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C–X Bond Formation

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C–X Bond Formation

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The series *Topics in Organometallic Chemistry* presents critical overviews of research results in organometallic chemistry. As our understanding of organometallic structures, properties and mechanisms grows, new paths are opened for the design of organometallic compounds and reactions tailored to the needs of such diverse areas as organic synthesis, medical research, biology and materials science. Thus the scope of coverage includes a broad range of topics of pure and applied organometallic chemistry, where new breakthroughs are being made that are of significance to a larger scientific audience.

The individual volumes of *Topics in Organometallic Chemistry* are thematic. Review articles are generally invited by the volume editors.

In references *Topics in Organometallic Chemistry* is abbreviated Top Organomet Chem and is cited as a journal.

Preface

Reactions resulting in the formation of C–X bonds were undoubtedly among the first experiments performed by synthetic organic chemists. With years, this area of research has matured and nowadays relies heavily on the use of transition metals. Most of the recent research in C–X bond-forming reactions has been focused on the late transition metal-catalyzed formation of aryl-nitrogen and aryl-oxygen bonds, reactions of primary importance to the pharmaceutical industry. Many highly efficient catalytic systems allowing for the formation of these bonds under mild conditions have been developed and thoroughly reviewed. Against this background, other C–X bond-forming reactions received considerably less attention. This volume is intended to highlight the recent advances in the formation of the C–X bonds other than aryl-oxygen or aryl-nitrogen.

While not comprehensive, it presents seven balanced chapters that summarize the synthetic and mechanistic studies of the formation of C–P, C–S, C–Halide, C–N, and C–O bonds. The reviewed research areas demonstrate great variety of metals and reaction mechanisms that can be involved in the formation of these bonds. I believe that this scope will only grow in the near future thus providing important information for chemists interested in making C–X bonds.

As editor, I wish to express my gratitude to all the experts who contributed to this volume.

Tel Aviv — Arkadi Vigalok

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Transition Metal Catalyzed Electrophilic Halogenation of C–H Bonds in Alpha-Position to Carbonyl Groups

Kilian Muñiz

Abstract Transition metals bearing chiral nonracemic ligands can act as efficient catalysts for the selective a-halogenation next to carbonyl groups in organic molecules. As a general reaction pattern, many of these reactions make use of 1,3-dicarbonyl or related functionalization readily, leading to enolization upon an interaction with Lewis acidic metal catalysts. Subsequent reaction with electrophilic halogenating reagents establishes the formation of new carbon-halogen bonds with asymmetric induction. This chapter discusses the state of the art of these reactions, including mechanistic details regarding catalytic cycles and models for stereoselection. It also includes recent progresses on substrates other than 1,3-dicarbonyls, selective monohalogenation of methylene groups and new mechanistic pathways, such as the use of nucleophilic fluorine sources.

Keywords Carbonyl compounds · Catalysis · Electrophilic substitution · Halogenation · Transition metals

Contents

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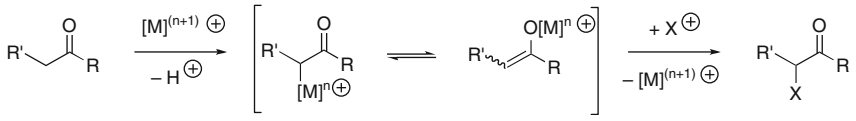
Abbreviations

Ar	aromatic substituent
Ee	enantiomeric excess
Et	ethyl
M	metal centre
Me	methyl
NBS	N-bromo succinimide
NCS	N-chloro succinimide
NF	N-fluoro
Np	naphthyl
OTf	triflate
R	organyl substituent
rt	room temperature
SET	single electron transfer
TADDOL	2,2-dimethyl-α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol
*t*Bu	tert-butyl
Tol	4-tolyl

1 Introduction

Over the past decades, the invention of asymmetric catalytic synthesis with transition metal complexes [1–3] has led to the development of a broad arsenal of methods for the defined creation of stereogenic centers [4–7]. Within this context, enantioselective halogenation reactions have entered the stage rather late as they have mainly been developed over the course of the past decade [8–14]. Parallel to transition metal catalysis, a significant part of this endeavor has been based on organocatalytic methodology [8, 9, 12]. Where transition metal catalysis is concerned, the best approach consists of enantioselective functionalization reactions at the α-position of carbonyl compounds (Scheme 1). This chemistry employs the general concept of transition metal complexes as catalysts for carbonyl activation and subsequent enolate formation. In order to arrive at carbon-halogen bond formations, electrophilic halogen sources are usually required to cleave the intermediary metal complex either at the stage of an α-metallated ketone or a metal enolate.



Scheme 1 General concept for transition metal catalyzed C–X bond forming processes

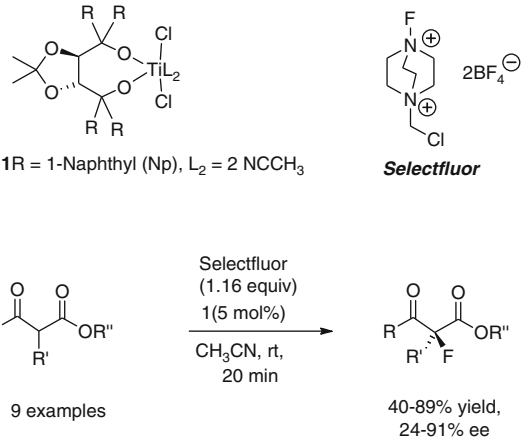
2 Transition Metal Catalysts

2.1 Titanium Catalysts

The first successful realization of this type of enantioselective halogenation catalysis was pioneered by Togni and coworkers [12, 15]. In their approach, they focused on chirally ligated titanium complexes bearing TADDOL-type ligands, and monosubstituted 3-keto esters were chosen as starting materials. The necessary enolization should be accelerated by catalytic amounts of oxophilic metal complexes. The naphthyl-substituted TADDOL complex **1** performed best in halogenating reactions both where rate and asymmetric induction are concerned. Typically, in the presence of 5 mol% of catalyst **1** and a slight excess of Selectfluor as the fluorinating agent [16], room temperature conversion to the fluorinated products occurred smoothly (Scheme 2).

Current understanding of the reaction suggests that an unprecedented mechanism is operating. Unlike in classical Lewis acid catalyzed reactions, the metal complex does not engage in simple activation of the carbonyl moiety, but is understood to directly enhance the degree of enolization and thus create the necessary nucleophilic enolate structure for reaction with the fluorinating agent. The enantioselection proceeds within the chiral environment of the octahedral coordination sphere of the titanium metal center in complete agreement with the selection rules established by Seebach for this class of ligands (Fig. 1) [17]. Although the active catalyst states prior to fluorination have so far escaped isolation, Togni has reported related TADDOLate-titanium bisenolate complexes. Their behavior in stoichiometric fluorination reactions resembles that of the in situ formed complexes from catalysis [12].

Calculations for the case of fluorination suggest that the reaction of the coordinated enolate substrate involves a single electron transfer (SET) process. Given the



Scheme 2 First general enantioselective metal catalyzed fluorination

oxidizing character of the participating NF reagents such as Selectfluor such a proposal appears reasonable, even in the absence of experimental evidence. The overall catalytic cycle for titanium catalyzed halogenation is depicted below for the fluorination reaction with Selectfluor (Fig. 2) [18]. It starts with the coordination of

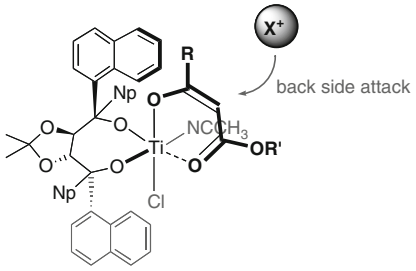


Fig. 1 Selection model for enantioselective halogenation of an (R,R)-TADDOLate–Ti catalyst

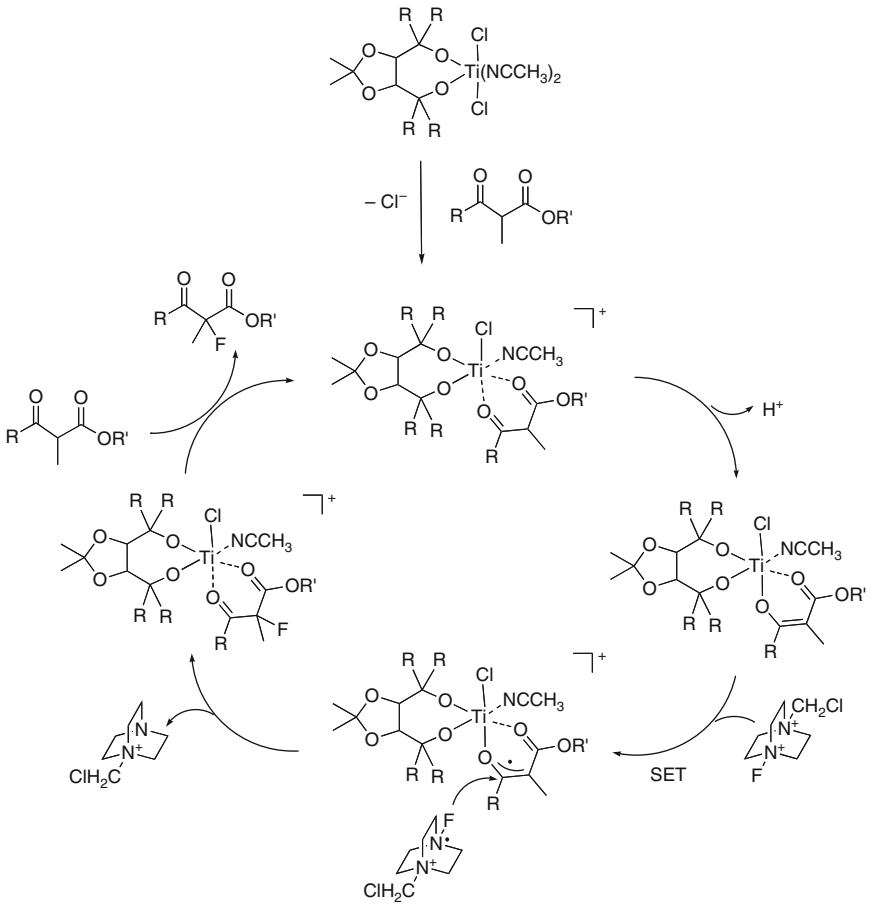
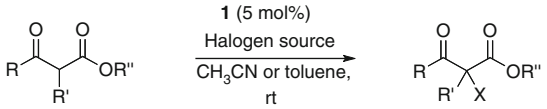


Fig. 2 Catalytic cycle for a-fluorination of 3-keto esters

Scheme 3 Enantioselective chlorination and bromination through TADDOLate–titanium catalysis



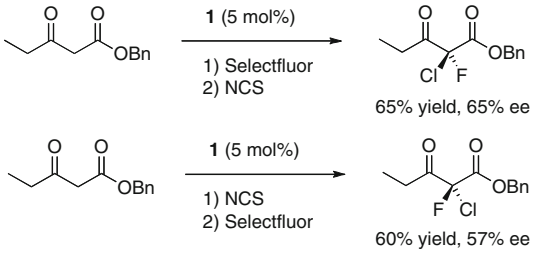
Chlorination (X = Cl): reagent = NCS	5 examples, 88-99% yield, 24-91% ee
Bromination (X = Br): reagent = NBS	2 examples, 84-90% yield, 3-6% ee
Chlorination (X = Cl): reagent = $TolICl_2$/pyridine	7 examples, 37-87% yield, 10-71% ee

the substrate to the chiral titanium catalyst followed by enolization within the coordination sphere of the catalyst. Subsequent SET interaction with the fluorinating reagent leads to the formation of a radical cation, which captures a fluorine atom from the reagent. This step forms the new C–F bond within the chiral environment of the catalyst. Displacement of the product from the coordination sphere by exchange with another substrate molecule closes the catalytic cycle.

Apart from fluorination the present catalyst is also able to promote other halogenation reactions such as chlorination and bromination [19]. These are again room temperature processes and *N*-chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS) were used initially as halogen sources (Scheme 3). The former one gave enantiomeric excesses comparable to the successful fluorination reactions discussed above. The ee could be slightly increased for the bromination reactions when a TADDOL ligand with phenyl instead of naphthyl substituents was used (up to 23% ee). The still large difference in ee when compared to chlorination and fluorination was suggested to originate from largely uncatalyzed background reaction in the case of bromination. Finally, the hypervalent iodine reagent $PhICl_2$ was introduced as chlorinating agent [20]. This procedure required the presence of additional base and led to slightly lower ee values.

Togni extended this work to an unprecedented geminal dihalogenation of 3-keto esters. In the presence of catalyst **1** a sequential reaction with Selectfluor and NCS gives the corresponding 2-chloro,2-fluoro derivatives in good enantiomeric excesses [21]. Importantly, reactions start with fluorination as the first halogenation suffers from only minor amounts of difluorination. Even more important is the fact that the absolute product stereochemistry depends on the sequence of halogenation. As shown for the example in Scheme 4, fluorination followed by chlorination leads to the (*S*)-configured product, while the opposite sequence, installs the (*R*)-configured product. The basis for this outcome is certainly the dominance of the second step of halogenation, which should occur with the same face selectivity as depicted in Fig. 1 and hence leads to opposite absolute configurations for both cases [22].

Scheme 4 Sequential halogenation toward geminal dihalogenated chiral products



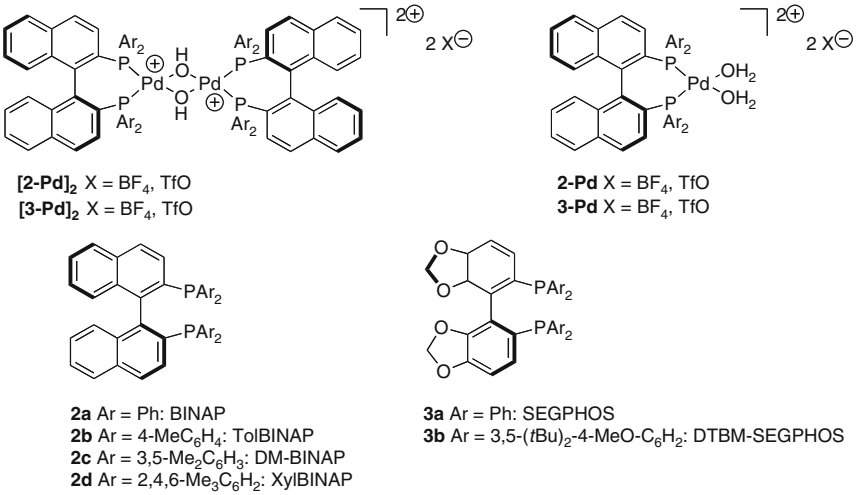
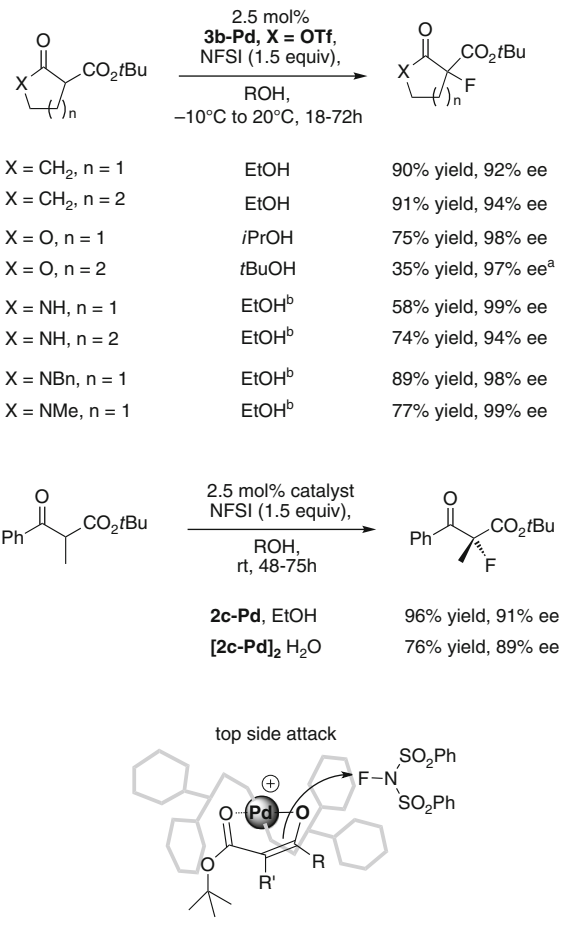


Fig. 3 Dimeric and monomeric palladium complexes for enantioselective halogenation. (*S*)-BINAP ligands and (*S*)-Segphos-ligand

2.2 Palladium Catalysts

Currently, a significant body of work deals with the use of chiral cationic palladium complexes bearing ligands of the BINAP type or related bisphosphine ligands such as SEGPHOS (Fig. 3). These are based on the pioneering work from Sodeoka on the direct formation of chiral palladium enolate complexes from the palladium precursors and 1,3-dicarbonyl compounds [10, 23]. Within this context, the combination of cationic BINAP-Pd complexes and *N*-fluoro-bis(phenylsulfonyl)imine (NFSI) was introduced by Sodeoka for the realization of an extremely efficient α-fluorination of 3-keto esters (Scheme 5).

The catalytic cycle resembles the one from the titanium catalysis. Again substrate coordination to the catalyst induces enolate formation. Interaction with the fluorinating reagent ultimately leads to the stereochemical installment of the new C–F bond and generates a dicationic catalyst state. Exchange of the product for a



Scheme 5 Fluorination of 3-keto esters with chiral bisphosphine palladium catalysts. (**a**) After aminolysis with benzylamine. (**b**) With 5 mol% catalyst and 50 mol% lutidine

substrate molecule leads to the regeneration of the initial enolate complex, thereby closing the catalytic cycle (Fig. 4).

Comparable results were achieved by Kim who used a BINAP-Pd(OH_2)(NCMe)(SbF_6)$_2$ catalyst precursor [24]. The same group reported the enantioselective fluorination of 2-chloro 1,3-dicarbonyls. Good enantiomeric excesses were obtained for the mixed halogenated products [25] (Scheme 6).

The chemistry of 1,3-dicarbonyl substrates was subsequently extended further to the class of 2-cyano acetates [26]. This class of substrates is more challenging since their monodentate coordination behavior would suggest a less rigid coordination mode and hence a decrease in face differentiation. While initial exploration of the reaction with BINAP-Pd complexes such as **2-Pd** led only to minor enantiomeric excesses of about 50% ee, Kim was able to devise a suitable protocol employing his cationic Pd complex [27] (Scheme 7).

Another interesting class of substrates was identified with β-keto phosphonates, as fluorinated phosphonates represent important mimics for phosphates in drug

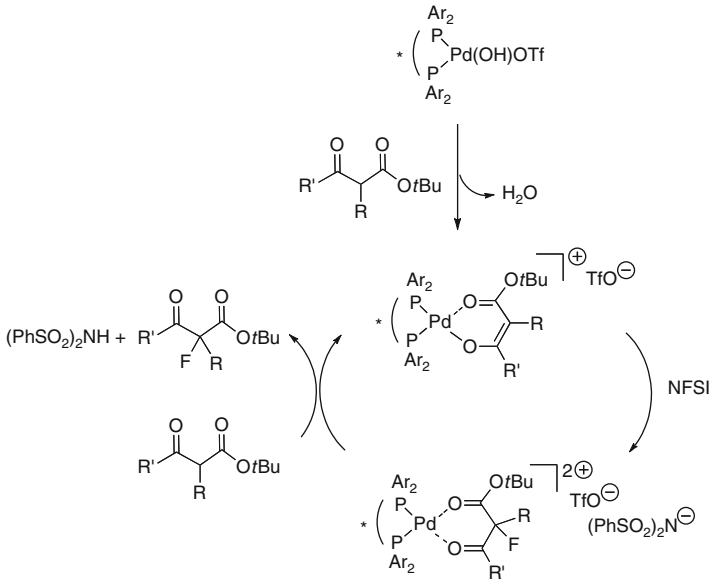
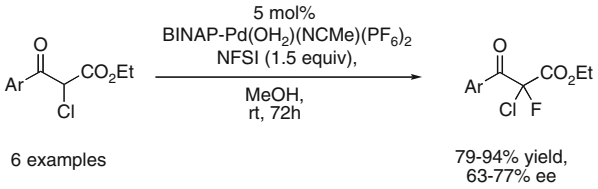
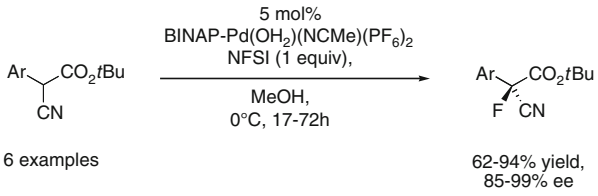


Fig. 4 Catalytic cycle for α-fluorination under BINAP-Pd catalysis

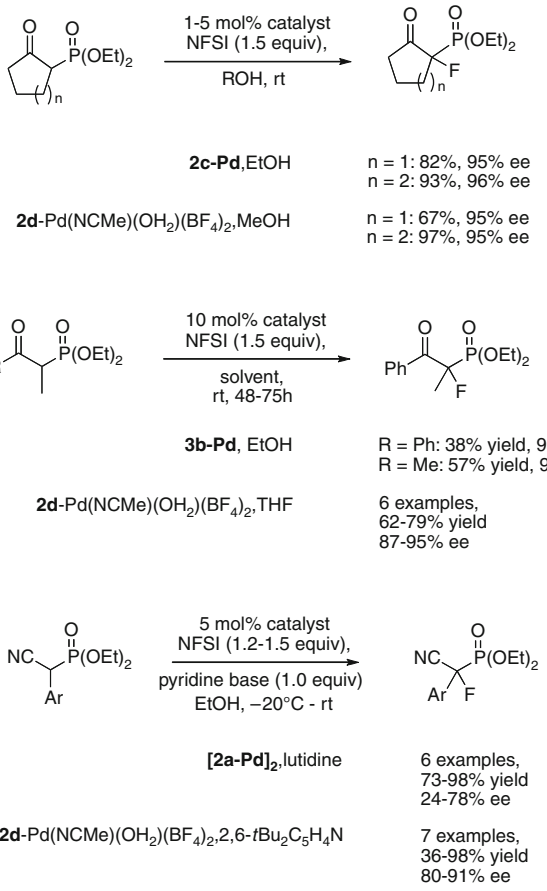


Scheme 6 Geminal dihalogenation of 3-keto esters



Scheme 7 Enantioselective fluorination of 2-cyano acetates

design. Several reports dealt with the use of β-keto phosphonates as substrates for catalytic enantioselective α-fluorination (Scheme 8). Again, Sodeoka employed her hydrated palladium cations bearing BINAP ligands to arrive at catalytic



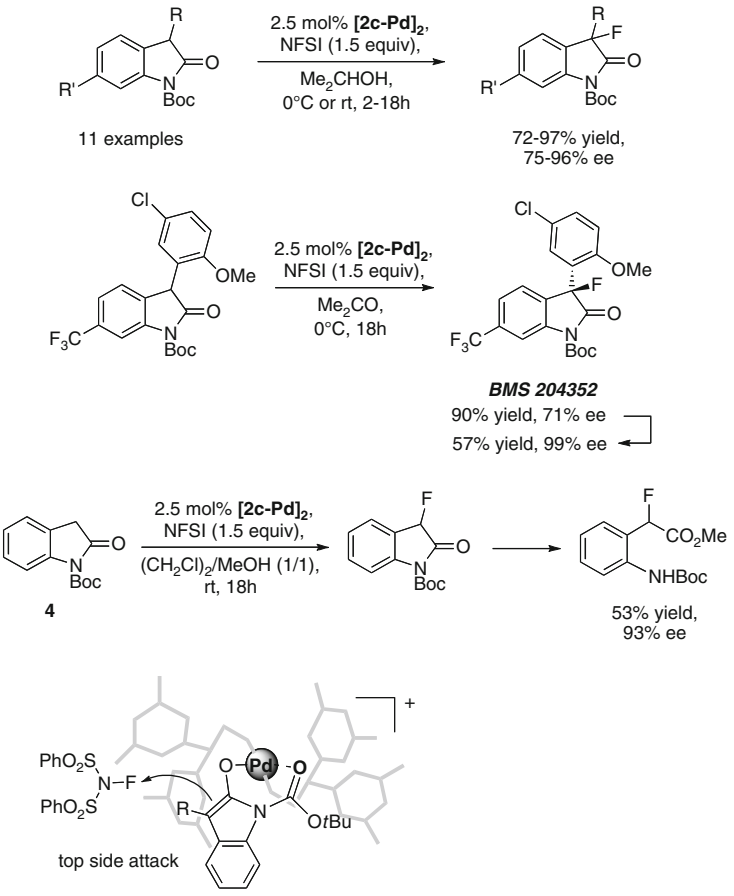
Scheme 8 Enantioselective fluorination of 3-keto and 2-cyano phosphonates

transformations with up to 96% ee [28]. Nearly identical performances were achieved by Kim for reactions with acetonitrile coordinated precatalysts (Scheme 8) [29, 30].

Likewise, 2-cyanophosphonates undergo enantioselective fluorination reactions to products with almost the same enantiomeric excesses. Due to the linear nitrile group, these reactions are believed to proceed without efficient chelation and hence require the presence of additional base. To this end, pyridine derivatives were found to be best. Sodeoka described a combination of lutidine and her dimeric hydroxyl-bridged palladium dimer as catalyst precursor, [31] while Kim relied on a sterically more congested pyridine in combination with a XylBINAP catalyst [29, 32].

In addition, Sodeoka and Kim described the successful reuse of BINAP-Pd complexes for reactions in ionic liquids. Recycled catalysts were reported to catalyze up to ten cycles without loss of ee [33, 34].

Recently, further important progress came again from the laboratories of Sodeoka [35]. In her studies on the asymmetric fluorination of oxindoles, two impressive findings were detailed. First, BINAP-palladium complexes were found to be capable of formally activating simple carbonyl groups as the amide in oxindoles. For a series of substrates, good to excellent enantiomeric excesses could be accomplished using the dimeric hydroxy palladium complex **[2c-Pd]$_2$** with DM-BINAP (Scheme 9). This reaction was also successfully applied in a short synthesis of BMS 204352, a promising compound for stroke treatment, which after recrystallization was obtained in enantiopure form. These reactions are believed to proceed through the general catalytic cycle with a bidentate binding of the substrate in the stereocontrolling transition state.



Scheme 9 Enantioselective fluorination of oxindoles and transition state model

Secondly, this sequence could be employed for the first catalytic synthesis of nonquaternary stereogenic centers in fluorination chemistry. Taking advantage of the observation that small alcohol molecules are capable of a rapid oxindole ring opening to give diaryl α-fluoro acetates, suitable reaction conditions were developed for the methylene containing oxindole **4**. While rapid epimerization was encountered in THF as solvent, a mixture of dichloroethane and methanol led to an irreversible ring opening and concomitant ester formation. As this process is faster than the epimerization reaction, the final product could be isolated in 93% ee. This transformation hence represents a useful approach to simple α-fluorinated esters.

2.3 Nickel Catalysts

The so far most advanced protocol employs a catalyst based on nickel instead of palladium, and the BINAP-complex **5** of nickel dichloride was identified as a suitable catalyst precursor [36]. The resulting catalysis readily converts ester equivalents into the corresponding monofluorinated derivatives. No difluorinated product is formed and the reaction proceeds with good to very good enantiomeric excesses of up to 88%, with no racemization encountered under the chosen conditions. Importantly, the thiazolidinone group could readily be removed within a two-step procedure as demonstrated for the phenyl-substituted product. Hence, enantiomerically enriched α-fluoro aryl acetates are now available from this protocol.

The role of the silyl triflate in the Sodeoka reaction is believed to be twofold. First, it converts the nickel dichloride into the corresponding ditriflate complex at the outset of the reaction. Secondly, on the basis of ^{1}H and ^{19}F NMR experiments the authors suggested that it exercises activation of the fluorinating agent by coordination of a triethylsilyl kation. This electrophilic flourinating agent is then attacked by a (*Z*)-enolate from within the coordination sphere of the nickel complex. The observed R configuration of the product matches a face selection from within the chiral BINAP scaffold as generally established for transition metal catalysis of this type.

The overall catalytic cycle is depicted in Fig. 5. It details the cooperativity of the chiral nickel catalyst, the lutidine base and the silyltriflate in this unique catalytic functionalization.

At the outset the Ni catalyst activates the substrate upon bidentate complexation followed by enolate formation upon porton abstraction with lutidine. Fluorination with the activated NFSI reagent through the transition state from Scheme 10 installs the fluorinated stereocenter leading to a dicationic nickel catalyst state, from which the product molecule dissociates.

This system was recently further optimized by Shibata who reported on the successful application of bisoxazline ligand **6** [37, 38]. An in situ generated

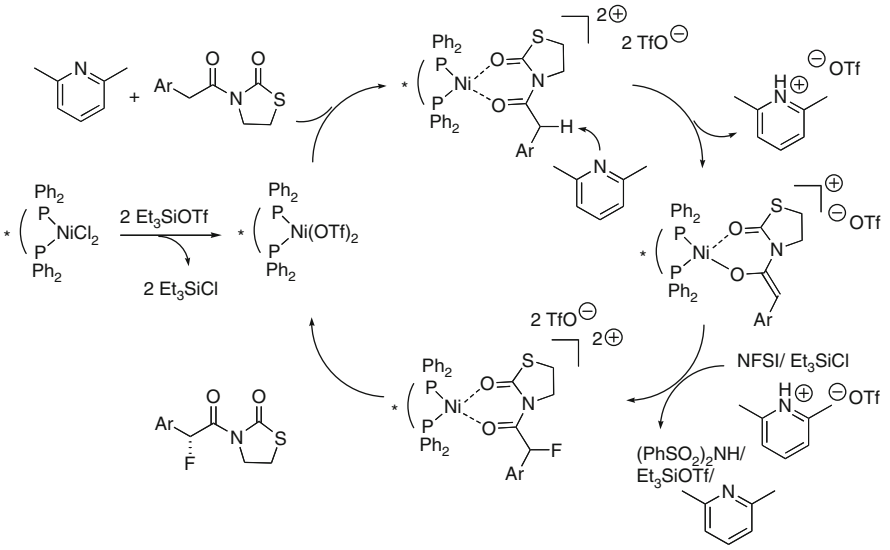
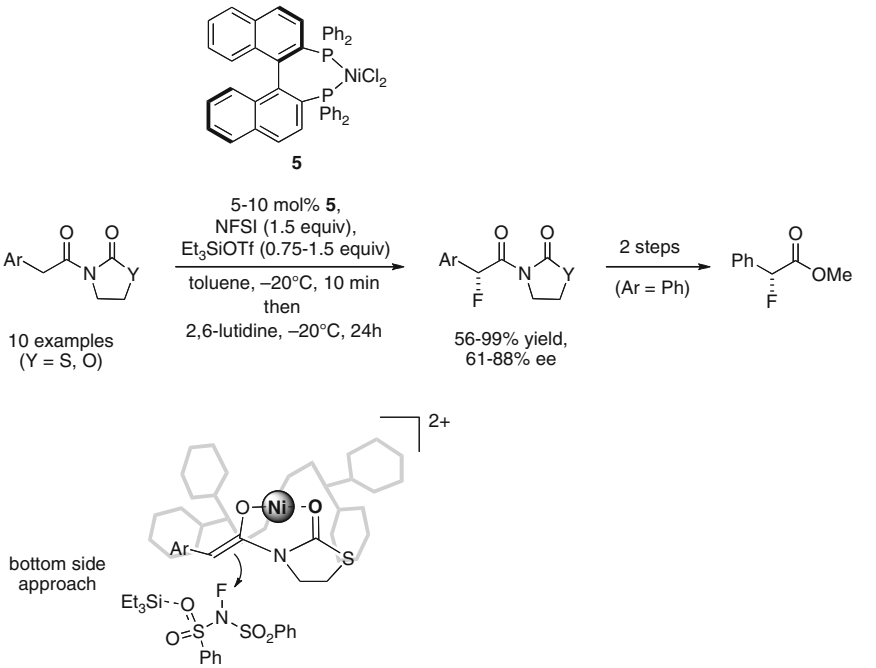
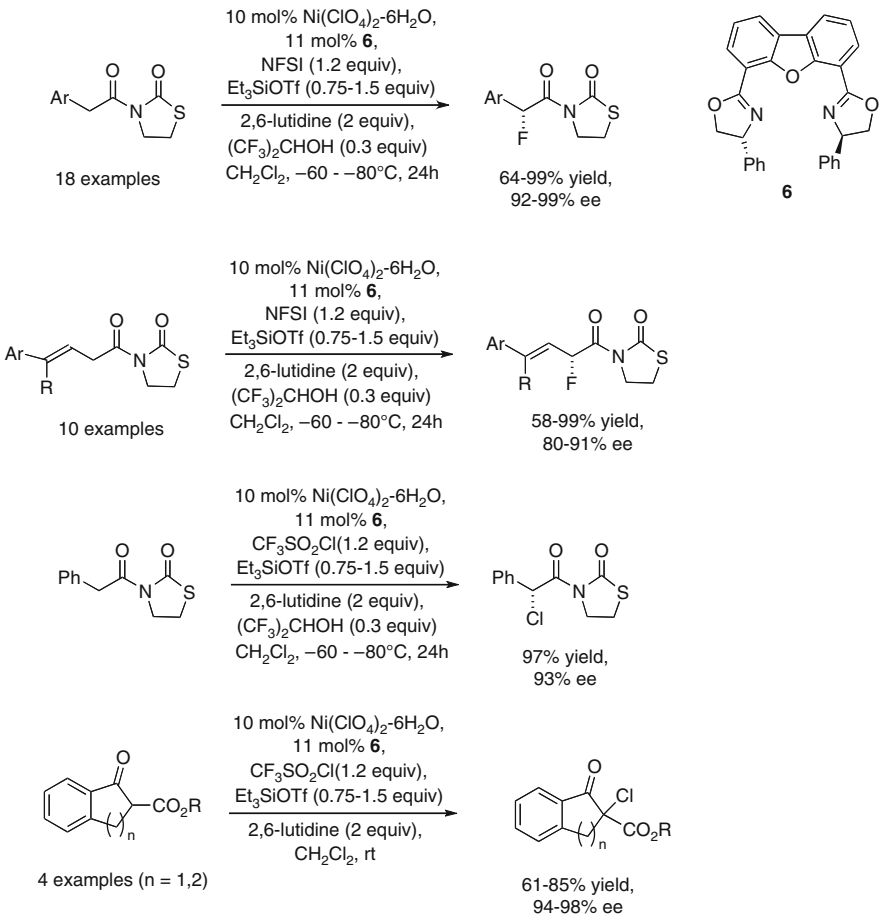


Fig. 5 Catalytic cycle for nickel-catalyzed monofluorination



Scheme 10 Enantioselective monofluorination with a BINAP-nickel catalyst and transition state model



Scheme 11 Enantioselective fluorination and chlorination reactions of 1,3-dicarbonyl compounds with a chiral nickel catalyst

nickel catalyst showed an impressive performance for a broad range of substrates in enantioselective halogenation. Apart from simple thiazolidinone derivatives, which gave up to 99% ee, the corresponding β,γ-unsaturated substrates also underwent clean fluorination with up to 91% ee. This transformation represents an important enantioselective entry into substituted allylic fluorine derivatives (Scheme 11).

The scope of nickel catalysis was further broadened by the demonstration that chlorination reactions become possible with trifluorosulfonylchloride as Cl source and provided an entry to the chlorination of 1,3-dicarbonyl compounds with excellent enantiomeric excesses. The observation of nonlinear effects in both fluorination as well as chlorination reactions suggest that the mechanism of all these reactions may be complicated and may involve more complex active

catalyst structures than simple monomeric adducts from the chiral catalyst and the enolized substrate [38].

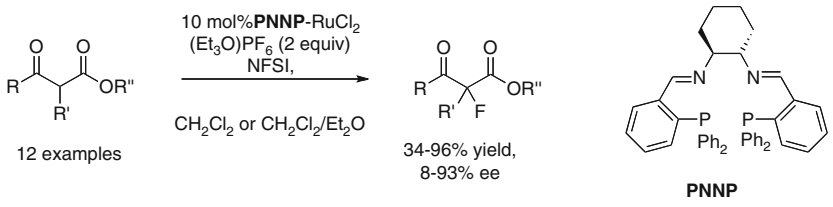
The same group had earlier described the use of bisoxazoline ligands for nickel catalyzed fluorination reactions of 1,3-dicarbonyl compounds, [39] which was also observed for an elaborate 2-oxazolinyl pyridine ligand bearing an axially chiral methylenylamine in 6-position [40].

2.4 Ruthenium Catalysts

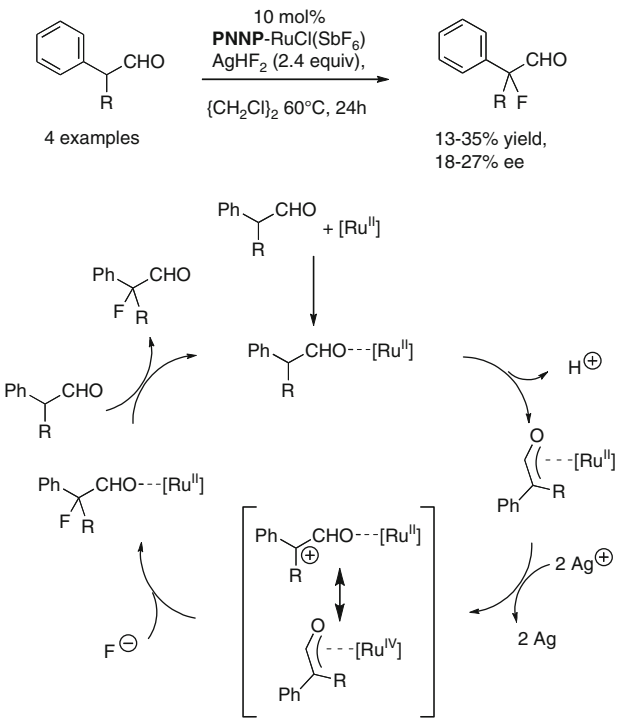
Togni and Mezzetti described a cationic ruthenium complex for enantioselective fluorination of 3-keto esters [41]. Again, NFSI turned out to be the halogenating agent of choice and the generality of this ruthenium-catalyzed reaction is impressive giving ee values of up to 93%. The active catalyst is believed to be a dicationic species, which is generated in situ from interaction of the PNNP-ruthenium dichloride precursor with triethyloxonium hexafluorophosphate. The reaction is further assumed to proceed through a catalytic cycle of two-point substrate binding, enolization, face selective fluorination and finally displacement of the fluorinated 3-keto ester by a still nonfluorinated substrate (Scheme 12).

The same complex type was employed in an impressive synthesis of fluorinated aldehydes (Scheme 13) [42]. In this reaction, a preformed cationic complex in the presence of the nucleophilic fluoride source $AgHF_2$ enables access to unprecedented reactivity. While yields and enantiomeric excesses are not satisfactory, this reaction bears enormous potential and devises new mechanistic pathways for future development of the field.

The mechanistic understanding is that a coordinated aldehyde undergoes enolization within the coordination sphere of the ruthenium catalyst. A subsequent oxidation of the metal upon interaction with the silver(I) complex provides a Ru(IV) catalyst state that is nucleophilically attacked by fluoride. This step installs the carbon-fluorine bond and reduces the ruthenium catalyst back to oxidation state II. Displacement of the product by another substrate molecule closes the overall catalytic cycle.



Scheme 12 Enantioselective fluorination of 3-keto esters employing Ru catalysis



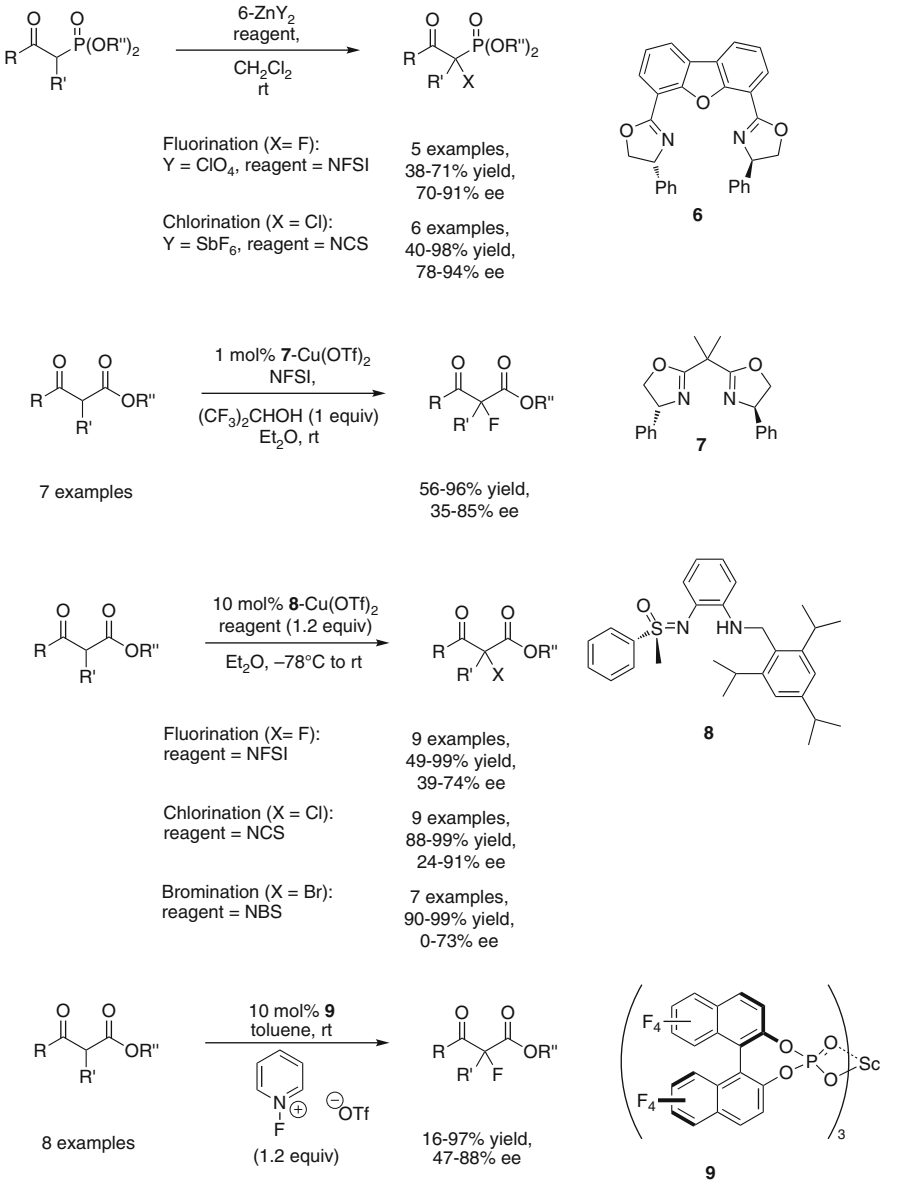
Scheme 13 Catalytic fluorination with a chiral ruthenium catalyst employing a nucleophilic fluorine source

2.5 Other Metal Catalysts

Additional work has described the use of copper, zinc and rare earth metals for halogenation reactions of chelating substrates. These reactions include another application of ligand **6**, which in a screening revealed high enantioselectivities for zinc, scandium and copper complexes, with the former one as the best. Hence, preformed zinc complexes of **6** showed good performances in chlorination and fluorination reaction of 3-keto phosphonates [43] (Scheme 14).

Copper complexes bearing bisoxazolines were described by Cahard [44]. Ligand **7** induces moderate to good enantiomeric excesses in the fluorination of 3-keto esters. Bolm described the application of chiral sulfoximine **8** as ligand for copper triflate and subsequent application of this catalyst in all three halogenation reactions of chlorination, bromination and fluorination employing various 3-keto esters [45].

Finally, Inanaga reported a rare example of scandium catalysis with a preformed complex bearing a fluorinated axial chiral phosphonate. This fluorination of 3-keto esters employed N-fluoro pyridinum triflate as reagent, a rare case in which NFSI did not represent the superior reagent [46].



Scheme 14 Enantioselective halogenation reactions with different chiral ligand/metal combinations

3 Conclusion

Over the past decade a series of chiral transition metal based catalysts have been introduced for enantioselective halogenation reactions. In particular, chiral Ti-TADDOLate catalysts, catalysts from the combination of nickel and palladium with chiral BINAP ligands and tetradentate ligands for ruthenium enabled the development of a series of enantioselective halogenation reactions that bear high generality. In particular, the important fluorination reactions have reached a high level enabling the synthesis of various fluorinated carbonyl compounds with nearly complete stereoinduction. For several classes of substrates, the corresponding chlorination and bromination reactions were also investigated, although to a lesser extent. As a consequence, some of these reactions still require additional optimization, especially in the case of bromination. As all currently employed halogenating agents are commercially available, future progress in this direction should derive from the screening of new ligand-metal combinations and reaction conditions.

In conclusion, the transition metal catalyzed enantioselective introduction of halogen atoms in the α-position of carbonyls has become a versatile synthetic tool and will continue to generate synthetic application.

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Late Transition Metal-Mediated Formation of Carbon–Halogen Bonds

Arkadi Vigalok and Ariela W. Kaspi

Abstract This chapter reviews the synthesis of nonactivated aromatic halides assisted by late transition metal complexes. Although some of these reactions have been known for over half-a-century, there was a tremendous progress in the stoichiometric and catalytic applications of late transition metals in halogenation of aromatic compounds. Both nucleophilic and electrophilic halogenation pathways have been explored, resulting in practical methods for making aryl-halides. The chapter provides a metal-by-metal discussion of the above reactions, including the possible mechanisms of the metal-promoted formation of C–Halogen bonds.

Keywords Aryl halides · Catalysis · Halide exchange · Reductive elimination · Transition metals

Contents

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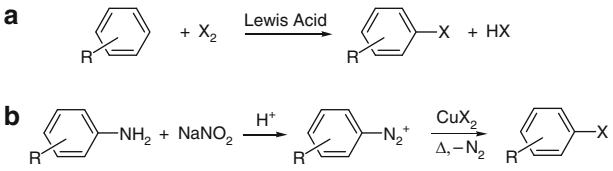
Abbreviations

Ac	acetyl
Ar	aryl
t-Bu	*tert*-butyl
cat	catalyst
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppe	bis(diphenylphosphino)ethane
equiv	equivalent(s)
Et	ethyl
h	hour(s)
L	liter(s)
Me	methyl
mol	mole(s)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
Nu	nucleophile
Ph	phenyl
i-Pr	isopropyl
py	pyridine
rt	room temperature
TBAF	tetrabutylammonium fluoride
Tf	trifluoromethanesulfonyl (triflyl)
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	tosyl, 4-toluenesulfonyl

1 Introduction

Organic halides represent a very important class of organic compounds, both on their own and due to the well-developed processes toward functionalization of carbon–halogen bonds in the synthesis of valuable chemicals [1]. Many of the organic halides, in particular fluorides and iodides, have also found applications in medicine and agriculture [2–5]. Such a prominence resulted in the development of numerous synthetic approaches for preparation of organic halides, some of these approaches becoming cornerstones of organic chemistry [6, 7]. For a long time, late transition metals were not considered particularly useful for the preparation of organic halides. Furthermore, they have grown to be very prominent in *breaking* carbon–halogen bonds to make way for a variety of functional groups at the carbon atom.



Scheme 1 Electrophilic halogenation and diazotization methods in synthesis of nonactivated aromatic halides

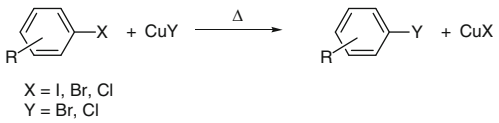
Yet, although a great deal of organic halides can (and should!) be prepared without utilizing transition metals, it is clear that there are cases when standard organic methods cannot produce the desired compounds and metal complexes have to come to the rescue. A particularly important class of organic compounds where typical synthetic approaches fail to deliver is the nonactivated aromatic halides, e.g., halides that have no electron-withdrawing groups in the *ortho*- or *para*-positions. Such halides are too unreactive to be involved in a halide exchange reaction under the nucleophilic aromatic substitution conditions [8] and are typically prepared via the direct electrophilic halogenation of the aromatic C–H bonds (Scheme 1a) [9] or diazotization of the corresponding anilines (Scheme 1b) [10]. Both approaches require rather harsh conditions which are often incompatible with a large variety of functional groups. In addition, the selectivity of electrophilic halogenation is predetermined by the directing properties of the substituents already present in the aromatic ring, while the laborious access to most synthetic anilines significantly limits the scope of the diazotization method. Finally, both classical methods often *do utilize* late transition metals, albeit not well-defined complexes, either as Lewis acids (iron salts) for electrophilic halogenation or source of the halide (copper salts) for the diazotization. In this chapter, we will focus on both stoichiometric and catalytic halogenation reactions of aromatic compounds that involve the participation of a late transition metal center.

2 Carbon–Halogen Bond Formation with Group 11 Metals

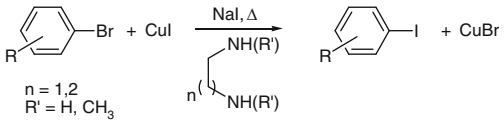
2.1 Copper

Copper salts have been used for nearly 100 years to introduce various nucleophiles into the aromatic ring. The first mentioning of copper-mediated halogenation reaction appeared over 50 years ago. Hardy and Fortenbaugh [11], and later Bacon and Hill [12] showed that heating haloaromatic compounds with a Cu(I) halide in pyridine or picoline results in the selective halogen exchange reaction (Scheme 2). Benzene derivatives as well as halogenated napthalenes or anthraquinones were used as substrates. The direction of the reaction followed the bond strength of the carbon–halogen bond: iodide could be replaced by bromide or

Scheme 2 Copper(I)-assisted halide exchange reactions



Scheme 3 Reversed halide exchange catalyzed by copper (I)/diamine mixture

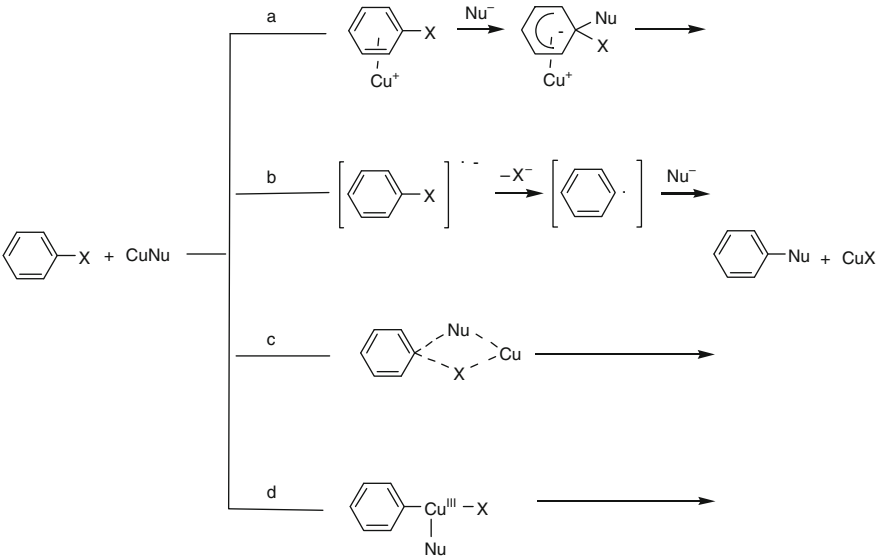


chloride, but not vice versa. Similarly, bromide could be replaced by the chloride-ion while the reverse reaction did not occur. Considering that aryl iodides are usually more valuable products than bromides or chlorides, this reaction had received little attention in the following 20 years when modified protocols leading to reverse selectivity, i.e., aryl iodides from bromides or chlorides have been reported [13, 14]. Use of polar aprotic solvents or solid-supported Cu precursors provided aryl iodides from the corresponding bromides in high yields. The use of aryl chlorides instead of bromides resulted in significantly reduced reactivity. By using the isotopically labeled Na*I as a source of iodide, the copper-catalyzed reverse halide exchange was also successfully applied to the synthesis of ^{131}I-enriched peptides in aqueous solutions [15]. In 2002, Klapars and Buchwald reported a catalytic method for converting aryl bromides into the iodides in quantitative yields and under relatively mild reaction conditions [16]. The key modification of this reaction was the addition of a bidentate secondary diamine ligand (Scheme 3). Lower yields were obtained when aryl chlorides were used as substrates. The reaction was later applied for in situ generation of iodoarenes for consequent catalytic transformations [17].

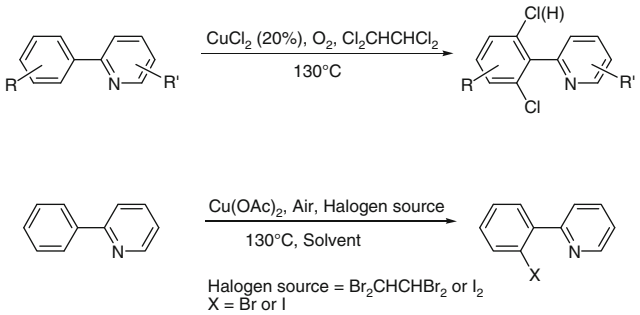
Finally, there was a recent report on the copper-mediated fluorination of nonactivated aryl chlorides using a heterogeneous copper aluminum fluoride system. The reactions were performed at very high temperatures and resulted in low-to-moderate yields of the fluoroaromatic products [18].

Mechanistic interpretations of the copper-catalyzed aromatic nucleophilic substitution reactions remain unsettled even after half-a-century of debate [19, 20]. Possible pathways involve an S_NAr reaction mediated by copper complexation to the pi-system (Scheme 4a), an electron transfer reaction followed by halide dissociation (Scheme 4b), four-centered σ-bond metathesis reaction (Scheme 4c) and Cu(I) oxidative addition to the Ar-X bond, followed by the nucleophile exchange and reductive elimination in the resulting Cu(III) system (Scheme 4d). There is presently a considerable body of experimental and theoretical data for and against each of the proposed mechanisms [21]. While the mechanistic studies were mostly related to the formation of C–C, C–O and C–N bonds, it is likely that the copper-catalyzed halogen exchange reactions follow a similar trend.

Although most of the copper-catalyzed halogenation involves the Ullmann-type halide exchange, Yu and coworkers recently reported an elegant aromatic



Scheme 4 Proposed mechanistic pathways for the copper-assisted halide exchange reactions in nonactivated aryl halides

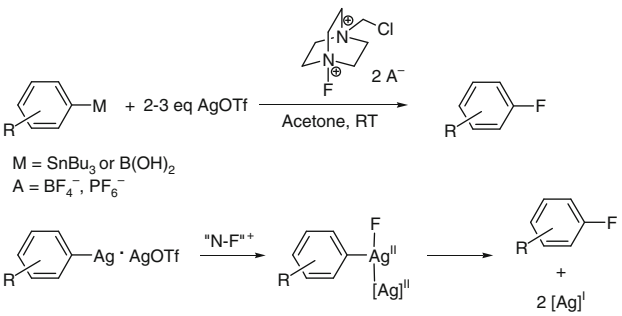


Scheme 5 Directing group-assisted copper-catalyzed electrophilic halogenation of aromatic C–H bonds

halogenation that proceeds via the ligand-directed C–H activation [22]. A variety of 2-arylpyridine derivatives could be selectively halogenated in good to excellent yields with dioxygen serving as an oxidant (Scheme 5).

2.2 Silver

Very recently, the Ritter group presented two examples of the silver-mediated fluorination of aryl stannanes and aryl boronic acids (Scheme 6) [23, 24]. Good yields were reported in both cases. The authors proposed the transmetallation



Scheme 6 Electrophilic fluorination of metal-aromatic compounds assisted by silver

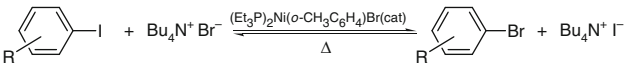
reaction leading to an Aryl-Ag(I) intermediate as the first step, followed by the one-electron two-metal oxidative addition–reductive elimination sequence. This mechanism can account for the necessary use of an excess of the silver salt (2–3 equiv.).

3 Carbon–Halogen Bond Formation with Group 10 Metals

3.1 Nickel

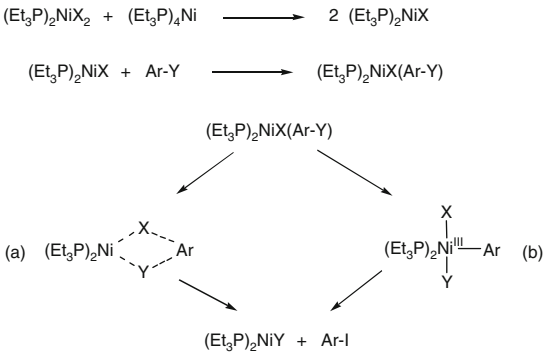
The preparation of chlorobenzene from bromobenzene catalyzed by a Ni(II) salt was reported by Cramer and Coulson in 1975 [25]. The reaction proceeded under harsh conditions (DMF, reflux or EtOH, 210°C), however, only small amounts of the Ni catalysts were sufficient to achieve good yields of the desired product. Use of stoichiometric amounts of the Ni(II) salt provided much better yields and allowed for the formation of the inverse halide exchange products, in addition to the normal ones. Employing microwave irradiation often facilitated the halide exchange [26].

Tsou and Kochi provided detailed mechanistic studies of the halogen exchange reaction in aryl- and vinyl halides catalyzed by Ni(II) complexes. Complexes of the formula $(Et_3P)_2Ni(Ar)I$ were found to be the active catalysts in this reaction (Scheme 7), although several Ni(II), Ni(I) or Ni(0) complexes could also be used instead [27]. Importantly, simple Ni(II) salts were inactive in catalysis and excess of the phosphine ligand was detrimental to the reaction. Both the direct and inverse halide exchange reaction required significant induction periods after which the reactions were complete within minutes in a number of solvents. Tsou and Kochi proposed the Ni(I) species $(Et_3P)_2Ni^{I}X$ as the catalytically active one which can undergo the halide exchange reaction with Ar-Y either via the concerted σ-bond metathesis mechanism (Scheme 8a) or via oxidative addition–reductive elimination pathway (Scheme 8b). The authors suggested that the latter mechanism was less likely in their system since they found no cross-over products, common for the



Scheme 7 Nickel-catalyzed halide exchange reaction

Scheme 8 Proposed mechanisms of the nickel-catalyzed halide exchange involving Ni(I) as the active catalytic species



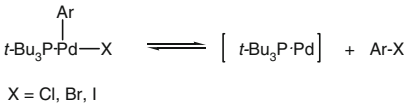
Ni(III) systems (Kochi), and the obtained ρ-value (∼ 0.6) was small compared to what was observed in oxidative addition reactions to a Ni(0) center.

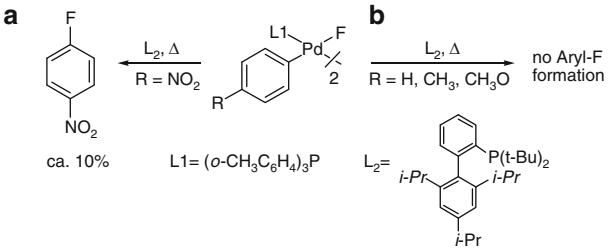
Ni(0) complexes were also employed in the halide exchange reactions in non-activated aryl halides. Both Ni powder and in-situ generated Ni(0) species (from Ni(II) and Zn dust) provided good yields of the exchange products, which included aryl iodides from the corresponding aryl bromides and chlorides [28–30]. In some cases, the reactions were accompanied by the formation of considerable amounts of C–C coupling products.

3.2 Palladium

Pd(0) complexes have traditionally been employed in the variety of aromatic nucleophilic substitution reactions that utilize aryl halides or sulfonates as starting materials. In these reactions, an electron-rich metal center oxidatively adds to either C–Halide or C–OSO_2R bond in the first step. However, until recently, very little was known about the reverse reaction of carbon–halogen bond formation from Pd(II) species. Roy and Hartwig demonstrated that building up the bulk around the metal using a sterically hindered phosphine ligand can result in the formation of a three-coordinate $(R_3P)Pd(Ar)X$ complex which is capable of the reductive elimination of the aryl halide molecule (Scheme 9) [31–33]. Although the elimination of aryl chlorides was the most thermodynamically favorable, the reactivity of the halide ligands followed the trend I>Br>Cl, indicating the importance of the kinetic factors in this reaction. The mechanistic studies suggested that the reductive Ar-X reductive elimination in a Pd(II) system takes place as the microscopic reverse of

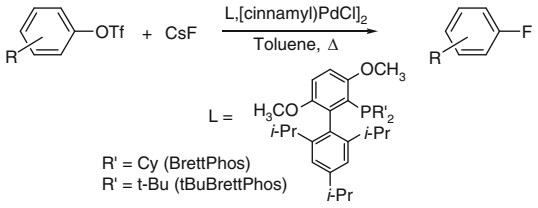
Scheme 9 Directly observed aryl-halide reductive elimination from sterically hindered Pd(II) complexes





Scheme 10 C–F bond formation from Pd(II) complexes: (**a**) Proposed reductive elimination step in the synthesis of p-fluoronitrobenzene, (**b**) No fluoroaromatic compound was observed for aryl groups lacking the strong electron-withdrawing nitro substituent

Scheme 11 Nucleophilic fluorination of aromatic triflates catalyzed by Pd(0) phosphine complexes



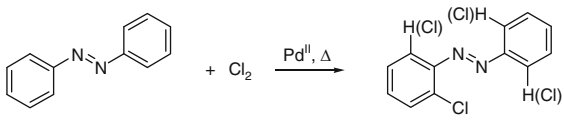
the Ar-X oxidative addition to the electron-rich Pd(0) complexes. No aryl fluoride reductive elimination was reported, however, it was recently proposed that the Ar-F reductive elimination results in the formation of small amounts of p-$NO_2C_6H_4F$ in a Pd(II) system upon the addition of a sterically hindered Buchwald ligand (Scheme 10a) [34]. The presence of the strongly activating nitro group in the reported system and absence of any aryl fluoride formation with other aryl groups (Scheme 10b) raised questions about the mechanism by which the Ar-F bond was formed. It was proposed that the cationic Meisenheimer-type intermediate could be formed during the reaction course [35]. Until recently, the considerable effort invested in making C–F bonds gave limited results despite the significant thermodynamic gain expected from the formation of the very strong C–F bond [36]. To advance in this goal, one also had to overcome the side-reactions leading to the formation of strong P–F and H–F bonds, often observed in the reactions of organometallic fluorides. Nevertheless, Buchwald and coworkers recently reported the first example of catalytic fluorination of unactivated aryl triflates (Scheme 11) [37]. The major factor in making the key step of the catalytic cycle – Ar-F reductive elimination – work was the development of an extremely bulky BrettPhos ligand (Scheme 11). The three-coordinate (BrettPhos)Pd(Ar)F intermediate was isolated

and crystallographically characterized, and was shown to undergo the Ar-F reductive elimination upon heating in toluene.

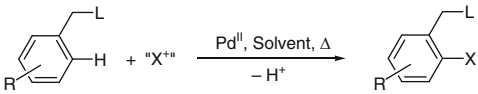
In addition to the formation of Ar-Halide bonds via the reductive elimination from Pd(II) complexes, there is much current interest in using palladium(II) complexes in combination with a source of an electrophilic halogen which usually results in Pd complexes in higher oxidation state (vide infra). Following the pioneering work of Fahey, who showed that Pd(II) complexes catalyze *ortho*-chlorination of azobenzene upon reaction with elemental chlorine (Scheme 12) [38, 39], several research groups developed synthetic methods for the *ortho*-directed halogenation of aromatic compounds using Pd(II) catalysts (Scheme 13).

The Sanford group developed a method for an electrophilic halogenation of a variety of aromatic substrates containing a nitrogen-based ligand that directs the halogenation reaction to the *ortho*-position. *N*-halosuccinimides were found to be the best reagents for the selective introduction of Cl, Br and I-substituents to the aromatic ring (Scheme 14a) [40, 41]. Interestingly, in many cases, the ligand-directed method is complementary to the metal-free halogenation of the same

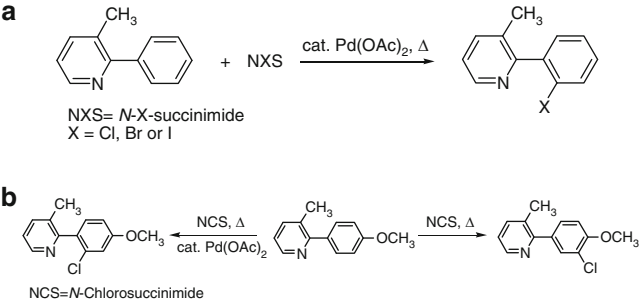
Scheme 12 Catalytic chlorination of azobenzene via the proposed Pd(II)/Pd(IV) catalytic cycle. The first directing group-assisted electrophilic halogenation reaction



Scheme 13 General approaches to the electrophilic halogenation of aromatic C–H bonds using a Pd(II) catalyst

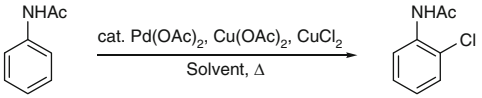


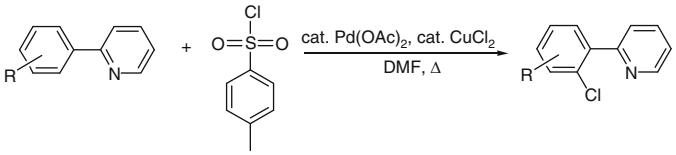
L= *N*- or *O*-donors
"X+" is usually a compound with an N-Halogen bond



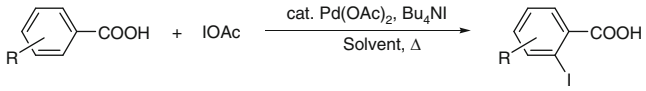
Scheme 14 Pyridyl group assisted halogenation: (**a**) General *ortho*-halogenation catalyzed by Pd(II). (**b**) Complementary Pd-catalyzed *ortho*-chlorination and electrophilic chlorination with NCS

Scheme 15 Pd(II)-catalyzed copper-promoted *ortho*-chlorination of acetanilide





Scheme 16 Pd(II)-catalyzed *ortho*-chlorination of 2-arylpyridines with arylsulfonyl chloride. The reaction requires copper(II) to give the chlorination product



Scheme 17 Pd(II)-catalyzed selective monoiodination of benzoic acids in the presence of a tertiary ammonium salt

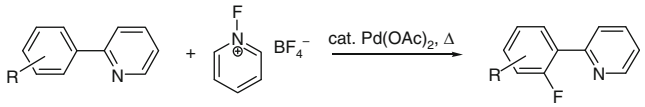
substrates under the identical reaction conditions which generally introduces the halogen atom to the most electron-rich position in the aromatic ring (Scheme 14b) [42].

More recently, the Shi group reported an *ortho*-halogenation of acetylanilide with copper(II) as oxidant (Scheme 15) [43]. Cu(II) salt was also found to be crucial to the formation of chloroarenes in the Pd(II)-catalyzed reaction of 2-phenylpyridine derivatives with arylsulfonyl chlorides. Only sulfonylation was observed when no copper was present in the system (Scheme 16) [44].

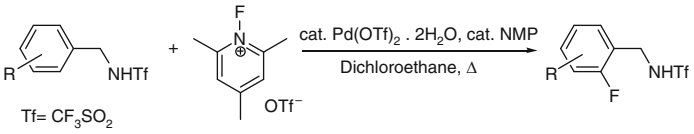
Very recently, Pd-catalyzed halogenation of various *N*-heterocyclic compounds was achieved under the electrochemical conditions with aqueous HX (X= Cl or Br) as the halogen source [45]. The reactions proceed without supporting electrolyte making the overall process more attractive from the environmental point of view.

Kodama et al. [46] and later Mei et al. [47] reported a selective *ortho*-halogenation of arylcarboxylic acids using the $Pd(OAc)_2$ precatalyst. Although both mono and dihalogenation products were usually obtained, especially in the iodination reaction, it was found that the presence of tertiary ammonium salts significantly improves the reaction selectivity mainly producing the monohalogenated product (Scheme 17) [47]. The bulky ammonium cation likely facilitates the displacement of the monohalogenated product from the metal coordination sphere, minimizing the competing formation of the dihalogenated side product.

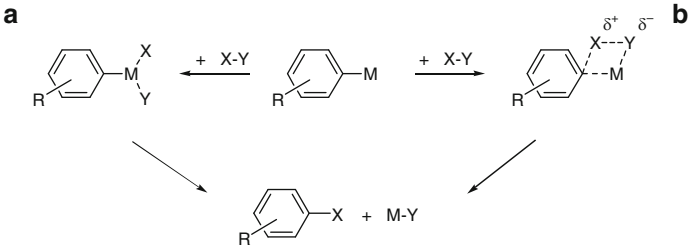
Considering that organofluorine compounds feature prominently in the pharmaceutical and agrochemical industries due to their important biological activities [2, 48], there were significant efforts to extend the above methods to making fluoroaromatic compounds. Sanford et al. reported a Pd-catalyzed C–H activation/*ortho*-fluorination of several 2-phenylpyridine derivatives with various N–F donors of "an electrophilic" fluorine (Scheme 18) [49]. Under the same conditions,



Scheme 18 Catalytic *ortho*-fluorination of 2-arylpyridines catalyzed by Pd(II)



Scheme 19 Pd(II)-catalyzed *ortho*-fluorination of triflamide-protected benzylamines. The triflamide group can later be converted to variety of synthetically important functional group

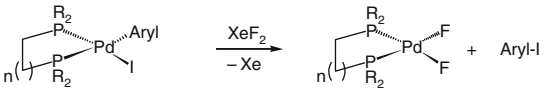


Scheme 20 Proposed mechanistic pathways of reaction of an organometallic compound with an electrophilic halogen source: (**a**) Oxidative addition–reductive elimination pathway. (**b**) Electrophilic Metal–Carbon bond cleavage

it was also possible to fluorinate the methyl group in 8-methylquinoline, thus making the method applicable to the synthesis of both $C(sp^2)$- and $C(sp^3)$-fluorinated products.

In a recent modification, Yu et al. described a Pd-catalyzed C–H activation/*ortho*-fluorination of triflamide-protected benzylamines with *N*-fluoro-2,4,6-collidinium cation (Scheme 19) [50]. The authors found that to achieve high yields it was crucial to use small amounts of NMP as a promoter. As the triflamide group can be easily converted to many other functional groups, such as aldehydes or azides, the reported method allows for an efficient synthesis of various *ortho*-fluorinated aromatic products.

The use of highly reactive electrophilic halogenation reagents can lead to the Pd(II) oxidation to give Pd(IV) complexes which can undergo the C–X reductive elimination reaction. Although this mechanism is often indistinguishable from the S_E2/metathesis mechanism [51], where no change in the metal oxidation state takes place (Scheme 20a, b), there is substantial evidence that the oxidative addition–reductive elimination path is viable in the Pd(II)-mediated halogenation of aromatic compounds [52, 53].



Scheme 21 Xenon difluoride-induced aryl-iodide reductive elimination from Pd complexes. The reaction is very general with regard to the aryl group involved

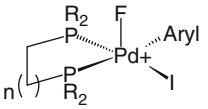
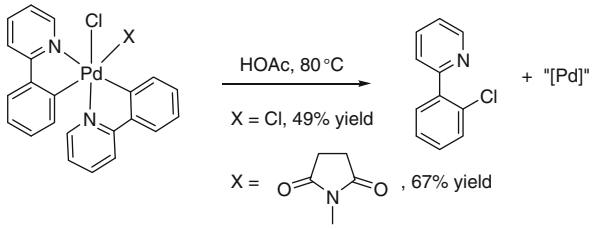


Fig. 1 Proposed cationic Pd(IV) intermediate in the reductive elimination of Aryl-I and Aryl-F in the reaction between the Pd(II) aryl iodo complexes and *N*-fluoro-2,4,6-collidinium cation

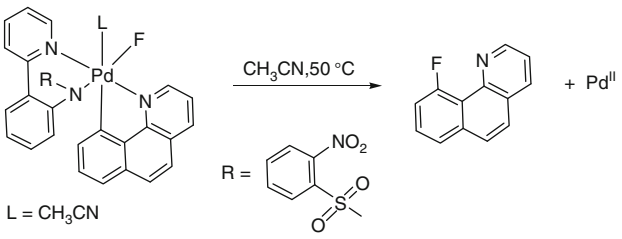


Scheme 22 Directly observed formation of an aryl-chloride bond from an isolated Pd(IV) complex

We recently reported an unexpectedly facile reductive elimination of aryl-iodides that takes place upon the reaction of Pd(II) aryl iodo complexes (P∼P)Pd(Ar)I with XeF_2 (Scheme 21) [54]. The reaction was very general in terms of the aryl ligand involved; even the pentafluorophenyl group readily eliminated from the metal coordination sphere to quantitatively give iodopentafluorobenzene and (P∼P)PdF_2. Interestingly, the reaction with *N*-fluoro-2,4,6-collidinium cation resulted in the mixture of Ar-I and Ar-F as organic products indicating the possibility of a single cationic Pd(IV) intermediate for both reductive elimination products (Fig. 1).

Whitfield and Sanford isolated di and monochloro Pd(IV) complexes of 2-phenylpyridine which upon heating in acetic acid gave substantial amounts of the chloroarene (Scheme 22) [55], although the fate of the transition metal remained unclear. More recently, Furuya and Ritter presented the first example of a reductive elimination of aryl fluoride from an isolated Pd(IV) center (Scheme 23) [56].

Although the C–X reductive elimination from Pd(IV) complexes has been established, it was recently suggested that Pd(III) dimers can also participate in the reductive elimination (Fig. 2) [57, 58]. Such, and relevant Pt(III) dimers, have been isolated and structurally characterized [59–63], however, it is not yet clear whether the mechanistic interpretation of the C–X elimination from these species should be treated differently from the established elimination from M(IV). As one



Scheme 23 Aryl-fluoride reductive elimination from an isolated Pd(IV) fluoro complex

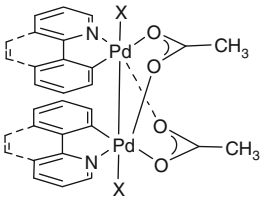
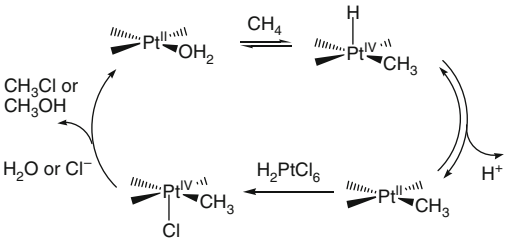


Fig. 2 Isolated Pd(III) dimer was shown to reductively elimination aryl-chloride. This and similar complexes were proposed to participate in the catalytic C–X bond formation catalyzed by $Pd(OAc)_2$

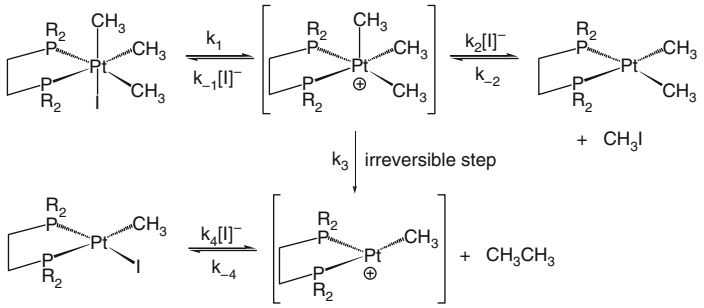


Scheme 24 Proposed catalytic cycle for the Shilov methane oxidation process. Under typical reaction conditions, chloromethane is formed parallel to methanol

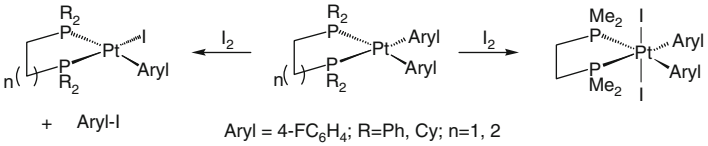
of the metal centers does not participate in the reductive elimination step, it can be viewed as a spectator ligand. It is also possible that the Pd(IV)–Pd(II) disproportionation takes place prior to the elimination step.

3.3 Platinum

CH_3–Halide bond formation is a side reaction in the Shilov methane oxidation process (Scheme 24) [64]. Mechanistic analysis of several catalytic steps by Bercaw and coworkers showed that the formation of the carbon–chlorine bond takes place in parallel to the formation of methanol, often being the major reaction pathway [65]. The reaction most likely involves a nucleophilic attack of the chloride-anion at the coordinated methyl group of the Pt(IV) intermediate [66]. Thus, the overall mechanism is closely related to the organic S_N2-type reaction. Further support for such a mechanism operating in Pt(IV) systems came from the Goldberg group which reported the competitive CH_3–I and CH_3–CH_3 reductive elimination reactions in platinum phosphine complexes (Scheme 25) [67, 68].



Scheme 25 Proposed mechanism of the kinetically controlled methyl iodide reductive elimination from Pt(IV). Due to the reversibility of the reductive elimination step, the thermodynamic products of CH_3–CH_3 coupling are eventually formed as the major species



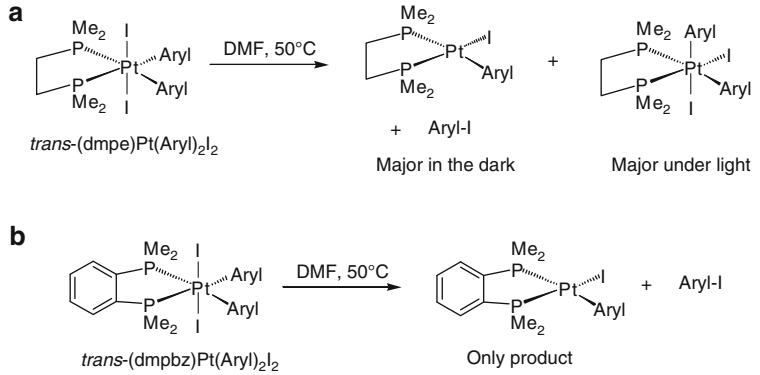
Scheme 26 Reactivity of Pt(II) diaryl complexes bearing chelating diphosphine ligands toward I_2

Goldberg et al. demonstrated that the reductive elimination of iodomethane is kinetically preferred over the much more common C–C reductive elimination in solution. As the resulting Pt(II) complex readily reacts with free CH_3–I to regenerate the starting material, the overall reaction eventually results in the products of the ethane reductive elimination.

$$\begin{aligned} &trans-(Et_3P_2)Pt(Ph)_2I_2 \overset{-I}{\underset{+I}{\rightleftharpoons}} trans-(Et_3P)_2Pt^{+}(Ph)_2I \\ &\rightarrow trans-(Et_3P)_2Pt(Ph)I + Ph\text{-}I \end{aligned} \quad (1)$$

The first example of Aryl-Halide reductive elimination from a Pt complex was reported by Ettorre in 1969 [69]. Following the reaction progress by UV-vis spectroscopy provided evidence for the iodide dissociation taking place prior to the reductive elimination step (1).

Our group recently showed that addition of I_2 to chelated Pt(II) diaryl complexes resulted in the formation of free iodoarene and Pt(II) aryl iodo complexes, with the exception of the small dmpe ligand system, where stable oxidative addition Pt(IV) complex *trans*-(dmpe)Pt$(Ar)_2I_2$ was isolated (Scheme 26) [70]. Heating this complex in polar solvents gave the mixture of products: the thermodynamically stable *cis*-isomer and Ar-I reductive elimination products (Scheme 27a) [71]. The isomerization reaction was light-assisted with the light triggering the diphosphine chelate



Scheme 27 Competitive aryl-iodide reductive elimination/isomerization reactions involving Pt(IV) diaryl diodo complexes: (**a**) The competition is light-dependent with dmpe as the ligand. (**b**) No isomerization takes place in the rigid dmpbz system suggesting that the diphosphine chelating opening is important for the isomerization reaction

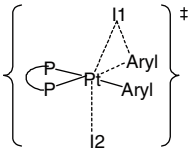
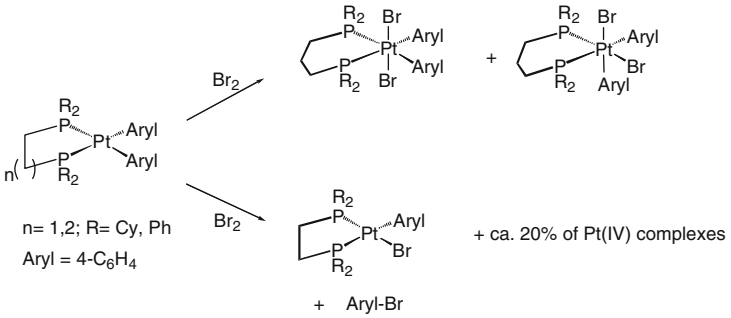


Fig. 3 Proposed transition state for the aryl-idiode reductive elimination from Pt(IV) complexes

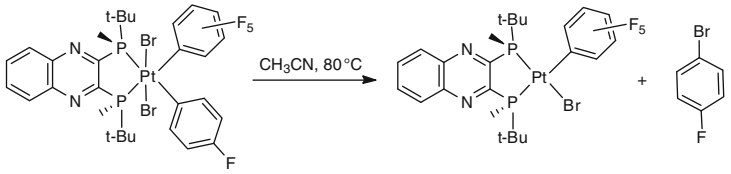
ring-opening. In the absence of light, the iodoarene reductive elimination reaction was the major one. Using a more rigid ligand dmpbz further hindered the ring-opening pathway leaving Ar-I reductive elimination the only observable reaction in DMF (Scheme 27b). The reaction proceeds via the concerted mechanism which was also confirmed by DFT calculations. There is a considerable cleavage of a Pt–I bond in the ion pair-like transition state (Fig. 3) [71]. Interestingly, the more stable *cis*-isomer of (dmpe)Pt(Ar)$_2$I$_2$, gave only C–C reductive elimination products upon prolonged heating at high temperatures.

We also reported that addition of Br_2 to chelated Pt(II) diaryl complexes gave product distribution dependent on the diphosphine bite angle. Use of larger chelates, dcpp or dppp, gave mainly Pt(IV) oxidative addition products, while smaller dppe or dcpe ligand systems gave mainly products of Ar-Br elimination, with very little of Pt(IV) products formed (Scheme 28) [70]. Heating these compounds at higher temperatures gave more of the Ar-Br, providing evidence for the first directly observed bromoarene reductive elimination from platinum.

More recently, we designed the system which can undergo selective Ar-Br elimination even when there is a possibility of C–C coupling. Using the quinoxaline-based ligand (Scheme 29) we were able to prepare a stable *trans* dibromo complex (P∼P)Pt(4-C_6H_4F)(C_6F_5)Br_2 which undergoes C–Br elimination upon heating in CH_3CN at 70ºC [72]. No C–C coupling was observed under these conditions.



Scheme 28 Chelate ring size-controlled oxidative addition – C–Br bond formation in bromination of Pt(II) diaryl complexes with Br_2



Scheme 29 Directly observed aryl-bromide formation from an isolated Pt(IV) complex

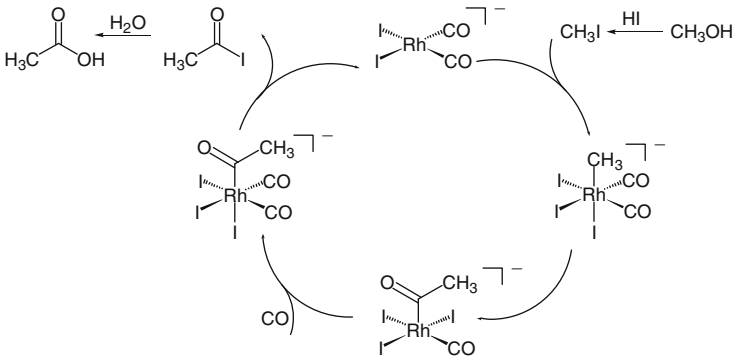
4 Carbon–Halogen Bond Formation with Group 9 Metals

4.1 Rhodium

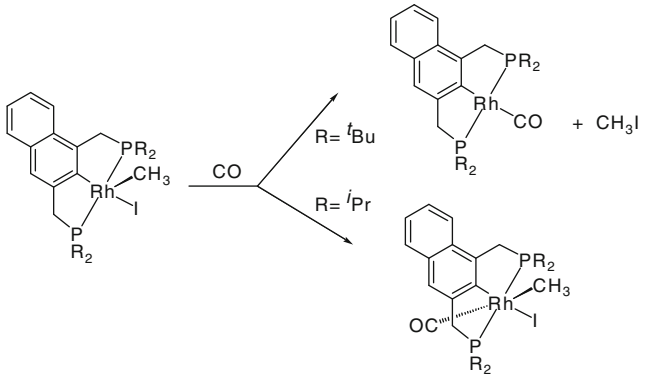
The proposed reductive elimination of acetyl iodide from the Rh(III) coordination sphere is an important step in the Monsanto methanol carbonylation process (2) [73]. In the proposed catalytic cycle (Scheme 30), the oxidative addition of iodomethane, formed from HI and methanol, is followed by the carbonyl insertion into the Rh–Me bond. The reductive elimination of acetyl iodide followed by its rapid hydrolysis furnishes the acetic acid and regenerates free HI.

$$CH_3OH + CO \xrightarrow{\text{Rh cat.}} CH_3COOH \qquad (2)$$

Recently, Milstein and coworkers reported an interesting CH_3–I reductive elimination chemistry from Rh(III) complexes (Scheme 31) [74]. The reactions, driven by steric bulk of the pincer ligands, represent the first example of the directly observed reductive elimination from metal complexes other than group 10. It was proposed that the reactions proceed via a concerted three-centered transition state rather than the S_N2-type back attack of the halide at the methyl group, as was proposed for the isoelectronic Pt(IV) complexes. To the best of our knowledge, no



Scheme 30 Proposed catalytic cycle for methanol carbonylation to acetic acid (Monsanto process). Acyl-iodide reductive elimination from a Rh(III) center is the key step toward the product formation



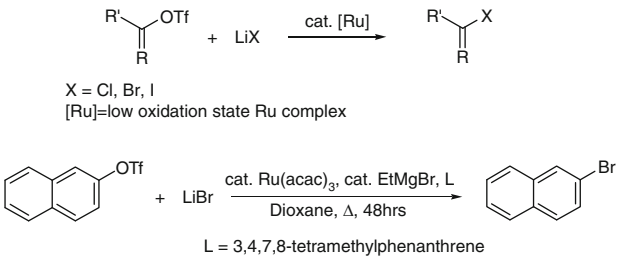
Scheme 31 Reductive elimination of methyl-iodide controlled by the steric bulk around the metal in Rh(III) complexes

confirmed examples of an aryl-halide bond formation assisted by group 9 metals have been reported.

5 Carbon–Halogen Bond Formation with Group 8 Metals

5.1 Ruthenium

There is a single recent report on the Ru-assisted formation of C(sp^2)–Halide bonds in vinylic substrates. Shirakawa et al. very recently reported that low valent Ru complexes are good catalysts for the triflate-for-halide exchange reaction for a great variety of alkenyl triflates (Scheme 32) [75]. The reaction was also successfully



Scheme 32 Ruthenium catalyzed nucleophilic halogenation of selected vinyl- and aryl-triflates

applied to the synthesis of 2-bromonaphthalene albeit under harsher conditions, although no exchange was observed with p-tolyl triflate as substrate.

6 Conclusions

The last several years saw a dramatic increase in interest in the metal-mediated formation of carbon–halogen bonds. Late transition metal complexes, which until recently were only considered as useful in breaking such bonds, are now recognized as playing an important role in making C–Halogen bonds, particularly the most challenging aryl-halide bonds. Naturally, nucleophilic substitution reactions received most of the attention; however, there were significant advances in the utilization of the electrophilic halogenation reagents in the synthesis of nonactivated aromatic halides. At present, the latter method still suffers from the necessity to use a directing group which significantly reduces its scope. Still, there were many instances when such a necessity was turned into a blessing. Both, the nucleophilic and electrophilic halogenation methods are likely to advance rapidly in the near future.

As expected from their relevance to the pharmaceutical and agrochemical industries, nonactivated aryl-fluorides received most of the attention, although other newly discovered aryl-halide bond forming reactions prepared the ground for the successful accomplishments in synthesis of fluoroaromatic compounds. In the middle of 2008, we published a Concept article [76] which concluded with: “Perhaps the most synthetically challenging, although also most rewarding, problem involving the C–Halide reductive elimination is the formation of carbon–fluorine bonds... Considering the recent awakening of the interest in the metal-assisted C–X bond formation, we are likely to see more of the interesting work in this area in the near future.” Within a year, two papers describing the formation of Aryl-F bonds from Pd(IV) and Pd(II) complexes appeared in the literature [37, 56]. Considering the timescale of a book publishing process, it is very likely that any prophecy regarding the near future now, in the middle of 2009, will become an accomplished fact by the time this Volume appears on the shelf. At present,

selective catalytic transformations using low cost late transition metals (Cu, Ni) leading to nonactivated aryl fluorides seems to be the next big challenge to address.

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Organometallic Approaches to Carbon–Sulfur Bond Formation

Paul Bichler and Jennifer A. Love

Abstract The transition metal mediated synthesis of carbon–sulfur (C–S) bonds is possible with a variety of simple and tailored metal complexes. This chapter serves to illustrate developments over the last decade involving the catalytic synthesis of C–S bonds with various transition metals, focusing on cross-coupling reactions and addition to π-bonds.

Keywords Carbon–sulfur · Cross-coupling · Catalysis · Bond activation

Contents

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Abbreviations

%	Mol %
Acac	Acetylacetonate
AcOH	Acetic acid
atm	Atmosphere
BINAM	1,1′-binaphthyl-2,2′-diamine
±BINAP	Racemic 2,2′-bis(diphenylphosphino)-1,1′-binapthyl
[bmim][OTf]	1-butyl-3-methylimidazolium triflate
Bn	Benzyl
Bu	Butyl
C–S	Carbon–sulfur
CH_3CN	Acetonitrile
cod	Cyclooctadiene
Conv.	Conversion
COX-2	Cyclooxygenase-2
CuI–bipy	Copper(I) iodide–bipyridine complex
CuMeSal	Copper(I) 3-methylsalicylate
Cy	Cyclohexyl
DIPEA	Diisopropylethyl amine
DCE	1,2-Dichloroethane
DIPPF	1,1′-Bis(diisopropylphosphino)ferrocene
DME	Dimethoxyethane
DMAD	Dimethylaceylene dicarboxylate
DMEDA	Dimethylethylenediamine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoixde
DPEphos	Oxydi-2,1-phenylene)bis(diphenylphosphine)
dppBz	1,2-Bis(diphenylphosphino)benzene
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
R-DTBM-Segphos	[(4R)-(4,4′-bi-1,3-benzodioxole)-5,5′-diyl]bis[bis (3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine]
ee	Enantiomeric excess
EtOH	Ethanol
HMPA	Hexamethylphosphoramide
Imes	1,3-bis(2,4,6-trimethylphenyl)-2,3-dihydro-1H-imidazaol-2-ylidene
i-PrOH	Isopropanol or 2-methylpropanol
Josiphos	(*R*)-1-[(S_P)-2-(Di-*tert*-butylphosphino)ferrocenyl]ethylbis (2-methylphenyl)phosphine
LiHMDS	Lithium bis(trimethylsilyl)amide
m-	*Meta* substitution
Me	Methyl
MLn	Transition metal complex
n-BuLi	*n*-Butyllithium
t-BuONa	Sodium *tert* butoxide

NHC	*N*-Heterocyclic carbine
o-	*Ortho* substitution
OAc	Acetate
OMs	Methanesulfonate
p-	*Para* substitution
P_2–Et	1-Ethyl-2,2,4,4,4-pentakis(dimethylamino)-2Λ^5-catenadi (phosphazene)
Pd_2dba_3	Tris(dibenzylideneacetone)dipalladium(0)
Ph	Phenyl
$PhCH_3$	Toluene
PhH	Benzene
PhCl	Chlorobenzene
$RhCl(PPh_3)_3$	Wilkinson's catalyst
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
t-Bu	*Tert*-butyl
t-BuOH	*Tert*-Butanol
t-BuOK	Potassium *tert* butoxide
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
Tp*	hydrotris(3,5-dimethylpyrazolyl)-borate
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

1 Introduction

A significant number of bioactive molecules contain sulfur, including β-lactam antibiotics (e.g., penicillins, cephalosporins), sulfonamide antibiotics, COX-2 inhibitors (e.g., Vioxx and Celebrex), the asthma drug Singulair and the antibiotic griseoviridin [1–5]. A wide variety of synthetic methods are needed to construct these molecules, given their apparent structural diversity. As such, the formation and further functionalization of C–S bonds have received considerable attention. Sulfides, thiols, and their oxidized derivatives are also widely utilized in a number of synthetic transformations, ranging from Diels–Alder cycloadditions [6, 7] to sigmatropic rearrangements [8], act as acyl anion equivalents [9] and are used in the synthesis of olefins [10].

The use of organometallic reagents for the catalytic formation of C–S bonds remains scarce compared to methods to form C–O and C–N bonds. Nevertheless, despite the oft-cited belief that sulfur poisons metal catalysts, methods for the construction of C–S bonds are becoming increasingly prevalent in the literature. Indeed, the use of metal catalysts, including copper, palladium, rhodium and gold, now represents a widely employed synthetic strategy for installation of C–S bonds. The functional group compatibility of these processes continues to increase [11–15], which has led to applications of metal-mediated C–S bond formation in complex molecule synthesis [16–18]. Despite these advances, there is continued pressure to develop more efficient and versatile methods.

This chapter is organized into two sections that highlight the main strategies to catalytic C–S bond formation: cross-coupling reactions and transformations across π-bonds. After a brief historical perspective, recent advances in these areas are covered. The reader is directed to a series of reviews that encompass aspects of these topics within the last decade [19–29].

2 Cross-Coupling Approaches to C–S Bonds

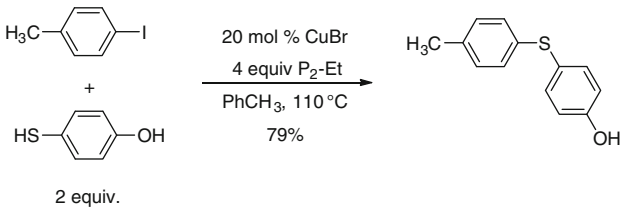
2.1 Cu-Catalyzed Cross-Coupling

2.1.1 Background

The Ullmann coupling [30] involves treatment of aryl halides with stoichiometric copper at high temperatures to yield biaryl compounds. Considerable effort has been made to lower the temperature necessary for initiation of the reaction, as well as decrease the required amount of copper salts. These advances served as the basis for extending this method for the synthesis of aryl heteroatom bonds, known as the Ullmann Condensation Reaction [22, 31, 32]. After several reports for C–O and C–N bond formation, methods for C–S bond formation began to emerge.

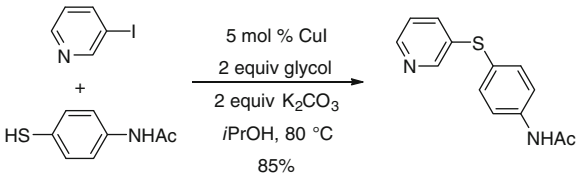
2.1.2 Ullmann Condensation Reaction

A major breakthrough in *S*-arylation was achieved by the discovery that phosphazene bases promote Cu-catalyzed Ullmann Condensation Reactions, by generation of highly reactive thiolates [29, 33]. A high degree of chemoselectivity was achieved using 4-mercaptophenol, indicative of the greater nucleophilicity of the thiol function (1). Despite this significant contribution, the major disadvantage of this method is the use of costly phosphazene base in excess (Eq. 1).



Equation 1 Chemoselectivity achieved with phosphazene bases [33]

Buchwald reported a more cost-effective, high-yielding method for aryl thioether formation, including substrates for which the Palomo conditions were ineffective (2). Notably, this process employs a relatively low loading of an air-stable catalyst (CuI) and K_2CO_3 as the base. The simplicity of the reported conditions, the high degree of chemoselectivity and the broad substrate scope render this process an attractive choice for C–S bond formation [35].



Equation 2 Cost-effective synthesis of arylthioethers [35]

These initial reports spurred considerable interest in Cu-catalyzed methods for *S*-arylation. Additional improvements continue to be made by modification of the reaction conditions, particularly the choice of ligand [36–54]. Typically, conditions found to be successful for *O*- and *N*-arylation were tested in *S*-arylation. A number of ligands have been successfully employed, including diamines, L-proline, β-keto esters, azaindolylmethanes and oxime phosphines, although the exact role of each of these ligands is not certain. For example, aliphatic and aromatic thiols were both effective using an oxime–phosphine ligand (**1**; Fig. 1), providing the corresponding thioethers in excellent yields [40]. The functional group diversity of the aryl iodide employed is similar to that reported by Buchwald, demonstrating the power of this ligand [35]. Pseudohalides, in particular tosylates, could be coupled using BINAM with a Cu(II) precatalyst, although the reaction is quite sensitive to electronic effects [50]. Lower catalyst loadings were achieved using bis(7-azaindolyl)methanes (**2**), which generate dinuclear complexes with bridging iodides and contained eight-membered chelate rings. The procedure is exceptionally high yielding and demonstrates the successful use of both sterically encumbered aryl iodides and aliphatic thiols, demonstrating a powerful method for *S*-arylation [53]. Improved mechanistic understanding is expected to permit predictions of which ligands would perform the best with a given substrate.

Ligand free methods have also been reported [55–58]. Likely, the function of each ligand is in solubilizing the copper precatalyst and preventing aggregation of any active copper species in solution [59]. Arylation can be promoted by the use of microwave or additives, including nanoparticles [60–65].

Ma recently demonstrated that 2-haloanilides can undergo coupling with metal sulfides; subsequent intramolecular condensation affords substituted benzothiazoles (3). Thioamides and thioureas also serve as precursors to benzothiazoles (vide infra). In addition to *S*-arylation reactions, alkenyl halides are also effective

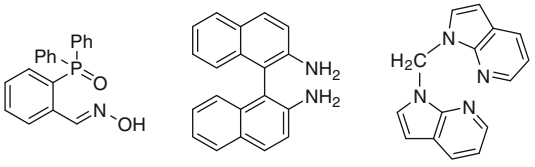
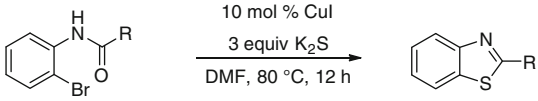


Fig. 1 Uncommon ligand classes for Ullmann Couplings [40, 50, 53]

electrophiles in Cu-catalyzed C–S bond formation, although there are considerably fewer reports for *S*-vinylation than for *S*-arylation [37, 51, 66–70].

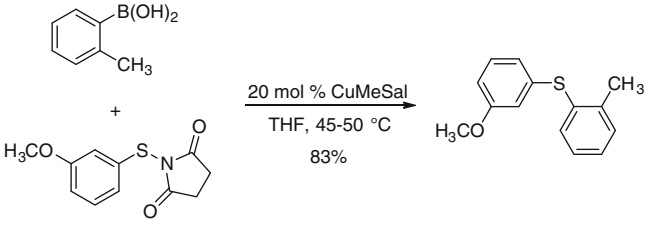
Equation 3 Synthesis of benzothiazoles with thioamide nucleophiles [70]



2.1.3 Chan–Evans–Lam-type Reactions

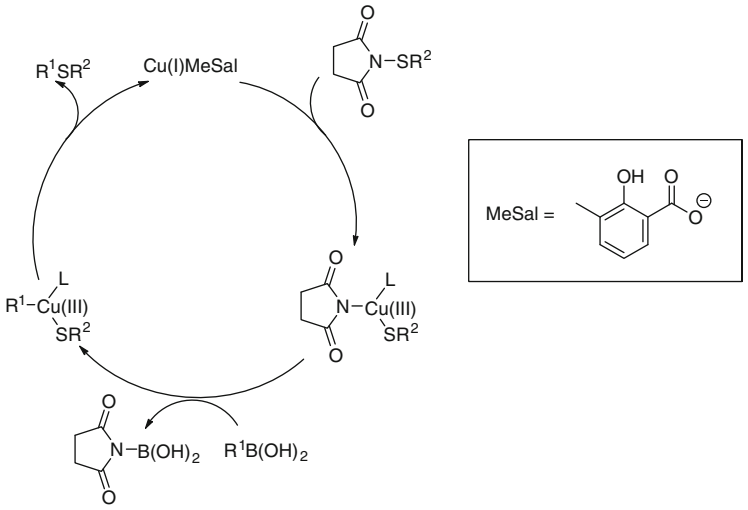
In 2000, Guy reported the stoichiometric coupling of alkane thiols and arylboronic acids, which was initially thought to be mediated by Cu(II) [71]. Liebeskind proposed that the reaction was more likely catalyzed by Cu(I), generated by oxidation of the alkane thiols into dialkyl disulfides. Based on this hypothesis, Liebeskind predicted that disulfides and disulfide equivalents should be effective reagents for thioether formation [34]. This process would constitute a modification of the Chan–Evans–Lam, which involves the coupling of arylboronic acids and amines or alcohols in the presence of tertiary amine bases, generating aryl amines and ethers, respectively. Indeed, the coupling of diphenyl disulfide with phenyl boronic acid would yield diphenyl sulfide.

Further study revealed thioimides to be effective nucleophiles in CuMeSal-catalyzed aryl, alkylaryl, and vinylarylthioether formation without the need for base (4) (MeSal = 3-methylsalicylate). Although the yields were lower than with other methods, the low temperature at which the reaction proceeds is particularly notable.



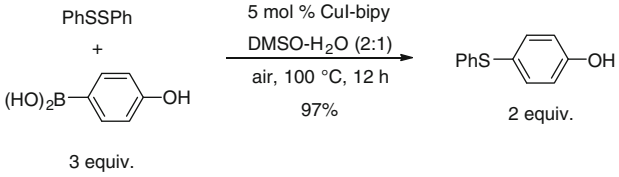
Equation 4 Thioimide nucleophiles in the Chan–Evans–Lam cross coupling [34]

The mechanism was postulated to involve a Cu(I)-carboxylate as the active species, which promotes oxidative addition of the thioimide. Subsequent transmetalation and C–S reductive elimination generates the thioether product. An excess of boronic acid is often required, as copper catalysts may competitively oxidize aryl substituted boronic acids to the corresponding phenol in the presence of adventitious water [21]. The rate of acceleration observed with amino acids and carboxylate-based ligands, such as 3-methylsalicylate, is attributed to stabilization of a π-Cu intermediate generated through a nucleophilic aromatic substitution type mechanism (Scheme 1) [72]. The amino acid or carboxylate ligand may also simply stabilize putative Cu(III) intermediates.



Scheme 1 Possible catalytic cycle for Cu-catalyzed *S*-arylation of arylboronic acids [34]

Catalytic cross-coupling of organoboronic acids with diaryldisulfides was subsequently demonstrated, using air as the terminal oxidant (5) [51, 73, 74]. The reaction is remarkably functional group tolerant, providing convenient access to a broad range of unsymmetrical diaryl- and arylalkylsulfides. Disulfides also can be coupled with arylsiloxane reagents under solvent free conditions [52].



Equation 5 Utilization of disulfides in the Chan–Evans–Lam cross coupling [74]

Inamoto and Doi reported that thiolenols can be coupled with arenes by C–H functionalization. The reaction is presumed to involve the intermediacy of disulfides, consistent with Liebeskind's proposal.

2.2 Group 10 Metal-Catalyzed Cross-Coupling with Thiols

2.2.1 Pd

Pd-catalyzed cross-coupling is one of the most widely used strategies for C–C and C–X bond formation [75, 76]. While not as widely studied as C–O or C–N bond formation, Pd-catalyzed methods to generate C–S bonds have also been achieved.

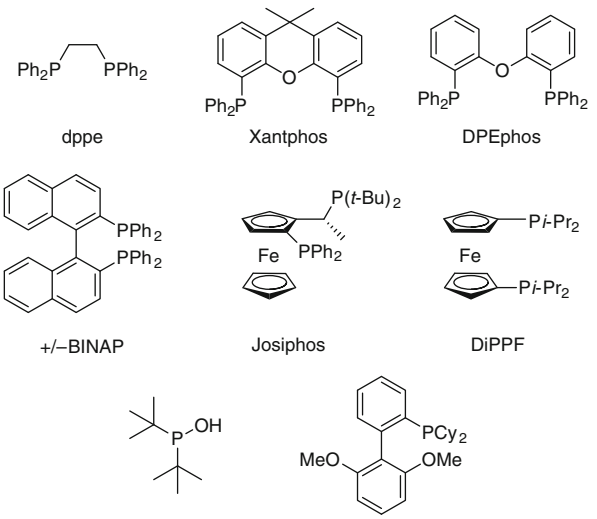
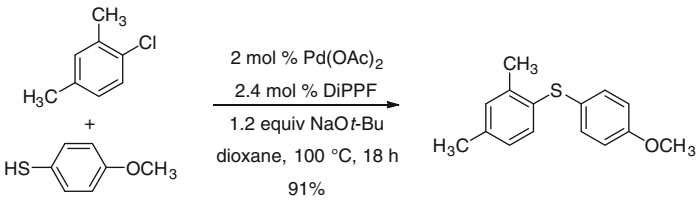


Fig. 2 Mono and bidentate phosphines for Pd catalyzed *S*-arylation

Since the initial report from Migita [77, 78] Pd-catalyzed cross-coupling to generate aryl and alkyl sulfides has been studied extensively [14, 15, 17, 18, 28, 77–111]. The large majority of this work is dedicated to developing synthetically useful protocols for the coupling of various thiols with an appropriate vinyl or aryl electrophile.

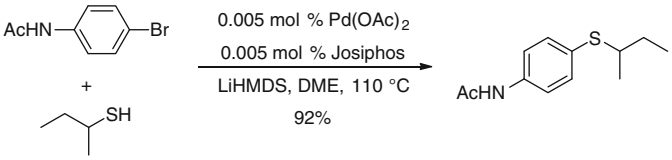
Not surprisingly, the use of bisphosphine ligands is common amongst successful methods for the synthesis of arylthioethers and alkylarylthioethers. Nevertheless, bulky monodentate phosphine ligands are successful in promoting *S*-arylation under relatively mild conditions, but typically require longer reaction times, or higher catalyst loading. The most frequently used bisphosphines and monophosphines are listed above (Fig. 2).

A notable advance over early methods was reported by Buchwald in 2004 [112]. Aryl bromides and chlorides reacted efficiently with thiols using $Pd(OAc)_2$ as the catalyst using DiPPF [1,1′-bis(diisopropyl-phosphino)ferrocene] as the optimal ligand (6).



Equation 6 $Pd(OAc)_2$/DiPPF mediated cross coupling of aryl thiols with aryl chlorides [112]

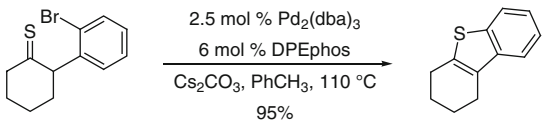
The next major breakthrough came from Hartwig, who discovered that the use of Josiphos as the ligand affords an exceptionally active catalyst, with loadings as low as parts per million (7) [14, 15]. This system had broad scope and functional group compatibility. Moreover, the methodology is suitable for hindered aliphatic thiols, which are typically difficult substrates for *S*-arylation [40]. Furthermore, the process reported demonstrates the first successful use of a tosylate as the electrophilic, albeit with more limited substrate scope. The use of more reactive aryl iodides and bromides led to the realization of reactivity even at room temperature, which remains a considerable challenge. This remarkable reactivity simply required an increase of the ligand and palladium loading to 0.5 mol% or longer reaction times [14, 15].



Equation 7 $Pd(OAc)_2$/Josiphos mediated thioetherification [14, 15]

The Josiphos ligand was selected based on detailed mechanistic investigations of reductive elimination from Pd-thiolate species [83, 85, 86, 106, 111]. Two factors were identified as crucial for the observed reactivity: the strong electron releasing nature of this bisphosphine ligand and the suppression of formation of less-reactive bridging thiolate complexes due to the steric demands of the ligand.

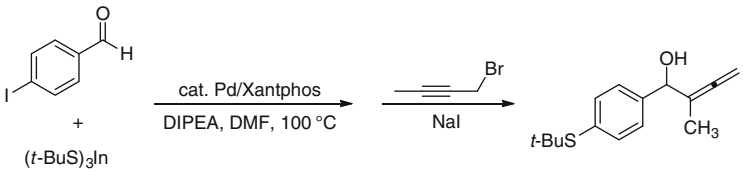
The general reaction mechanism has been shown to involve typical steps for cross-coupling [98, 113]. Oxidative addition of an aryl halide generates a Pd(II) species that undergoes transmetalation to form a Pd(II)-thiolate. C–S reductive elimination provides the aryl sulfide and regenerates the Pd(0) catalyst. More recently, Hartwig reported a detailed mechanistic analysis of the Pd/Josiphos system derived from different Pd precursors. The dominant Pd species were found to be off the catalytic cycle, which accounted for differences in rates between stoichiometric and catalytic reactions [114]. Thioketones are also effective thiolate nucleophiles for C–S bond formation. The reaction involves tandem Pd-catalyzed thioenolate alkylation, followed by *S*-arylation (8) [102]. Presumably, the arylation process proceeds by a similar mechanism to related Pd-catalyzed transformations.



Equation 8 Palladium mediated thioenolate cross coupling [102]

Progress in this area is anticipated to continue. Lee reported that indium tri (organothiolates) can be used in conjunction with Pd catalysts for C–S bond

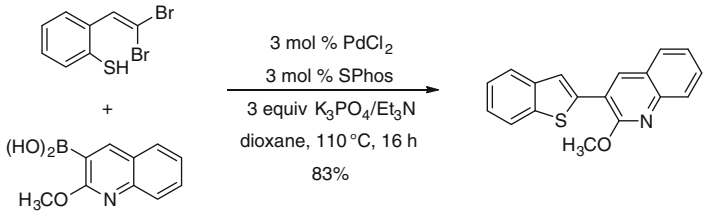
formation [107, 109, 115, 116]. In addition to the ability to couple aryl and vinyl halides, aryl and vinyl triflates were also effective coupling partners. Moreover, the procedure is amenable to sequential C–S bond formation/In-mediated addition reaction (9).



Equation 9 Sequential C–S, C–C bond formation using indium tri(organothiolates)

Stambuli found that addition of a substoichiometric amount of zinc chloride permits the use of Pd-phosphine catalysts that are typically inactive for cross-coupling of aryl bromides. This system has excellent functional group tolerance, high yields and can even be used for vinyl bromide cross-coupling.

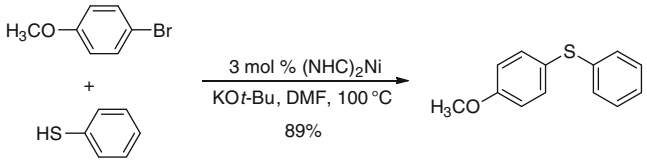
Lautens recently reported a novel strategy for benzothiophene synthesis, employing intramolecular Pd-catalyzed vinylation of thiols. Concomitant C–S and C–C bond formation can be achieved in the presence of organoboronic acids (10) [116].



Equation 10 $PdCl_2$/SPhos mediated tandem cross couplings [116]

2.2.2 Reactions with Ni

Ni catalysts have also found use in C–S bond forming reactions [117–126]. A variety of ligands are effective, including bipyridines, pincer ligands, and *N*-heterocyclic carbenes. For example, Zhang and Ying reported that aryl bromides undergo efficient cross-coupling with thiols in the presence of a bis-*N*-heterocyclic carbene Ni species (11) [124].

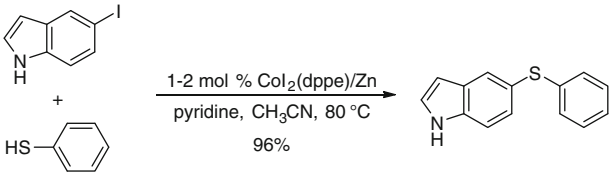


Equation 11 Nickel catalyzed arylthioetherification [124]

2.3 Group 9 Metal-Catalyzed Cross-Coupling with Thiols

2.3.1 Co-Catalyzed Cross-Coupling of Thiols with Aryl Halides

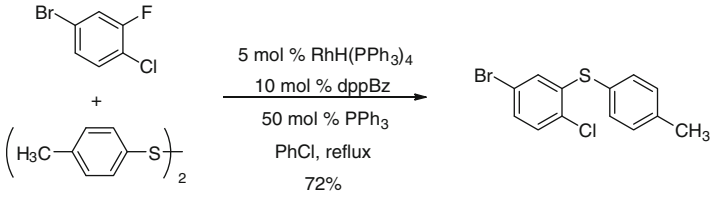
An example of Co-catalyzed coupling of thiols with aryl bromides and iodides recently emerged [127]. CoI_2(dppe) was identified as the optimal catalyst and can be used at relatively low loadings (12). This process has excellent scope, with alkane thiols reacting in high yields.



Equation 12 Cobalt/zinc catalyzed arylthioether formation [127]

2.3.2 Rh-Catalyzed Cross-Coupling of Thiols with Aryl Halides

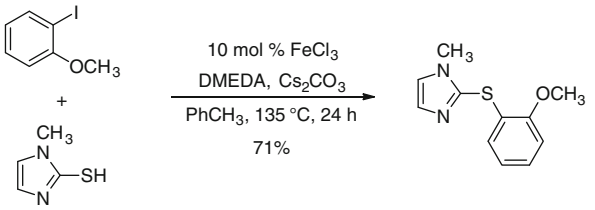
The first examples of Rh-catalyzed C–S bond formation were reported by Yamaguchi in 2008 [128]. The process involves the coupling of disulfides with aryl fluorides, which remain atypical electrophiles for cross-coupling. These conditions afford excellent selectivity for C–F bond cleavage over other C–X bonds (13) (dppBz = 1,2-bisdiphenylphosphinobenzene). A potential advantage of this process is that the use of disulfides precludes the need for strong base. Catalyst loadings as low as 0.25 mol% could be used.



Equation 13 Rhodium catalyzed disulfide, aryl fluoride cross coupling [128]

2.4 Group 8 Metal-Catalyzed Cross-Coupling with Thiols

Bolm reported that $FeCl_3$ is effective for *S*-arylation reactions [13]. A variety of thiols, including functionalized ones, react efficiently with aryl iodides (14) (DMEDA = *N*, *N*′-dimethylethylenediamine). Alkane thiols do not react under these conditions.



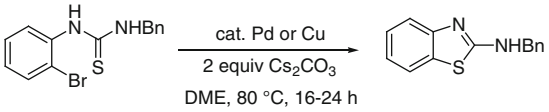
Equation 14 $FeCl_3$ mediated arylthioetherification [13]

2.5 *Cross-Coupling with Nonthiolate Nucleophiles*

2.5.1 Thioureas and Thioamides

Thioureas and thioamides have also been useful nucleophiles in intramolecular metal-catalyzed cross-couplings to generate benzathiazoles, which display a broad range of bioactivity [129, 130]. Initial studies focused on Pd and Cu catalysts [43, 131–133]. With aryl bromides, CuI was found to provide higher yields, although comparable results could be obtained with $Pd(PPh_3)_4$ when more activated aryl iodides were employed (Scheme 2). A one-pot method to generate aminobenzothiazoles directly from the corresponding isothiocyanate was also reported.

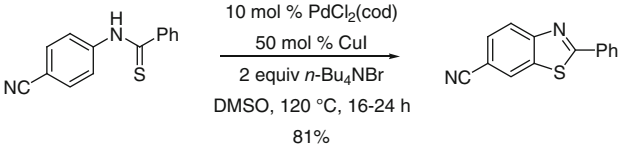
Subsequent studies revealed that the pre-activation of the arene was not required when an oxidant was present (15) [134, 135]. While the mechanism has yet to be fully investigated, preliminary studies have ruled out both radical and electrophilic palladation pathways.



5 mol % $Pd(PPh_3)_4$ 95%

5 mol % CuI, 10 mol% 1,0-phenanthroline quant.

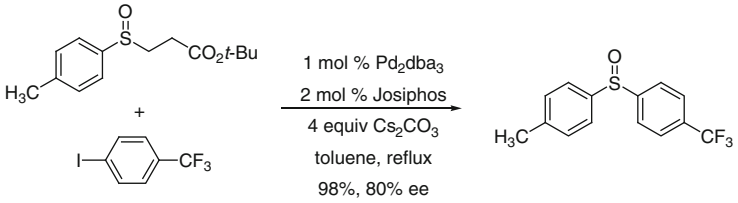
Scheme 2 Thioamides as nucleophiles for C–S bond formation [43]



Equation 15 Thioamides as nucleophiles for C–S bond formation [134]

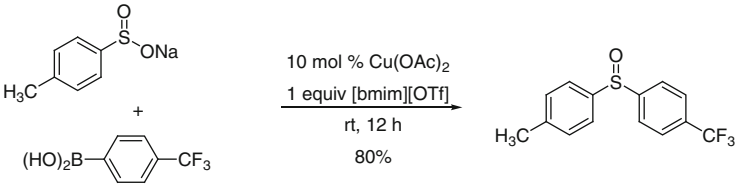
2.5.2 Sulfenates and Sulfinates

Madec and Poli recently reported that sulfenate anions can also be used as nucleophiles in catalytic formation of C_{aryl}–S bonds, generating sulfoxides [103]. The sulfenate anions are generated *in situ* by base-induced elimination of β-sulfinylesters [136]. These groups subsequently developed an enantioselective variant, allowing the asymmetric synthesis of sulfoxides with up to 83% ee (16) [105]. Chiral sulfoxides are present in a variety of pharmaceuticals and are widely used in asymmetric catalysis [137–141]. Likewise, Madec and Poli found that sulfenate anions can be used to generate $C_{sp}{}^3$–S bonds in Pd-catalyzed allylic alkylation [142].



Equation 16 Cross-coupling of sulfinyl esters and iodoarenes with Pd(0) [105]

Sulfinate anions have been used as nucleophiles in palladium-catalyzed allylic alkylation [143]. More recently, both Cu- and Pd-catalyzed couplings of sulfinate anions with aryl halides have also been reported as a means to generate unsymmetrical diaryl sulfones, which are common motifs in bioactive molecules [38, 93, 144–148]. Similarly, Cu-catalyzed coupling of arylboronic acids with sulfinate anions has been reported [95, 149, 150]. Notably, Kantam and co-workers found that the use of ionic liquids permits $Cu(OAc)_2$-catalyzed sulfone synthesis at ambient temperature and with convenient product separation and catalyst recyclability (17) [150].



Equation 17 Ionic liquids as solvents for sulfinate ion cross-couplings [150]

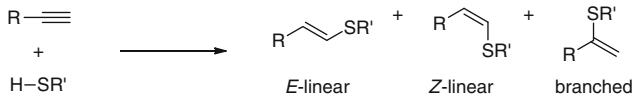
3 Reactions of Sulfur-Containing Reagents Across π-Bonds

3.1 Reactions with Alkynes

3.1.1 Hydrothiolation

The direct installation of an S–H bond across the π-system of an alkyne represents an atom economical approach to the synthesis of vinyl sulfides. This method typically avoids the need for excess base or ligand that is common to cross-coupling

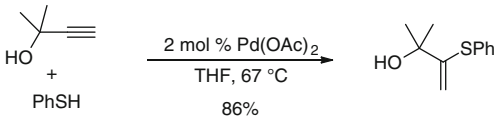
strategies. The activation of the weak S–E bonds (E = S, Se, etc) can also be achieved and leads to the formation of olefins that possess both components of the organochalcogen reagent. A common challenge in developing a successful method for the hydrothiolation of alkynes is controlling the regioselectivity of the reaction (18). In addition, aliphatic thiols frequently display lower reactivity than aryl thiols, paralleling the strength (both hetero- and homolytic) of the S–H bond. The use of aliphatic alkynes poses a separate problem, where metal catalyzed isomerization of the incipient olefin can occur, thus eroding any observed selectivity.



Equation 18 Regioselectivity in the hydrothiolation of alkynes

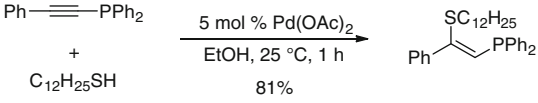
These inherent difficulties have elicited considerable attention, which has led to the emergence of synthetically viable protocols. The first catalytic alkyne hydrothiolation was reported by Ogawa in 1992 [151]. A number of late transition metal salts were found to be effective. In particular, $Pd(OAc)_2$ demonstrated excellent selectivity for the branched olefin. High yields were obtained even with sterically demanding substrates and potentially reactive functional groups (19).

Equation 19 Observed regioselectivity in the Pd $(OAc)_2$ catalyzed alkyne hydrothiolation [151]

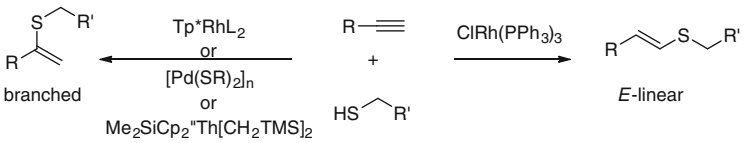


Since this initial report, significant advances have been made with Ni [121, 152–159], Pd [160–189], Pt [187, 190–201], Rh [202–212] and Ir [204, 211]. In general, group 10 metals generate the branched isomer and proceed by *syn*-insertion of the alkyne into an M–S bond, followed by protonolysis of the resulting M–C bond, although this is dependent on the reaction conditions. For example, under photolytic conditions, certain Pt complexes react through a *trans*-insertion mechanism [192, 200]. Likewise, Pd-catalyzed reactions of thiols with 1-alkynylphosphines proceeds by *anti*-hydrothiolation (20) [213].

Equation 20 Anti-addition of thiols to 1-alkynylphosphines [213]

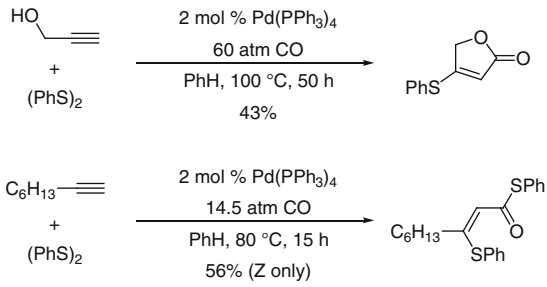


In comparison, group 9 metals can generate either the linear or the branched isomer, depending on the nature of the ancillary ligands and are thought to proceed by oxidative addition/*syn*-insertion/reductive elimination. Reactions of alkane thiols were achieved for the first time with Rh and later with Pd and actinides. Depending on the metal and ligand choice, either the branched or linear product can



Scheme 3 Regioselectivity achieved with various transition metals [151, 206, 209, 214]

Scheme 4 Complexity generated through hydrothiolation carbonylation cascades [160, 165]



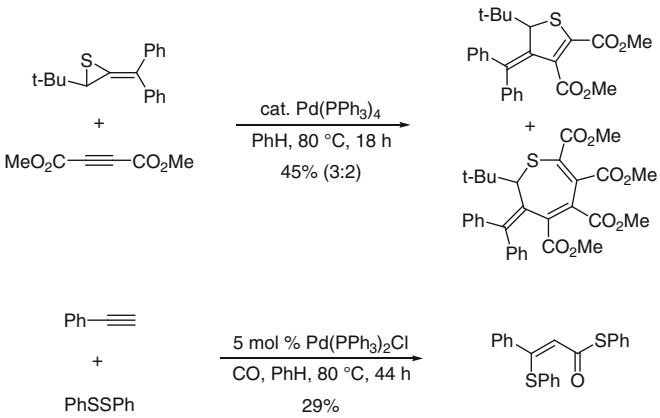
be generated with high selectivity (Scheme 3). Overall, these studies have provided convenient strategies for the synthesis of a broad range of vinyl sulfides [151, 172, 206, 207, 209, 214].

In some cases, alkyne hydrothiolation can be achieved in the absence of transition metal catalysts. Examples include the use of indium halides, selenium halides and salts, bases and β-cyclodextrin [215–226]. In particular, Cesium bases yield exclusively the anti-Markovnikov product and frequently give high regioselectivity for the *Z*-linear olefin, which is complementary to transition metal catalysis. While these approaches as yet lack the generality of the transition metal-catalyzed systems, the ability to achieve hydrothiolation without the need for a metal catalyst is attractive. Undoubtedly, this area of research will continue to yield promising results.

Interception of reactive intermediates provides access to an even broader range of products. For example, insertion of CO leads to conjugated lactones and thioesters (Scheme 4). A wide variety of sulfur derivatives can be used in these processes producing an array of interesting synthetic intermediates. These organosulfur compounds can be: free thiol [164, 167–170, 175, 190, 193, 197, 202, 204], disulfide [160, 165, 183, 207], thiocyanate [179, 182, 186], thioborate [161], thiostannane [196], sulfenamide [180], and thioester [187, 189, 191, 194, 195]. Palladium catalyzed thiocarbonylation, and the development of multicomponent reactions centering on hydrothiolation with free thiols and disulfides has been reviewed extensively [19, 20, 23–26, 167, 227–231].

3.1.2 Carbothiolation

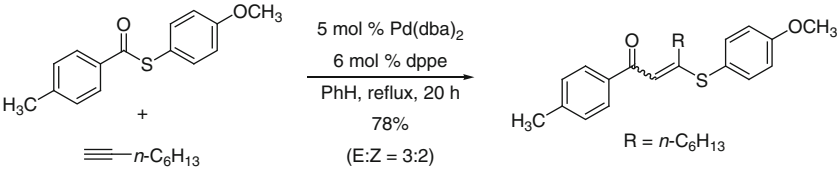
Carbothiolation affords an opportunity to install C–C and C–S bonds in a single reaction, thereby rapidly generating molecular complexity. This process is



Scheme 5 First examples of carbothiolation [160, 232]

analogous to hydrothiolation and is thought to involve transition metal-mediated activation of a C–S bond with subsequent addition to an appropriate alkyne. This process has been recently reviewed [23]. The first report of a carbothiolation involved the insertion of a vinylepisulfide with DMAD, which proceeded with a catalytic amount of $Pd(PPh_3)_4$ (Scheme 5) [232]. Similarly, Ogawa independently reported the carbonylative chalcogenation of an alkyne [160].

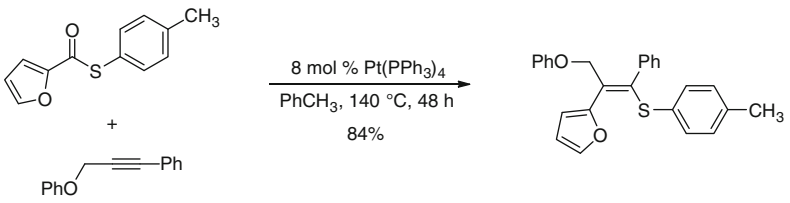
This interesting transformation likely inspired the use of thioesters, which effectively generates an organometallic species analogous to the carbonylative chalogenation (21). The use of thioesters represents the modern approach to carbothiolation. The reactivity of thioesters is similar to acid anhydrides, where the C–S bond can easily be activated by an appropriate low-valent transition metal [187, 233, 234]. Moreover, this approach circumvents the need for high pressures of carbon monoxide and is typically high yielding for the analogous carbonylated products. Thus, the use of thioesters represents a considerable advance in carbothiolation. Similar is the case with disulfides, vinylsulfides, thiocyanates, and allylic sulfides in carbothiolation type processes [157, 158, 179, 235].



Equation 21 Use of thioesters as replacement for CO in Pd catalyzed carbothiolation [233]

A Pt(0) complex was shown to catalyze decarbonylative arylthiolation of alkynes using thioesters (22). The reaction proceeds in good-to-excellent yields and with high selectivity. In comparison, the use of a Pd(0) catalyst resulted in

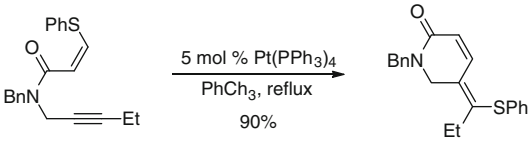
retention of the carbonyl group (23) [233].



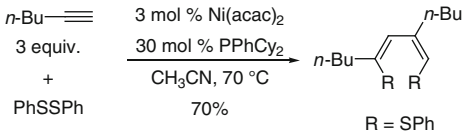
Equation 22 Use of thioesters in the analogous decarbonylative arylthiolation reaction [233]

The products of standard hydrothiolation processes are capable of further undergoing subsequent transformations, such as Pt-catalyzed Heck reactions with appropriately tethered alkyne acceptors (23) [235]. Furthermore, Beletskaya demonstrated that following the organometallic intermediates formed in addition of disulfides to terminal alkynes may be intercepted; these were found to undergo further carbon–carbon bond formation in the presence of a suitable ligand and excess alkyne (24) [158].

Equation 23 Use of vinylsulfides in carbothiolation processes [235]



Equation 24 Use of disulfides in carbothiolation processes [158]



3.2 *Reactions with Allenes*

A number of similar transformations of allenes have been reported. As with alkyne hydrothiolation, the key to the utility of this process is the ability to control regio- and stereoselectivity. A few key recent discoveries are highlighted below. For related reactions, see the following references [165, 168, 197, 236–243].

Ogawa reported in 1996 the Pd(II)-catalyzed regioselective addition of thiols to allenes [163]; Yamamoto subsequently discovered that tosylhydrazines can serve as a source of sulfur [244]. At the time, $Pd(PPh_3)_4$ was found to be less effective than $Pd(OAc)_2$, by generating a mixture of regioisomers. However, because $Pd(PPh_3)_4$ is typically useful for related additions of heteroatoms to allenes, Ogawa explored the use of this catalyst in greater detail. Through solvent optimization, it was determined that the use of acetonitrile rendered the reaction regioselective (25) [245]. It is noteworthy that a regioisomeric product is obtained when $Pt(PPh_3)_4$ is used (Fig. 3) [245].

Equation 25 Optimized regioselectivity for allene hydrothiolation [245]

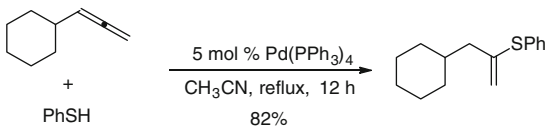
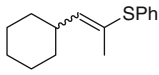
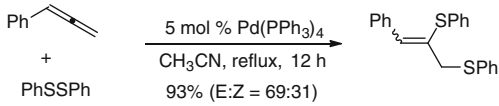


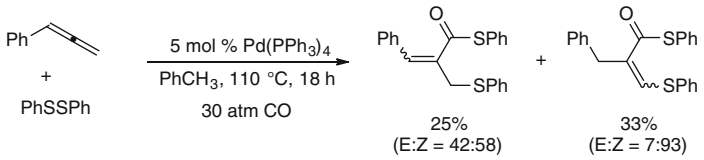
Fig. 3 Regioisomeric product formed with $Pt(PPh_3)_4$ in place of $Pd(PPh_3)_4$ [245]



Monothiolation can be achieved with disulfides using $RhH(PPh_3)_4$ as the catalyst [246]. Likewise, monothiolation is obtained when disulfides are used with $Pd(PPh_3)_4$ when H_2O is present [245]. This process is thought to involve H_2O and PPh_3-mediated reduction of the disulfide to the corresponding thiol. In support of this hypothesis, dithiolation is obtained in the absence of H_2O (26) [183]. In the presence of CO, thiocarbonylation occurs (27) [183]. Further advances are expected to improve the selectivity of this process. In addition, this discovery opens the possibility of using reagents other than CO in multi-component transformations.

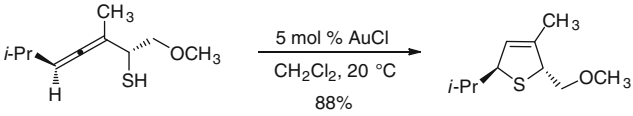
Equation 26 Dithiolation of allenes with $Pd(PPh_3)_4$ in the absence of water [183]





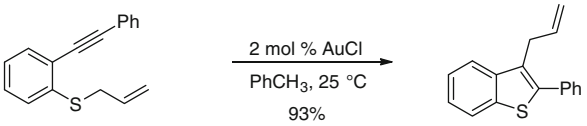
Equation 27 $Pd(PPh_3)_4$ allene hydrothiolation carbonylation sequence [183]

In 2006, Krause and Nakamura independently reported the first examples of Au-catalyzed transformations of sulfur-containing reagents [11, 247]. These reports are particularly notable, as they dispel the myth of sulfur–gold incompatibility. Krause's approach involves intramolecular cyclization of a thiol onto an allene (28). Au(I) salts were found to be superior to Au(III), with AuCl being the optimal choice with respect to yield and cost. Both Cu and Ag salts were ineffective. The reactions proceed in high yield and are thought to be catalyzed by a Au(I) species, although mechanistic studies are just underway.



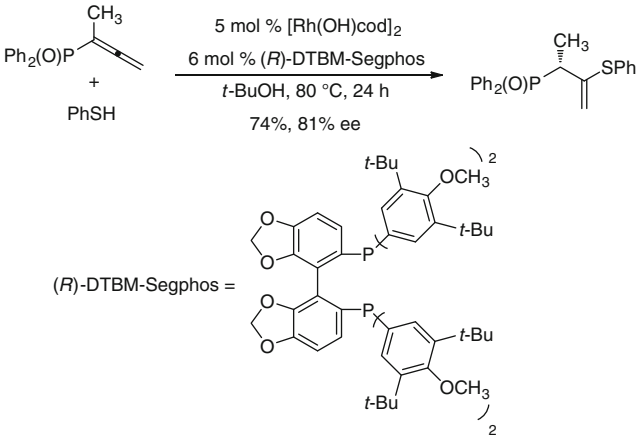
Equation 28 Au(I) mediated intramolecular allene hydrothiolation [11]

Nakamura's discovery of Au-catalyzed C–S bond formation is not thought to involve an allene moiety, but is grouped in this section for continuity. An example is given in (29). In this case, Au(III) and Pt(II) were also found to be effective catalysts. It is notable that this process represents both catalytic C–S bond cleavage and formation. Further applications of this reaction are anticipated.



Equation 29 Au(I) catalyzed C–S bond cleavage and subsequent rearrangement [247]

Very recently, the asymmetric hydrosulfenylation of diphenylphosphinylallenes were reported [248]. Although only two examples were reported, both reactions proceeded in high yield and with good enantioselectivity, demonstrating the feasibility of this transformation (30). Undoubtedly, further advances based on this exciting result are on the horizon.



Equation 30 Intermolecular hydrothiolation of diphenylphosphinylallenes [248]

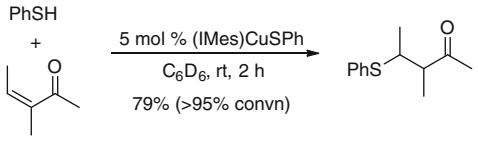
3.3 *Reactions with Alkenes*

Thiols can be added to alkenes under radical, acidic and basic conditions, as well as by use of main group metal catalysts. In particular, Dunach demonstrated high yields of inter- and intramolecular In(III)-catalyzed hydrothiolation [249]. Both aliphatic and aromatic thiols react efficiently, as do sterically hindered olefins. Functional group compatibility remains to be demonstrated. In addition, these approaches lack selectivity, functional group compatibility and generality.

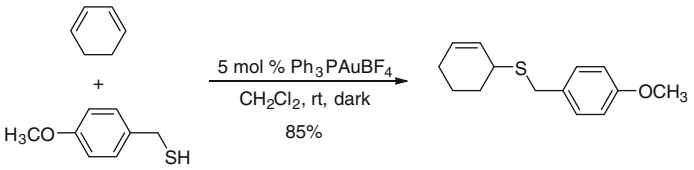
Transition metal catalysis has the potential to alleviate these shortcomings. Nevertheless, while catalytic alkene hydrothiolation has been achieved, the number of reports is still limited [250–254].

Gunnoe recently demonstrated the addition of thiols to electron-deficient alkenes using well-defined Cu–NHC thiolate complexes (31) [255, 256]. The preliminary scope is broad, with a number of potentially reactive electron-withdrawing groups being well-tolerated. Both alkane thiols and arene thiols are effective. In addition, sterically hindered olefins also react efficiently.

Equation 31 Thiolation of electron-deficient alkenes with Cu–NHC thiolate complexes [255]

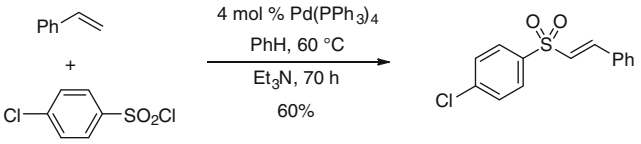


Building from Krause's study with allenes,it was discovered that Au(I) catalysts can effect intermolecular hydrothiolation of unactivated olefins (32) [12]. 2-Mercaptoethanol reacts exclusively with sulfur, demonstrating chemoselectivity and functional group compatibility. As with the other systems, both aliphatic and aromatic thiols work well.



Equation 32 Hydrothiolation of unactivated alkenes with Au(I) catalysts [12]

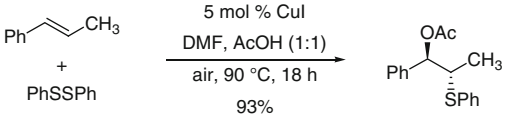
The Pd-catalyzed transformation of sulfonyl chlorides and styrenes typically involves desulfitive Mizoroki-Heck type coupling. At lower temperature, Vogel discovered that the putative Pd–SO_2Ar intermediate, which would arise from cleavage of the S–Cl bond, does not undergo elimination of SO_2 [257]. Insertion of an olefin into the presumed Pd–S bond would generate, after β-hydride elimination, the vinyl sulfone (33). Importantly, unlike a previous study using Ru, this alkene sulfonylation is not radical-induced [258].



Equation 33 Pd mediated vinyl sulfone formation from styrenes [257]

Taniguchi reported the regio- and stereoselective 1,2-hydroxysulfenylation of alkenes catalyzed by Cu(I), using disulfides and acetic acid (34) [259]. The Cu species is thought to generate RS^+, which then reacts with an olefin to form an episulfonium intermediate. Ring opening yields the product.

Equation 34 CuI catalyzed hydroxylsulfenylation of alkenes [259]



4 Summary and Conclusion

Despite the belief that sulfur reagents poison transition metal catalysts, myriad examples of transition metal-catalyzed C–S bond formation have been reported. This review has hopefully captured recent advances in the most widely used strategies for catalytic C–S bond formation. In particular, cross-coupling methods are highly effective for generating C–S bonds, with a broad range of functional groups being tolerated. The use of commercially available precatalysts and ligands allow for procedural simplicity. A need still exists to develop more efficient systems that operate at lower temperatures. Insertions into π-bonds are also a highly effective method for generating C–S bonds in a catalytic fashion. In both areas, multi-component reactions and tandem processes are beginning to emerge. These developments are particularly exciting, by generating densely functionalized molecules. The main limitation of catalytic C–S bond formation seems to be that mechanistic studies are relatively scarce. Increased efforts in this area are expected to yield considerable insight that will facilitate future reaction design.

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Recent Advances in Metal-Catalyzed C–P Bond Formation

David S. Glueck

Abstract This chapter describes recent advances in metal-catalyzed C–P bond formation, which may be classified into two types of reactions. In hydrophosphination and related processes, P–H groups add across unsaturated C–X (X = C, N, O) bonds. Phosphination of electrophiles typically results in substitution at sp^2 or sp^3 carbon; the P–H group is removed, often by a base. The scope of both nucleophilic and electrophilic partners in these processes is surveyed, and the proposed mechanisms and intermediates in the metal-catalyzed reactions are described.

Keywords Cross-coupling · Hydrophosphination · Mechanism · Palladium · Phosphination · Phosphine

Contents

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1 Introduction

Metal-catalyzed formation of carbon–phosphorus bonds is an important method for synthesis of organophosphorus compounds, including ligands for metal-catalyzed reactions and compounds with biological activity. This review summarizes recent synthetic advances from the viewpoint of organometallic chemistry, with a focus on the proposed mechanisms and intermediates in the catalytic reactions. An understanding of the mechanistic details of metal-catalyzed C–P bond formation should enable improvement of known reactions and design of new ones. This general area has been the subject of recent reviews, which the reader can consult for more information [1, 2].

1.1 Substrates

Figure 1 shows typical organophosphorus substrates, which usually act directly, or after activation at a metal center, as nucleophiles. Most include a reactive P–H bond, which, for P(V) substrates, is involved in an important tautomerization equilibrium which interconverts four- and three-coordinate compounds **1** and **2**. The source of electrophilic carbon for C–P bond formation is usually unsaturated (alkynes, alkenes, aldehydes, etc), or contains a good leaving group (aryl and alkyl halides, allyl acetates).

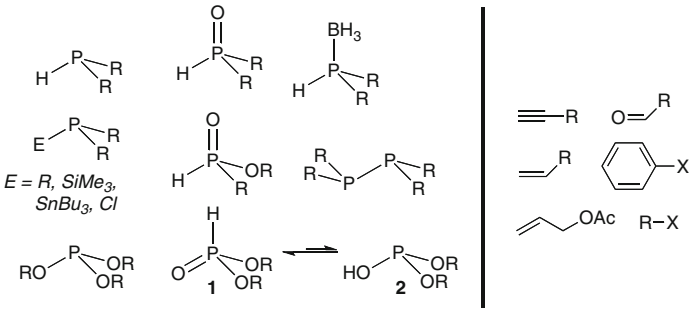
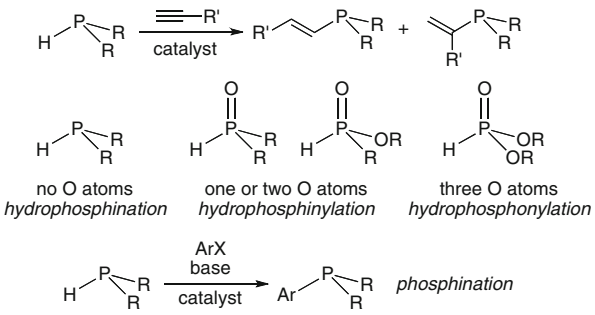


Fig. 1 Substrates for metal-catalyzed C–P bond formation



Scheme 1 Typical metal-catalyzed reactions for C–P bond formation

1.2 Reactions

Metal-catalyzed C–P bond-forming reactions may be divided into two types. In hydrophosphination, a P–H bond is added across a C–X multiple bond (X = C, N, O), as reviewed recently [3–7]. Scheme 1 shows a typical reaction of a terminal alkyne, showing the two possible regiochemical outcomes. Related reactions are defined in terms of the number of O atoms bound to P in the substrate (Scheme 1). Phosphination (cross-coupling) typically involves substitution at sp^2 or sp^3 carbons with removal of the PH group, often by a base (Scheme 1).

2 Hydrophosphination and Related Reactions; Mechanisms of C–P Bond Formation

Depending on the metal catalyst and the substrate, C–P bond formation in hydrophosphination and related reactions may occur by different pathways, including insertion into an M–P bond, P–C reductive elimination, and attack of a P-nucleophile on an electrophile. These typical mechanisms, ordered further by the electrophile, are surveyed below.

2.1 Insertion, then Reductive Elimination

2.1.1 Alkynes

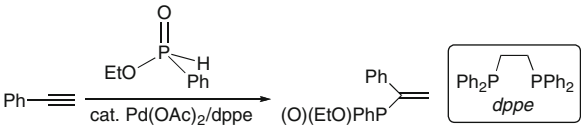
Markovnikov or anti-Markovnikov selectivity in hydrophosphination of alkynes (Scheme 1) depends on the metal catalyst and reaction conditions; it is thought to be controlled by the regioselectivity of insertion of an alkyne into an M–H or M–P bond.

For example, Pd-catalyzed addition of $PH(OR)_2(O)$ to a terminal alkyne was branched-selective, while $PHPh_2(O)$ preferentially gave linear products. However, a Pd(dppe) catalyst resulted in Markovnikov selectivity both for diphenylphosphine oxide [8] and for the mixed substrate PH(Ph)(OEt)(O) (Scheme 2). For the latter, linear products were favored with the ligand P(*t*-Bu)$_3$ and with PPh_3 in a protic solvent, ethanol. However, the mechanistic basis for this selectivity was not elucidated [9].

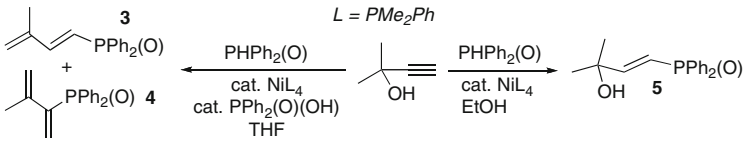
In related Ni-catalyzed hydrophosphination of propargyl alcohols, the addition was anti-Markovnikov in ethanol. But, when the catalyst was modified with $PPh_2(O)(OH)$, butadiene derivatives **3** and **4** formally derived by dehydration of **5** were obtained; **5** was not an intermediate in this process (Scheme 3) [10].

Similar hydrophosphination of alkynes has been used for addition polymerization of diynes, where the regiochemistry could be controlled by the choice of metal catalyst (Scheme 4) [11, 12].

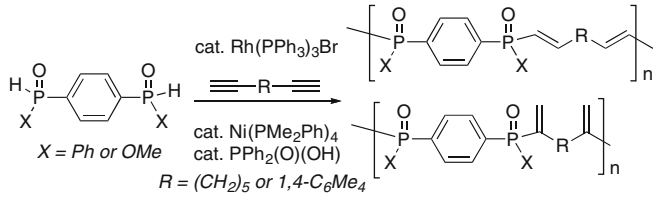
Addition of diphenylphospholane oxide **6** to terminal alkynes was catalyzed by $Pd(PPh_3)_4$ with complete Markovnikov selectivity, while the precursor $[Rh(cod)Cl]_2$ was anti-Markovnikov selective. With Rh, a sequence of P–H oxidative



Scheme 2 Markovnikov-selective Pd-catalyzed hydrophosphinylation of phenylacetylene



Scheme 3 Dependence of the products in nickel-catalyzed hydrophosphinylation of a propargyl alcohol on reaction conditions



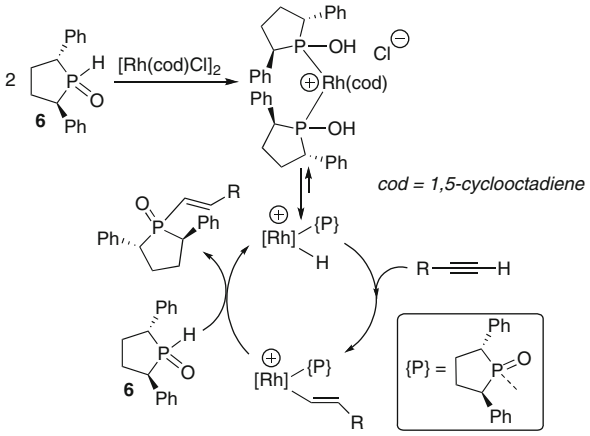
Scheme 4 Control of regiochemistry by metal catalyst in hydrophosphinylation polymerization of diynes

addition and alkyne insertion into the Rh–H bond was suggested to yield a Rh–alkenyl intermediate. P–C reductive elimination would then form the product and regenerate the Rh(I) catalyst (Scheme 5) [13].

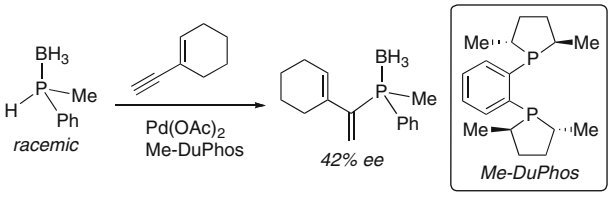
Although no mechanism was proposed, the Pd(Me-DuPhos)-catalyzed asymmetric hydrophosphination of an alkyne with a phosphine–borane under kinetic resolution conditions (Scheme 6) presumably involves similar insertion and reductive elimination steps [14].

Recently, a low PPh_3/Pd ratio (2:1) and a catalytic amount of trifluoroacetic acid (TFA) led to high regioselectivity on addition of H-phosphonates to alkynes (Scheme 7). However, the role of acid was not elucidated [15].

Noble metals like Pd and Rh are not always required; a CuI/ethylenediamine catalyst precursor promoted regioselective addition of diphenylphosphine oxide to terminal alkynes to yield *E*-alkenylphosphine oxides (Scheme 8) [16]. When

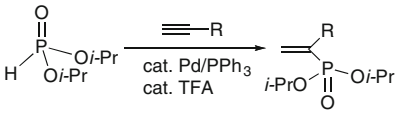


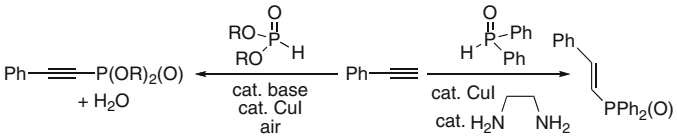
Scheme 5 Proposed mechanism for Rh-catalyzed hydrophosphinylation of an alkyne



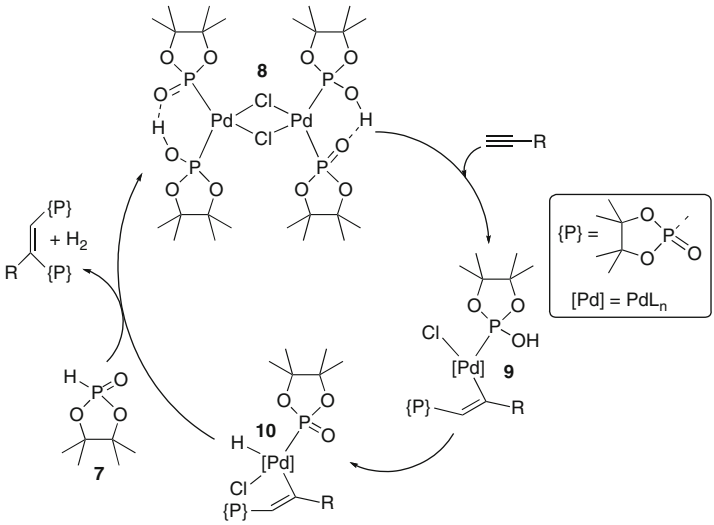
Scheme 6 Pd-catalyzed asymmetric alkyne hydrophosphination

Scheme 7 Pd-catalyzed alkyne hydrophosphonylation with a trifluoroacetic acid additive





Scheme 8 Copper-catalyzed reactions of substrates containing P–H bonds with phenylacetylene

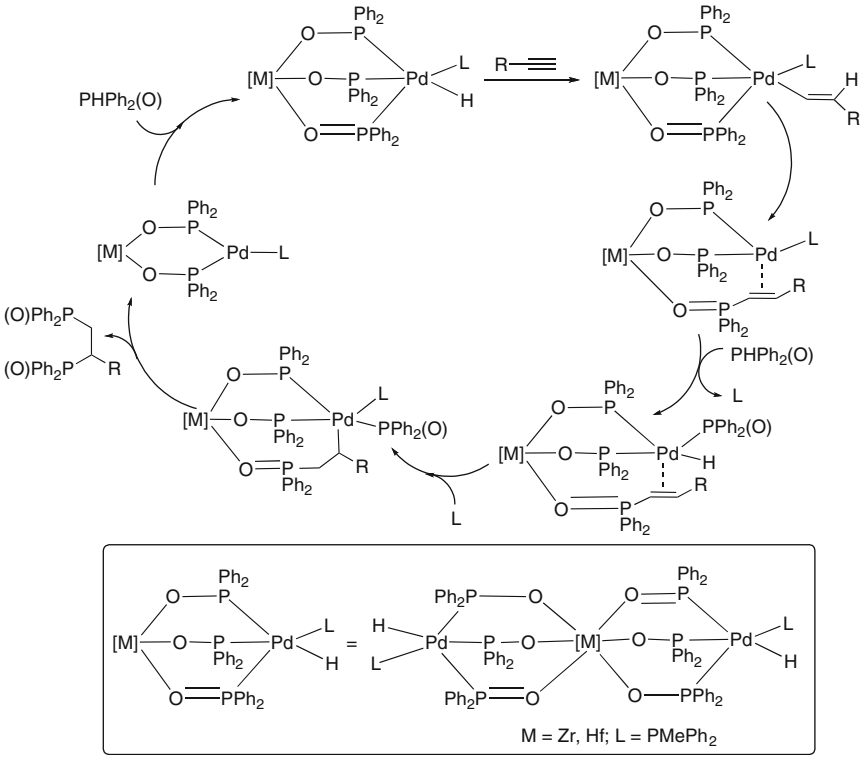


Scheme 9 Proposed mechanism for Pd-catalyzed dehydrogenative double *cis* phosphonylation of an alkyne

similar reactions were carried out under air instead of nitrogen, aerobic oxidation of terminal alkynes with H-phosphonates gave alkynylphosphonates [17]. As with other copper-catalyzed reactions discussed below, little is known about the mechanisms of these processes.

Similar reactions can lead to the formation of two P–C bonds. For example, Pd-catalyzed addition of **7** (a privileged substrate which is often more reactive than other H-phosphonates) to terminal alkynes led to dehydrogenative double *cis* phosphonylation (Scheme 9). A Pd(II)/Pd(IV) cycle was proposed. Reaction of $[Pd(allyl)Cl]_2$ with **7** gave chloro-bridged dimer **8**. Alkyne insertion into the Pd–P bond was then proposed to give alkenyl intermediate **9**. P–H oxidative addition would then yield hydride **10**, whose reaction with **7** was proposed to lead to P–C bond formation and loss of H_2 [18].

Similarly, Pd-catalyzed double hydrophosphinylation of 1-octyne was promoted by a novel metalloligand (Scheme 10) [19]. Oxidative addition of diphenylphosphine oxide to Pd(0) was proposed to yield a Pd hydride in which a phosphido–oxide ($PR_2(O)$) ligand was stabilized by O-coordination to zirconium. After alkyne

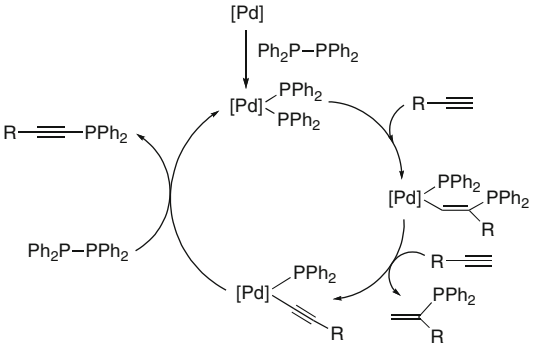


Scheme 10 Proposed mechanism for Pd-catalyzed double hydrophosphinylation of 1-octyne

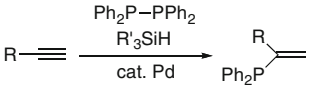
insertion into the Pd–H bond to yield a Pd–alkenyl group, P–C reductive elimination was suggested to yield the alkene complex. After a related sequence of oxidative addition and alkene insertion, reductive elimination of the resulting Pd–alkyl gives the product and regenerates Pd(0). Interestingly, a crossover experiment using PH(O)(*p*-Tol)$_2$ gave a product containing both tolyl and phenyl groups, suggesting exchange of the "ligand" and substrate groups.

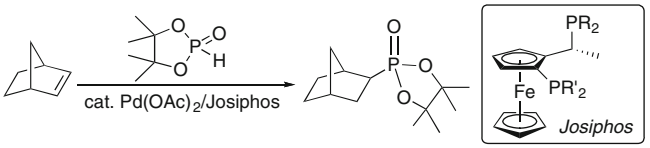
Pd-catalyzed hydrophosphination has also been reported without P–H bonds in the substrate. Addition of tetraphenyldiphosphine (Ph_2P–PPh_2) to alkynes gave vinylphosphines; the alkyne was the source of the "missing" H [20]. Scheme 11 shows the proposed mechanism. P–P oxidative addition to Pd(0) gives a bis(phosphido) intermediate; alkyne insertion into a Pd–P bond then yields a Pd–alkenyl complex. Protonation of the Pd–C bond by the alkyne then yields a vinylphosphine and a palladium acetylide, whose reductive elimination regenerates Pd(0); the alkynylphosphine byproduct required by this mechanism was observed by NMR spectroscopy. When deuterated PhCCD was used, the product contained two deuteriums on the terminal vinylic carbon, consistent with this mechanism.

Scheme 11 Proposed mechanism for Pd-catalyzed alkyne hydrophosphination using a diphosphine



Scheme 12 Pd-catalyzed hydrophosphination of an alkyne using a diphosphine and a silane





Scheme 13 Pd(Josiphos)-catalyzed asymmetric hydrophosphinylation of norbornene

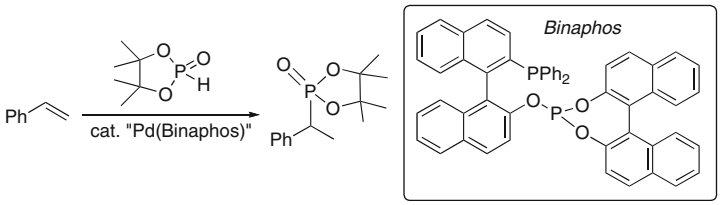
Since this process is not atom-economical, a silane was used instead as the source of hydrogen (Scheme 12) [21]. Oxygen was required, and a speculative mechanism to explain its role was suggested.

2.1.2 Alkenes

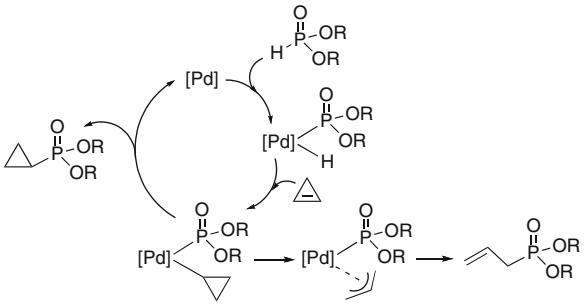
Similar additions to alkenes have been reported with the same metals, Pd and Rh, including several Pd-catalyzed *asymmetric* syntheses. For example, Pd(Josiphos) catalysts enabled enantioselective hydrophosphinylation of norbornenes (Scheme 13) [22].

Similar reactions of styrenes have also been reported. For example, up to 74% ee for the favored branched isomer was observed with a Pd(Binaphos) catalyst (Scheme 14) [23, 24].

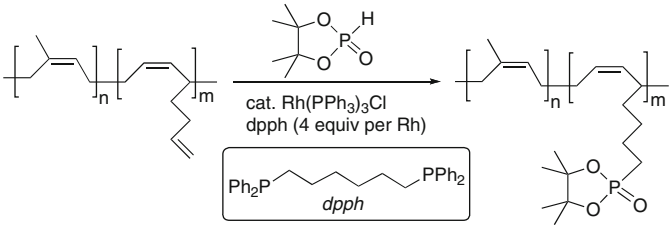
P–H bonds in H-phosphonates and secondary phosphine oxides could also be added to special alkene derivatives, cyclopropenes, with Pd catalysts [25]. Scheme 15 shows the proposed mechanism, including P–H oxidative addition, insertion into the Pd–H bond, then P–C reductive elimination. The observed



Scheme 14 Pd(Binaphos)-catalyzed asymmetric hydrophosphonylation of styrene



Scheme 15 Pd-catalyzed hydrophosphonylation of cyclopropene



Scheme 16 Rh-catalyzed hydrophosphonylation of a polymeric alkene

allylphosphonate byproducts might form via ring-opening of a Pd–cyclopropyl intermediate to form an allyl ligand, followed by reductive elimination.

A Rh catalyst mediated anti-Markovnikov hydrophosphonylation of alkenes in a polymer to give a linear product (Scheme 16). A catalyst formed from Wilkinson's complex and four equiv of dpph was the most active; this ligand was suggested to be bidentate, but the active Rh species was not identified [26, 27].

2.1.3 Isocyanides

$Pd_2(dba)_3$-catalyzed hydrophosphinylation of isocyanides has also been described (dba = dibenzylideneacetone). The proposed mechanism is similar to that for

alkynes and alkenes, involving P–H oxidative addition, isocyanide insertion into the Pd–H bond, and P–C reductive elimination (Scheme 17) [28]. In contrast, Wilkinson's complex catalyzed formation of *two* P–C bonds to yield **11**.

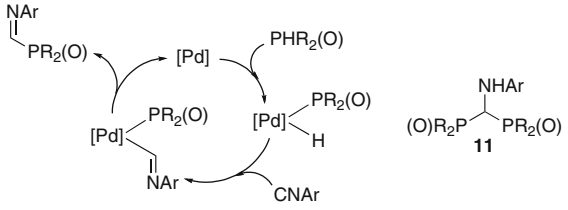
2.2 *Insertion, then Protonolysis*

This is a common mechanism for P–C bond formation using lanthanide and alkaline earth metal catalysts; instead of oxidative additions, as in Sect. 2.1, σ-bond metathesis is a key step.

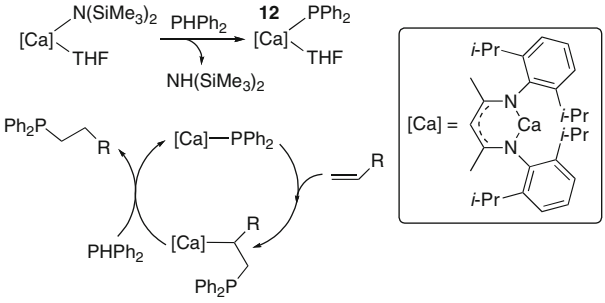
2.2.1 Alkenes

The catalyst precursor Ca(nacnac)($N(SiMe_3)_2$)(THF) reacted with diphenylphosphine to yield the phosphido complex **12** [29], which was proposed to undergo alkene insertion. Protonolysis of the resulting Ca–alkyl complex with diphenylphosphine via σ-bond metathesis then completes the catalytic cycle (Scheme 18).

If the alkene is connected to the phosphine, hydrophosphination results in cyclization, as observed for a series of lanthanocene catalysts. DFT and experimental studies were consistent with the mechanism of Scheme 19, where P–C bond formation occurs by the approximately thermoneutral insertion of an alkene into a

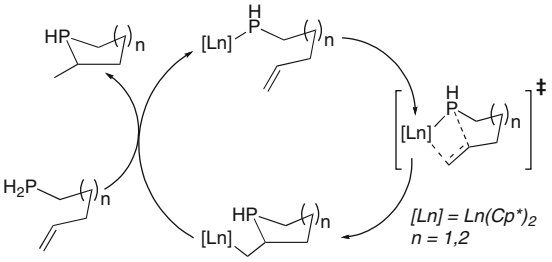


Scheme 17 Proposed mechanism for Pd-catalyzed hydrophosphinylation of isocyanides

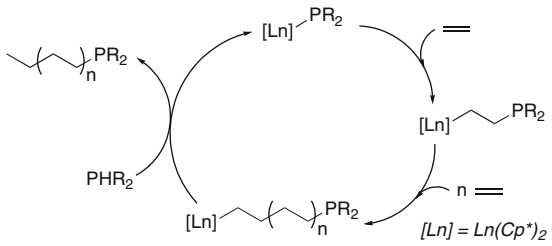


Scheme 18 Proposed mechanism for calcium-catalyzed alkene hydrophosphination (for simplicity, coordinated THF is not shown in **12** or other intermediates)

Scheme 19 Proposed mechanism for organolanthanide-catalyzed hydrophosphination/cyclization



Scheme 20 Lanthanide-catalyzed hydrophosphination/polymerization of ethylene



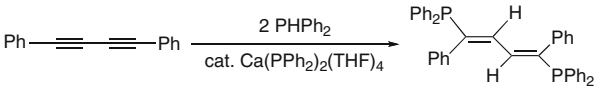
lanthanide–P bond. Exothermic protonolysis then yields the product and regenerates the phosphido intermediate [30].

Phosphine-terminated polyethylenes have been prepared in related organolanthanide-catalyzed reactions [31, 32]. After initiation by insertion of ethylene into the Ln–P bond of a phosphido complex, polymerization occurs by repeated ethylene insertion. Termination results from protonolysis of the growing polymer chain via a four-centered σ-bond metathesis transition state, as seen in Scheme 19, to give a polymeryl-phosphine and regenerate the lanthanum phosphido complex (Scheme 20).

More recently, hydrophosphination of butadiene with PH_3 catalyzed by the precursor Cp_2EuH was investigated computationally [33]. Consistent with the previous experimental work on alkene hydrophosphination, the active species was proposed to be the phosphido complex $Cp_2Eu(PH_2)$, and P–C bond formation occurred by insertion into the Eu–P bond. Hydrophosphination of such conjugated dienes by f-element catalysts does not appear to have been studied in the laboratory, but dienes have been prepared from alkyne hydrophosphination, as described below.

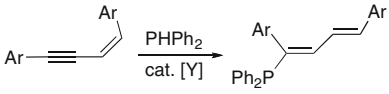
2.2.2 Alkynes

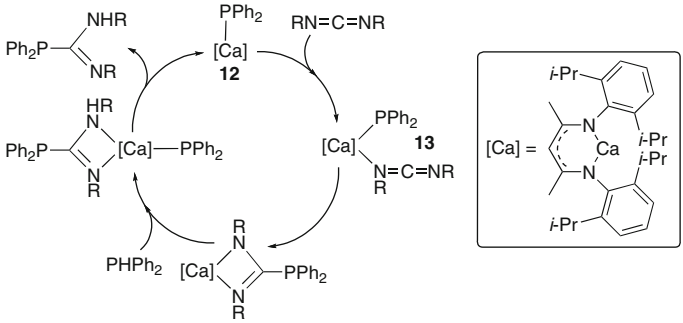
The complex $Ca(PPh_2)_2(THF)_4$ catalyzed hydrophosphination of phenyl-substituted alkynes with diphenylphosphine (Scheme 21). The proposed mechanism includes insertion of the alkyne into the Ca–P bond and protonolysis of the new



Scheme 21 Calcium-catalyzed hydrophosphination of a diyne

Scheme 22 Yttrium-catalyzed hydrophosphination of an enyne





Scheme 23 Proposed mechanism for calcium-catalyzed hydrophosphination of carbodiimides (for simplicity, coordinated THF is not shown in **12** or related intermediates)

Ca–C bond with $PHPh_2$ to form the product and regenerate the catalyst [34]. Similar chemistry had been observed earlier with ytterbium–phosphido catalysts [35].

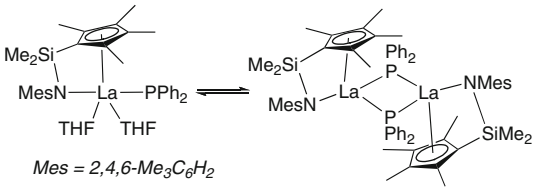
Butadiene derivatives were also prepared by hydrophosphination of enynes catalyzed by Y(HMPA) complexes, which was selective for addition to the triple bond (Scheme 22, HMPA = hexamethylphosphoramide) [36].

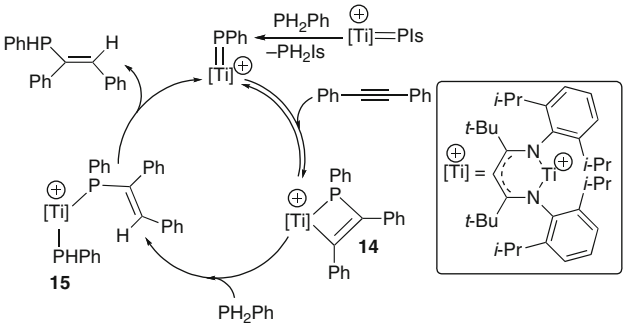
2.2.3 Carbodiimides

Hydrophosphination of carbodiimides to yield phosphaguanidines was catalyzed by several related metal complexes. For example, after carbodiimide coordination by the calcium phosphido complex **12** (see Scheme 18 above), P–C bond formation involving a four-centered transition state and rearrangement was proposed to yield the N,N-bound intermediate **13**. Addition of the P–H bond across the Ca–N bond, followed by dissociation of the product, then regenerates the phosphido intermediate (Scheme 23) [37]. Related chemistry was reported recently using the calcium phosphido complex $Ca(PPh_2)_2(THF)_4$ [38].

A similar mechanism was proposed for the same reaction catalyzed by alkali metal complexes, such as $KN(SiMe_3)_2$ [39], or organolanthanides, where both monomeric and dinuclear phosphido intermediates could be isolated (Scheme 24) [40, 41].

Scheme 24 Dimerization of a constrained-geometry lanthanum phosphido complex, an intermediate in carbodiimide hydrophosphination





Scheme 25 Ti-catalyzed hydrophosphination of an alkyne via a phosphinidene intermediate

2.3 Metal–Phosphinidene Intermediates

Although M–P single bonds are involved in all the transformations above, complexes with M–P double bonds may also be intermediates in hydrophosphination catalysis. In the only example of this type of reactivity (Scheme 25), the cationic titanium phosphinidene complex [Ti(nacnac)(PIs)][$MeB(C_6F_5)_3$] (Is = 2,4,6-(i-Pr)$_3C_6H_2$) was proposed to react with two equivalents of phenylphosphine to yield PH_2Is and the more-reactive, less sterically hindered phenylphosphinidene complex. [2+2]-cycloaddition, as observed for related imido complexes, then gives metallacycle **14**, whose protonation with phenylphosphine yields Ti–bis(phosphido) complex **15**. α-elimination would then yield the alkenylphosphine product and regenerate the catalyst [42].

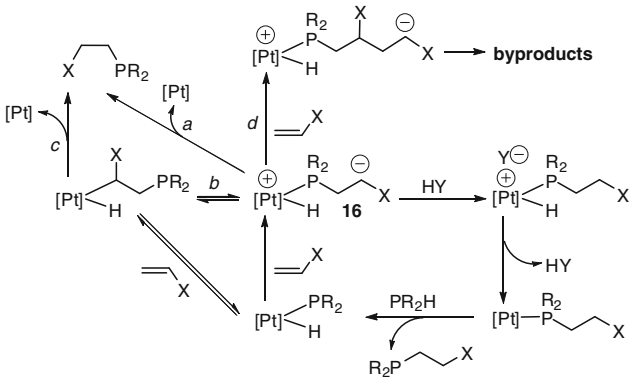
2.4 Activation of a P-Nucleophile

The previous sections have described C–P bond formation by classical organometallic processes, such as migratory insertion and reductive elimination. However, there is evidence in some other systems that the metal catalyst activates the organophosphorus substrate for *direct* nucleophilic attack on an electrophile [43].

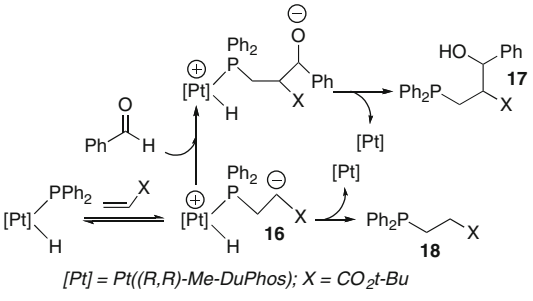
For example, this mechanism was proposed in Pt-catalyzed hydrophosphination of acrylonitrile and acrylates. P–H oxidative addition gave Pt–phosphido hydride

complexes. Nucleophilic attack on the Michael acceptor alkenes was suggested to give zwitterion **16**. It could yield the product via two complementary pathways shown in Scheme 26: (a) deprotonation of the cationic platinum hydride by the carbanion or (b) attack of this anion at Pt, Pt–P dissociation, and reductive elimination (c) of the resulting alkyl hydride. Alternatively, attack of the zwitterion on additional alkene (d) could result in oligomerization and the formation of phosphine products derived from more than one equivalent of alkene, which is commonly observed in these reactions. Evidence for this mechanism was provided by trapping experiments. Protic additives (*t*-BuOH or water), which were intended to compete with alkenes in reactions with zwitterion **16**, reduced the amount of byproducts. They also altered the rate and selectivity of the reactions, perhaps because P–C bond formation was reversible, but carbanion protonation was not [44].

Addition of benzaldehyde led to a Pt-catalyzed three-component coupling related to the Morita–Baylis–Hillman reaction, which could be explained mechanistically in terms of competition for the zwitterionic nucleophile **16** between an external electrophile (benzaldehyde) and an internal one (Pt–H). Consistent with this idea, increasing the concentration of benzaldehyde led to a larger ratio of **17**–**18** (Scheme 27) [45].



Scheme 26 Proposed nucleophilic mechanism for Pt-catalyzed hydrophosphination of Michael acceptor alkenes (X = CN or CO_2R); formation of byproducts and the effect of protic additives (HY = *t*-BuOH or H_2O)



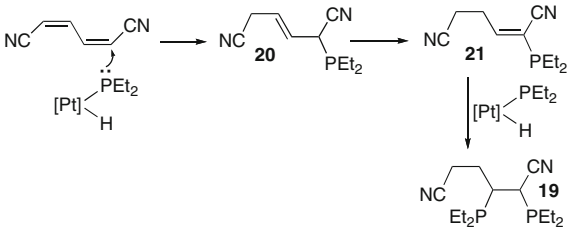
Scheme 27 Proposed mechanism of Pt-catalyzed three-component coupling of $PHPh_2$, a Michael acceptor alkene, and benzaldehyde

Similarly, the diene muconononitrile underwent Pt(Me-DuPhos)-catalyzed hydrophosphination with diethylphosphine to yield the diphosphine **19** via alkene intermediates **20** and **21**, which were observed by NMR spectroscopy. Nucleophilic 1,4-attack of a Pt–phosphido group on the diene was proposed to give **20**. After isomerization to **21**, another Pt-catalyzed hydrophosphination via Michael addition gives **19** (Scheme 28) [46].

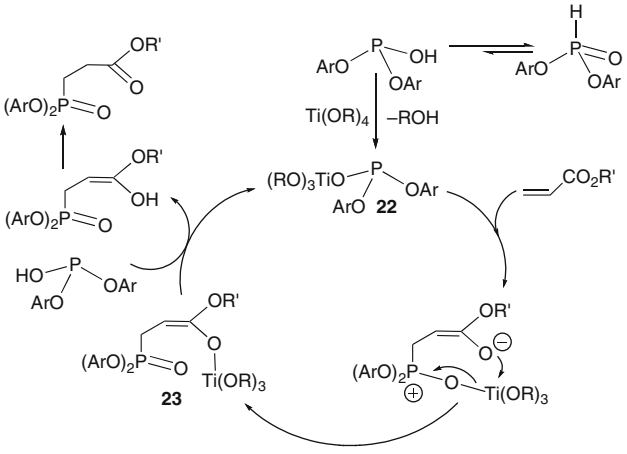
Scheme 29 shows a different method to activate a P-nucleophile for attack on a Michael acceptor alkene. Reaction of an H-phosphonate, after tautomerization, with the catalyst precursor $Ti(OR)_4$ was proposed to give intermediate **22** [47]. Nucleophilic attack on an acrylate, followed by Ti–O and P=O bond formation, would then yield titanium alkoxide **23**, whose protonolysis by the substrate yields the product and regenerates the catalyst.

In a simpler example, hydrophosphination oligomerization of the bifunctional substrate **24** was mediated by catalytic *n*-BuLi, presumably by nucleophilic attack of the secondary phosphido anion on the alkyne of another molecule (Scheme 30) [48, 49].

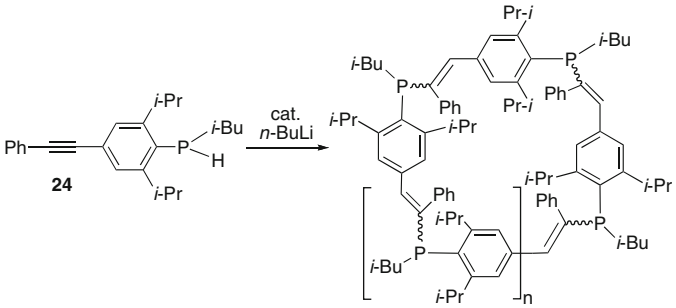
Nucleophilic attack of a metal–phosphido complex on an alkyne was also proposed in copper-catalyzed *anti*-hydrophosphination of 1-alkynylphosphines



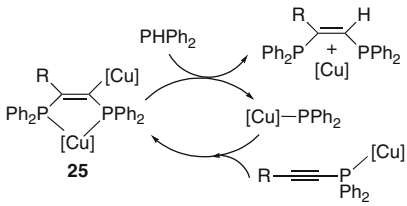
Scheme 28 Proposed mechanism for Pt-catalyzed hydrophosphination of muconononitrile ([Pt] = Pt((*R*, *R*)-Me-DuPhos))



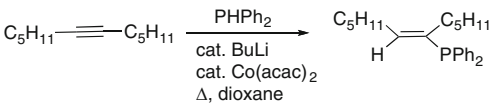
Scheme 29 Proposed mechanism for Ti-catalyzed hydrophosphonylation of activated alkenes



Scheme 30 Lithium-catalyzed hydrophosphination/oligomerization of a secondary phosphine/alkyne



Scheme 31 Proposed mechanism for copper-catalyzed *anti*-hydrophosphination of 1-alkynylphosphines with diphenylphosphine



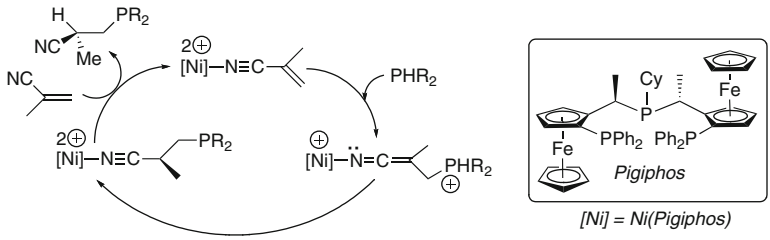
Scheme 32 Cobalt-catalyzed alkyne hydrophosphination

with diphenylphosphine, which formed *Z*-1,2-diphosphino-1-alkenes (Scheme 31). After generation of a soluble form of $[Cu(PPh_2)]_n$ [50] from $CuI/Cs_2CO_3/PHPh_2$ in DMF, nucleophilic (*anti*) attack on the alkynylphosphine substrate, perhaps activated by coordination to copper, could then yield bidentate complex **25**. The analogous alkynylphosphine oxide and sulfide did not undergo hydrophosphination, suggesting the importance of Cu–P coordination. Finally, protonation of the vinylcopper group by diphenylphosphine regenerates the catalyst and forms the alkene product [51].

In contrast, *syn*-hydrophosphination of alkynes was accomplished using a catalyst obtained by treatment of $Co(acac)_2$ with a mixture of $LiPPh_2$ and $PHPh_2$ (Scheme 32). The nature of the catalyst and mechanism of P–C bond formation were not reported, but the *syn* stereochemistry is consistent with an insertion step [52].

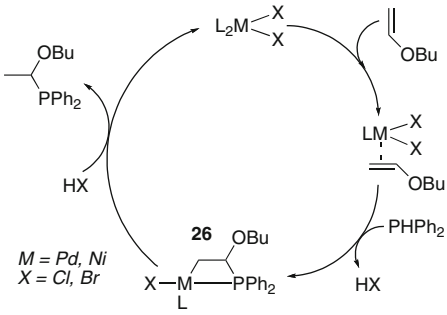
2.5 *Activation of an Unsaturated Electrophile*

While the examples so far have featured activation of nucleophiles, metal catalysts can also promote hydrophosphination by complexation of an electrophile.



Scheme 33 Proposed mechanism for nickel-catalyzed asymmetric hydrophosphination via attack on a methacrylonitrile complex

Scheme 34 Proposed mechanism for nickel- or palladium-catalyzed hydrophosphination via attack on a complex of an electron-rich alkene

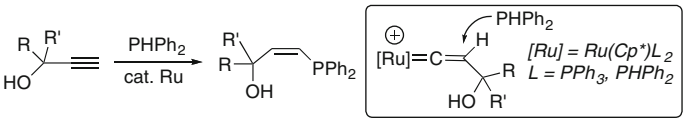


For example, a chiral nickel Lewis acid catalyst bound methacrylonitrile and activated it for nucleophilic attack by a secondary phosphine. Subsequent proton transfer resulted in enantioselective hydrophosphination (Scheme 33) [53, 54].

Similarly, activation of a coordinated alkene was suggested in Markovnikov-selective addition of diphenylphosphine to alkyl vinyl ethers promoted by Ni(II) and Pd(II) precatalysts such as $NiBr_2(PPh_3)_2$. Nucleophilic attack on bound alkene, followed by loss of HX to form chelate **26** and protonolysis of the M–C bond would form the product and regenerate the catalyst (Scheme 34). This mechanism was consistent with the observation that added Et_3N shut down the reaction [55, 56].

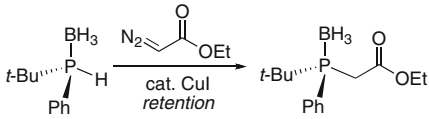
Beyond simple coordination, metal catalysts may transform unsaturated substrates to enable C–P bond formation. For example, Ru-catalyzed hydrophosphination of propargyl alcohols was proposed to proceed via nucleophilic attack of diphenylphosphine on the Ru=C group in a vinylidene complex (Scheme 35) [57].

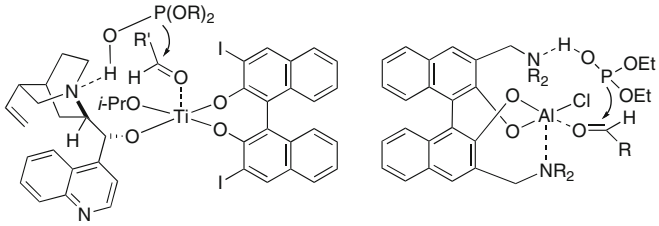
Similarly, a copper catalyst is thought to mediate transformation of a diazo substrate to a carbene, which inserts into P–H bonds in phosphine–boranes. When PHPh(*t*-Bu)(BH_3) of 99% ee was used, the reaction proceeded with retention of configuration at phosphorus (Scheme 36); other chiral phosphine–boranes behaved similarly [58].



Scheme 35 Proposed mechanism for ruthenium-catalyzed hydrophosphination of a propargyl alcohol via nucleophilic attack on a vinylidene complex

Scheme 36 Copper-catalyzed addition of a P–H bond to a carbene





Scheme 37 Proposed bifunctional activation in Ti- and Al-catalyzed asymmetric hydrophosphonylation of aldehydes

2.6 *Bifunctional Activation of Nucleophile and Electrophile*

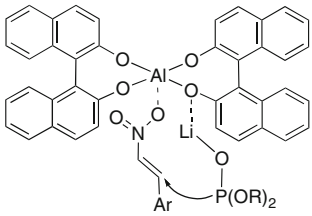
A logical extension of these themes is for one catalyst to activate both the P-nucleophile and the unsaturated electrophile. This approach has been especially popular in asymmetric hydrophosphonylation of aldehydes and imines, which has been reviewed recently [59].

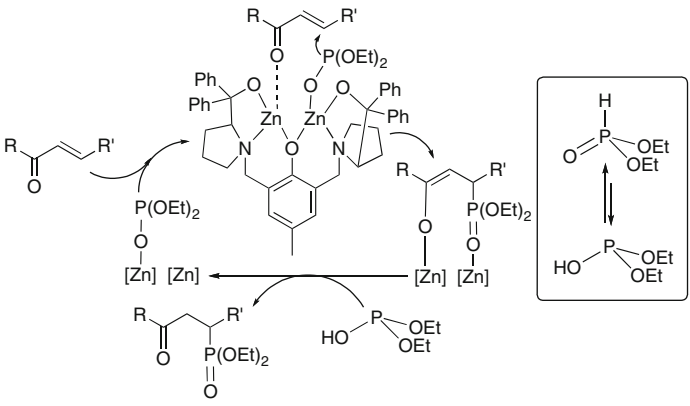
A few related recent examples are included in this section. Tautomerization of a H-phosphonate to the three-coordinate nucleophilic form (as in Fig. 1 and Schemes 5 and 29) is an important step in these reactions. Scheme 37 shows how a Ti catalyst was proposed to bind an aldehyde, while the P–OH nucleophile was simultaneously activated by hydrogen bonding to a pendant quinuclidine Lewis base, derived from a cinchona alkaloid [60]. The same two types of interactions were suggested in related Al-catalyzed reactions (Scheme 37) [61].

In a variation on this theme, addition of dialkyl phosphites to nitroalkenes was catalyzed by an Al–Li–Binol species (ALB) [62]. Coordination of the nitro group to aluminum and activation of the phosphite tautomer by Li binding was proposed to lead to selective P–C bond formation (Scheme 38).

Using two metal centers for such complementary tasks was also suggested in enantioselective 1,4-addition of diethyl phosphite to enones mediated by a dinuclear zinc catalyst (Scheme 39) [63]. Coordination of the nucleophile to one zinc,

Scheme 38 Proposed bifunctional activation in ALB-catalyzed hydrophosphonylation of nitroalkenes





Scheme 39 Proposed mechanism for enantioselective hydrophosphonylation of enones catalyzed by a dinuclear zinc complex

and the electrophile to the other, enables templated P–C bond formation. Proton transfer to diethyl phosphite then regenerates the catalyst and yields the product (Scheme 39).

3 Phosphination

These reactions involve the same organophosphorus substrates, but, in contrast to hydrophosphination and related reactions, the P–H group is not transferred to the electrophile.

3.1 Pd- and Ni-Catalyzed Reactions

As reviewed recently, the most popular phosphination reaction is synthesis of tertiary phosphines via Pd- or Ni-catalyzed cross-coupling of aryl halides or triflates with P–H substrates, which has become a routine procedure to form P–C bonds [64].

Comprehensive coverage is not possible, so this section emphasizes new approaches and recently reported mechanistic information.

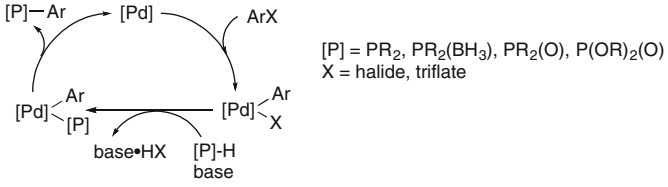
The standard mechanism (Scheme 40) includes oxidative addition, Pd–P bond formation, and P–C reductive elimination. When silyl- or stannylphosphines are used, [65] no base is required for Pd–P bond formation, which instead yields R_3E–X (E = Si, Sn). Since these P-substrates are often made from secondary phosphines, and because of the toxicity of organotins, they are used less often.

Occasionally, other organophosphorus substrates are used in these reactions; Scheme 41 shows how Ph_2PCl was converted electrochemically to Ph_2PMgCl, which was cross-coupled with aryl bromides using the catalyst precursor $NiBr_2$(bipy) [66].

3.2 Cu-Catalyzed Reactions

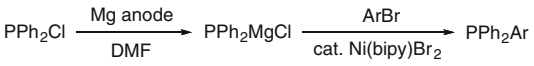
Copper-catalyzed P–C bond formation has recently become quite popular as a complement to Pd-catalyzed reactions [67–69]. Figure 2 shows some ligands which have been used with Cu(I) precursors. Little is known about the mechanism of these reactions, but, by analogy with Scheme 40, they may proceed by Cu(I)/Cu (III) cycles involving oxidative addition and reductive elimination [70].

Recently, this approach was used to make phosphinooxazoline ligands (Scheme 42) [71].



Scheme 40 Proposed mechanism for Pd-catalyzed phosphination of aryl halides and triflates

Scheme 41 Ni-catalyzed phosphination of aryl bromides using electrochemically generated Ph_2PMgCl



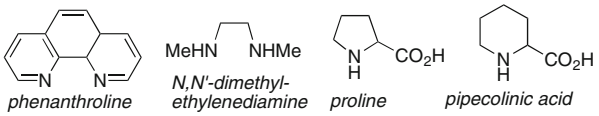
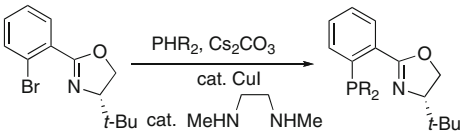
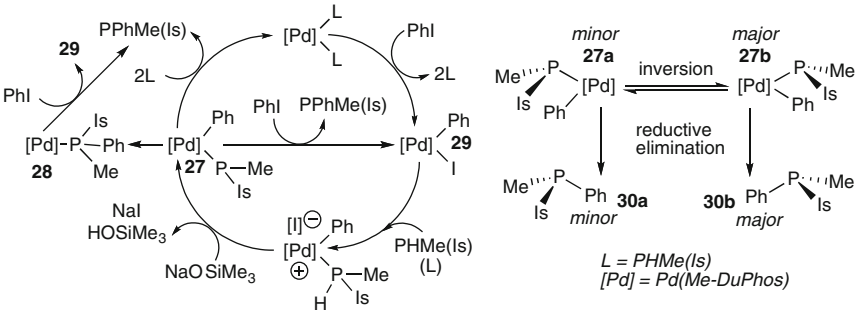


Fig. 2 Some ligands used in Cu-catalyzed phosphination of aryl halides

Scheme 42 Synthesis of phosphinooxazolines by copper-catalyzed phosphination





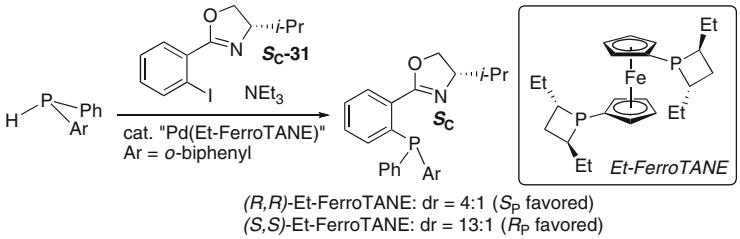
Scheme 43 Proposed mechanism and origin of enantioselectivity in Pd-catalyzed asymmetric phosphination

3.3 Asymmetric Phosphination

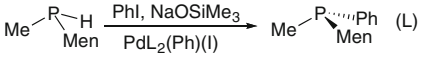
Recently, chiral metal catalysts have been used in enantioselective phosphination, yielding P-stereogenic phosphines [72–74]. In the first such example, asymmetric phosphination was catalyzed by Pd(DuPhos) complexes. In a mechanistic study of the cross-coupling of PhI and PHMe(Is) (Is = 2,4,6-(i-Pr)$_3$C$_6$H$_2$), P–C bond formation by first-order reductive elimination of the phosphido complex Pd((*R*,*R*)-Me-DuPhos)(Ph)(PMeIs) (**27**) was observed directly by ^{31}P NMR spectroscopy. This reaction gave three-coordinate Pd((*R*,*R*)-Me-DuPhos)(PPhMeIs) (**28**), which was rapidly trapped by PhI to yield the catalyst precursor **29**. Fast pyramidal inversion at phosphorus in the Pd–phosphido group interconverted the diastereomers of **27**; stereochemical studies suggested that the major product enantiomer **30b** was formed from the major diastereomer **27b**, although P–C bond formation occurred more quickly from minor intermediate **27a** (Scheme 43) [75].

A related Pd(Et-FerroTANE) catalyst was used for preparation of chiral triarylphosphines, including phosphinooxazolines; added LiBr enhanced both rates and selectivities [76]. Although the presence of a chiral oxazoline in substrate **31** affected the diastereoselectivity of P–C bond formation, the catalyst controlled the preferred P configuration (Scheme 44).

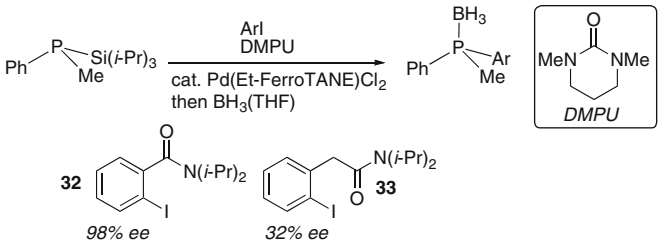
In contrast, cross-coupling of the chiral substrate PHMe(Men) (Men = (–)-menthyl) with an achiral Pd catalyst led to diastereoselective formation of PPhMe(Men) (L, Scheme 45) [77]. The catalyst precursor PdL$_2$(Ph)(I), containing diastereomerically pure L, promoted diastereoselective formation of more L, an example of "chirality breeding".



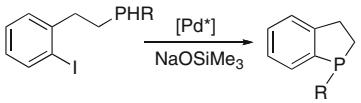
Scheme 44 Catalyst control in Pd(Et-FerroTANE)-catalyzed asymmetric phosphination of a chiral oxazoline derivative



Scheme 45 Formal chirality breeding in Pd-catalyzed asymmetric phosphination



Scheme 46 Effect of a substrate amide group in Pd-catalyzed asymmetric phosphination



Scheme 47 Pd-catalyzed intramolecular asymmetric phosphination: synthesis of benzophospholanes

Silylphosphines were coupled with a class of privileged aryl iodides by a Pd(Et-FerroTANE) catalyst to give tertiary phosphines in high yield and ee. Although benzamide **32** and several analogs with substituted aryl groups gave high ee values, moving the amide group one carbon further away in **33** led to reduced enantioselectivity (Scheme 46). It was logically suggested that coordination of the amide to Pd enhanced the selectivity of P–C bond formation, but structural details have not yet been elucidated [78].

Similar cross-couplings have been used in enantioselective ring-closing to form benzophospholanes (Scheme 47) [79].

3.4 Scope of Electrophilic Partners

3.4.1 Aryl Halides

Aryl iodides and bromides are most commonly used in cross-coupling, but several other electrophiles may be employed; this section describes some recent examples.

A Pd(dippf) catalyst enabled cross-coupling with aryl bromides and one aryl chloride; notably, these reactions used dialkylphosphines instead of the usual arylphosphines (Scheme 48) [80].

3.4.2 Vinyl Substrates

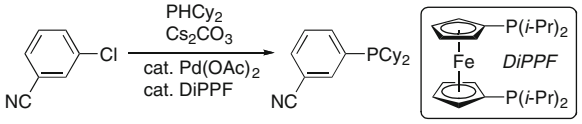
Nickel-catalyzed phosphination of a vinyl chloride is shown in Scheme 49 [81].

A related Cu-catalyzed cross-coupling of vinyliodonium salts (Scheme 50) was, for some substrates, superior to Pd-catalyzed reactions [82].

3.4.3 Alkyl Halides

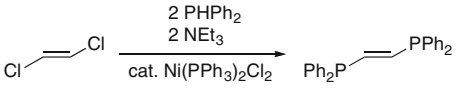
As in Pd-catalyzed C–C bond formation, alkyl halides are less common substrates in cross-coupling. However, coupling of Ph_2PCF_2Br with Ph_2PSiMe_3 was catalyzed by the precursor $Ni(dippf)Cl_2$, or related Ni(0) complexes (Scheme 51). A similar microwave-promoted coupling of CF_2Br_2 with $(i\text{-Pr})_2PSiCl_3$ gave the bisphosphine directly, along with some monophosphine [83].

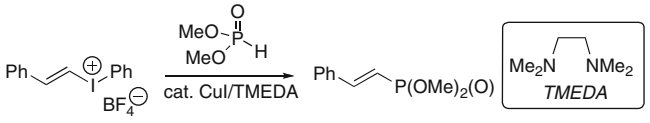
Even perfluoroalkyl iodides have recently been used in related reactions with phosphinostannanes. Generating the latter in situ reduced the hazards of isolating



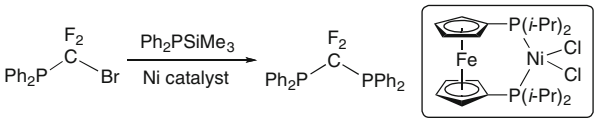
Scheme 48 Pd-catalyzed phosphination of an aryl chloride

Scheme 49 Ni-catalyzed phosphination of 1,2-dichloroethene



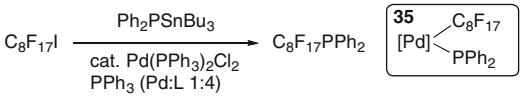


Scheme 50 Cu-catalyzed cross-coupling of a vinyliodonium salt

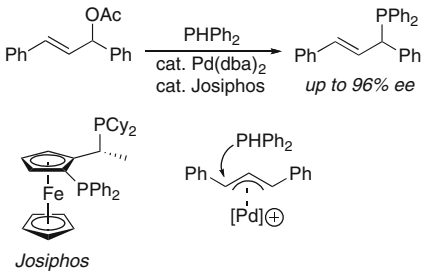


Scheme 51 Ni-catalyzed cross-coupling of a functionalized bromofluorocarbon

Scheme 52 Pd-catalyzed cross-coupling of a perfluoroalkyl iodide



Scheme 53 Pd(Josiphos)-catalyzed asymmetric allylic phosphination

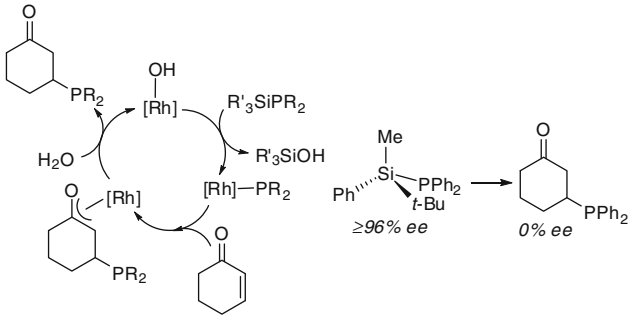


and purifying organotins, but remains undesirable. Although yields in these reactions were generally low, the mechanistic implication (P–C bond formation by the rare reductive elimination of a Pd–fluoroalkyl group from intermediate **35**, Scheme 52) is interesting [84, 85]

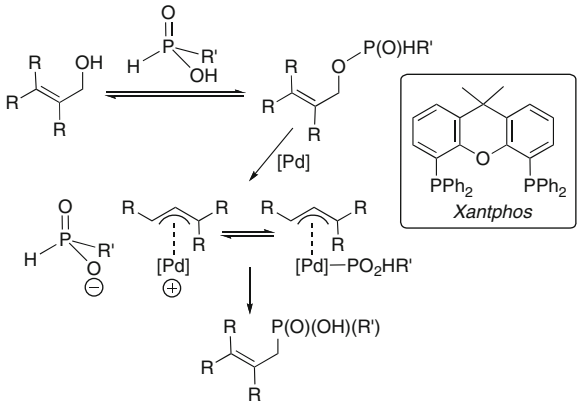
3.4.4 Allyl Substrates

Enantioselective allylic phosphination was catalyzed by Pd(Josiphos) complexes. As with related nucleophiles, these reactions presumably occur by nucleophilic attack of a secondary phosphine on a Pd-allyl intermediate (Scheme 53) [86].

Similar π-allyl intermediates were proposed in Rh-catalyzed conjugate addition of phosphido groups to enones [87–89]. Silylphosphine substrates were suggested to generate Rh–phosphido intermediates from a Rh–OH catalyst precursor. Nucleophilic attack at the alkene, accompanied by formation of a Rh-π-oxyallyl group, could be followed by protonolysis to yield the phosphine–ketone and regenerate a rhodium hydroxide. To differentiate this mechanism, in which only the Rh(I) oxidation state is involved, from one in which P–Si oxidative addition to yield Rh (III) occurs [90], the chiral Si-stereogenic substrate $Ph_2PSiMe(Ph)(t\text{-}Bu)$ was prepared. If oxidative addition occurred, then the presence of a chiral Rh–silyl group might be expected to result in asymmetric induction in the catalytic reaction. None was observed, arguing against this pathway (Scheme 54).



Scheme 54 Proposed mechanism of Rh-catalyzed conjugate addition to enones



Scheme 55 Proposed mechanism for Pd(Xantphos)-catalyzed allylation of an H-phosphinic acid

A related Pd-catalyzed allylation relied on the excellent leaving group ability of the H-phosphinate anion. Instead of the allyl acetate shown in Scheme 53, unfunctionalized allyl alcohol was used directly. Transesterification yields an allyl phosphonate, whose oxidative addition to a Pd(Xantphos) catalyst yields a π-allyl complex, with the H-phosphinate group present as a counter ion or bound to Pd. P–C bond formation might then take place either by nucleophilic attack, or by P–C reductive elimination (Scheme 55) [91]. A similar mechanism was suggested for cross-coupling of H_3PO_2 with benzylic alcohols [92].

3.5 Scope of Nucleophilic Partners

As is evident from Scheme 55, the nucleophilic partner in cross-coupling need not be a phosphine. This section surveys recent results with other P-nucleophiles.

3.5.1 Phosphine–Boranes

Pd-catalyzed cross-coupling of secondary phosphine–boranes and aryl iodides has been carried out in ionic liquids using a ligand immobilized with a pyridinium substituent (Fig. 3). Catalyst recycling at least six times without significant loss of activity was possible [93].

Pd-catalyzed asymmetric arylation of a phosphine–borane, under kinetic resolution conditions, gave enantioenriched phosphine–borane **36**. Slowing reductive elimination with a Pd–C_6F_5 group enabled isolation and separation of the diastereomers of an analog of the key intermediate (Scheme 56) [94]. The stereochemical details of Pd–P bond formation and P–C reductive elimination, which both proceed with retention at phosphorus, had been elucidated earlier in related Pd(Chiraphos) complexes [95, 96].

3.5.2 Phosphine Oxides and H-Phosphonates

Cross-coupling of a diastereomerically pure phosphine oxide (**37**) proceeded with retention of configuration at P, consistent with earlier work. After oxidative addition, Pd–P bond formation was proposed to occur from the nucleophilic tautomer of the phosphine oxide, with retention at P, to give the intermediate shown in the box. Deprotonation of the O–H group and retentive P–C reductive elimination then follows (Scheme 57) [97].

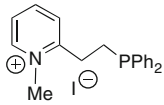
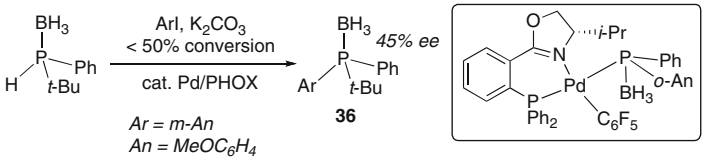
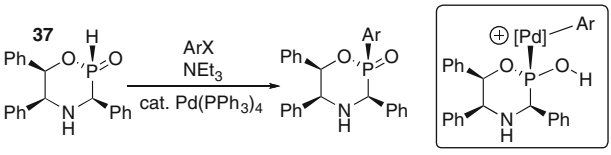


Fig. 3 Pyridinium-tagged phosphine for Pd-catalyzed cross-couplings in ionic liquids



Scheme 56 Pd-catalyzed asymmetric phosphination with a secondary phosphine-borane

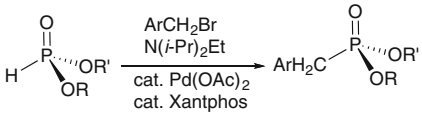


Scheme 57 Retention of P stereochemistry in Pd-catalyzed cross-coupling

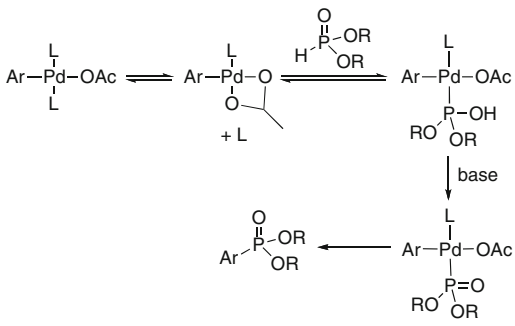
In related Pd(Xantphos)-catalyzed cross-couplings of benzyl halides, reductive elimination was proposed as the slow step, since the overall rate increased with large bite angle ligands [98]. P–C bond formation with isolated diastereomers of dinucleoside H-phosphonates was stereospecific, likely with retention of configuration at phosphorus, as above (Scheme 58).

Added acetate ion promoted the Hirao coupling of $PH(O)(OR)_2$ with aryl bromides and iodides. Formation of a bidentate acetate ligand was suggested to result in PPh_3 dissociation, yielding a more reactive Pd electrophile for coordination (followed by deprotonation) of the H-phosphonate. P–C reductive elimination would then yield the product (Scheme 59) [99, 100].

A related Pd(DPEPhos)-catalyzed cross-coupling used a silver phosphonate, instead of a base and an H-phosphonate, for the Pd–P bond-forming step [101]. To understand ligand and substituent effects in such reactions better, stoichiometric reductive elimination of arylpalladium phosphonate complexes was studied in detail [102]. Diphosphine ligands with larger bite angles promoted the reaction; intermediates with dppe and dppp were detected (Fig. 4), but reductive elimination of the DPEPhos complex was too fast to observe. Unusually, reductive elimination was faster with electron-donating aryl groups, in contrast to related Pd-mediated



Scheme 58 Stereospecific Pd-catalyzed cross-coupling of benzyl bromides with a diastereomerically pure H-phosphonate



Scheme 59 Proposed role of acetate in promoting Pd-catalyzed Hirao couplings

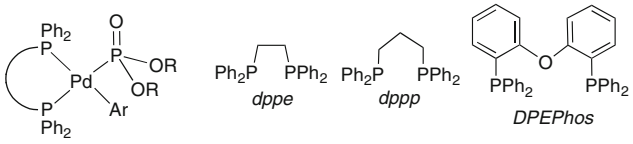


Fig. 4 Ligands used in mechanistic study of the P–C reductive elimination step in cross-coupling of H–phosphonates

reactions which form C–N, C–S and C–P bonds. Attack of the ipso aryl carbon on the phosphonate P is a possible explanation, although concerted reductive elimination could not be ruled out. A computational study was consistent with the experimental Hammett plot ($\rho_I = -2.7$).

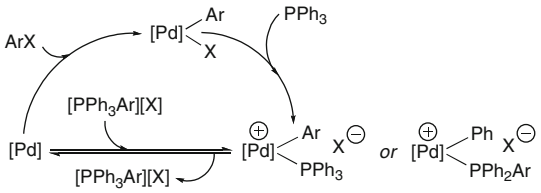
3.5.3 Phosphonium Salts

Cross-coupling may yield phosphonium salts (from PPh_3 and aryl halides or triflates) [103, 104]. In the reverse process, phosphonium salts have been used to make phosphines [105]. The key step in both reactions is thought to be reversible oxidative addition/reductive elimination of the P–C bond (Scheme 60). Switching the solvent to make the salt insoluble avoids this reversible process and is useful in the preparation of the salts.

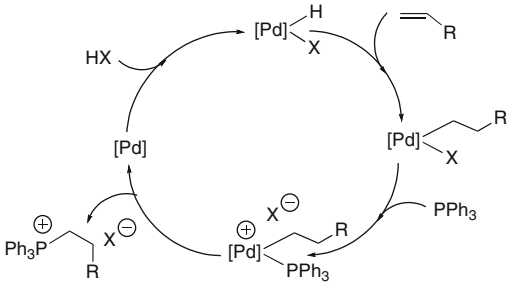
Scrambling of aryl groups between Pd and P by this mechanism has resulted in the formation of byproducts in cross-couplings [106]. More recently, in $Pd(OAc)_2$/PPh_3-catalyzed coupling of $PH(O)(OEt)_2$ with bromoanilines, $PPh(O)(OEt)_2$ was seen as a byproduct [107].

In a related synthesis of phosphonium salts, $Pd_2(dba)_3$ catalyzed addition of alkenes and the acid Tf_2NH to PPh_3 to yield anti-Markovnikov adducts (Scheme 61) [108]. By analogy to related chemistry with alkynes [109], a plausible mechanism involves protonation of Pd, alkene insertion, and P–C reductive elimination.

Coordinated phosphites may also be modified by metal catalysis to act as nucleophiles. For example, in the nickel-catalyzed Arbuzov reaction [110, 111], after oxidative addition of an aryl halide, attack of free or metal-bound halide at

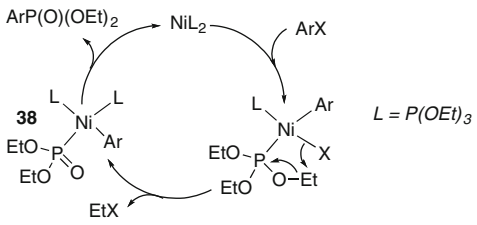


Scheme 60 Proposed mechanism for reversible Pd-catalyzed formation and decomposition of phosphonium salts



Scheme 61 Proposed mechanism for Pd-catalyzed synthesis of phosphonium salts from PPh_3 and an alkene

Scheme 62 Proposed mechanism of cross-coupling in a nickel-catalyzed Arbuzov reaction of aryl halides



carbon in the OEt group of a complexed phosphite was proposed. This process yields ethyl halide and intermediate **38**, which undergoes P–C reductive elimination to form the product and regenerate Ni(0) (Scheme 62).

3.6 Cross-Coupling Without Oxidative Addition

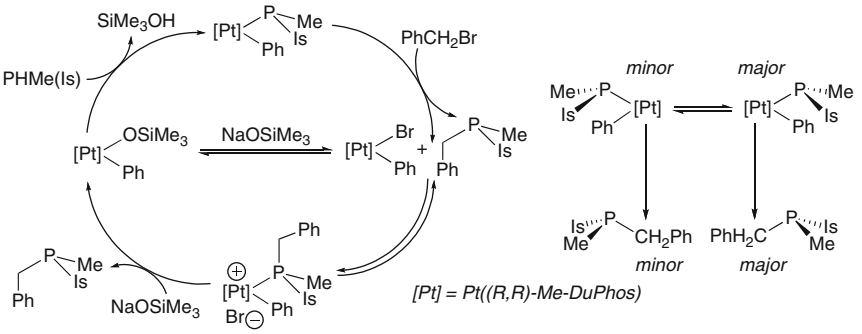
Nucleophilic aromatic substitution often requires metal catalysis, as described above. In contrast, alkyl halides undergo reactions with phosphines directly. Nevertheless, metal-catalyzed cross-couplings of these reactive electrophiles have been developed by activation of the nucleophile.

3.6.1 Alkyl Halides

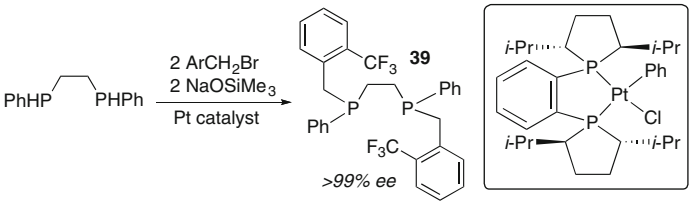
Catalytic symmetric synthesis of P-stereogenic phosphines by cross-coupling of secondary phosphines with benzyl or other alkyl halides was promoted by chiral Pt and Ru complexes [112–114]. The key step is believed to be the nucleophilic attack of a metal–phosphido complex on a free electrophile; the background reaction of the unactivated nucleophilic substrate is much slower. The origin of enantioselectivity, as in the Pd-catalyzed asymmetric cross-couplings described above, is the interconversion of diastereomeric phosphido complexes, whose speciation and relative rates of nucleophilic attack determine the product ratio. In the case of Pt ((*R*,*R*)-Me-DuPhos)(Ph)(PMeIs), as with the Pd analog in Scheme 43 above, the major product phosphine was formed from the major diastereomeric phosphido complex (Scheme 63) [112–113].

Pt-catalyzed alkylations of bis(secondary) phosphines were diastereo- and enantioselective, yielding enriched mixtures of C_2-symmetric *rac* and *meso* bis(tertiary) phosphines. Removal of the *meso* isomer by recrystallization of a phosphine–-borane adduct enabled synthesis of the enantiomerically pure DiPAMP analog **39** by this approach (Scheme 64) [115].

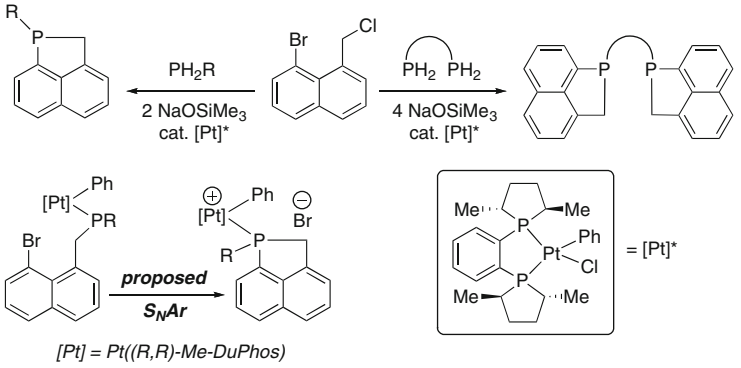
This chemistry has been extended to the tandem alkylation/arylation of primary phosphines with bifunctional naphthalene derivatives. In this case, intermolecular benzylation of a primary phosphine is followed by intramolecular arylation,



Scheme 63 Proposed mechanism and origin of enantioselectivity in Pt-catalyzed asymmetric phosphination of benzyl bromide with PHMe(Is) (Is = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$)



Scheme 64 Synthesis of an enantiomerically pure diphosphine by Pt-catalyzed asymmetric phosphination of a benzyl bromide



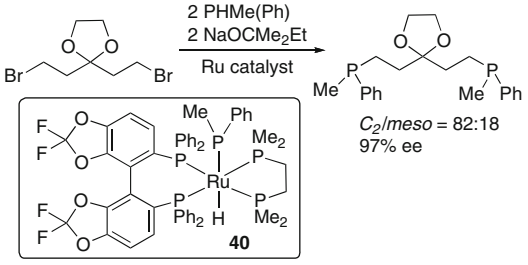
Scheme 65 Enantioselective synthesis of 1-phosphaacenaphthenes by Pt-catalyzed tandem alkylation/arylation of primary phosphines

presumably via nucleophilic aromatic substitution, to yield the novel 1-phosphaacenapthene ring system enantioselectively. With bis(primary) phosphines, formation of four P–C bonds gave potential bidentate ligands (Scheme 65) [116].

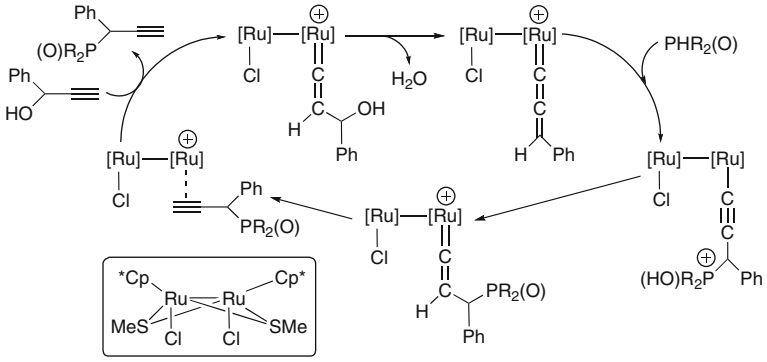
Related ruthenium catalysts contain much more nucleophilic phosphido groups. For example, in a stoichiometric reaction, the phosphido group in $Ru(dmpe)_2(P\text{-}MePh)(H)$ (dmpe = $Me_2PCH_2CH_2PMe_2$) was smoothly alkylated with neopentyl bromide! While this enabled the use of less reactive electrophiles (benzyl chlorides instead of benzyl bromides), the resulting catalytic reactions had to be carried out at low temperature [114]. More recently, phosphination of other electrophiles gave bis (tertiary) diphosphines with good selectivity [117]. Catalysts containing one achiral and one chiral diphosphine were used; Scheme 66 shows an example. Although the catalytic intermediates were not identified, it is likely that phosphido complex **40** is the active species, whose selective nucleophilic attack yields the products.

3.6.2 Other Electrophiles

As shown in Scheme 55 above, electrophiles in phosphination need not include a halide leaving group. Related chemistry with formal nucleophilic substitution of an OH group was reported in cross-coupling of diphenylphosphine oxide with a propargyl alcohol mediated by a dinuclear ruthenium catalyst (Scheme 67) [118–120]. After conversion of the propargyl alcohol to an allenylidene complex

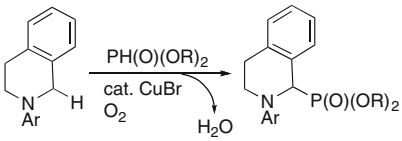


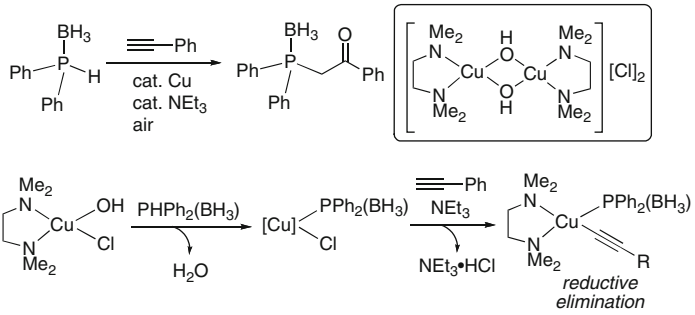
Scheme 66 Diastereo- and enantioselective synthesis of a diphosphine by Ru-catalyzed asymmetric phosphination



Scheme 67 Proposed mechanism for Ru-catalyzed cross-coupling of propargyl alcohol and diphenylphosphine oxide via an allenylidene complex

Scheme 68 Copper-catalyzed cross-coupling of an H-phosphonate and an isoquinoline





Scheme 69 Proposed mechanism of C–P bond formation in Cu-catalyzed cross-coupling of a phosphine-borane and phenylacetylene

via a vinylidene, γ-nucleophilic attack, followed by a series of proton transfers, liberates the alkyne and regenerates the catalyst.

A more unusual leaving group (H) was employed in copper-catalyzed aerobic phosphonation of sp^3 C–H bonds in an isoquinoline derivative (Scheme 68). A speculative mechanism involving nucleophilic attack on a Cu-complexed imine was proposed [121].

In another copper-catalyzed reaction, cross-coupling of alkynes with phosphine–boranes was followed by surprising oxidation to yield ketones (Scheme 69) [122]. The active species was proposed to be a copper phosphido–borane complex, formed by proton transfer to a Cu–OH group. Formation of a Cu-acetylide followed by P–C reductive elimination would then yield a phosphino-alkyne, whose subsequent Cu-mediated air oxidation yields the ketone.

The final step in Scheme 69 is similar to that suggested for nickel or palladium-catalyzed cross-coupling of terminal alkynes with chlorophosphines to give phosphinoalkynes. After P–Cl oxidative addition, Sonogashira-style formation of a metal–alkynyl group and P–C reductive elimination were proposed [123, 124].

4 Conclusion and Future Outlook

This chapter has examined recent advances in metal-catalyzed C–P bond formation. Both reactions in which P–H bonds are added to an unsaturated substrate (hydrophosphination and related processes) and those in which the P–H group is removed

(phosphination) have been reported for a range of metal catalysts, and it is probable that the scope of these transformations will be extended in the future.

Likely growth areas in future research include asymmetric catalysis for synthesis of chiral organophosphorus compounds and more detailed investigation of Cu-catalyzed phosphination, which would be much cheaper than the well-established Pd chemistry. Although some mechanistic information about metal-catalyzed C–P bond formation is available, further studies might assist the development of additional synthetically useful processes.

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C–O Reductive Elimination from High Valent Pt and Pd Centers

Andrei N. Vedernikov

Abstract Reactions of high valent platinum and palladium complexes leading to the formation of C(sp^2)-O and C(sp^3)-O bonds are involved in various catalytic applications such as oxidative functionalization of hydrocarbons, which are especially rich in the case of palladium chemistry. This Chapter emphasizes on the mechanisms of C–O reductive elimination from octahedral d^6 Pt(IV) and, in part, from Pd(IV) complexes. The nature of the leaving groups, the metal center, the presence of soft/hard spectator ligands, the number of hydrocarbyl ligands at the metal, and some other factors affecting the reactivity of such complexes are considered. As shown here, there are still uncharted territories in the area of high valent organoplatinum and organopalladium chemistry: C(sp^2)-O reductive elimination from Pt^{IV}, reactivity and reaction mechanisms of Pt^{III} and Pd^{III} organometallic derivatives, synthesis and reactivity of monoalkyl and monoaryl palladium(IV) complexes stabilized by O-donor ligands, and others. The rapid progress observed in this field of chemistry suggests that some of these areas will soon be explored.

Keywords C–O reductive elimination · Mechanism · Palladium · Platinum

Contents

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1 Introduction

Transition metal mediated carbon–oxygen bond forming reactions constitute an essential tool available to synthetic organic chemists [1]. A classical example is the formation of an aryl ether from an aryl halide and a metal aryloxide or alkoxide catalyzed by Pd^0 complexes. Recent works by Buchwald [2] and Hartwig [3] have contributed significantly to our understanding of the substrate scope of this catalytic C–O coupling reaction, the mechanism of the catalysis, and the structure-reactivity relationship. A simplified reaction sequence leading from an aryl halide Ar–X to a product of a formal nucleophilic substitution of the halogen, Ar–OR, (R = Ar′, Alk), is shown in Fig. 1.

The reaction sequence includes (1) an oxidative addition of C–X bond of the aromatic substrate Ar–X to a Pd^0 center, (2) a substitution of OR for X in the $L_nPd^{II}(Ar)X$ intermediate, and (3) a reductive elimination of the C–O bond from the Pd^{II} center. The ability of palladium(II) alkoxides bearing β-hydrogen atoms to undergo β-hydride elimination imposes some limitations on the type of alkoxide groups that can be involved in these C–O coupling reactions [2]. The C(sp^2)-O reductive elimination reactions from Pd^{II} and Pt^{II} centers have also been studied computationally [4]. The reactions were suggested to proceed via a concerted three-center mechanism.

Recent wide-spreading of the concept of atom economy in chemical synthesis, and economical and ecological requirements have fueled significant interest to selective oxidative functionalization of substrates with C–H and C=C bonds. Catalytic functionalization of CH bonds or olefin C=C bonds with a platinum(II) or a palladium(II) complex leading to products with new C–O bonds may represent a mechanistically more complex case as compared to the reaction sequence shown in Fig. 1. A C–H or C=C bond activation step by a transition metal complex leading

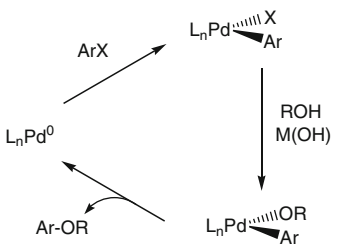

Fig. 1 The mechanism of Pd^0-catalyzed C–O coupling of an aryl halide Ar–X and a metal aryl (alkyl)oxide M(OR)

to a monohydrocarbyl metal intermediate is typically involved in such functionalization reactions. The ability of platinum(II) and palladium(II) compounds to activate alkane and arene C–H bonds is well established.

The subsequent functionalization of an M–C bond present in the resulting organometallic intermediate is the next reaction step. Not much is known about the ways that would allow for an oxy-functionalization of transient monohydrocarbyl palladium(II) and platinum(II) complexes. Both Pd^{II}-C and Pt^{II}-C bonds are relatively inert toward electrophiles. In particular, oxygen, the most abundant and one of the most practically attractive oxidants, is usually unreactive toward such species. As a result, dioxygen activation with organoplatinum(II) and organopalladium(II) complexes is of significant current interest [5–7].

Depending on the nature of an oxidizing agent and an organometallic species involved in the functionalization of a M^{II}-C bond (M = Pd or Pt), an oxidation process can lead either to the formation of a higher-valent organometallic species containing Pt^{IV} [5, 8, 9], Pd^{IV} [10–12], or Pd^{III} [13, 14] complexes (metal-centered oxidation), or to an oxygenated product containing a new C–O bond (dioxygen insertion into M–C bond) [6, 7]. If a metal-centered oxidation occurs, a subsequent C–X reductive elimination of an organic product from a high-valent metal center completes the reaction sequence resulting in a M^{II}-C bond functionalization (see an example in Fig. 2, X = O, Cl). Any advanced knowledge of the possible pathways of C(sp^3)-O and C(sp^2)-O reductive elimination of oxygenated alkyl and aryl derivatives, respectively, from a high valent metal center might be very beneficial for designing more selective and efficient oxidative functionalization reactions. The mechanisms of C–O reductive elimination from high-valent Pt and Pd centers are not limited to a concerted three-center process typical for C–O elimination from Pt^{II} and Pd^{II} compounds [4, 15]. For instance, an S_N2-mechanism of C(sp^3)-O reductive elimination from Pt^{IV} center was suggested for one of the steps of the Shilov reaction [16–18] (Fig. 2). A methyl platinum(IV) transient **3** generated as a result of methane activation with a platinum(II) aqua complex **1** and subsequent oxidation of methyl platinum(II) intermediate **2** with $H_2Pt^{IV}Cl_6$ is a subject to an C(sp^3)-O reductive elimination reaction leading to methanol with water acting as an external nucleophile [18, 19].

The reactivity of platinum(IV) and palladium(IV) hydrocarbyls can be noticeably different from that of their counterparts containing metal(II) centers.

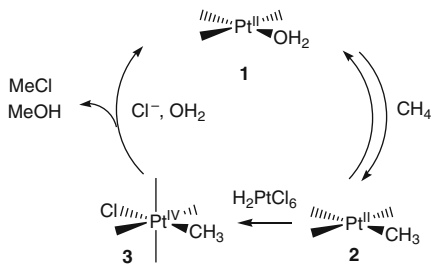

Fig. 2 The proposed mechanism of the Shilov reaction

In particular, in contrast to metal(II) alkyls β-hydride elimination from alkyl metal (IV) species with alkyls bearing β-hydrogen atoms does not typically constitute a problem [20, 21]. As a result, a greater variety of alkyl metal(IV) intermediates might be accessible compared to their alkyl metal(II) analogs.

The C–O reductive elimination chemistry of high valent metal species discovered and matured over the last four decades is being actively explored now. The goals of this Chapter are to overview the C–O bond elimination reactivity of organoplatinum and organopalladium complexes with the metal in an oxidation state greater than +2 and to discuss the C–O reductive elimination mechanisms involving these complexes.

2 General Consideration of C–O Bond Elimination Reactions

2.1 C–X Oxidative Addition and Reductive Elimination Reactions Involving d^8/d^6 Metal Complexes: Microscopic Reversibility

2.1.1 Oxidative Addition of C–X Bonds to Square Planar d^8 Metal Complexes

Reductive elimination of a C–X bond to form an organic product R–Z from a high-valent metal complex $L_nM(R)Z$ is a microscopic reverse of a corresponding process involving C–X oxidative addition to a lower oxidation state metal complex L_nM leading to the high-valent metal compound $L_nM(R)Z$ [15]. In the case of square planar d^8 metal complexes, the C–X oxidative addition reactions (X = halogens, O, N) most often proceed via either an S_N2 mechanism resulting in a trans-addition of R–Z to the metal (Fig. 3, path **a**) or a concerted three-center mechanism resulting in a *cis*-addition of R–Z to the metal (Fig. 3, path **b**), depending on the nature of Z, the hydrocarbyl R, and the metal M. Homolytic pathways are also known for some organic bromides and iodides, as well as reactions involving two metal centers (binuclear oxidative addition) [15].

An oxidative addition reaction to a single metal center usually results in an octahedral metal complex as shown in Fig. 3, but five coordinate reaction products $L_nM(R)$ can also form. For instance, dimethyl Pt^{II} complexes supported by sterically bulky anionic N-acetyl-N-acetonate ligands can react with methyl iodide to produce stable five coordinate Pt^{IV} complexes [22]. Square planar d^8 metal complexes use electrons located on the metal d_{z2} orbital to make a bond to an electrophilic carbon atom. In turn, a lone pair of electrons on X is ultimately donated to a metal empty orbital directed either trans- (Fig. 3, path **a**) or *cis*- (Fig. 3, path **b**) with respect to the M–C bond. Based on the principle of microscopic reversibility, a sequence of the same elementary reactions but occurring in the reverse order is expected for the corresponding reductive elimination reaction. Note that for a

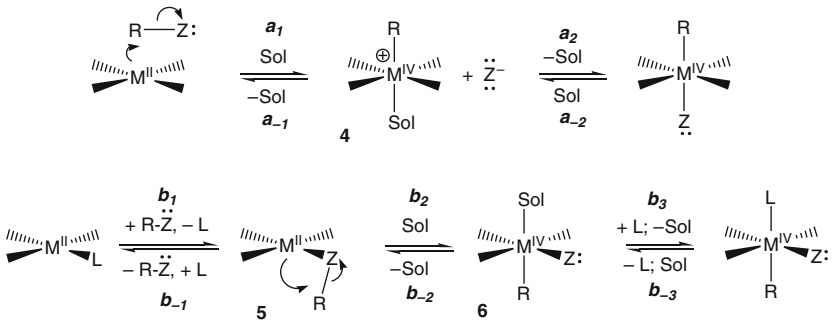

Fig. 3 Two mechanisms of oxidative addition of a C–X bond (X = halogen, O, N) of an organic reagent R–Z to a square planar d^8 metal complex (M = Pd, Pt). *Sol* designates a potential solvento ligand

particular combination of reagents R–Z and L_nM and product $L_nM(R)Z$, one of the two reactions, either forward or reverse, can be virtually unobservable. In particular, when a R–Z oxidative addition reaction to a metal complex L_nM to produce $L_nM(R)Z$ is very favorable thermodynamically, which is often the case for L_nM containing a low valent metal M, the reverse process, a R–Z reductive elimination from $L_nM(R)Z$ may be difficult to observe. In such a case, a detailed mechanistic study of the readily observable oxidative addition reaction can be used to analyze the mechanism of the corresponding reverse process.

Consider two mechanisms of a C–X oxidative addition reaction involving a square planar d^8 metal complex (Fig. 3).

If an S_N2 oxidative addition mechanism is realized (path **a**), the M–C and M–X bonds are formed during two separate steps of the reaction (steps a_1 and a_2) resulting in a reaction product with an octahedral metal configuration. An expected five coordinate intermediate can actually be stabilized by coordination of a solvent molecule (*Sol*) as shown in structure **4**. The configuration of the carbon atom in R–Z is inverted at the step a_1. Importantly, from both synthetic and mechanistic points of view, if a ligand Y^- more nucleophilic than Z^- is present in the reaction mixture in sufficient concentration, the intermediate **4** can be intercepted by Y^- to produce a $L_nM^{IV}(R)Y$ complex (1):

$$L_nM^{II} + R - Z + Y^- \rightarrow L_nM^{IV}(R)Y + Z^- \quad (1)$$

If a concerted three-center oxidative addition mechanism is realized (path **b**), first a lone electron pair of an atom X (X = O, N) is used to form the M–X bond resulting in a complex **5** (step b_1). Formation of the M–C bond and cleavage of the C–X bond constitute a concerted process resulting in a five coordinate intermediate, which can be stabilized by coordination of a solvent molecule (*Sol*) as in structure **6** (step b_2) similar to **4**. Finally, by coordination of ligand L, the intermediate **6** can produce an octahedral reaction product (step b_3) shown in Fig. 3, **b**. The configuration of the carbon atom present in R–Z is retained during oxidative addition to the metal.

2.1.2 Reductive Elimination of C–X Bonds from Octahedral d^6 Metal Complexes

Consider now Fig. 4 showing two mechanisms of C–X reductive elimination from an octahedral d^6 metal species. According to the principle of microscopic reversibility, the mechanisms in Fig. 4 are the microscopic reverse of those in paths **a** and **b** in Fig. 3.

The two key steps of an S_N2 reductive elimination mechanism (Fig. 4, path **a**) are dissociation of Z^- from a high valent metal center (step a_{-2}) and a nucleophilic attack of Z^- at the metal-bound carbon in the intermediate **4** (step a_{-1}). The reaction leads to a product of trans-elimination of R–Z with the inversion of the configuration of the metal-bound carbon atom.

The key steps of a concerted three-center reductive elimination mechanism (Fig. 4, path **b**) are dissociation of the ligand L trans- to the hydrocarbyl R (step b_{-3}), a concerted M–C bond cleavage and C–X bond formation (step b_{-2}), and a displacement of the organic product R–Z by the ligand L (step b_{-1}). The reaction leads to the product of *cis*-elimination of R–Z with the retention of the configuration of the metal-bound carbon atom.

2.2 *General Trends in the Reactivity of Pt^{IV} and Pd^{IV} Complexes in C–O Reductive Elimination Reactions*

2.2.1 M^{IV}/M^{II} Redox Potentials

The reactivity of Pt^{IV} and Pd^{IV} complexes in a C–O reductive elimination reaction depends on a number of factors, including structural and solvent effects. One of the factors is the tendency of a particular high valent metal center M^{IV} to be reduced to

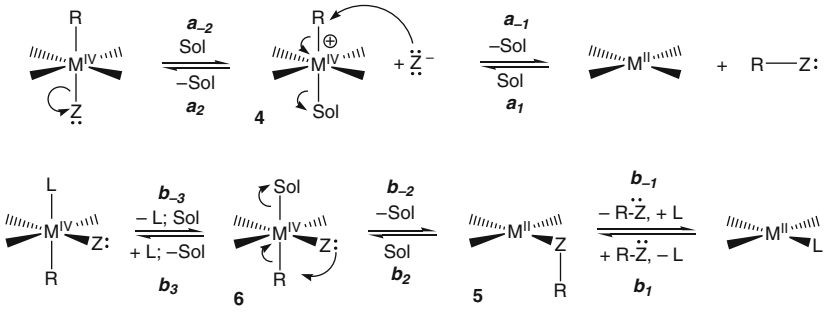

Fig. 4 Two mechanisms of the reductive elimination of a C–X bond (X = O, N) from an octahedral d^6 metal complex (M = Pd, Pt) leading an organic product R–Z. Mechanisms **a** and **b** are the microscopic reverse of those in the paths **a** and **b** in Fig. 3, respectively. *Sol* designates a potential solvento ligand

the M^{II} state. The standard redox potentials for aqueous solutions of Pt^{IV} and Pd^{IV} chloro complexes $[M^{IV}Cl_6]^{2-}$ are 0.73 and 1.29 V, respectively (2 and 3):

$$[PtCl_6]^{2-} + 2e^- \rightarrow [PtCl_4]^{2-} + 2Cl^- \quad E^\circ = 0.73\ V \tag{2}$$

$$[PdCl_6]^{2-} + 2e^- \rightarrow [PdCl_4]^{2-} + 2Cl^- \quad E^\circ = 1.29\ V \tag{3}$$

Therefore, one has to expect a greater thermodynamic driving force for a C–O reductive elimination from Pd^{IV} complexes compared to their Pt^{IV} analogs. Though this trend might not necessarily be reflected in kinetics, in fact, it is usually observed for high valent derivatives of these metals: for both inorganic and organometallic compounds, the reactivity in reductive elimination reactions is higher for Pd^{IV} analogs. Compounds containing Pd^{IV} are more difficult to prepare compared to their Pt^{IV} counterparts.

2.2.2 Hard Vs. Soft Spectator Ligands

As the redox potentials for the majority of organopalladium(IV) and organoplatinum(IV) complexes are unavailable, to be able to analyze some reactivity trends, it may be useful to consider the structural factors that affect the relative stability of the high- and low- valent organoplatinum and organopalladium derivatives. One of these factors is the nature of the donor atoms in the ligands stabilizing the high-valent metal complex. N- and O-donor ligands are hard Lewis bases that tend to stabilize better a high valent metal center than a lower valent metal center found in the product of a reductive elimination reaction. A high valent metal is a harder Lewis acid than its lower-valent precursor. Therefore, the former is a better match to the hard spectator ligands. The opposite is true for ligands – soft Lewis bases such as phosphines. Soft Lewis bases are a better match to a lower valent metal center than to a higher oxidation state metal atom. The overall effect of spectator ligands – hard bases is a decrease of the driving force for a C–X bond elimination reaction from a M^{IV} center, whereas ligands – soft bases increase the driving force for elimination reactions. An activation barrier for a C–X reductive elimination reaction from N- or O-donor stabilized Pt^{IV} or Pd^{IV} complexes may be noticeably higher as well, as compared to their phosphine analogs.

For instance, a cationic aqua complex *fac*-$[PtMe_3(OH_2)_3]^+$ is indefinitely stable in aqueous solutions at elevated temperatures, whereas diphosphine – supported trimethyl platinum(IV) complexes such as *fac*-(dppbz)$Pt^{IV}Me_3(OR)$ and *fac*-(dppe)$Pt^{IV}Me_3(OR)$ shown in Fig. 5 undergo concurrent C–C and C–O reductive elimination at 120°C [21, 23, 24].

2.2.3 The Number and the Nature of Hydrocarbyl Ligands

The number and the nature of hydrocarbyl groups at a high valent metal center have also a profound impact on the tendency of a particular M^{IV} compound to undergo a

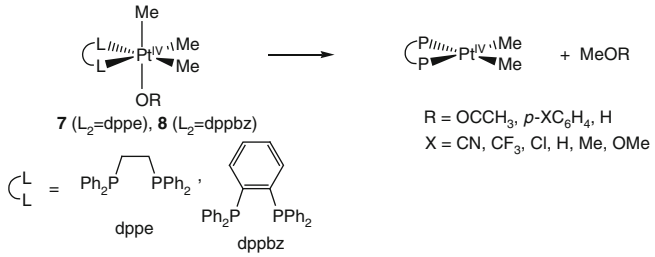

Fig. 5 An S_N2 reductive elimination of a C(sp^3)-O bond from model trimethyl Pt^{IV} complexes [21, 23, 24]

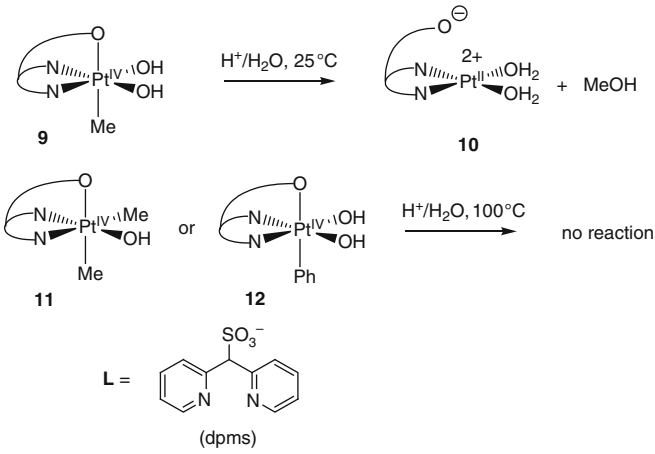

Fig. 6 Formation of methanol as a result of a C(sp^3)-O reductive elimination from symmetric complex (dpms)$Pt^{IV}Me(OH)_2$ in acidic aqueous solutions

reductive elimination. Trihydrocarbyl derivatives are less oxidizing compared to structurally similar dihydrocarbyl complexes, whereas monohydrocarbyls are more oxidizing and more reactive in C–O reductive elimination than dihydrocarbyls. For example, an unsymmetric dimethyl hydroxo Pt^{IV} complex supported by di(2-pyridyl)methanesulfonate ligand (dpms), **11**, is indefinitely stable in acidic aqueous solutions at 100°C, whereas its monomethyl analog (dpms)$Pt^{IV}Me(OH)_2$, **9**, produces methanol and a diaqua Pt^{II} complex **10** in acidic solutions in water in >95% yield at room temperature (Fig. 6) [9].

The phenyl complex **12** of a similar structure is kinetically more resistant to C–O reductive elimination than the methyl analog **9** as different reductive elimination mechanisms are expected to be operational in these two cases, concerted three-center in the case of the aryl derivative and an S_N2 mechanism in the case of the alkyl complex. In particular, the symmetric phenyl complex (dpms)$Pt^{IV}Ph(OH)_2$, **12**, in Fig. 6 is completely inert in acidic aqueous solutions at 100°C [25], whereas its methyl analog **9**, (dpms)$Pt^{IV}Me(OH)_2$, eliminates methanol via an S_N2 mechanism at room temperature [9].

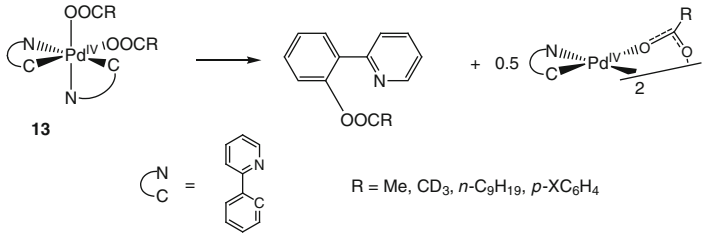

Fig. 7 Concerted three-center reductive elimination of C(sp^2)-O bonds from model diaryl dicarboxylato Pd^{IV} complexes [11, 12]

2.2.4 Pt^{IV} Vs. Pd^{IV} Hydrocarbyls

As a result of the combined effect of the factors mentioned above, Pd^{IV} monoalkyl complexes are expected to be the least stable among M^{IV} hydrocarbyls (M = Pd, Pt). Such complexes are currently unknown, whereas monoalkyl Pt^{IV} complexes were among the first compounds characterized in C(sp^3)-O reductive elimination reactions [16–19]. Among monoaryl Pd^{IV} derivatives only few were isolated to date; all of them are stabilized by fluoride ligands [26, 27]. No monohydrocarbyl Pd^{IV} complexes supported by O-donor ligand have yet been reported and characterized. The most studied O-ligated organopalladium(IV) complexes are diaryl dicarboxylates **13** shown in Fig. 7 [11, 12].

These relatively stable and well characterized complexes can exhibit C(sp^2)-O reductive elimination reactions leading to corresponding arylcarboxylates in high yield.

2.3 Mechanisms of C–O Reductive Elimination

2.3.1 S_N2 Mechanism. C(sp^3)-O Elimination

An S_N2-type mechanism is typical for alkyl derivatives R–Z (Fig. 4); their reactivity decreases in the following sequence of R: Me > 1° > 2°. Hence, for alkyl derivatives it is most common to discuss C(sp^3)-O elimination reactions. The reactivity of octahedral d^6 metal complexes in C(sp^3)-O reductive elimination reactions that proceed via S_N2 mechanisms was studied in detail for Pt^{IV} complexes. High valent alkyl palladium complexes with O-donor ligands are much less stable and less synthetically accessible. A stereochemical evidence exists that high valent alkyl palladium acetate complexes might undergo C(sp^3)-O reductive elimination via an S_N2 mechanism involving an inversion of configuration of the metal-bound carbon atom [28]. A similar report discussing possible involvement of high valent palladium alkyls in a C(sp^3)-O – forming S_N2 reductive elimination has been published [29].

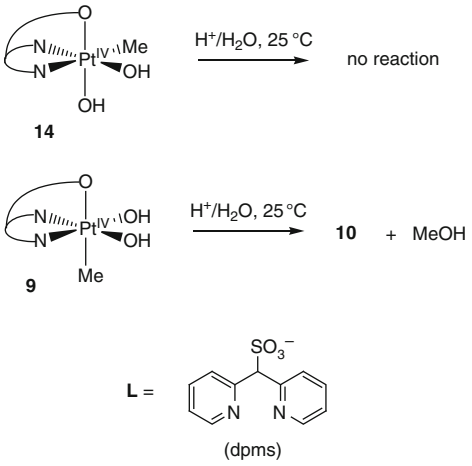

Fig. 8 The effect of the quality of a leaving group in trans- C(sp^3)-O elimination reactions

In the case of an S_N2 mechanism leading to a trans-elimination (path **a**, Fig. 4), the ability of Z^- to serve as a good leaving group (Fig. 4, step a_{-2}) and/or the electrophilicity of the metal-bound carbon atom in the intermediate **4** (step a_{-1}) are the key parameters.

For example, the reactivity of an unsymmetric monomethyl Pt^{IV} complex **14** in the C(sp^3)-O reductive elimination of methanol is at least three orders of magnitude lower than that of the symmetric complex **9** (Fig. 8) [9]. The former compound has a pyridine ligand as a leaving group trans- to the Pt^{IV} – bound methyl, whereas in the latter complex **9** the leaving group trans- to the methyl is the sulfonate. The dramatic difference in the reactivity of **14** and **9** is due to the different quality of the leaving group, py $<<$ SO_3^-.

Typically, though not always, the abilities of a ligand to be a good leaving group (step a_{-2}) and to be a good nucleophile (step a_{-1}) are not the qualities observed simultaneously. If a ligand Z^- is a relatively good leaving group but not a strong nucleophile, the nucleophilic attack of Z^- at **4** (step a_{-1}) is the rate-limiting step.

Figure 9 shows a schematic representation of the potential energy profiles for a two-step C–X reductive elimination from a M^{IV} center with step a_{-1} being the rate limiting (*solid line*). A one-step C–X reductive elimination with an external nucleophile Z^- is also presented (*dashed line*). The two-step reaction path in Fig. 9 includes a five coordinate intermediate or a six-coordinate solvento-complex **4** and leads to a lower energy transition state $\mathbf{TS_S}$ compared to the transition state $\mathbf{TS_{S6}}$ that corresponds to a direct nucleophilic attack of Z^- at the metal-bound carbon of the starting six coordinate compound.

The main factors that favor greater reactivity of **4** compared to that of the starting complex can be (1) the cationic nature of the intermediate **4**, which enhances the electrophilicity of the metal-bound carbon and its susceptibility to nucleophilic attacks, and (2) the weak M-*Sol* bond (if any) that will be partially broken in the transition state $\mathbf{TS_S}$ and completely broken in the reaction product.

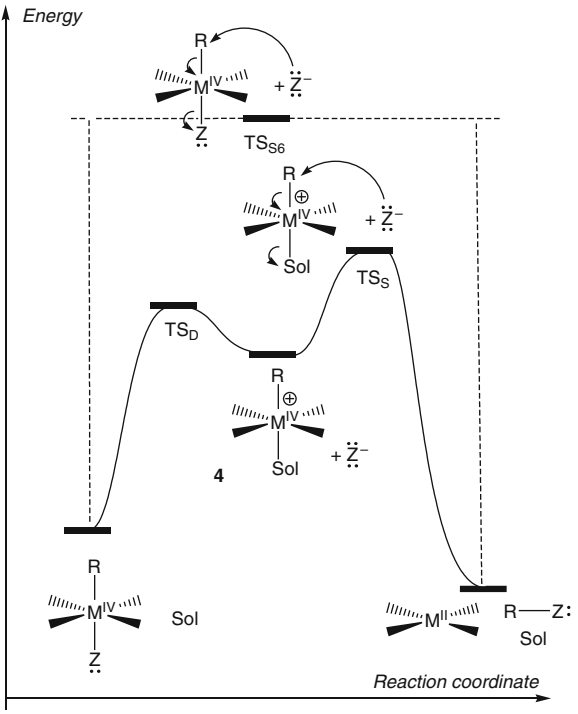

Fig. 9 A schematic representation of two possible potential energy profiles for an S_N2 reductive elimination reactions of an organic product R–Z from a M^{IV} center: a two-step C–X bond elimination (*solid line*) and one-step C–X reductive elimination (*dashed line*). *Sol* designates a potential solvento ligand

A one-step elimination mechanism via $\mathbf{TS_{S6}}$ was suggested to be not viable for a series of complexes *fac*-$L_2PtMe_3(Z)$, where L_2 = dppe (**7**) or dppbz (**8**) and Z = OAc or OAr (Fig. 5) [23, 24]. It was shown that additives of nucleophiles in the form of *n*-$Bu_4N(OAc)$ (Z = OAc) or [K@18-crown-6](OAr) (Z = OAr) in THF solutions of the complexes above do not affect the rate of the C–O elimination from the Pt^{IV} center. On the basis of the absence of a linear dependence between the C–O elimination rate and concentration of nucleophile additives in solution as well as some other considerations, it was concluded that the reaction does not follow a one-step mechanism including a direct nucleophilic attack upon six coordinate starting complex (Fig. 9, *dashed line*) but rather follows a two-step nucleophilic mechanism (Fig. 4, path **a**; Fig. 9, *solid line*).

Improving the quality of the leaving group, $Z^- = ArO^-$, in complex **8** by introducing electron-withdrawing substituents to the *para*-position of an aryloxide ArO^- leads to a faster C–O reductive elimination kinetics (*p*-CN > *p*-CF_3 > *p*-Cl > H > *p*-Me ~ *p*-OMe). It was suggested that the energy of the transition state $\mathbf{TS_D}$ (Fig. 9) and the rate of dissociation of an aryloxide from the Pt^{IV} center are more

sensitive to the nature of such substituent than the nucleophilic reactivity of ArO^- and the related energy of the corresponding transition state $\mathbf{TS_S}$.

In general, in the case of an S_N2 C–O reductive elimination reaction with the rate limiting step a_{-1} (Fig. 4), the presence of a different nucleophilic species Y^- in the reaction mixture in sufficient concentrations can lead to elimination of the product R–Y which results from an interception of the intermediate **4** by Y^- (4):

$$L_nM^{IV}(R)Z + Y^- \rightarrow L_nM^{II} + R - Y + Z^- \quad (4)$$

As both nucleophiles, Z^- and Y^-, can participate in a reductive elimination reaction, a mixture of reaction products, R–Z and R–Y, forms. Such behavior is observed in the Shilov reaction (Fig. 2). Formation of a mixture of methanol and methyl chloride is considered in Shilov chemistry as a result of occurrence of two concurrent S_N2 processes with water and chloride anion as competing nucleophiles [18, 19]. The rate of the formation of chloromethane in aqueous solutions of $[MePt^{IV}Cl_5]^-$ in this reaction was shown to be first order in chloride ion concentration.

Figures 4 and 9 can also be used for a comparative analysis of the S_N2-type reactivity of Pd^{IV} alkyl complexes *vs*. their Pt^{IV} analogs. The former are expected to react at much faster rates. The major reasons for that are (1) a greater kinetic lability of palladium compounds compared to their platinum counterparts that would increase the rate of reductive elimination from Pd^{IV} intermediate **4** (Fig. 4, step a_{-2}) and lower the energy of the transition state $\mathbf{TS_D}$ (Fig. 9), and (2) greater oxidizing power of Pd^{IV} compared to Pt^{IV}. The latter factor would decrease the activation barrier for the step a_{-1} and the energy of the transition state $\mathbf{TS_S}$. Some available reports on C(sp^3)-O reductive elimination from presumed high valent palladium intermediates are consistent with this analysis [10, 28].

Electrophilicity of an alkyl metal(IV) complex is an important factor affecting its reactivity toward external nucleophiles (4). Protonation of symmetric (dpms) $PtMe^{IV}(OH)_2$ complex **9** (Fig. 6) in water was shown to enhance its susceptibility to nucleophilic attacks [9, 30]. In the absence of strong acid additives, the C–O reductive elimination is sluggish even at 90°C [9], whereas in the presence of 1 equivalent of HBF_4 the reaction proceeds at a noticeable rate at room temperature.

2.3.2 S_N2 Elimination with Hydroxo Pt^{IV} Complexes as External Nucleophiles

The Shilov reaction is an example of an S_N2 – type C(sp^3)-X reductive elimination reaction where several nucleophiles compete for the same electrophilic high-valent metal complex [18, 19]. A detailed analysis of C(sp^3)-O reductive elimination from symmetric (dpms)$Pt^{IV}Me(OH)_2$, **9**, in aqueous solutions shows that this reaction also follows a complex mechanism characterized by the involvement of several competing nucleophilic Pt^{IV} hydroxo and methoxo complexes (Fig. 10) [30].

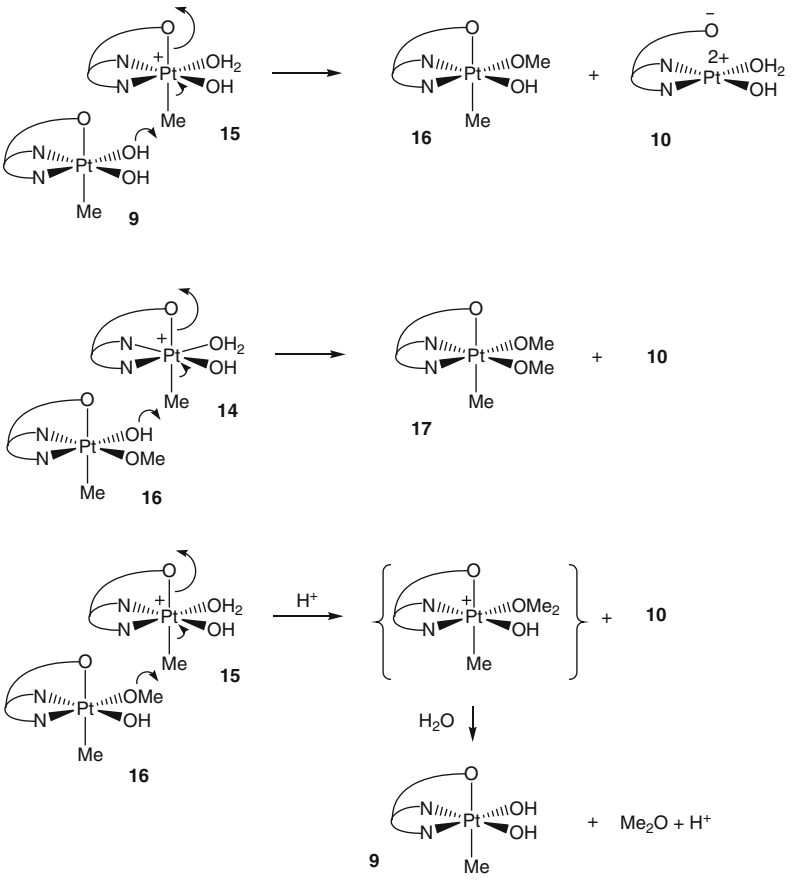

Fig. 10 Nucleophilic attack of hydroxo and methoxo complexes, (dpms)$Pt^{IV}Me(OH)_2$ and (dpms)$Pt^{IV}Me(OH)(OMe)$, at the protonated electrophilic (dpms)$Pt^{IV}Me(OH)(OH_2)^+$ species

One of the indications of a complex reaction mechanism is the fact that, besides methanol, the reaction produces dimethyl ether in the amount of up to 5%.

Another important observation is that the reaction carried out in 98%-enriched ^{18}O-labeled water produces, along with the expected ^{18}O-labeled methanol, a significant, up to 50 mol %, fraction of non-labeled methanol, $Me^{16}OH$. The $Me^{16}OH : Me^{18}OH$ ratio is proportional to the concentration of the starting complex which is the only other major source of non-labeled oxygen atoms present in the reaction mixture besides residual $H_2{}^{16}O$ in the solvent.

These observations could be accounted for assuming that complex **9** and two complexes shown in Fig. 10, (dpms)$Pt^{IV}Me(OH)(OMe)$, **16**, and (dpms)$Pt^{IV}Me(OMe)_2$, **17**, are the nucleophiles that compete with water in this system. The nucleophilicity of complex **9** was estimated to be about 10^3 greater than that of water, allowing for an efficient competition with the solvent for protonated

electrophilic (dpms)$Pt^{IV}Me(OH)(OH_2)^+$, **15**. Both (dpms)$Pt^{IV}Me(OH)(OMe)$, **16**, and (dpms)$Pt^{IV}Me(OMe)_2$, **17**, could be detected in reaction mixtures and were shown to be kinetically competent reaction intermediates.

These results suggest that alkyl M^{IV} complexes bearing nucleophilic O-donor ligands and, presumably, other nucleophilic ligands such as amides, can compete successfully with other nucleophiles present in a reaction mixture. The consequences of this competition are (1) formation of a complex mixture of reaction intermediates, (2) formation of "unexpected" products of C–X elimination such as Me_2O in the case above, and (3) observation of a complex rate law.

2.3.3 Concerted Three-Center Mechanisms. C(sp^2)-O and C(sp^3)-O Elimination from Pd^{IV}

Concerted three-center C–O reductive elimination is most common for aryl Pd^{IV} complexes. Up to date, the most studied reaction of this type is C(sp^2)-O reductive elimination of aryl carboxylates from diaryl dicarboxylato Pd^{IV} complexes (Fig. 7) [11, 12]. It is presumed that C(sp^3)-O reductive elimination from high valent alkyl palladium intermediates can also occur [31]. Reactions involving C(sp^2)-O reductive elimination from Pt^{IV} compounds are currently unknown.

On the basis of the analysis of the stereochemical outcome of oxidatively induced palladium-catalyzed C(sp^3)-O forming reactions leading to substituted tetrahydrofurans, it was suggested that high valent alkyl palladium intermediates can react via a concerted three-center reductive elimination mechanism to form C (sp^3)-O bonds [31]. No characterization of these presumed high valent species or mechanistic studies of their reactions have been carried out.

An interesting pertinent question to answer is whether or not concerted three-center C–O elimination reactions proceed via a dissociation – elimination mechanism involving a formally five coordinate intermediate or its solvento adduct such as **6** (Fig. 11, *solid line*) or a direct elimination from the six coordinate starting complex (Fig. 11, *dashed line*) takes place.

In the case of the C(sp^2)-O elimination reaction shown in Fig. 7, it was established that a dissociation of the carboxylate ligand trans- to the aryl from the starting Pd^{IV} complexes **13** does occur at temperatures much lower than those required for the C–O reductive elimination reaction. This observation suggests that the reaction might proceed via a cationic intermediate **6** and follow a reaction path shown in Fig. 11 with a *solid line*. If so, the transition state $\mathbf{TS_D}$ which corresponds to the carboxylate dissociation is of a noticeably lower energy compared to the $\mathbf{TS_C}$ corresponding to the R–Z elimination step. A Hammett analysis of the kinetics of the reaction in Fig. 7 showed that increased nucleophilicity of the benzoate *p*-XC_6H_4COO in complexes **13** leads to a faster kinetics (*p*-OMe > *p*-Me > H > *p*-OPh > *p*-F > *p*-Cl > *p*-Ac > *p*-CF_3 > *p*-CN > *p*-NO_2), a trend opposite to that observed for trimethyl Pt^{IV} complexes **8** involved in an S_N2-type reaction shown in Fig. 5. As the electronic requirements to the nucleophilicity of Z for the

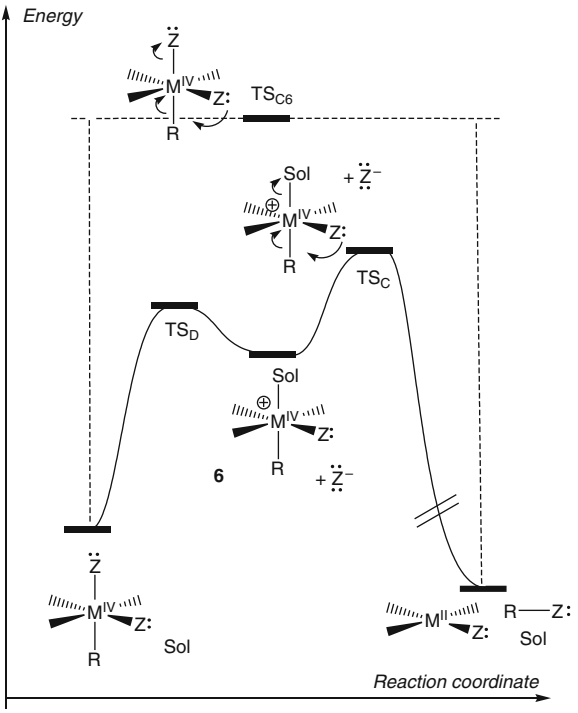

Fig. 11 A schematic representation of the potential energy profiles for a concerted three-center C–X reductive elimination of an organic product R–Z via a cationic intermediate **6** (*solid line*) and directly from the six coordinate reactant (*dashed line*). *Sol* designates a potential solvento ligand

mechanisms in steps a_{-1} and b_{-2} in Fig. 4 may be different, this observation does not look to be alarming.

At the same time, when choosing between the dissociation – reductive elimination reaction path (Fig. 11, *solid line*) and the reaction path including a direct elimination from the six coordinate starting complex (Fig. 2, *dashed line*), it is worth to note that there might exist a continuum of structures of potential transition states corresponding to a concerted C–O reductive elimination, ranging from $\mathbf{TS_{C6}}$ to $\mathbf{TS_C}$ shown in Fig. 11. These structures may differ by the degree of dissociation of the ligand trans- to R, with M–Z bond length ranging from an elongated one as in $\mathbf{TS_{C6}}$ (such tight ion-pair like structures for C(sp^2)-I elimination from Pt^{IV} diphosphine complexes have been analyzed previously [32]) to a very large one corresponding to a solvent-separated ion pair as in $\mathbf{TS_C}$. The presence of a metal-coordinated solvent ligand separating M and Z^- allows to distinguish between $\mathbf{TS_C}$ and $\mathbf{TS_{C6}}$ already on a qualitative level. If solvent cannot coordinate to the metal because of some steric or electronic effects, the actual transition state for a particular system might be closer to either $\mathbf{TS_C}$ or $\mathbf{TS_{C6}}$. In that case, a complete dissociation of the ligand Z from the metal will not be required (the transition state $\mathbf{TS_D}$ will be absent), and it is impossible to distinguish between two mechanisms

shown in Fig. 11. The nature of the metal, ligand Z, solvent, and additives to the reaction mixture might be among the factors affecting the mechanism of concerted three-center C–O elimination as well as the structure and energy of the corresponding transition states.

In the case of either of the two mechanisms of concerted three-center C–O reductive elimination, one involving six coordinate complex or another involving a potentially five coordinate transient **6**, a better leaving group Z would favor a faster elimination reaction. For instance, di(-2-pyridyl)methanesulfonate ligand shown in Fig. 6 has a good leaving group, the sulfonate. This ligand was shown to be a suitable platform for a number of platinum complexes active in C–H activation and C–O reductive elimination reactions, the latter including S_N2 and concerted three-center mechanisms [5].

2.3.4 Concerted Three-Center Mechanisms. C(sp^3)-O Elimination from Pt^{IV}

Examples of C(sp^3)-O reductive elimination of olefin oxides from Pt^{IV} center have been reported recently (Fig. 12) [33]. In the case of Pt^{IV} oxetanes derived from strained cycloolefins, norbornene and cyclooctene, the elimination reactions can proceed readily at 40−60°C in a number of solvents and even in the solid state. The reaction is highly stereoselective; formation of a single isomer of an olefin oxide is observed for norbornene. Importantly, as for complexes **9** and **14** (Fig. 8), the reactivity of the Pt^{IV} oxetane **19** with an alkyl ligand trans- to the sulfonate is much higher than that of an isomeric compound **18** where the pyridine ligand, a poorer leaving group is trans- to the alkyl.

A computational study of the concerted C(sp^3)-O reductive elimination of olefin oxides from complexes **19a** and **19b** showed that the Gibbs activation energy of epoxide elimination increases in the following order of **19a** ∼ **19b** ≪ **20** [33]. In other words, migration of a secondary alkyl from the Pt^{IV} center to the oxetane oxygen atom is a more facile process than that involving a primary alkyl group.

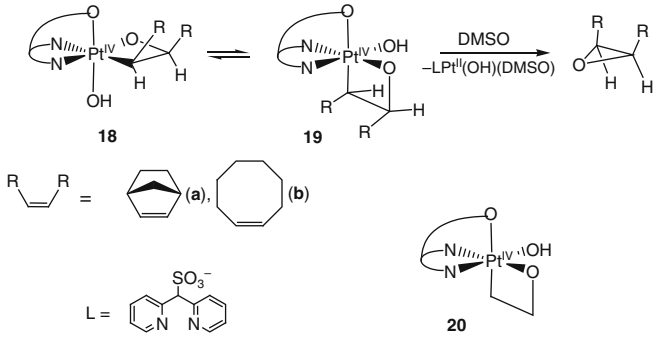

Fig. 12 Concerted three-center C(sp^3)-O reductive elimination of olefin oxides from Pt^{IV} oxetane complexes [33]

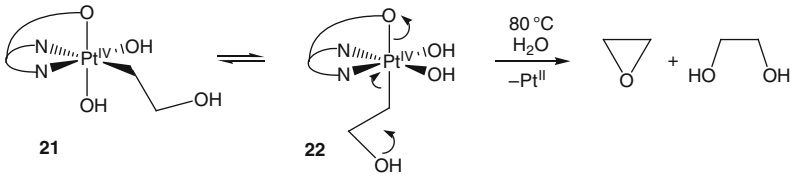

Fig. 13 Nucleophilic C(sp^3)-O elimination of ethylene oxide from a Pt^{IV} 2-hydroxoethyl complex [34]

This trend is different from that known for S_N2 – type C(sp^3)-O reductive elimination reactions observed earlier for alkyl Pt^{IV} complexes.

Interestingly, an epoxide also forms as a primary reaction product along with the product of its hydrolysis, ethylene glycol, in C(sp^3)-O reductive elimination from (dpms)$Pt^{IV}(C_2H_4OH)(OH)_2$ complex **21** in aqueous solutions (Fig. 13) [34]. No Pt^{IV} oxetane intermediates could be detected in this system. Even if the oxetane **20** did form, the expected low reactivity of this compound would preclude the epoxide elimination at relatively low temperatures. It was assumed that a three-center C–O elimination mechanism is not involved in this transformation.

The reaction was proposed to include an intramolecular nucleophilic attack of the oxygen atom present in the 2-hydroxyalkyl fragment at the Pt^{IV} – bound carbon. The reaction involves an isomerization of a less reactive dpms complex **21** to a more reactive isomeric **22** with the alkyl trans- to the sulfonate.

3 Dinuclear Pt^{III} and Pd^{III} Systems

An oxidative functionalization of M^{II}-C bonds, which was discussed in the Introduction, can be performed in the case of Pt^{II} alkyl complexes using dioxygen as oxidant and dpms as a ligand which enables both dioxygen activation and C(sp^3)-O reductive elimination in hydroxylic solvents. Corresponding alkyl Pt^{IV} hydroxo complexes could be isolated and thoroughly characterized in the C–O elimination reactions [5]. In some specific cases, dioxygen can also be used for ligand-enabled functionalization of benzylic C-Pd^{II} bonds [35]. In contrast, much stronger oxidants, Oxone or iodine(III) compounds such as $PhI(OAc)_2$, are used to functionalize Pd^{II}-C bonds in aryl and non-activated alkyl palladium complexes [36]. The initial hypothesis of the authors was that unstable hydrocarbyl palladium(IV) intermediates are involved in this reaction [28, 29, 31, 37]. These reactive monohydrocarbyl Pd^{IV} species that have never been isolated from or observed in the reaction mixtures were considered as a subject to a facile C–O reductive elimination. In support to this idea, studies involving diaryl Pd^{IV} dicarboxylates **13** showed that a C(sp^2)-O reductive elimination can readily occur in this model system. In spite of this fact, in the most recent communications from the Sanford [14] and other [13] groups the plausible mechanism of Pd^{II}-C bond functionalization in the presence of $PhI(OAc)_2$

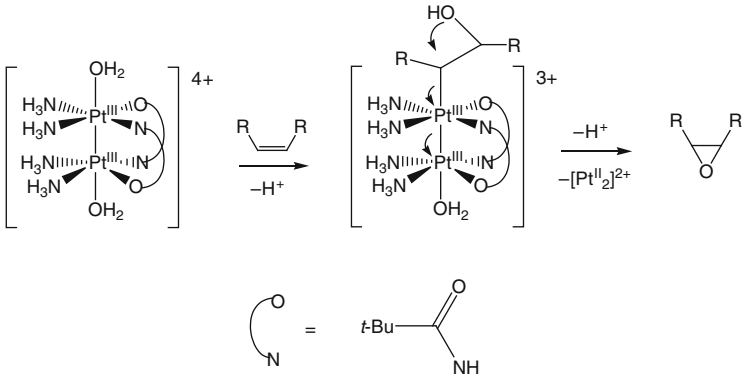

Fig. 14 Formation of β-hydroxyalkyl diplatinum(III) complexes and a proposed mechanism of the C(sp^3)-O reductive elimination of epoxides [38]

and similar iodine(III) compounds has been revised. The observed second-order dependence in palladium concentration for Pd^{II}-catalyzed catalytic oxidative CH functionalization and the isolation of dinuclear Pd^{III} complexes that are competent in C(sp^2)-X reductive elimination suggest that Pd^{IV} complexes may be not viable intermediates in a number of cases where they were thought previously to be involved [28, 29, 31, 37]. These new findings do not question the value of the previously discovered synthetic protocols but open new horizons for further improvement of the catalytic systems found and development of new ones.

Interestingly, dinuclear Pt^{III} systems have long been known to allow for catalytic aerobic oxidation of olefins leading to the corresponding olefin oxides and carbonyl compounds [38]. Formation of epoxides, in particular, was thought to be a result of an intramolecular C(sp^3)-O attack similar to the one in Fig. 13 where the oxygen atom of a β-hydroxoalkyl intermediate attacks the metal(III)-bound carbon atom (Fig. 14). No studies of C–O reductive elimination have been performed for these systems.

The C–O reductive elimination reaction shown in Fig. 14 can be viewed as a intramolecular version of nucleophilic elimination reactions with one of the Pt^{III} atoms as a leaving group Z (Fig. 9). As in the case of S_N2 processes discussed above, one can consider a mechanism involving an attack of the nucleophile upon a six coordinate Pt^{III} atom (Fig. 9, *dashed line*) or a dissociation – elimination mechanism involving a formally five coordinate Pt^{IV} transient (Fig. 9, *solid line*) that forms upon a heterolytic cleavage of the Pt^{III}-Pt^{III} bond.

4 Conclusions

Reactions of high valent platinum and palladium complexes leading to the formation of C(sp^2)-O and C(sp^3)-O bonds are important for both our understanding of fundamental reactivity of organometallic compounds and various catalytic

applications such as oxidative functionalization of hydrocarbons, which are especially rich in the case of palladium chemistry. Discovery of new roles of a metal in an unusual oxidation state or a previously unobservable reaction mechanism is especially inspiring. The material reviewed in this Chapter suggests that there are still uncharted territories in the area of high valent organoplatinum and organopalladium chemistry: C(sp^2)-O reductive elimination from Pt^{IV}, reactivity and reaction mechanisms of Pt^{III} and Pd^{III} organometallic derivatives, synthesis and reactivity of monoalkyl and monoaryl palladium(IV) complexes stabilized by O-donor ligands, and others. A rapid progress observed in this area of research might suggest that some of the questions listed above will soon find their answers.

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Recent Developments in Metal-Catalyzed Additions of Oxygen Nucleophiles to Alkenes and Alkynes

Lukas Hintermann

Abstract Progress in the field of metal-catalyzed redox-neutral additions of oxygen nucleophiles (water, alcohols, carboxylic acids, and others) to alkenes, alkynes, and allenes between 2001 and 2009 is critically reviewed. Major advances in reaction chemistry include development of chiral Lewis acid catalyzed asymmetric oxa-Michael additions and Lewis-acid catalyzed hydro-alkoxylations of nonactivated olefins, as well as further development of Markovnikov-selective cationic gold complex-catalyzed additions of alcohols or water to alkynes and allenes.

Keywords Alkenes · Alkynes · Catalysis · Heterofunctionalization · Oxygen nucleophiles

Contents

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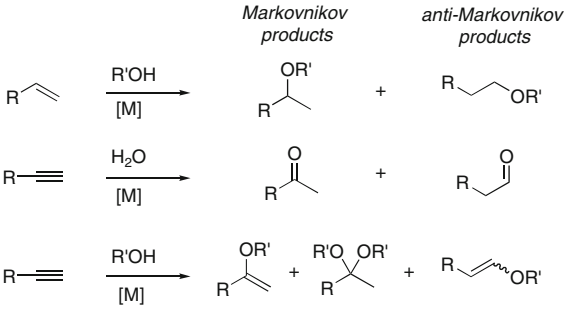
Abbreviations

AZARYPHOS	aza-aryl-phosphanes
BHT	2,6-di-*tert*-butyl-4-methylphenol
BINAP	2,2′-bis-diphenylphosphino-1,1′-binaphthyl
BINOL	2,2′-dihydroxy-1,1′-binaphthyl
cod	(*Z*,*Z*)-1,5-cyclooctadiene
DMAP	4-(dimethylamino)-pyridine
dppb	1,4-bis-(diphenylphosphino)butane
dppe	1,2-bis-(diphenylphosphino)ethane
dppm	1,1-bis-(diphenylphosphino)methane
IPr	1,3-bis-(2,6-diisopropylphenyl)imidazolylidene
MOM	methoxymethyl
MVK	methyl vinyl ketone
TMEDA	*N*,*N*,*N*′,*N*′-tetramethyl-ethane-1,2-diamine
TolBINAP	2,2′-bis-(di-{4-methylphenyl})phosphino-1,1′-binaphthyl
Tf	trifluoromethanesulfonyl
TPPH	tetraphenylporphyrine
p-Ts	(*or*: Ts) para-toluenesulfonyl

1 Introduction

The addition of oxygen nucleophiles such as water, alcohols, or carboxylic acids to alkenes produces alcohols, ethers, and esters, whereas their addition to alkynes gives rise to carbonyl compounds, enol ethers (or acetals), and enol esters (Scheme 1). This group of reactions, which belongs to the larger family of hetero-functionalizations [1], generates oxygenated products from unsaturated precursors with atom economy. Application of such reactions in synthesis is desirable, because the starting materials (olefins, alkynes, oxygen nucleophiles) are abundant, and because current methodology to produce oxygenated compounds is often based on energy-consuming oxidation/reduction methodology with low atom-economy [2].

In the past, some of those reactions were performed under harsh conditions including strongly acidic media and high temperatures, particularly in the case of alkenes. Having access to catalysts, which would achieve those conversions under



Scheme 1 Types of heterofunctionalization reactions of (shown here, but not restricted to:) terminal alkenes and alkynes with oxygen nucleophiles

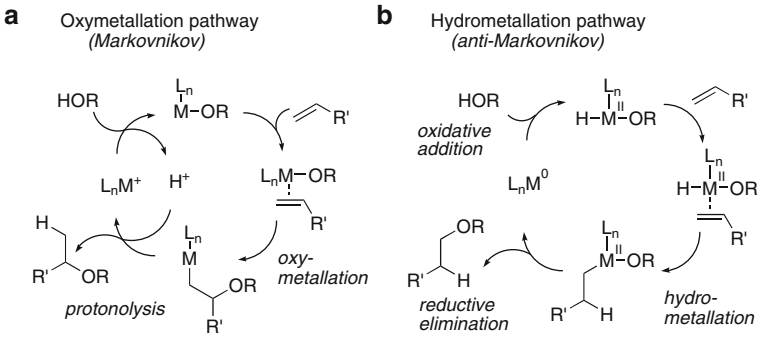
mild conditions with control of regioselectivity and stereoselectivity, is very desirable. The redox-neutral additions of water, alcohols, or carboxylic acids to terminal olefins in an anti-Markovnikov fashion would be synthetically very powerful reactions. Currently, such chemistry requires non-atom-economic hydroboration/oxidation sequences, preventing large-scale applications.

Work in the field of oxygen heterofunctionalization via organometallic and catalytic approaches has been reviewed up to the year 2000 [3]. Other reviews covering aspects of heterofunctionalization with oxygen nucleophiles have appeared [4, 5]. We have also published an extended review on catalytic hydrations of alkynes [6]. The present text provides not only an update of methodological progress made in the 8 years since Tani and Kataoka's review [3], but also references to older work, where adequate. The focus is more on new catalysts or catalytic conditions and less on discussions of the detailed substrate scope or purely synthetic application examples. Work on catalytic oxa-Michael type additions with small molecule organic catalysts (organocatalysts) has been reviewed elsewhere [7].

2 Mechanistic Aspects

Mechanistic hypotheses play an important role in developing new catalytic and selective heterofunctionalizations of alkenes. Two basic reaction cycles for metal-catalyzed hydroalkoxylation (and hydration, for R = H) of alkenes can be postulated (Scheme 2). One pathway leads to Markovnikov products via activation of the nucleophile, oxy-metallation, and protonolysis (hydro-de-metallation) (Scheme 2a). Alternatively to the inner sphere *syn*-oxymetallation depicted in Scheme 2a, external *anti*-attack of the nucleophile to coordinated olefin is plausible. The oxidation state of the metal remains constant in this cycle. The alternative hydrometallation pathway (Scheme 2b) proceeds via oxidative addition of the H–OR bond, hydrometallation of the olefin, and reductive elimination to the anti-Markovnikov addition product [3, 4].

For alkynes, an electrophilic activation/insertion pathway leads to the Markovnikov product, whereas an alkyne/vinylidene isomerization pathway is specific towards anti-Markovnikov addition products [4–6]. Some insightful studies on elementary steps of the above mechanisms will now be presented.



Scheme 2 Projected catalytic hydroalkoxylation cycles: (**a**) Oxymetallation pathway giving Markovnikov products. (**b**) Hydrometallation pathway leading to anti-Markovnikov products

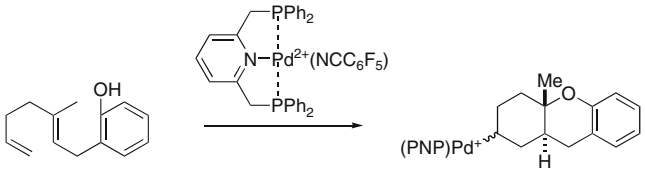
2.1 The Oxymetallation Pathway

2.1.1 Oxymetallation: Insertion of Alkoxide

The addition of water to a metal–alkene complex is an important reaction step in the Wacker oxidation [8]. Both inner and outer sphere mechanisms have been discussed for this step [9]. The intermediary 2-hydroxyethylpalladium(II) species is not observed because β-H-elimination is fast. However, insertion of ethylene into the Ir–OH bond of Cp*IrPh(OH)(PMe_3) to give Cp*IrPh(PMe_3)CH_2CH_2OH was observed spectroscopically in solution [10]. A series of outer sphere additions of water, alcohols or alkoxides, and other nucleophiles to dicationic palladium(II) olefin complexes of PNP–pincer ligands have been reported [11]. The 2-(alk)oxyethyl complexes formed in this reaction are stable, because the pincer ligand sterically blocks β-hydrogen-elimination. Examples of alkoxide attack to coordinated olefins have been reported for the complex [(TMEDA)PtCl(styrene)]ClO_4 [12]. Addition of methoxide is observed in the benzylic (internal) as well as the terminal position, depending on the electronic properties of the styrenes and the reaction solvent. A theoretical analysis of insertion of alkenes into rhodium hydroxo complexes has been undertaken [13]. The energy barrier for insertion into the Rh–OH bond was found to be lower than that for insertion into a Rh–Me bond. For propene as substrate, a preferred regioselectivity of insertion towards the 2-hydroxy-1-propylrhodium intermediate was predicted.

2.1.2 Protonolysis Versus β-Hydrogen-Elimination

The protonolysis (proto-de-metallation) of organometallic species is often postulated in discussions of potential mechanisms in the current research literature. However, in contrast to the hydrolysis of Grignard reagents and the like, the reaction is rather slow for electrophilic or cationic organometallic species of



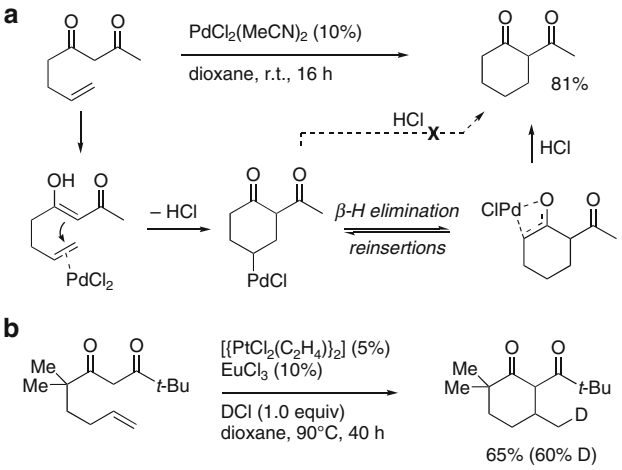
Scheme 3 Oxympalladation without β-hydrogen elimination

heavier transition metals. The protonation of electrophilic platinum dimethyl complexes typically stops at the stage of the monomethyl complex, and protonolysis of the second Pt–C bond is difficult [14], although acceleration by suitable spectator ligands can be achieved [15]. An interesting case-study concerns the reaction-mechanism of the enzyme organomercurial lyase (MerB), which mediates the difficult protonolysis of the Hg–CH_3 bond in methyl mercury(II) cations. Coordination of two cysteine thiolates at mercury generates an anionic methyl mercurate complex, followed by rate-limiting protonation of the Hg–C bond by an asparagine carboxylic acid residue [16]. The case of the Wacker reaction already implies that β-hydrogen-elimination from 2-oxyalkylmetal species is generally preferred over proto-de-metallation. Elimination can be prevented in the presence of steering ligands that occupy free coordination sites: a dicationic pincer complex of palladium(II) induces telomeric oxy-metallation to an organometallic species that is stable in solution and does not undergo β-hydrogen-elimination up to 100°C (Scheme 3) [17]. Neither is the organometallic species prone to protonolysis; a reductive cleavage of the C–Pd bond with $NaBH_4$ was achieved, instead [17].

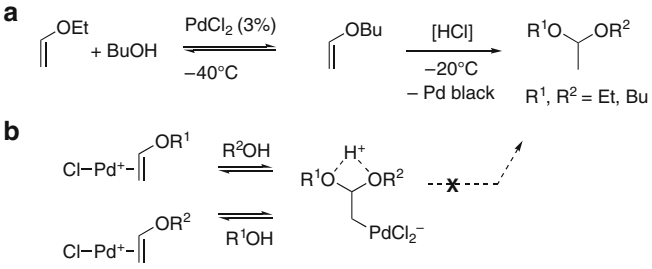
In an instructive example from the Widenhoefer group, the hydroalkylative cyclization of unsaturated β-keto esters was shown to proceed along a pathway of multiple hydro-metallations and β-H-eliminations. Protonolysis of the C–Pd(II) bond eventually occurred at the α-position to a carbonyl group, facilitated by the strongly polarized palladium(II) enolate (Scheme 4a) [18].

On the other hand, the closely related platinum(II)-catalyzed reaction of substrates with a geminal dimethyl "block" that prevents similar isomerizations provides contrary evidence in favor of a proto-de-metallation of an alkylplatinum intermediate (Scheme 4b) [19]. Additional evidence for protonolysis of the C–Pd (II) bond as rate-limiting step has been collected in the case of an intramolecular catalytic hydroamidation [20].

The metal-catalyzed transvinylation of vinylacetates or vinyl ethers with alcohols is initiated by an oxy-metallation reaction. With $PdCl_2(PhCN)_2$ as the catalyst and at low temperature, transvinylation takes place exclusively (Scheme 5a). At higher temperatures, acetal formation is observed after an induction period, in addition to precipitation of palladium (Scheme 5b). It is probable that the acetalization step is catalyzed exclusively by traces of Brønsted acid (HCl), rather than via proto-de-metallation of a Pd(II) alkyl species [21, 22]. Consequently, a recent report on the protection of primary alcohols as tetrahydropyranyl- (THP-)ethers by addition to 2,3-dihydropyrane in the presence of $PdCl_2(MeCN)_2$ as catalyst



Scheme 4 Widenhoefers work on hydrometallation with palladium(II) and platinum(II) catalysts

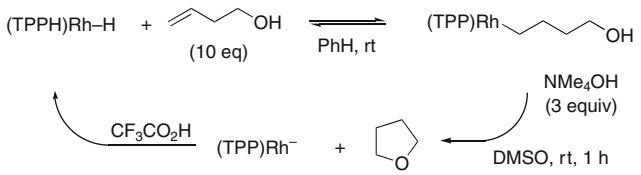


Scheme 5 Transvinylation and acetalization from vinyl ether substrates

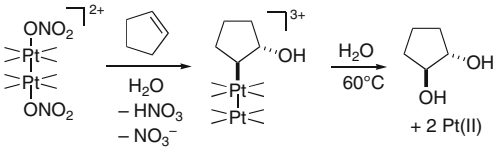
could be ascribed to protic acid catalysis rather than palladium-catalysis via proto-de-metallation [23]. Concluding from the available experimental data, oxy-metallation/hydro-de-metallation sequences may be less common than generally assumed and should only be postulated after careful evaluation of alternative pathways, or if favorable experimental evidence is available.

2.2 The Hydrometallation Pathway

The (postulated) hydrometallation pathway of hydroalkoxylation (or hydration) of olefins (Scheme 2b) relies on O–H bond activation by oxidative addition of RO–H to metal centers, a process that is studied eagerly in the organometallic chemistry community [3, 24]. However, the insertion of olefins into the M–H bonds of metal



Scheme 6 Stoichiomeric hydrometallation/oxy-de-metallation reactions with outer sphere reductive elimination, leading to anti-Markovnikov hydroalkoxylation products



Scheme 7 Olefin dioxy-functionalization with a dinuclear platinum complex

hydrido–hydroxo and hydrido–alkoxo complexes, derived from RO–H oxidative additions, is little documented. According to Sanford and Groves, a porphyrine rhodium(III) hydride (TPPH = tetraphenylporphyrine) reacts with 3-butenol (and other alkenes) to give a linear hydroxy-alkyl-rhodium(III) species (Scheme 6) [25]. An oxy-de-metallation via back-side attack of internal alkoxide, corresponding to an outer-sphere reductive elimination, releases tetrahydrofuran. The overall process is an anti-Markovnikov hydroalkoxylation, resembling the catalytic cycle of Scheme 2b. However, the basic reaction conditions of the S_N2 type oxy-de-metallation are not compatible with the acidic conditions required for regenerating the Rh–H species, which currently prevents the process from becoming a catalytic one.

The topic of outer sphere reductive oxy-de-metallation is also prominent in work on the difunctionalization of alkenes [26]. The reaction of a dinuclear Pt(III) complex with olefin and water gave a hydroxy–alkyl complex; next, the dinuclear metal unit serves as an electron sink and leaving group in an oxy-de-metallation at carbon, presumably via double inversion and an epoxide intermediate (Scheme 7) [26]. The process currently remains a stoichiometric oxidation.

Extension of this work to stoichiometric hydroxyplatination of open-chain olefins or alkynes gave 2-hydroxy-1-alkyl or 2-oxo-1-alkyl-diplatinum(III) species, respectively. In a direct competition experiment, 1-petnyne reacted nine times faster than 1-pentene [27].

3 Reactions of Alkenes

Progress in catalytic additions of oxygen nucleophiles to alkenes (Sect. 3), alkynes (Sect. 4), and allenes (Sect. 5) will now be discussed.

3.1 Addition of Oxygen Nucleophiles to Nonactivated Alkenes

3.1.1 Catalytic Hydration of Alkenes?

The topic of transition-metal catalyzed hydration of alkenes is still dominated by a somewhat infamous 1986 report on a $Pt(H)Cl(PMe_3)_2$-catalyzed anti-Markovnikov hydration of terminal alkenes to give primary alcohols [28, 29]. This work could not be reproduced [30, 31]. The original paper has not been retracted, and has inspired some fairly inconclusive follow-up work over the years [32, 33]. One study analyzes the original work under the optimistic assumption that the inactive complex $Pt(H)Cl(PMe_3)_2$ may have contained impurities from its preparation, which would have been responsible for the originally reported catalytic activity [33]. Dinuclear and trinuclear hydrido platinum complexes were prepared and tested as potential catalysts. In such experiments, oxygenated products including 2-octenal, 2-octen-1-ol, or octanons were indeed observed in small amounts, but they appeared to be derived from peroxide impurities in autoxidized samples of the starting alkene! When carefully purified 1-octene and a trinuclear platinum hydrido complex were used as substrate and catalyst, respectively, the authors claim to have observed "typically 50 TON" of methanol addition to give 1-methoxyoctane, "sometimes accompanied by 2-methoxyoctane" [33]. Unfortunately, these authors did not establish a correlation between the amount of added catalyst and the yield of product. Reaction products were not isolated, and only qualitative reaction data based on GC/MS-analyses were provided. In our opinion, future experiments on the catalytic hydration of alkenes should be performed on preparative scale with isolation of the products rather than on small-scale with chromatographic analyses in the absence of internal standards. Already, the 1986 paper on a presumed anti-Markovnikov hydration had suffered from such methodological limitations [28].

In a similar vein, a series of papers published between 2002 and 2008 contains spectacular claims of highly enantioselective asymmetric additions of water to styrenes, unsaturated carboxylic acids, or simple terminal alkenes [34–41]. The catalysts used are of the heterogeneous type and based on chiral biopolymers such as wool, gelatin, or chitosan as solid supports (sometimes in combination with silica or ion-exchange resins) that are doped with transition metal salts. This series of papers contains spectacular claims, insufficient experimental data, and erroneous chemical structures for the biopolymers used. As earlier work from the same group of authors on asymmetric catalysis on bio-polymeric supports is irreproducible [42], one is well advised to await independent confirmation of those results.

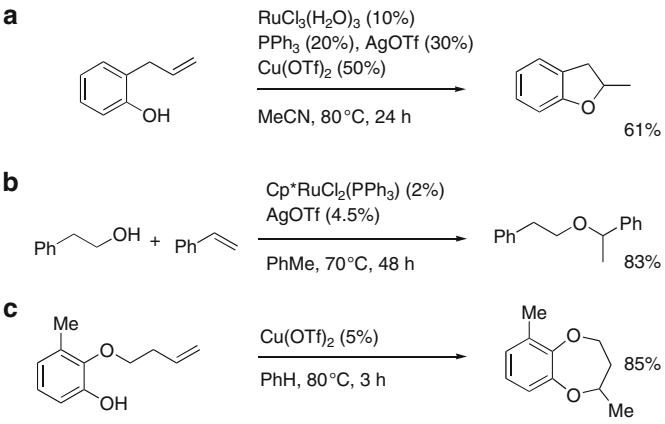
3.1.2 Lewis Acid Catalyzed Additions of Alcohols to Alkenes

The metal-catalyzed hydroalkoxylation of nonactivated olefins has seen much activity recently. Numerous publications on electrophilic metal-triflate catalysts have appeared, and a general picture of Lewis-assisted Brønsted type acid catalysis

[43] emerges. The results achieved with those catalysts are often comparable in terms of substrates, reaction conditions, and selectivities, irrespective of the metal center. In many cases, the results obtained with Lewis acid catalysts can also be reproduced using trace amounts of Brønsted acid like triflic acid (HOTf) or bis-trifluoromethanesulfonylimide ($HNTf_2$) as catalyst.

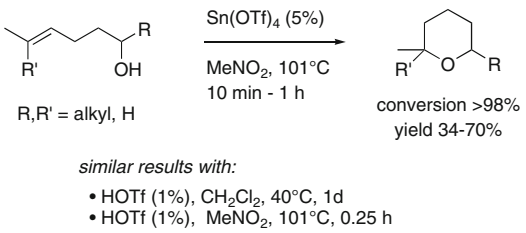
Ruthenium: In one of the earliest examples of a transition metal-catalyzed hydroalkoxylation reaction from 1998, the cyclization of 2-allylphenols to benzodihydrofurans was catalyzed by a cocktail of ruthenium chloride, silver- and copper triflates, and a phosphane ligand (Scheme 8a) [44]. A control experiment implied that triflic acid alone was ineffective as catalyst, but this experiment is at variance with a later report where 2-allylphenol was cyclized using only 5 mol% of triflic acid as catalyst (CH_2Cl_2, 40°C, 3 h) [45].

The cyclization of allylphenols was also performed with Cp*$RuCl_2$/AgOTf and a phosphane ligand in benzene (Scheme 8b) [46]. This catalyst system was also used in additions of electron-rich carboxylic acids to norbornene, with dppe as chelating phosphine coligand [47]. The latter reaction is also catalyzed by triflic acid alone (10 mol%), which appeared to give the product in lower yield and stereoselectivity. Alcohols were added to styrene, norbornene, or 1-octene by this catalyst [48]. Later, these authors found that salts like $Cu(OTf)_2$, $Cu(ClO_4)_2{\cdot}6H_2O$, $CuOTf{\cdot}C_6H_6$, AgOTf, $AgClO_4$, or $AlCl_3$ alone showed catalytic activity in the cyclization of allylphenol or other alkenols in hot chloroform, rather than acetonitrile, as solvent (Scheme 8c) [49]. As a matter of fact, a recent report highlights that when heated in organic solvent, $Cu(OTf)_2$ decomposes with release of triflic acid [50]. This finding casts doubt on the catalytic activity of copper, and possibly on that of other metals as well. Considering this ambiguity, it is then surprising that an asymmetric catalytic hydroalkoxylation of allylphenol has been realized when starting from Cp*$RuCl_2$ (2 mol%), AgOTf (4 mol%), and a chiral chelating bis-phosphane ligand (2 mol%) in hot toluene. With (*S*)-TolBINAP as the ligand,



Scheme 8 Ruthenium and copper catalyzed hydroalkoxylations

Scheme 9 Tin versus triflic acid aluminium catalyzed hydroalkoxylations

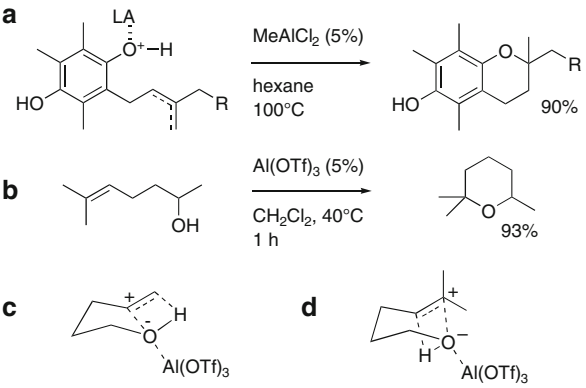


2-methyldihydrobenzofuran was reported to be formed in 65% ee (37% conversion) or 33% ee (80% conversion) [46]. On repetition of this reaction, we have obtained racemic product [193].

Tin: Coulombel and coworkers have used tin(IV) triflate as catalyst in the hydroalkoxylation of unsaturated alcohols (Scheme 9a) [51]. The substrate reactivity decreases along the order trisubstituted olefins ≈ 1,1-disubstituted olefins > 1,3-disubstituted > monosubstituted olefin. Incidentally, this is a typical reactivity profile for most Lewis acid catalysts discussed in this section. The catalyst loading could be reduced down to 0.1% in favorable cases and in the absence of a solvent. As triflic acid alone (5%) also catalyzed the reaction in Scheme 9 efficiently, and because $Sn(OTf)_4$ is readily hydrolyzed, a control experiment with cocatalytic amounts (5% each) of $Sn(OTf)_4$ and 2,6-lutidine as proton quencher was performed, in which catalytic activity was retained. We do not believe that this experiment is sufficient proof of tin catalysis, as $Sn(OTf)_4$ may release more than a single equivalent of triflic acid upon hydrolysis. In any case, the selectivity profile of the tin-catalyzed reaction matches that of the triflic acid-induced hydroalkoxylation reactions studied earlier in the same research group [45].

Tin(IV) triflate also was effective in intermolecular additions of alcohols to trisubstituted olefins (5 mol%, 80°C, 24 h) [52], for which $Sn(NTf_2)_4$, $Al(OTf)_3$, or $In(OTf)_3$ gave only partial, but triflic acid or $HNTf_2$ (5 mol%) considerable conversions.

Aluminium: The catalytic activity of the aluminium Lewis acid $MeAlCl_2$ in the cyclization of isomeric phytyl-trimethylhydroquinones to tocopherol was similar to that of toluene sulfonic acid (Scheme 10a) [53]. The authors of the study referred to work by Yamamoto who had earlier postulated a mechanism of Lewis-acid assisted Brønsted acid catalysis for Lewis acids coordinated to hydroquinone hydroxy groups [54, 55]. More recently, $Al(OTf)_3$ was used as catalyst for cyclizations of alkenols (Scheme 10b) with di- and trisubstituted double bonds (CH_2Cl_2, 40°C), or with less substituted double bonds in nitromethane (101°C, 1.5–3 h) [56]. The general reactivity profile of trisubstituted ≈ 1,1-disubstituted > 1,2-disubstituted > monosubstituted alkenes was noted. Reactions with $AlCl_3$ or $AlBr_3$ as catalysts proceeded more slowly. As in the tin case, the retention of catalytic activity by a mixture of cocatalytic amounts of 2,6-lutidine and $Al(OTf)_3$ (5 mol % each) was taken as an indication that triflic acid (released e.g. by hydrolysis) was not the actual catalyst, although this argument is not convincing (see the comment above concerning the tin case). The authors observed major ^{13}C NMR shift

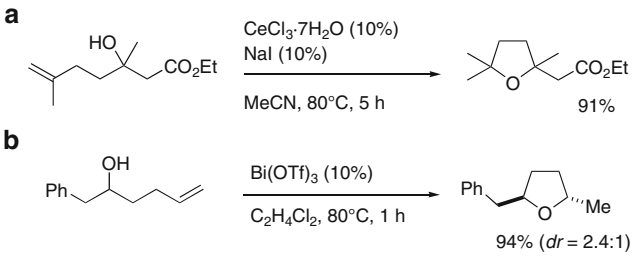


Scheme 10 Aluminium catalyzed hydroalkoxylations: Lewis acid assisted Brønsted acidity

differences at C-1 when $Al(OTf)_3$ was combined with the substrate in CD_3NO_2, concluding that the catalyst interacts more strongly with the alcoholic function rather than the double bond. Assuming precoordination of the Lewis acid to the hydroxy group, 4-membered ring transition states with advanced proton transfer from the acidified OH group to the alkene π-electrons and concomitant approach of oxygen to the double-bond were assumed (Scheme 10c, d). The transition states have carbenium ion character, explaining the Markovnikov regioselectivity and the similarity of the reaction outcome when compared to that with Brønsted acid-catalysis (Scheme 10b, c) [56].

This picture resembles Yamamoto's Lewis acid assisted Brønsted acidity [43]; furthermore, the strategy of increasing the nucleophilicity of alcohols and water by precoordination to Lewis acids is generally found in enzymatic reaction mechanisms [57]. The mechanistic alternative of an alkoxy-alumination, followed by protonolysis of a C–Al bond was investigated by calculation. The transition state for alkoxy-alumination was at an accessible level, but the proto-de-alumination step was kinetically hindered, excluding this alternative mechanism [56]. This example places once more emphasis on the earlier notation that oxy-metallation/proto-de-metallation sequences should not be postulated without specific evidence (Sect. 2.1.2).

Cerium: In a series of unsaturated β-hydroxyesters capable of cyclizing to tetrahydrofurans or tetrahydropyrans, this cyclization could be induced by a catalyst combination of $CeCl_3$ and NaI (Scheme 11a) [58]. The alkenol substrates contained 1,1-di- or trisubstituted olefin units. In cases where the hydroxy group of the β-hydroxyester donor is attached to stereogenic carbon, the configuration of the latter is retained in the product of cyclization. Hydrated CeI_3 was also an effective catalyst, but pure $CeCl_3 \cdot 7H_2O$ failed to induce the reaction. We believe that the characteristics of the reaction are compatible with a Lewis assisted Brønsted acid catalysis, additionally aided by binding of the Lewis acid to the substrate through chelation. Conversely, there appears to be insufficient experimental evidence supporting the original author's assumption of an oxy-ceration/protonolysis pathway.



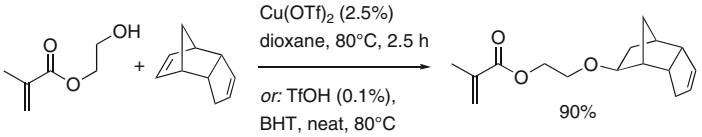
Scheme 11 Alkenol cyclizations catalyzed by cerium and bismuth Lewis acids

Zinc: The cyclization of 2-homoallylphenols to chromanols is mediated by zinc chloride (1.5 equiv) in the ionic liquid $(BuPy)_2SnCl_4$ at 70°C [59]. *Zirconium:* zirconium tetrachloride brings about the cyclization of 2-allylphenols to 2-methyldiyhdrobenzofurans (0°C, CH_2Cl_2, 10–12 h), but the substrate range appears to be limited to phenols with π-acceptor substituents [60].

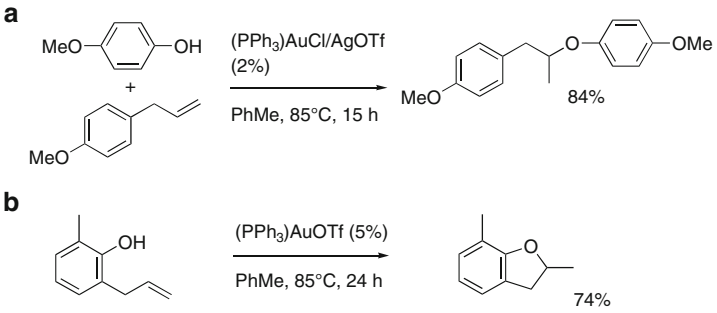
Bismuth: The Lewis acid $Bi(OTf)_3$ brings about cyclizations of a range of alkenols, including those bearing tertiary alcohol functions, without elimination [61]. The authors find strong support for a triflic acid background catalysis by observing that a variety of metal catalysts including AgOTf, $AuCl(PPh_3)$/AgOTf, $Al(OTf)_3$, $FeCl_3$/AgOTf, and also triflic acid itself catalyze the reaction with identical diastereoselectivity of 2.4:1 for the test-substrate in Scheme 11b.

Copper: The catalytic activity of copper(II) triflate for cyclizations of alkenols or intermolecular additions of alcohols and carboxylic acids to norbornene has been reported [62, 63]. In dioxane at 80°C, high conversions were achieved at prolonged reaction times, and those were superior to those obtained with Lewis acids such as $Yb(OTf)_3$, though the latter also displayed catalytic activity [62]. In a control experiment with triflic acid (10 mol%) only little product (29%) resulted with low stereoselectivity. However, it is now clear that this control experiment was flawed, as too much triflic acid and overly long reaction times had been applied. The previously mentioned study by Carpentier and coworkers on copper triflate catalyzed hydroalkoxylations has established that $Cu(OTf)_2$ decomposes to CuOTf and triflic acid when heated in organic solvents [50]. Triflic acid is catalytically active in hydroalkoxylation at levels down to 0.1 mol%, if a polymerization inhibitor is present to prevent consumption of the olefinic substrate. Indeed, $Cu(OTf)_2$ is an excellent reagent for releasing small amounts of triflic acid in this case, because the coreleased CuOTf acts as polymerization inhibitor for the acrylic substrate (Scheme 12) [50]. Other metal triflates like $Sc(OTf)_3$ or $Yb(OTf)_3$ displayed catalytic activity at the 1 mol% level in the reaction of Scheme 12. Additional experiments were presented to support the conclusion that triflic acid is the actual catalyst in this and other Lewis acid catalyzed hydroalkoxylations [50].

Gold: The finding that an in situ cationic gold(I) complex of the type (PPh_3)AuCl/AgOTf catalyzes additions of phenols and carboxylic acids to alkenes certainly aroused interest in 2005 (Scheme 13) [64, 65]. These findings must now be regarded with skepticism as far as the involvement of metal catalysis is concerned,



Scheme 12 Copper triflate catalyzed intermolecular hydroalkoxylation of dicyclopentadiene

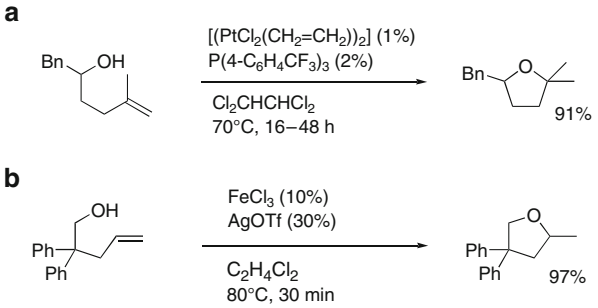


Scheme 13 Gold complex catalyzed hydroalkoxylations

because the author's assumption that triflic acid is not a catalyst for the reaction was disproved by Hartwig and coworkers, who found that an "overdose" of triflic acid in the control experiment had consumed the substrate (or possibly the product) via polymerization [66]. He and coworkers agree with a triflic acid catalyzed background reaction, but they suggest, on the basis of minor deviations in the catalytic activity of HOTf versus $AuCl(PPh_3)/AgOTf$, that other catalytic species may also be at work [67].

Iridium: In addition to gold(I) [65], a sequence of Claisen-rearrangement and hydroalkoxylation has been catalyzed with a range of catalysts including $RuCl_3$/AgOTf, $Cu(OTf)_2$, $Yb(OTf)_3$/AgOTf, or $IrCl_3$/2AgOTf. The latter catalyst displayed the highest activity, whereas both $IrCl_3$ and AgOTf alone were ineffective. Control experiments with triflic acid have not been carried out [68]. On the other hand, silver triflate alone in dichloromethane at reflux was found to cyclize 4-alkenoic acids to 5- and 6-membered lactones or 4-alkenols to tetrahydrofurans or tetrahydropyrans [69]. As those reactions display the same selectivity as that expected for acid-catalyzed conversions, one cannot help assuming that triflic acid-catalysis is possibly involved here, too.

Platinum: A less clear-cut case is the observation of the Widenhoefer group of a platinum(II) catalyzed hydroalkoxylation of 4- and 5-alkenols (Scheme 14a) [19, 70]. An electrophilic activation mechanism with final protonolysis of a Pt–C bond is discussed, but the substrate range and reactivity of this catalyst system are again close to that expected for an acid catalyst. On the other hand, the authors have performed control experiments to exclude that HCl is a catalyst of the reaction.



Scheme 14 Platinum, iron, -catalyzed hydroalkoxylations

Iron: An iron-catalyzed hydroalkoxylation reaction of alkenols with the system $FeCl_3$/3AgOTf has been reported (Scheme 14b) [71]. The catalyst is prepared from $FeCl_3$ (10 mol%) and AgOTf (30 mol%) in dichloroethane, and the reaction proceeds at 80°C over 30–45 min to give tetrahydrofurans. The compounds $FeCl_3$, $FeCl_3{\cdot}6H_2O$, $FeCl_3/AgClO_4$, $FeCl_2{\cdot}4H_2O/AgOTf$, and $AgClO_4$ are also catalytically active. There are hints of hidden Brønsted acid catalysis, even though a control experiment with triflic acid generated a different reaction product, but this appears to be due to an over-reaction (Friedel-Crafts alkylation) in the presence of the more active HOTf catalyst [71]. Similarly, the addition of carboxylic acids to alkenes including norbornene, cyclohexene, and 1-octene by means of $Fe(OTf)_3$ (2 mol%, neat) at 80° proceeds in 3 h, but is also catalyzed by triflic acid [72]. The stability of $Fe(OTf)_3$ under reaction conditions is certainly questionable.

Lanthanoids: As mentioned in several cases above, some lanthanoid triflates displayed more or less catalytic activity for alkenol cyclizations. In one optimized case, several alkenol cyclizations were performed with $Ln(OTf)_3$, $Sm(OTf)_3$, and $Yb(OTf)_3$ as catalysts (1 mol%) at 120°C in an ionic liquid as solvent (*N*-ethyl-*N*-methyl-imidazolium triflate) [73]. Addition of 2,6-di-*tert*-butylpyridine blocked the activity of $Yb(OTf)_3$; nevertheless, the authors argue that triflic acid, even though it catalyzed the reaction in a blind test, could not have been the "hidden" active catalyst, because triflic acid was not found by NMR spectroscopy in a vacuum transfer of volatiles from the reaction solution.

3.1.3 Lewis- Versus Brønsted-Acid Catalysis

The ambiguity of Lewis acid versus Brønsted acid catalysis has been mentioned repeatedly above. Following up on Spencers study of oxa-Michael type reactions (see below) [74], Hartwig and coworkers have shown that many of the model reactions for metal-catalyzed hydroalkoxylation or hydrocarboxylation are also catalyzed by strong Brønsted acids like triflic acid (HOTf) and bis-trifluoromethanesulfonimide ($HNTf_2$) [66]. The results of the reactions catalyzed by triflic acid mirror closely those obtained with metal triflate Lewis acids, although the loadings

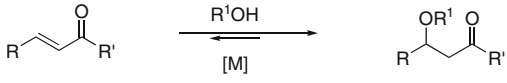
of triflic acid usually have to be lower than the loading of the metal catalysts so as to suppress acid induced side-reactions such as olefin polymerization. Failure to observe this in control experiments aimed at excluding background acid-catalysis has led to false conclusions. It now appears that many of the hydroalkoxylation reactions in Sect. 3.1.1 could be Brønsted-acid- rather than metal-catalyzed. This is not to say that the presence of the metal is irrelevant in all catalyses. Lewis-acid assisted Brønsted acidity may still be operating, and asymmetric catalysis with chiral metal Lewis acids might still be achieved.

3.2 oxa-Michael Addition Reactions

The conjugate addition of oxygen nucleophiles to acceptor-substituted olefins is the oxa-Michael reaction (Scheme 15). The term is derived from heteroatom replacement nomenclature, meaning that oxygen takes the place of a CH_2 unit ($RCH_2^- \rightarrow RO^-$). Oxa-Michael reactions have been known for many years and are often catalyzed by bases or acids [7]. Catalysis by metals has been reported sporadically in the older literature, e.g. for the case of alcohol addition to vinyl ketones with a Nieuwland catalyst (HgO, $BF_3{\cdot}OEt_2$, ROH) [75–77]. A patent describes a $PdCl_2$-catalyzed addition of alcohols to acrolein or methacrolein [78].

3.2.1 Lewis- Versus Brønsted-Acid Catalyzed oxa-Michael Reactions

In 1989, Hosokawa and coworkers reported on $PdCl_2(MeCN)_2$ catalyzed additions of alcohols to various alkenones [79]. The kinetics of this reaction has been investigated by Abu-Omar and coworkers for the case of MVK and benzyl alcohols [80]. Dicationic palladium(II) catalysts with two labile acetonitrile ligands are more reactive catalysts, and acetonitrile is a competitive inhibitor of the reaction. The results of Hosokawa have been reinterpreted by Spencer and coworkers, who noted with surprise that copper- and palladium-catalyzed aza-Michael additions of carbamates [81, 82] were catalyzed just as efficiently by Brønsted acids like TfOH, Tf_2NH [83], or acidic Nafion resin [84]. They concluded that the comparable reaction characteristics observed with many Lewis acids and protic acids might be explained by the presence of a common catalytic species, namely the proton [74]. An equilibrium between 2,6-di-*tert*-butylpyridine and its conjugate acid in the presence of two equivalents of Lewis acid and water could be quantified by ^1H NMR measurements in CD_3CN. A rough correlation of catalytic oxa-Michael addition activity with the extent of pyridine protonation or metal acidity (approximated by the pK_a values of



Scheme 15 oxa-Michael type reactions

the metal aquo ions) was noted. Spencer and coworkers believe that a majority of the Lewis acid catalyzed hetero-Michael additions can be ascribed to protic background catalysis, and they predict that attempts to perform asymmetric catalysis with chiral Lewis acids might be futile [74]. This prediction cannot be true for all types of Lewis acids or nucleophiles, as examples of chiral Lewis acid catalyzed oxa-Michael additions have been found, as discussed below in Sect. 3.2.3.

3.2.2 New Metal-Catalyzed oxa-Michael Reactions

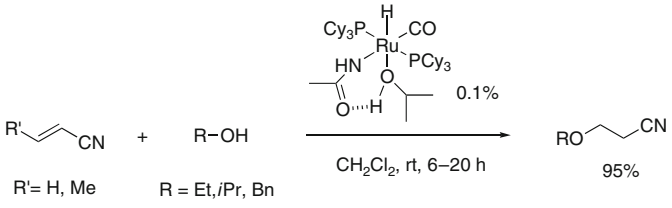
Lithium: The addition of benzyl alcohol to cyclohexenone is catalyzed by LiCl (10 mol%) and DMAP (10 mol%). The product yield is 56% after 85 h at room temperature, but under 2,000 bar pressure at –20°C, the yield rises to 97% [85].

Vanadium: Vanadinyl (VO^{2+}) salts catalyze the addition of alcohols to α,β-unsaturated ketones [86].

Gold: A gold-catalyzed oxa-Michael addition has been discussed as one step in a multi-step sequence involving alkyne hydration, β-elimination of methanol, and intramolecular oxa-Michael addition [87, 88].

Ruthenium: An amido ruthenium(II) complex catalyzes the addition of primary and secondary alcohols to acrylonitrile, crotononitrile, methacrylonitrile, and other unsaturated nitriles at ambient temperature and a low catalyst loading of 0.1 mol% (Scheme 16) [89]. ^{1}H NMR experiments indicate that the basic amido ligand at ruthenium deprotonates the alcohol to give a cationic amido complex [$(MeCONH_2)RuH(CO)(PCy_3)_2(S)]^+$ (S = nitrile substrate). The authors assume that the nitrile substrate is activated by coordination to ruthenium via the nitrile unit and then attacked by external alkoxide [89].

The addition of primary alcohols to MVK is catalyzed by a bridged dinuclear methoxy complex of rhodium, [{Rh(cod)OMe}$_2$] (2 mol% [Rh], 60°C, 2 h, 60–90%), in toluene [90]. A corresponding iridium-complex induced transfer-hydrogenation instead. *Copper*: The addition of ethanol or phenol to Michael acceptors like acrylonitrile or MVK is catalyzed by *N*-heterocyclic carbene complexes of copper(I) alkoxides such as (IPr)CuOEt (IPr = 1,3-bis-{2,6-diisopropylphenyl}imidazolylidene) [91]. External attack of Cu-alkoxide to olefin without substrate coordination was proposed. Acrylates reacted only after addition of *tert*-butyl isonitrile to the reaction mixture; this donor ligand might provoke dissociation of alkoxide from copper, inducing an ionic reaction. The role of copper other than that



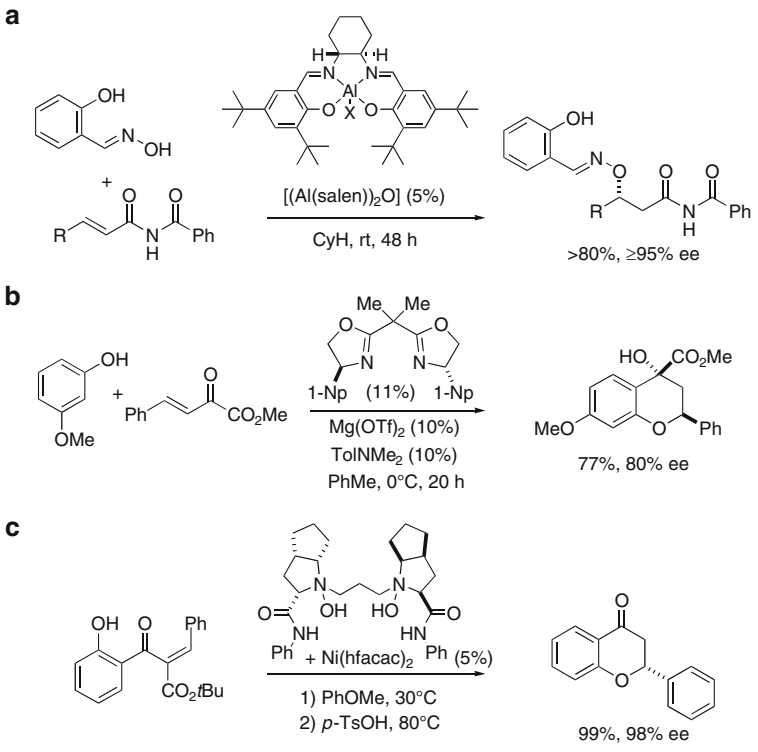
Scheme 16 Ruthenium-catalyzed cyanoalkylation

of a counter-cation in this catalysis is not evident. Base-induced oxa-Michael reactions can also be performed in the absence of metals, e.g. by using PBu_3 as precatalyst, where in situ generated phosphonium alkoxide acts as Brønsted base catalyst [92–94]. For this reason, the validity of an older catalytic addition of water to acrylonitrile and crotono-nitrile must be questioned [95]: The use of zerovalent PtL_n complexes with electron-rich phosphane ligands may have provoked dissociation of the phosphane ligands, the latter acting as precatalyst [95].

3.2.3 Asymmetric Catalytic oxa-Michael Additions

Asymmetric catalytic reactions are, in addition to their synthetic value, interesting mechanistic tools. In case of a presumed "hidden" general base or acid catalysis, the occurrence of an enantiomeric excess in the reaction product indicates that an added chiral metal-complex was indeed involved in the catalytic cycle.

Vanderwal and Jacobsen have used an aluminium complex of the Jacobsen salene to catalyze asymmetric additions of salicylaldehyde-oxime to alkenoylamides (Scheme 17a) [96]. The peculiar oxime nucleophile was needed as ordinary alcohols



Scheme 17 Asymmetric catalytic oxa-Michael type additions

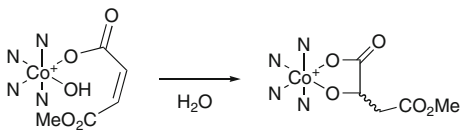
did not react. Hydrogenolysis of the oxime N–O bond released β-hydroxyimides, which are products of a formal asymmetric addition of water to the imide double bond.

Phenols have been condensed with alkenoylesters to give chromans by an oxa-Michael addition/electrophilic aromatic addition sequence with magnesium(II)- or copper(II)-bis-oxazoline complexes as chiral Lewis acid catalysts (Scheme 17b) [97]. This reaction may be initiated by an oxa-Michael reaction, followed by a hydroarylation of a carbonyl group. The authors suggest that the initial stereo-determining oxa-Michael addition is followed by a fast diastereoselective aromatic substitution [97]. A nickel Lewis acid, derived from $Ni(hfacac)_2$ (hfacac = 1,1,1,5,5,5-hexafluoro-3,5-dioxopentane enolate) and chiral *N*-oxide ligands, catalyzes the enantioselective oxa-Michael cyclization of 2-*tert*-butyloxycarbonyl-2′-hydroxy-chalcones to 3-*tert*-butoxycarbonyl flavanones, which can be decarboxylated to flavanons in a separate step (Scheme 17c) [98]. A Lewis acid activation of the unsaturated β-ketoester unit can be assumed.

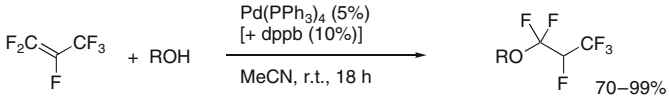
3.2.4 Hydration of Maleinate

A Michael acceptor of biochemical relevance is maleinic acid (or: maleinate). Additions of oxygen nucleophiles in the presence of metal salts have been studied repeatedly. Some of the best catalysts (or: mediators) for the addition of water, polyols, or hydroxy–carboxylic acids are multivalent metal ions of La(III), Nd(III), Eu(III), Ho(III), Yb(III), Fe(II/III), Co(II), Ni(II), Cu(II), Zn(II), Al(III), Ga(III), In(III), Zr(IV), and Ti(IV) [99, 100]. Hydration of maleic acid in the presence of $CrCl_3 \cdot 6H_2O$ or $AlCl_3$ or other metal salts in water at 170°C gave variable yields of malic (2-hydroxysuccinic) and fumaric acids. A blank reaction with dilute sulfuric also gave considerable yields of malic acid under those conditions [101, 102]. If maleate is coordinated to a chromium(III) aquo complex, a stoichiometric inner-sphere hydration to give chelating malate is observed [103]. Similarly, a cobalt aquo complex with coordinated methylmaleate adds water in an inner-sphere reaction (Scheme 18) [104]. Such reactions are discussed as models for the mechanism of the enzyme aconitase, which hydrates (*Z*)-aconitate to citrate or iso-citrate [105]. An x-ray crystal structure of aconitase with bound citrate or isocitrate reveals comparable coordination geometries at an iron center at the edge of an Fe_4S_4-cluster [106].

Palladium-catalyzed hydration of dimethyl maleate has been described with the complex $[\{Pd(\mu\text{–}OH)(dppe)\}_2](BF_4)_2$ (1 mol% [Pd]) in water/THF (140°C, 30 h),



Scheme 18 Inner-sphere hydration of methyl maleinate



Scheme 19 Synthesis of perfluorinated ethers

but the turnover number remained low and the reaction has not been optimized for preparative use [107, 108]. The activity and selectivity of the reaction is rather low, and there is a general acid catalyzed background reaction. Similar hydration experiments were later performed with palladium(II) and platinum(II) dichloro complexes of tetraaryl-bisphosphane ligands, which displayed low activity [109].

3.3 Addition of Alcohols to Perfluorinated Alkenes

A catalytic addition of acidic alcohols or phenols to hexafluoropropene is induced by the complex $Pd(PPh_3)_4$ [110]. Catalytic activity is increased in the presence of cocatalytic 1,4-bis-(diphenylphosphino)butane (dppb) (Scheme 19). The authors propose a mechanism involving external protonation of a Pd(0)-coordinated olefin and reductive elimination to the ether product, but both steps appear improbable. There is literature precedence for insertion of tetrafluoroethylene into the Pt–O bond of (dppe)PtMe(OMe) to give (dppe)PtMe(CF_2CF_2OMe), but proto-de-metallation of the resulting complex has not been reported [111, 112].

In our opinion this reaction may not be catalyzed by palladium at all. The addition of 1,1,1-trifluoroethanol to hexafluoropropene is catalyzed by a range of simple Brønsted-bases including mildly basic counter-ions such as acetate, bicarbonate, or carbonate in ionic liquids [113] or by the fluoride anion [114]. The generation of olefinic side-products in older potassium-base catalyzed reactions has been ascribed to effects of the potassium cation [115]. Taking these findings into account, a critical analysis suggests that the palladium phosphane complex (or the phosphane alone) may be a precatalyst generating fluoride or alkoxide anions as the true catalyst under reaction conditions.

4 Catalytic Addition of Oxygen Nucleophiles to Alkynes

4.1 Catalytic Hydration of Alkynes

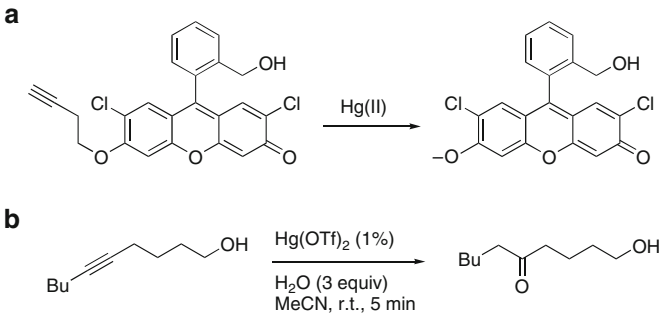
The topic of alkyne hydration has been covered in our recent review [6]. The current section presents an update of new methodology and mechanistic work that has appeared after publication of that review, but straightforward synthetic application examples are not covered.

4.1.1 Catalytic Hydrations with Markovnikov Selectivity

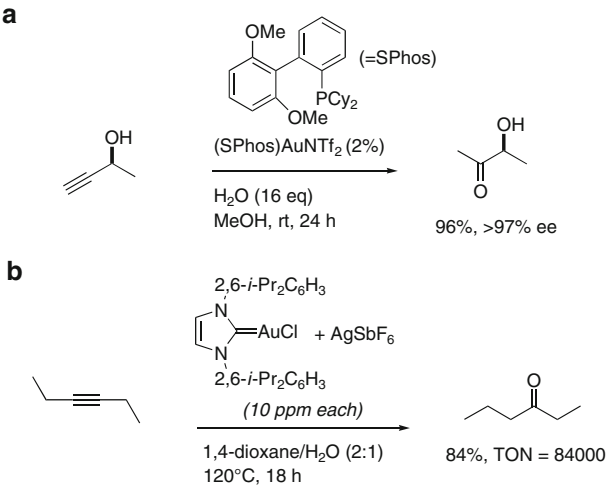
Mercury: A short account of the discovery of metal-catalyzed hydration of alkynes by Kucherov (1881) appeared on the occasion of its 125th anniversary [116]. Mercury-catalyzed hydration of alkynes has been used as mechanistic principle for devising fluorogenic probes for mercuric ions by two research teams. In one system, a 3-butyn-1-yl group at the phenolic oxygen of a fluorescein dye was cleaved via catalytic oxymercuration and elimination to releases a fluorescent dye (Scheme 20) [117]. In another system the mercury-catalyzed hydration of an ethynyl to an acetyl group provoked the quenching of fluorescence in a coumarine-based dye [118].

Nishizawa and coworkers have extended their work on use of mercury(II) triflate as alkyne hydration catalyst [119]. Alkynols of varying chain lengths are hydrated with accelerations at catalyst loadings down to 0.05 mol%. The regioselectivities are as expected for reactions via 5- and 6-membered oxacyclic intermediates, and the selectivity profile is similar to that of the less reactive palladium(II) catalysts already in use for reactions profiting from anchimeric assistance [6]. *Gold*: The use of Au(I) or Au(III) compounds as catalysts for alkyne hydration continues to be a major research area. The hydration of phenylacetylene in acidic aqueous media with water-soluble phosphane complexes of gold(I) acetylides was observed [120]. The regioselective hydration of 3-alkynoates to 4-oxo-carboxylates with neighboring group participation has been realized using the established [6] $NaAuCl_4$ hydration catalyst [121]. Notable methodological improvements have been reported by Leyva and Corma, who used stable complexes of the type $(PR_3)AuNTf_2$ in aqueous methanol as highly active single component hydration catalysts [122]. Neutral reaction media can be used, and enol ethers are then observed as reaction intermediates, and this explains the need for methanol as cosolvent (Scheme 21a).

Nolan and coworkers applied cationic gold(I) complexes of *N*-heterocyclic carbenes at elevated temperatures in the catalytic hydration of terminal and internal alkynes at very low catalyst loadings of 1,000 ppm (0.1%) down to 10 ppm (0.001%). The thermal stability of the gold(I) carbene complex appears to be critical to achieve those results [123] (Scheme 21b). *Iron*: Iron(III) chloride catalyzes



Scheme 20 Applications of mercury catalyzed alkyne hydration



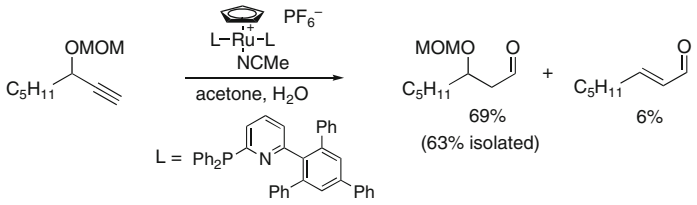
Scheme 21 Methodological improvements in gold(I) catalyzed hydration

(10 mol%) the hydration of terminal alkynes to methyl ketones in refluxing dichloroethane (85°C, 67 h for phenyl acetylene) with three equivalents of water [124]. Whether an iron-specific catalysis is operating, as opposed to hidden Brønsted acid catalysis, is not evident from the available data.

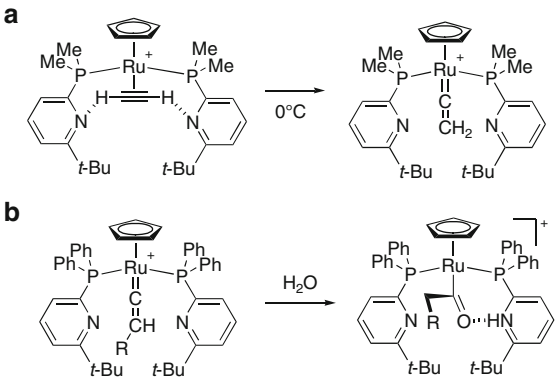
4.1.2 Anti-Markovnikov Hydration of Alkynes

New catalysts for the anti-Markovnikov hydration of terminal alkynes have not been reported since our previous review [6]. Currently, the most active catalysts are of the type $[CpRu(AZARYPHOS)_2(NCMe)]PF_6$ (AZARYPHOS = aza-aryl-phosphane), introduced by Grotjahn [125] and further optimized in our group [126]. Those complexes were based on the first generation catalyst CpRuCl(dppm) introduced by Wakatsuki [127]. New AZARYPHOS ligands have been tested in the ruthenium-catalyzed hydration of 1-octyne to octanal [128]. Propargyl-alcohols have been hydrated to mixtures of unsaturated aldehydes and aldols, but *O*-acetal-protected propargyl alcohols gave mainly *O*-protected aldol derivatives with retention of configuration at the propargylic center (Scheme 22) [129].

Grotjahn and coworkers have continued their studies into the mechanism of anti-Markovnikov hydration of terminal alkynes. A bifunctional mechanism in which the ligand acts both as a donor to the metal via phosphorus and as a hydrogen-bond acceptor via its nitrogen lone-pair is postulated [130]. Recent mechanistic studies have been reviewed [131]. NMR spectroscopic investigations give support for hydrogen bonding between the C(sp^1)–H bond of side-on coordinated alkynes and the nitrogen lone-pair of the heterocyclic ligand, which may be responsible for acceleration of the alkyne to vinylidene rearrangement (Scheme 23a) [132].



Scheme 22 Catalytic hydration of propargyloxy- to aldol-derivatives



Scheme 23 Anti-Markovnikov hydration; catalytic intermediates

These studies imply that allenylidene cations $[CpRu(=C=CHR)(AZARYPHOS)_2]^+$ are reaction intermediates; their attack by water produces a tautomeric metal acyl species with a hydrogen-bond to the pyridine nitrogen (Scheme 23b), as proven by multidimensional NMR experiments involving ^{15}N markers [133]. Current work is addressing the details of reductive elimination of aldehyde from the acyl complex.

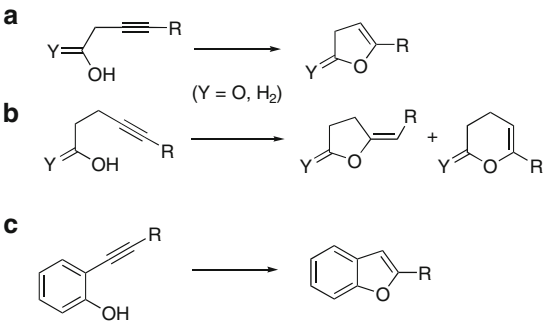
4.2 Cycloisomerizations of Alkynols or Alkynoic Acids

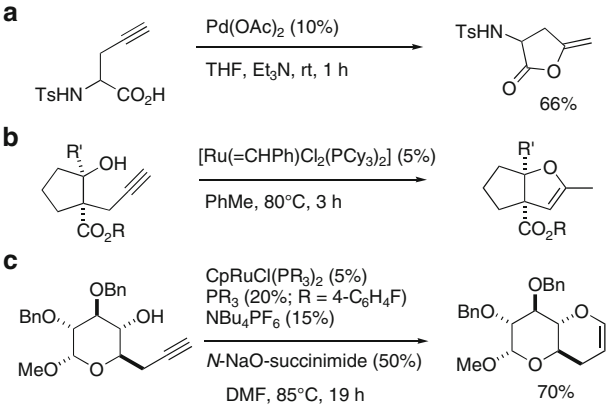
Several catalysts for additions of either alcohols or carboxylic acids to nonactivated alkynes are known [3–5], and those reactions are particularly easy in case of cyclizations to 5- or 6-membered rings. A review addressing palladium-catalyzed cyclizations of alkynols to acetals and furans has appeared [134].

4.2.1 Catalytic Cycloisomerizations to Enol–Ethers or Enol–Lactones

Common model reactions for the title conversion include cyclizations of alkynoic acids to lactones, with variable degrees of regioselectivity [3–5]. Another model-reaction is the cyclization of ortho-alkynyl-phenols to benzofurans. The reaction is

Scheme 24 Common reactions for studying intramolecular hydroalkoxylation or hydrocarboxylation





Scheme 25 Catalytic alkynol hydroalkoxylation

mediated by strongly basic conditions, or catalyzed by several transition metals under both basic and (Lewis-) acidic reaction conditions (Scheme 24).

For the cyclization of 2-alkynyl-phenols to benzofuranes, a Rh(I) catalyst from $[Rh(CO)_2(acac)]$ (10 mol%) and BINAP (11%) has been reported (toluene/water, 100°C, 1 h, >90% yield). The intermediacy of organometallic vinylrhodium species was proven by performing a tandem conjugate addition to acrylate [135]. Similarly, the homologous 2-propargyl-phenols cyclize in a 5-exo-dig manner to 2-alkenyl-benzodihydrofuranes by use of a silver-catalyst under basic conditions [136]. Alkynoic acids have been cyclized to lactones by several metal catalysts. Gold-catalysts (AuCl 10 mol%, with K_2CO_3 in acetonitrile at rt over 2 h) show the usual kinetic preference for ring-sizes of 5>6 >> 7 [137, 138]. Amino-acids with alkynyl groups in the side-chain are substrates of relevance in bioorganic chemistry. The cyclization of *N*-protected amino-acids is catalyzed by palladium(II) salts in basic medium (Scheme 25a) [139].

Similar cyclizations of *N*-protected amino acids are mediated under surprisingly mild conditions by CuBr (10 mol%) in aqueous *tert*-butanol (1:1) at ambient

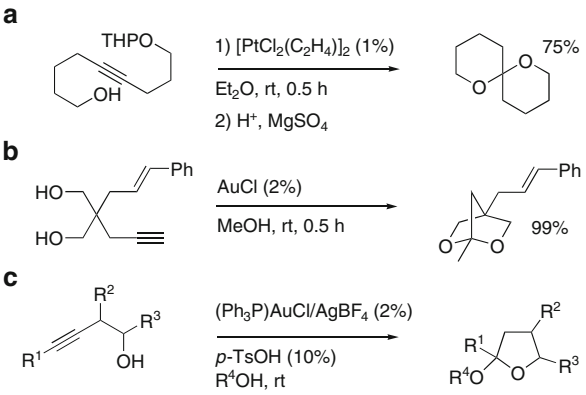
temperature [140]. Such cyclizations may interfere with "click-chemistry" in a bioorganic environment. Copper(I) catalysts based on CuI (10 mol%) and the ligand *N,N*-dimethylcyclohexane-1,2-diamine (20 mol%) and cocatalytic potassium carbonate (10 mol%) also cyclize simple alkynoic acids in refluxing THF (0.3–20 h) [141]. This reaction, with 4-pentynoic acid, was also catalyzed by a nickel-capped molybdenum sulfide cluster at the 0.33 mol% level of loading [142]. 2-Propargyl-1-cycloalkanols cyclize to bicyclic dihydrofuranes via Markovnikov addition and double-bond shift to the endocyclic position in the presence of Grubbs I metathesis catalyst (Scheme 25b) [143]. Related 5-dig-endocyclizations in *cis*-4-hydroxy-5-alkynylpyrrolidines have been catalyzed by either $AgNO_3$ or $(Ph_3P)AuCl$ or $PdCl_2(PPh_3)_2$/CuI in *N,N*-dimethyl formamide or ethanol [144], whereas simple open-chain 4-alkynols are cyclized by lanthanoid tris-hexamethyldisilazides (5 mol% $Ln\{N(SiMe_3)_2\}$, PhH, 60–120°C) [145, 146]. Alken-yn-ols cyclize to furans by means of gold(I) or gold(III) catalysts [147, 148]. An intermolecular version of the reaction is the palladium(0)-catalyzed addition of phenols to 1,3-diynes [149].

Anti-Markovnikov cyclizations: For anti-Markovnikov cyclizations of 4-alkynols to dihydropyrans such as glycals, the catalysts or reagents introduced by McDonald [150] remain synthetically important [151, 152]. Another catalyst based on ruthenium was presented by the Trost group. A rather finely tuned catalyst based on a $CpRuCl(PAr_3)_2$ complex (Ar = aryl) achieved similar reactions like the McDonald catalyst (Scheme 25c) [153].

4.2.2 Acetals by Double Addition of Alcohols to Alkynes

Several new catalyst systems for the synthesis of acetals from alkynes have been presented over the past few years. A palladium(II) catalyst with iodide additives (0.5 mol% PdI_2, 1 mol% KI) cyclizes 4-alkyn-1-ols in alcohols to 2-alkoxy-tetrahydrofuranes [154]. The platinum compounds $PtCl_2$ and $[PtCl_2(H_2C{=}CH_2)]_2$ (1 mol %) catalyze the intermolecular addition of alcohols (MeOH, EtOH; THF, 12 h, rt) to internal alkynes such as 4-octyne, but only in the presence of cocatalytic additives such as Na_2SO_4, $MgSO_4$, or 2,6-di-*tert*-butylpyridine. In the absence of such additives, no appreciable reaction is said to take place [155]. Intramolecular hydroalkoxylations of alkynyl-diols to spiroacetals, or of alkynols with external alcohols to cyclic acetals have also been catalyzed with $[PtCl_2(H_2C{=}CH_2)]_2$ (1 mol %) in ethyl ether. Keto-alcohols appear to be intermediates, but were acetalized in a separate acid-catalyzed step under dehydrating conditions to give a uniform reaction product (Scheme 26a) [156].

Gold: Cationic gold(I) catalysts are also active (Scheme 26b, c) [156–158]; factors controlling the selectivity in substrates that can cyclize either to 5- or 6-membred oxacycles were discussed [156]. Intermolecular acetalizations of alkyne-diols have been realized with $(PPh_3)AuCl/AgBF_4$ (2 mol%) in toluene (100°C, 0.2–6 h, 80%) [159]. The reaction is accelerated by cocatalytic toluenesulfonic acid. The cyclization of 2-propargyl-1,3-diols to bicyclic acetals is



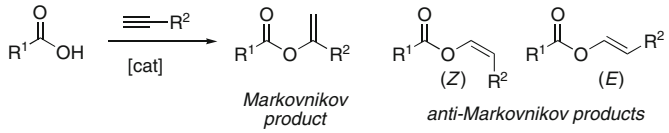
Scheme 26 Cyclizations of alkyne-diols and alkynols to acetals

catalyzed by AuCl (2%) or $AuCl_3$ (Scheme 26b) [160], and the cyclization of 3-alkynols and 4-alkynols in alcoholic solvents to 2-alkoxytetrahydrofuranes is mediated by cationic gold(I) catalysts with a Brønsted acid additive (Scheme 26c); if $HAuCl_4$ is used as catalyst, no additional acidic additive is needed [158]. Related gold-catalyzed cyclizations of 3-butyne-1,2-diols proceed via oxymetallation and β-elimination to dihydrofuranes [161, 162]. The iridium(I) complex $[\{IrCl(cod)\}_2]$ (1–2.5 mol%) converts 2-substituted 2-propargyl-1,3-propanediols in alcoholic solvent to 2-alkoxy-4-hydroxymethyltetrahydrofuranes (rt, 0.5–24 h) in high yield under neutral conditions [163]. Ruthenium carbonyl $Ru_3(CO)_{12}$ (2 mol%) promotes the addition of catechol to alkynes in the Markovnikov sense, at elevated temperatures [164].

4.3 Intermolecular Addition of Carboxylic Acids to Alkynes

The state of the art in catalytic intermolecular additions of carboxylic acids to terminal alkynes (Scheme 27) prior to 2000 has been reviewed by Dixneuf and Bruneau, who conclude that complexes $[(p\text{-cymene})RuCl_2(PR_3)]$ are catalysts for Markovnikov additions (toluene, 80–100°C), whereas $[(dppb)Ru(methallyl)_2]$ is the preferred catalyst for anti-Markovnikov hydrocarboxylations of alkynes with predominant selectivity for (*Z*)-enol esters (toluene, 50–60°C) [165, 166].

Goossen and coworkers found optimal conditions for the Markovnikov hydrocarboxylation by combining $(p\text{-cymene})RuCl_2$ (0.8 mol% [Ru]) with trifuryl phosphane (0.8 mol%) and Na_2CO_3 (1.6 mol%) in toluene at 50°C for 16 h. Those conditions often gave enol esters in excess of 90% yield [167]. Astonishingly, combination of the same metal precursor (2 mol% [Ru]) with tris-(4-chlorophenyl)-phosphane (3 mol%) and 4-dimethylaminopyridine (4 mol%) as additive produced



Scheme 27 Products of terminal alkyne hydrocarboxylation

anti-Markovnikov addition product as (*Z*)-isomer selectively under similar conditions (toluene 60°C, 16 h). The role of DMAP for blocking a coordination site at ruthenium was discussed [167].

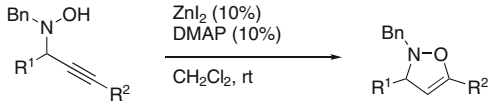
It should be mentioned that many transition metal complexes will catalyze the addition of carboxylic acids to alkynes at a suitably high temperature. Depending on reaction conditions and product selectivities, such catalysts are not always practically useful.

Rhenium: A hydrocarboxylation with high selectivity for anti-Markovnikov addition and predominant (*Z*)-enol ester product is mediated by $ReBr(CO)_5$ (1 mol%, 110°C, 15 h) [168]. The π-activation mechanism proposed by the authors does not fit to the observed anti-Markovnikov selectivity. *Iridium*: The precursor complex $[\{IrCl(cod)\}_2]$ (1 mol%) combined with $P(OMe)_3$ (4 mol%) and Na_2CO_3 (2 mol%) produces a catalyst that adds carboxylic acids to terminal alkynes (toluene, 100°C, 15 h) to give a mixture isomers with variable selectivities, although the Markovnikov product is usually formed in excess (ca 5:1) [169]. The complex $[\{IrCl(cod)\}_2]$ (1 mol%) in the presence of Na_2CO_3 (0.6 equiv) is also a catalyst for the transvinylation of vinylacetate with diverse alcohols [170].

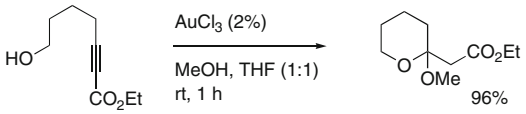
4.4 Additions of Other Nucleophiles to Alkynes

The reaction of *para*-toluenesulfonic acid with alkynes to give vinyl sulfonates is catalyzed by the gold complex $(Ph_3P)AuNO_3$ (2 mol%) in the presence of phthalimide (4 mol%) in dichloroethane at 100°C [171]. *ortho*-Alkynyl-phenylphosphonic acids cyclize in a 6-endo dig manner to give phosphorus heterocyles in the presence of a copper catalyst (CuI, 10 mol%) in DMF (90°C, 4 h). Addition of triethylamine increased the yield [172]. Cyclic 4-propargyl-1,3-diketones react via their enol-form to give bicyclic dihydrofurans or dihydropyrans in the presence of several catalysts including $Pd(OAc)_2$ (2 mol%), $W(CO)_5(THF)$ (10 mol%), or $PtCl_2$ (all in THF at rt). Also $CpRuCl(PPh_3)_2$ (10 mol%) induced a slow cyclization (7 days). The reaction was sensitive to the ring-size of the diketone starting material [173]. In a variation of the alkynol cyclization theme, in situ generated hemiacetals are nucleophiles in a cationic gold-complex-catalyzed cyclization of 4-alkynylketones with alcohols [174]. Acid catalyzes the cyclization of 3-alkynones to furanes; this conversion has now also been realized with a $ZnCl_2$ (10 mol%) catalyst under mild conditions [175].

Scheme 28 Cyclization of *N*-propargylhydroxylamins to 2,3-dihydroisoxazoles



Scheme 29 Acetals from ω-hydroxy-propiolates



N-Propargyl-hydroxylamine Dihydroisoxazole Cyclizations: A catalyst composed of zinc iodide and DMAP catalyzes the cyclization of *N*-propargyl-*N*-benzylhydroxylamines to 2,3-dihydroisoxazoles (Scheme 28) [176]. In a related cyclization with $ZnMe_2$ as catalyst or stoichiometric reagent, the intermediacy of vinylzinc species has been made plausible [177]. For carbamate protected *N*-propargyhydroxylamines, the cyclization to 2,3-dihydroisoxazoles is catalyzed by $NaAuCl_4{\cdot}2H_2O$ (5 mol%) with DMAP as cocatalyst (20–30%) in CH_2Cl_2 (40°C, 2 h) [178].

4.5 Addition Reactions to π-Acceptor Alkynes

π-Acceptor alkynes are particularly reactive towards nucleophilic additions. They are readily hydrated via stoichiometric hydroamination to an enamine, followed by acidic hydrolysis [6]. A gold-catalyzed hydroalkoxylation of conjugate alkynoates in alcoholic solvents gives cyclic acetals via enol ethers (Scheme 29). Aside from $AuCl_3$, $AuCl(PPh_3)$/AgOTf, $PtCl_4$, $\{PtCl_2(C_2H_4)\}_2$, and $PdCl_2(MeCN)_2$/AgOTf were also efficient catalysts [179].

5 Reactions of Allenes

5.1 Hydration

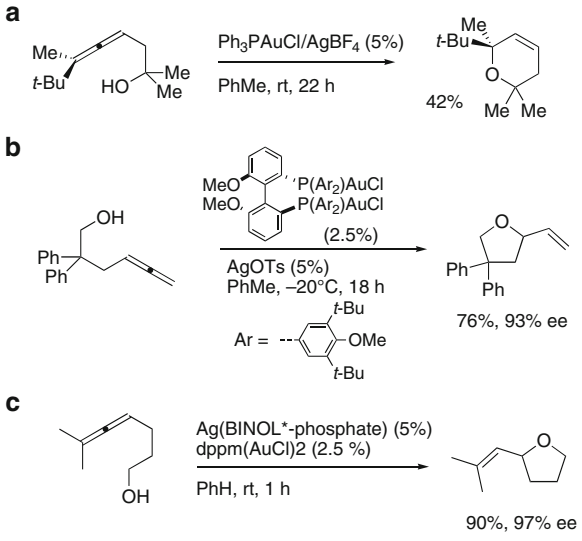
Catalytic conversions of allenes are sometimes considered models for catalytic reactions of alkenes, even though allene reactivity is more closely comparable to that of alkynes rather than alkenes. The catalytic hydration of allenes was achieved by means of a cationic gold(I) complex with a carbene steering ligand, (IPr)AuCl/AgOTf (5 mol%), in dioxane (rt, 4–9 h) in fair yield [180]. Attack of water is selective for the terminal carbons, whereas regioselectivity in nonsymmetric substrates is controlled by steric, electronic, and solvation factors.

5.2 *Additions of Alcohols and Carboxylic Acids to Allenes*

Cyclizations of 2-allenoic acids have been investigated by Ma and coworkers [181]. These studies were mostly based on palladium-catalysts and were aimed at in situ generation of organometallic derivatives via carboxy-metallation, for use in coupling reactions to C-5 functionalized butenolides. Straightforward cyclizations were realized with a Cu(I) catalyst (CuCl 4 mol%, MeOH, reflux 2 h). Older work on silver(I)-catalyzed cyclizations of 2-allenols to 2,5-dihydrofurans was also referred to [181]. *Gold*: Cyclizations of 3-allenols to 5,6-dihydro-2*H*-pyrans were realized with both gold(I) and gold(III) catalysts; the reaction proceeds with chirality-transfer from the allene axis to an sp^3 center in the product (Scheme 30a) [182].

4-Allenols cyclize to 2-vinyl-tetrahydrofurnas by means of (t-Bu$_2$P{2-biphenyl})-AuCl/AgOTs (5 mol%) in toluene at room temperature. The tosylate counter-ion induced higher regioselectivity than triflate [183]. By using chiral chelating phosphanes of the biaryl type, this reaction could be performed asymmetrically with high enantiomeric excess (Scheme 30b) [184]. Another asymmetric catalytic cycloisomerization of allenols was induced by a catalyst combining an achiral bisphosphine-di-gold(I) complex with the chiral counter-ion 3,3′-bis(2,4,6-triisopropylphenyl)-binaphthol-phosphate (Scheme 30c) [185].

Other cyclizations of allenols have been realized by means of gold-catalysts [186, 187], gold and platinum catalysts [188], and with lanthanum amide catalysts [189]. Intermolecular additions of alcohols to allenes were also catalyzed by cationic gold(I) complexes with carbene [190] or phosphane spectator ligands



Scheme 30 Catalytic and asymmetric hydroalkoxylation of allenols

[191]. An intermolecular rhodium(I)-catalyzed asymmetric addition of alcohols to diphenylphosphinyl-allenes has just been reported [192].

6 Conclusions

The synthesis of oxygen-functionalized products by conceptually simple redox-neutral heterofunctionalizations from simple and abundant precursors is a challenge for catalysis development.

For alkynes (and in part, allenes), synthetically useful protocols for Markovnikov and anti-Markovnikov selective hydrations, hydroalkoxylations (mainly intramolecular), and hydrocarboxylations are available and find increasing applications in organic synthesis. In the past decade, the research focus on cationic gold(I) complexes has led to new additions to the catalysis toolbox. It can be predicted that a further refining of such tools for alkyne functionalization with respect to catalytic activity and functional group tolerance will take place.

On the other hand, there is a lack of methodology for regio- and stereoselective catalytic additions of water, alcohols, or carboxylic acids to nonactivated alkenes. In the past decade, progress has been made in the fields of stereoselective oxa-Michael type additions to electron-poor alkenes. Also, Lewis-acid catalyzed hydroalkoxylations, mainly of higher substituted alkenes in an intramolecular fashion, have been investigated and numerous catalysts have been identified. The reactivity profile of those Lewis acid catalysts is similar to that of strong, protic acids. Even if this observation casts doubt on the true nature of the catalytically active species, it cannot be denied that some practically useful protocols for Markovnikov-selective hydroalkoxylations have been devised. The problem of redox-neutral anti-Markovnikov heterofunctionalization of alkenes is still largely unsolved. Recent work on a stoichiometric hydrometallation/oxy-de-metallation sequence [25] raises, once more, hopes that this long postulated catalytic cycle might eventually be realized. For the time being, we state that new approaches towards and breakthrough discoveries in catalytic anti-Markovnikov oxyfunctionalization of nonactivated alkenes are very much needed.

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Catalytic C–N, C–O, and C–S Bond Formation Promoted by Organoactinide Complexes

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Abstract Throughout this last decade, we have witnessed impressively how the chemistry of electrophilic d^0/f^n actinides has been prospering either in their new synthetic approaches reaching very interesting compounds or in their use in stoichiometric and catalytic reactions leading to high levels of complexity. The unique rich and complex features of organoactinides prompted the development of this field toward catalysis in demanding chemical transformations. In this review, we present a brief and selective survey of the recent developments in homogenous catalysis of organoactinide complexes, especially toward the formation of new C–N, C–O, and C–S bonds. We start by presenting the synthesis and characterization of the corresponding organoactinide complexes, followed by the homogeneous catalytic chemical transformations that include the hydroamination of terminal alkynes, the polymerization of ε-caprolactone and *L*-lactide, the reduction of azides and hydrazines by high-valent organouranium complexes, the hydrothiolation of terminal alkynes, and the catalytic Tishchenko reaction. For each reaction, the scope and the thermodynamic, kinetic, and mechanistic aspects are presented.

Contents

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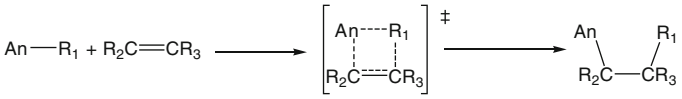
1 Introduction

During the last three decades, the chemistry of organoactinides has arrived at an exquisite level of sophistication. The uses of organoactinides as stoichiometric or catalytic complexes have increased because of their rich, complex, unique, and highly informative organometallic chemistry promoting synthetically important organic transformations. Among the unique features exhibited by actinides, the first to be pointed out is the remarkably sizeable ionic radii, which give rise to large formal coordination numbers and unusual coordination geometries. The presence of 5f valence orbitals is an additional characteristic of actinides that differs distinctly from the characteristics of d-block elements. Taking into consideration these differences, it can be said that actinides exhibit parallel but primordially different reactivities for similar organic processes when compared to early or late transition-metal complexes. In various cases, the reactivity of organoactinide complexes challenges the activities of the transition metals, illustrating their unique and plausible reactivities. Moreover, in many instances, the regio- and chemo-selectivities displayed by the organoactinide complexes are complementary to that observed for other transition-metal complexes. Several recent review articles [1–8] dealing mostly with the synthesis of new actinide complexes confirm the broad and rapidly expanding scope of this field. This review is aimed to be a brief and selective survey of the catalytic chemistry of organoactinide complexes. This review covers the new literature for the last decade and focuses on the reactivity of organoactinide complexes as catalysts for challenging organic transformations, especially in the homogeneous catalytic reactions for the C–N, C–O, and C–S bond formation. For other catalytic processes, recent reviews are also available [9–12]. We start the presentation with the synthesis of organoactinide catalysts, followed by a survey of the organic transformation catalyzed by these organoactinides. The reactivity of organoactinide complexes is based on their ability to perform bond-breaking and bond-forming reactions of distinct functional groups. The factors influencing such processes are the steric and electronic effects. With reference to the steric hindrance, a number of articles have been dedicated to deal with the geometric control in organo-5f-complexes. For example, Xing-Fu et al. have developed a rule for packaging saturation, showing that the stability of a complex is governed by the sum of the ligand cone angles [13–15]. In this model, highly coordinative

"oversaturated" complexes will display low stability. An additional model regarding steric environments was proposed by Pires de Matos [16]. This model assumes pure ionic bonding, and is based on cone angles defining the term "steric coordination number." A more important and unique approach to the reactivity of organo-5f-complexes considers the utilization of thermochemical studies. The knowledge of the metal–ligand bond enthalpies is of fundamental importance to allow the estimation of new reaction pathways [17–24]. In addition, neutral organoactinides have been proved to follow a four-center transition state (1) because of the high-energy orbital impediment to undergo oxidative addition and reductive elimination. Such a transition state allows the predictions of new actinide reactivities, while taking into account the negative entropies of activation [25]. It is important to indicate that recently organoactinides were found to be active in the insertion of isonitriles into actinides following a three center transition state. The difference in activity of the thorium compounds as compared to the corresponding uranium complexes, in this process, indicates also the importance of the 5f electrons participating in the bonding and in the chemistry as compared to the inner core 4f electrons that do not participate in the chemistry of the lanthanides [26].



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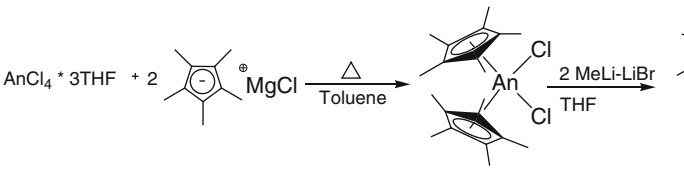
2 Synthesis of Organoactinide Catalysts

2.1 Synthesis of Actinide (An(IV)) Based Complexes

In this review we concentrate on the catalytic activity of well characterized organoactinide complexes: the neutral metallocene–alkyl complexes $Cp^*_2AnMe_2$ (An = Th (**1**) or U (**2**), $Cp^* = C_5Me_5$), $Me_2Si(C_5Me_4)_2AnR_2$ (**3** – An = Th, R = ^{n}Bu; **4** – An = U, R = Me; **5** – An = U, R = $CH_2C_6H_5$), and the cationic trisamido complex $[(NEt_2)_3U][BPh_4]$ (**6**).

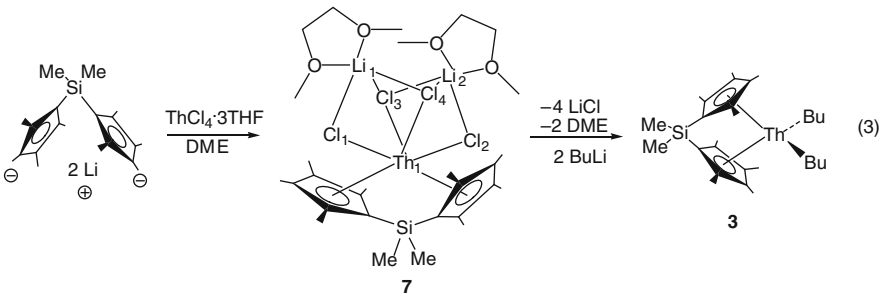
The synthesis of the metallocene complexes **1** and **2** (2) was reported by Fagan et al. [27] and involves two major steps: (1) reaction of the actinide chloride with 2 equiv of Cp*MgCl to form the corresponding dichloride complex, and (2) reaction of the latter with 2 equiv of MeLi•LiBr to obtain the corresponding dimethyl complex. The spectroscopic characterization of the complexes was fully disclosed; however, the crystal structure for complex **2** was reported only recently [28].



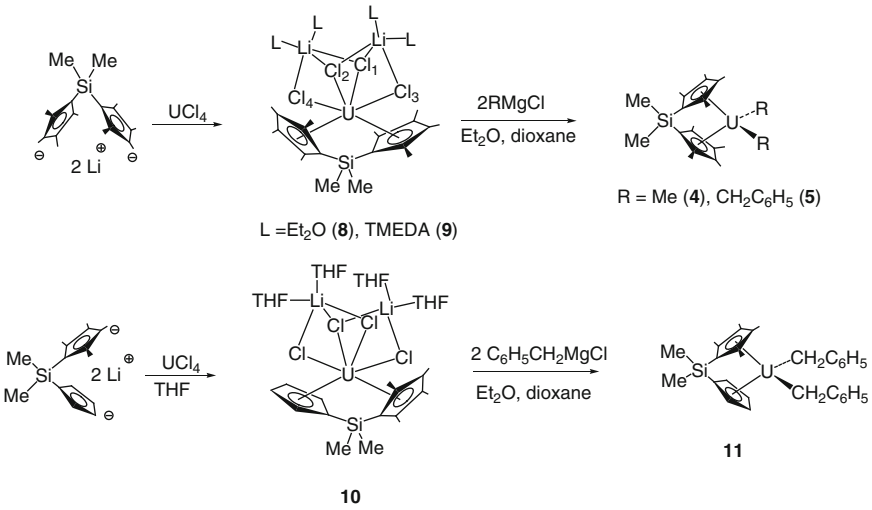
(2)

An = Th (**1**) , U (**2**)

As can be expected, the stoichiometric and catalytic properties of the organo-f-element complexes are deeply affected by the nature of the σ−ancillary ligands [29–33]. It is known that opening of the metal coordination sphere (frontier orbitals) [34] at the surrounding equatorial sash, where the σ -ligation is disposed, is achieved by using a bridge ligation forming the *ansa*-$Me_2Si(C_5Me_4)_2MR_2$ type of complexes [35–38]. The effect of opening the coordination geometry sphere in some organo-f- complexes toward catalytic processes was observed for organo-lanthanides, which allows an increase (10–100 fold) in the corresponding rates for olefin insertion into a M–R bond [36, 37, 39, 40], and in organoactinides, it spurs an increase (10^3 fold) in their catalytic activity for the hydrogenation of 1-hexene [38, 40] or in the hydrosilylation of alkynes [41]. The synthetic procedures for the formation of complexes $Me_2Si(C_5Me_4)_2ThCl_2$ (**7**) and $Me_2Si(C_5Me_4)_2Th^nBu$ (**3**) are presented in 3 [40, 41]. The complex $Me_2Si(C_5Me_4)_2ThCl_2$•LiCl was isolated in 82% yield. Single crystal x-ray diffraction studies show that the complex exhibits a classical bent metallocene geometry. The ring-centroid-Th-centroid angle (113.3°) is smaller, as expected, when compared to the unhindered bis(pentamethylcyclopentadienyl) thorium complexes (130–138°) [42], and similar, although slightly smaller, to the corresponding angle encountered for the bridged thorium dialkyl complex $[Me_2Si(C_5Me_4)_2Th(CH_2SiMe_3)_2]$ (118.4°) [38]. Because of the strain generated by the Me_2Si- motif, as reported for other *ansa* type of complexes, the thorium–carbon (carbon = C_5Me_4 ring carbons) bond lengths are not equidistant. The shorter distance is found between the metal and the first carbon adjacent to the silicon bridge [43].

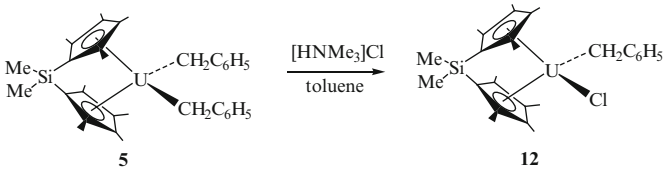


X-ray analysis of complex **7** showed that two of the metal–chloride bonds are shorter than the other two Th(1) – Cl(1) = 2.770(2)Å, Th(1) – Cl(2) = 2.661(2)Å, Th (1) – Cl(3) = 2.950(2)Å, and Th(1) – Cl(4) = 2.918(2)Å. The longer Th–Cl distances are those belonging to the chlorine atoms encountered in the threefold bridging positions and connected to the lithium atoms. The other two chlorine atoms are coordinated only to one lithium atom. All the Th–Cl distances are longer than those observed for terminal Th–Cl distances (Th–Cl = 2.601Å for $Cp_2^*ThCl_2$ or 2.65Å for $Cp_2^*Th(Cl)Me$). *Ansa*-chelating bis(cyclopentadienyl) complexes of uranium have been prepared as presented in Scheme 1. Burns et al. have described an efficient high yield procedure for the required U(IV) complexes [44].



Scheme 1 Synthetic routes for the preparation of *ansa*-organouranium complexes

The uranium complexes **8**, **9,** and **10** are obtained as dark-red, air and moisture sensitive materials. These complexes were found to be soluble in aromatic solvents but insoluble in hexane. No dynamic behavior was observed for these complexes in solution. The single crystal x-ray diffraction studies on the molecular structure of complex **8** reveal a normal bent metallocene with a ring centroid-metal-ring centroid angle of 114.1°. This angle is somewhat smaller than the same type of angle in the nonbridge uranium complexes (133–138°) [27, 45–48]. The uranium atom is bonded to four bridging chloride ligands for which two bonds are much longer U-(Cl(1)) = 2.885(3), U-(Cl(2)) = 2.853(3), U-(Cl(3)) = 2.760(3), U-(Cl(4) = 2.746(3) Å. For the synthesis of the dialkyl complexes, the corresponding chloride-TMEDA complex (**9**) was utilized as a precursor. The alkylation of the halo-precursors with Grignard reagents indeed produced the corresponding alkyl complexes; however, large excess of dioxane was needed as the solvent. Interestingly, complex **4** is very stable in contrast to the instability of the corresponding dimethyl thorium complex [38]. The dimethyl complex of the mixed cyclopentadienyl precursor (**10**) was not obtained; however, in the synthesis, concomitant precipitation of an insoluble material and evolution of gas were observed. On the contrary, the dibenzyl complexes **5** and **11** were achieved in excellent yields. The mixed benzyl-chloride complex **12** was obtained by protonolysis of the dibenzyl complex **5** with $[HNMe_3]Cl$ (4).

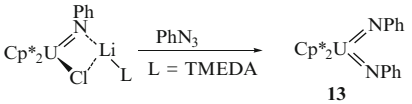


(4)

As will be presented in the course of this review, some of the work has been dedicated towards catalytic reactions using the cationic complex $[(Et_2N)_3U][BPh_4]$ (**6**) [49]. The synthesis of this and other cationic complexes, reported by Berthet et al., is on the basis of the reaction of $U(NEt_2)_4$ with $[NHEt_3][BPh_4]$ in THF.

2.2 Synthesis of High-Valent Organouranium Complexes

It has been shown over the course of the last two decades that the reactivity of organoactinide (IV) complexes toward unsaturated organic substrates such as olefin, alkynes, and nitriles follows a four-center transition state as described in 1. The synthesis, characterization, and reactivity studies of high-valent organouranium complexes are of fundamental importance. The ability to transform U(IV) to U(VI) and vice-versa can originate complementary modes of activation exhibiting unique and novel reactivities. The first high-valent organouranium(VI) bis-imido complex (**13**) was prepared by Burns et al. by the oxidation of the lithium salt of an organoimido uranium chloride complex with phenylazide (5) [50].



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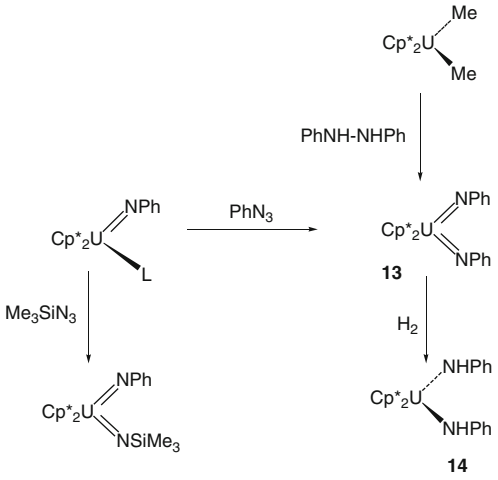
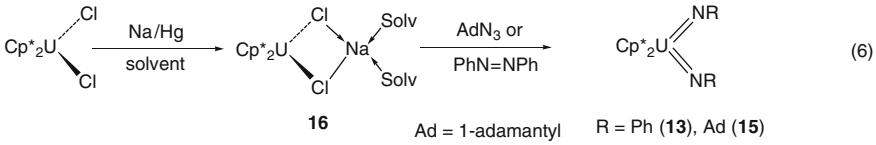
Other bis(imido) organouranium (VI) complexes have been prepared, and for a metallocene complex, a general pathway is represented in Scheme 2. The reactions involve the oxidation of uranium (IV) bis-alkyl or uranium (IV) imido complexes



Scheme 2 Synthetic routes for the synthesis of high-valent organouranium-bis (imido) complexes and their reductive reactivity with dihydrogen

with two-electron atom transfer reagents, in high yield. Other pathways as well are now described in the literature but are beyond the scope of this review [51–53].

A very elegant and simple procedure for the generation of high-valent bis(imido) organouranium (VI) complexes **13**, and **15** was described starting from the organometallic uranium (III) complex **16**. The reaction involves the direct reduction of diazenes or azides (**6**) [54].

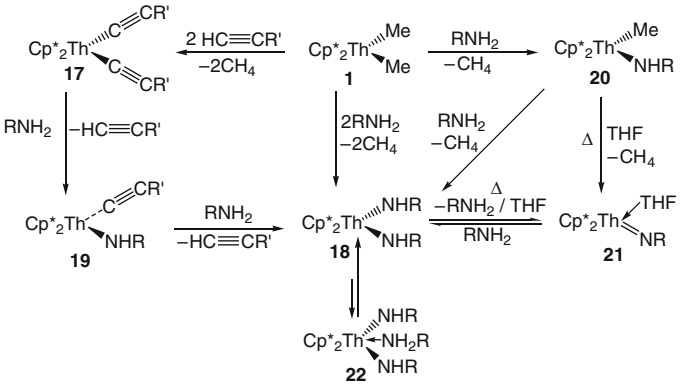


(6)

2.3 *Stoichiometric Reactivity of Cp*$_2$AnMe$_2$ Towards Terminal Alkynes and Primary Amines*

The different catalytic reactivity found for structurally similar organoactinides, which is unprecedented in the chemistry of organoactinides, is always a driving force to studying the stoichiometric reactivity of these complexes, Cp*$_2$AnMe$_2$ (An = Th (**1**), U (**2**)) [55] as outlined in Schemes 3 and 4 for Th and U, respectively.

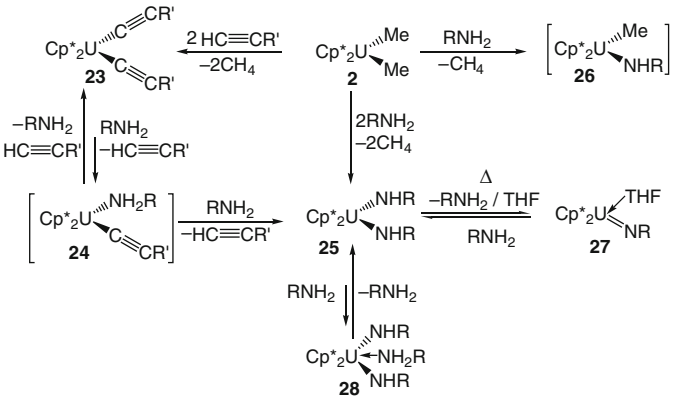
Cp*$_2$ThMe$_2$ (**1**) was found to react with terminal alkynes producing the bis (acetylide) complexes Cp*$_2$Th(C≡CR′)$_2$ (**17**) (R′ = ^{t}Bu, SiMe$_3$). The reaction of these bis(acetylide) complexes with equivalent amounts of amine yields the bisamido complexes Cp*$_2$Th(NHR)$_2$ (**18**); the starting bis(acetylide) complex indicates



Scheme 3 Stoichiometric reactions of the complex Cp*$_2$ThMe$_2$ (**1**) with primary amines and terminal alkynes

that the second amine insertion into the thorium monoamido monoacetylide complex **19** is faster than the first insertion. However, the reaction of complex **1** with an equimolar amount of amine, allowed the formation of the monoamido thorium methyl complex **20**, which upon subsequent reaction with another equivalent of amine produced the same bisamido complex **18**. Complex **18** can eliminate an amine on heating of its THF solution affording the thorium imido complex **21**. Complex **21** can also be formed by the elimination of methane on heating complex **20** [56]. In an excess of amine, the bisamido complex **18** was found to be in rapid equilibrium with the bisamido–amine complex **22** [57], resembling the lanthanide complexes [39, 58, 59]; however, when the equilibrium was studied, it was found to favor the bisamido complex.

The organouranium complex **2** displays a similar reactivity as that found for complex **1** for the stoichiometric reaction with primary amines and/or terminal alkynes (Scheme 4). The reaction with alkynes produced the bis(acetylide) complexes $Cp^*_2U(C{\equiv}CR')_2$ (**23**) (R' = Ph, $SiMe_3$), but in contrary to the thorium reactivity, these bis(acetylide) complexes were found to be extremely stable and the bisamido complex **25** can be formed only by adding large excess of the amine, indicating that the equilibrium between complexes **23** and **24** lies preferentially toward the bis(acetylide) complexes, instead of either the monoamido monoacetylide **24** or the bisamido complexes **25**. Efforts to isolate the monomethyl–amido complex **26**, by reacting complex **2** with one equivalent of an amine afforded only half equivalent of the bisamido complex **25**. Similar to the thorium bisamido complex **18**, with an excess of amine, complex **25** was found to be in fast equilibrium with complex **28**, with the equilibrium favoring the bisamido complex. Heating of the bisamido complex **25** in THF eliminates an amine molecule, allowing the formation of the corresponding uranium imido complex **27** [60].

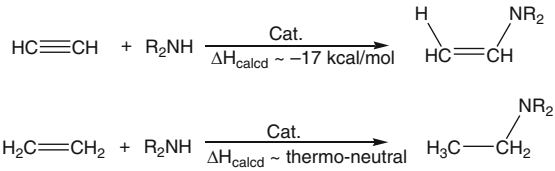


Scheme 4 Stoichiometric reactions of the complex $Cp^*_2UMe_2$ (**2**) with primary amines and terminal alkynes

3 Intermolecular Hydroamination of Terminal Alkynes Catalyzed by Neutral Organoactinide Complexes

3.1 Scope of the Intermolecular Hydroamination

The hydroamination reaction (7) is known as an atom-economic transformation towards the introduction of the R_2NH moiety across a C–C double or triple bond. This field is nowadays widely studied with different organometallic compounds, including late transition-metals [61–68], early transition-metals [69–76], and lanthanides [77–83]. The catalytic C–N bond formation is a chemical reaction of primordial significance in modern synthetic organic chemistry. The hydroamination of terminal alkynes results in the formation of enamines or imines, which are significant synthons in organic chemistry, with at least two active organic group functionalities (double bond and nitrogen lone pair).



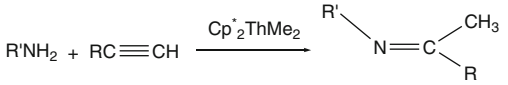
(7)

Thermodynamically, the addition process of amines to alkynes is known to be exothermic, while addition to alkenes is closer to thermo-neutral. Therefore, the hydroamination of alkynes, where the mechanism is indeed a four center transition state, is more promising from a catalytic viewpoint. It is important to indicate that the expected negative entropy of activation of the reaction may prevent the use of high temperatures. Organolanthanide complexes have been found to be extremely good catalysts for the intramolecular hydroamination/cyclization of aminoalkenes, aminoalkynes, and aminoallenes [39, 58, 84–97], and enantioselective intramolecular amination has been performed using chiral organolanthanide precatalysts [39]. Interestingly, many years ago, the intermolecular functionalization of olefins and alkenes with simple amines was mentioned as one of the ten most important challenges in catalysis [98] and still remains a major challenge in some cases (secondary and tertiary amines).

The organoactinide complexes $Cp^*_2AnR_2$ (An = Th, U; R = Me, NHR′; R′ = alkyl) and the bridge complexes **3–6** were found to be excellent precatalysts for the intermolecular hydroamination of terminal aliphatic and aromatic alkynes in the presence of primary aliphatic amines to yield the corresponding imido compounds [56, 99]. The reactivity exhibited for the thorium complexes was different, depending on the alkynes, from that for organouranium complexes.

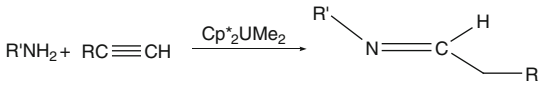
The intermolecular process (8 and 9) showed two hydroamination regioselectivities depending on the precatalyst. The intermolecular hydroamination catalyzed by the metallocene thorium catalyst yielded the methyl alkyl-substituted imines in

moderate yields with the attendant formation of the corresponding alkyne *gem* dimer. However, with the utilization of the uranium catalyst, the reaction exhibited large regio- and chemo-selectivity towards the imine in which the amine and alkyne substituents are allocated, almost always, in an *E* regio-chemistry.



(8)

R = H; R' = Et
R = ^{n}Bu; R' = Me, Et
R = Ph; R' = Et
R = ^{i}Pr; R' = Ph

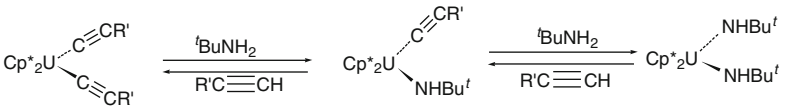


(9)

R = $SiMe_3$, ^{t}Bu; R' = Me, Et, ^{n}Pr, ^{i}Pr, ^{n}Bu, ^{i}Bu
R = ^{n}Bu; R' = Me, Et, ^{n}Pr, ^{i}Pr, ^{i}Bu
R = Ph; R' = Me, Et
R = ^{i}Bu; R' = Et
R = C_5H_{11}; R' = Et

when R = $SiMe_3$, both imine isomers (E and Z) are obtained

It is important to address the fact that when the alkyne reactions catalyzed by the uranium complexes were performed using the bulky $^{t}BuNH_2$, as the primary amine, no hydroamination products were obtained. The product achieved in each case was, selectively, the corresponding dimer (*geminal)* of the starting alkyne. This result indicates that probably the active species involved in the intermolecular hydroamination with $^{t}BuNH_2$ was not obtained. Utilizing this bulky amine, the only obtained organouranium complex in solution was either the organoactinide uranium bis (acetylide) complex (**23**) or the corresponding uranium bis(amido) (**25**) complex. These two complexes were found to be in rapid equilibrium with the mono-amido, mono-acetylide complex (**24**), which is known to be the active species responsible for the oligomerization of alkynes in the presence of amines (10).



23 **24** **25**

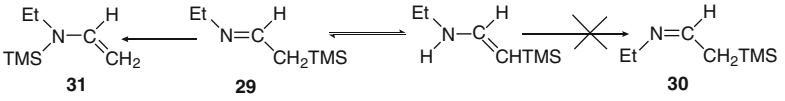
(10)

When comparing some of the hydroamination rates utilizing the various amines for a specific alkyne, it was found that the bulkier the amines, the lower the turnover frequency of the reaction. In addition, when comparing the hydroamination rates for a particular amine ($MeNH_2$) using various alkynes, similar N_t were observed.

The lack of electronic and/or steric effects of the alkyne suggested that the alkyne is not involved in the rate determining step of the reaction.

When the intermolecular hydroamination was catalyzed by the analogous organothorium complex $Cp^*_2ThMe_2$, reactivities similar to $Me_3SiC{\equiv}CH$ and $MeNH_2$ or $EtNH_2$ were obtained when compared with those observed with the corresponding uranium complex (9). However, in the intermolecular hydroamination with $PhC{\equiv}CH$ or $^nBuC{\equiv}CH$ using $MeNH_2$ or $EtNH_2$, a surprising change in the regioselectivity of the reaction was achieved generating the unexpected imines (8). For both organoactinides of the corresponding bridged organoactinide complexes, the use of internal alkynes or secondary amines yielded no hydroamination products. However, utilizing secondary amines, chemo-selective oligomerization of alkynes toward the corresponding dimers, and in some cases trimers, was obtained.

The catalytic hydroamination of $^nBuC{\equiv}CH$ or $TMSiC{\equiv}CH$ with $EtNH_2$ with either the organothorium complex **1** or the bisamido complex **18** gave equal, in every respect, results (yields, stereochemistry of the products, rate, and kinetic curves), implying that both complexes are forming mutually active species. This behavior was also encountered in the corresponding organouranium complexes. It is interesting to note that following the product formation as a function of time reveals that when mixtures of imines **29** and **30** were obtained, the imine **29** was found to undergo a noncatalyzed Brook silyl rearrangement to form the corresponding enamine **31** (11) [100]. The rearrangement followed a first order kinetics in imine **29** to form **31,** leaving the concentration of **30** unaffected.

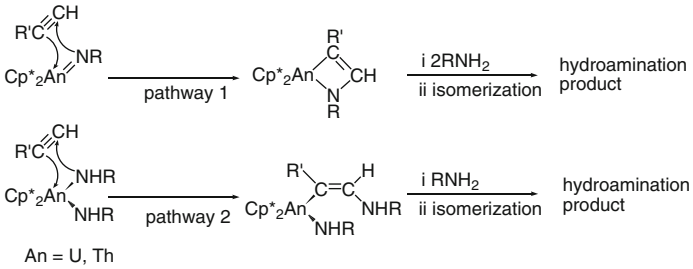


(11)

3.2 *Kinetic and Mechanistic Studies of the Hydroamination*

The formation of alkyne oligomers that are concomitantly formed in the hydroamination reactions catalyzed by the thorium complexes indicates that two possible different complexes can be considered as active, conceivably with inter-conversion causing the occurrence of the two parallel processes. The discernment between these two most probable mechanistic pathways to find the key organometallic intermediate, responsible for the hydroamination process, was achieved by kinetic and thermodynamic studies (Scheme 5). The first pathway proposed the insertion of an alkyne into a metal–imido (M=N) bond, as observed for early transition metal complexes [101]. The second pathway suggested the insertion of an alkyne into a metal–amido bond, as found in some lanthanide compounds [39, 58, 84, 85]

Kinetic measurements on the hydroamination of $Me_3SiC{\equiv}CH$ with $EtNH_2$ were conducted by monitoring the reaction via ^1H NMR. The results showed that the reaction has an inverse first order dependence in amine, first order dependence in

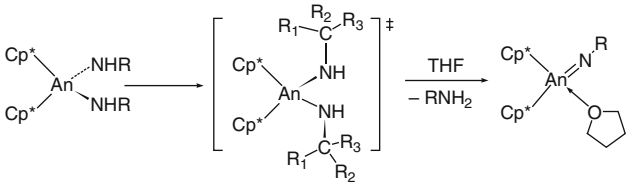


Scheme 5 Pathways proposed for the organoactinide-catalyzed intermolecular hydroamination of terminal alkynes with primary amines. For Thorium the approach of some alkynes was inverted before insertion

precatalyst, and as shown before, a zero order dependence in alkyne concentration, resulting in the rate law for the hydroamination of terminal alkynes promoted by organoactinides as presented in 12. The derived $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ parameter values from a thermal Eyring analysis (in the range 60–120°C, error values are in parenthesis) were 11.7(3) kcal mol^{-1} and −44.5 (8) eu, respectively.

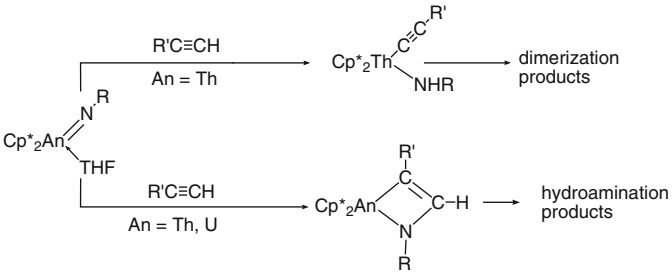
$$v = \mathrm{k[An][amine]}^{-1}\mathrm{[alkyne]}^{0} \tag{12}$$

The lack of alkyne effect on the kinetic hydroamination rate implies that the second pathway (Scheme 5) cannot be considered a major operative route. The zero kinetic order with respect to an alkyne can be predicted for pathway 1 (Scheme 5) and is consistent with the high coordinative unsaturation of the imido complexes, allowing a fast insertion of the different alkynes with indistinct rates. This first pathway can also support the lack of reactivity when performing the reaction with bulky amines as the formation of the corresponding imido complexes is thwarted because of the hindered transition state (13), reaching the highest steric hindrance with ^{t}BuNH$_2$



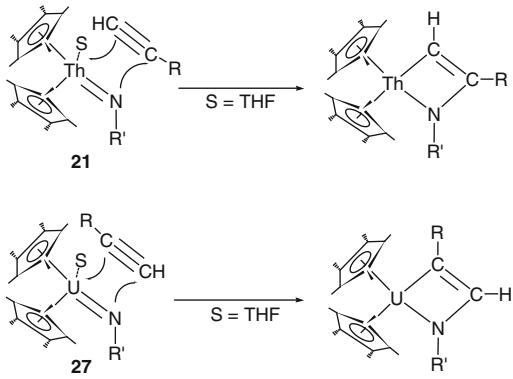
(13)

The different modes of activation for the different organoactinides are indeed very unusual. For both organoactinide–imido complexes, a selective metathesis with the alkyne π-bond is operative (yielding the hydroamination products), whereas for the thorium complex a competing protonolysis reaction also takes



Scheme 6 Representative mode of activation for the organoactinide-imido complexes in the presence of terminal alkynes

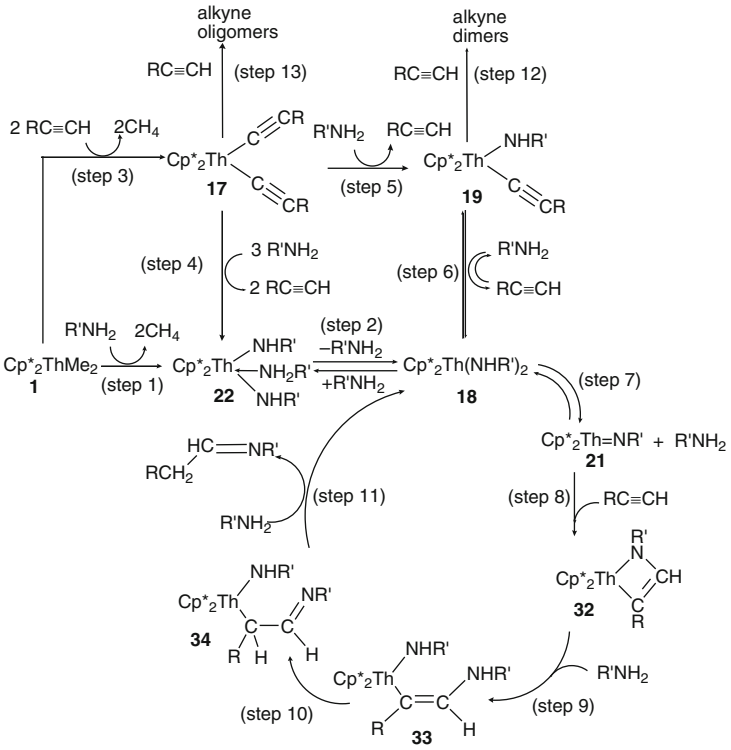
Scheme 7 Contrasting reactivity of the different organoactinide-imido complexes in their metathesis reactions with terminal alkynes



place. This competing reaction is responsible for the selective dimerization of the terminal alkynes (Scheme 6).

The formation of different products on using different organoactinide catalysts in the hydroamination reaction is a result of a contrasting stereochemistry in the metathesis of the alkyne, toward the imido complex (Scheme 7). It is plausible that the regio-chemistry of the intermolecular hydroamination is governed by the organometallic differences in their imido-electronic configurations rather than by the difference in their thermodynamic characteristics (plausibly involving the f^2 electrons of the uranium complex).

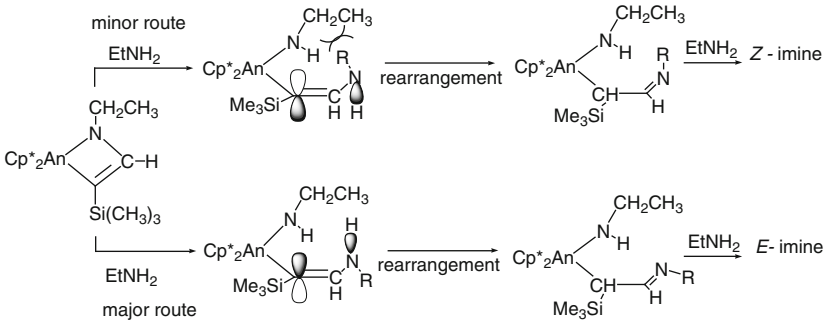
Scheme 8 presents a plausible mechanism for the intermolecular hydroamination of terminal alkynes promoted by the organothorium complex **1**. The first step in the catalytic cycle involves the N–H σ-bond activation of the primary amine by the organothorium complex yielding the bisamido-amine complex $Cp_2^*Th(NHR')_2$ (H_2NR') (**28**) and two equivalents of methane (step 1). Complex **22** was found to be in rapid equilibrium with the corresponding bis(amido) complex **18** (step 2) [57, 60]. An additional starting point involved a similar C–H activation of the terminal alkyne with complex **1** yielding methane and the bis(acetylide) complex **17** (step 3).



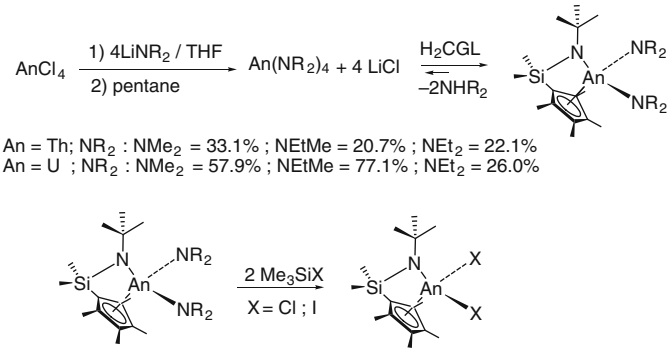
Scheme 8 Plausible mechanism for the intermolecular hydroamination of terminal alkynes and primary amines promoted by $Cp^*_2ThMe_2$

Complex **17** can react rapidly, in the presence of amines in either an excess amount (step 4) or equivalent amounts (step 5), yielding complexes **22** or **19**, respectively. Complex **18** may follow two competitive equilibrium pathways. The σ-bond metathesis with a terminal alkyne yielding complex **19** (step 6), which is responsible for the production of selective dimers when reacted with more alkynes (step 12), or the second pathway (step 7) as the rate-limiting step, eliminates an amine producing the corresponding imido complex **21**. This imido complex **21** follows a rapid σ-bond metathesis with an additional alkyne producing the metallacycle complex **32** (step 8). Rapid ring opening of complex **32** via protonolysis by an amine yielded the actinide–enamine amido complex **33** (step 9), which is isomerized to the actinide-alkyl(imine) amido, **34**, by an intramolecular 1,3 sigmatropic hydrogen shift (step 10). An additional protonolysis of complex **34** by an amine produces the imine product and regenerates the bis(amido)complex **18** (step 11).

To shed some light on the formation of larger amounts of the *E* imine isomer as compared to that of the *Z* isomer, it is indispensable to take into account the steric hindrance of the amine substituents in the isomerization pathway as described in Scheme 9.



Scheme 9 Formation of *E* and *Z* imines via a 1,3 – sigmatropic hydrogen shift. The curves show the steric interaction between the amine substituents



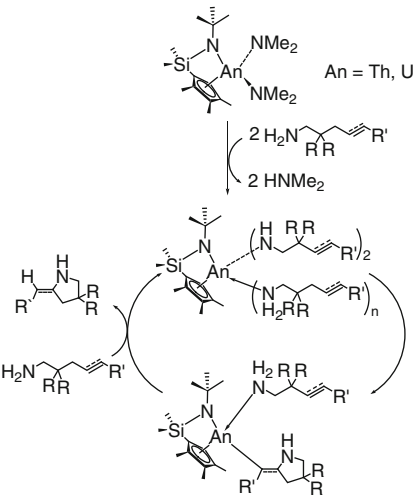
Scheme 10 Synthesis of the constrained geometry organoactinide complexes (H_2CGL = neutral constrained geometry ligand)

The hydroamination reaction using other types of organoactinide complexes was recently disclosed as containing a constrained geometry ligand, which was prepared by reacting the appropriate neutral ligand and the corresponding homoleptic amido–actinide complex (Scheme 10) [102]. High yields were achieved by controlling the dialkylamine concentration and removal of the accompanying by-products [103].

Kinetic studies in the intramolecular hydroamination/cyclization reaction show first order dependence on the precatalyst and zero order dependence on the substrate, making the kinetic rate law as described in 14 [104].

$$v = k_{obs}[\text{precatalyst}]^1[\text{substrate}]^0 \tag{14}$$

This result indicates that the protonolysis of the amido-complex by the substrate is rapid, and the rate determining step includes the insertion of the olefin into the



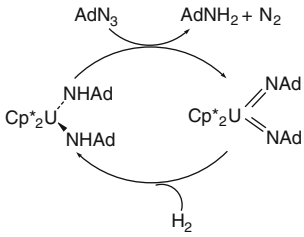
Scheme 11 Proposed mechanism for the organoactinide-catalyzed intramolecular hydroamination/cyclization of terminal and disubstituted aminoalkenes, aminoalkynes, aminoallenes, and aminodienes

An–NHR bond. As for aminoalkenes, it was found that the reaction is faster with organoactinides with larger ionic radii, while the opposite is true for aminoalkynes. However, both constrained complexes (Th and U) were found to react faster with aminoalkenes and aminoalkynes than the corresponding metallocenes. A plausible mechanism is presented in Scheme 11 [104].

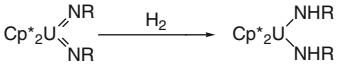
4 Catalytic Reduction of Azides and Hydrazines by High-Valent Organouranium Complexes

Organoactinide metallocene compounds (U(IV) and/or Th(IV)) often display reactivities similar to those observed for similar types of group IV early transition metal and lanthanide metallocenes. The comparable pathways in the catalytic cycles, as presented above, include olefin insertion, σ-bond metathesis, and protonolysis. In contrast to the lanthanides and group IV metals, uranium can also access the +6 oxidation state, giving rise to the possibility of two-electron (+4/+6) redox processes. The reaction of the complexes $Cp^*_2U(=NR)_2$ (R = Ph, **35**, R = Ad = 1-adamantyl, **36**) to an atmosphere of hydrogen, resulted in their reduction to the corresponding bis(amido) complexes $(Cp^*)_2U(NHR)_2$ (**25**) (R = Ph, Ad,) (15). The rate of the hydrogenation of complex **36** was much faster than that of complex **35**. Interestingly, when AdN_3 was added to $(Cp^*)_2U(NHR)_2$ (**25**), the corresponding bis(imido) **36** complex and $AdNH_2$ were formed. Therefore, when complex **25** (R = Ad) was reacted with AdN_3 under a dihydrogen

Scheme 12 Catalytic reduction of azide by a U(VI) complex



atmosphere, catalytic hydrogenation of AdN_3 to $AdNH_2$ was observed (Scheme 12) [105].

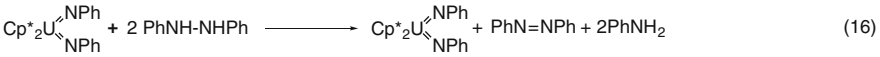


(15)

35 (R = Ph)
36 (R = Ad)

25

N,*N*′-diphenylhydrazine was also utilized as a good oxidant for the conversion of $Cp^*_2UMe_2$ (**2**) to **35**. The reaction begins with protonolysis of the organoactinide methyl groups, liberating methane. However, when the complex $Cp^*_2U(=NPh)_2$ was reacted with an excess of *N*,*N*′-diphenylhydrazine under starving hydrogen conditions, the reaction came to completion, producing aniline and azobenzene in a 2:1 ratio (16). This disproportionation illustrates that the *N*,*N*′-diphenylhydrazine is functioning both as oxidant and reductant. The formation of aniline during this reaction suggested that the U(IV) bis(amide) complex **25** should be present to oxidize the hydrazine, although the only observed uranium species in solution throughout the reaction was $Cp^*_2U(=NPh)_2$, indicating that the oxidation from U (IV) to U(VI) must be much faster than the subsequent reduction.



(16)

From the thermodynamic point of view, the reaction with diphenylhydrazine should be favored by enthalpy and entropy as well. The calculated enthalpy of the reaction to produce two molecules of aniline and one molecule of azobenzene from two *N*,*N*′-diphenylhydrazine molecules is $\Delta H_f = -14.6$ kcal/mol. Entropy considerations also qualitatively favor product formation; two molecules of starting material are converted to three molecules of product.

The reaction of $Cp^*_2U(=NPh)_2$ with *N*,*N*′-diphenylhydrazine was claimed to proceed via the protonation of U(IV) bis(amide) by *N*,*N*′-diphenylhydrazine. Therefore, it was proposed that for the reaction of $Cp^*_2U(=NAd)_2$ (**36**) with *N*,*N*′-diphenylhydrazine, the initial products would include 1-adamantylamine and azobenzene, with the concomitant formation of $Cp^*_2U(=NPh)_2$. When the reaction was performed, $Cp^*_2U(=NAd)_2$, aniline, and azobenzene were the products observed, indicating that the

imido ligands might operate as sites for mediating H-atom transfer. No reaction in the stoichiometric reaction of **35** with 1-adamantanamine was observed. This result rules out the possibility of U-N bond break in which complex **35** is formed and undergoes subsequent rapid reaction with 1-adamantanamine regenerating $Cp^*_2U(=NAd)_2$ (**36**) [105].

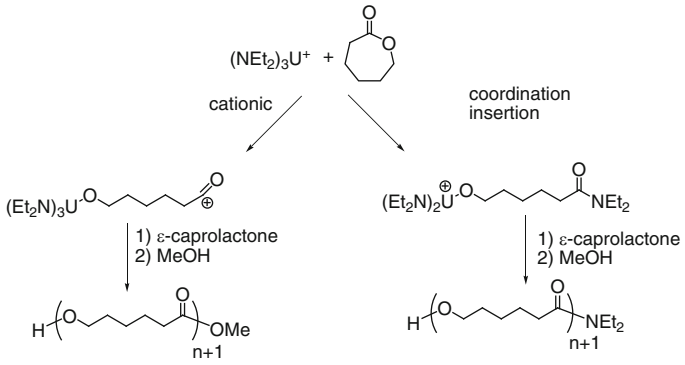
This two-electron oxidation/reduction catalytic process represents a novel type of reactivity for organoactinide complexes. The involvement of U(VI) species strongly argues again for the participation of the f-orbitals in the catalytic process.

5 Polymerization of ε-Caprolactone and L-Lactide by Organoactinide Complexes

Main group metals and lanthanide complexes are well known as excellent catalysts for the ring opening polymerization of cyclic esters to form poly-L-Lactide (PLLA) and polycaprolactone (PCL) polymers. These families of polyesters are generously utilized in everyday life because of their beneficial biodegradable and biocompatible properties. It was expected, however, that actinide complexes will be excluded from any catalysis that included alkoxy reactants, as it was assumed that these substrates will significantly reduce their catalytic activity, because of the high oxophilic nature of the early actinides. For example, Lin et al. showed that the use of alkoxy ligands induces a decreased catalytic activity in the organoactinide-catalyzed hydrogenation of olefins, when compared to the use of alkyl ligands [106].

The first example using an organoactinide in the polymerization of ε-caprolactone was recently reported by Barnea et al. [107] The activities of the three organoactinide complexes ($Cp^*_2ThMe_2$ (**1**), $Cp^*_2UMe_2$ (**2**) and $[(Et_2N)_3U][BPh]_4$ (**6**)) were studied.

Barnea et al. found that the cationic complex **6** exhibits the highest activity in comparison with complexes **1** or **2**. This result was explained by a higher steric hindrance implied by the Cp* ligands in complexes **1** and **2**. The thorium complex **1** was found to be more active than the corresponding uranium complex **2** probably because of the higher oxophilic nature of the uranium forming some inactive metal-oxygen aggregates. Increasing the catalyst/monomer ratio induced an increase in the Mn (Number Molecular Weight) of the obtained polyesters. Very high ratios (1:2400) caused a reduced catalytic reactivity very likely because of the obtained high viscosity of the polymerizing solution. In all cases the molecular weight distribution (MWD) was found to be very narrow, suggesting a living polymerization. Spectroscopic ^{1}H-NMR and GC/MS studies revealed that upon quenching of the reaction with methanol using the cationic complex **6,** the chain end of the polymer contains a methoxy group, suggesting a cationic mechanism (Scheme 13). However, as evident from the high Mn and low MWD, it is suggested that the cationic chain end must stay close to the metal center as no termination is observed.



Scheme 13 Different activations of the cationic catalyst **6** in the polymerization of ε-caprolactone

The polymerization of *L*-lactide (*L*-LA) was also investigated with the three organoactinide complexes **1**, **2,** and **6**. The cationic complex **6** showed the highest activity at 70°C in THF. The cationic complex also formed polymers with narrow polydispersities (1.06–1.21), which substantiates the hypothesis that the polymerization proceeds in a living fashion at least in the early stages of the reaction [107]. At higher conversions (more than 60%), the reaction gradually slows down because of the viscosity and stickiness of the solution. In contrast to complexes **1** and **2** that produce only CH_4 at room temperature, complex **3** was found to be active for the polymerization of *L*-LA at room temperature, yielding living polymers with high *M*n and low MWD. The initial catalyst to monomer ratio and the GPC results for complexes **1**, **2,** and **6** suggested that the polymerization proceeds with only one main active site.

Recently, it was shown that the polymerization of ε-caprolactone can be also performed using a homoleptic amidinate uranium (III) complex (17 and 18); however, the activity of the complex was found to be more sluggish as compared to that of other actinide complexes or similar homoleptic lanthanide complexes [108].

$$UCl_4 + 1.5\,[Li\{RC(NCy)_2\}(THF)]_2 \xrightarrow[R = Me,\ nBu]{THF} U\{RC(NCy)_2\}_3Cl + 3\,LiCl \quad (17)$$

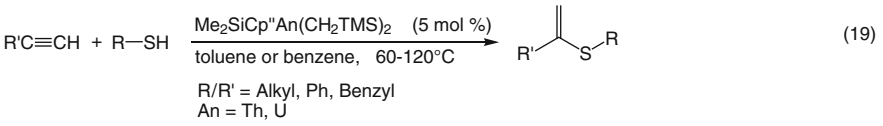
$$U\{RC(NCy)_2\}_3Cl + Li \xrightarrow[R = Me,\ nBu]{THF} U\{RC(NCy)_2\}_3 + LiCl \quad (18)$$

Interestingly, the polymerization of caprolactone or lactide using the bridge organoactinide complexes (**3–5)** was found to be much faster ($\times 10^4$) than that using the complex **1** or **2**, proceeding in a living fashion producing very high molecular weight polymers.

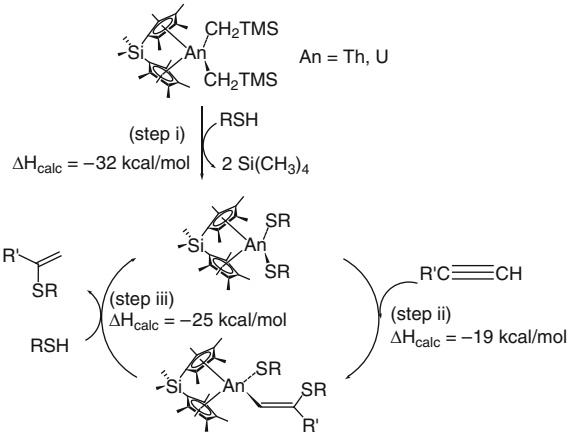
6 Catalytic Hydrothiolation of Terminal Alkynes Promoted by Organoactinide Complexes

As shown above, metal-complex-catalyzed hydro-elementation is a versatile and atom-efficient method for catalytically installing heteroelements in small molecules and macromolecules. While significant advances have been achieved using amines, less is known about the use of thiols because of the high affinity of sulfur for many metal catalysts. Sulfur is a constituent of many important polymeric materials, natural products, and synthetic reagents. Radical and nucleophilic thiol addition across alkynes in an antiMarkovnikov fashion is well-known [109]; however, Markovnikov addition presents a significant challenge. The calculated bond enthalpy for the hydrothiolation predicts an exothermic reaction for the RSH addition to alkynes, allenes, and alkenes mediated by organoactinide complexes. The insertion of an alkyne into an An−S bond is predicted to be exothermic (step ii, Scheme 14); however, with alkenes, the insertion is calculated to be endothermic. The final protonolysis (step iii, Scheme 14) is expected to be highly exothermic for all substrates, reflecting the C−H and An−S bond enthalpies.

The reaction of the $Me_2SiCp''_2Th(CH_2TMS)_2$ ($Cp'' = Me_4C_5$) with 1-pentanethiol and 1-hexyne proceeds to completion in ~3.5 h at 90°C in the presence of an excess of alkyne. The conversion is quantitative in thiol for a range of alkyl, aryl, and benzyl thiols and for alkyl, aryl, and vinyl alkynes (19), and similar transformations are observed for the corresponding uranium complex [110].



(19)



Scheme 14 Proposed catalytic cycle for the hydrothiolation of terminal alkynes promoted by an organoactinide complex

Kinetic analysis of the reaction between 60 and 110°C yields $\Delta H^{\ddagger} = +9.1(0.7)$ kcal/mol and $\Delta S^{\ddagger} = -45(2)$ eu, suggesting a highly ordered transition state and an intermolecular, turnover-limiting step. The hydrothiolation processes exhibits a high Markovnikov selectivity. This is presumably reflecting a four-membered transition state with the alkyne insertion regio-chemistry dictated by the transition state steric hindrance and the bond polarity orientation.

It is interesting to point out that the thiol nature has a major influence on the hydrothiolation rates. Hence, changing the aliphatic thiol from primary to secondary resulted in significant rate depression, consistent with a steric impediment at the turnover-limiting alkyne insertion (step ii, Scheme 14). The use of benzyl mercaptan allows an increase of the rate by nearly three times. The effect on the alkyne was found to be minor and by increasing the alkyne steric encumbrance minor changes in rates were observed.

Kinetic studies indicate that the reaction follows the kinetic rate law described in 20. The reaction follows first order kinetics in alkyne at low concentrations and zero order at high concentration, and zero-order in thiol concentration. In addition, the turnover-limiting step is the insertion of an alkyne into the An−S bond.

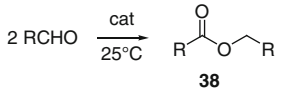
$$v = \mathrm{k[catalyst]}^{1}\mathrm{[alkyne]}^{x}\mathrm{[thiol]}^{0} \tag{20}$$

7 Catalytic Tishchenko Reaction Catalyzed by Organoactinides

We have shown in this review that neutral and cationic organoactinide complexes have been extensively studied, in the last decade, as catalysts for several organic transformations [9–12, 111]. Polymerization of alkenes[112, 113], oligomerization of terminal alkynes [55, 114], hydrosilylation of terminal alkynes [41], and 1,1-insertion of isonitriles into terminal alkynes [28] comprise some other studied processes not presented here. However, due to the high oxophilicity of the actinide complexes (as mentioned above), substrates containing oxygen have been excluded because of the expected and predictable oxygen−actinide interaction.

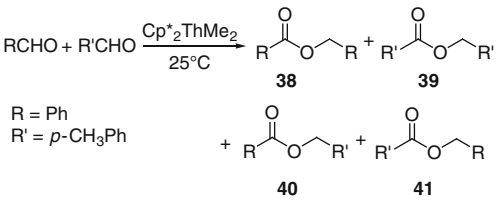
In attempts to discover new challenging catalytic reactions for actinide based complexes, Barnea et al. reported their surprising activity towards the polymerization of cyclic mono- and diesters [107]. This discovery arouses the conceptual question about the activity of actinide–alkoxo complexes. Hence, to expand the scope of the actinides in catalysis, the Tishchenko reaction (dimerization of aldehydes to give the corresponding esters) was studied. The catalytic Tishchenko reaction was investigated between similar (21) or different (22) aldehydes to give the symmetric or asymmetric esters, respectively. In order to show the generality of the process and to be able to propose a suitable mechanistic pathway, two

organoactinide complexes $Cp^*_2ThMe_2$ (**1**) ($Cp^* = C_5Me_5$) and $Th(NEtMe)_4$ (**37**) [102] were studied in addition to kinetic and thermodynamic studies using complex **1**.



38 (21)

cat = $Cp^*_2ThMe_2$ (**1**); $Th(NEtMe)_4$ (**37**)
R = Ph; *p*-ClPh; *m*-ClPh; *o*-ClPh; *p*-CH_3Ph; *m*-CH_3Ph; *o*-CH_3Ph;



38 **39** (22)

40 **41**

The two organoactinide complexes were found to be active (yields 65−85%) in the catalytic dimerization of benzaldehyde, and gave the corresponding ester with no other side products. Interestingly, the activity of the complexes was found to be dependent on the proximity of the substituents at the phenyl group to the metal center. For the different tolualdehydes, the *ortho* compound has a lower activity as compared to *p*-tolualdehyde (see entries 6–8, 11–13; in Table 1). A different behavior was observed with the chloride substitution, in which the same yields were obtained for the *para* and *ortho* substituted compounds but lower yields were obtained for the corresponding *meta* substitution (entry 2–4 in Table 1).

Table 1 Product distribution for the dimerization of aldehydes by thorium complexes **1** and **37**

Entry	Cat	R	Cat:RCHO	38%			
1	**1**	Ph	1:100	65			
2	**1**	*p*-ClPh[b]	1:100	60			
3	**1**	*m*-ClPh[b]	1:100	57			
4	**1**	*o*-ClPh[b]	1:100	50			
6	**1**	*p*-CH_3Ph	1:100	25			
7	**1**	*m*-CH_3Ph	1:100	20			
8	**1**	*o*-CH_3Ph	1:100	10			
9	**37**	Ph	1:100	85			
10	**37**	*p*-ClPh[b]	1:100	85			
11	**37**	*p*-CH_3Ph	1:100	82			
12	**37**	*m*-CH_3Ph	1:100	75			
13	**37**	*o*-CH_3Ph	1:100	55			
Entry	Cat	R, R′	Cat:RCHO: R′CHO	**38**[c]%	**39**[c]%	**40**[c]%	**41**[c]%
14	**1**	Ph, *p*-CH_3Ph	1:100:100	15	4	6	6
15	**1**	Ph, *p*-CH_3Ph	1:100:50	25	2	5	5
16	**1**	Ph, *p*-CH_3Ph	1:50:100	9	6	6	6

When mixed experiments were performed by reacting a mixture of benzaldehyde and *p*-tolualdehyde, four possible esters were obtained. As expected, the ester *p*-tolyl 4-methylbenzoate **39**, which is produced only from *p*-tolualdehyde (less reactive) was obtained in lower extents and the symmetrical ester **38** was always obtained as the major product (entry 15 in Table 1). The ratio between the four different products was partially controlled by manipulating the ratio between the reactants.

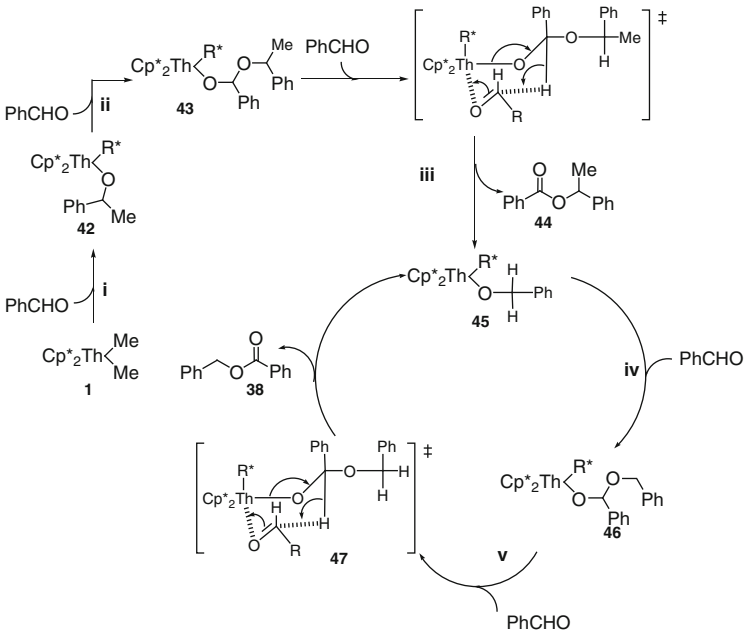
In order to get an insight on the plausible mechanism for the reaction and learn about the influence of aldehyde, catalyst, and temperature on the reaction rate, kinetic and thermodynamic measurements were performed. Kinetic studies of the $Cp_2^*ThMe_2$-catalyzed Tishchenko reaction of benzaldehyde indicates that the reaction follows a first order dependence on both catalyst and aldehyde (23) [115].

$$v = k[\text{catalyst}]^1[\text{aldehyde}]^1 \tag{23}$$

Thermodynamic studies show that the energy of activation (Ea), enthalpy of activation ($\Delta H^{\ddagger}$), and entropy of activation ($\Delta S^{\ddagger}$) for the rate determining step are 7.16 $\pm$ 0.40 kcal/mol, 6.5 $\pm$ 0.4 kcal/mol, and -48.8 ± 0.4 eu, respectively. The high negative entropy value indicates an ordered transition state at the rate determining step. A primary isotopic effect was also observed when using α-deuterated benzaldehyde with kH/kD = 2.7, which suggests that a hydride transfer is involved at the rate determining step. Stoichiometric reactions between the actinide complexes with benzaldehyde yield the 2-phenetylbenzoate (step 1–3 in Scheme 4), corroborating the fact that an aldehyde is able to insert into complex **1** producing the active alkoxo species.

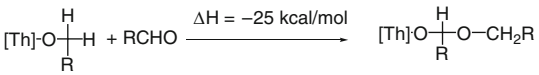
On the basis of the kinetic and thermodynamic data, a plausible mechanism for the Tishchenko reaction is presented in Scheme 15. In the first step of the reaction, the precatalyst **1** reacts with two equivalents of the aldehyde to give exothermically the alkoxo complex **42** (Step i in Scheme 15; $\Delta H_{calc} = -68$ kcal/mol). A second insertion of an aldehyde into the thorium–alkoxide bond yields complex **43** (step ii in Scheme 15). The concomitant hydride transfer from complex **43** to an additional aldehyde releases the ester **44** and produces the active catalytic species **45** (step iii in Scheme 15). The insertion of an aldehyde into complex **45** (step iv, $\Delta H_{calc} = -25$ kcal/mol) gives complex **46,** and its hydride transfer reaction (step v, rate determining step, ΔHcalc $= -22$ kcal/mol) with an additional aldehyde via a plausible six-centered chair-like transition state (**47**) produces the ester **38** and regenerates the active complex **45**.

It is possible to expect a *β*-hydrogen elimination in steps iii and v of the mechanism presented in Scheme 15 producing the same results; however, the kinetic data do not corroborate with a *β*-hydrogen elimination mechanism. From a thermodynamic point of view, the calculated enthalpy of the reaction for a *β*-hydrogen elimination was found to be much higher than that of the hydride transfer following a six-centered transition state mechanism (+6 and -47 kcal/mol

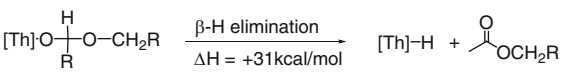


Scheme 15 Plausible mechanism for the catalytic Tishchenko reaction mediated by $Cp^*_2ThMe_2$. R* is used instead of $PhCH(CH_3)O^-$ or $PhCH_2O^-$ for clarity

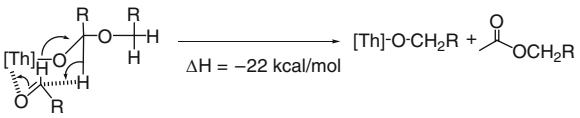
respectively, (24–26)), suggesting that the β-hydrogen elimination is not the main termination pathway.



(24)



(25)



(26)

The effect of the substitution on the phenyl ring can be illustrated by considering two parallel effects: (1) the steric "obstacle" created by both the chloride and the methyl groups, which hinder the approaching of an aldehyde to the metal–alkoxide bond when disposed in the *ortho* position and (2) the electrostatic interaction between the metal and the chloride, which may facilitate the approach of the aldehyde to the metal center, and hence the activity (Fig. 1).

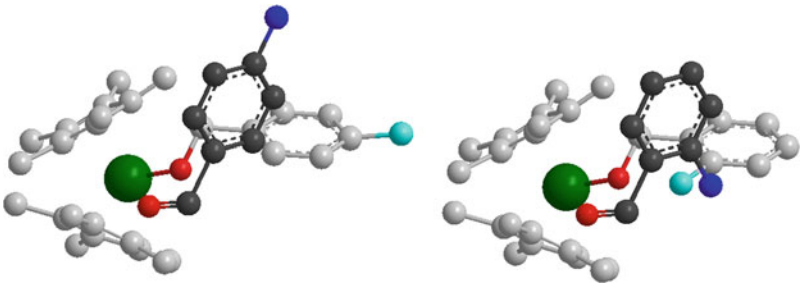


Fig. 1 Illustration exhibiting the steric hindrance between the two methyl groups, on the *ortho* positions, (*blue* and *light blue* atoms, *right* molecule) as compared to that between two on the *para* positions (*left*)

This first example of the catalytic coupling of aldehydes mediated by actinide complexes proceeding via an actinide-alkoxo bond activation, which was believed to be a dead-end, opens new routes for the use of organoactinides in new catalytic processes.

8 Conclusions and Future Outlook

As presented through this review, the properties of the actinides and especially the catalytic chemistry of the organometallic actinides complexes are new, challenging, and sophisticated. The ability to tailor a catalytic reaction with these complexes by a rational design of their electronic and steric features is an outcome of the basic reactivities of these complexes that may stimulate new processes or achieve different stereoselectivities as compared to similar reactions with other transition-metal complexes. The use of polar substrates in catalytic reactions using organoactinides is still a basic challenge that upon succeed will offer many potential returns. The use of organoactinide complexes in industrial processes is still far, and their incorporation will depend on public safety and economical advantage (radioactive compounds are to date part of medical practices and industrial processes). We can expect and hopefully believe that the findings presented here will inspire this new progressive field.

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