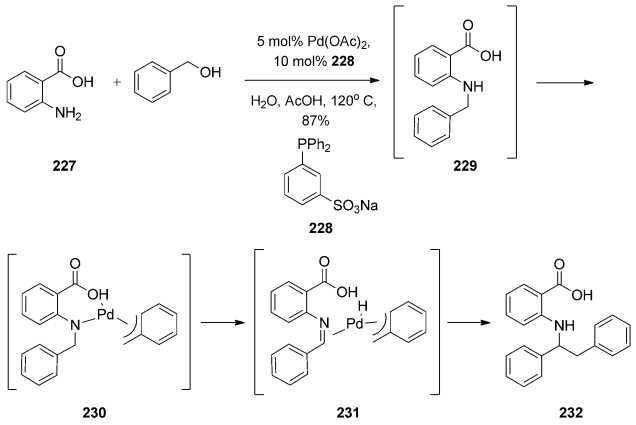


Scheme 53. Palladium-catalyzed domino reaction to form 3,3-disubstituted oxindoles.

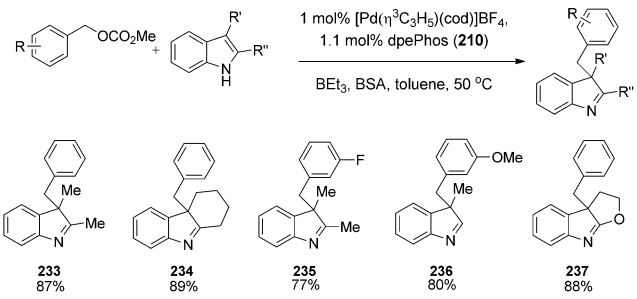
followed, and the cation was trapped by the generated enolate to furnish **222.** Nine total examples were disclosed, including those utilizing electron-rich alcohols (**223**), heterocyclic benzylic alcohols (**224**), and diaryl alkyne partners (**225**–**226**).

A second recently-reported domino process showed that anthranilic acid nucleophiles such as **227** undergo bisbenzylation with benzyl alcohol acting as the electrophile in aqueous solution (Scheme 54).[124] A water-soluble phosphine ligand (**228**) was utilized, and the first step in the proposed mechanism is N-benzylation to **229**. Coordination of a second palladium-benzyl cation would form **230**, which proceeds to **231** following β-hydride elimination. Addition of a benzyl group to the imine would provide **232**, which was isolated in 87% yield.

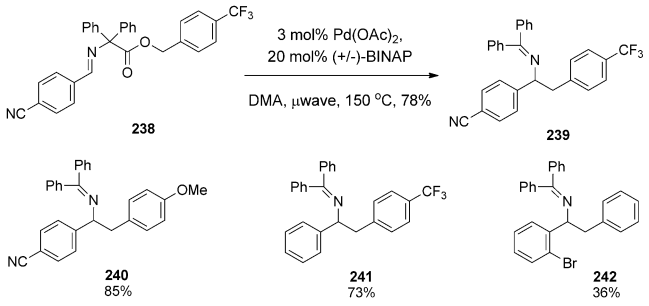
The 3-substituted indole represents a new class of carbon nucleophile for palladium-catalyzed benzylation, the study of



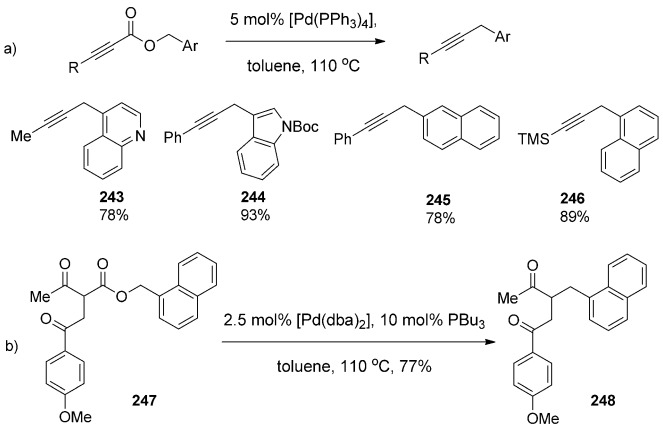
Scheme 54. Bisbenzylation of anthranilic acids in aqueous solution.



Scheme 55. Palladium-catalyzed benzylation of 3-substituted indoles.



Scheme 56. Decarboxylative benzylation of diphenylglycinate imines. DMA = *N*,*N*-dimethylacetamide.



Scheme 57. Decarboxylative benzylation to form a) benzylated alkynes and b) an α-benzylated ketone with high regioselectivity.

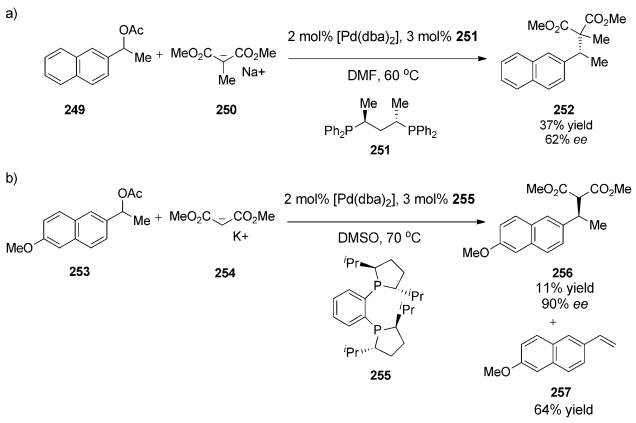
which was reported by Rawal in 2012.[125] Methyl carbonates reacted with unprotected indoles to yield dearomatized products (Scheme 55). Substitution at the 2-position of the indole was not required, and 23 examples, all in at least 70% yield, were disclosed.

Decarboxylative allylic alkylation is a pseudo-intramolecular process wherein ionization of the allyl moiety generates a palladium carboxylate that forms the active nucleophile upon loss of CO_2.[126] This process has been widely studied for allylation of enolates, especially its asymmetric variant. Successful decarboxylative benzylic alkylation has been achieved only recently with carbon nucleophiles.[127] Fields and Chruma reported decarboxylative benzylation of diphenylglycinate imines such as **238** under microwave conditions (Scheme 56).[128] Both electron-rich and electron-poor aryl components were well-tolerated, but the reaction was sensitive to steric bulk.

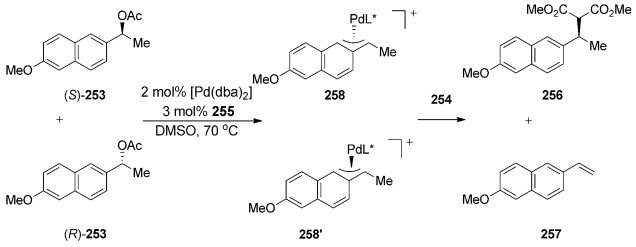
Further studies in decarboxylative benzylation were performed by Tunge and co-workers.[129] Benzyl propiolates reacted to form products of net benzylic alkynylation (Scheme 57a). While monocyclic benzyl esters were unreactive, a number of heterocyclic (**243, 244**), and naphthalene-containing (**245, 246**) esters were utilized. Benzyl β-ketoesters led to net enolate benzylation (Scheme 57b). In an interesting experiment, the authors used tricarbonyl substrate **247** and observed benzylation solely at the site of carboxylate connection (**248**). The process offers an improved means to access monobenzylated diketones relative to classical enolate alkylations due to the high regioselectivity of the process.

If palladium-catalyzed benzylic alkylation proceeds through a mechanism analogous to asymmetric allylic alkylations, asymmetric induction can be achieved at any point in the catalytic cycle. Initial studies towards enantioenriched benzylation products was conducted by Fiaud, investigating the reaction between naphthylethyl electrophiles and malonate nucleophiles.[130] The effects of leaving group, bisphosphine ligand, and nucleophile structure were studied, and Fiaud found that the an acetate leaving group (**249**), a (2*S*,3*S*)-(−)-2,4- bis(diphenylphosphino)pentane ligand (BDPP, **251**), and a dimethyl sodiomethylmalonate (**250**) nuleophile were optimal parameters. The isolated yield of **252** was 37%, and an enantiomeric excess of 62% was observed (Scheme 58a). Further studies revealed that high product enantioselectivity could be achieved in the reaction between **253** and **254** using chiral DuPhos ligand **255**; the benzylated product **256** was obtained in 90% *ee*.[131] However, the isolated yield of 11% was quite low, and stryrene product **257** was the major product, isolated in 64% yield (Scheme 58b).

The two enantiomers of **253** will form diastereomeric π-benzyl interemediates (**258**) upon ionization, the structure of which does not allow for racemization via equilibration through the σ-intermediate (Scheme 59). Therefore, the only way to achieve a single diastereomer of the intermediate



Scheme 58. Palladium-catalyzed benzylic alkylation of malonates towards enantioenriched products; a) first and b) second-generation conditions. DMSO = dimethylsulfoxide.

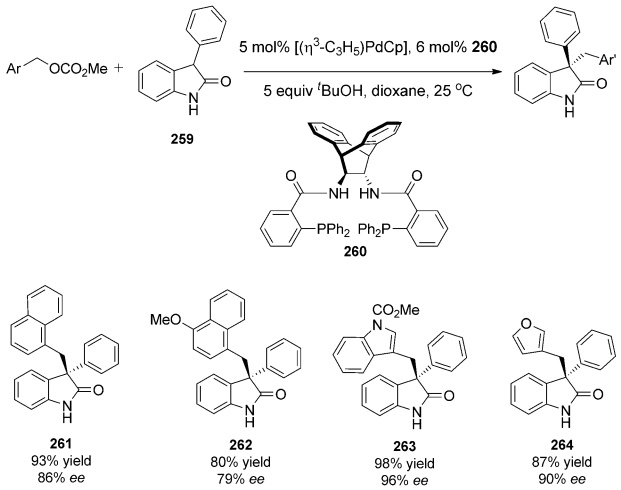


Scheme 59. Enantiodivergent reactivity in palladium-catalyzed benzylation of substituted naphthyl electrophile.

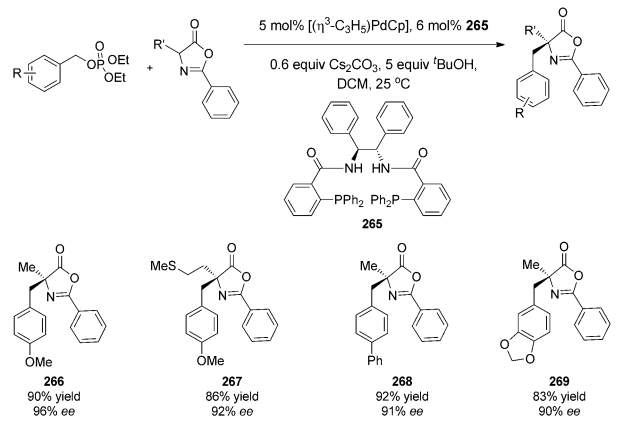
would be through palladium-palladium substitution, a process that would not be facile under catalytic conditions. Fiaud and co-workers concluded that a kinetic resolution was occurring and have been able to demonstrate that substrate/catalyst match and mismatch behavior leads to enantiodivergent alkylation or elimination.[132]

An alternate means of asymmetric induction which avoids the need for racemization of a benzylic center is attack on an achiral electrophile by a prochiral nucleophile. Trost and Czabaniuk reported such a method using 3-aryl oxindoles as nucleophiles in 2010 (Scheme 60).[133] Naphthalene- (**261**, **262**) and heteroarene-based (**263**, **264**) electrophiles were demonstrated to benzylate the oxindole nucleophile **259** with high enantioselectivities in the presence of chiral bisphosphine **260**. The high levels of asymmetric induction are particularly remarkable given the distances between the chiral information on the ligand and the incoming nucleophile.

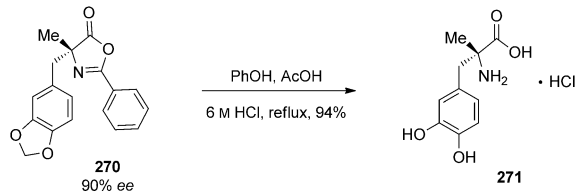
Extension of electrophile scope to monocyclic benzylic electrophiles, for which the energetic barrier to formation of the dearomatized intermediate is higher, required the use of a phosphate leaving group.[134] For the benzylation of azlactones, it was found that the reaction was sensitive to the electron density on the benzene ring. For electron-rich substrates, a diethyl phosphate leaving group was employed (Scheme 61). Studies in reaction scope demonstrated high reactivity and enantioselectivity with unhindered azlactone nucleophiles (**266**, **267**), as well as both mono- and disubti-



Scheme 60. Asymmetric benzylation of prochiral 3-aryl oxindole nucleophiles.



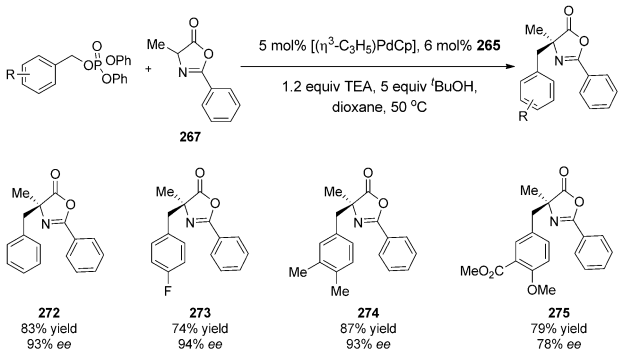
Scheme 61. Asymmetric benzylation of azlactone nucleophiles with electron-rich benzylic phosphates.



Scheme 62. Azlactone hydrolysis to α-methyl-D-DOPA (**271**).

tuted electrophiles (**268**, **269**). Azlactone **270** was completely hydrolyzed to α-methyl-D-DOPA (**271**), the enantiomer of an anti-hypertensive pharmaceutical (Scheme 62).

For electron-neutral electrophiles, an even more labile diphenyl phosphate leaving group was required for high levels of reactivity (Scheme 63). Reactions of diphenyl benzyl phosphates bearing a number of substitution patterns were performed with alanine-derived azlactone **271.** Of note is the ability to place an electron-withdrawing group at the *meta* position of the benzene ring provided that an electron-



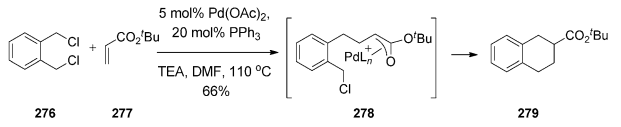
Scheme 63. Asymmetric benzylation of azlactone nucleophiles with monocyclic electron-neutral benzylic electrophiles.

donating group at the *para* position is present to balance arene electron density.

These observations are consistent with the possibility that there are two mechanisms for ionization. Using benzyl systems wherein loss of aromaticity in the ionization stage is less formidable (naphthyl, indolyl, furyl, etc.), coordination of the π-system with palladium(0) precedes ionization of the benzylic leaving group, thereby requiring a less reactive one. On the other hand, using a simple benzyl group wherein loss of aromaticity by binding palladium(0) with the π-system is rather high, the oxidative addition involves direct attack of the palladium(0) at the benzylic carbon. Thus, a better leaving group is required to generate a σ-benzyl complex which subsequently relaxes to the η^3-benzyl complex. This interpretation is consistent with early results of Stille on the mechanism of the oxidative addition of palladium(0) to simple benzyl systems.[65,66] The fact that ligands which induce high asymmetric induction with π-allyl palladium complexes also work well with benzyl systems is consistent with the notion that η^3-benzyl complexes are involved in the enantiodiscriminating steps.

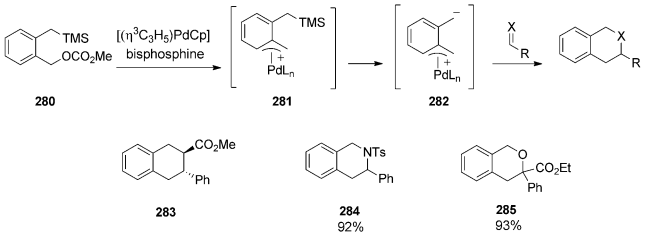
8.4. Palladium-Catalyzed Formal Cycloaddition

The *o*-quinodimethane moiety is a reactive diene for [4+2] cycloadditions, offering access to tetralins and analogous heteroatom-containing 6,6-bicycles. O*rtho*-substituted benzyl electrophiles have emerged as a means to generate similar products by palladium catalysis. Initial work by Bruneau reacted bis-benzylic chloride **276** with polarized olefin acceptors such as **277** in the presence of catalytic palladium.[135] Bruneau proposed that initial Heck-type addition to the enoate occurred, followed by displacement of the second chloride with resultant palladium enolate **278** to furnish tetralin **279** (Scheme 64).



Scheme 64. Bisbenzylic chlorides as substrates for formal [4+2] cycloaddition.

A second strategy for using benzyl chlorides as precursors for [4+2] coupling reactions was developed by Kuwano. Substrate **280** is proposed to generate a 1,4-dipole by ionization of the benzylic carbonate (**281**) followed by desilylation (**282**) (Scheme 65).[136] Kuwano's initial report

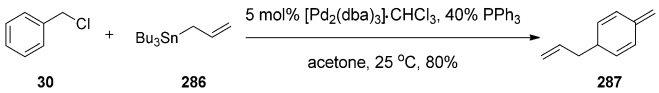


Scheme 65. Benzylic carbonate/silane substrates for formal [4+2] cycloaddition.

used polarized olefins as coupling partners (**283**) and subsequently disclosed the reaction with *N*-tosyl imines (**284**)[137] and activated ketones (**285**).[138] Substrates containing additional benzene substitution led to mixtures of isomeric products.

8.5. Palladium-Catalyzed Arene Functionalization

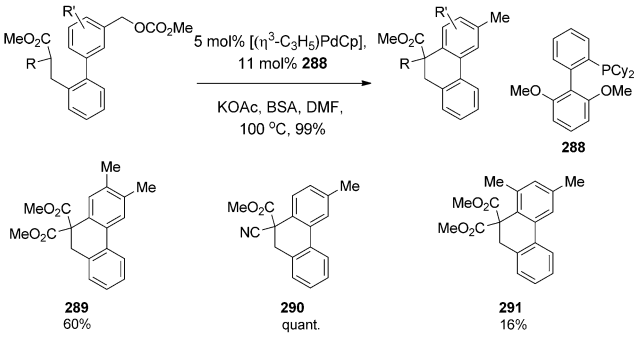
In all palladium-catalyzed reactions discussed thus far, attack of the nucleophilic moiety has occurred at the benzylic carbon, which is energetically favorable as aromaticity is immediately restored. However, functionalization at an arene carbon has been reported. Yamamoto and co-workers disclosed a report of *para*-selective allylation of benzyl chlorides.[139] Benzyl chloride was reacted with stannane **286**, yielding **287** in 80% isolated yield (Scheme 66). The authors



Scheme 66. Palladium-catalyzed allylative dearomatization.

noted that isolation under neutral conditions was required to prevent the aromatization but that **287** was stable in chloroform for three days. DFT studies were performed to probe this interesting reactivity pattern, and it was proposed that the terminal carbon of the allyl group is transferred to the *para*-position of the benzene ring, this allyl inversion process being geometrically favorable.[140]

Attack of a nucleophile at the *para*-position of a benzene ring has also been observed by Kuwano.[141] Methyl carbonates containing a *meta*-substitution pattern between the carbonate and pendant active methine were utilized. Nucleophilic attack occurred selectively at the *para*-position relative to the benzylic site, leading to fused tricycles as a single regioisomer due to the geometric constraints

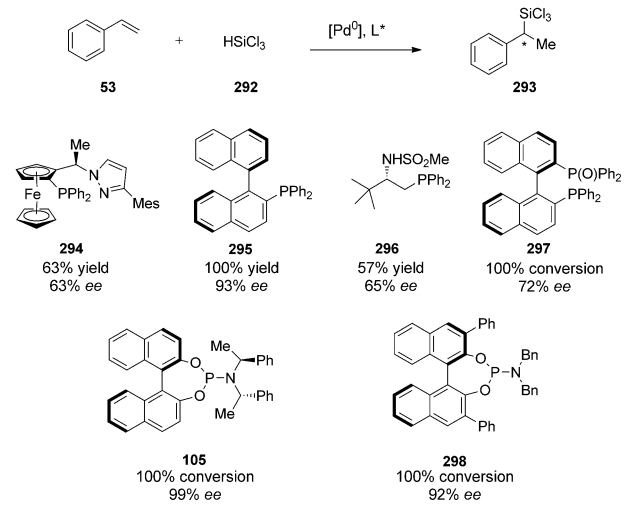


Scheme 67. Nucleophilic attack at the *para*-position of a π-benzyl followed by rearomatization.

prohibiting benzylic carbon attack (Scheme 67). In this case, reaomatization occured to provide the biphenyl product in quantitative yield. The reaction scope included malonate (**289**) and cyanoester (**290**) nucleophiles, while substitution *ortho* to the reaction site was not well-tolerated (**291**).

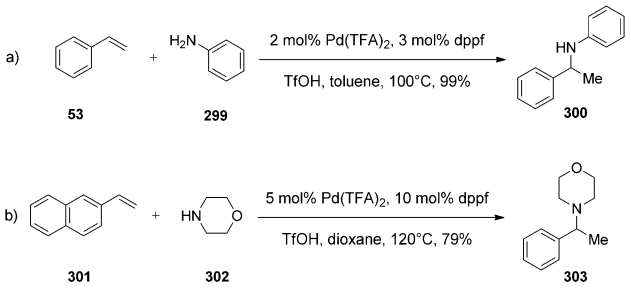
8.6. Palladium-Catalyzed Addition Across Vinylarenes

The early findings that migratory insertion of palladium(II) across vinylarenes selectively places the palladium at the benzylic carbon to take advantage of η^3 coordination have been translated into catalytic regioselective formal additions of hydrogen and an X moiety, proceeding through a hydropalladation/reductive elimination sequence. Products of hydrosilylation are versatile substrates for further functionalizations such as oxidation, protonolysis, and cross-coupling.[142] Because these transformations are stereospecific, the asymmetric installation of silicon is of great importance. Asymmetic palladium-catalyzed hydrosilylation of vinyl arenes with **292** to yield chiral silane **293** been studied by a number of groups, generally focusing on ligand design for the process (Scheme 68). Monophosphines (**294**, **295**, **296**), bisphosphines (**297**), and phosphoramidites (**105**, **298**) have been developed and utilized in the catalytic hydrosilylation of styrene.[143]



Scheme 68. Palladium-catalyzed hydrosilylation of styrene and selected ligands used for the process.

Palladium catalyzed hydroamination of vinylarenes with either aryl- or alkylamines has been developed by Hartwig (Scheme 69).[144] The observed Markovnikov regioselectivity

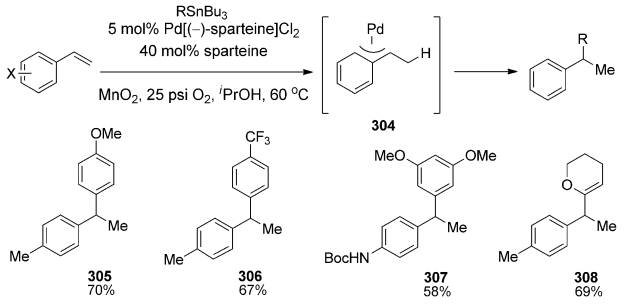


Scheme 69. Palladium-catalyzed hydroamination of vinylarenes with a) anilines and b) secondary alkylamines.

was attributed to formation of an η^3-benzyl intermediate upon hydropalladation, and this hypothesis was further supported by stoichiometric mechanistic studies. Palladium-π-benzyl complexes were prepared, characterized by NMR and crystallography, and demonstrated to lead to amination products upon treatment with an amine.[145] Additionally, it was found that addition occurred to the ligated benzyl group as opposed to exogenous styrene. Reaction of enantiomerically pure benzyl complexes yielded inversion products, suggesting an outer sphere attack by amine or aniline. Studies on various catalyst parameters showed rate acceleration using bisphosphine ligands with larger bite angles.[146] Additionally, a counterion effect was observed in that less coordinating counterions led to enhanced reactivity. Use of a phosphine with a large bite angle or a non-coordinating counterion would disfavor ligation of a third ligand to palladium, which in turn would favor the η^3-benzyl complex, which was implicated as the catalyst resting state. Informed by these observations, Hartwig developed a second-generation catalyst for palladium-catalyzed hydroamination of styrenes, $[Pd(MeCN)_4](BF_4)_2$ with Xantphos ligand. Improved yields were observed for electron-poor amines that had previously been slow to react.

Sigman and co-workers have studied reductive coupling of styrenes and organometallic agents. Using isopropyl alcohol as a hydride source, stannane organometallics were first investigated (Scheme 70).[147] Stannane electron density did not affect reaction efficiency (**305**, **306**), and acid-sensitive functional groups were well-tolerated (**307**). Vinyl stannyl enolethers were also demonstrated to be competent reaction partners (**308**). The perfect regioselectivity of addition was hypothesized to arise due to formation of a π-benzyl intermediate formed following hydropalladation of the styrene starting material (**304**).

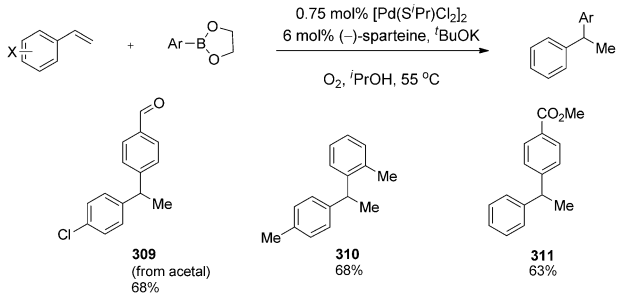
It was later disclosed that arylboronic esters were also capable of participating in hydroarylation.[148] The reaction was tolerant of an aryl chloride (**309**), steric bulk (**310**), and an



Scheme 70. Palladium-catalyzed hydroarylation of styrenes with stannane reagents. Boc = *tert*-butoxycarbonyl.

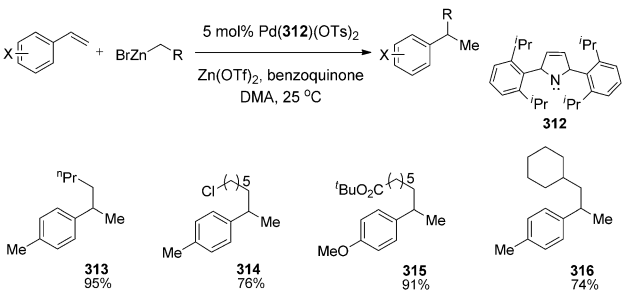
ester substituent (**311**) (Scheme 71). In contrast to the stannanes, vinylboronic esters were unreactive.

Extension of scope to hydroalkylation was achieved through use of organozinc reagents.[149] Alkylzinc bromides were used in excess as both a hydride and alkyl source, which was confirmed by isotope labeling (Scheme 72). Straight-



Scheme 71. Palladium-catalyzed hydroarylation of styrenes with boronic ester reagents.

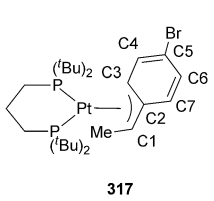
chain alkyl groups bearing a halogen (**314**) and an ester (**315**) were compatible under the reaction conditions, as was β-branching (**316**). Sigman and co-workers have also studied regioselective difunctionalization of *ortho*-vinyl phenols, but in this case the formation of an *ortho*-quinone methide is hypothesized to direct the selectivity.[150]



Scheme 72. Palladium-catalyzed hydroalkylation of styrenes with organozinc reagents.

9. Platinum

Protonation of a platinum(0)-styrene complex yielded π-benzyl-platinum salt **317** (Figure 18).[151] X-Ray crystallography showed the characteristic *ortho*-carbon binding as well as delocalization within the dearomatized ring. In contrast to allyl complexes, the methyl group adopts an *anti*-conformation. These complexes were somewhat unstable, readily forming bridged hydride dimers in the absence of excess styrene.



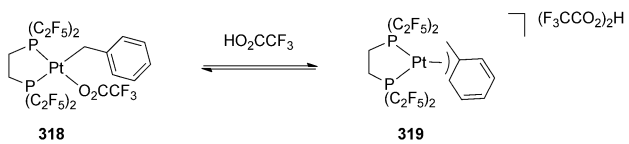
Atoms	Distance
Pt-C1	2.163
Pt-C2	2.242
Pt-C3	2.446
C3-C4	1.429
C4-C5	1.373
C5-C6	1.421
C6-C7	1.333

Figure 18. Structure of η³-benzyl-platinum complex with selected bond lengths.

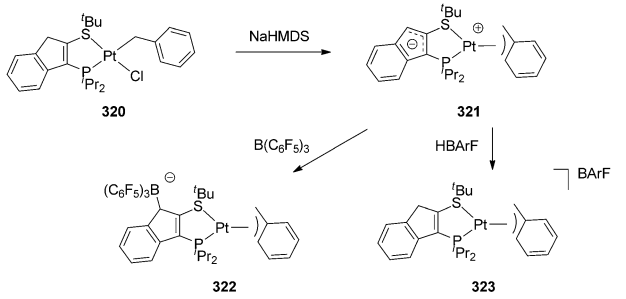
Spencer and co-workers synthesized a number of platinum-benzyl complexes containing varying bisphosphine steric bulk and bite angle and, the dynamic behavior of these complexes was studied by variable temperature NMR.[152] Based on their findings, mechanisms of π–σ–π isomerization as well as β-hydride elimination followed by reinsertion after olefin rotation are operative. Comparing the complexes, it was found that as steric bulk and bite angle increased, the temperature at which signals coalesced decreased. In a direct comparison between palladium and platinum complexes containing the same ligands, rates of exchange were higher in platinum complexes.

Another study performed by Spencer and co-workers investigated electronic effects on platinum–benzyl binding.[153] To this end, *para*-substituted styrenes were utilized, and the degree of asymmety in benzyl binding was invesigated through Pt–P coupling constants in NMR. More electron-donating substituents led to more asymmetric binding, and subsequently lower stability.

Ligand abstraction has been demonstrated to yield π-benzyl platinum complexes. In neat thrifluoroacetic acid, Roddick and co-workers obsrved the transformation of η¹-benzyl-platinum complex **318** to η³-coordinated **319** (Scheme 73).[154] The structure of the salt was assigned based upon NMR analysis, namely the change in Pt–P coupling constants. Equivalence of benzyl protons suggested dynamic coordination in this compound, which was not able to be isolated.



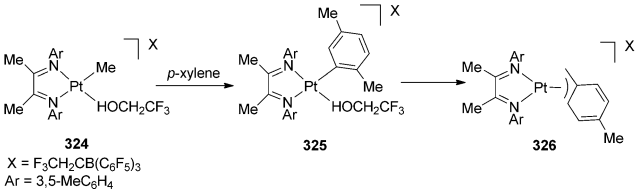
Scheme 73. Synthesis of η³-benzyl-platinum complex by ligand abstraction.



Scheme 74. Synthesis an of η^3-benzyl-platinum complex by dehydrohalogenation and subsequent transformations.

Stradiotto and co-workers performed dehydrohalogenation on **320** to obtain π-benzyl complex **321** (Scheme 74).[155] This zwitterionic species could be tranformed to compound **322** through indene protonation. Additionally, treatment with a borane yielded complex **323**. Analysis of structures solved by X-ray crystallography confirmed the η^3-benzyl hapticity and indicated more asymmetric binding in **323** than in **322**, perhaps a function of the neutral ligand.

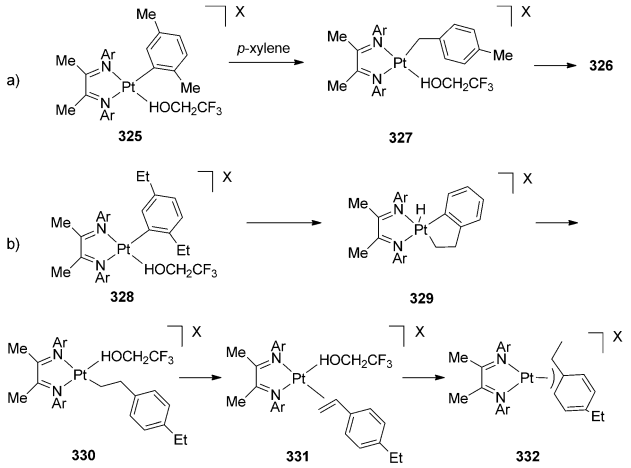
Benzylic C-H activation has been demonstrated with platinum(II) complexes. Bercaw and co-workers reacted diimine-ligated compounds such as **324** with aromatic hydrocarbon solvents and observed a mixture of arene and benzylic C–H activation, the ratio of which depended on the hydrocarbon and diimine ligand.[156] Using *p*-xylene, **325** and **326** were formed initially as a 6:1 mixture, followed by slow conversion to **326** (Scheme 75).[157] It was hypothesized that the thermodynamic stability of **326** relative to **325** was due to the η^3-hapticity of the benzyl group.



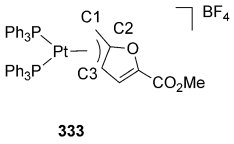
Scheme 75. Synthesis of an η^3-benzyl-platinum complex by C–H activation.

Further kinetic studies suggested that for methyl-substituted arenes, initial C–H activation was a combination of arene and benzylic activation, and an intermolecular pathway led to conversion (Scheme 76a).[158] For ethyl-substituted arenes, arene insertion occurred first, followed by an intramolecular pathway involving cyclometalated intermediate **329** to provide the η^3-benzyl product (Scheme 76b).

Expanding on previous work with π-furfuryl-palladium complexes, Dewhurst and co-workers synthesized the platinum analogue.[159] Oxidative addition of a furfuryl chloride followed by chloride abstraction furnished complex **333** (Figure 19). Compared to palladium, the furfuryl group exhibited less symmetric binding to platinum, evidenced by the greater difference between bond lengths from platinum to



Scheme 76. Proposed formation of η^3-benzyl-platinum complexes from a) *p*-xylene and b) 1,4-diethylbenzene.



Atoms	Distance
Pt-C1	2.132
Pt-C2	2.223
Pt-C3	2.316

Figure 19. Structure of η^3-furfuryl-platinum complex with selected bond lengths.

C1 and C3 (0.184 vs 0.126 Å). Thienyl complexes were also synthesized and studied by NMR, but were too unstable to be isolated.

10. Conclusions

Since the first disclosure of an η^3-benzyl-metal complex, that with molybdenum in 1968, a diverse group of transition metal complexes displaying this binding pattern with dearomatized arenes have been synthesized and characterized. Major strategies towards these products have utilized substitution with a benzyl organometallic, oxidative insertion into a benzylic carbon–heteroatom bond, and addition to a vinylarene, which occurs in a regioselective manner. Studies on the dynamics of these complexes suggest mechanisms for equilibration of the benzyl fragment via changes in hapticity. Currently, the development of catalytic transformations that may proceed through a π-benzyl intermediate has found greatest success with rhodium, nickel, and palladium. The future of catalytic benzylations and additions to vinylarenes will likely focus on more efficient reaction protocols as well as the improvement of asymmetric processes. Knowledge of the nature of the reactive intermediate will prove useful in ligand design and modulation of the coordination sphere.

We thank the U.S. National Science Foundation for their generous support of our programs in catalysis. L.C. thanks the Evelyn Laing McBain Fellowship for financial support. We

thank Dr. Dennis Koester for his help in proofreading this manuscript.

Received: July 10, 2013
Revised: September 17, 2013
Published online: February 19, 2014

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