Review

CHEMICAL REVIEWS
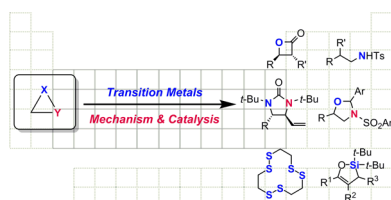
The Chemistry of Transition Metals with Three-Membered Ring Heterocycles

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CONTENTS

1. INTRODUCTION

The chemistry of three-membered ring heterocycles has played a dominant role in the history of organic synthesis.[1] Countless classic and modern protocols exist for their preparation from simple starting materials. At the same time, the intrinsic ring strain of these compounds primes them for facile ring-opening. As a result, much attention continues to be given to the discovery of reactions that harness the reactivity of three-membered ring heterocycles as entry points to the synthesis of complex heteroatom-containing products.

Transition metal chemistry is another field that has seen a long history of development. A detailed understanding of the properties of organometallic complexes and the mechanisms of their reactions has facilitated the design of practical methodologies that are widely utilized in synthetic chemistry.

Combining organometallic chemistry with reactions of three-membered ring heterocycles therefore represents a logical and potentially fruitful direction for reaction discovery. Indeed, transition metals have the potential to render known ring-opening reactions viable under mild conditions, impart complementary selectivity to the chemistry of three-membered ring heterocycles, and enable unprecedented bond constructions. In this work, we review the chemistry of transition metals with O, N, S, Si, P, and Ge-containing three-membered ring heterocycles. Much of this field is still centered on stoichiometric reactions. However, these studies, and the fundamental knowledge gained from them, have recently given way to the development of the broad range of catalytic methods that will be discussed herein. In many cases, these methods represent conceptually novel and immensely practical approaches to organic synthesis. There are many additional examples in which transition metals simply serve as Lewis acids, or as heterogeneous and polymerization catalysts, which will not be covered in this discussion.[2] Furthermore, due to the distinct reactivity of vinyl epoxides and aziridines,[3] their

chemistry will not be reviewed. Similarly, we refer the reader to leading reviews on the chemistry of dioxiranes.[4]

2. EPOXIDES

2.1. Carbonylations

Given the availability of both epoxides and carbon monoxide, carbonylation of epoxides has become a powerful strategy to prepare β-hydroxycarbonyl compounds, which are themselves versatile intermediates in chemical synthesis.[5] There are three different types of transformations available to epoxides and CO: (1) ring-expansive carbonylations that afford β-lactones, (2) alkoxycarbonylations or aminocarbonylations that yield β-hydroxyesters or β-hydroxyamides, and (3) hydroformylations that give β-hydroxyaldehydes (Scheme 1). Recent synthetic advances and mechanistic insight have centered upon ring-expansive carbonylations.

### Scheme 1. General Mechanism of Transition Metal-Catalyzed Epoxide Carbonylations
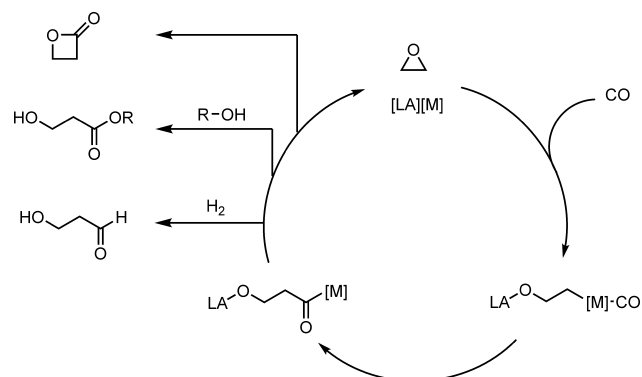
A series of early reports from the 1960s first demonstrated the potential of transition metals to facilitate CO insertion into epoxides. Eisenmann,[6] Heck,[7] McClure,[8] and Watanabe[9] independently reported carbomethoxylation[10] of aliphatic epoxides to afford methyl β-hydroxycarboxylate products. Additionally, Watanabe,[11] Orchin,[12] and Rosenthal[13] showed that β-hydroxyaldehydes can be obtained through hydroformylation processes.[14] Subsequently, the Alper group found that the efficiency of these processes can be enhanced by phase-transfer catalysts.[15] The most broadly utilized catalyst among these examples is $Co_2(CO)_8$. Although these reports were not accompanied by in depth mechanistic studies, it was suggested that an anionic species such as $Co(CO)_4^-$ is generated in the reaction and serves as the nucleophile[16] for epoxide ring-opening. It was further proposed that ring-opening is facilitiated by Lewis acid activation of the epoxide.

Unfortunately, most of the early synthetic protocols suffered from harsh conditions, limited substrate scope, and low chemoselectivity. Polymer or ketone byproducts were commonly observed. Because the reaction is proposed to proceed by nucleophilic attack of the metal catalyst on a Lewis-acid activated epoxide, endeavors to improve the efficiency of these reactions under milder conditions have been focused on identifying a more suitable Lewis acid. Following a patent by Drent and Kragtwijk,[17] a series of catalysts of the form $[LA^+][Co(CO)_4^-]$ were examined. Alper and co-workers first reported the use of PPNCo(CO)$_4$ (PPN = bis-(triphenylphosphine)iminium) in combination with BF$_3$·Et$_2$O or B(C$_6$F$_5$)$_3$.[18] This catalyst combination affords β-lactones in

good yields (Scheme 2). Subsequently, the Coates group reported three structurally distinct cobalt complexes that display superior reactivity and enable broader substrate scope (Scheme 2).[19]

Scheme 2. Catalysts for Epoxide Carbonylation
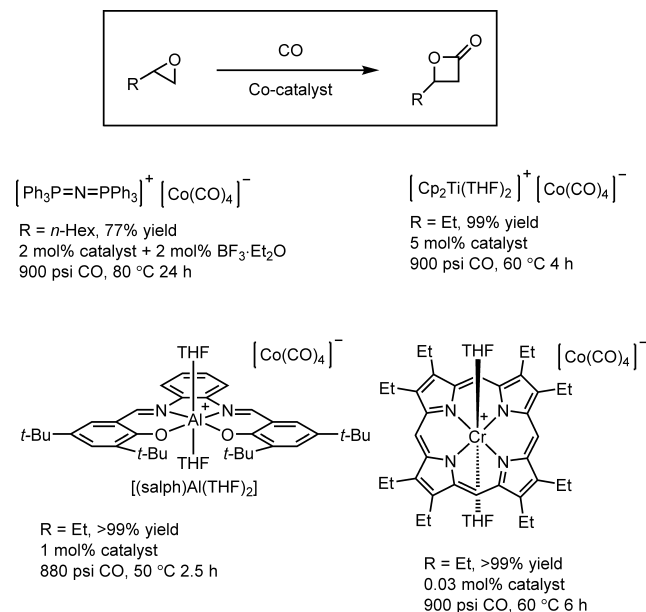
When simple alkyl epoxides are used as the substrates, the formation of β-lactone products corresponding to CO insertion at the less substituted C–O bond is favored. This regiochemical outcome is consistent with $[Co(CO)_4^-]$ performing a nucleophilic attack through an S_N2 mechanism. Further support for this mechanistic proposal with the Co system can be found in Coates's studies with 1,2-disubstituted epoxides (Scheme 3).[19e] For example, cis-substituted epoxides such as 1 provide

Scheme 3. Co-Catalyzed Ring-Expansive Carbonylation of 1,2-Disubstituted Epoxides
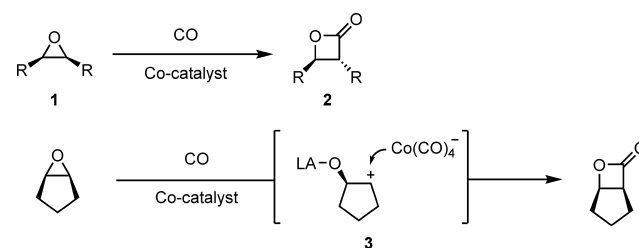
trans-β-lactones 2 through inversion of the stereocenter undergoing carbonylation. One exception to this observation is that cyclopentene oxide gives rise to a cis-lactone product. The Coates group accounts for this observation by invoking a change in mechanism due to the inaccessibility of the trans-lactone product. Instead, ring-opening is suggested to proceed via a carbocation intermediate 3.

In addition, when enantiopure epoxides are utilized, enantiopure β-lactones can be isolated.[20] This property of the reaction is particularly interesting because enantiopure epoxides can be easily prepared through various methods. For instance, the Jacobsen group took advantage of this reactivity in preparing enantiopure β-hydroxyesters and β-hydroxyamides

via carboalkoxylation and carboamidation of enantioenriched terminal epoxides (Scheme 4).[20a,b]

Scheme 4. Co-Catalyzed Carbonylation of Enantiopure Epoxides
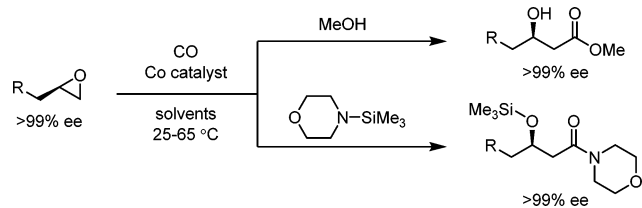
Detailed mechanistic investigations have been conducted in the context of the Co-catalyzed ring-expansive carbonylation reaction. It was established through in situ IR kinetics experiments and computational studies that lactone ring closure is rate determining (Scheme 5).[21] In the original publication by
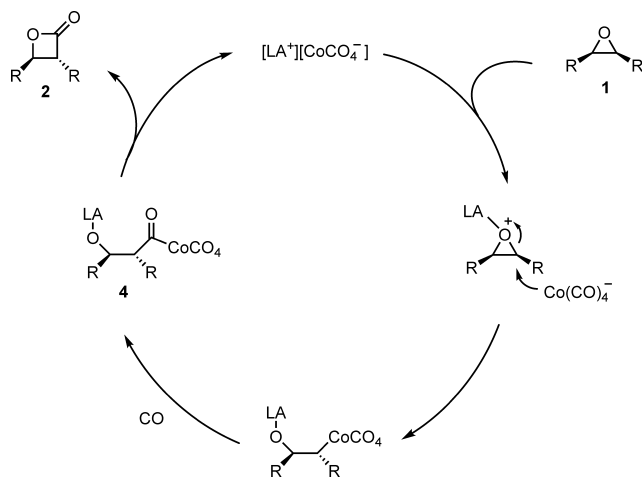
Scheme 5. Mechanism of Ring-Expansive Epoxide Carbonylations

Heck,[7] a β-hydroxycobaltcarbonyl compound was obtained by mixing ethylene oxide, cobalt hexacarbonyl, and CO at 0 °C, and this species was analyzed spectroscopically upon complexation with PPh₃. Intermediate trapping experiments with isocyanates conducted by the Coates group were also informative in suggesting **4** as the resting state in the catalytic cycle.[19d] These studies demonstrate the importance of utilizing an adequate Lewis acid that is strong enough to activate the epoxides but labile in nature to allow for lactone ring closure.

Catalyst development and mechanistic understanding have significantly expanded the substrate scope of the Co-catalyzed ring-expansive carbonylation reaction. In Coates's systems,[19] alkyl epoxides with various substitution patterns, as well as those containing Lewis basic functional groups, are successfully converted into β-lactones, and in certain examples,[22] under only 1 atm of CO. The synthetic power of this methodology is manifested by its wide application in natural product[23] and polymer synthesis.[5c] On the other hand, to date styrenyl-type epoxides remain a limitation of the Co system. Despite the report by Ohta and co-workers in 1980 showing that RhCl(CO)(PPh₃)₂ is an active catalyst for the carbonylation of styrenyl epoxides,[24] this system has not yet seen much development in the literature. Instead, for vinyl- and aryl-

substituted epoxides, Pd, Rh, or Fe catalysts promote selective insertion of CO at the position adjacent to the π-system due to the formation of π-allyl or π-benzyl species.[5a]

2.2. Carboxylations

The cycloaddition of epoxides and CO_2 provides five-membered cyclic carbonates as products (Scheme 6).[25] This

**Scheme 6. Transition Metal-Catalyzed Ring-Expansive Carboxylation of Epoxides**
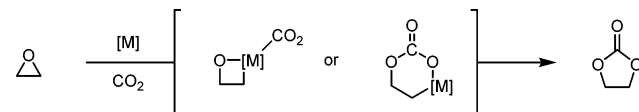
process has gained significant recent attention due to the surging interest in carbon dioxide sequestration and utilization. Many different types of catalysts are known to facilitate this transformation, including transition metals. In this Review, we will only discuss examples in which the transition metal catalyst is suggested to react by a redox mechanism rather than as a Lewis acid.

A paper in 1973 by Pasquale and co-workers represents the earliest contribution to this area.[26] In this work, various Ni catalysts were shown to promote the conversion of simple alkyl epoxides to cyclic carbonates under 500 psi CO_2 at 100 °C. Among the Ni catalysts examined, the more electron-rich Ni(PCy₃)₂ was found to induce higher rate and efficiency than Ni(PPh₃)₂ and Ni(cod)₂. The authors account for this observation by proposing that the Ni catalyst engages the epoxide via nucleophilic attack. The fact that less hindered epoxides react faster than more hindered ones is also in line with this proposal. A few years later, Saegusa and co-workers discovered that a Cu(I) cyanoacetate complex can act as a CO_2 carrier and can be used to carboxylate propylene oxide in a stoichiometric manner.[27] The group suggested that the electron-withdrawing nature of the cyanoacetate ligand was critical in decarboxylation of the (NCCH₂CO₂)Cu complex and that the resulting intermediate, (NCCH₂)Cu, may play an important role in the process. More recently, Wu and co-workers carried out a DFT study of this system and suggested a stepwise mechanism in which CO_2 binding to (NCCH₂)Cu precedes the epoxide ring-opening.[28]

In 1980, Backvall and co-workers conducted an investigation on the stereochemical outcome of these two carboxylation reactions using trans-1,2-dideuterioethene oxide **5** as the substrate (Scheme 7).[29] With Ni(PCy₃)₂ as the catalyst, a 1:1 mixture of trans and cis cyclic carbonates **6** was obtained, whereas the (NCCH₂CO₂)Cu complex provided only the trans isomer **6**. The authors thus proposed a radical-based oxidative addition for the Ni(0) system, which would lead to

Scheme 7. Studies on trans-1,2-Dideuterioethene Oxide
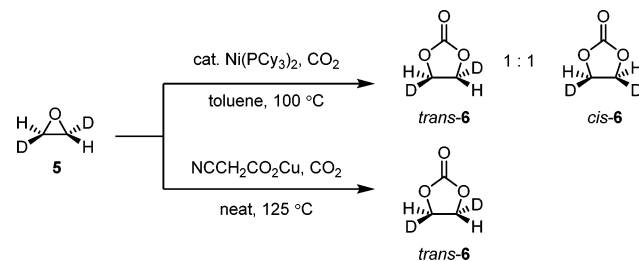
epimerization. The Cu(I) complex may instead undergo insertion and CO_2 incorporation by either a double retentive or a double invertive mechanism. Furthermore, utilizing nickel catalysis under electrochemical conditions or in the presence of chemical reductants, carboxylations of epoxides have also been accomplished by the Dünach and the Xia groups.[30]

In addition, a system based on a $Re(CO)_5Br$ catalyst and supercritical CO_2 has been reported by the Hua group (Scheme 8).[31] A range of terminal epoxides undergo carboxylation in

Scheme 8. Carboxylations of Epoxides with Rhenium Catalysts
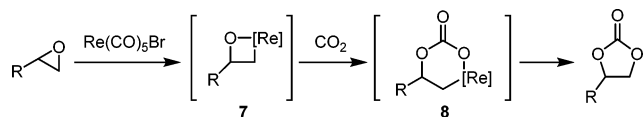
good yields, while disubstituted epoxides are not suitable substrates. Computational work performed by the Wu group supports a mechanism proceeding through an oxametallacyclo-butane intermediate **7**.[32]

Puddephatt and co-workers provided experimental support for the intermediacy of a cyclic metallacarbonate (Figure 1).[33]
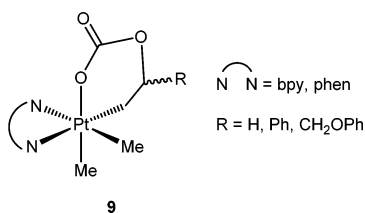

Figure 1. Cyclic platinacarbonate.

Oxidative addition of bis-methyl-diimineplatinum to the unsubstituted side of various epoxides and subsequent CO_2 incorporation provides the six-membered platincarbonate species **9**. When a substituted terminal epoxide (R ≠ H) was utilized, a mixture of diastereomeric metal complex was obtained. The kinetics of this reaction are dependent on the concentration of the Pt complex and the epoxide but not on the CO_2 pressure. A stepwise mechanism is most consistent with these data wherein a rate-determining insertion to the epoxide precedes fast CO_2 incorporation.

In 1986, Behr and Kanne published a related Pd-catalyzed three-component coupling between butadiene, CO_2, and epoxides that affords product structures such as **13** (Scheme 9).[34] Although these products could arise via a direct epoxide carboxylation pathway, no cyclic carbonate was observed in this system at intermediate conversion; instead, side products originating from the oligomerization of butadiene and CO_2 were observed. As such, the authors proposed the mechanism depicted in Scheme 9 wherein CO_2 reacts with butadiene to generate **10** prior to reaction with the epoxide.

Synthetically, epoxide carboxylation offers an entry to 1,2-diol derivatives. However, possibly due to the numerous alternative methods for epoxide ring-opening, including nonmetal catalysis and Lewis acid-induced transformations, the transition metal insertion pathway has not been fully exploited as a synthetic tool.

Scheme 9. Mechanism of Pd-Catalyzed Three-Component Coupling
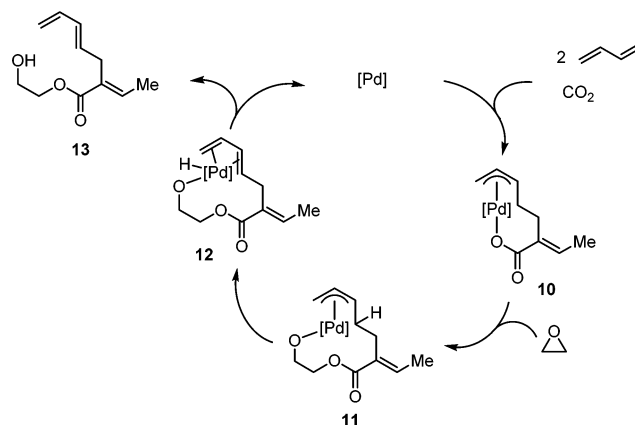

2.3. Deoxygenations

Formally, deoxygenation of epoxides generates alkenes as products and is the reverse reaction of alkene epoxidation. This transformation is occasionally responsible for the olefin side products observed in various transition metal-catalyzed reactions. The topic has been discussed extensively in a recent review by Dauth and Love.[35]

2.4. Isomerizations

The isomerization of epoxides to aldehydes or ketones is mediated by a wide variety of reagents. In transition metal catalysis, this transformation intercepts the elementary steps of a number of other synthetically desirable reactions, and is therefore sometimes regarded as an unwanted side pathway. However, recent methodological developments suggest that this reaction can potentially be a useful alternative to the synthesis of carbonyl compounds from readily available epoxide substrates.

A few general considerations are important to note: when an unsymmetrically substituted epoxide is utilized, two regioisomeric carbonyl compounds can be produced. Some possible side products include alkenes through deoxygenation and allylic alcohols through epoxide rearrangement (Scheme 10). The distribution of products can often be altered by the catalyst and reaction conditions.

Scheme 10. Transition Metal-Catalyzed Epoxide Isomerizations
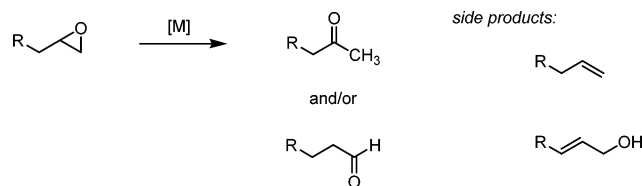
The first report of such a process was communicated by Eisenmann in 1962.[36] Eisenmann showed that a methanol solution of $Co_2(CO)_8$ efficiently converted epoxide substrates such as propylene oxide, butylene oxide, and cyclohexene oxide into ketones. This paper is relevant to the later report on Co-catalyzed carbomethoxylation of epoxides by the same author (section 2.1). Related Co systems were subsequently reported by the research groups of Kwan,[37] Kagan,[38] Cabrera,[39] and

Kauffmann.[40] Other examples based on Ni and Mo have also been presented by Fukuoka,[41] Miyashita,[42] and Alper.[43]

In the 1970s, the Blum group conducted a series of detailed studies on the isomerization of aryl-substituted epoxides under Rh(I) catalysis.[44] Specifically, the authors showed that stilbene oxide isomerizes to 2-phenylacetophenone with RhCl(PPh₃)₃ as catalyst. When the two aryl groups in the stilbene oxide have different electronic properties, the ketone forms preferentially at the position adjacent to the electron-poor aryl group (Scheme 11). The authors also reported that any electron-rich

Scheme 11. Rh-Catalyzed Epoxide Isomerizations
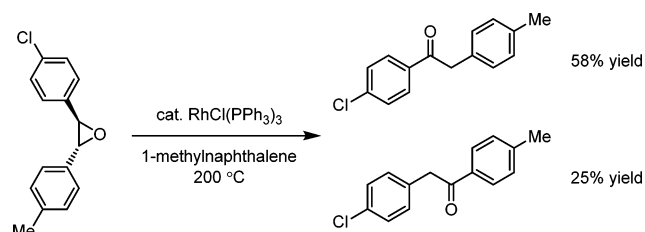
substituent on the aryl ring of the epoxide leads to rate acceleration. Furthermore, isomerization with *trans-α,α′-*dideuteriostilbene oxide revealed a normal kinetic isotope effect.

Three different mechanisms were discussed by the authors to account for these observations. First, Rh may serve as a Lewis acid and promote epoxide rearrangement via a carbocation intermediate. However, an examination of a series of RhCl-(PAr₃)₃ catalysts revealed that less Lewis acidic catalysts bearing electron-rich phosphine ligands promoted faster reactions. A second mechanism was considered in which the Rh catalyst acts as a nucleophile for epoxide ring-opening. However, the regioselectivity and substrate structure/rate dependencies of the reaction are not consistent with this proposal. Thus, the authors proposed the C−H insertion mechanism shown in Scheme 12. Loss of PPh₃ from Wilkinson's catalyst would generate the active catalyst **14**. This 16 e⁻ complex then undergoes oxidative addition into the α C−H bond of the stilbene oxide substrate to form intermediate **15**. Hydride transfer via transition structure **16** would afford the alkoxy complex **17**. On the basis of the obtained kinetic isotope effect

Scheme 12. Mechanism of RhCl(PPh₃)₃-Catalyzed Epoxide Isomerization
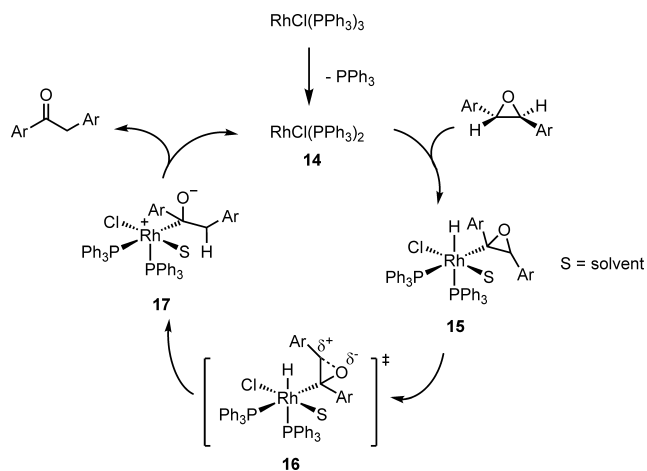
data, the authors suggest that this step is rate determining. Finally, formation of the ketone product by elimination would regenerate the Rh(I) catalyst. Buildup of a partial positive charge on the carbon of the transition structure **16** explains the observed regioselectivity and substituent effect trends. As support for this C−H insertion mechanism, a publication by the Bergman group in 1989 documented the generation of a complex related to the proposed intermediates **15**.[45]

An interesting example by the Berchtold group showed that in the presence of a catalytic amount of [Rh(CO)₂Cl]₂, arene oxides yield a mixture of a phenol derivative and the parent arene (Scheme 13).[46] The formation of the phenol derivative

Scheme 13. Rh-Catalyzed Isomerizations of Arene Oxides
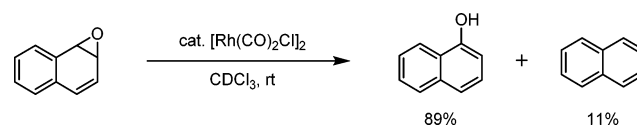
was proposed to occur by a 1,2-hydride shift of an alkoxyrhodium species and subsequent tautomerization, whereas a rhodaoxetane intermediate may be responsible for arene formation through deoxygenation.

In 1980, Noyori and co-workers reported the isomerization of α,β-epoxy ketone substrates to 1,3-diketones using catalytic Pd(PPh₃)₄ and 1,2-bis(diphenylphosphino)ethane (dppe).[47] Vankar and co-workers showed that Pd(PPh₃)₄ can promote the isomerization of 2,3-epoxy alcohols to β-hydroxy ketones and also that the same Pd catalyst can convert nitroepoxides into 1,2-diketones in the presence of Et₃N.[48] Reports by the Hirao group showed that α,β-epoxysilanes can be isomerized to α,β-unsaturated carbonyl compounds when Pd(II) salts and oxidants are utilized.[49]

Later, the research group of Kulawiec described in-depth investigations of the palladium system.[50] They showed that a combination of Pd(OAc)₂ and monophosphines such as PBu₃ and PPh₃ effectively catalyzed the isomerization of aryl-substituted epoxides to ketones or aldehydes in excellent selectivity (Scheme 14). A variety of functional groups, such as nitriles, free alcohols, and esters, as well as substitution patterns

Scheme 14. Pd/PR₃-Catalyzed Epoxide Isomerization
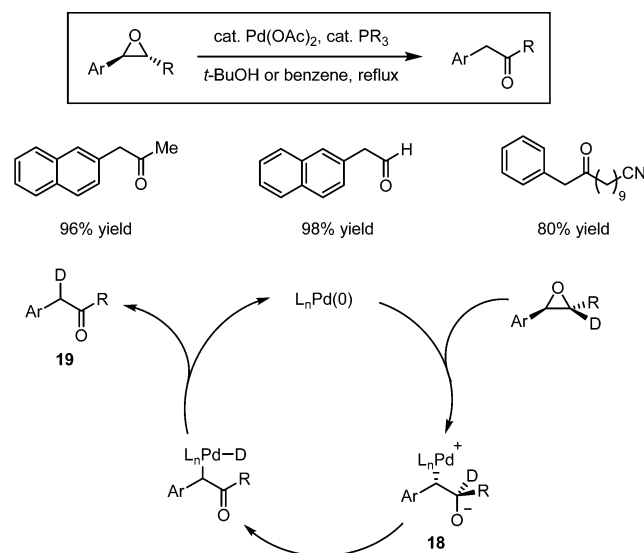
are tolerated. Although the reaction proceeds at the highest rate in *t*-BuOH, the authors showed that a range of solvents can also be utilized. Data from a mechanistic study led the authors to suggest that S_N2 attack by the Pd(0) species at the benzylic position of the arene oxide is rate determining (Scheme 14). Furthermore, stoichiometric migration of a deuterium label from the homobenzylic position of **18** to the benzylic position of **19** during the course of the reaction supports an intramolecular transfer of hydride. The protic solvent may facilitate the reaction by stabilizing intermediate **18** through hydrogen bonding.

Very recently, Mazet and co-workers reported a protocol based on a palladium−hydride complex **20** that features even broader substrate scope (Scheme 15).[51] Interestingly, the

Scheme 15. Epoxide Isomerization with Pd-Complex 20
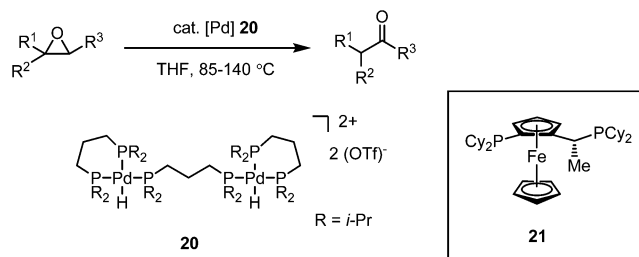
authors reported the utilization of a chiral bisphosphine ligand **21** to achieve kinetic resolutions of 1,1-disubstituted epoxides, providing both the ketone and the epoxide in modest enantioselectivity.

Stoichiometric investigations have been reported and provide a closer look at the process of metal-mediated epoxide isomerization. Milstein and co-workers studied the oxidative addition of Ir- and Rh-complexes and isolated the resulting formylmethyl- and acylmethyl intermediates **22** (Scheme 16).[52]

Scheme 16. Oxidative Addition of Transition Metals to Epoxides
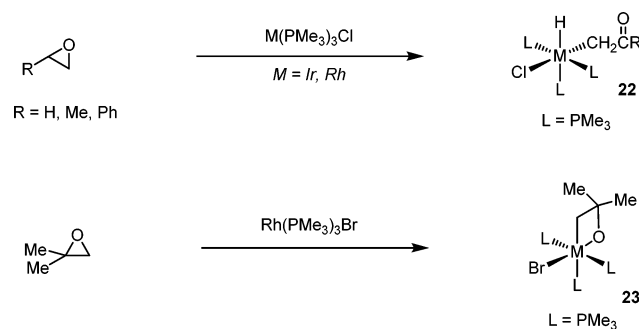

Subsequent reductive elimination to form the C−H bond was shown to be slow and dependent on phosphine dissociation. By contrast, when an epoxide void of *β*-hydrogens was subjected to the reaction conditions, the metallaoxetane **23** could be obtained.

2.5. Hydrogenations

As one of the most studied processes in organometallic chemistry, homogeneous hydrogenation has also been applied to epoxide substrates. Following the early examples by Kwiatek[53] using $[Co(CN)_5H]^{3-}$ as catalyst and by McQuillin[54] using a $RhCl_3py_3$−$NaBH_4/H_2$ system, the major focus of

subsequent work has concentrated on Rh-based catalysts. In contrast to olefin hydrogenation in which neutral rhodium complexes such as Wilkinson's catalyst, $Rh(PPh_3)_3Cl$, display high activity, epoxide hydrogenation was found to be catalyzed primarily by cationic rhodium complexes. Fujitsu and co-workers reported studies utilizing $[Rh(NBD)(PR_3)_2]^+(ClO_4)^-$ (NBD = norbornadiene) in the hydrogenation of styrenyl epoxides (Scheme 17).[55] Linear α-phenylethylalcohol was

**Scheme 17. Mechanism of Rh-Catalyzed Epoxide Hydrogenation**
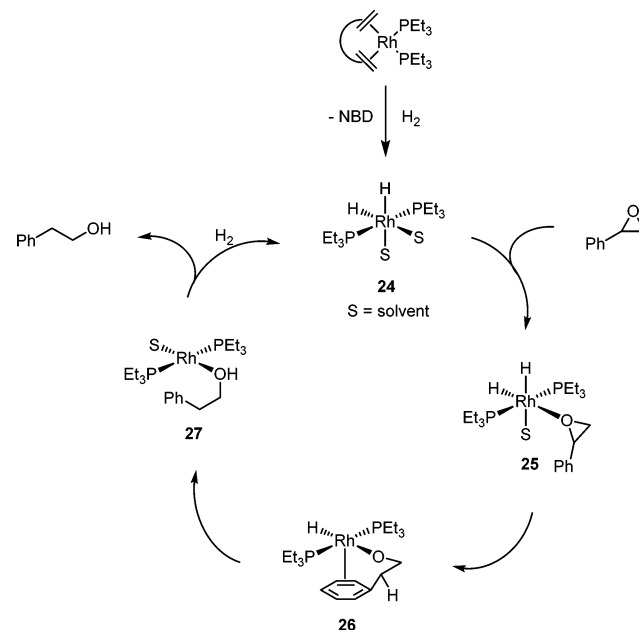
obtained as the sole regioisomeric product with phenyl-acetaldehyde and dimers or oligomers as the major byproducts. Electron-rich PEt_3 induced the highest reactivity, whereas PPh_3, PMe_3, and bisphosphines were less effective. Replacement of ClO_4^- with BPh_4^-, which may interrupt π-interactions between the Rh center and aryl group on the substrate, completely inhibited reactivity. Nonstyrenyl-type epoxides were also inert in this protocol. The proposed mechanism is shown in Scheme 17. After loss of the diene ligand, the cationic Rh complex undergoes oxidative addition to H_2 to afford **24**. Epoxide coordination followed by hydride insertion to the benzylic position would deliver **26**. Stabilization of **26** via π-coordination was mentioned by the authors as an explanation for the regioselectivity of the reaction, the substrate scope, and the inactivity of BPh_4^- catalyst. Finally, reductive elimination forms the O−H bond; this step may be assisted by the presence of H_2O, which was shown to enhance the overall reactivity. Furthermore, the authors noted that an alternative pathway proceeding through phenylacetaldehyde may be operative because the buildup of such an intermediate was observed when PPh_3 was used as the ligand.

Attempts to develop asymmetric hydrogenation of epoxides have been reported by the Chan group[56] and the Bakos group.[57] Moderate enantioselectivity can be obtained using cationic Rh complexes and chiral bisphosphine ligands with epoxysuccinate substrates. In addition, Ricci and co-workers successfully applied transfer hydrogenation conditions to the hydrogenation of epoxide substrates with $Rh_2(OAc)_4·4H_2O$ and *i*-PrOH as the hydride source.[58]

In 2003, the research group of Ikariya reported a Ru(II) system featuring metal/NH bifunctionality and demonstrated selective production of branched alcohols from the hydrogenation of a range of epoxides.[59] The concerted transfer of 2 H's via six-membered transition state **29** was proposed to account for the regioselectivity (Scheme 18). The authors also suggested that the use of a P−N chelating ligand was necessary to achieve the appropriate conformation for this transition state.

**Scheme 18. Mechanism of Ru-Catalyzed Epoxide Hydrogenation**
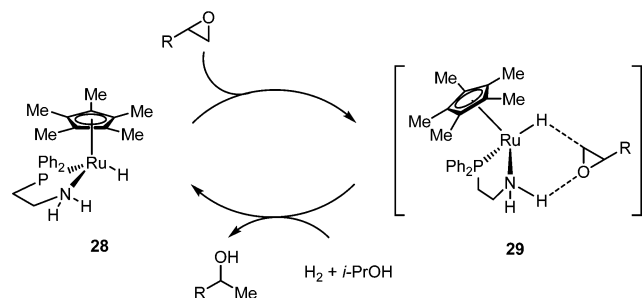
Examples with Pd catalysts have recently been thoroughly reviewed by Muzart et al.[60]

2.6. Cross-Coupling Reactions

Utilizing epoxides as electrophiles in cross-coupling reactions represents an attractive strategy for bond construction, especially for the formation of C−C bonds. A great challenge in this endeavor is facile β-hydride elimination as seen in the epoxide isomerization chemistry (Section 2.4). To date, most catalytic C−C bond-forming methods with epoxides have involved carbonylative couplings in which CO insertion can outcompete β-hydride elimination (Section 2.1). Alternatively, copper-mediated nucleophilic addition of lithium or Grignard reagents to epoxides and the addition of organic cuprate reagents are common processes to enable C−C bond formation; these reactions have been discussed extensively in several reviews and will not be covered herein.[61]

In 1967, Corey and Semmelhack reported a sole example showing that methallylnickel bromide dimer **30** undergoes C−C bond formation with styrene oxide (Scheme 19).[62] The

Scheme 19. Allylation of Styrenyl Epoxide with Complex 30
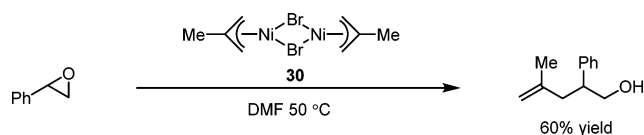
regioselectivity was such that a β-substituted instead of an α-substituted alcohol was obtained exclusively via C−C bond formation at the benzylic position. In a later paper by Hegedus and co-workers, the same complex **30** was shown to have modest reactivity with cyclopentene oxide.[63]

The Jamison group has developed some of the most synthetically valuable cross-coupling reactions with epoxides in the form of alkyne reductive couplings (Scheme 20).[64] Catalyzed by Ni(cod)₂ and PBu₃, the transformation of alkynes and epoxides to homoallylic alcohols can be accomplished in the presence of BEt₃ as the terminal reductant. Both styrenyl

Scheme 20. Reductive Coupling with Epoxides
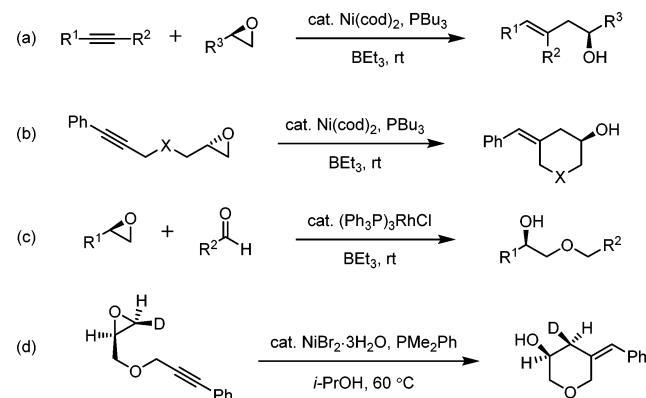
and alkyl epoxides are suitable substrates. Notably, ring-opening at the unsubstituted position of the epoxide is favored (Scheme 20a). Intramolecular reductive couplings can also be achieved and afford access to alcohols containing exocyclic olefins (Scheme 20b). In addition, the group showed that reductive couplings between epoxides and aldehydes can be promoted by (Ph₃P)₃RhCl (Scheme 20c).

Recently, the same group reported the use of a Ni(II) precatalyst and i-PrOH as the reductant to allow for more practical variants of these reactions (Scheme 20d). Taking advantage of this system, the authors studied the mechanism of oxidative addition of Ni to epoxides via a deuterium labeling experiment and found that an S_N2-type insertion of the metal with inversion of configuration was operative. The proposed mechanism is shown in Scheme 21. Coordination of Ni(0) to

Scheme 21. Mechanism of Reductive Coupling with Epoxides
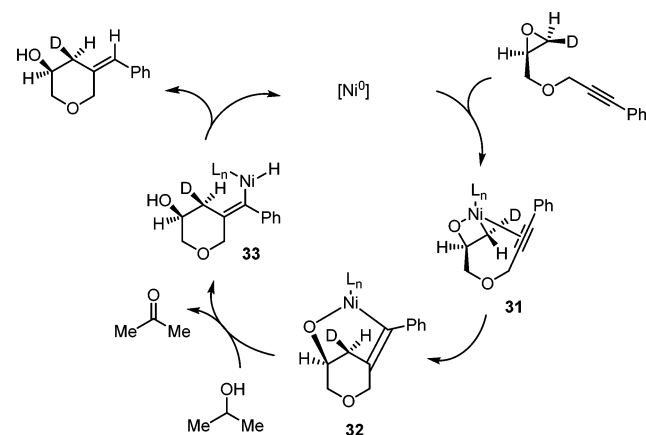
the alkyne of the substrate is accompanied by an S_N2-like oxidative addition to afford intermediate **31**. Next, migratory insertion of the alkyne provides a bicyclic complex **32**. Ligand exchange with i-PrOH precedes β-hydride elimination, forming an alkenyl nickel species **33**. Finally, reductive elimination generates the allylic alcohol and returns the Ni(0) catalyst.

In contrast to the Jamison work, most other transition metal-catalyzed methods using epoxides as substrates occur by β-hydride elimination followed by the desired C−C bond formation. The Lu group[65] and subsequently the Roy group[66] reported that aryl epoxides can be allylated through a Barbier-type reaction with allyl bromide in the presence of a Pd(0)

catalyst and a stoichiometric amount of InCl or SnCl$_2$ (Scheme 22). Roy and co-workers also showed that propargylation was

Scheme 22. Allylation and Propargylation of Epoxides
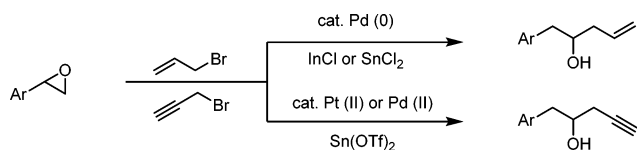
possible with Pd(II) or Pt(II) catalysts. A deuterium labeling experiment performed by the Lu group suggested that epoxide isomerization to an aldehyde, possibly promoted by the Lewis acid, occurs prior to C−C bond formation. In this example, the role of the Pd catalyst is to generate an allylindium intermediate via transmetalation.

In the reaction of butadiene, styrene oxide, Ni(cod)$_2$, and PCy$_3$, Ogoshi and co-workers isolated an allyl nickel complex **34** (Scheme 23).[67] The regioselectivity of the epoxide ring-

Scheme 23. Coupling of Butadiene and Epoxide

opening indicates that the epoxide has isomerized to the aldehyde prior to C−C bond formation. Indeed, when the authors combine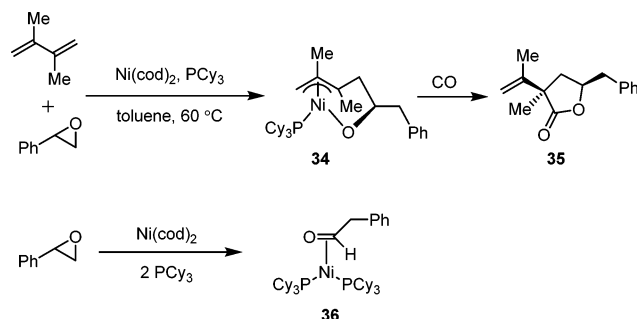d the same epoxide and Ni catalyst in the absence of butadiene, they isolated complex **36**, which features the nickel bound to the aldehyde carbonyl through a π-interaction.

In 1988, Miyashita and co-workers described a regioselective methylation of epoxides using MeI in the presence of Ni(PPh$_3$)$_4$, Pd(PPh$_3$)$_4$, or Pt(PPh$_3$)$_4$ (Scheme 24).[68] It was

Scheme 24. Regioselective Methylation of Epoxides
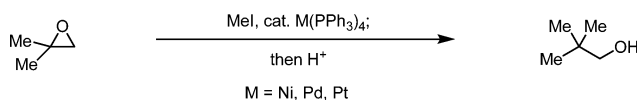
proposed in this paper that the product of oxidative addition between the transition metal and MeI, (Me)M(PPh$_3$)$_2$I, promotes epoxide rearrangement. Next, insertion of the methyl group and protonolysis yields the alcohol product. However, the authors did not suggest a mechanism by which the catalysts are regenerated.

In 2011, the Doyle group reported a method involving the Ni-catalyzed Suzuki−Miyaura cross coupling of styrenyl epoxides with aryl boronic acids (Scheme 25).[69] A ligand evaluation revealed that the bulky, electron-rich phosphine BrettPhos gave optimal yields. A variety of *ortho-*, *meta-*, and *para*-substituted epoxides can be used in this protocol. The authors suggested that the α-substituted alcohol products arise

Scheme 25. Ni-Catalyzed Suzuki−Miyaura Cross Coupling of Epoxides
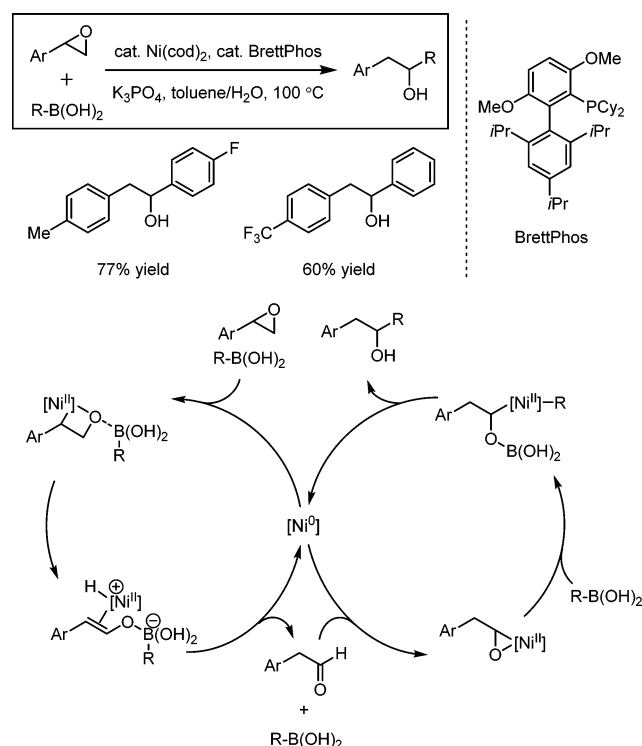
by β-hydride elimination-initiated isomerization of the styrene oxides followed by 1,2-arylation of the intermediate aldehydes (Scheme 25). The authors isolated a red crystal from the reaction mixture, and by X-ray analysis, the structure of this complex **37** was found to be composed of Ni, styrene oxide, boroxine, and the ligand BrettPhos with equal stoichiometry (Figure 2). Interestingly, the bottom ring of the ligand in this
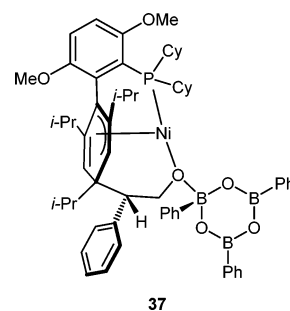
Figure 2. Nickel complex **37**.

complex had undergone dearomatization and formed a C−C bond with the epoxide. This crystal was catalytically active, albeit displayed an induction period, showing that the complex was not directly on the catalytic cycle.

The cross coupling of epoxides can also be achieved by radical mechanisms. Although the generation of carbon-based radicals from epoxides by means of alkali metals is a viable route, the strongly reducing conditions hamper its synthetic utility. Nugent and RajanBabu have hence devised a system utilizing the mild reductant, Cp$_2$TiCl, that promotes rapid reduction of epoxides to form radical intermediate **38**.[70] This mode of activation has allowed a wide variety of subsequent transformations such as deoxygenation, reduction, and, more

importantly, addition to alkenes and other π-systems (Scheme 26).[71,72] C−C bond formation by way of this mechanism has been exploited as a powerful method for constructing complex alcohols.

Scheme 26. Generation of Radical Intermediates from Epoxides
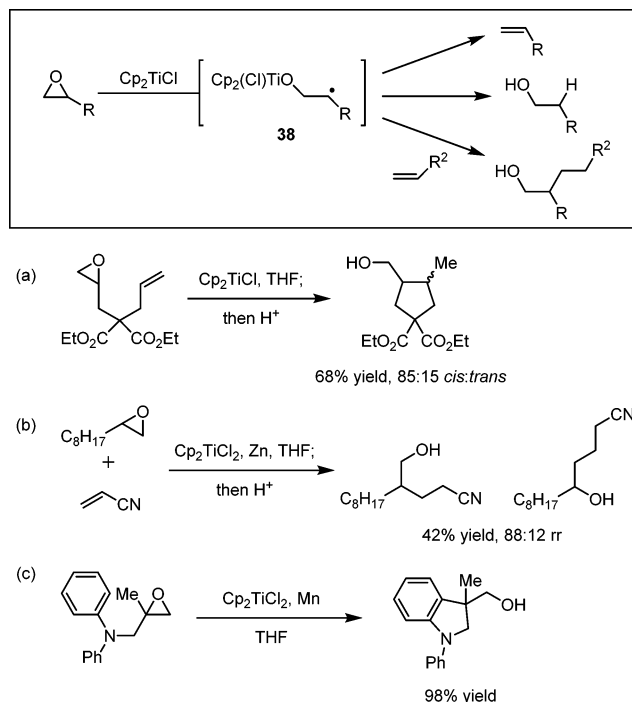
In 2004, the Oshima group developed a Co-catalyzed Mizoroki−Heck-type reaction with epoxides (Scheme 27).[73]

Scheme 27. Co-Catalyzed Mizoroki−Heck-type Reactions of Epoxides
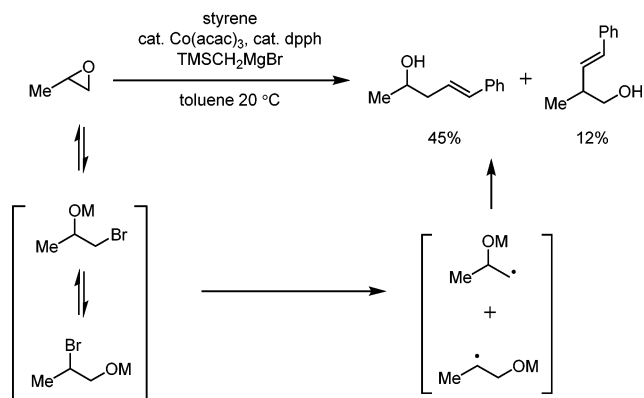
With monosubstituted epoxides, regioisomeric mixtures of products were obtained, favoring the terminal addition isomer. To account for this outcome, the authors put forth a mechanism involving reversible formation of bromoethoxides followed by the generation of intermediates bearing a carbon-based radical. In their proposal, the distribution of equilibrating bromoethoxide derivatives determines the regioselectivity of C−C bond formation.

In 2014, the Weix group reported Ni-catalyzed reductive couplings of epoxides with aryl bromides. Most notably, the

reaction design enables them to achieve both terminal and internal arylation depending on the reaction conditions (Scheme 28).[74] For terminal addition, iodide additives were

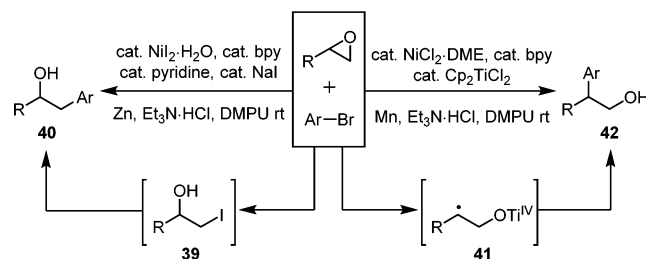**Scheme 28. Ni-Catalyzed Reductive Couplings of Epoxides**

used as promoters, presumably to facilitate the generation of adduct **39** that subsequently undergoes oxidative addition with the Ni catalyst. On the other hand, internal coupling was achieved with the use of Cp_2TiCl_2 and Mn as reductant. This additive can facilitate the generation of radical intermediate **41** as demonstrated by Nugent and RajanBabu.[70] Interception of this intermediate by Ni leads to the generation of product **42**.

2.7. Miscellaneous Isolated Organometallic Complexes from Epoxides

Although products from the oxidative addition of transition metals[35] to simple epoxides have seldom been isolated due to their instability, investigations with cyano-substituted epoxides have been fruitful. In the 1970s and 1980s, Graziani, Lenarda, Ibers, and co-workers reported the formation of metal-laoxetanes **43** from tetracyanoethylene oxide and a series of low valent metals (Scheme 29).[75] Upon ligand substitution

Scheme 29. Oxidative Additions to Cyano-epoxides
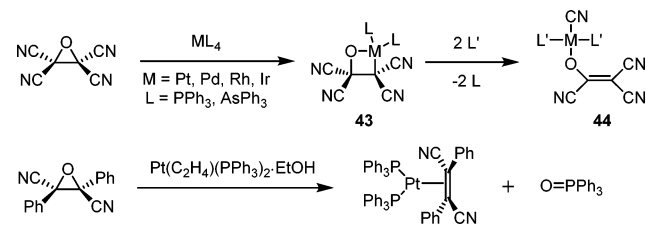
with trialkylphosphines, heat, or photolysis, the complexes underwent β-cyanide elimination to afford the corresponding metal alkoxy compounds **44**. Later, Ibers and co-workers carried out similar reactions with phenyl dicyanoepoxides and discovered that deoxygenation occurs instead of elimination.[76] Furthermore, studies with gaseous ethylene ferraoxetane were carried by the Kafafi and Jørgensen groups.[77]

Angelici, Singh, Michelin, and co-workers reported the synthesis of a series of metal carbene complexes from metal carbonyl compounds and epoxides (Scheme 30).[78] In these reactions, bromide additives and brominated alcohol solvents were utilized. Two mechanisms were put forth to explain the formation of these metal carbenes, one involving addition of the epoxide to CO mediated by the metal (path a), and the other occurring first by bromide ring-opening of the epoxide (path b). Becasue of the relatively low nucleophilicity of epoxides, the latter pathway (b) was favored. Similarly, the Michelin group prepared analogous complexes starting from metal isocyanide compounds.

Scheme 30. Preparation of Metal—Carbene Complexes from Epoxides
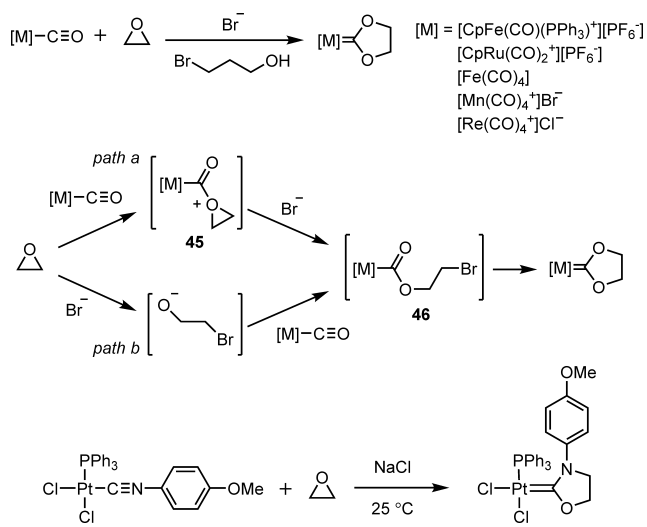
In 2005, the Bergman group prepared a zirconium imido complex **47** and showed that it underwent insertion into epoxides (Scheme 31).[79] A stereochemical investigation, Hammett study and radical clock experiment, implicated zwitterionic intermediate **48** in the transformation.

Scheme 31. Reaction of Zirconium Imido Complex with Epoxides
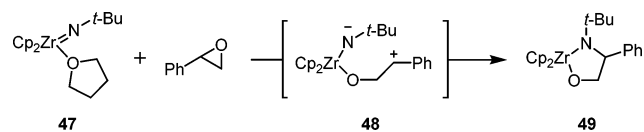
3. AZIRIDINES

3.1. Carbonylations

Ring-expansive carbonylation of aziridines constitutes a direct and modular approach to the preparation of β-lactams, ubiquitous moieties found in many bioactive molecules.[5] Similar to epoxide carbonylations, the formation of β-lactams can be mediated by nucleophilic transition metals according to the general mechanism in Scheme 32.

Scheme 32. General Mechanism of Transition Metal-Catalyzed Ring-Expansive Aziridine Carbonylation

The Alper group pioneered the development of these methods, with their first paper on the topic reported in 1983.[80] Subsequent studies have led to methods of broad synthetic application.[81] Their approach utilizes catalytic 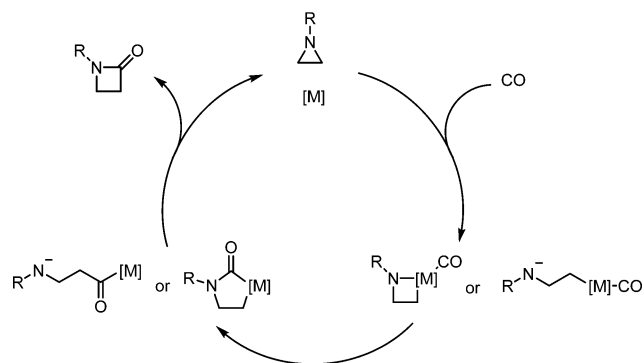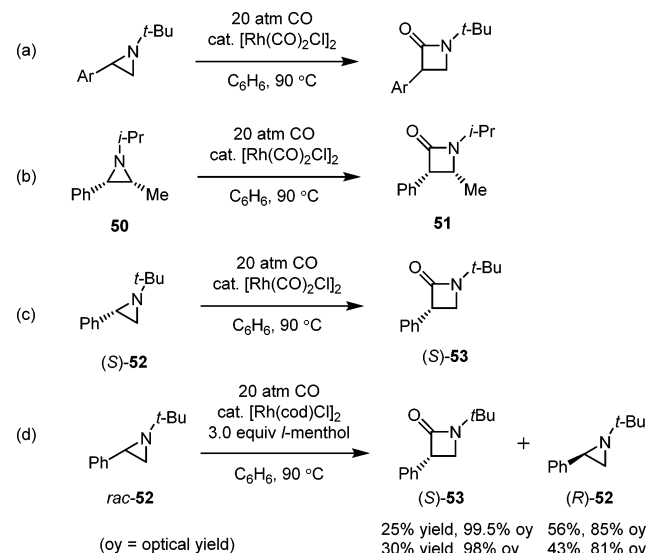[Rh-(CO)$_2$Cl]$_2$ to carbonylate aryl-substituted aziridines regioselectively at the benzylic position (Scheme 33). This process is

Scheme 33. Rh-Catalyzed Ring-Expansive Aziridine Carbonylation: Scope

also diastereoselective and stereospecific. Thus, when the *cis*-disubstituted aziridine **50** is subjected to the reaction conditions, the *cis*-β-lactam **51** is obtained exclusively (Scheme 33b). Furthermore, when (*S*)-**52** is used, (*S*)-**53** is isolated, in which the stereocenter has undergone retentive carbonylation (Scheme 33c). In addition, this protocol was expanded to enable a kinetic resolution process that provides enantioenriched β-lactams and aziridines (Scheme 33d). With the use of a superstoichiometric amount of *l*-menthol and [Rh(cod)Cl]$_2$ as the catalyst, the product β-lactams **53** can be isolated in >98% optical yield (oy) and 20−30% chemical yield, and the starting material aziridines **52** could be recovered in >81% oy.

The authors proposed that the following mechanism can account for these data: the reaction initiates by precoordination of the metal to the aryl ring, perhaps as a π- or benzyl complex (Scheme 34). This precoordination event explains the regioselectivity of the carbonylation. Indeed, a computational paper by Sordo and co-workers indicated that metal arene precoordination weakens benzylic C−N bonds through hyperconjugation.[82] The fact that simple alkyl aziridines are not suitable substrates for the Alper methodology is also consistent with a key role for catalyst precoordination. Next, a stereoretentive oxidative addition from **54** provides intermediate **55**. Rapid CO insertion followed by reductive elimination generates the β-lactam product.

In a mechanistically distinct approach, Pinhas and co-workers have reported a reaction variant using stoichiometric Ni(CO)$_4$ with LiI (Scheme 35).[83] The protocol calls for the aziridine substrates to react with LiI for a given time, followed by the addition of Ni(CO)$_4$, and finally an oxidative workup provides the β-lactam products. The proposed mechanism is depicted below (Scheme 35). S$_N$2 attack by the I$^-$ additive generates intermediate **57**, which then reacts with Ni(CO)$_4$ to afford the

Scheme 34. Rh-Catalyzed Ring-Expansive Aziridine Carbonylation: Mechanism
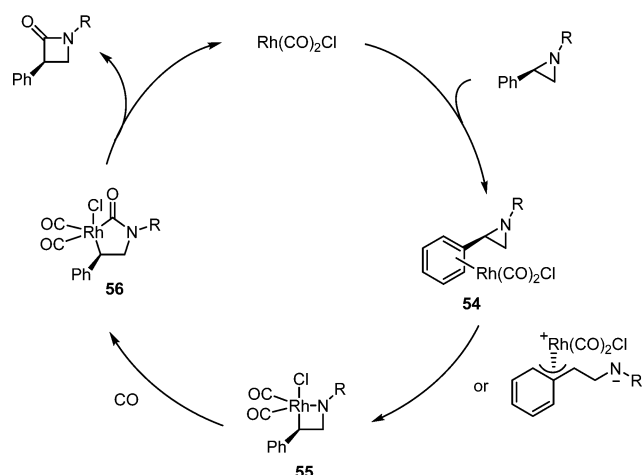
Scheme 35. Ni(CO)$_4$/LiI-Mediated Ring-Expansive Aziridine Carbonylation Reactions
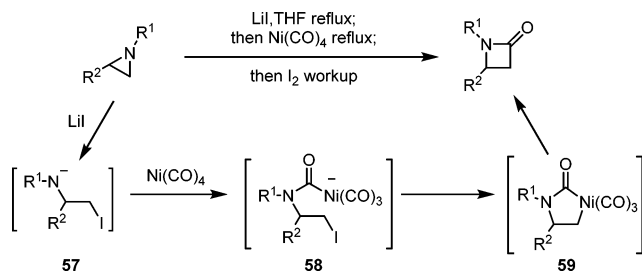
nickel acylate complex **58**. Notably, CO insertion occurs regioselectively at the less substituted position of the aziridine, presumably due to the selectivity of S$_N$2 attack by LiI. Consistent with this initial step is the observation that monosubstituted aziridines react faster and in higher yield than disubstituted ones. To complete the cycle, another S$_N$2 reaction on the alkyl iodide may form the five-membered nickel metallacycle. Finally, reductive elimination provides the desired β-lactam. This double inversion mechanism on the terminal position assures that when a *cis*-disubstituted aziridine is used, the resulting β-lactam also has a *cis*-configuration.

Later, the research groups of Alper[84] and Coates[19b,85] reported the successful application of a cobalt catalyst system to aziridine carbonylations (Scheme 36). This catalyst system has been studied extensively in epoxide carbonylation reactions, where it is proposed that [Co(CO)$_4$]$^-$ serves as the nucleophile in the ring-opening step (section 2.1). In 1996, Alper and co-workers reported that Co$_2$(CO)$_8$ was effective in converting aziridines into β-lactams.[84] Unlike their previously described Rh-system,[80,81] the cobalt catalyst is also productive in carbonylating simple alkyl aziridines. Furthermore, CO insertion occurs at the less substituted carbon of the aziridine substrate, which is consistent with a proposal in which the cobalt catalyst undergoes nucleophilic attack on the three-membered heterocycle. Various mono- and disubstituted aziridines are suitable substrates, and aziridines bearing a wide variety of N-substituents can be used, including alkyl and aryl groups. However, when a benzoyl-protected aziridine was utilized, a mixture of regioisomers was obtained. From this result, the authors proposed an alternative single-electron

Scheme 36. Co-Catalyzed Ring-Expansive Aziridine Carbonylations
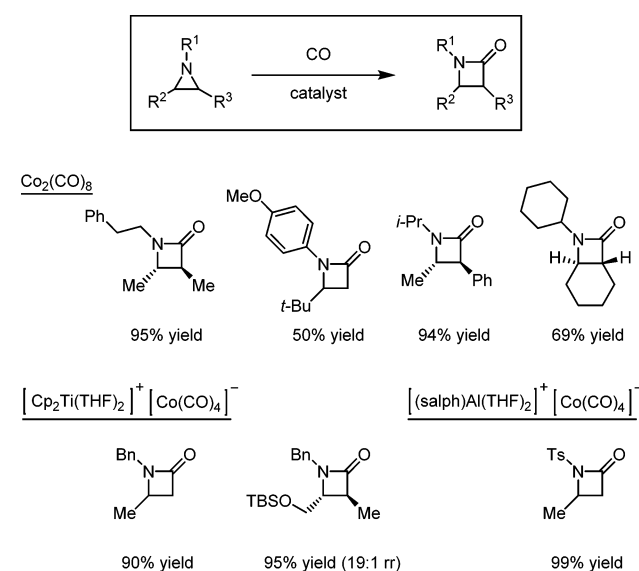
transfer (SET) oxidative addition pathway to explain the regioselectivity of this particular substrate.

In 2002, Coates and co-workers disclosed that two of their previously developed Lewis acid-cobalt catalysts, [Cp$_2$Ti-(THF)$_2$][Co(CO)$_4$] and [(salph)Al(THF)$_2$][Co(CO)$_4$] (section 2.1), promote the carbonylation of aziridines (Scheme 36).[19b,85] Remarkably, these catalysts, along with the Alper Co system, are sufficiently reactive to facilitate the synthesis of strained *trans*-bicyclic β-lactams.

The mechanism of these ring-opening reactions is proposed to commence with nucleophilic attack by Co(CO)$_4$$^-$, which would result in inversion of configuration at the electrophilic carbon of the aziridine undergoing reaction (Scheme 37). The

Scheme 37. Mechanism of Co-Catalyzed Ring-Expansive Aziridine Carbonylation Reactions
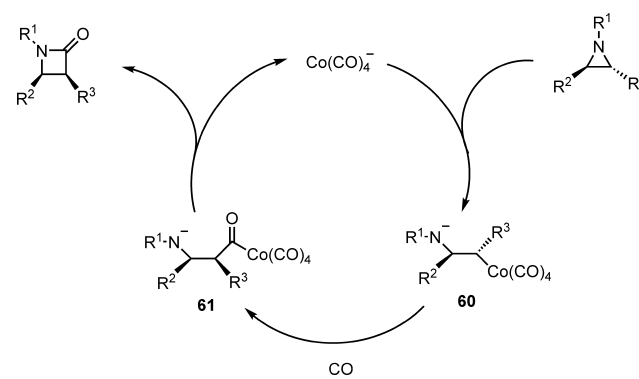
organocobalt intermediate **60** may then undergo CO insertion of the Co–C bond. Finally, acyl transfer to the nitrogen would afford the β-lactam products. A theoretical study by López and co-workers provides support for this proposed pathway, and suggests that nucleophilic ring-opening is the rate-determining step.[86] The latter observation is striking because for epoxide carbonylation with this same catalyst class, the final ring-closing step is instead proposed to be rate-determining.

Two other related classes of substrates, aziridinones[87] and methyleneaziridines,[88] have also been shown by the Alper

group to undergo ring-expansive carbonylation with the aid of transition metal catalysts (Scheme 38). Either a stoichiometric

Scheme 38. Ring-Expansive Carbonylations of Aziridinones and Methyleneaziridines
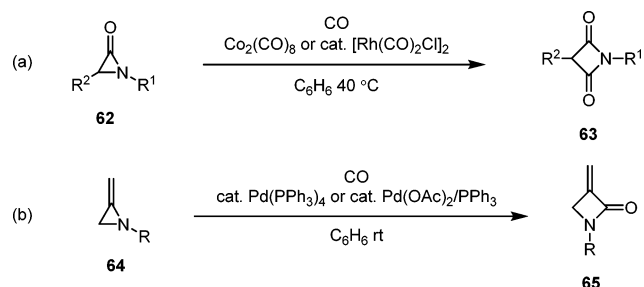
amount of $Co_2(CO)_8$ or a catalytic amount of $[Rh(CO)_2Cl]_2$ was shown to intercept aziridinones **62** in the generation of azetidine-2,4-diones **63** (Scheme 38a). Regioselective insertion of the carbonyl group into the C_{sp3}–N bond can be accounted for by a reversible unselective oxidative addition that is followed by selective CO insertion into the metal–C_{sp3} over the metal–C_{sp2} bond. Carbonylation of methyleneaziridines **64** has also been accomplished using a Pd catalyst (Scheme 38b). In this case, CO insertion into the C_{sp2}–N bond is favored. Treatment of methyleneaziridines with $Pd(PPh_3)_4$ or $Pd(OAc)_2/PPh_3$ as catalyst affords α,β-unsaturated 2-azetidinones **65** as products.

Stoichmetric reactions between aziridines and metal carbonyl hydride complexes were reported by Höfer, Beck, and co-workers (Scheme 39).[89] Monosubstituted aziridines gave five-

Scheme 39. Reactions of Aziridines with Metal Carbonyl Hydride Complexes

membered metallacycles **66** or **67** with regioselectivity dependent on the substituent. The authors proposed a mechanism involving intermediate **68**, which may be formed by protonation and subsequent aziridine ring-opening with the metal center.

Recently, Xi and co-workers reported the carbonylation of 2,6-diazasemibullvalene **69** with a stoichiometric amount of $Co_2(CO)_8$ (Scheme 40).[90] This reaction was carried out under much milder conditions than the typica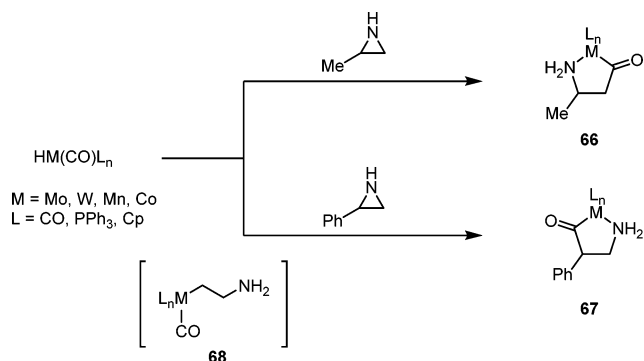l Co-catalyzed processes, presumably due to the intrinsic strain of this aziridine substrate. Also, in the same report, the authors isolated an azametallacyclobutane **71** resulting from the insertion of a Ni(0)–NHC species into the 2,6-diazasemibullvalene.

Scheme 40. Reactions with 2,6-Diazasemibullvalene
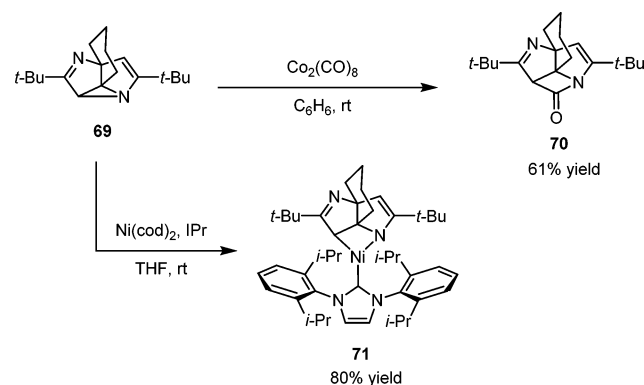
3.2. Cycloadditions[91]

A variety of heterocumulenes have been demonstrated to undergo cycloaddition with aziridines in the presence of transition metal catalysts (Scheme 41).[92] In reports by the

Scheme 41. Pd-Catalyzed Cycloadditions of Heterocumulenes with Aziridines
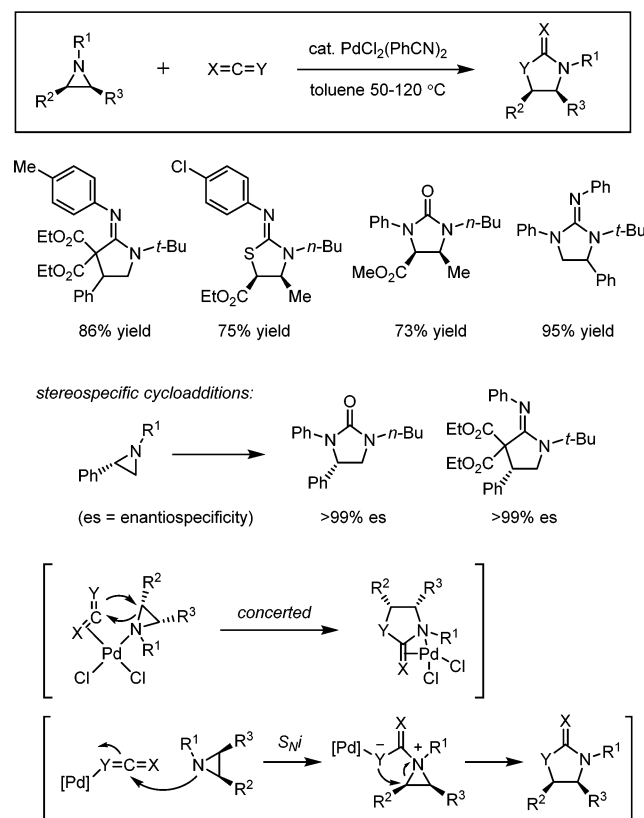
Alper group from the 1990s, $PdCl_2(PhCN)_2$ has been used as a catalyst. Under optimized conditions, a wide array of five-membered heterocycles are obtained in good yields, and, in general, the cycloadditions proceed regioselectively wherein the direction of insertion depends on the aziridine substituents as well as the heterocumulene partners utilized. Additionally, these processes are stereospecific, delivering products with >99% enantiospecificity (es). To account for this result, the authors proposed two mechanistic possibilities, a concerted and an S_Ni process (Scheme 41). A related reaction was reported by Saito

and co-workers in 2006 using isocyanates as the cycloaddition component and NiI$_2$ as the catalyst.[93] It is worth noting, however, for these and the accompanying examples described in this section that the transition metal catalysts may simply serve as Lewis acids without undergoing oxidative addition into the aziridine C−N bonds.

Interestingly, the Alper group showed that when sulfur diimides are used as the cycloaddition partners, unique imidazolidinethione compounds **72** are isolated instead of the expected thiadiazolidenimine **73** products (Scheme 42).[94] [13]C labeling studies revealed that the additional carbon originates from the incorporation of another molecule of the aziridine starting material into the cycloadduct.

Scheme 42. Pd-Catalyzed Cycloadditions of Sulfur Diimides with Aziridines
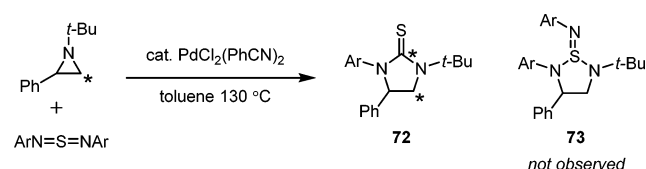
Related cycloaddition reactions can be effected through the addition of zwitterion-type reagents. In 2003, Harrity and co-workers reported that palladium-trimethylenemethane (Pd-TMM) **75**, generated from 2-[(trimethylsilylmethyl)-2-prop-1-enyl **74** and a palladium catalyst, can undergo cycloaddition with sulfonyl aziridines (Scheme 43).[95] This methodology

Scheme 43. Piperidine Synthesis through Pd-Catalyzed Cycloadditions with Aziridines
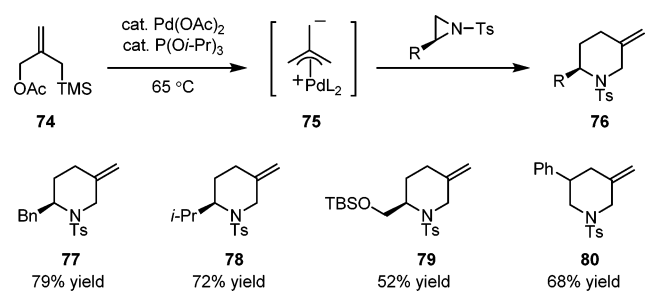
constitutes a rapid route for the synthesis of piperidines **76**. All of the products are obtained as single regioisomers with C−C bond formation occurring at the nonsubstituted end of the aziridine. An exception to this observation is that a styrenyl aziridine undergoes cycloaddition to give piperidine **80** in 1.6:1 regioisomeric ratio (rr).

The Shintani group has utilized a similar strategy for the synthesis of medium-sized N-containing heterocycles (Scheme 44).[96] Intermediate **82** can be generated from lactone **81** in the presence of palladium. Cycloaddition of **82** with a N-Ts-aziridine provides a range of 10-membered azlactones. Alternatively, the authors note that, depending on the substituents R^1 and R^2, intermediate **82** can also undergo decarboxylation and subsequent cycloaddition of **83** with aziridines to instead produce azepane derivatives. Furthermore, this reaction has been rendered enantioselective under the influence of a chiral phosphoramidite ligand **85**.

Scheme 44. Azlactone and Azepane Synthesis through Pd-Catalyzed Cycloadditions with Aziridines
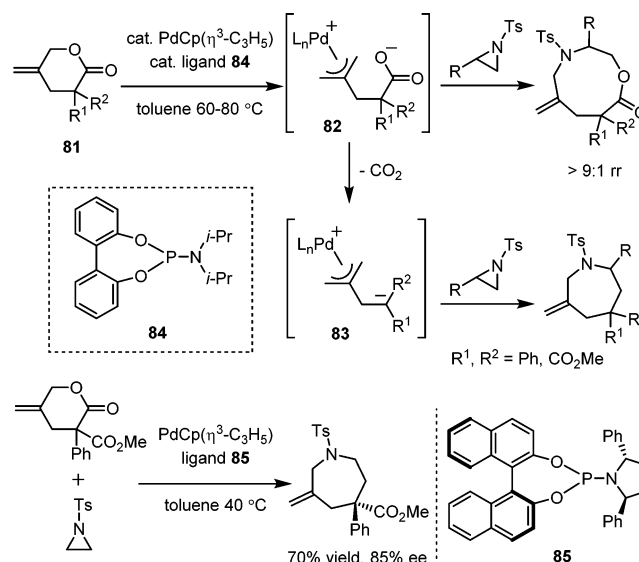
3.3. Isomerizations

In 2003, Wolfe and co-workers published a paper describing the palladium-catalyzed isomerization of aziridines to ketimines (Scheme 45).[97] It was shown in this report that a Pd(0) catalyst

Scheme 45. Pd-Catalyzed Isomerizations of Aziridines
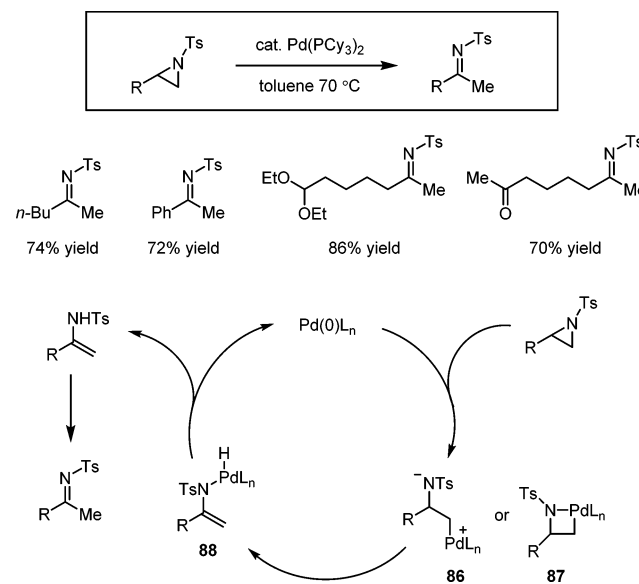
in combination with an electron-rich trialkyl phosphine ligand promotes the reaction with the greatest efficiency. Also, the protocol is compatible with various alkyl- and aryl-substituted terminal N-Ts-aziridines. The authors put forth the following mechanistic proposal. Pd(0) undergoes oxidative addition to the aziridine by an S$_N$2 mechanism, accessing either a zwitterion complex **86** or an azametallacyclobutane intermediate **87**. Subsequent β-hydride elimination affords palladium-amido species **88**. The ketimine products are then generated by reductive elimination followed by tautomerization. Because Pd is expected to add selectively to the less-substituted carbon of the electrophile in an S$_N$2 mechanism, this proposal is

consistent with the observed regioselectivity, in which ketimines instead of aldimines are produced.

3.4. Hydrogenations

The hydrogenation of aziridines is commonly mediated by various heterogeneous Pd or Ni catalysts to produce amine products. This chemistry has been previously discussed in a review by Hu[98] and will therefore not be mentioned in any detail herein.

3.5. Cross-Coupling Reactions

Nucleophilic ring-openings of aziridines by cuprates, Grignard, or lithium reagents in the presence of copper promoters represent a common strategy to achieve C−C bond formation with this electrophile class. However, because these processes are not thought to proceed via a redox mechanism with copper, an in-depth discussion of the literature in this area will not be covered. Readers are instead directed to two recent reviews on the topic.[98,99] The identification of transition metal catalysts that can achieve cross coupling between aziridines and organometallic reagents, on the other hand, has proven to be particularly challenging. This type of transformation is attractive because it offers the opportunity to effect catalyst-controlled chemo-, regio-, and stereoselective C−C bond formation in a manner impossible to achieve by conventional substitution chemistry.

The recent developments in this area have been inspired in large part by seminal reports from the Hillhouse and Wolfe laboratories on the stoichiometric chemistry of Ni and Pd with N-Ts-aziridines. In 2002, Hillhouse and co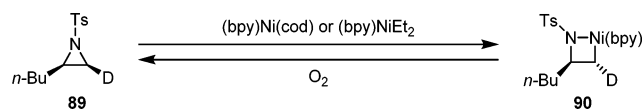-workers demonstrated that Ni(0) complexes were capable of undergoing oxidative addition into alkyl aziridines, and the resulting azametallacyclobutane intermediates 90 could be isolated and characterized (Scheme 46).[100] Using a deuterium labeled

Scheme 46. Oxidative Addition of Ni(0) to Aziridines

aziridine 89, the Hillhouse group demonstrated that oxidative addition proceeds by an S_N2 mechanism involving the attack of the unsubstituted end of the aziridine by Ni(0). Exposure of the metallacycle complex 90 to oxygen triggered reductive elimination. Notably this step also proceeded by a stereopecific mechanism with inversion, affording the starting aziridine with overall retention of configuration.

In 2006, another example of stoichiometric oxidative addition of a group 10 transition metal into aziridines was reported by the Wolfe group (Scheme 47).[101,100b] They showed that a Pd(0) catalyst can undergo oxidative addition

Scheme 47. Oxidative Addition of Pd(0) to Aziridines
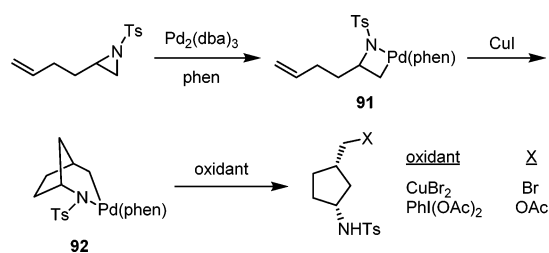
into N-Ts-aziridines that bear a tethered olefin. Both the tether length and the electronic properties of the olefin influenced this reactivity, and the authors proposed that precoordination of the olefin with Pd(0) played a critical role in facilitating the rather difficult oxidative addition. When the azametallacyclobutane intermediate 91 was treated with CuI, bicyclic complex 92 was obtained. Further transformation with oxidants cleaved the metallacycle, and a 1,3-disubstituted cyclopentane could be generated.

Reactions performed with the deuterium-labeled aziridine 93 informed the mechanism of this process (Scheme 48).

Scheme 48. Oxidative Addition of Pd(0) to Deutered-Aziridine
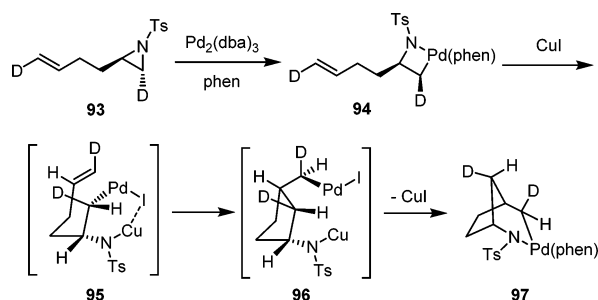
Examination of the metallacycle 94 revealed that oxidative addition proceeds through an S_N2-like mechanism. Subsequent stereospecific alkene insertion would then generate 96, which upon loss of CuI delivers product 97.

A decade after the first report by Hillhouse, the Doyle group described the development of a Negishi cross coupling with N-Ts-aziridines.[102] Styrenyl aziridines were shown to undergo C−C bond formation with alkyl zinc reagents under the influence of nickel catalysis (Scheme 49). The key to this protocol is the use of an electron-deficient olefin ligand, dimethyl fumarate 98, which is proposed to favor reductive elimination over β-hydride elimination. This reaction is regioselective, with C−C bond formation occurring exclusively at the benzylic position. The functional group tolerance is also broad, and in line with more traditional sp^2 Negishi reactions: aldehyde, secondary N−H, and silyl ether functional groups are all well-tolerated. When an enantioenriched aziridine substrate (R)-99 was utilized, C−C bond formation proceeded with racemization (Scheme 49a). Either an S_N2 oxidative addition followed by Ni−C bond homolysis or a single-electron transfer (SET) mechanism can account for this observation. This result in combination with the observation that cross coupling with the 1,2-disubstituted aziridine 100 gives product in high cis diastereoselectivity provides support for the intermediacy of an azametallacyclobutane species 101 (Scheme 49b).

Later, the Doyle group extended the aziridine scope to include simple alkyl aziridines (Scheme 50).[103] This electrophile class showed no reactivity under the originally developed reaction conditions using N-Ts-aziridines. To enhance the reactivity of the substrates, the authors developed a new protecting group, cinsyl (Cn), which contains an electron-deficient olefin on the aryl sulfonyl group. With a Cn rather than Ts protecting group, aliphatic aziridines deliver cross-coupled products with aromatic and aliphatic zinc reagents in good yield as a mixture of regioisomers favoring the linear products. As compared to their original protocol, dimethylfumarate is no longer included as a ligand, but a super-

Scheme 49. Ni-Catalyzed Cross Coupling of Styrenyl Aziridines

Scheme 50. Ni-Catalyzed Cross Coupling of Alkyl Aziridines
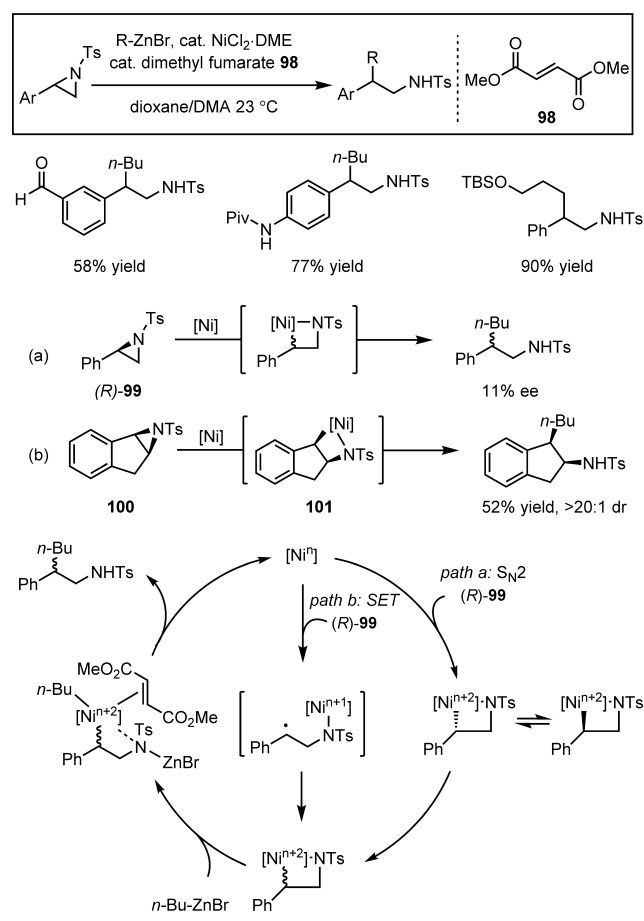
stoichometric amount of LiCl additive is used to increase the reaction efficiency. To better understand the mechanism, an enantiopure aziridine **102** was subjected to the standard reaction conditions and was found to afford the linear product **103** with no erosion in ee, whereas the branched product **104** underwent significant racemization under the reaction conditions (Scheme 50a). Similarly, an aziridine **105** labeled with deuterium at the terminal position gave a mixture of diastereomeric cross-coupled products **106** arising from epimerization at the terminal position (Scheme 50b). Finally, a cyclopropane-substituted aziridine **107** delivered ring-opened products **108** and **109**, which supports the presence of a radical intermediate (Scheme 50c). These results suggest that cross couplings of the styrenyl and aliphatic aziridines share a common mechanism.

After this report, Michael and co-workers described a distinct system for the cross coupling of alkyl aziridines (Scheme 51).[104] A palladium catalyst was shown to induce regioselective arylation of alkyl *N*-nosyl (*N*-Ns) aziridines with aryl boronic acids under exceptionally mild conditions. The authors found that inclusion of phenol additive **112** was critical to the reaction efficiency. They proposed that **112** facilitates dissociation of metallacyclic intermediate **111** through sulfonamide protonation and accelerates transmetalation of the boronic acid coupling partner. On the basis of a deuterium labeling study, the authors put forward a catalytic cycle featuring an S_N2 mechanism for oxidative addition similar to that described by Hillhouse[100a] and Wolfe.[101]
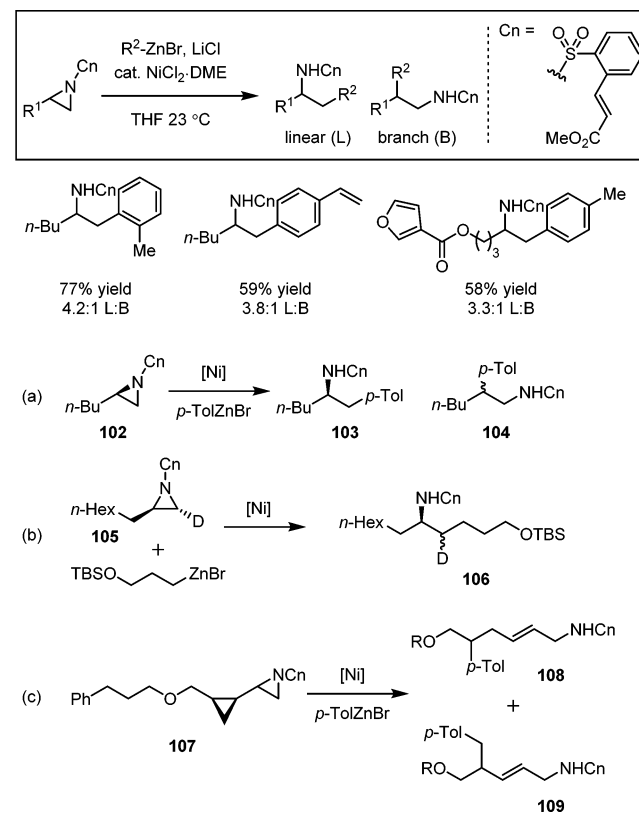
Scheme 51. Pd-Catalyzed Cross Coupling of Alkyl Aziridines
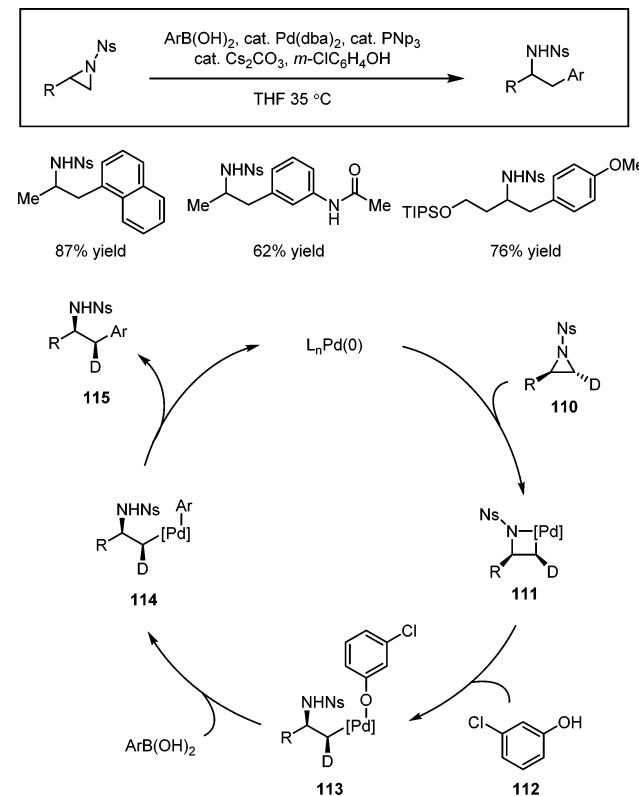
In 2013, Li and co-workers applied a C−H activation strategy to achieve cross coupling with styrenyl aziridines (Scheme 52).[105] By utilizing a Rh(III) catalyst, C−H bonds *ortho* to a

Scheme 52. Rh-Catalyzed Cross Couplings of Styrenyl Aziridines through C−H Insertions

Scheme 53. Mechanism of Rh-Catalyzed Cross Coupling of Styrenyl Aziridines

Scheme 54. Co-Catalyzed Mizoroki−Heck-type Reaction of Aziridines

directing group could be activated. The authors showed that the corresponding organorhodium species participates in C−C bond formation at the benzylic position of aziridines. A kinetic isotope effect experiment demonstrated that insertion of rhodium into the C−H bond serves as the rate-determining step. When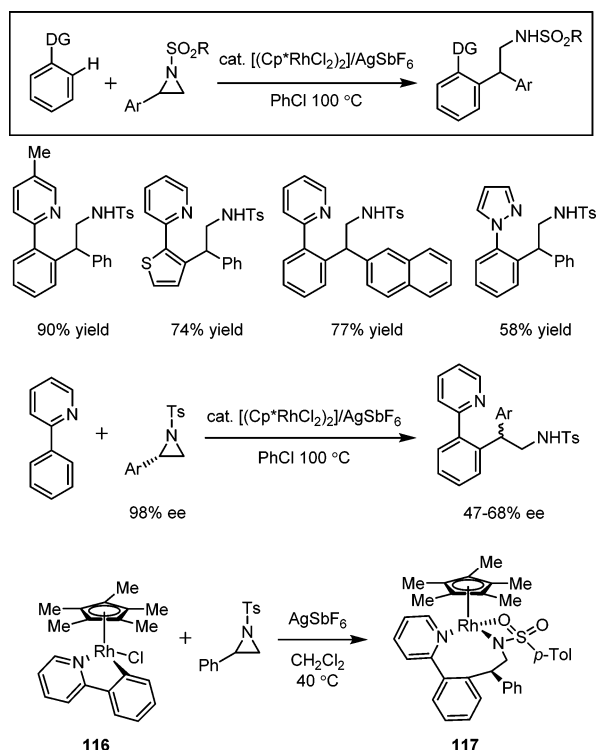 enantioenriched aziridine was used as the substrate, racemic product was obtained. The authors account for this stereochemical outcome by invoking an S$_N$1 mechanism for ring-opening. To further probe the mechanism, the C−H inserted complex **116** was prepared and then reacted with N-Ts styrenyl aziridine. The resulting complex **117** was characterized by single crystal X-ray diffraction. Upon the addition of 2-phenylpyridine, complex **117** converts to the cross-coupled product. Taken together, a catalytic cycle can be proposed as shown in Scheme 53. In the presence of AgSbF$_6$, [(Cp*RhCl$_2$)$_2$] undergoes C−H insertion directed by the pyridine to form intermediate **118**. Complexation with the aziridine, followed by C−C bond formation, gives **119**. Finally, displacement by 2-phenylpyridine provides the cross-coupled product.

Mizoroki−Heck cross coupling with aziridines has also been achieved by the Oshima group (Scheme 54).[73] In the presence of a cobalt catalyst and trimethylsilylmethylmagnesium bromide, aziridines react with styrenes to afford a mixture of regioisomeric amines. A mechanistic discussion of this transformation is included in section 2.6.

3.6. Miscellaneous Isolated Organometallic Complexes from Aziridines

In studies performed by the Angelici group, metal carbonyl species have also been shown to react with N-H aziridines.[78] Specifically, in the presence of bromide mediators, metal carbene complexes are formed in a fashion similar to that with epoxides (section 2.7). However, being more nucleophilic than
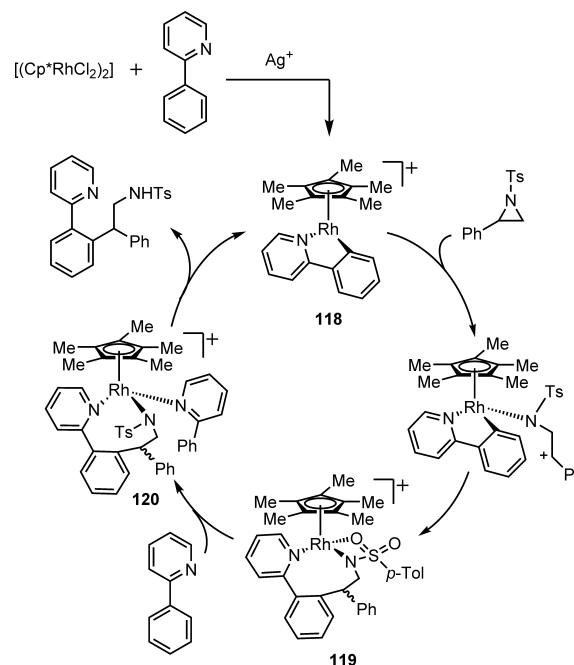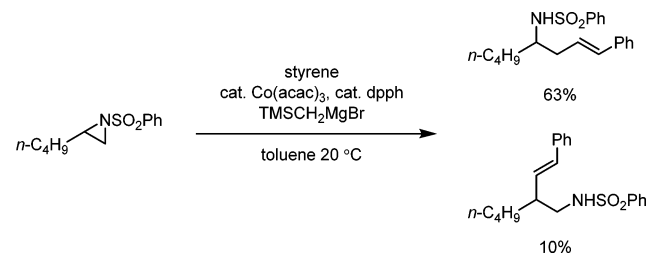
the oxygen of an epoxide, the nitrogen of the aziridine is proposed to react first with CO, generating adduct **121** (Scheme 55). Subsequent attack by bromide followed by ring closure affords the isolated complex. Reactions with metal thiocarbonyl complexes were also reported by the authors, and, through competition studies, were shown to be faster than the reactions promoted by metal carbonyls.

Michelin and co-workers later published a related process involving metal isocyanide complexes and N-H aziridines

Scheme 55. Preparation of Metal−Carbene Complexes from Metal Carbonyl Complexes and Aziridines
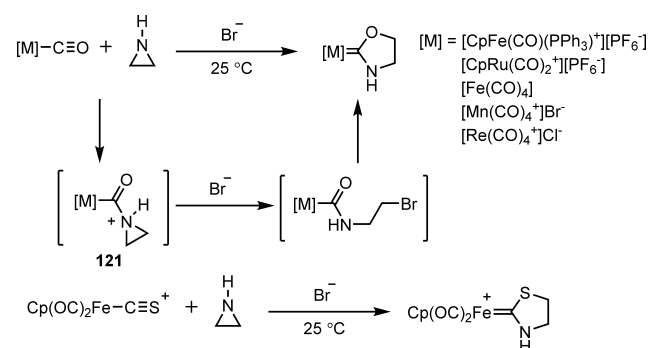
(Scheme 56).[78] A concerted mechanism for the cyclization process was proposed in this study.

Scheme 56. Preparation of Metal–Carbene Complexes from Metal Isocyanide Complexes and Aziridines
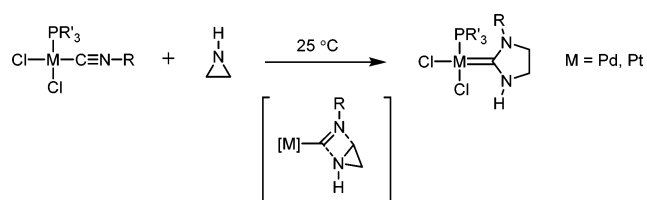
The Bergman group demonstrated the feasibility of nitrene transfer from aziridines utilizing low valent tantalum species **122** (Scheme 57a).[106] This process was shown by the authors

Scheme 57. Nitrene Transfer and Aziridines
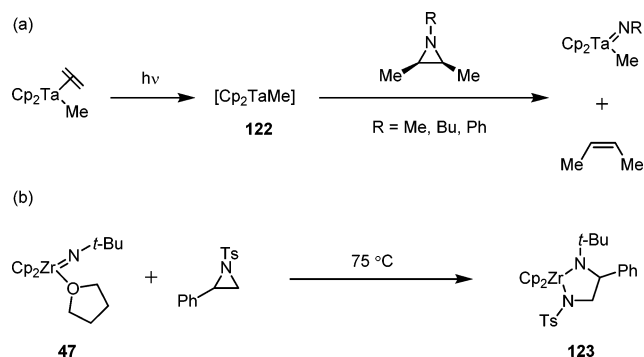
to be stereospecific in that *cis*-aziridines gave *cis*-olefins. Furthermore, the same group showed that the related zirconium nitrene complex **47** was capable of inserting into aziridines to form five-membered complex **123** (Scheme 57b).[79]

4. 2H-AZIRINES

The presence of an additional π-bond in 2*H*-azirines as compared to aziridines contributes to their higher strain energy and corresponding unique reactivity.[5a,107] Under thermal or photolytic conditions, azirines can form two intermediates: vinyl nitrenes **124** or nitrile ylides **125** (Scheme 58). Transition

Scheme 58. Reactivity of 2H-Azirines
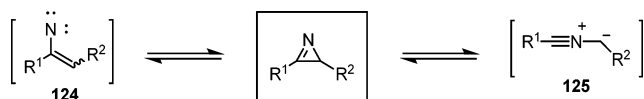
metal species have been shown to accelerate the generation of these intermediates, enabling a wide range of chemistry under milder conditions than possible in uncatalyzed processes. These reactions provide attractive platforms for the synthesis of larger ring nitrogen-containing heterocycles.

4.1. Isomerization and Related Reactions

Much of the early work on transition metal-induced isomerization of azirines centered on the use of metal carbonyl compounds. In 1975, Alper and co-workers reported that group 6 metal carbonyls $M(CO)_6$ (M = Cr, Mo, W) are capable of promoting dimerizations of azirines **126** to form a mixture of

pyrazine derivatives **127–129** (Scheme 59).[108] These dimerizations were proposed to go through a bis(2-azaallyl)metal

Scheme 59. Group 6 Metal Carbonyl-Mediated Dimerization of Azirines
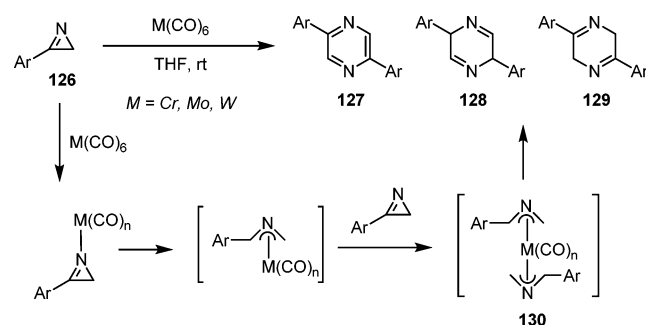
species **130**. As support for this proposal, a related bis(2-azaallyl)metal has been observed by Schuchardt and co-workers using $(PhCN)_2PdCl_2$ as the metal precursor, and the authors showed that the complex could be converted to a pyrazine.[109] Later, the Alper group described the use of substoichiometric $[CpFe(CO)_2]_2$ to promote the identical transformation.[110]

On the other hand, when an azirine possessing an sp²-hybridized C2 substituent is utilized as the substrate, intramolecular cycloaddition is observed instead of dimerization. As shown in Scheme 60, the Alper group found that aldehydes,

Scheme 60. Group 6 Metal Carbonyl-Mediated Intramolecular Cycloaddition of Azirines
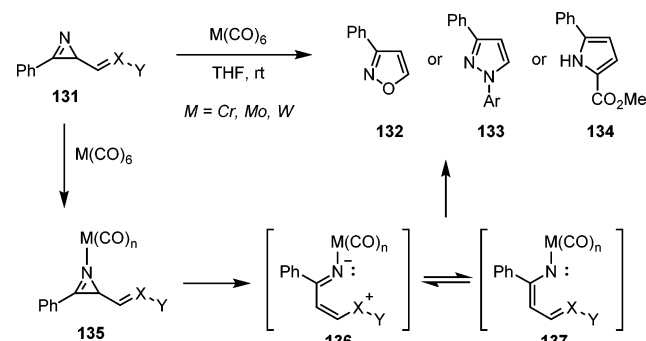
imines, and alkenes could serve as the C2 substituent to form five-membered ring heterocycles **132–134**.[111] A similar transformation was later achieved by the Padwa group with the use of the Grubbs first generation catalyst, $(PCy_3)_2Cl_2Ru=CHPh$.[112]

Curiously, when a similar reaction was attempted with trisubstituted azirines **138**, Bellamy, Nitta, and their co-workers found that, in addition to oxazepines **139**, pyrrole products **140–142** and pyridines **143** were generated (Scheme 61).[113] The formation of pyrroles **140–142** is in direct analogy to Alper's previous report, except that the presence of a benzoyl group induces a subsequent sigmatropic rearrangement, ultimately producing three different isomeric products **140–142**. On the other hand, oxazepine **139** may arise by a Claisen rearrangement from **138**. In the report by Nitta and co-workers, it was found that oxazepine **139** is formed in the absence of $Mo(CO)_6$, whereas the pyrrole and pyridine products **140–143** are only generated in the presence of the transition metal.

Scheme 61. Mo(CO)$_6$-Mediated Rearrangement of Trisubstituted-Azirine 138
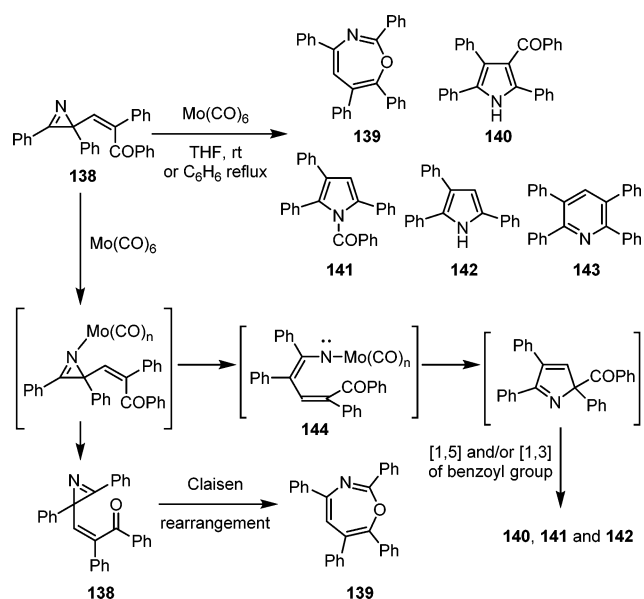
Interestingly, iron carbonyl complexes have been shown to display distinct reactivity from group 6 metal carbonyls. In studies by the Alper group and the Schmid group, pyrrole product **146** was isolated along with three other iron complexes **147**−**149** when azirine **145** was reacted with Fe$_2$(CO)$_9$ (Scheme 62).[114] The production of all of these compounds can be viewed as originating from a common iron-vinyl nitrene intermediate **150**.

Scheme 62. Reaction of Fe$_2$(CO)$_9$ and Azirine 145
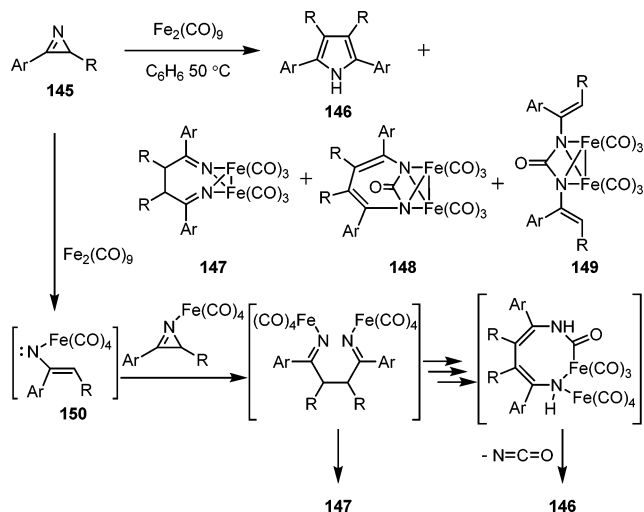
The intermediacy of an iron-vinyl nitrene complex **151** in these reactions is supported by work from the Nitta group (Scheme 63).[115] The authors showed that reactions of either an azirine or a vinyl azide with the Fe$_2$(CO)$_9$ in MeOH provided identical mixtures of carbamate and ketone products **152** and **153**.

Stoichiometric studies carried out by Green and co-workers revealed that the reaction of azirines and [CpMo(CO)$_2$]$_2$ produces a molybdenum allyl complex **155** (Scheme 64).[116]

Scheme 63. Reactions of Fe$_2$(CO)$_9$ with Vinyl Azide or Azirine
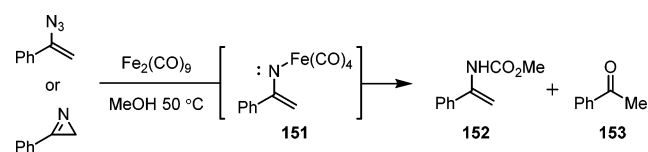
This complex undergoes a hydrogen shift to afford complex **156**.

Scheme 64. Stoichiometric Reactions of [CpMo(CO)$_2$]$_2$ with Azirine
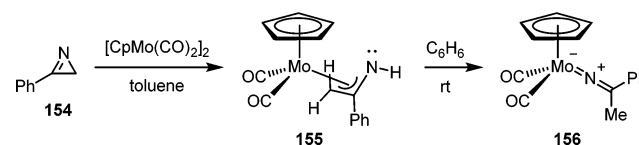
In addition, the research group of Curtis performed a series of stoichiometric experiments with azirines **157** and [CpW-(CO)$_2$]$_2$ or [Cp*Mo(CO)$_2$]$_2$ (Scheme 65).[117] Complexes **158** and **159** were obtained, which possess metal−nitrogen triple bonds.

Scheme 65. Stoichiometric Reactions of [CpM(CO)$_2$]$_2$ with Azirine
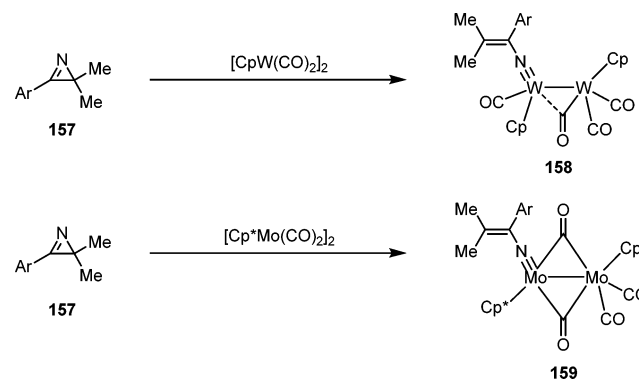
Other transition metal complexes have also been shown to promote the isomerization of azirines. For example, a report by the Alper group showed that aryl azirines **145** dimerize to form pyrazines **160** in the presence of AgClO$_4$ (Scheme 66).[118] The authors proposed that the silver salt serves as an oxidant in this reaction.

Scheme 66. Dimerizations of Azirines with AgClO$_4$
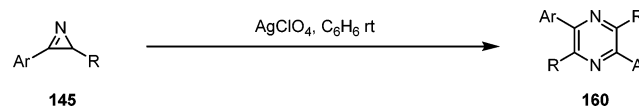
In 1982, Alper and co-workers reported an isomerization protocol of allyl azirines **161** under the influence of palladium catalysts (Scheme 67).[119] Two products, pyridine **162** and pyrrole **163**, were obtained in this reaction, and their formation was rationalized by the generation of a palladium allyl intermediate **164**. Interestingly, running the reaction under

Scheme 67. Pd-Catalyzed Isomerization of Allyl Azirines
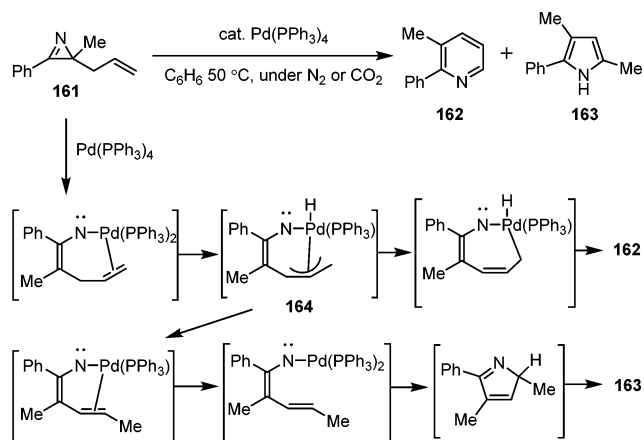
CO_2 atmosphere increases the yield and alters the product distribution.

When metal halides are used as promoters, the incorporation of halides into the products has been observed. For example, in 1975 Taniguchi and co-workers reported azirine isomerizations with $CuBr_2$ (Scheme 68).[120] In cyclohexane as solvent, azine

Scheme 68. CuBr₂-Promoted Isomerization of Azirines
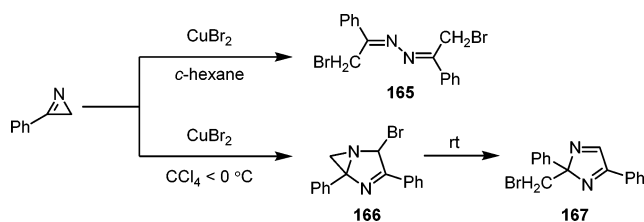
165 was isolated, whereas in CCl_4 at low temperature, a bicyclic compound **166** was obtained. When the reaction in CCl_4 was warmed to room temperature, **166** isomerized to a 2H-imidazole **167**.

As a second example, the Alper group reported the interaction of azirines **145** with $TiCl_4$ and found that α-chloroketones **168** are formed as the major product along with pyridazines **169** as a minor component of the reaction mixture (Scheme 69).[111] $TiCl_4$ likely serves as a Lewis acid to activate the azirine, which is then primed for attack by chloride ion. Hydrolysis of the imine would form the observed ketone **168**.

Auricchio and co-workers investigated the use of $FeCl_2$ instead of $TiCl_4$ and discovered that the major products were 2H-imidazoles **170**, pyridazines **171**, and pyrazines **172**

Scheme 69. TiCl₄-Promoted Isomerization of Azirines
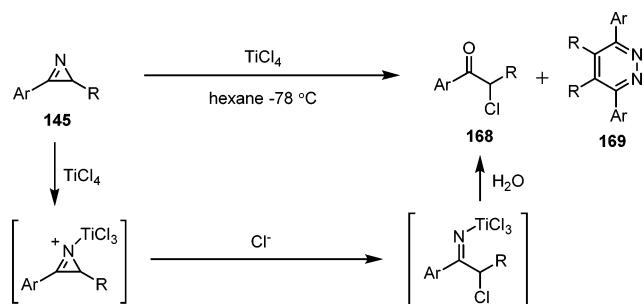
(Scheme 70).[121] The authors proposed a radical mechanism for the generation of these dimerized products.

Scheme 70. FeCl₂-Promoted Dimerization of Azirines
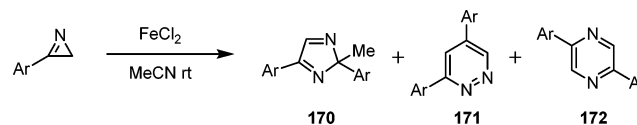
$FeCl_2$ has also been used in the isomerization of azirines to form pyrazolopyridine derivatives **173**, as shown in a patent by Fitzgerald and co-workers, and, later, a publication by Stevens and co-workers (Scheme 71).[122]

Scheme 71. Synthesis of Pyrazolopyridines from Azirines
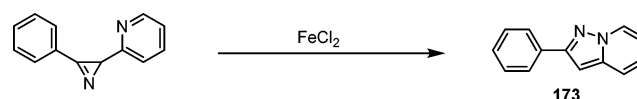
In 2012, the research group of Ohe reported a Ni-catalyzed reaction with 2,3-diarylazirines **174** to form 2-azabutadienes **175** and aryl nitriles **176** (Scheme 72).[123] The proposed

Scheme 72. Ni-Catalyzed Isomerization of Azirines
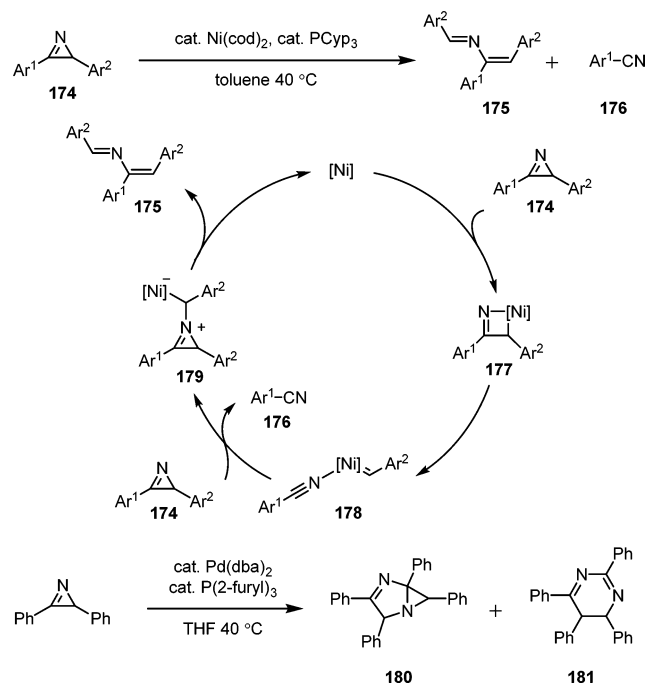
mechanism commences with oxidative addition of Ni(0) to the N−C2 single bond of **174** to give metallacycle **177**. Retrocycloaddition forms the complex **178** bearing a coordinated aryl nitrile group. Next, nucleophilic attack by another molecule of azirine on the nickel−-carbene species would provide intermediate **179**. Regeneration of Ni(0) can occur upon rearrangement of **179** to the desired product **175**. The results of a crossover experiment were consistent with this mechanism. By contrast, replacing the nickel catalyst with palladium generated the dimers **180** and **181**, presumably because the reaction proceeded via a vinyl nitrene intermediate.

When Wilkinson's catalyst, RhCl(PPh₃)₃, was used, the Padwa group showed that azirines can be converted into α,β-unsaturated oximes **182** (Scheme 73).[112] This process was proposed to go through the rhodium vinyl nitrene intermediate **183**.

Scheme 73. Rh-Catalyzed Conversion of Azirines to Oximes
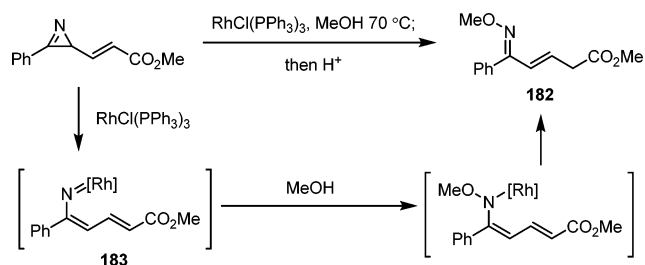
The isomerization of azirines has also been exploited as a synthetic tool to prepare indoles. Although such transformations can be accomplished at high temperature without the use of a catalyst, transition metal catalysis often enables the reactions to occur at milder conditions. Early work by the Alper group utilized Co₂(CO)₈ or [Rh(CO)₂Cl]₂ to dimerize phenyl azirine **154** in the formation of 2-alkenylindole **184** (Scheme 74).[124]

Scheme 74. Metal-Mediated Indole Formation from Azirines
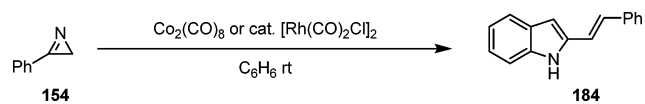
Later, Taniguchi and co-workers reported that PdCl₂(PhCN)₂ was effective in rearranging azirines to indoles without dimerization (Scheme 75).[125] The Narasaka group and the Zheng group expanded upon Taniguchi's protocol to achieve broader synthetic scope by using Rh₂(TFA)₄ and FeCl₂, respectively, as the catalysts.[126] The mechanism is thought to proceed through metal vinyl nitrene species **187** as shown in Scheme 75.
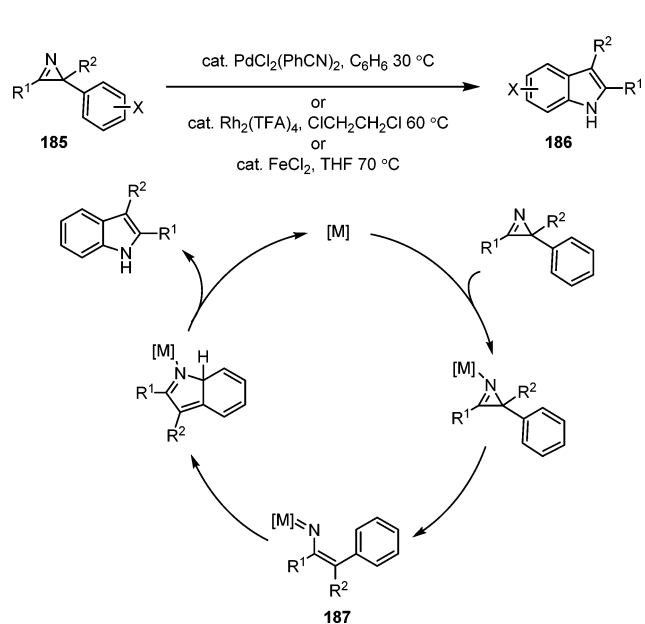
4.2. Carbonylations

In contrast to the chemistry of aziridines, metal-catalyzed carbonylations of azirines do not provide direct CO-inserted, four-membered ring products. Instead, rearrangement or dimerization often occurs in the process of CO incorporation. The Alper group reported an interesting product dependence on the metal and ligand used in these processes (Scheme 76).[127] When a stoichiometric amount of [Rh(CO)₂Cl]₂ or a

Scheme 76. Metal-Catalyzed Carbonylation of Azirines
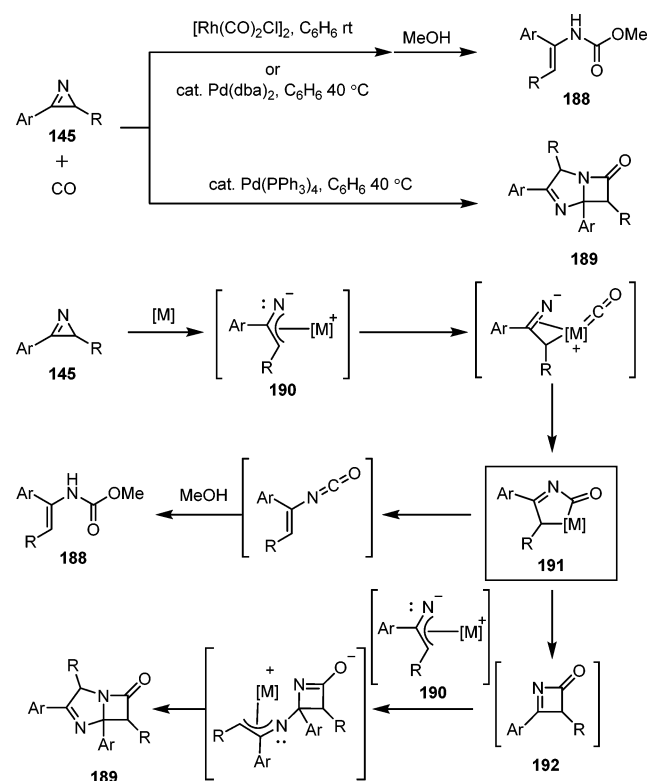
catalytic amount of Pd(dba)₂ is used in the reaction of aryl azirines and CO, vinyl isocyanates are generated, and upon methanolysis, carbamates **188** were obtained. On the other hand, when catalytic Pd(PPh₃)₄ is utilized, the products observed are the bicyclic compounds **189**. The authors proposed the following mechanism: Formation of the metal allyl complex **190**, followed by CO insertion, affords common intermediate **191**. Extrusion of the metal and subsequent reaction with MeOH gives the carbamates **188**. Alternatively, starting from the common intermediate **191**, reductive elimination affords the four-membered complex **192**, which is susceptible to nucleophilic attack by another molecule of metal allyl complex **190**. Ring closure of the resulting intermediate provides the isolated bicyclic compound **189**.

4.3. Cycloadditions

Intermolecular cycloaddition of π-systems with azirines represents another important class of reactions promoted by transition metal complexes. Heimgartner and co-workers showed that pyrroles **193** can be formed from azirines and alkynes under the influence of Mo(CO)₆ (Scheme 77).[128] A mechanism involving the formation of a azacyclobutene

Scheme 75. Metal-Catalyzed Indole Formation from Azirines

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intermediate **194** and subsequent rearrangement was postulated by the authors.

Scheme 77. Cycloaddition of Alkynes with Azirines
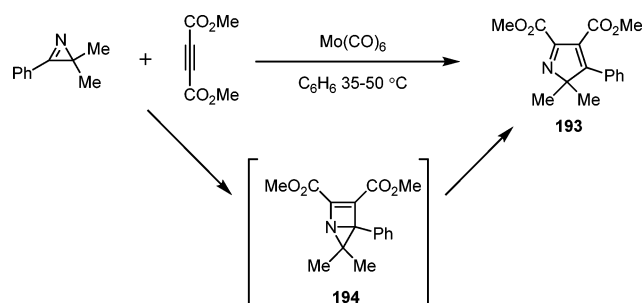
In 1995, Sheridan and co-workers reported a [6 + 3] cycloaddition between azirines and cycloheptatrienes coordinated with the $Cr(CO)_3$ group **195** under irradiation conditions in the formation of compounds **196** (Scheme 78).[129]

Scheme 78. [6 + 3] Cycloaddition of Azirines
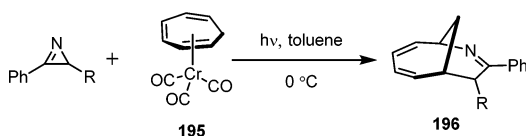
The use of metal chlorides as the promoters in cycloadditions with azirines was reported by Auricchio and co-workers in 2012 (Scheme 79).[130] When imines **197** were used

Scheme 79. Metal Chloride-Promoted Cycloaddition of Azirines
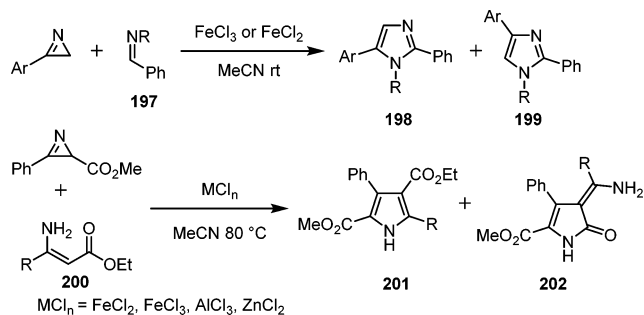
as the partners, two regioisomeric imidazoles **198** and **199** were obtained. The authors argued that $FeCl_2$ serves dual roles, as a Lewis acid and as a single-electron donor, leading to **198** and **199** through two distinct pathways. In the case wherein enamine species **200** are the cycloaddition partner, the metal chloride is thought to serve solely as a Lewis acid to promote the formation of **201** and **202**.

In 2013, Novikov, Khlebnikov, and co-workers reported a copper-catalyzed reaction of azirines with diazotetramic and diazotetronic acids that forms triazole derivatives **203** and **204** (Scheme 80).[131]

4.4. Hydrogenations

Hydrogenation of azirines with H_2 normally cleaves the C_{sp3}–N bond, rather than adding across the C–N double bond, as can

Scheme 80. Formation of Triazole Derivatives from Azirines
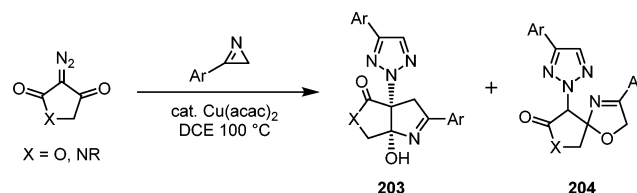
be seen in early examples by Cram, Harvey, and Rees (Scheme 81).[132]

Scheme 81. Hydrogenation of Azirines with H_2
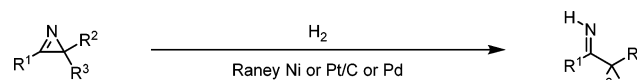
However, under transfer hydrogenation conditions with a Ru catalyst, Somfai and co-workers demonstrated that reduction of the C–N double bond occurs (Scheme 82).[133] Furthermore, in

Scheme 82. Enantioselective Transfer Hydrogenation of Azirines
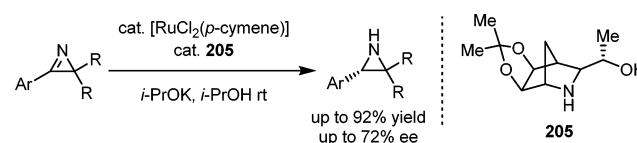
the presence of a chiral aminoalcohol ligand **205**, the method can be rendered enantioselective, serving as a valuable approach to the asymmetric synthesis of aziridines.

4.5. Reactions with Carbenoids

Another common reaction type in azirine chemistry involves their reaction with metal carbenoids. In 1973, Hassner and co-workers described the formation of *N*-vinylimines **206** from the reaction of dichloro carbenes and azirines (Scheme 83).[134]

Scheme 83. Early Examples of Reactions between Azirines and Metal Carbenoids
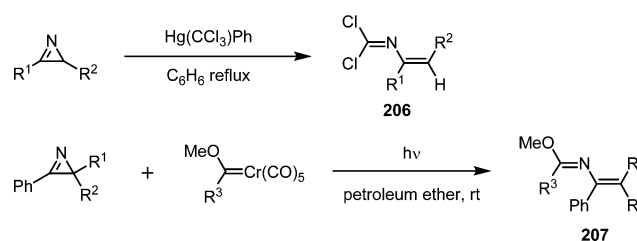
Another early report by the Hegedus group in 1985 revealed that when azirines are allowed to react with Fischer carbenes, a series of *N*-vinylimidates **207** can be obtained (Scheme 83).[135]

Subsequently, Khlebnikov, Novikov, and co-workers conducted a series of studies on the reaction of azirines with metal carbenoids generated from rhodium catalysts and diazo compounds (Scheme 84).[136] Depending on the structures of the azirines and the diazo compounds, distinct products were obtained. Mechanistically, it is believed that the azirines undergo nucleophilic attack on the rhodium carbenoids to afford a common zwitterionic intermediate **208**, which then rearranges to the *N*-vinylimine complex **209** (Scheme 85). At

Scheme 84. Reactions between Azirines and Metal Carbenoids

Scheme 85. General Mechanism of Reactions between Azirines and Metal Carbenoids
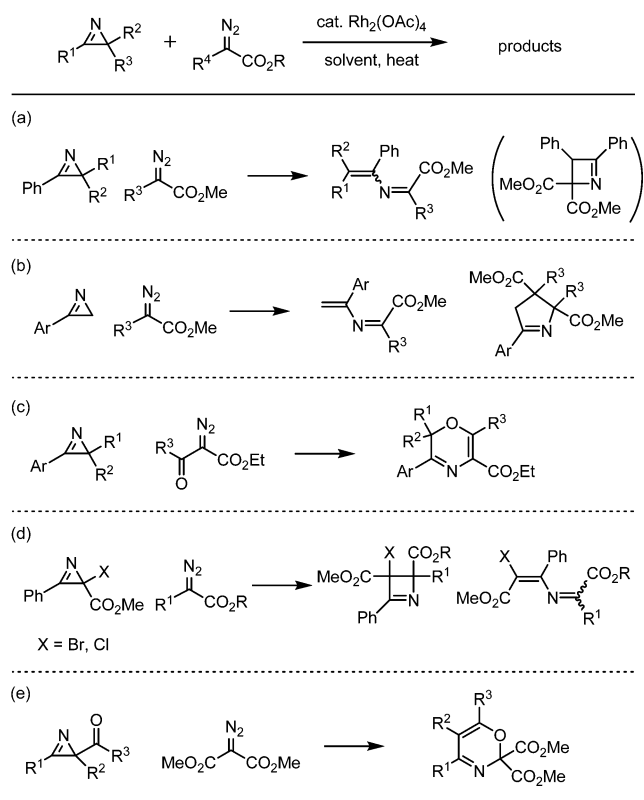
this stage, the proximal functional groups can engage complex **209** in further transformations to afford the variety of products illustrated in Scheme 84.
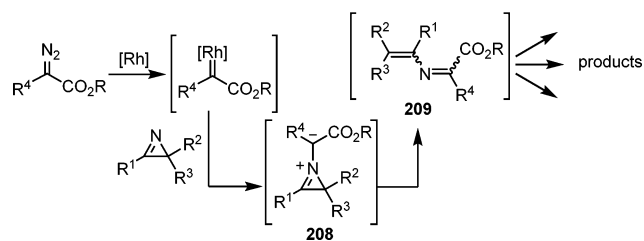
In 2013, Park and co-workers reported a method for the preparation of pyridine derivatives that harnesses the reactivity of azirines and metal carbenoids (Scheme 86).[137] With the use of Rh$_2$(esp)$_2$ as catalyst, 1,4-dihydropyridines **212** are formed initially, and a subsequent one-pot DDQ oxidation provides the pyridine products **213**. Although the scope is limited to substrates containing electron-withdrawing substituents at the 2-position, a wide range of functional groups are tolerated in this protocol. A mechanism similar to that in Scheme 85 was put forth to account for the transformation (Scheme 86). Generation of zwitterionic intermediate **210** occurs by nucleophilic attack of the azirines on the metal carbenoid. Rearrangement of this intermediate, followed by 6π-electro-cyclization, then forms the dihydropyridine **212**.

Okamoto, Ohe, and co-workers pursued azirine carbenoid reactions wherein the metal carbenoid is generated by an approach distinct from diazocarbonyl decomposition (Scheme

Scheme 86. Formation of Pyridines from Azirines and Diazo Compounds

94% yield   78% yield   71% yield
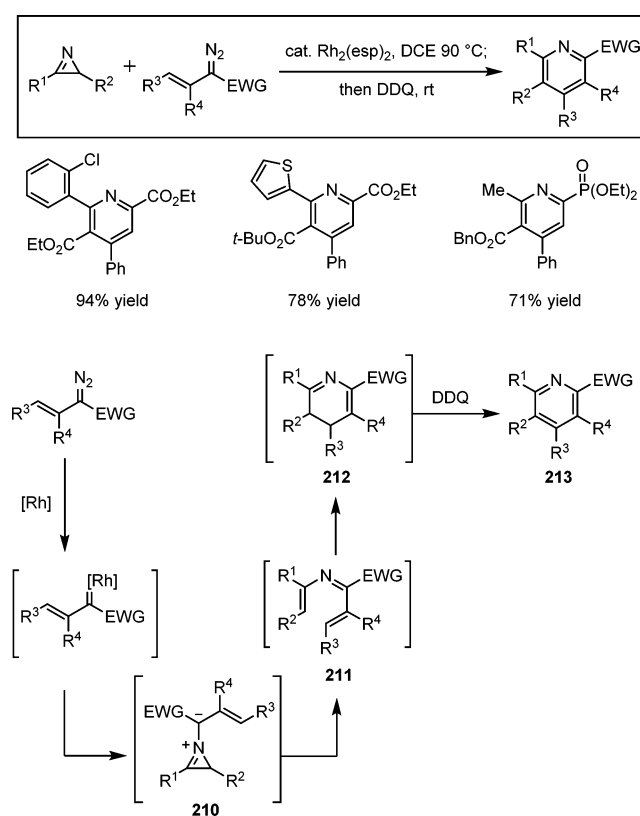
87).[138] Specifically, starting from carbonyl-ene-ynes **214**, the authors showed that Rh$_2$(OAc)$_4$ facilitates the formation of azadiene products **215**. The intermediacy of furylcarbene **216** was put forth to account for the mechanism.

Scheme 87. Generation of Furyl-Azadiene Compounds from Azirines
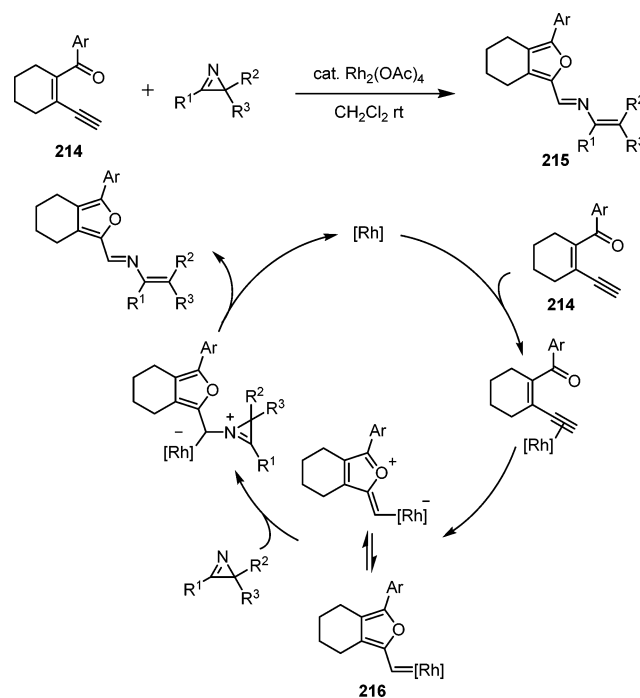
In 1992, the Curtis group conducted stoichiometirc studies involving the reaction of azirines and metal carbenoid complexes (Scheme 88).[117] In particular, Fischer-type tungsten

Scheme 88. Stoichiometric Reactions of Metal Carbenoids with Azirines
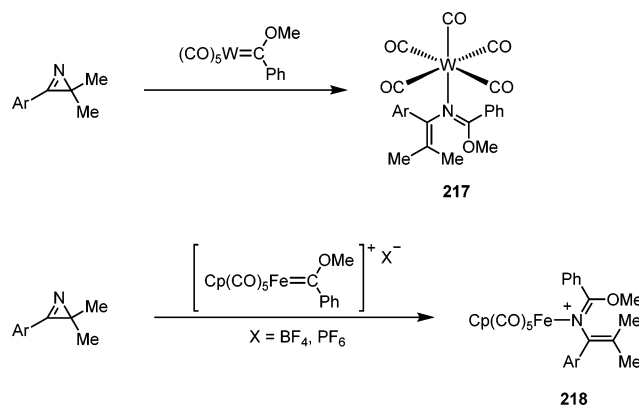
and iron carbenoids were utilized. Isolation of complexes **217** and **218** showed that azirines can undergo isomerization to azabutadienes in the presence of these reagents.

4.6. Reactions with Enolates

Azirines also react with enolates under the influence of transition metals. In 1977, Schuchardt and co-workers described the nickel-catalyzed preparation of pyrroles **219** from azirines and 1,3-diketones (Scheme 89).[139]

Scheme 89. Ni-Catalyzed Reactions between Azirines and Enolates
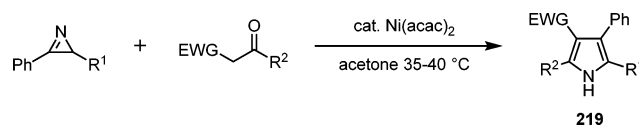
Later, the Alper group published a method with $Mo(CO)_6$ as the promoter, obtaining instead cyclic imides **220** (Scheme 90).[140] The mechanism is proposed to proceed by nucelophilic attack of the enolate on the C−N double bond of a Mo-coordinated azirine. Intramolecular acyl transfer would then provide the bicyclic intermediate **222**. Access to the imide products **220** from **222** would follow upon rearrangement and hydrolysis.

4.7. Miscellaneous Reactions

In 2010, the Lautens group successfully effected a palladium-catalyzed domino reaction with azirine substrates that involves norbornene mediated C−H bond activation (Scheme 91).[141] This methodology enables the synthesis of indoles **223** from aryl iodides and azirines. On the basis of their prior work, the authors proposed the following mechanism: Oxidative addition of Pd(0) to the aryl iodide followed by olefin insertion to norbornene sets the stage for the C−H activation event. Directed *ortho* C−H activation delivers intermediate **224**, which can then undergo insertion into the azirine to form eight-membered metallacycle **225**. β-Aryl elimination generates complex **226**, which then reductively eliminates to form indole **223** and return norbornene.

Scheme 90. Imide Formation from Azirines and Enolates
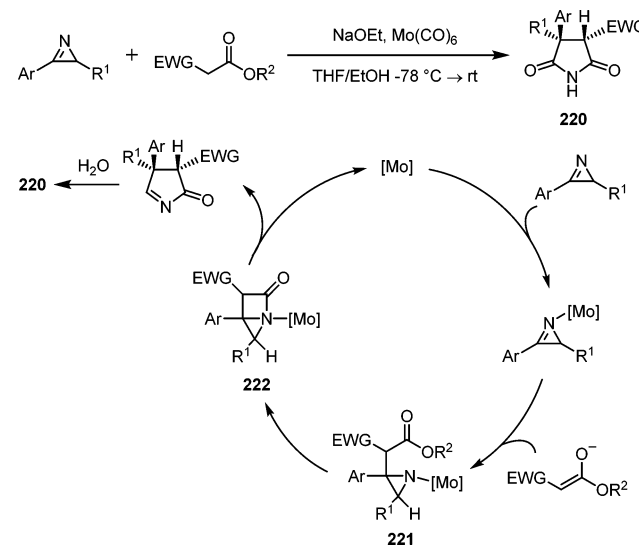
Scheme 91. Pd-Catalyzed Domino Reactions between Azirines and Aryl Iodides
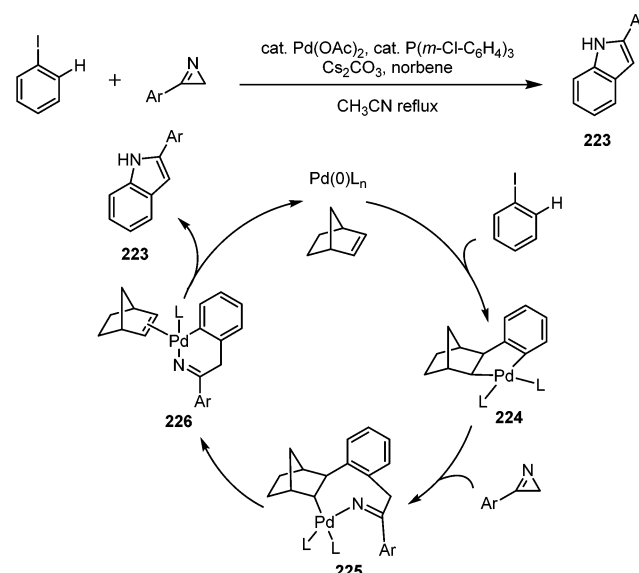
Tanaka and co-workers reported a Pt-catalyzed dehydrogenative double silylation reaction with an azirine to form the bissilyl enamine compound **227** (Scheme 92).[142]

5. DIAZIRIDINES[143]

Although the chemistry of diaziridines has not been studied as extensively as that of aziridines, examples documenting the interaction of diaziridines with transition metals and their application in catalysis have been reported.

Scheme 92. Pt-Catalyzed Dehydrogenative Double Silylation of Azirine
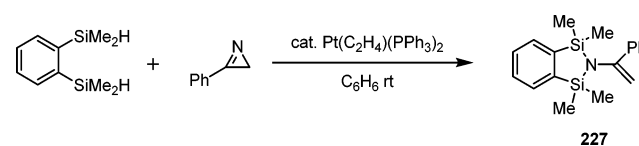
An early example by the Alper group showed that bisaroyl diaziridines **228** undergo isomerization in the presence of $Co_2(CO)_8$ (Scheme 93).[144] 4,5-Dihydro-oxadiazoles **229** are formed upon loss of benzoic acid.

Scheme 93. Co-Mediated Isomerization of Diaziridines
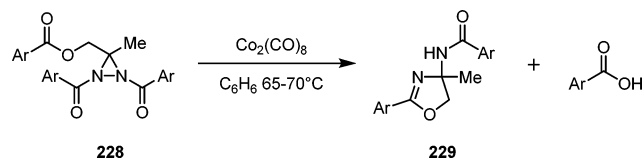
Reports by Beck and co-workers pointed instead to the possibility of effecting transition metal-catalyzed carbonylations of diaziridines with metal carbonyl complexes.[145] They showed that various carbonyl metal–hydride species react with diaziridines **230** to yield metal carbamoyl complexes **231**, in which CO insertion occurs adjacent to the less hindered nitrogen (Scheme 94). Complexes **231** are subject to further isomerization and ultimately afford imino metal compounds **232**.

Scheme 94. Formation of Metal Carbamoyl Complexes from Diaziridines
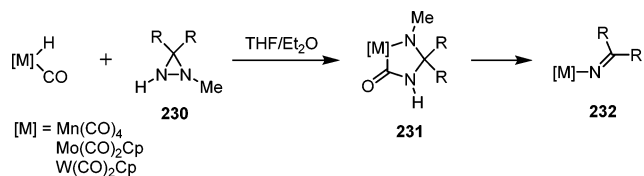
Alper and co-workers subsequently published a Pd-catalyzed diaziridine carbonylation method (Scheme 95).[146] Under the

Scheme 95. Pd-Catalyzed Carbonylation of Diaziridines
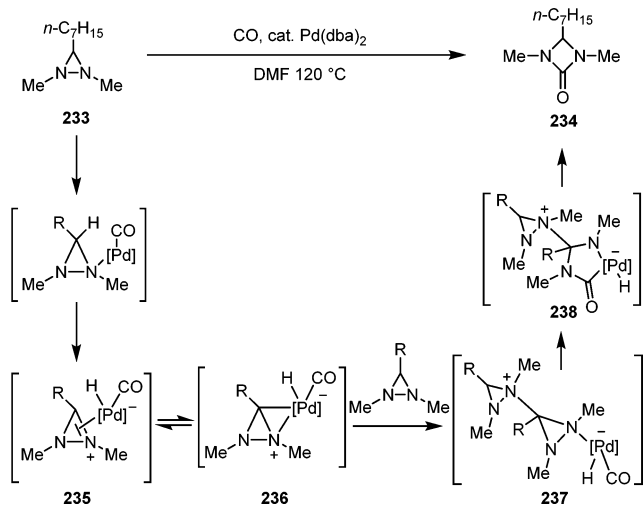
action of $Pd(dba)_2$ as catalyst, 3-monosubstituted diaziridine **233** is converted to 1,3-diazetidinone **234** by regioselective CO insertion into the N–N bond. The authors proposed that the mechanism begins by association of the diazridine to Pd, followed by β-hydride elimination to generate the equilibrating complexes **235** and **236**. Next, nucleophilic attack by another equivalent of diaziridine yields intermediate **237**, which can

rearrange to **238**. Reductive elimination provides the product **234**. This mechanism is consistent with the observation that 3,3-disubstituted diaziridines lacking an available β-hydrogen are inert under these conditions.

On the other hand, the Alper group has also shown that 3,3-disubstituted diaziridines are subject to carbonylation under cobalt catalysis (Scheme 96).[147] In particular, diaziridine **239**

Scheme 96. Co-Mediated Carbonylation of Diaziridines
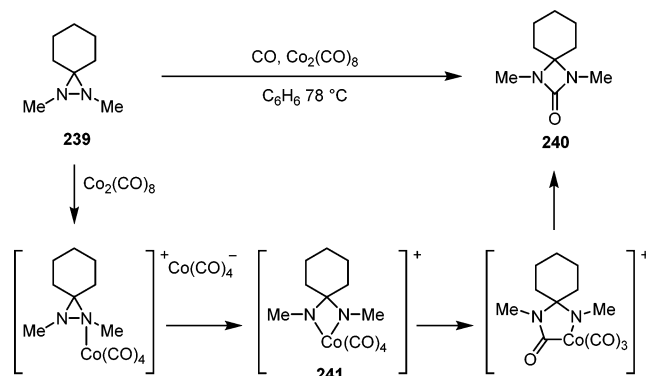
was converted into 1,3-diazetidinone **240** in the presence of $Co_2(CO)_8$. A different mechanism proceeding through metallacycle intermediate **241** was proposed for this system.

Later, Komatsu and co-workers reported an analogous reaction using $Ni(CO)_4$ or $Pd(PPh_3)_4$ (Scheme 97).[147] A

Scheme 97. Ni- and Pd-Mediated Carbonylation of Diaziridines
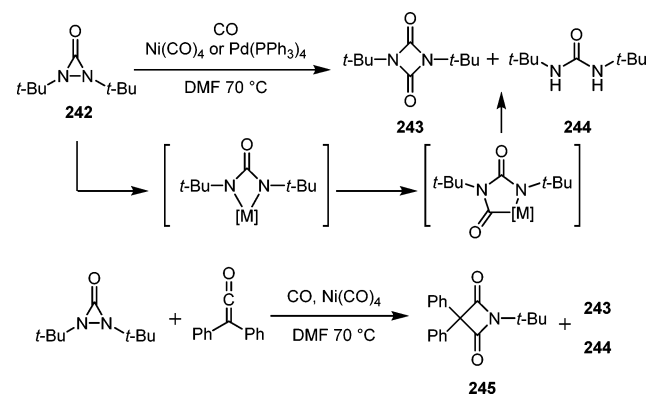
mechanism involving metallacyclic intermediates was also proposed. In this paper, the authors show that with the addition of ketene to the reaction, azetidinedione **245** can be obtained in addition to the carbonylative products **243** and **244**.

Starting in 2007, the Shi group published a series of reports describing metal-catalyzed diamination of olefins and related substrates utilizing diaziridinone **242**. Initial examples featured the use of Pd catalysts with conjugated dienes or trienes as substrates (Scheme 98).[148] Both phosphines and NHCs were effective supporting ligands for the palladium catalyst. Notably, diamination occurs in a regioselective and diastereoselective manner at the internal olefin to afford *trans* cyclic ureas **246**. Furthermore, with the use of chiral ligands such as **247**, this methodology was rendered enantioselective. Mechanistic studies carried out by the same group revealed that oxidative

Scheme 98. Pd-Catalyzed Diamination of Dienes

Scheme 99. Cu-Catalyzed Diamination of Dienes
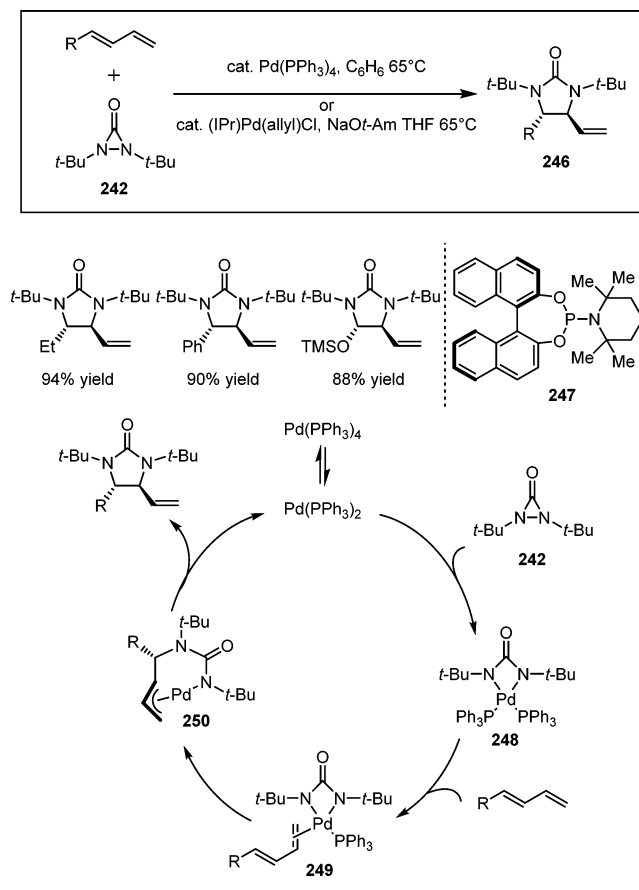
addition of a bis-ligated palladium species to the diaziridinone **242** is rate-determining, and the intermediate **248** has been detected. The rest of the catalytic cycle likely proceeds by coordination of the alkene followed by migratory insertion to form the allyl intermediate **250**, which then undergoes C−N bond reductive elimination to provide the observed products.

Later, the Shi group disclosed a Cu-catalyzed method that induces regioselective diamination of either the terminal or the internal olefin of a conjugated diene (Scheme 99).[149] With CuCl and phosphine ligands, terminal cyclic ureas **251** are formed, whereas with CuBr, internal cyclic ureas **246** are generated. A reaction with deuterium-labeled substrate **252** showed that isomerization occurs in the process of addition to the terminal olefin but not for diamination of the internal site. To account for this outcome, the authors proposed that internal addition proceeds through intermediate **254** as in the Pd-catalyzed protocol, but terminal addition involves a radical intermediate **253**. The intermediacy of this species was supported by spectroscopic experiments and substituent studies. Further mechanistic experiments suggested that cleavage of the N−N bond is rate determining.

The Shi group subsequently expanded the substrate scope to terminal olefins[150] and carbonyl substrates,[151] as well as probed the synthetic utility of the product heterocycles.[152]

A similar strategy was also applied to thiadiaziridine **255** to afford compounds **256** or **257** with selectivity that mirrors that obtained with diaziridine **242** and the corresponding copper catalysts (Scheme 100).[150e,153]
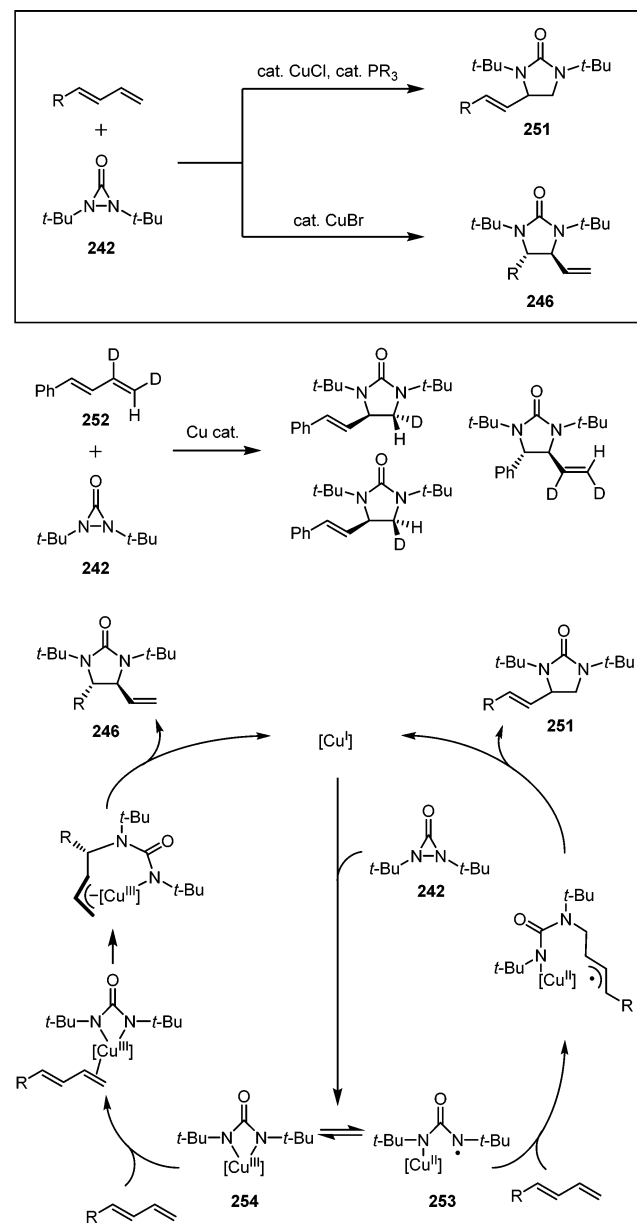
Scheme 100. Cu-Catalyzed Diamination of Dienes with Thiadiaziridine 255
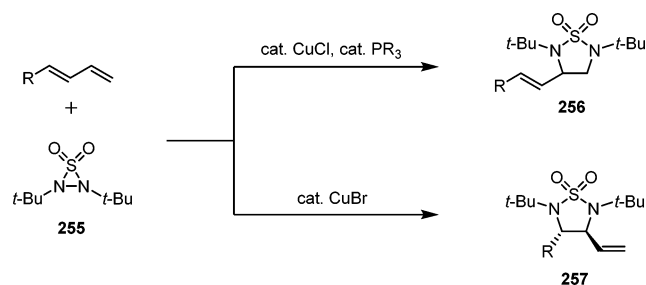
6. DIAZIRINES

Early reports by Beck, Danzer, Kisch, and co-workers studied the interaction between diazirines **258** and **259** and metal carbonyl compounds (Scheme 101).[154] When Cr, Mo, W, and Mn-carbonyl compounds were combined with diazirines, η^1- or

Scheme 101. Reactions of Diazirines with Metal Carbonyls
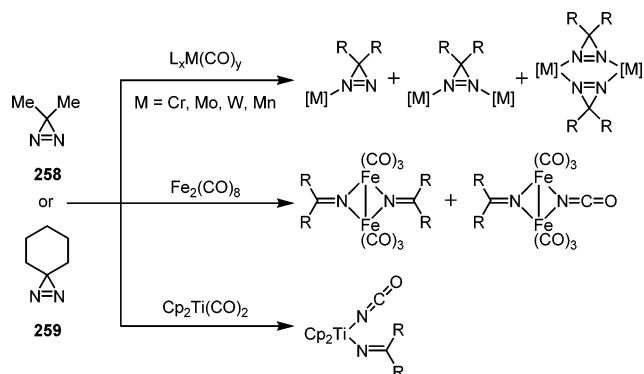
η^2-diazirine−metal complexes were obtained without ring cleavage. On the contrary, in the cases of Fe- and Ti-carbonyl compounds, diazirines underwent isomerization to afford metal-coordinated isocyanates and imines.

However, with the use of diazirine **260** bearing aryl and methoxy substituents, Chaloner and co-workers observed the formation of metal carbene complexes **261** from metal carbonyl compounds (Scheme 102).[155] The authors suggest that a free

Scheme 102. Reactions of Aryl Diazirine with Metal Carbonyls
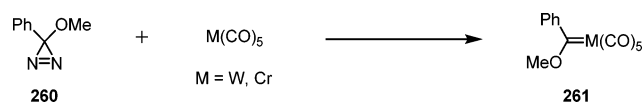
carbene intermediate is not involved because the metal-mediated reaction occurs at a temperature lower than that necessary for the uncatalyzed reaction.

Chaloner and co-workers further demonstrated that these diazirine-derived carbene-type intermediates undergo addition to metal−metal double bonds (Scheme 103).[156] Thus, the

Scheme 103. Reactions of Diazirines with Metal−Metal Double Bonds
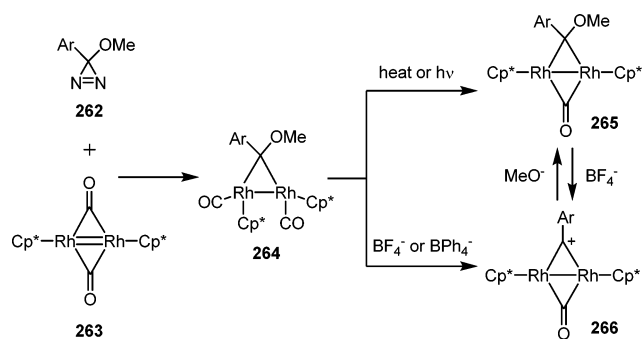
reaction of diazirine **262** with [Cp*Rh(CO)]₂ **263** affords complex **264**, in which the η-CO has isomerized to a terminal CO with conconcomitant formation of a three-membered ring metallacycle. Complex **264** is converted into the η-CO complex **265** with loss of 1 equiv of CO under heat or photolysis conditions. In addition, methoxide abstraction by a borate additive provides a cationic species **266**. The same research group carried out similar studies with [Cp*Co(CO)]₂.

In 1980, Vol'pin and co-workers prepared a Ru−diazirine complex **267**, and upon treatment with an oxidant under acidic

conditions, they observed the corresponding ketone as well as a ruthenium dinitrogen compound **268** (Scheme 104).[157] The fact that the diazirine substrate did not decompose to the ketone in the absence of ruthenium suggests that this process was mediated by the metal.

Scheme 104. Decomposition of Diazirines to Ketones
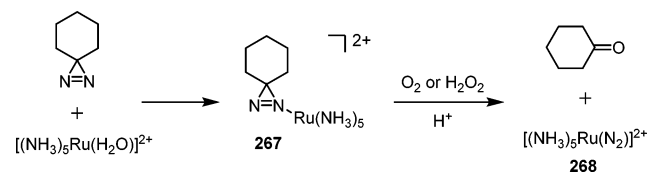
Later, Filho and co-workers treated diazirine **259** with (PhCN)₂PdCl₂ and in addition to observing the evolution of nitrogen, a cyclohexene-palladium dichloride dimer **269** was obtained (Scheme 105).[158] This dimer **269** was also found to

Scheme 105. Decomposition of Diazirines into Alkenes
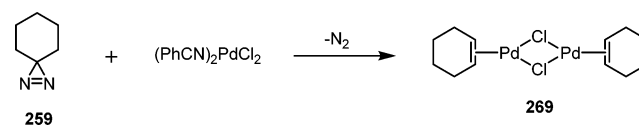
be catalytically active in decomposing the diazirine into cyclohexene. The authors proposed that loss of dinitrogen from the diazirine results in carbene-type intermediates, which then decompose into alkenes.

The first metal-catalyzed reaction with diazirines was reported in 2010 by the Wang group (Scheme 106).[159] They

Scheme 106. Pd-Catalyzed Cross Coupling of Diazirines and Aryl Halides
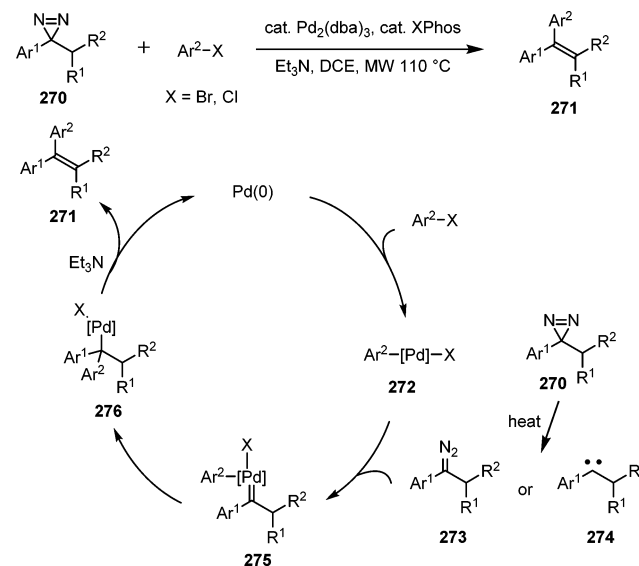
showed that in the presence of a palladium catalyst, aryl diazirines **270** can serve as nucleophilic cross-coupling partners with aryl halides to form olefin products **271**. The authors proposed that diazirines decompose under the reaction conditions into diazo compounds **273** or carbene species **274** and then combine with the oxidative adduct **272** to form intermediate **275**. Migratory insertion of the aryl group affords

complex **276**, which then undergoes elimination to give the olefin products.

7. OXAZIRIDINES

7.1. Isomerizations and Related Reactions

Oxaziridines have been widely utilized in organic synthesis for *O*- or *N*-atom transfer and other oxidative transformations. Because of their ring strain and relatively weak N−O bond, oxaziridines are subject to isomerization under thermal or photolytic conditions as well as in the presence of transition metal species. Normally, a low valent metal compound promotes the reductive ring cleavage of oxaziridines, and the resulting radical intermediate undergoes subsequent isomerization.

In a seminal paper by Emmons from 1957, oxaziridine **277** was shown to react with ferrous ions to form complex mixtures including formyl amides (Scheme 107).[160] The author proposed that an *O*-centered radical **278** was a common intermediate in this process.

Scheme 107. First Observation of Oxaziridine Isomerizations with Fe^{2+} Ions
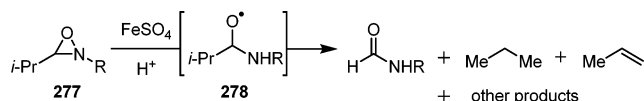
Many groups have since reported detailed investigations of the isomerization of oxaziridines and related processes with Fe as well as other transition metals. The research groups of Murawski, Dupin, Minisci, and Hawkins showed that in the presence of Fe^{2+} species, dimerization products of putative radical intermediates are generated (Scheme 108).[161] In the case of oxaziridine **279**, the radical intermediate undergoes ring cleavage before the formation of dimer **280**.

Scheme 108. Fe^{2+}-Promoted Isomerization/Dimerization of Oxaziridines
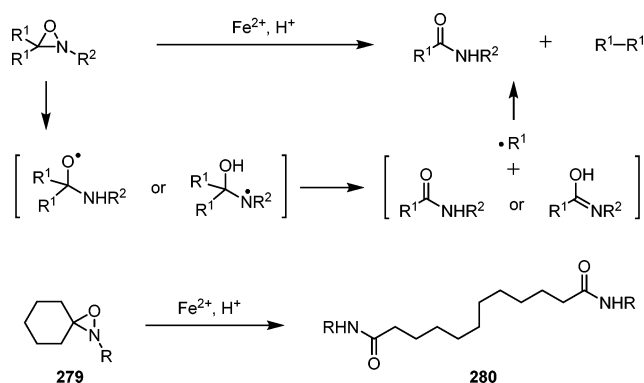
Black and co-workers later demonstrated that the product distribution of oxaziridine isomerization depends on the C3-substituent and its ability to stabilize radicals (Scheme 109).[162] The radical intermediate **282** decomposes by hydrogen atom elimination to form amide **283** if the R group radical is poorly stabilizing. Conversely, if the R group is capable of forming a relatively stable radical, then **282** decomposes to form formamide **284**. The same group also identified a similar system with pyrroline-derived oxaziridines **285** (Scheme 109b).

Scheme 109. Structure−Reactivity Relationship of Oxaziridine Isomerizations
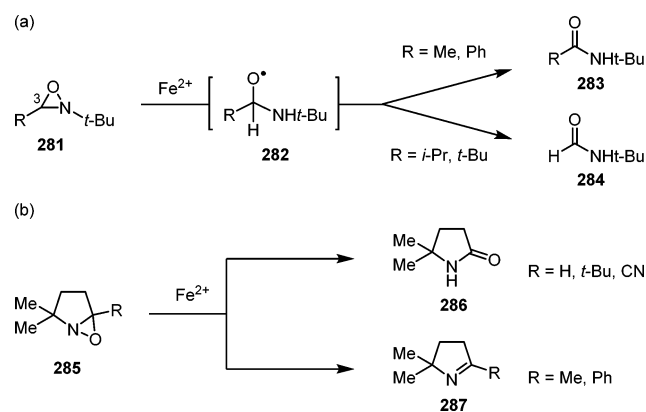
Either pyrrolidinones **286** or pyrrolines **287** were obtained depending on the structures of the oxaziridine substrate.

The research groups of Lorenz, Suda, and Crabtree investigated the use of other transition metals to catalyze the isomerization of oxaziridines into amides as an alternative to the Beckmann rearrangement (Scheme 110).[163] Mn(TPP)Cl (TPP = tetraphenylprophyrin) and VO(acac)$_2$ were found to be the most effective catalysts.

Scheme 110. Isomerization of Oxaziridines to Amides
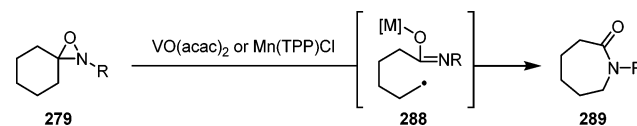
The Aubé group conducted a series of studies on the Cu(I)-catalyzed reduction of oxaziridines containing a pendant alkene (Scheme 111).[164] Curiously, depending on the diastereomeric configuration and the tether length of the substrate, either cyclization, aziridination, or allylic oxidation was observed. The authors rationalized these distinct outcomes by the difference in configuration of the radical intermediates as shown in the following scheme.

The Boer group described that both Ag$_2$O and PbO$_2$ are able to convert oxaziridine **279** into cyclohexanone (Scheme 112a).[165] A stoichiometric strudy was also presented by Beck and co-workers, who isolated complex **291** from oxaziridines and tungsten carbonyl compounds (Scheme 112b).[155] In addition, it has also been shown by Iskii and co-workers that oxaziridines can serve as oxidants, and, in combination with FeCl$_2$, promote polymerization of olefins.[166]

7.2. Oxyaminations

Utilizing sulfonyl oxaziridines **292**, the Yoon research group developed Cu- and Fe-catalyzed oxyaminations of olefins (Scheme 113).[167] Interestingly, the two catalytic systems display complementary regioselectivity: copper catalysts afford oxazolidines **293**, whereas iron yields the isomeric products **294**. With Cu(TFA)$_2$ or CuCl$_2$, both unactivated olefins and strenyl olefins are competent substrates. However, a halide additive is necessary to effect efficient conversion with the unactivated substrates. Notably, utilizing chiral bisoxazoline ligands, asymmetric oxyaminations were achieved with both iron and copper catalysts.

Scheme 111. Cu-Catalyzed Reductive Cleavage of Oxaziridines Containing an Appended Alkene
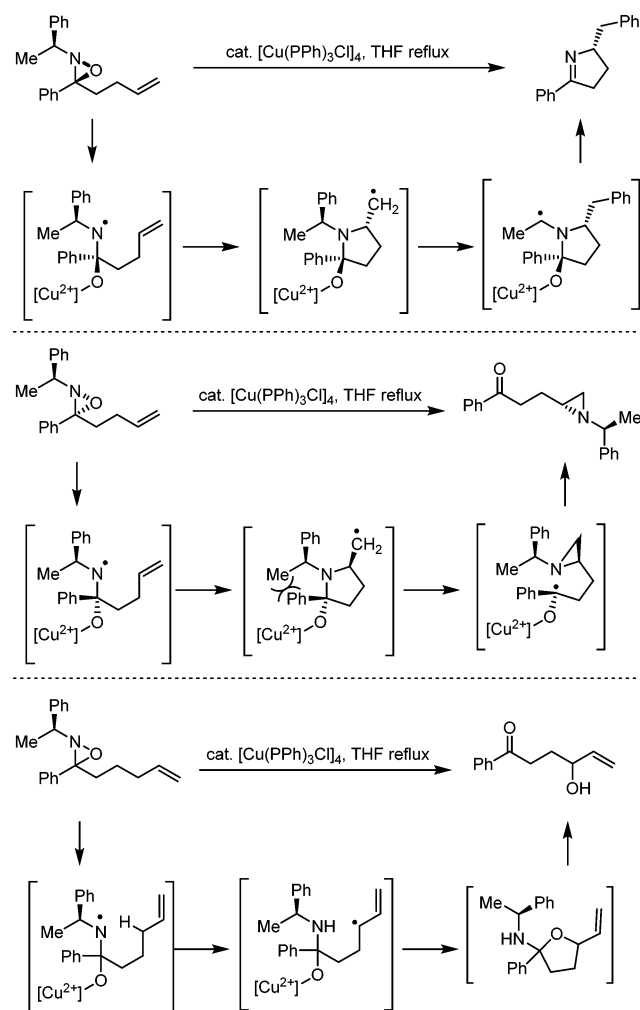
Scheme 112. Two Studies on Interactions between Metals and Oxaziridines
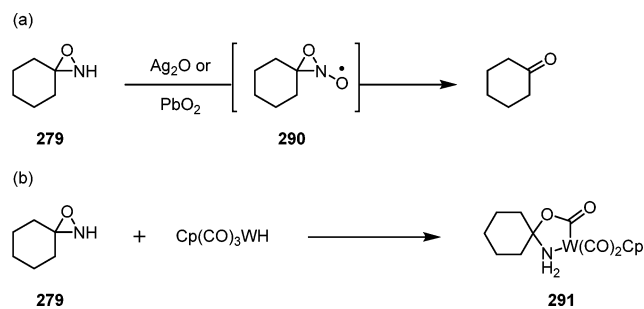
Initially, the authors proposed that the copper catalyst serves as a Lewis acid, promoting the formation of a carbocationic intermediate by coordination to the oxaziridine. However, the authors later revised this proposal as shown in Scheme 114 on the basis of radical clock and radical trap experiments.

In an exciting extension of this reactivity, the Yoon group identified that a copper catalyst also effects intramolecular C–H functionalization of oxaziridine (Scheme 115).[168] In the presence of CuCl$_2$ and LiCl, oxaziridine **298** undergoes C–N bond formation, and upon reduction, tetrahydroisoquinoline **300** is obtained.

Scheme 113. Cu- and Fe-Catalyzed Oxyamination of Olefins with Oxaziridines
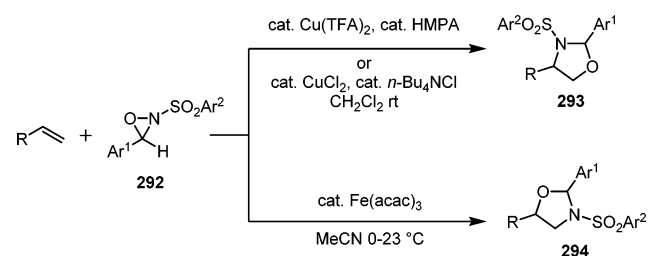
Scheme 114. Proposed Mechanism of Cu-Catalyzed Oxyaminations
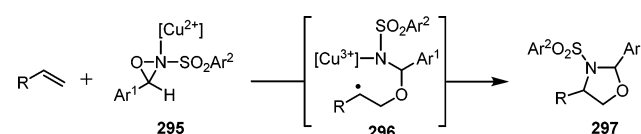
Scheme 115. Cu-Catalyzed Cyclizations through C–H Activation
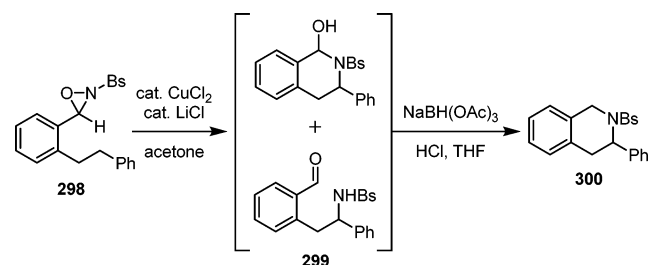
7.3. Miscellaneous Reactions

The Shi group utilized oxaziridine **301** and a Pd catalyst to effect C–H ethoxycarbonylation of 2-phenylpyridines and related compounds (Scheme 116).[169] The authors proposed a Pd(II/IV) mechanism featuring O–N bond insertion followed by CO$_2$Et group transfer.

8. THIIRANES

8.1. Desulfurizations and Sulfur Group Transfers

The most prevalent transformation of thiiranes mediated by transition metals is desulfurization and subsequent sulfur group transfer. This technique has been widely utilized to prepare sulfur-containing organometallic complexes (Scheme 117).[170]

In the 1960s, Hieber and Gruber, and King disclosed that treatment of cyclohexene sulfide **306** with Fe$_3$(CO)$_{12}$ resulted in the formation of a complex of molecular formula Fe$_3$(CO)$_9$S$_2$ (Scheme 118a).[171] The structure of **307** was proposed by King. Later, the Trost group noted that desulfurization with Fe$_2$(CO)$_9$ or Fe$_3$(CO)$_{12}$ proceeds in a stereoretentive manner, and the authors postulated an intermediate of structure **309** to account for the reaction outcome (Scheme 118b).[172] Schunn, Treichel, and Wilkes performed similar studies but using instead CpV(CO)$_4$ and [CpMo(CO)$_3$]$_2$ complexes.[173]

In later studies, Beck, Danzer, Höfer, and Thiel reported the desulfurization of propylene sulfides **310** with metal hydride complexes (Scheme 119).[174] First, the authors found that (CO)$_5$MnH could be converted into thiol **311** with the extrusion of propylene. Removal of CO provided manganese

Scheme 116. Pd-Catalyzed C–H Ethoxycarbonylation with Oxaziridines
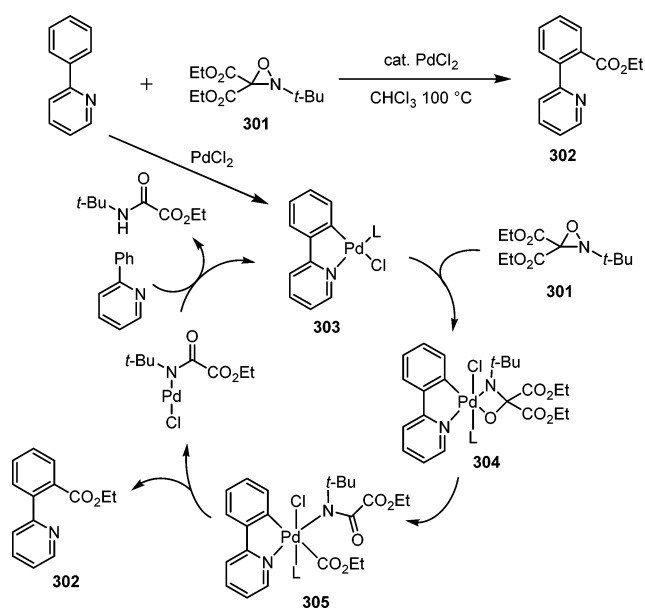
Scheme 117. Common Modes in Sulfurizations of Organometallic Complexes with Thiiranes
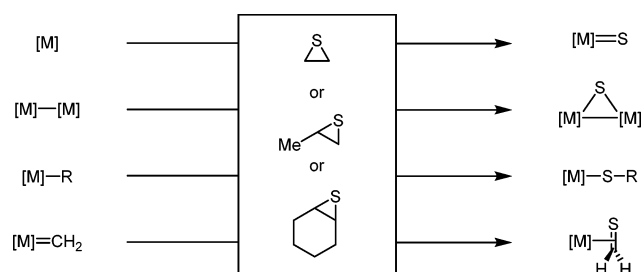
Scheme 118. Reaction of Thiirane 306 with Iron Carbonyls

Scheme 119. Reaction of Metal Hydride Compounds with Thiiranes
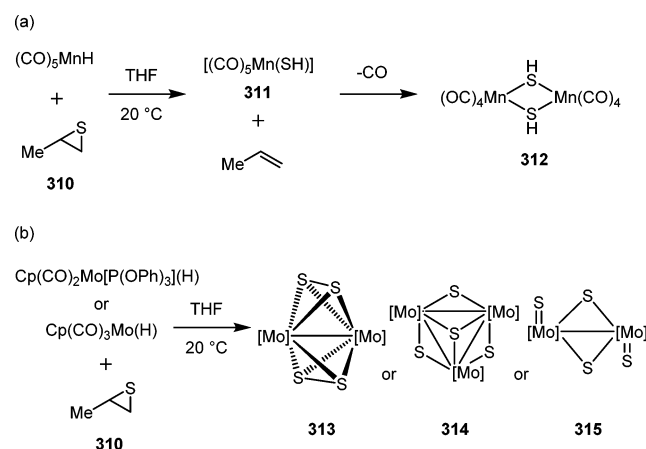
Scheme 120. Formations of Metal–Thioformaldehyde Complexes

complex **312** bridged with two thiol groups (Scheme 119a). They then reported that three possible complexes **313**–**315** are obtained when different stoichiometries of molybdenum hydride are reacted with propylene sulfide **310** (Scheme 119b). Related studies with metal hydride compounds, including $Cp(CO)_3W(H)$ and $(CO)_4Fe(H)_2$, were later published by the same group.[175]

In addition to these examples that result in the formation of metal complexes with bridging thiolate ligands, desulfurization reactions can also result in metal complexes bound by thioformaldehyde. Gladysz and co-workers reacted thiirane **306** with rhenium complex **316** and isolated the thioformaldehyde adduct **318** (Scheme 120a).[176] The Adams group observed that when osmium complex **319** was treated with

thiiranes **320** or **306**, two compounds **321** and **322** were obtained in which **321** possessed a metal–thioformaldehyde motif (Scheme 120b).[177] Additionally, Grubbs and co-workers reported the synthesis of titanium–thioformaldehyde complex **323**, and through a deuterium-labeling experiment determined that the process was not stereospecific (Scheme 120c).[178]

Furthermore, in the studies by Adams and co-workers, complex **325** featuring an ethylene dithiol ligand was isolated from the reaction between osmium compound **324** and thiirane **320** (Scheme 121).[179] The authors proposed that the formation of the ethylene dithiol motif originated from ring-opening between metal thiolate intermediate **326** and another molecule of thiirane.

The Bergman group has documented the preparation of sulfur-bridged heterobimetallic complexes (Scheme 122).[180] First, a W–S–Zr bridged complex **328** was obtained from the reaction of $Li[Cp(CO)_2W(PMe_3)]$ and Cp_2ZrCl_2 with propylene thiirane **310**; the authors proposed that ring-opened intermediate **327** is involved. Furthermore, the authors converted pregenerated Zr–Ir complex **329** into compound **331**, in which a new sulfur bridge is formed, in the presence of

Scheme 121. Formations of Metal−Ethylene Dithiol Complex
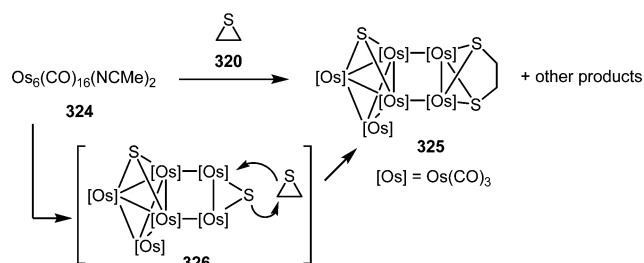
Scheme 122. Formations of Sulfur-Bridged Heterobimetallic Complexes
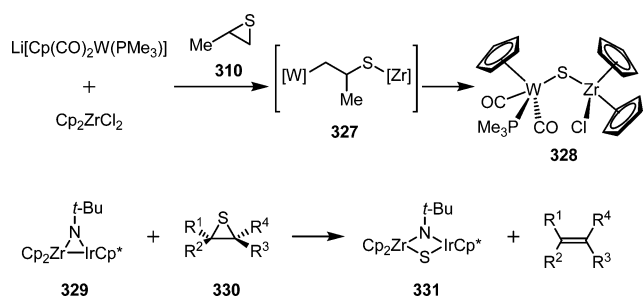
various thiiranes **330**. This desulfurization reaction was found to be stereospecific.

Another investigation of a heterobimetallic system was conducted by the Komiya group (Scheme 123).[181] Curiously,

Scheme 123. Stereochemical Course of Desulfurization with Heterobimetallic Complexes
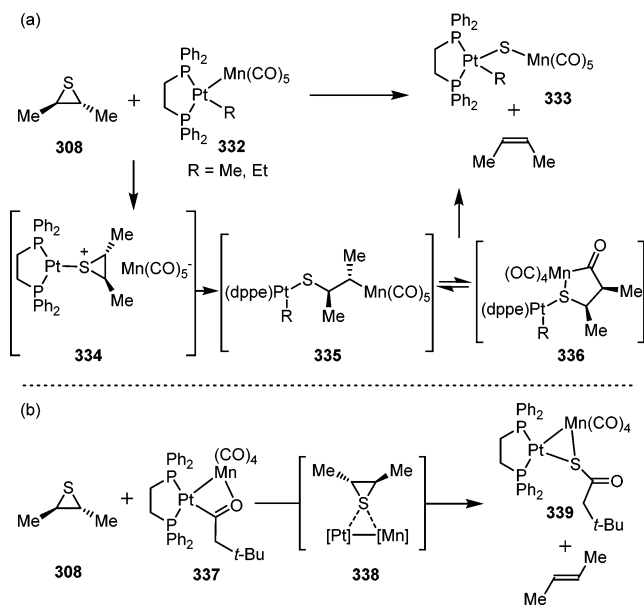
two different Pt−Mn complexes **332** and **337** were found to give opposite stereochemical outcome with the same *trans*-thiirane **308** starting material. When the complex **332**, in which the platinum bears a methyl or ethyl group, was utilized, the configuration of the *trans*-thiirane **308** was inverted and *cis*-2-butene was obtained (Scheme 123a). To account for this reaction outcome, the authors proposed an S_N2 mechanism involving dissociation of the metal−metal bond and coordina-

tion of the thiirane. Nucleophilic attack occurs with inversion to form intermediates **335** and **336**; the subsequent reductive elimination step is presumably stereoretentive. On the other hand, complex **337**, possessing a Mn-coordinated carbonyl group, facilitates the formation of *trans*-2-butene as the major product via the concerted loss of sulfur (Scheme 123b).

Furthermore, the Bergman group showed that stereospecific desulfurization can be achieved with tantalum complex **122** (Scheme 124).[106] Thus, thiiranes were converted selectively

Scheme 124. Formations of Tantalum Sulfido Complexes
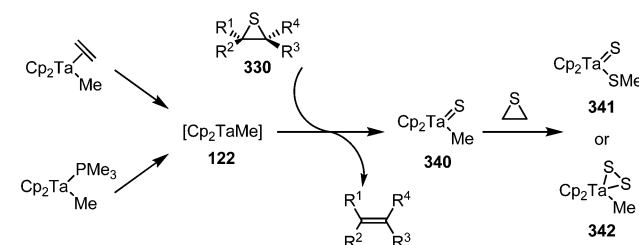
into alkenes with concomitant generation of tantalum sulfido complex **340**. Treatment of compound **340** with an additional equivalent of thiirane yielded complexes **341** or **342**. In view of the stereospecificity, the authors proposed a concerted mechanism for the sulfur abstraction step.

A report by the Dickson group showed that the desulfurization of thiiranes by a dirhodium complex **343** first proceeds through a coordinated intermediate **344**, which then slowly converts to the bridged sulfido complex **345** with CO migration (Scheme 125).[182]

Scheme 125. Desulfurization with Complex 343
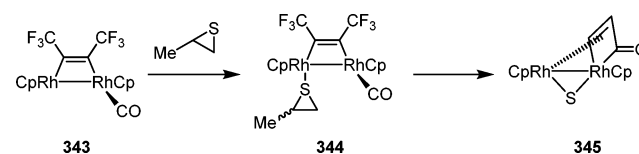
In the study by the DuBois group, the dimolybdenum complex **346** was found to efficiently desulfurize thiirane **320** with elimination of ethylene (Scheme 126).[183] The authors proposed a mechanism that commences with ligand displacement of Me_2S by the thiirane. Ring-opening by the neighboring sulfido group provides intermediate **349**, which then extrudes one molecule of ethylene. Attempts by the authors to independently prepare the complex **349** also led to the evolution of ethylene. The generation of bismetallic bridged sulfido and ethylene dithiol complexes with thiiranes has also been observed by the Lorenz group with $CpCo(CO)_2$.[184]

Chaudret and co-workers prepared a cationic ruthenium complex **350** and found that it promotes desulfurization as well as dehydrogenation of thiirane **306** (Scheme 127).[185] Complex **351** containing a benzene ligand was obtained, and the production of H_2S and H_2 gases was detected.

In 2002, the Groves group presented a Ru-based catalyst for thiirane desulfurizations (Scheme 128).[186] Interestingly, in addition to the common olefin products, 1,2,3-trithiolanes **353** and 1,2,3,4-tetrathianes **354** were also isolated in the reactions. A crossover experiment with the coordinated complex **355** showed that after the first equivalent of thiirane is consumed, additional thiirane equivalents only serve as sulfur atom donors.

Scheme 126. Desulfurization with Complex 346
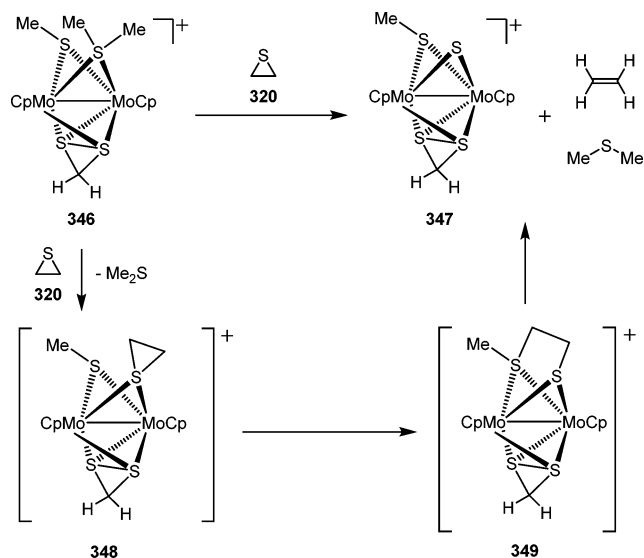
Scheme 127. Desulfurization with Cationic Ruthenium Complex 350

Scheme 128. Desulfurization and Formation of Trithiolanes and Tetrathianes

Scheme 129. Rh-Catalyzed Desulfurization of Thiiranes

Scheme 130. Re-Catalyzed Desulfurization of Thiiranes
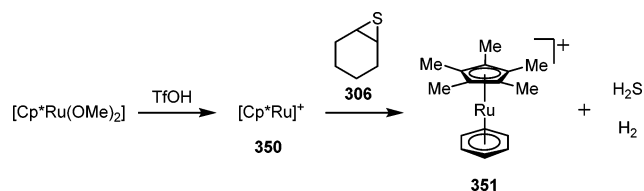
Furthermore, formation of the olefin products is stereo-retentive, whereas the trithiolanes and tetrathianes compounds are generated with inversion of stereochemistry. A mechanistic proposal is depicted in Scheme 128.

Catalytic desulfurization of thiiranes have also been reported. In 1986, the research group of Alper communicated a protocol using $[Rh(CO)_2Cl_2]_2$ as catalyst that converted thiiranes into alkenes in a stereoretentive manner (Scheme 129).[187] Running the reactions under an atmosphere of CO was found to improve the reaction efficiency. To explain this result, the authors proposed a mechanism involving oxidative addition of the thiirane to the rhodium catalyst and subsequent CO insertion to form intermediates **361** or **362**. Loss of OCS would provide the alkene products.

Systems relying on phosphorus(III) compounds as the sulfur acceptor have also been developed (Scheme 130).[188] Although sulfur transfer from thiiranes to phosphines can proceed without any catalyst, Arterburn and Espenson found that rhenium complexes induce significant rate accelerations. The Arterburn group found that a wide array of phosphorus(III) compounds, including phosphines, phosphites, and phosphor-amides, could be used as the sulfur atom acceptor. The protocol developed by the Espenson group features addition of H_2S, which is proposed to facilitiate generation of the active $MeO_3Re=S$ species.

Drawing upon knowledge gained in the development of these metal-catalyzed desulfurizations, research groups have recently discovered methods that allow sulfur-group transfer to other organic molecules. In 1998, the Simpkins group showed that $Rh_2(OAc)_4$ promotes episulfidation of norbornenes or norbornadienes, using propylene thiirane as the sulfur donor.[189]
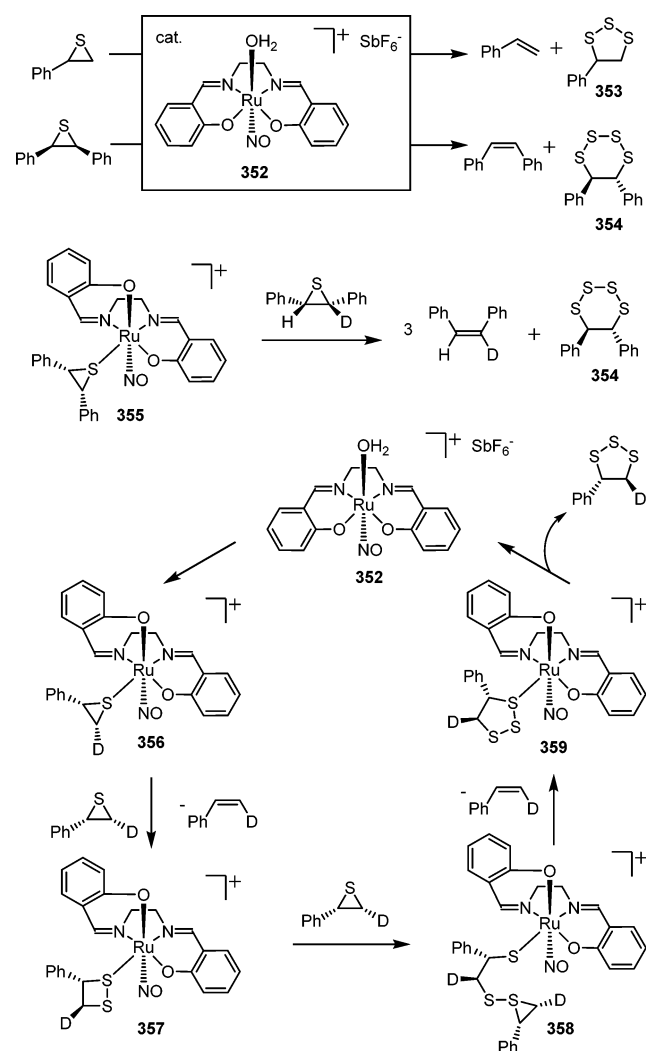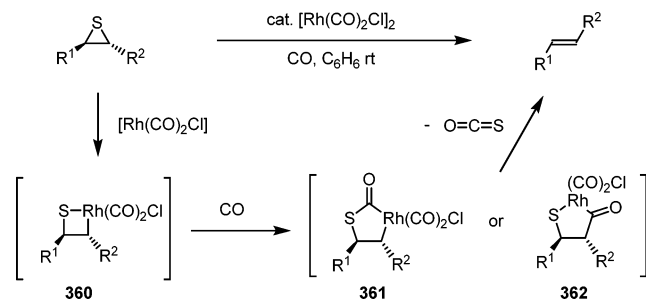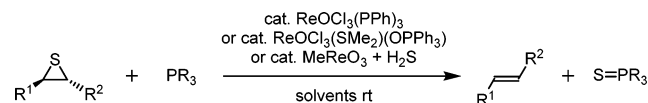
In 2003, Bargon and co-workers described a method with expanded scope that uses a molybdenum oxo catalyst (Scheme 131).[190] A collection of alkenes and allenes were suitable substrates in this methodology. Although catalyst **365** is most active, the authors conducted mechanistic studies with catalyst

Scheme 131. Mo-Catalyzed Episulfidation of Olefins with Thiiranes

63% yield   43% yield   58% yield   12% yield   52% yield
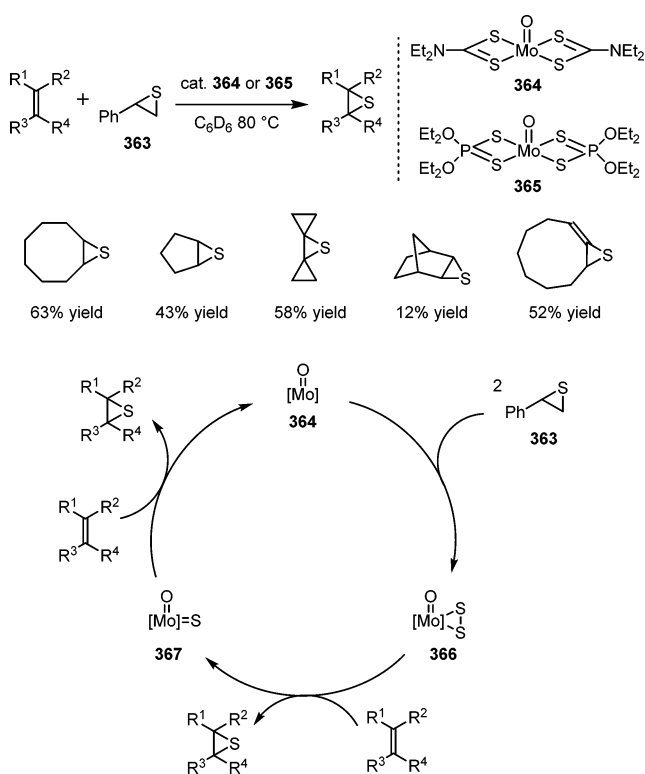
364, which enabled detection of various reaction intermediates by virtue of its attenuated catalytic activity. The authors hypothesized the following mechanism: 2 equiv of thiirane converts catalyst **364** into oxo-sulfido complex **366**, which then undergoes double episulfidation to regenerate the oxo-compound **364**.

Bargon and co-workers have also documented the sulfurization of isonitriles with thiiranes **310** utilizing molybdenum catalyst **364** (Scheme 132).[191]

Scheme 132. Mo-Catalyzed Sulfurization of Isonitriles with Thiiranes
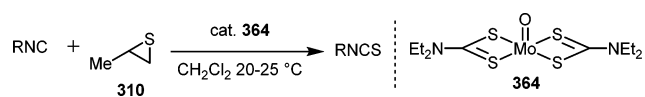
In 2010, Huy and co-workers reported an example describing the sulfurization of complex **368** with propylene thiirane **310** (Scheme 133).[192]

Examples of desulfurization of thiirane oxides and sulfur monoxide transfer have also been described in the literature. Reports by the groups of Lorenz and Schenk showed that the metal sulfur monoxide complexes **371**−**373** and **375** can be prepared via reactions with thiirane oxide **370** (Scheme 134).[193]

Scheme 133. Sulfurization of Complex 368
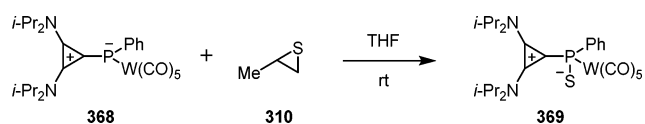
Scheme 134. Sulfur Monoxide Transfer
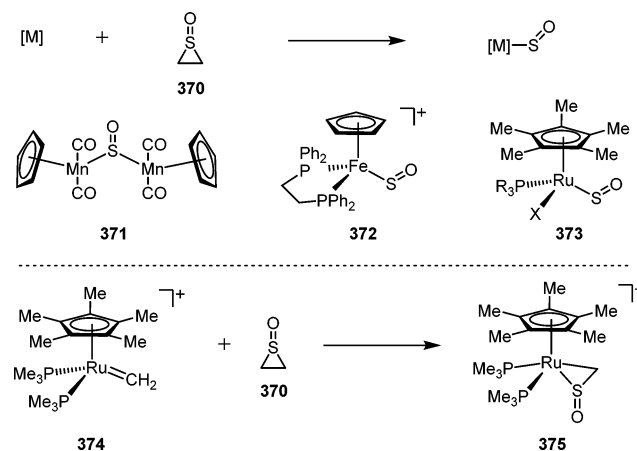
A system utilizing $Rh_2(OAc)_4$ as catalyst was reported by Simpkins and co-workers to be effective in sulfur monoxide transfer from thiirane oxide **376** to norbornene or nobornadiene; in these reactions, a diastereomeric mixture of products **377** and **378** was formed (Scheme 135).[190,194]

Scheme 135. Rh-Catalyzed Sulfur Monoxide Transfers
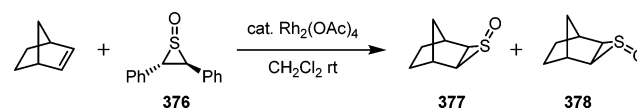
8.2. Cycloadditions

Whereas epoxides and aziridines readily form metal carbenes with a variety of transition metal carbonyl complexes as described in sections 2.7 and 3.6, the generation of metal carbenes from thiocarbonyl compounds and thiiranes has been limited to iron complex **379** (Scheme 136).[78a,b] The proposed mechanism is similar to that for epoxides and aziridines, in which the formation of adduct **381** precedes attack by bromide ion to afford the observed products.

Scheme 136. Cycloaddition of Thiiranes with an Iron Thiocarbonyl Compound
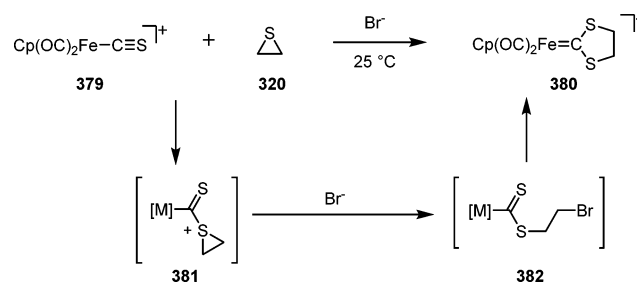
Later, the Michelin group reported examples of cycloadditions between thiiranes **320** and palladium isonitrile complexes **383** to provide the corresponding palladium carbenes **384** (Scheme 137).[78e]

The research group of Ando carried out a series of studies on allene thiiranes **385** (Scheme 138).[195] When this substrate class was treated with iron carbonyl compounds, (thioallyl)iron complexes **386** were isolated. Depending on the substitution pattern of the organic fragment, the complex **386** underwent

Scheme 137. Cycloaddition of Thiiranes with Palladium Isonitrile Compounds
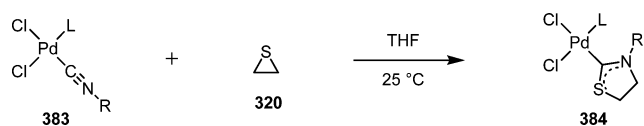
Scheme 138. Reactions with Allene Thiiranes
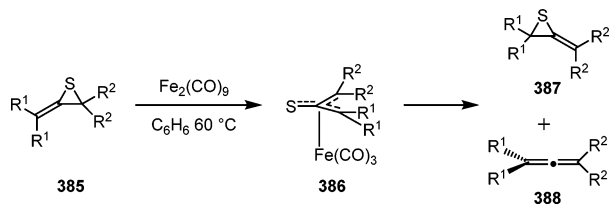
reaction to deliver either isomerized allene thiirane **387** or the desulfurized product allene **388**.

Later, the Ando group extended this chemistry to inter- and intramolecular cycloadditions of allene thiiranes with alkynes and alkenes (Scheme 139).[196] The Pd-catalyzed cycloaddition

Scheme 139. Cycloadditions with Allene Thiiranes
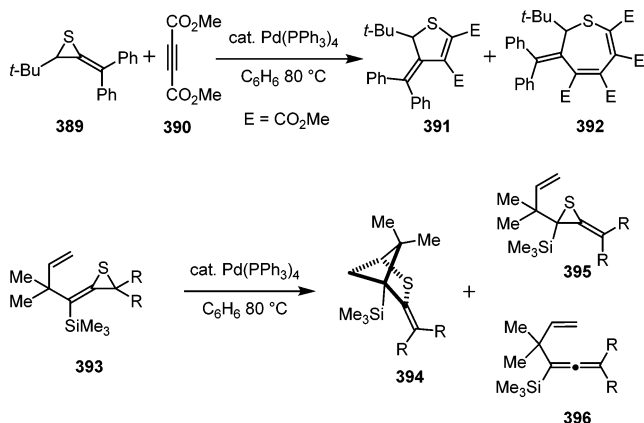
of alkynes **390** with thiiranes **389** afforded both the mono-adduct **391** and the bis-adduct **392**. Furthermore, under similar conditions, thiiranes **393** were cyclized to form **394**, although the isomerized products **395** and desulfurized product **396** were also formed.

In 2001, Alper and co-workers reported a Pd-catalyzed cycloaddition between vinyl thiiranes **397** and heterocumulenes **398** (Scheme 140).[197] Carbodiimides, isocyanates, ketenimines, and ketenes were all successfully utilized as coupling partners. Furthermore, in the presence of chiral bisphosphine ligands, the cycloadditions with carbodiimides could be rendered asymmetric with promising levels of enantioselectivity. These reactions are proposed to proceed by the addition of Pd(0) to the vinyl thiiranes, affording allyl species **400** or **401**. Addition of one of these intermediates to the heterocumulene reaction partner would then generate intermediate **402**, which can cyclize to afford the product.

8.3. Formations of Polydisulfides and Thiacrowns

The Adams research group discovered that thiiranes can be used in the synthesis of polydisulfides and thiacrowns.[198] In their first report from 1996 and in several subsequent publications, the researchers achieved the preparation of

Scheme 140. Cycloaddition of Vinyl Thiiranes with Heterocumulenes
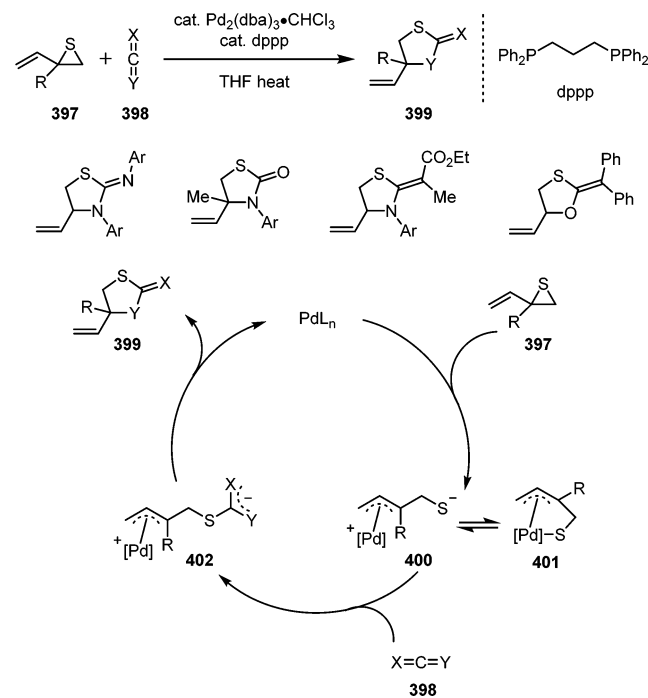
polydisulfides **403–406** using W(CO)$_5$(NCMe) as catalyst and ethylene thiirane **320** as substrate (Scheme 141).[199] The proposed mechanism, which consists of a series of nucleophilic additions by the thiirane followed by loss of ethylene to form the disulfide bonds in the products, is depicted in Scheme 141. The authors argued that the use of a tungsten catalyst

Scheme 141. Formation of Polydisulfides from Thiiranes

8185

dx.doi.org/10.1021/cr500036t | Chem. Rev. 2014, 114, 8153–8198
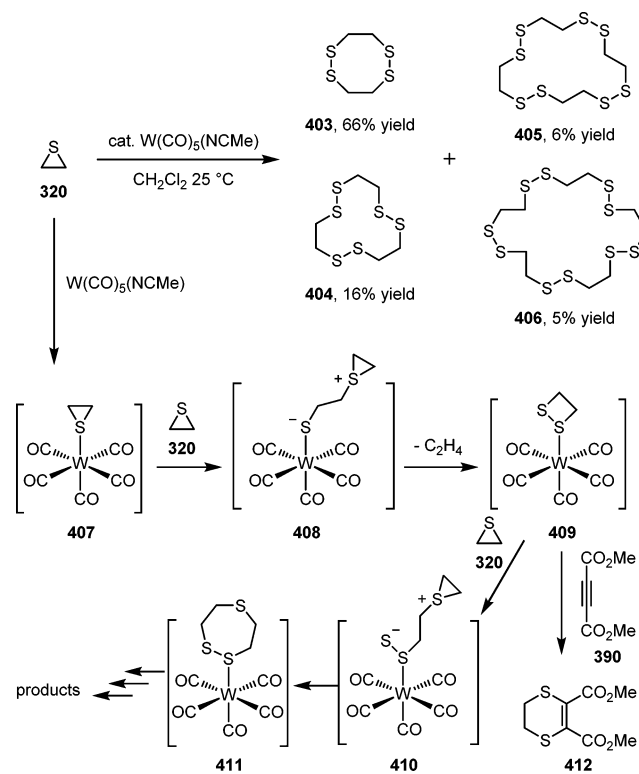
possessing a labile ligand, NCMe, was critical to forming the key thiirane-coordinated complex **407**. To support their proposal, complex **407** was isolated and shown to be an active catalyst in the protocol. Furthermore, the presence of intermediate **409** was postulated on the basis of the observation of product **412** when alkyne **390** was dosed into the reaction mixture.

When manganese complexes were used instead of tungsten, thiacrowns **413**–**415** were generated as the main products (Scheme 142).[200] In these reactions, polydisulfides **403**–**406**

Scheme 142. Formation of Thiacrowns from Thiiranes
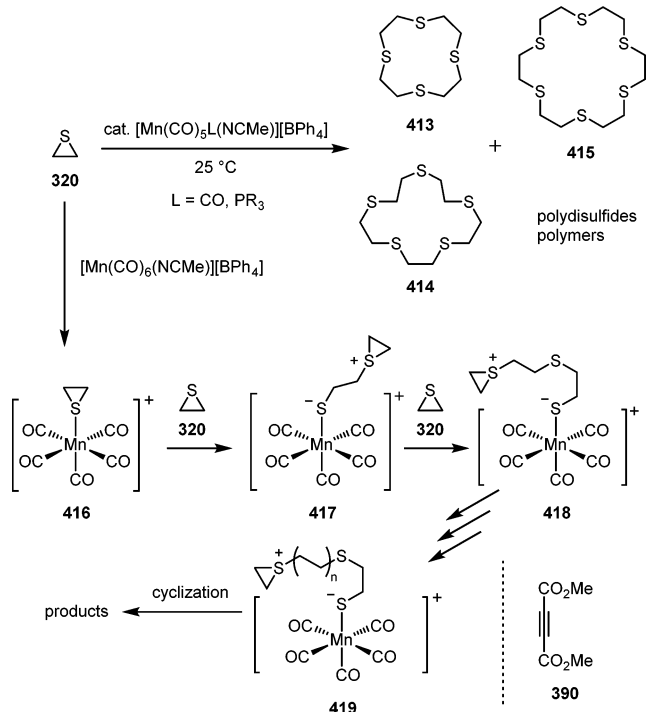
and polymer side products comprised the mass balance, and their ratio could be altered by changing the identity of the catalyst. Furthermore, addition of alkynes such as **390** to the reaction was found to suppress the formation of these polydisulfides and favor the generation of thiacrowns. The role of the alkyne is presumably to disfavor extrusion of ethylene from intermediates **417** and **418** by occupying a coordination site. This in turn would encourage chain lengthening by favoring addition of another equivalent of the thiirane monomer. Cyclization from species **419** would provide the thiacrown products.

When vinyl thiiranes **420** were used as substrates, Adams and co-workers found that dihydrodithiins **421** were isolated with loss of butadiene (Scheme 143).[201] The authors proposed the intermediacy of **424**, which can be generated either from the zwitterionic complex **423** followed by addition of vinyl thiirane **420** or by direct attack of the thiirane on complex **422**. The extrusion of butadiene would then give complex **425**. The Adams group initially favored path a, but a later report by the Taylor group[202] argued for path b (Scheme 143).

8.4. Miscellaneous Reactions

Transition metal-mediated chlorinations of thiiranes have been documented in the literature. In 1963, Arbuzov and Nuretdinova reported that in the presence of $HgCl_2$, thiiranes

Scheme 143. Formation of Dihydrodithiins with Thiiranes
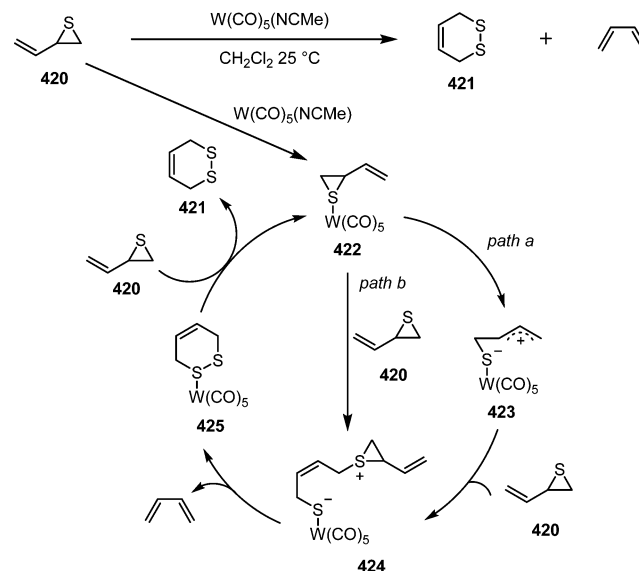
reacted with chloroalkyl ether **426** to afford a regioisomeric mixture of chlorinated products **427** and **428** (Scheme 144a).[203] DuBois and co-workers reported that when they reacted a rhenium chloride complex **429** with thiiranes, compound **430** containing a disulfide ligand was isolated (Scheme 144b).[204]

Scheme 144. Metal-Mediated Chlorination of Thiiranes

(a)

(b)
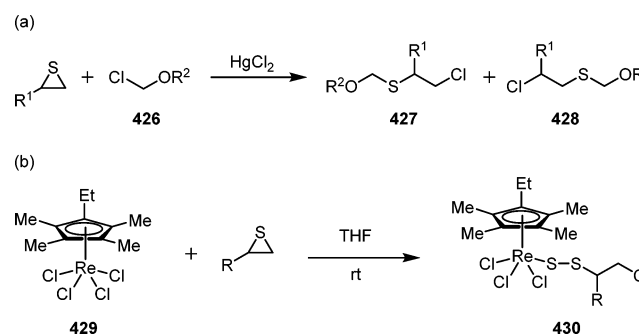
In 1973, Meneghini and co-workers showed that the addition of Ag^+ ion rendered the ammonolysis of thiiranes viable under mild conditions (Scheme 145).[205] The reactions with silver also

Scheme 145. Ag-Mediated Ammonolysis of Thiiranes
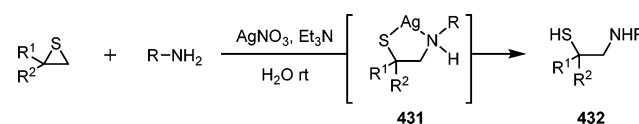
displayed complementary regioselectivity to the uncatalyzed process, with the terminal adducts **432** being formed exclusively. It was postulated that formation of complex **431**, in which silver is coordinated to both sulfur and nitrogen, plays a critical role in this chemistry. A similar proposal has also been put forward by Kuranova and Snetkova.[206] Consistent with the intermediacy of **431**, in their syntheses of taurines, Xu and co-workers utilized silver salts for the ammonolysis of thiiranes and found that polymerization was suppressed.[207]

The research group of Komiya published a study describing the alkoxymetalation of thiiranes with gold complexes **433** (Scheme 146).[208] Monosubstituted thiiranes **310** gave mixtures

Scheme 146. Au-Mediated Alkoxymetallation of Thiiranes
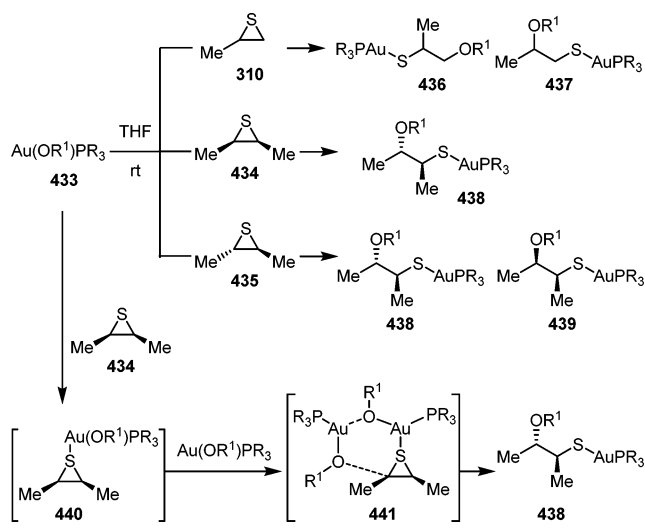
of regioisomeric products **436** and **437**. Whereas *cis*-disubstituted thiiranes **434** yielded a single diastereomeric product **438**, the *trans*-isomer **435** afforded a mixture of diastereomers **438** and **439**. To account for the observed second-order dependence of reaction rate on the concentration of gold, the authors proposed intermediate **441**, in which one gold species is coordinated to the thiirane and the other delivers the alkoxy group.

A rare example reported by the Bergman group showed that it is possible to isomerize thiiranes into allyl thiols.[79] Specifically, a stoichiometric reaction between the zirconium complex **47** and propylene thiirane **310** gave a zirconium compound **442** bearing the allylic thiol group (Scheme 147).

Scheme 147. Formation of a Zirconium Allylic Thiol Complex
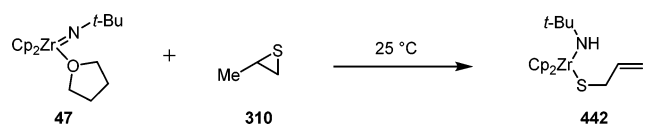
Furthermore, in the presence of metal hydride species, thiiranes can be reduced to the corresponding thiol compounds. Leblanc and co-workers found that when the tantalum trihydride complex **443** was heated with excess thiiranes, the sulfide−thiolate complex **444** was obtained (Scheme 148).[209]

In 2007, the Njardarson group developed a Cu-catalyzed isomerization of vinyl thiirane derivatives **445** for the

Scheme 148. Reduction of Thiiranes with Tantalum Trihydride Complex
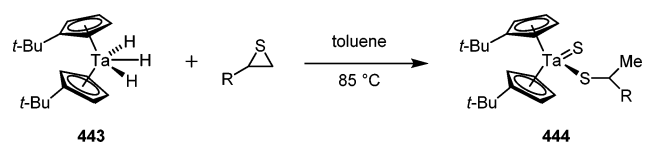
preparation of 2,5-dihydrothiophenes **446** (Scheme 149).[210] A variety of substitution patterns were shown to be compatible with this methodology.

Scheme 149. Cu-Catalyzed Isomerization of Vinyl Thiiranes
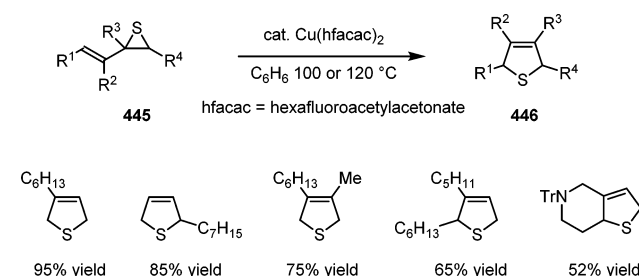
Alper and co-workers reported Co-catalyzed carbonylations of thiiranes under the influence of phase-transfer catalysis to afford β-mercapto acids **447** (Scheme 150).[211] The authors

Scheme 150. Co-Catalyzed Carbonylation of Thiiranes
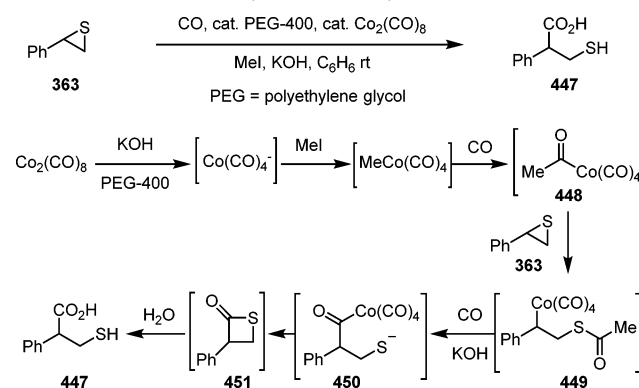
proposed that methyl iodide facilitates the generation of intermediate **448**, which undergoes nucleophilic ring-opening to form complex **449**. Ring closure from **450** gives β-thiolactone **451**, and, upon hydrolysis, affords the product **447**. The regioselectivity is such that insertion of CO at the benzylic position is favored.

The research group of Hillhouse published an example demonstrating oxidative addition of Ni(0) into thiiranes (Scheme 151).[212] In contrast to their analogous report with

Scheme 151. Oxidative Additions of Ni(0) into Thiiranes
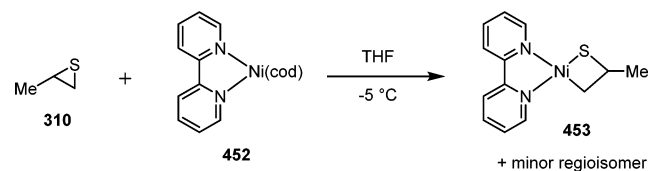
aziridines (section 3.5), a regioisomeric mixture of thiametalla-cyclobutanes **453** was obtained from monosubstituted thiirane **310**, where the major isomer originated from the addition at the unsubstituted end.

9. SILIRANES, SILIRENES, AND SILAAZIRIDINES

In the 1970s and 1980s, the research groups of Sakurai, Seyferth, and Ishikawa reported a series of Pd- and Ni-catalyzed reactions between silirenes **454** and alkynes (Scheme 152).[213]

Scheme 152. Pd- and Ni-Catalyzed Cycloaddition of Alkynes and Silirenes
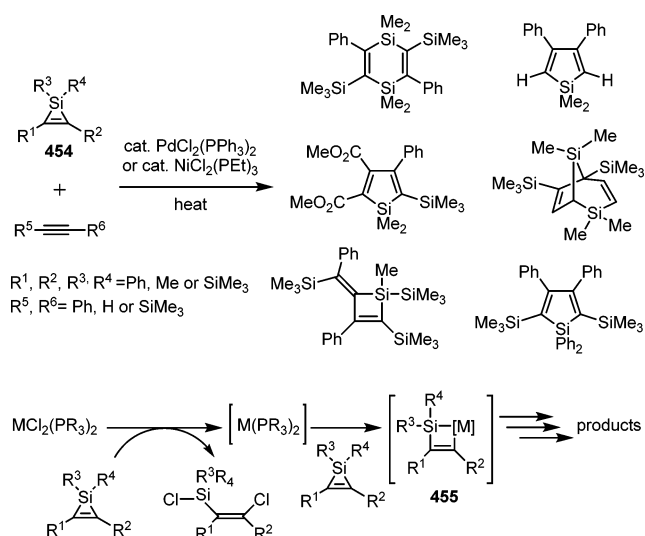
The reaction outcome showed a dramatic dependence on the substituents of both reactants. A wide variety of products are obtained, with some suggesting that silirene rearrangement has occurred in addition to alkyne insertion. Although detailed mechanistic studies have not been completed, the authors proposed that reduction of Pd(II) or Ni(II) to M(0) by the silirene initiates the chemistry. The low valent metal species then undergo oxidative addition into the silirene to form four-membered metallacycles **455**, which serve as common intermediates in the subsequent transformations.

Support for the intermediacy of these metallacycles has been obtained by Ishikawa and co-workers (Scheme 153).[214] When

Scheme 153. Isolation and Reactions of Nickellacycle 457
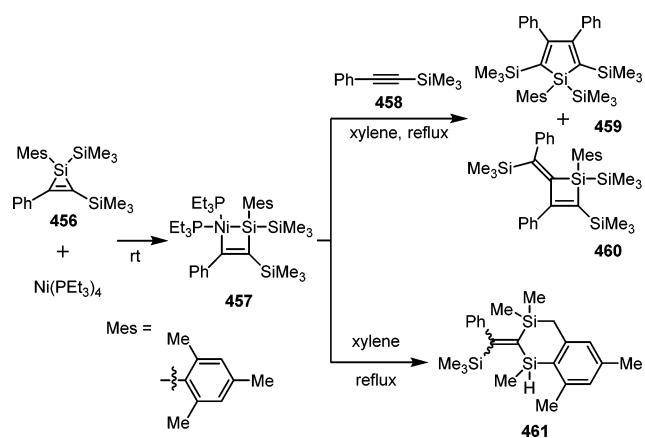
silirene **456** was combined with Ni(PEt₃)₄ at room temperature, the four-membered nickellacycle **457** was obtained. Furthermore, heating **457** in the presence of 1-phenyl-2-trimethylsilylacetylene **458** yielded two cycloadducts **459** and **460**. Instead, if **457** is heated in the absence of the alkyne, it undergoes isomerization to **461**.

In 1988, the Ando group reported palladium-catalyzed cycloadditions of alkylidenesilacyclopropanes **462** and alkynes or alkenes (Scheme 154a).[215] The authors discovered that two different palladium catalysts induced complementary regioselectivity in the alkyne insertion, affording isomeric cycloadducts

Scheme 154. Pd- and Ni-Catalyzed Cycloaddition of Alkylidenesilacyclopropanes
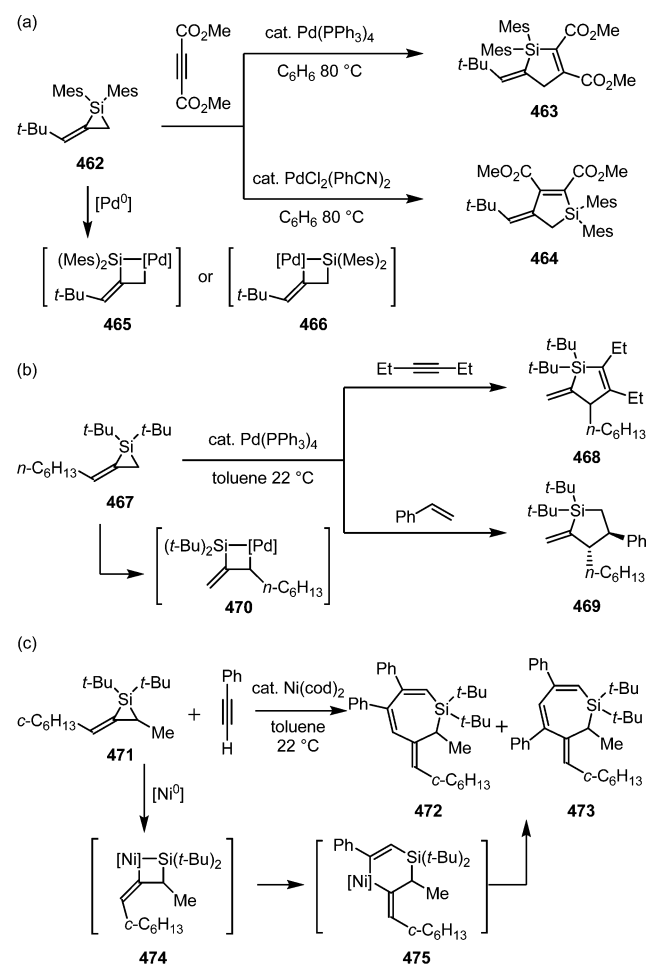
463 or **464**. This result was explained by the interplay between electronic effects of the ligand and steric effects of the substituents on the siliranes. Later, the Woerpel group published a more extensive study utilizing palladium and nickel catalysts.[216] In the case of Pd-catalysis, when poorly reactive alkynes or alkenes were used as the cycloaddition partners, double bond transposition products such as **468** and **469** were obtained (Scheme 154b). Intermediate **470** was proposed to be involved in this process. On the other hand, a nickel catalyst was effective for the reaction of disubstituted alkylidenesilacyclopropanes **471**, and when a terminal alkyne was utilized, products of double cycloaddition **472** and **473** were isolated (Scheme 154c). Complexes **474** and **475** were put forward as intermediates in this transformation.

Silanes **476** derived from alkenes rather than allenes were also the subject of study in the Woerpel laboratory.[217] The Pd-catalyzed reaction with these silanes and distinct alkynes afforded three major products **477**−**479** in varied ratios (Scheme 155). The authors proposed the reaction pathways shown in Scheme 155 to account for the formation of these products, and that the electronic and steric properties of the alkynes dictated the preferred pathways.

The Woerpel group also communicated a Cu-catalyzed cycloaddition between silanes **480** and carbonyl compounds (Scheme 156).[218] When amides or α,β-unsaturated aldehydes were utilized, the diasteroselective synthesis of **481** was achieved. The authors proposed that a stereospecific insertion

Scheme 155. Pd-Catalyzed Cycloaddition of Siliranes with Alkynes
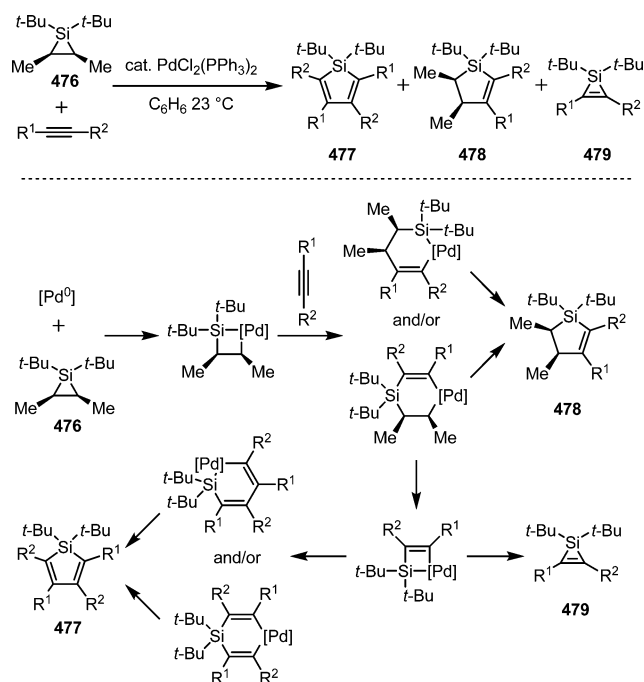
Scheme 156. Cu-Catalyzed Cycloaddition of Siliranes with Carbonyl Compounds
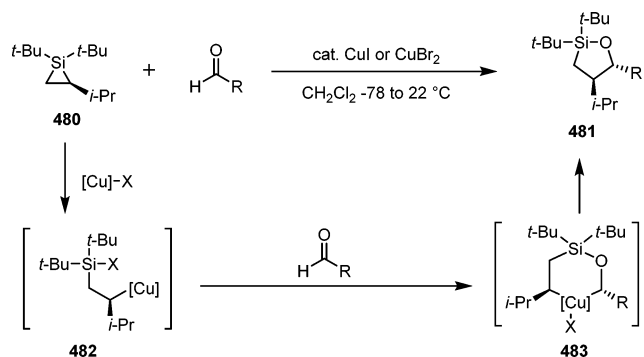
of copper to the siliranes affords cuprate **482**, which can then react with the carbonyl substrates to form **483**. Reductive elimination would provide the observed heterocyclic products.

In a distinct set of transformations, Berry and co-workers reported that desilylation of hexamethylsilacyclopropane **484** and concurrent silylene group transfer occurs using molybdenum and tantalum hydride compounds (Scheme 157).[219] Lewis basic solvents or additives such as THF and PMe₃ were found to accelerate the reactions. A radical ring-opening mechanism was postulated by the authors.

The Woerpel group has further expanded the concept of silylene group transfer and developed a series of synthetically useful methods to prepare silicon compounds (Scheme 158).[220] The key to obtaining productive chemistry was the use of a strained silirane **485** as the group transfer reagent in the presence of a Ag(I) catalyst. The researchers evaluated a range of silylene group acceptors, including alkenes, alkynes, α,β-unsaturated carbonyls, allylic ethers, and allylic epoxides. In addition, they have demonstrated that the methods afford access to building blocks of value in the construction of complex molecules.[221]

Scheme 157. Desilylations and Silylene Group Transfer of Hexamethylsilacyclopropane
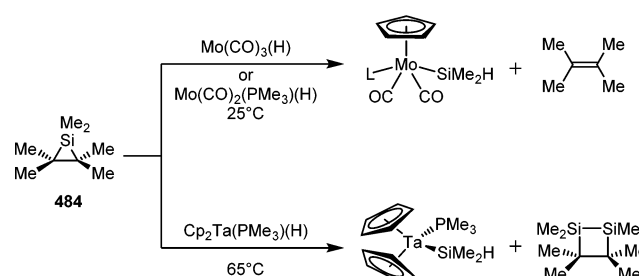
Scheme 158. Ag-Catalyzed Silylene Group Transfer Reactions
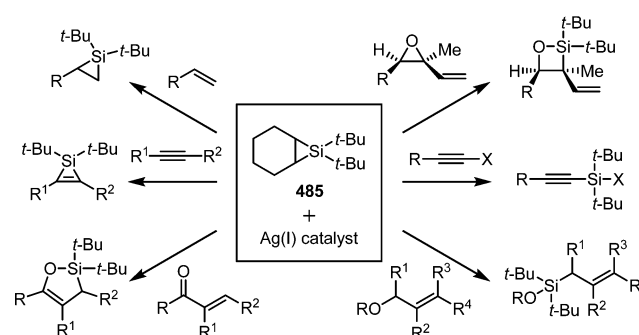
Woerpel and co-workers also investigated the mechanism of this silylene transfer reaction (Scheme 159).[221e] The authors

Scheme 159. Mechanism of Ag-Catalyzed Silylene Group Transfer to Alkenes
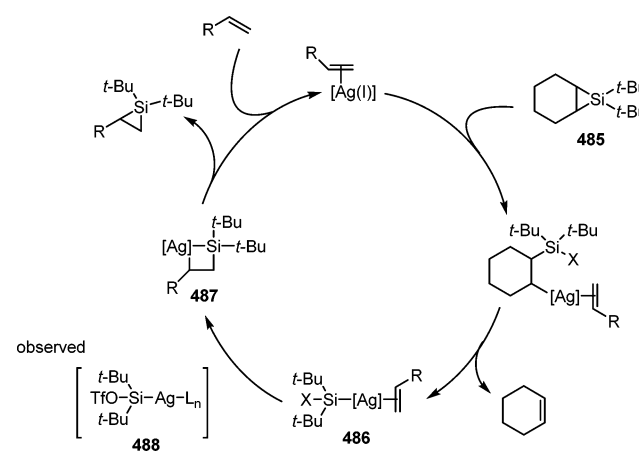
proposed the following mechanism, which commences by ring-opening of silirane **485** with the silver catalyst. Olefin exchange to afford complex **486** may occur next. The intermediate **486** then undergoes rate-determining migratory insertion to form four-membered complex **487**, which delivers the silirane product upon reductive elimination. The triflate version of silylsilver intermediate **488** was observed by NMR when (Ph₃P)₂Ag(OTf) was added to silirane **485**. This intermediate was shown to be competent as a silylene transfer reagent upon mixing with alkenes. The authors also conducted a linear free energy study with a range of olefins that suggests that the key silylsilver intermediate is electrophilic in nature.

In 2007, the Woerpel group extended these methodologies to silaaziridines (Scheme 160).[222] First, silaaziridines **489** were

Scheme 160. Studies on Silaaziridines
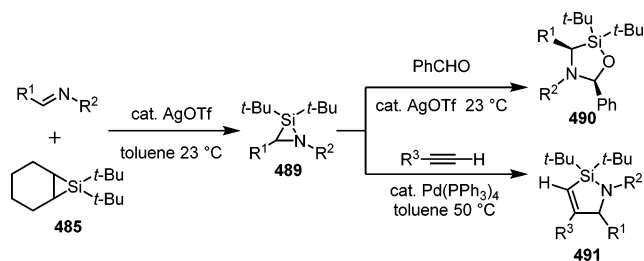
synthesized through Ag-catalyzed silylene transfer from siliranes **485** to imines. The silaaziridines were then subjected to Ag-catalyzed cycloaddition with benzaldehyde as well as Pd-catalyzed cycloaddition with alkynes to afford products **490** and **491**.

10. PHOSPHIRANES, PHOSPHIRENES, OXAPHOSPHIRANES, AND AZAPHOSPHIRENES

Phosphiranes and related phosphorus-containing three-membered ring heterocycles readily form complexes with tungsten and other metal carbonyls through *P*-coordination, and these complexes have been shown to be involved in various types of transformations as described herein.[223]

Mathey, Regitz, Streubel, Lammertsma, and Sterenberg have pursued the generation of phosphinidene species and evaluated their synthetic utility (Scheme 161).[224] Metal-stabilized phosphinidene **492** can be prepared by several different protocols, the most common of which is copper-promoted decomposition of 7-phosphanorbornadiene complexes such as **493** (Scheme 161). In addition, thermal decomposition of phosphirane complexes **494** or azaphosphirene complex **495**

Scheme 161. Generation and Reactivity of Phosphinidenes
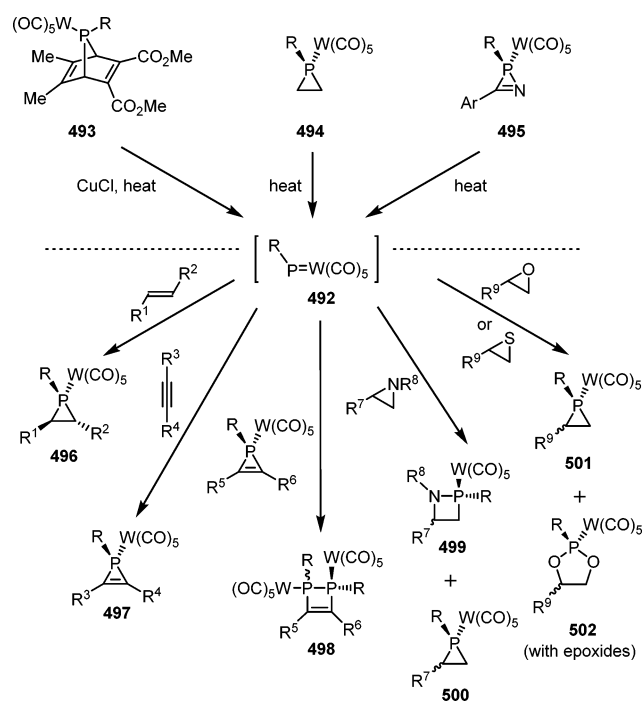
also affords **492**. Phosphinidene **492** has been shown to engage in various addition and insertion reactions (Scheme 161). For example, addition to alkenes or alkynes provides new phosphiranes **496** or phosphirenes **497**, respectively. Furthermore, insertion into tungsten-phosphirene complexes, aziridines, epoxides, or thiiranes yields products **498–502**.

The Streubel group has studied in detail the cycloaddition reaction between tungsten-azaphosphirenes and alkynes, nitriles, and aldehydes (Scheme 162).[225] They found that in the process of generating phosphinidene **504**, the ylide **503** can also engage in cycloaddition to afford products **505** and **507**.

Scheme 162. Reactions with Tungsten-Azaphosphirenes
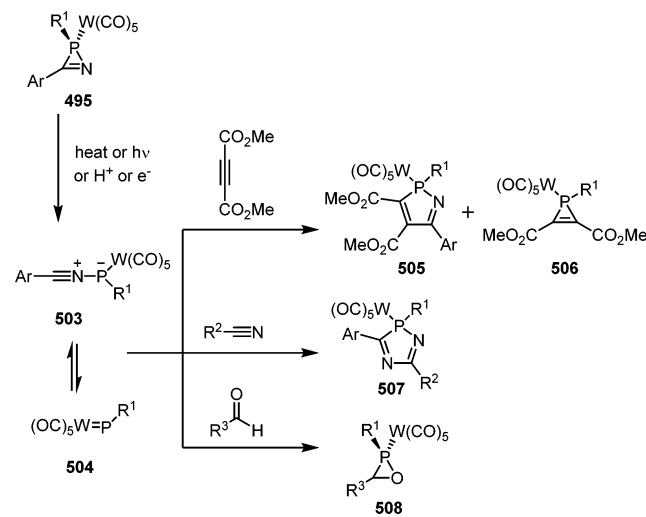
Similarly, cycloadditions of aldehydes and nitriles with tungsten-oxaphosphirane complexes **509** have been evaluated by Streubel and co-workers (Scheme 163).[226] In addition, deoxygenation of oxaphosphirane **509** was achieved with titanium and zinc as the reducing reagents.[227]

Scheme 163. Reactions with Tungsten-Oxaphosphiranes
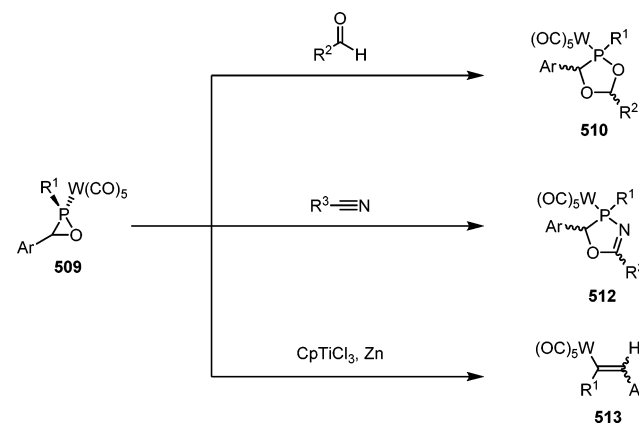
Nixon and co-workers showed that Pd(0) and Pt(0) undergo oxidative addition into phosphirenes and phosphiranes (Scheme 164).[228] When tungsten-phosphirene complexes **514** were subjected to palladium or platinum, four-membered metallacycles **515** were isolated (Scheme 164a). The free phosphirene **516** is also reactive, and with Pt(PPh₃)₂(C₂H₄), a bis-coordinated complex **517** was observed at low temperature (Scheme 164b). Furthermore, insertion into phosphirane **519**

Scheme 164. Oxidative Addition of Pd(0) and Pt(0) into Phosphirenes and Phosphiranes

(a)

(b)

(c)
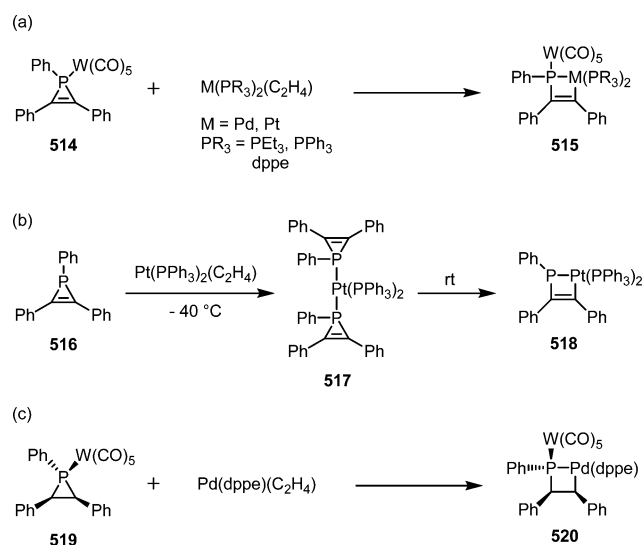
by Pd(dppe)(C₂H₄) was found to proceed in a stereoretentive manner, yielding complex **520**; a concerted oxidative addition mechanism was put forth by the author to account for this result (Scheme 164, c).

Ritcher and Mathey reported isomerizations of phosphiranes initiated by oxidative addition with low-valent transition metals, and in both cases, metal π-allyl intermediates such as **522** and **526** were proposed to be involved in the reaction (Scheme 165).[229]

Scheme 165. Isomerization of Phosphiranes
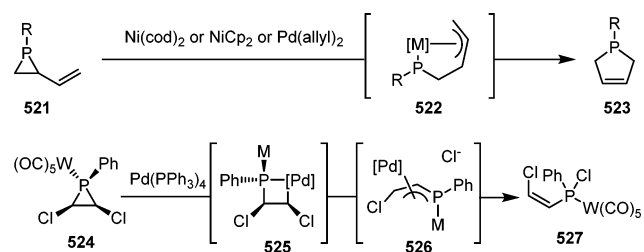
In light of these demonstrations that a transition metal can insert into phosphiranes, various researchers have pursued carbonylation reactions of these heterocycles (Scheme 166). The Mathey group reported that when complexes **528** were heated under 1 atm of CO, products **529** were obtained, and the authors proposed a mechanism involving metal insertion followed by CO migration (Scheme 166a).[230] Later, relevant intermediates were observed by Nixon and co-workers.[229] When the complexed phophiriene **514** was subjected to Ni(0), a metallacyclobutane **532** formed. The addition of CO at low temperature then converted **532** into the five-membered metallacycle **533**, which upon warming to room temperature underwent reductive elimination to furnish **534** (Scheme 166b). However, a similar process with Rh(I) only afforded dimer **536** as the product (Scheme 166c).

In addition to intramolecular cycloaddition between alkene and phosphirenes under thermal conditions, Mathey and co-workers published examples of intermolecular Pd-catalyzed alkene and alkyne cycloadditions with tungsten-phosphirenes and -phosphiranes (Scheme 167).[231]

Scheme 166. Carbonylation of Phosphirenes

(a)

(b)

(c)
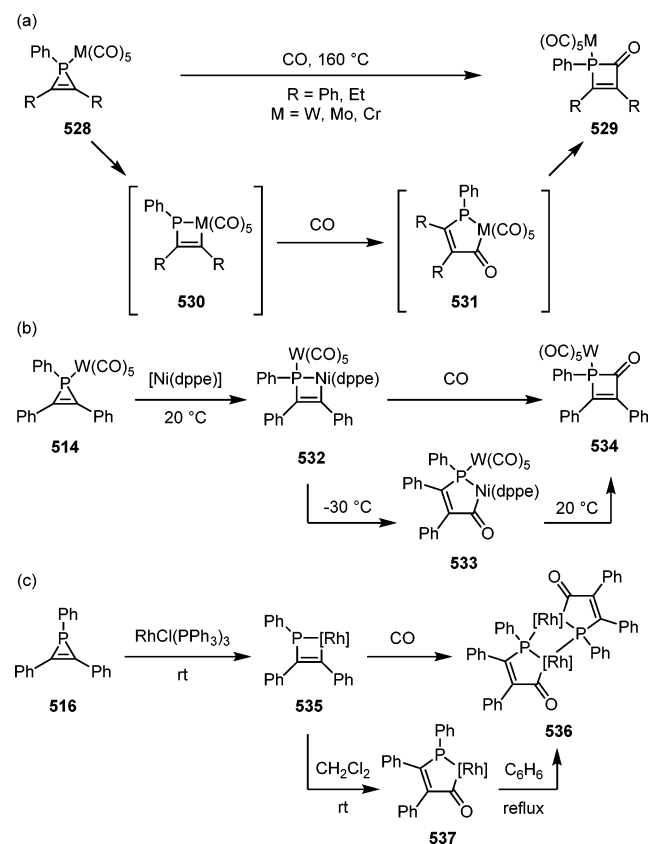
Scheme 167. Cycloadditions with Phosphirenes and Phosphiranes

(a)

(b)

(c)
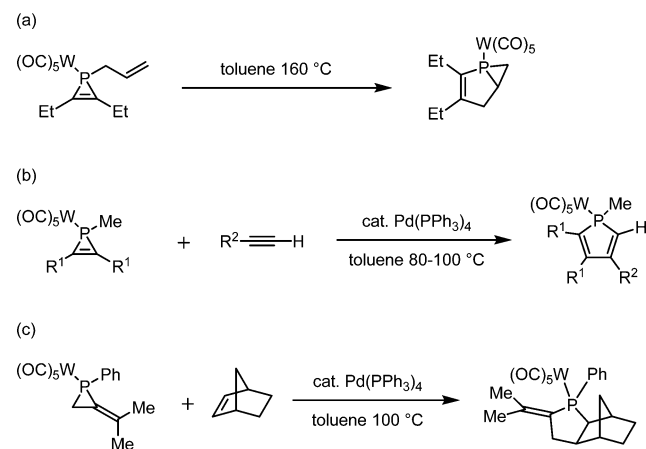
11. GERMIRANES

The research group of Takitoh reported reactions of germacyclopropabenzene **538** with metal carbonyls.[232] Notably, the reaction outcome was influenced by the identity of the metal (Scheme 168). For example, when chromium, molybdenum, or tungsten carbonyls were used, the corresponding metal carbene complexes **539** were isolated. On the other hand, use of manganese carbonyl resulted in rearrangement of the germirane to yield four-membered germacycle **540**. Finally, direct CO insertion occurred with the cobalt carbonyl to afford product **541**.

Scheme 168. Reactions of Germacyclopropabenzene 538
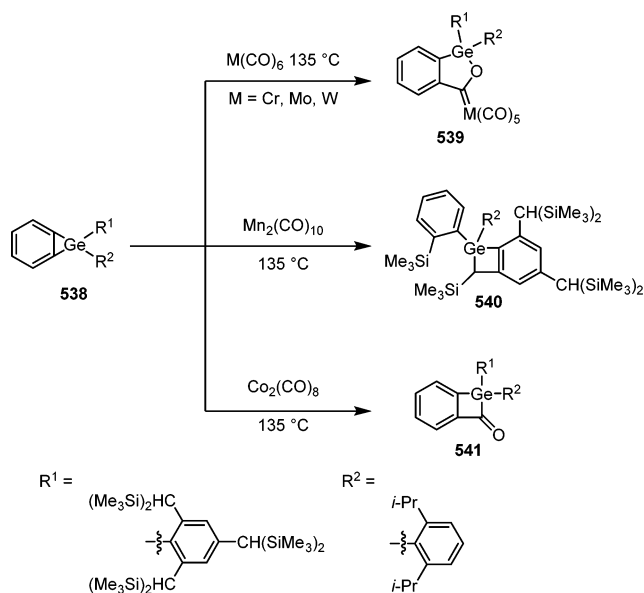
12. CONCLUSION

In this Review, we describe the chemistry of transition metal complexes with each class of three-membered ring heterocycle. A focus of early research in this area involved reactions of metal carbonyl compounds, where it was shown that CO insertion and occasionally isomerization of the heterocylic substrates are the predominant outcomes. On the basis of these early stoichiometric studies, chemists were able to develop various metal-catalyzed carbonylation reactions, mostly with epoxides and aziridines as substrates, and these transformations have proven extremely valuable to the synthetic community. This is a representative example of how practical synthetic methods can evolve from merging the reactivity of heterocyclic compounds and transition metals. Recently, attention has been directed to co-opting cross-coupling techniques to enable general methods for carbon–carbon and carbon–heteroatom bond construction with these electrophiles. Early stoichiometric examples provide a compelling mechanistic basis for the development of such reactions, and the past five years have witnessed exciting developments in this area.

Nonetheless, further research is still required in this field because many early discoveries have not seen significant development. To faciliate the design of new methods, a better fundamental understanding of the underlying principles govering the reactivity of organometallic complexes with these heterocyclic substrates is necessary. In addition, application of recent advances in transition metal catalysis should be useful in expanding the existing chemistry of three-membered ring heterocycles. With these advances, it may be possible to develop highly chemo- and stereoselective methods for the preparation of a diverse array of valuable heteroatom-containing molecules. It is our hope that this Review will motivate the interest of the community on this topic and serve as an entry point for reaction discovery in the future.

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Notes

The authors declare no competing financial interest.

Biography

Chung-Yang (Dennis) Huang (left in photo) was born in Kaohsiung, Taiwan in 1988. He received his B.S. in Chemistry in 2010 from Massachusetts Institute of Technology, where he conducted undergraduate research with Professor Rick Danheiser in the area of natural product synthesis. He also spent a summer at The University of Tokyo with Professor Eiichi Nakamura investigating fullerene derivatives. In 2012 he started his graduate studies at Princeton University working in the laboratory of Professor Abigail Doyle. His graduate work focuses on the development of electron-deficient olefin ligands for nickel-catalyzed aziridine cross-coupling reactions.

Abigail G. Doyle (right in photo) was born in Princeton, NJ in 1980. She obtained her A.B. and A.M. degrees summa cum laude in Chemistry and Chemical Biology from Harvard University in 2002. After spending the subsequent year at Stanford University working with Professor Justin Du Bois, she joined the laboratory of Professor Eric Jacobsen at Harvard University for her doctoral studies, which were centered in the area of enantioselective catalysis. Abby began as an Assistant Professor in the Department of Chemistry at Princeton University in 2008. In 2013, she was promoted to Associate Professor. Research in the Doyle group is centered in the area of catalysis, with specific interests in the development of novel nickel-catalyzed cross-coupling reactions and the identification of new reagents and strategies for catalytic nucleophilic (radio)fluorination.

ACKNOWLEDGMENTS

ABBREVIATIONS

acac	acetylacetonate
Bs	benzenesulfonamide
Cn	cinsyl
cod	1,5-cyclooctadiene
Cp	cyclopentadiene
Cp*	pentamethylcyclopentadiene
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DME	dimethoxyethane
dppe	1,2-bis(diphenylphosphino)ethane

dpph	1,6-bis(diphenylphosphino)hexane
dppp	1,3-bis(diphenylphosphino)propane
es	enantiospecificity
esp	$\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionic acid
hfacac	hexafluoroacetylacetonate
HMPA	hexamethylphosphoramide
MW	microwave
NBD	norbornadiene
NHC	N-heterocyclic carbene
Ns	nosyl
oy	optical yield
PEG	poly(ethylene glycol)
phen	phenanthroline
PNp$_3$	tri-1-naphthylphosphine
PPN	bis(triphenylphosphine)iminium
py	pyridine
rr	regioisomeric ratio
salph	N,N'-bis(salicylidene)-1,2-phenylenediamine
SET	single-electron transfer
TFA	trifluoroacetic acid
TMM	trimethylenemethane
TPP	tetraphenylprophyrin
Ts	tosyl
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

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