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Transition-Metal-Catalyzed Laboratory-Scale Carbon–Carbon Bond-Forming Reactions of Ethylene

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Abstract

Ethylene, the simplest alkene, is the most abundantly synthesized organic molecule by volume. It is readily incorporated into transitionmetal–catalyzed carbon-carbon bond-forming reactions through migratory insertions into alkylmetal intermediates. Because of its D_{2h} symmetry, only one insertion outcome is possible. This limits byproduct formation and greatly simplifies analysis. As described within this Minireview, many carbon–carbon bond-forming reactions incorporate a molecule (or more) of ethylene at ambient pressure and temperature. In many cases, a useful substituted alkene is incorporated into the product.

Keywords

C–C coupling; ethylene; fine chemicals; homogeneous catalysis; synthetic methods

1. Introduction

Worldwide, more than 140 million tons of ethylene are produced annually, mostly from kerogen and shale gas cracking, but also from ethanol dehydration. This production level makes ethylene the most abundantly prepared organic molecule by volume.[1] More than half of this material is incorporated into various higher olefins and polyethylene materials.[2] Other high-volume uses of ethylene are in the production of ethylene oxide, which is further converted into many different commodity chemicals such as ethylene glycol, and in the production of other common feedstocks such as propionic acid, acetaldehyde, ethylbenzene, ethylene dichloride, and specialized polymers.[2,3] Considering the diversity of commodities that incorporate ethylene as a fundamental building block, it is somewhat surprising that ethylene is not employed as a standard alkene in modern synthetic method discovery and development. While this may be due to apprehensions about working with gas-phase reactants, the abundance of this two-carbon building block should make ethylene a very attractive substrate for new transition-metalcatalyzed functionalization reactions. Moreover, because functionalization reactions of alkanes (methane and ethane in particular) are challenging, ethylene remains the simplest, readily functionalized hydrocarbon synthon.[4] The goal of this Minireview is to highlight the intersection of modern synthetic methods

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development with the use of ethylene in the production of nonpolymeric small-molecule products of enhanced value. We will focus on seminal reactions and also detail recent efforts in the field. Classical industrially applied reactions of ethylene, including the Wacker oxidation,[2,5] hydroacylation,[6] and hydroformylation[7] reactions, are beyond the scope of this Minireview.

2. Mizoroki–Heck-Type Reactions of Ethylene

The Mizoroki–Heck reaction was one of the earliest transition-metal-catalyzed carbon–carbon bond-forming reactions to extensively employ ethylene as a substrate for fine chemicals synthesis. As discussed below, this reaction has found use in the preparation of useful material feedstocks and pharmaceutical intermediates.

2.1. Palladium-Catalyzed Mizoroki–Heck Reactions Using Aryl Electrophiles

The palladium-catalyzed reaction of alkenes and aryl halides, also known as the Mizoroki–Heck reaction, is a general method for the synthesis of a wide range of alkene-bearing aromatic compounds.[8] The use of ethylene as the reactant alkene was disclosed in several of the pioneering studies by Mizoroki and co-workers[9] and Heck and co-workers[10] for the preparation of styrenes (Scheme 1). For example, Mizoroki and co-workers reported the reaction of iodobenzene (**1**) with ethylene at elevated pressure and temperature to access styrene (**2**) under palladium catalysis. They also observed the formation of stilbene (**3**). Heck and Plevyak used alternative reaction conditions to access *o*-vinyltoluene (**5**), which is a common co-monomer in styrene polymerization.[10a] The conventional route to *o*-vinyltoluene is tedious, as it involves multiple steps such as the alkylation of toluene with ethylene, separation of *o*-ethyltoluene from other alkylated products, and subsequent steam cracking. The method developed by Heck and Plevyak involved the reaction of *o*-bromotoluene (**4**) with ethylene using triethylamine as a base in the presence of 1 mol% palladium acetate and 2 mol% tris(*o*-tolyl)phosphine as a catalyst. The efficiency of the reaction as well as the selectivity for the formation of *o*-vinyltoluene was shown to be pressure dependent, as increasing the pressure from 20 to 120 psi substantially suppressed the formation of the stilbene **6**. At reduced pressures of ethylene, arylation of the resultant styrene becomes competitive, thus affording the corresponding stilbene product. Thus, the key drawback of this method is the requisite high pressure of ethylene. Improved reaction efficiency (reduction of the catalyst load and pressure of ethylene) have been realized through extensive optimization by DeVries and Mendoza using DMF/H_2O as the solvent.[11] Kiji and co-workers have also reported aqueous systems for Heck reactions of ethylene with certain aryl halides.[12]

In 1983, Spencer reported a decarbonylative Mizoroki–Heck reaction which involved the use of benzoyl chlorides as electrophiles.[13] As with the original Heck report discussed above, the selectivity of styrene to stilbene products can be improved by increasing the pressure of ethylene (Scheme 2).

Chaudhari and co-workers have recently described the use of C,N-palladacycles as catalysts for the Mizoroki–Heck arylation of ethylene.[14b] Because of their superior thermal stability relative to the $Pd(OAc)_2/PAr_3$ system, such complexes were intended for palladium(0)-

catalyzed reactions which require temperatures of 140 °C or greater.[15] However, ethylene arylation products undergo polymerization at this temperature. As such, Chaudhari and co-workers optimized the reaction of 2-bromo-6-methoxynaphthalene (**10**) with ethylene, thus resulting in 98% selectivity for the polymerization-prone Naproxen precursor **11** at 90 °C using the catalyst **12** (Scheme 3). The reaction required 290 psi of pressure and was performed on 5.3 mmol of substrate. The following year, RajanBabu and co-workers reported a similar reaction with broader substrate scope.[14a]

Despite their promising utility, Mizoroki–Heck reactions of ethylene have not found widespread use because of their high operating pressure and temperature. Such reaction conditions promote polymerization of the desired products.

2.2. Nickel-Catalyzed Mizoroki–Heck-Type Reactions Using Allylic and Benzylic Electrophiles

Nickel has found use in Mizoroki–Heck-type reactions of sp^3 electrophiles. In 2010, Matsubara and Jamison reported nickel-catalyzed allylic substitution reactions utilizing ethylene.[16] The protocol enables the use of a variety of allylic alcohol derivatives (**13**) as electrophiles which, upon reaction with ethylene in the presence of silyl triflates, afford synthetically useful skipped dienes (**14**; Scheme 4). Both *trans*- and *cis*-allylic alcohol derivatives are good substrates for the reaction (**13a**). The *E/Z* selectivity of the resultant product is generally high for disubstituted alkenes such as **13a**, **13b**, and **13e**, but is somewhat diminished for trisubstituted examples such as **13c** and **13d**. The reaction was also conducted on gram scale using the allylic carbonate **13 f**, which afforded the desired skipped diene **14 f** in 81% yield upon isolation. For ease of chromatographic purification, the conjugated 1,3-diene product isomer (not shown), which is typically formed in less than 5% yield in these reactions, was consumed by a [4+2] cycloaddition reaction with tetracyanoethylene (TCNE).

The proposed mechanism of the reaction reported by Jamison and co-workers is depicted in Scheme 5. After formation of the nickel/p-allyl species **15**, triethylsilyl triflate is used to generate the ethylene-associated cationic species **16**, which then undergoes migratory insertion to furnish **17**. Finally, β-hydride elimination leads to the product-bound species **18**, from which the product **14 f** and nickel(0) are liberated.

Jamison and co-workers reported related reaction conditions for the benzylation of ethylene (Scheme 6).[17] Benzyl chlorides substituted with either electron-rich or electron-poor groups, were smoothly converted into allylbenzene derivatives (**20a–c**). In addition, hetereobenzylic chlorides including benzofuran, benzothiophene, and *N*-tosylpyrrole led to the corresponding products (**20d–f**) in good to excellent yields.

These nickel-catalyzed Mizoroki–Heck-type reactions are inherently limited to allylic and benzylic electrophiles, which serve to stabilize the resultant nickel/alkyl intermediates. Such electrophiles limit the general synthetic applicability of this methodology. However, it would appear that the use of secondary allylic or benzylic electrophiles, such as **13e**, could allow for the development of kinetic resolution reactions if a suitable chiral ligand can be identified.

3. Multicomponent Coupling Reactions of Ethylene

The following examples show how ethylene can be incorporated into multicomponent coupling reactions at ambient pressure to rapidly increase molecular complexity.

3.1. Palladium-Catalyzed Three-Component Reductive 1,1-Difunctionalization Reactions of Ethylene with Vinyl Electrophiles and Boronic Acids

In 2012, Saini and Sigman developed a palladium(0)-catalyzed three-component reaction using vinyl triflates or vinyl nonaflates, and aryl or alkenylboronic acids to functionalize ethylene (Scheme 7).[18] This can be thought of as a three-component interrupted Mizoroki–Heck reaction, in that after oxidative addition and ethylene migratory insertion, the resultant palladium–alkyl intermediate is trapped by an organometallic species before it can undergo β-hydride elimination. The net result of the transformation is a substantial increase in molecular complexity, including the generation of a chiral center. The reaction conditions are mild, including ambient pressure of ethylene, and 5 mol% of [Pd$_2$dba$_3$], plus 15 mol% of added dibenzylideneacetone (dba). The scope of the reaction is broad in terms of the nucleophilic coupling partners as demonstrated by the use of both electron-rich (as in **23a**) and electron-poor boronic acids (as in **23b**–**e**), all of which give good to excellent yields of the ethylene 1,1-difunctionalization product. Cyclic triflates and nonaflates are required as electrophiles because they enable selective formation of the difunctionalization products **23** through the formation of the thermodynamically more stable endocyclic double-bond-containing product. The byproduct **24** arises from isomerization of the intermediate palladium/p-allyl species (not shown) prior to transmetallation.

Alkenyl boronic acid derivatives, such as that from which **23 f** is derived, were also found to be compatible under the reaction conditions, although the regioselectivity for the formation of the ethylene difunctionalization product is attenuated. In addition, vinyl nonaflates can also be used as the electrophile. These electrophiles are advantageous in terms of their lower cost and higher thermodynamic stability compared to vinyl triflates.[19]

Nitrogen-containing heteroaromatic boronate coupling partners pose a great challenge in palladium-catalyzed Suzuki-Miyaura cross-coupling reactions because of their Lewis basicity, slow rate of transmetallation, and propensity to decompose by protodeborylation.[20] Therefore, it was not surprising that the use of 4-pyridyl boronic acids under the aforementioned optimized reaction conditions resulted in diminished conversion. However, the use of 4-pyridyl boronic acid pinacol ester instead of the free boronic acid led to the efficient 1,1-difunctionalization of ethylene to afford **26a** (Scheme 8). A slight increase in the reaction temperature and duration enabled the use of a pyrazolyl boronic ester and 2-chloro-4-pyridyl boronic ester, thus affording **26b** and **26c**, respectively. However, the catalyst proved to be far less efficacious for the reaction of 2-pyridyl boronic esters, as this substrate is highly prone to protodeborylation. To circumvent this problem, 2-pyridyltributylstannane was used to access the corresponding product **26d**. Surprisingly, each of the reactions with heteroaromatic cross-coupling partners yielded a single regioisomer.

In summary, Saini and Sigman have developed a mild, functional-group-tolerant catalyst system for the three-component coupling of ethylene to vinyl electrophiles and a variety of sp²-hydridized boronic acids and esters. Although the scope of the reaction is broad in terms of organometallic reagents, the reaction is presently limited to the use of six-membered cyclic alkenyl electrophiles, and has not yet been rendered enantioselective.

3.2. Nickel-Catalyzed Three-Component Coupling Reactions of Ethylene to Aldehydes and Silyl Triflates for Allyl Silyl Ether Synthesis

In 2005, Ng and Jamison reported the nickel-catalyzed three-component coupling of ethylene (and terminal alkenes) to aldehydes and silyl triflates to access the allyl silyl ethers **29** (Scheme 9).[21] The reaction is generally high yielding under mild reaction conditions, including ambient pressure and temperature. Sterically hindered, non-enolizable aldehydes work best, including those leading to **29a–d**, and a wide variety of alkyl silyl triflates are well tolerated. Despite pre-existing examples utilizing stoichiometric amounts of transition metals,[22] this was the first example of a catalytic intermolecular coupling of ethylene to aldehydes. The mechanism was proposed to involve an initial cyclometallation of ethylene and the aldehyde with nickel(0), with subsequent Lewis acid activation of the alkoxide, and finally b-hydride elimination.

It should be noted that, while pre-existing examples utilizing stoichiometric amounts of transition metals are known, catalyst loadings are still relatively high and the reaction has not yet been rendered enantioselective.

4. Hydrovinylation Reactions

Ethylene has been extensively employed in hydrovinylation reactions of alkenes. These reactions involve the addition of hydrogen and ethylene groups across a double bond in a 1,2-fashion, are an appealing and formally atom-economical means of C–C bond formation.[23] Such reactions involve the coupling of ethylene to stabilized alkenes, such as styrenes, or strained alkenes such as norbornene, and lead to the formation of a chiral center. The catalytic asymmetric variant is particularly appealing because the products formed are intermediates in the synthesis of 2-arylpropionic acids, which are an important class of nonsteroidal anti-inflammatory drugs (NSAIDs).[24] Below is a summary of key advances in asymmetric catalytic hydrovinylation reactions.[25]

4.1. Nickel-Catalyzed Hydrovinylation Reactions

Wilke and co-workers reported the first asymmetric hydrovinylation of 1,3-cyclooctadiene (**30**) with ethylene in 1972 using an allylnickel catalyst, Lewis acid co-catalyst, and chiral phosphine, although neither the catalyst loading, product yield, nor reaction pressure (presumably 1 atm) were reported.[26] The skipped diene product (*S*)-**31** was determined to have been formed in 70% enantiomeric excess (Scheme 10). The observed complete regioselectivity of vinyl installation at the allylic position is likely a result of a relatively stable nickel/π-allyl resting state. The following year, Wilke reported the hydrovinylation of norbornadiene using 3.5 mol% of the allylnickel dimer and a slightly bulkier chiral phosphine at −65 °C.[27] In this instance, the hydrovinylation product (5*R*)-**33** was formed in

49% yield with 78% enantiomeric excess (*ee*). The *E*- and *Z*-ethylidene derivatives **34** were also formed in 13% yield, and ethylene oligomerization products, likely arising from β-hydride elimination after ethylene migratory insertion,[25,28] were also observed. Although these examples exhibited less than desirable catalytic activity and enantioselectivity, this work inspired others in the field to perform rigorous studies which would address these shortcomings.

Subsequent studies by Wilke et al. established excellent control of both the regio- and enantioselectivity of styrene hydrovinylations through the use of the pinene-derived 1-azaphospholene ligand (*R,R*)-**36** (Scheme 11).[29] In 1999, Wegner and Leitner developed a variant of Wilke's reaction which employs supercritical carbon dioxide as opposed to dichloromethane.[30] Additionally, they observed that combustible $Et_3Al_2Cl_3$ could be replaced by comparatively mild sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) salt for the activation of the catalyst. Both the chemoselectivity and enantioselectivity were comparable to that observed by Wilke and co-workers.

Rajanbabu and co-workers identified superior chiral ligands for the hydrovinylation of 2-methoxy-6-vinylnaphthalene (**11**), a precursor to Naproxen.[31] Excellent yields and modest enantioselectivities resulted from the use of hemibidentate phosphine ligands of type **38** previously developed by Hayashi and co-workers[32] in the presence of NaBARF (Scheme 12). A hemilabile Lewis-basic functional group tethered to the ligand was found to be crucial for the efficiency of the reaction. Whereas ether-containing ligands **38a** and **38b** resulted in good activity and selectivity, removal of the ether, as in **38c**, rendered the catalyst incompetent.

After revealing the utility of hemibidentate ligands bearing weakly coordinating ether groups in asymmetric hydrovinylation reactions, Rajanbabu and co-workers sampled a number of 1-aryl-2,5-dialkylphospholanes with pendant ethers for activity in hydrovinylation.[25d,33] The *o*-benzyl-oxymethyl derivative **39a** effects styrene hydrovinylation in the presence of a BARF counterion, thus affording 98% yield but just 50% enantiomeric excess (Scheme 13). A slight increase in enantioselectivity was observed by increasing the steric bulk of the phospholane substitutents, as in **39b**. Expectedly, the yield and enantioselectivity were found to be strongly dependent on the nature of the counteranion. More recent developments in this reaction have described the use of phosphinite and phosphite ligands, including sugarderived examples, which are easily tuned.[34]

In 2009, Joseph, Rajanbabu, and Jemmis undertook an extensive theoretical investigation of the mechanism of the nickel(II)/phospholane-catalyzed hydrovinylation reaction (Scheme 14).[33a] This elegant study provided evidence that nickel hydride intermediates, long implicated as the active species in the aforementioned hydrovinylations, may not be formed at all. Instead, their studies suggest that the precatalyst **40** undergoes multiple ligand exchanges to give the ethylene-bound **41** with subsequent insertion of ethylene to give the nickel/alkyl **42**. Although the authors anticipated that β-hydride elimination would generate the nickel hydride **43** and liberate 1,4-pentadiene (**44**), quantum mechanical calculations using the B3LYP/6-31G* data set revealed that the transition-state energy of β-hydride

elimination leading to **43** is high because of the *trans* orientation of hydrogen and phosphine about the nickel center. As such, β-hydride transfer directly to styrene, leading to the nickel/benzyl complex **45**, is substantially lower in energy. After ethylene coordination and insertion, another favorable β-hydride transfer from **47** affords the product. The absence of a nickel hydride intermediate may account for the lack of isomerization of the product alkene, and therefore the generally excellent yields of nickel-catalyzed hydrovinylations.

In 2002, Leitner and co-workers developed an efficient system for asymmetric hydrovinylations using phosphoramidite ligands in combination with NaBARF or [Al{OC-(CF$_3$)$_2$Ph}$_4$] counterions.[35] They reported the hydrovinylation of styrene using [{(allyl)NiCl}$_2$], the phosphoramidite **50**, and NaBARF at −65 °C in 89% yield and 91% enantiomeric excess (Scheme 15). The use of 4-chlorostyrene afforded similar yield and enantiomeric excess, whereas 4-isobutylstyrene reacted in low yield and with diminished enantio-selectivity. In the last decade, phosphoramidite ligands have been used to expand the substrate scope of hydrovinylation reactions.[36] The use of phosphoramidite ligands holds great potential for the future development of these reactions because of the modular fashion in which they are prepared.

It should be noted that nickel-catalyzed hydrovinylations have enabled the enantioselective synthesis of many other biologically active compounds, such as trikentrin,[37] various pyrrolidinoindolines,[38] and pseudopterosins.[39]

4.2. Other Transition-Metal-Catalyzed Hydrovinylation Reactions

A common problem in palladium-catalyzed hydrovinylation reactions is the isomerization of the desired hydrovinylation products through side reactions with palladium hydride intermediates.[40] In 1998, Vogt and co-workers described a palladium-catalyzed hydrovinylation reaction of styrene using menthol-derived phosphonite ligands, including **52** (Scheme 16).[41] A weakly coordinating cosolvent such as ethyl acetate was required to maintain the catalytic activity, presumably by acting as a ligand and therefore preventing the agglomeration of palladium nanoparticles. Relatively poorly coordinating counteranions such as PF$_6$ and SbF$_6$ were shown to be most effective at delivering good yields and enantio-selectivities, and minimized alkene isomerization. Recently, the group of Rocamora has reported the use of chiral diamidophosphite ligands for hydrovinylations proceeding with high enantioselectivity (up to 90% *ee*).[42] Many others have used palladium with chiral phosphine ligands to accomplish alkene hydrovinylation with low to moderate enantioselectivity.[40,43]

Although cobalt-catalyzed hydrovinylations of various 1,3-dienes with alkenes are known,[44] Vogt and co-workers were the first to report enantioselective hydrovinylations of styrene using chiral bidentate phosphine ligands.[45] In this report, the use of (*S,S*)-**53** [(*S,S*)-diop] or (*S,S*)-**54** [(*S,S*)-dipamp] resulted in moderate activity and low enantioselectivity (Scheme 17). The use of (*R,R*)-**55** [(*R,R*)-dach] led to a promising near-doubling of the enantioselectivity, to 47% *ee*. Conjugated dienes have been shown to be more amenable substrates towards highly enantioselective cobalt-catalyzed hydrovinylations through the use of chiral analogues of dppb and dppp (dppp = 1,3-bis(diphenylphosphino)propane)ligands. In one case, (*E*)-1,3-nonadiene was hydrovinylated in quantitative yield and 95%

enantiomeric excess in the presence of [{(*R,R*)-diop}CoCl$_2$] and AlMe$_3$ at –45 ° C (not shown).[46]

Recently, Page and Rajanbabu have developed highly enantio-and regioselective 1,4-hydrovinylation reactions of 1-vinylcycloalkenes (**56**) leading to synthetically useful skipped 1,4-dienes [(*S*)-**57**; Scheme 18].[47] Excluding 1-vinylcyclohexene (**57a**), the regioselectivity for the formation of the 1,4-hydrovinylation products (*S*)-**57** over 1,2-hydrovinylation products **58** has been found to be greater than 95%. The efficiency of the reaction is largely unperturbed by cycloalkene ring size, as five-, six-, seven-, and eight-membered rings afford excellent yields and enantio- and regioselectivities [(*S*)-**57a**–**d**]. Saturated heterocycloalkenes, such as (*S*)-**57e**, also work in this reaction.

Recently, Jiang and List developed the first rutheniumcatalyzed enantioselective hydrovinylation reaction through the use of chiral-counterion-directed catalysis.[48] The selectivity observed for the hydrovinylation of styrenes was excellent but enantioselectivities were modest. Other reports of ruthenium-catalyzed symmetric hydrovinylation reactions are also known.[49]

In conclusion, while substantial progress has been made in the asymmetric hydrovinylation of styrenes with ethylene, a general method for the regio- and enantioselective hydrovinylation of alkenes remains elusive. Regardless of the transition metal employed, only alkenes which result in the formation of a stabilized metal–alkyl intermediate (i.e., π-allyl or π-benzyl) have been used as substrates.

5. Directed C–H Functionalization Reactions

5.1. Pyridine-Directed Three-Component Propionylation of C–H Bonds using Ethylene and Carbon Monoxide

In the synthetic interest of step and atom economy, C–H bond functionalization is an area of intense investigation. The cleavage of unactivated $C_{sp}3$–H bonds poses a great challenge to organic chemists because of their thermodynamic and kinetic inertia.[50] However, $C_{sp}3$–H bonds adjacent to heteroatoms are more reactive than those adjacent to carbon atoms. Bearing this in mind, in 1997 the group of Murai reported a dehydrogenative [Rh$_4$(CO)$_{12}$]-catalyzed three-component acylation reaction which occurs at a C–H bond a to α piperazine nitrogen atom and in proximity to a directing pyridine group [Eq. (1)].[51] However, in this reaction it is
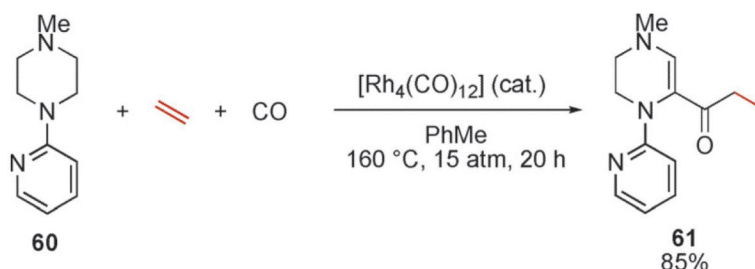
believed that dehydrogenation takes place first, with subsequent propionylation by ethylene coordination and CO insertion of an $C_{sp}2$–H bond rather than an C_{sp}^3–H bond. Other examples of $C_{sp}2$–H bond carbonylation and alkylation have been reported.[52]

Murai and co-workers later accomplished the desired three-component $C_{sp}3$–H bond acylation of a pyrrolidine substrate (**62**) using rhodium catalysis (Scheme 19).[53] Mechanistically, it was proposed that rhodium coordinates to the nitrogen atom in **62**, then cleaves the adjacent C–H bond to form the rhodium/alkyl complex **64**. Ethylene insertion and then CO insertion gives the acyl rhodium complex **66**, from which reductive elimination liberates the product **63**.

5.2. Pyridine-Directed Ethylation of C–H Bonds using Ethylene

Attempts to extend the directing-group-assisted C–H acylation of pyrrolidinyl substrates to the use of other transition metal complexes, such as [$Ru_3(CO)_{12}$], were not successful because of reductive elimination from ethylene insertion. The efficiency of this directed C–H ethylation is highly sensitive to the nature of the substituents on the pyridine ring (Scheme 20).[54] For example, double α-ethylation predominantes for substrate **62**. When the coordinating ability of the pyridine nitrogen atom is diminished through steric encumbrance from the 6-position, as in **67a**, the yield is decreased and the monoethylation product predominates. Substituting with an electron-withdrawing group at the 4-position of the pyridine, as in **67b**, resulted in no reaction.

Other N-directing groups were also evaluated, including an acetyl group (**70a**) and a pivaloyl group (**70b**), but no reaction was observed (Scheme 21). The use of other amine substrates was also described, thus providing access to mono- and diethylated products in the case of **70c**. The scope of the reaction for acyclic N-pyridyl amines is also limited, as only one secondary amine, **70d**, was found to react efficiently, albeit under modified conditions.

While the products of direct C–H ethylation may not be particularly interesting because no functional handle is installed, a potential asymmetric ethylation may find synthetic use.

6. Ethylene in Olefin Metathesis Reactions

Olefin metathesis is a transition-metal-catalyzed reaction class in which two alkenes or alkynes combine and rearrange into two new unsaturated carbon–carbon bond-containing products, one of which is often ethylene. For example, in the case of ring-closing alkene metathesis reactions of terminal alkenes, widely used in natural product synthesis, a single desired alkene is established in the product while ethylene is liberated as a conveniently labile byproduct.[55] However, ethylene may also be used as a substrate from which carbon atoms are incorporated into value-added products by enyne metathesis reactions,[56] some of which are described below.

6.1. Intermolecular Enyne Methatesis Reactions Employing Ethylene as the Ene Component

In 1997, Mori and co-workers applied ethylene as a substrate in ruthenium-catalyzed intermolecular enyne metathesis reactions with various alkynes (**72**), thus affording the 1,3-dienes **73** in good-to-excellent yields (Scheme 22).[57] The synthetic protocol is very attractive in that a solution of the alkyne and ruthenium catalyst is simply stirred at room temperature under 1 atmosphere of ethylene. The overall transformation appends a carbon atom from ethylene onto each sp-hybridized alkyne carbon atom. Mechanistically, it is believed that the 14-electron ruthenium alkylidene **75** undergoes a [2+2] cycloaddition with ethylene to give a ruthenacyclobutane (**76**), with subsequent cycloreversion with ethylene to generate the active ethylidene **77**. Another [2+2] cycloaddition/cycloreversion sequence, this time involving the alkyne, generates the alkylidene intermediate **79**, onto which a third and final [2+2] cycloaddition/cycloreversion sequence with ethylene affords the product **73**.

In terms of scope, both internal and terminal alkynes containing a wide variety of functional groups, such as a silyloxy group (**72a**), an ester (**72b**), and a ketal (**72c**) were tolerated. Interestingly, an alkyne bearing an alkylsulfonamide at the propargylic position (**72d**) gave the corresponding product in 81% yield, while the homopropargylic variant **72e** afforded just an 11% yield. The diminished yield could be due to coordination of the N atom to ruthenium in the cycloadduct **78**, which could prevent cycloreversion to **79**.[58] Recently, related ethylene–alkyne cross-metathesis reactions have been used for the synthesis of variety of 1,3-dienecontaining products.[59]

6.2. Ethylene in Tandem Ring-Closing/Ring-Opening Enyne Metathesis Reactions

When a cyclic alkene is added to the alkyne substrate, as with the substrate **81**, a five-membered ring is formed in the process of cycloheptene ring opening, thus leading to the terminal ruthenium alkylidene **85**, and subsequently the diene **82** (Scheme 23).[60] This may be thought of as an ene–ene–yne metathesis reaction. The carbon atoms from ethylene are introduced into the product as shown in **82**. The yield is still surprisingly high in this reaction despite the proclivity of the product towards further reaction. Notably, under an atmosphere of argon, only substrate polymerization was observed. Recently, the scope of this reaction has been extended to cyclopentene-yne substrates, thus leading to the efficient synthesis of variety of carbo- and heterocycles including, pyrrolizidine, indolizidine, and quinolizidine derivatives.[61]

6.3. Ethylene-Promoted Intermolecular Alkyne–Ene Cross-Metathesis Reactions

In 2003, an elegant three-component cross-enyne reaction was described by Diver and co-workers [Eq. (2)].[62] In one
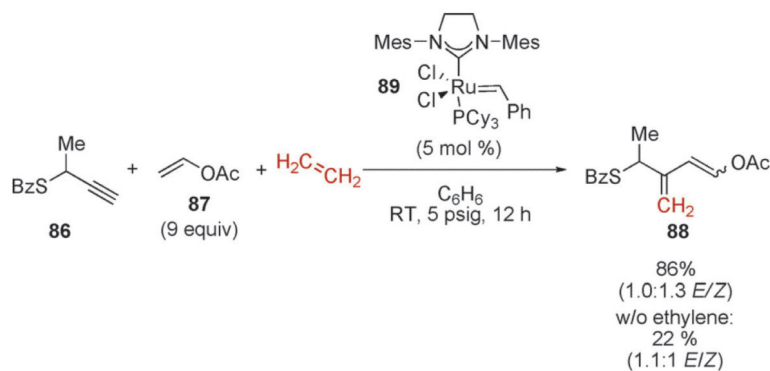
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example, the reaction between the propargyl thiobenzoate **86**, vinyl acetate **87**, and ethylene afforded the diene **88** in very good yield in the presence of Grubbs s second-generation catalyst (**89**), albeit with poor alkene stereoselectivity. The active species in this reaction may be either the methylidene $[LCl_2Ru=CH_2]$ or the acetoxyalkylidene $[LCl_2Ru=CHOAc]$. Interestingly, it was found that the methylene carbon atom in the product may arise either from ethylene or from vinyl acetate, since in the absence of ethylene, the desired product is still formed in 22% yield. This result suggests multiple reaction mechanisms may be operating simultaneously by either of the aforementioned active species. The synthesis of various substituted dienes using similar cross-enyne metathesis reactions have been reported by other groups.[63]

6.4. Ethylene in Intramolecular Ring-Closing Enyne Metathesis Reactions

There have been numerous reports describing the use of ethylene as a facilitator of inter- and intramolecular enyne metathesis processes.[64] For example, in 1998, Mori and co-workers observed a dramatic reactivity difference in the intramolecular ring-closing enyne metathesis (RCEYM) of terminal-alkyne-bearing substrates such as **90** in the presence of ethylene (Scheme 24).[65] They noted a low yield of **91** under an argon atmosphere, but under an atmosphere of ethylene quantitative yield was observed in just 2.5 hours. Several other enyne substrates reacted cleanly under the optimized reaction conditions to give five-, six-, or seven-membered carbo- or heterocycles in excellent yields.

In 2011, Fogg and co-workers provided significant mechanistic insight by finding that the alkene terminus of enyne substrates such as **90** reacts faster than the alkyne terminus, thus leading to the ruthenium alkylidene **93**.[66] In the presence of ethylene, the ruthenacyclobutane **94** and finally product **91** are formed. In the absence of ethylene, however, **93** reacts with the alkyne portion of **90** to form the alkylidene **95**, which can cyclize to form the ruthenacycle **96**. Fogg and co-workers detected similar ruthenacycles derived from different enyne substrates by MALDI-TOF mass spectrometry.

Surprisingly, the use of Grubbs s second-generation catalyst in the reaction between **90** and ethylene afforded a mixture of the anticipated product **91** (38%), but also the diene

byproduct **97** (12%, Scheme 25).[67] The authors attributed the formation of **97** to an initial ruthenacyclization to form the ruthenacyclopentene **98** with subsequent ethylene insertion to form the ruthenacycloheptene **99**. Subsequent β-hydride elimination could afford the ruthenium hydride **100**, which could reductively eliminate to give the exocyclic diene **97**.

Ethylene-incorporating RCEYM has been applied to the synthesis of the natural product (−)-longithorone A by Shair and co-workers (Scheme 26).[68] Although the RCEYM of **101** gave the macrocyclic 1,3-diene **102** with greater than 25:1 atropdiastereoselectivity and greater than 25:1 *E/Z* selectivity, an inseparable internal conjugated diene was observed. The benzylic silyl ether stereocenter is required for atropselectivity, as removal of the silyl protecting group led to a complex mixture of products. Using a similar metathesis protocol, the other macrocyclic diene product **104** was isolated from the substrate **103** in 31% yield. The yield is diminished because of modest atropdiastereoselectivity and alkene stereoselectivity (2.8:1 atropdiastereoselectivity, 3.9:1 *E/Z* selectivity). After a series of protections and deprotections, a Lewis-acid-mediated [4+2] cycloaddition of the 1,3-diene led to installation of one of two product cyclohexene rings.

Ethylene is a competent substrate, and is also kinetically suitable for the prevention of catalyst decomposition in enyne metathesis reactions. Since the seminal reports by Mori and co-workers, the reaction has been extensively used for the synthesis of a wide variety of unsaturated compounds.

7. Nonmetathetic Ethylene-Incorporating Ruthenium(II)-Catalyzed Functionalization Reactions of Alkynes via Ruthenacyclopentene Intermediates

7.1. Ruthenium(II)-Catalyzed Ethylene-Incorporating Oxidative Cyclizations of Enynes

Intrigued by the formation of **97** above (Scheme 25), Mori and co-workers optimized a reaction to access exocyclic conjugated dienes using **106** as a model substrate (Scheme 27).[67] The use of 5 mol% of non-alkylidenyl [Cp*RuCl(cod)] significantly enhanced the yield of the exocyclic diene **107** at room temperature within 3 hours. In fact, none of the metathesis product **108** was observed. The reaction was found to be quite general, as a wide variety of five-membered carbo- and heterocyclic products were accessed using this method. For example, the amides **97** and **109**, as well as the tertiary amine **110**, were formed in high yield. Highly conjugated products, such as **111**, arising from an ynone substrate, were formed in modest yield. Even the six-membered quinoline derivative **112**, derived from a 1,7-enyne substrate, was obtained under similar reaction conditions, with an improved yield at slightly lower temperature. To improve the understanding of the mechanism of the reaction, the deuterated enyne **113** was subjected to the optimized reaction conditions. The deuterated cyclized product **114** was obtained in 85% yield (with 90% deuterium incorporation), thus implying that a ruthenacycloheptene (similar to **99** above) may be an intermediate in this reaction.

Yet another unexpected result was observed by the Mori group while investigating the substrate scope of the above exocyclic diene formation.[69] They found that under identical

reaction conditions the 1,6-enyne **115**, featuring an acetylsubstituted internal alkyne, affords the bicyclic, cyclopropane-containing product **116** in quantitative yield (Scheme 28). None of the anticipated exocyclic diene **117** was observed. Enynes having different carbonyl substituents gave the corresponding bicyclic products in excellent yields, including *n*-propylcarbonyl and cyclohexylcarbonyl functional groups (**118** and **119**, respectively). However, substrates having a heteroatom in the tether between the alkene and alkyne reacted differently: the dienylcyclopentanes **120** and **121** were the only products observed. The reason for this discrepancy in reaction outcomes is unclear.

Mechanistically, the initial step of the dual ring-forming reaction could again be the formation of the ruthenacylclopentene **123** by oxidative cyclization of the enyne with [Cp*RuCl(cod)]. It was proposed that the oxygen atom of the carbonyl binds to ruthenium, thereby increasing the acidity of the proton at the ring junction and leading to the dienol **124**. Cleavage of the Ru–C bond could lead to the ruthenacyclobutene **125**, which is in equilibrium with the ruthenium alkylidene **126**. Subsequent ethylene insertion, followed by reductive elimination could yield the desired compound **128**.

7.2. Ruthenium(II)-Catalyzed Alkyne Hydrovinylation Reactions of Ynamides

Recently, a highly regio- and stereoselective rutheniumcatalyzed intermolecular hydrovinylation of ynamides with ethylene, leading to amino-1,3-dienes, has been reported (Scheme 29).[70] Although the oxidative cyclization of ruthenium(II) with ethylene and the ynamide **129** could give two possible regioisomeric ruthenacyclopentenes, **130** and **132**, only the former was likely formed under the reaction conditions: sequential b-hydride elimination and reductive elimination would account for the formation of **131**. The authors proposed that the ruthenium catalyst preferentially interacts with the relatively electrophilic β-carbon atom of the ynamide.[71]

As shown above, ruthenium(II)-catalyzed alkyne functionalization reactions proceeding through an oxidative ruthenacyclopentenation step provide selective access to interesting and potentially useful products.

8. The Synthesis of para-Xylene from Ethylene

para-Xylene is a central feedstock chemical in the polymer industry. It is primarily obtained by the catalytic reformation of petroleum, although its separation from common side products, including benzene, toluene, and other xylenes, is challenging.[72] In a recent report, Brookhart and co-workers have developed a selective synthesis of *para*-xylene using ethylene as the sole carbon-atom source (Scheme 30).[73] The reaction involves the initial formation of 1-hexene (**134**) by a homogeneous chromium-catalyzed trimerization of ethylene.[74] Subsequent transfer dehydrogenation using the iridium pincer complex **138** results in disproportionation into an inseparable mixture containing 15% of the desired 2*E*, 4*E*-hexadiene (**135**), which undergoes a Diels–Alder reaction with ethylene to give **136**. Finally, dehydrogenation over Pt/Al$_2$O$_3$ gives *para*-xylene, which is contaminated with ethylbenzene that has carried over from the Diels–Alder reaction of 1,3-hexadiene, which itself arose from the iridium-catalyzed transfer dehydrogenation. It should be noted that the Diels-Alder and dehydrogenation steps are amenable to a single-pot procedure.

The substantial increase in global energy demand requires adaptability to certain fuel supply shortages to meet our commodity chemical needs. This work by Brookhart and co-workers is an intriguing route to the synthesis of an industrially important fine chemical, namely *para*-xylene, from an ethylene feedstock that is increasing in supply.

9. Summary

As the most widely produced and readily functionalized hydrocarbon, ethylene has seen steady use as a feedstock for small-molecule synthesis, including in numerous recent reports of Mizoroki–Heck-type reactions. One promising but underdeveloped area in which ethylene may be especially useful is in asymmetric catalytic transformations, particularly those in which the double bond of ethylene is retained for subsequent functionalization. With respect to alkene hydrovinylation reactions, there are only a handful of substrate classes which can be transformed with high enantio- and regioselectivity since the product yield and enantioselectivity are marred by isomerization and oligomerization of the product. Therefore, the development of catalysts of superior efficiency, in terms of both yield and selectivity, is of high importance. Recent advances in chiral ligand design and synthesis could streamline rapid development in this field. The role of ethylene in enyne metathesis reactions is deeply rooted in the progress of this field, thus influencing not only synthetic utility, but also catalytic performance. The minimization of competing metathesis reactions in the presence of ethylene is notable.

Although significant efforts have been made to incorporate ethylene into fine chemicals and complex small molecules, the use of such reactions on an industrial scale is sorely lacking. This suggests that the use of ethylene in transitionmetal-catalyzed bond-forming reactions is still early in its evolution. We anticipate that sophisticated reactions of ethylene, amenable to diverse applications, will be reported with increasing frequency in years to come.

Acknowledgments

Biography

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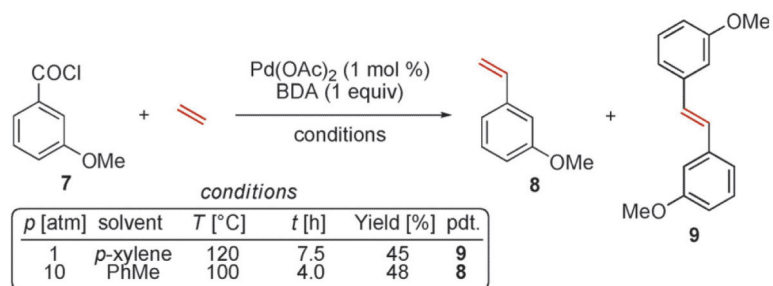
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a) Mizoroki Protocol (1971):

b) Heck Protocol (1978):

p [psi]	Yield [%]	**5/6**
20	88	61:39
120	90	96:04
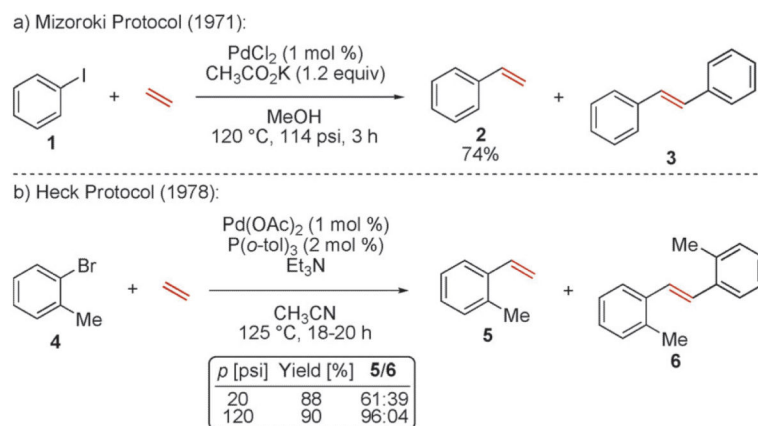
Scheme 1.
Palladium-catalyzed Mizoroki–Heck arylations of ethylene.

p [atm]	solvent	T [°C]	t [h]	Yield [%]	pdt.
1	p-xylene	120	7.5	45	**9**
10	PhMe	100	4.0	48	**8**

Scheme 2.
Palladium-catalyzed Mizoroki–Heck arylations of ethylene using benzoyl chloride electrophiles. BDA=benzyldimethylamine.
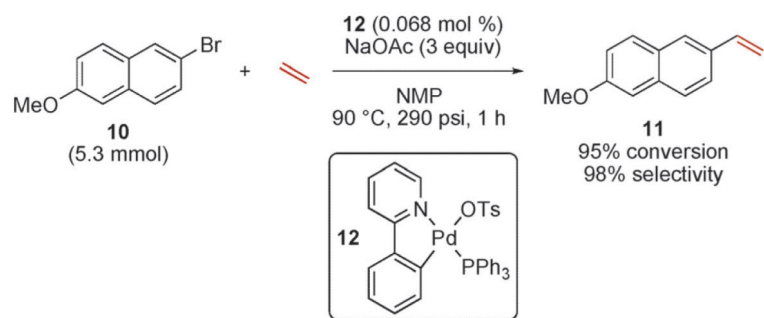
Scheme 3.
The C,N-palladacycle-catalyzed Mizoroki–Heck arylation of 2-bromo-6-methoxynaphthalene. NMP=1-methyl-2-pyrrolidone, Ts = 4-toluenesulfonyl.
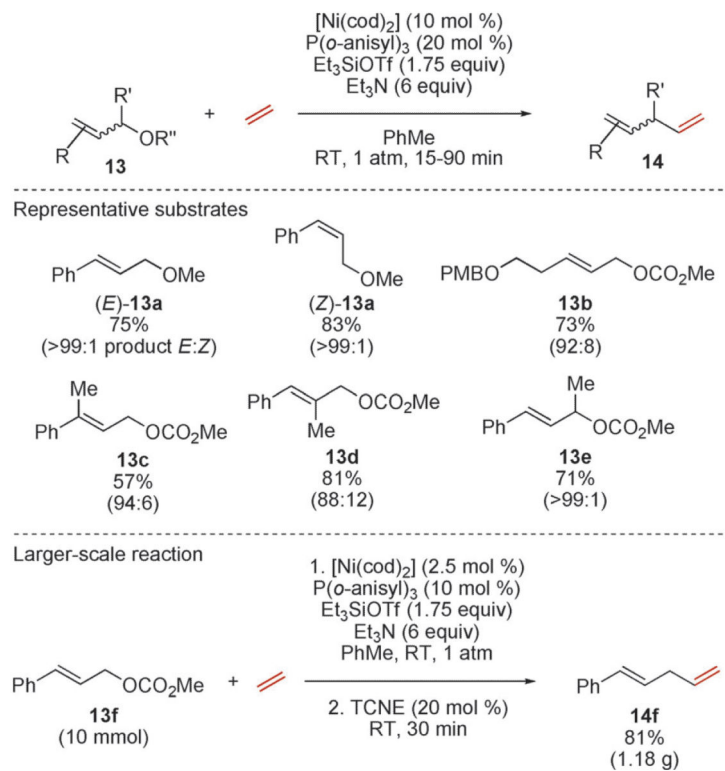
Scheme 4.
Nickel-catalyzed substitution reactions of allylic electrophiles with ethylene. cod = 1,5-cyclooctadiene, PMB = *para*-methoxybenzyl, TCNE = tetracyanoethylene, Tf = trifluoromeethanesulfonyl.
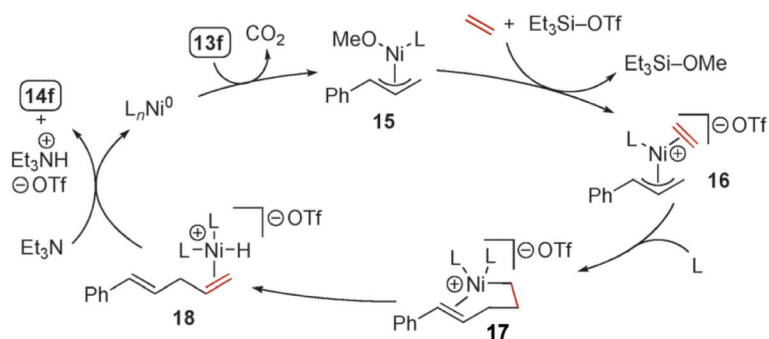
Scheme 5.
Proposed mechanism of the nickel-catalyzed allylic substitution reactions using ethylene.
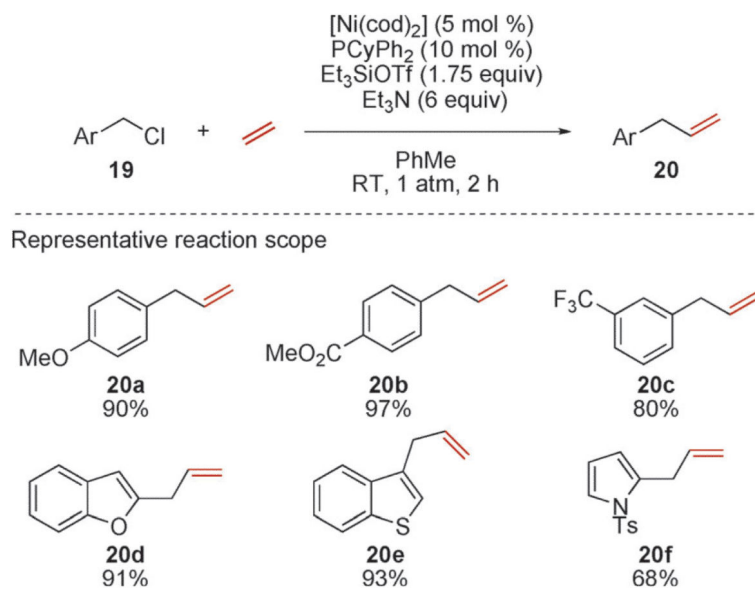
Scheme 6.
Nickel-catalyzed benzylation and heterobenzylation reactions of ethylene.
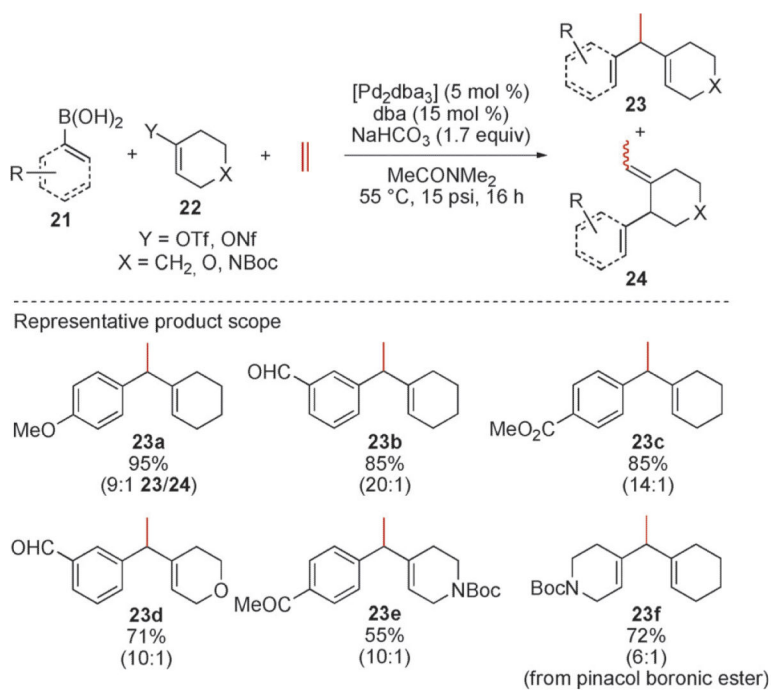
Scheme 7.
Palladium-catalyzed three-component couplings of ethylene to boronic acids and vinyl triflates and vinyl nonaflates. Boc=*tert*-butoxycarbonyl.
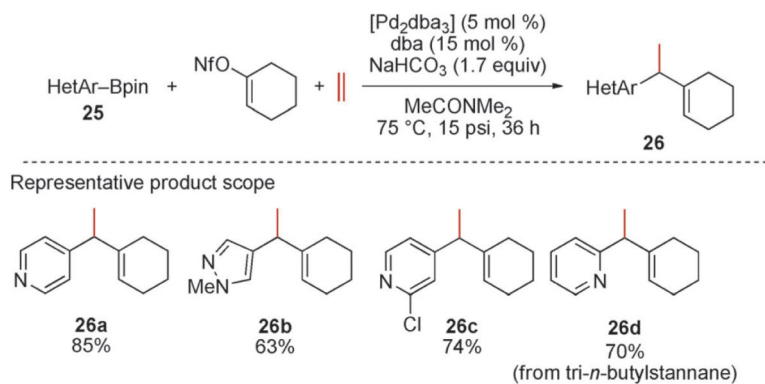
Scheme 8.
The use of heteroaromatic transmetalating reagents in palladium-catalyzed three-component couplings of ethylene to boronic acids and vinyl nonaflates. pin=pinacol.
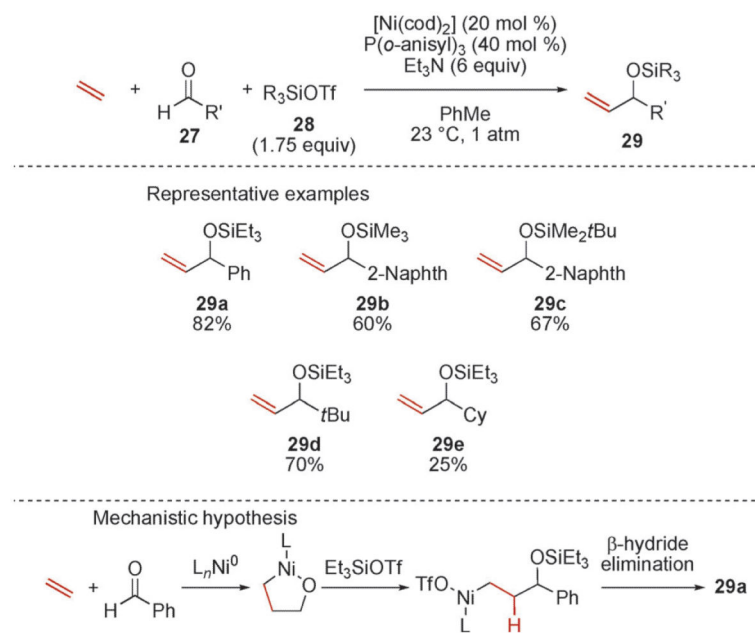
Scheme 9.
Nickel-catalyzed three-component couplings of ethylene to aldehydes and silyltriflates.

a) 1972

	[(allyl)NiCl]₂ (cat.)
30	PR₃ (3.8:1 P/Ni)
	Et₃Al₂Cl₃ (2.5:1 Al/Ni)
	CH₂Cl₂, 0 °C, 1 atm

PR₃ = (–)-dimenthylmethylphosphine

(S)-31
70% ee

b) 1973

[(allyl)NiCl]₂ (3.5 mol %)
PR'₃ (3.8:1 P/Ni)
Et₃Al₂Cl₃ (2.5:1 Al/Ni)
CH₂Cl₂, –65 °C, 1 atm, 3 h

32

(5R)-33
49%
78% ee

34
13%

PR'₃ = (–)-dimenthylisopropylphosphine
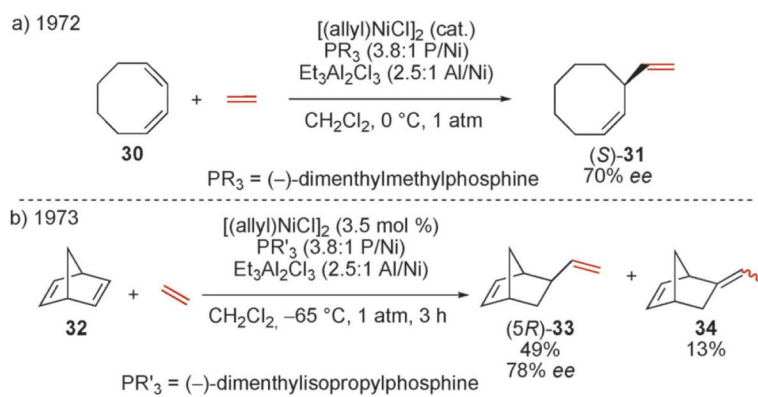
Scheme 10.
Wilke's protocol for the asymmetric hydrovinylation of biased alkenes.
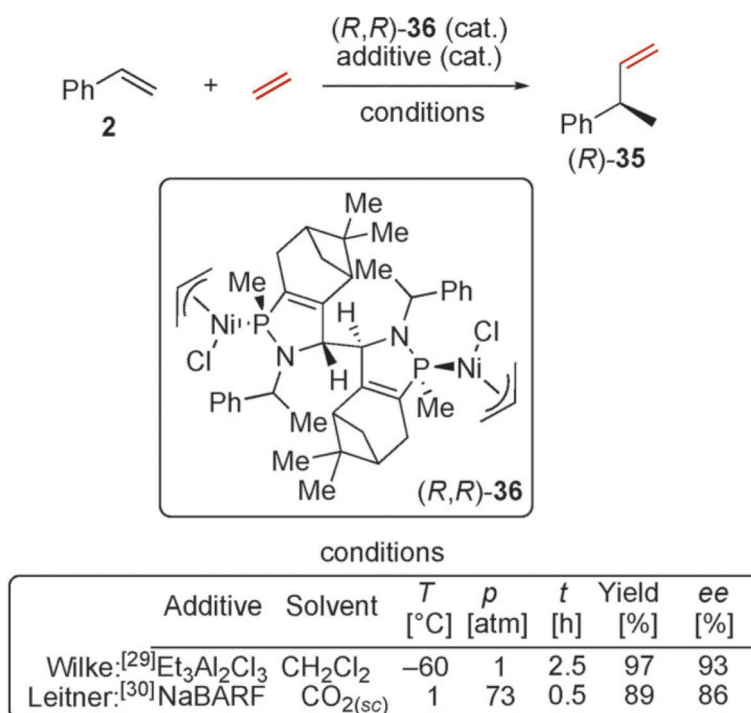
Scheme 11.
The use of pinene-derived azaphospholene ligands in asymmetric hydrovinylation reactions of styrene.
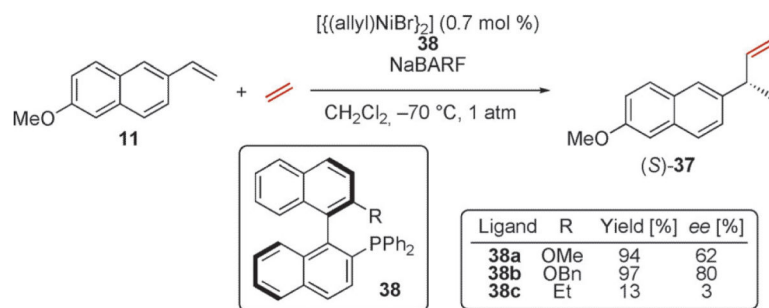
Scheme 12.
The use of hemibidentate phosphine ligands in asymmetric hydrovinylation reactions.
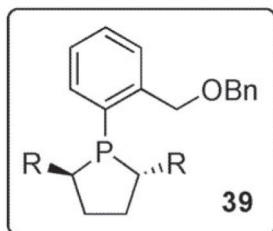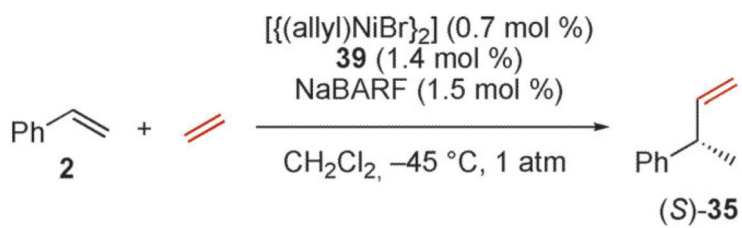
Scheme 13.
Use of dialkylphospholanes in asymmetric hydrovinylation reactions of styrene.
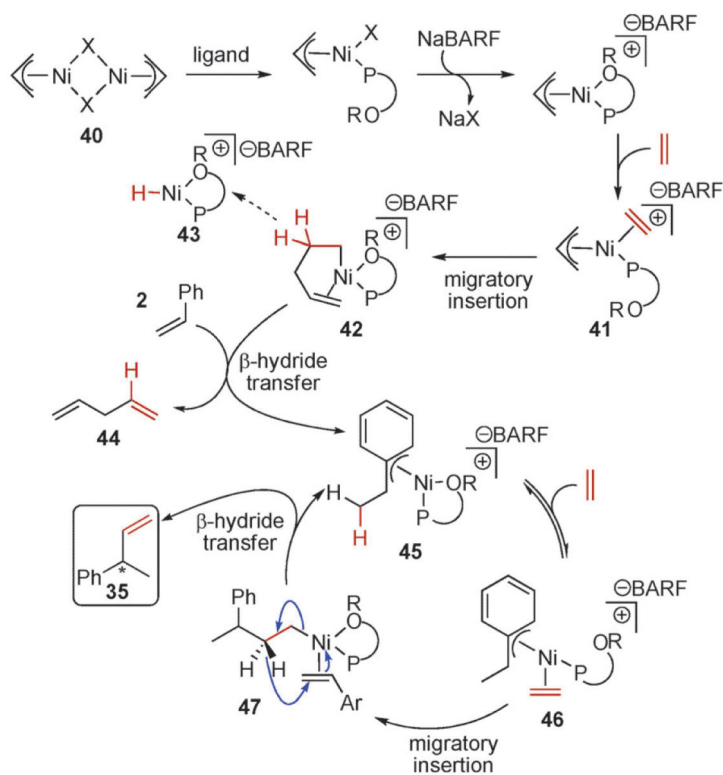
Scheme 14.
The proposed mechanism of nickel-catalyzed hydrovinylation reactions of styrenes using hemilabile phosphine ligands.
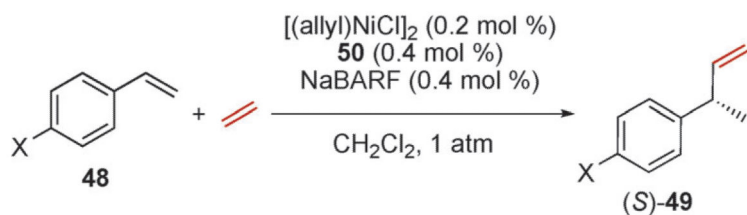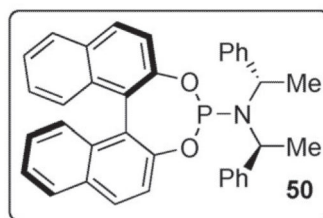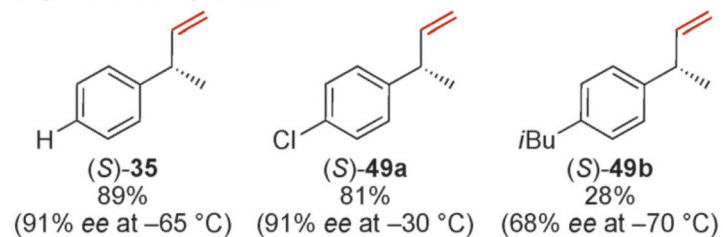
Scheme 15.
The use of phosphoramidite ligands in the asymmetric hydrovinylation of styrenes.
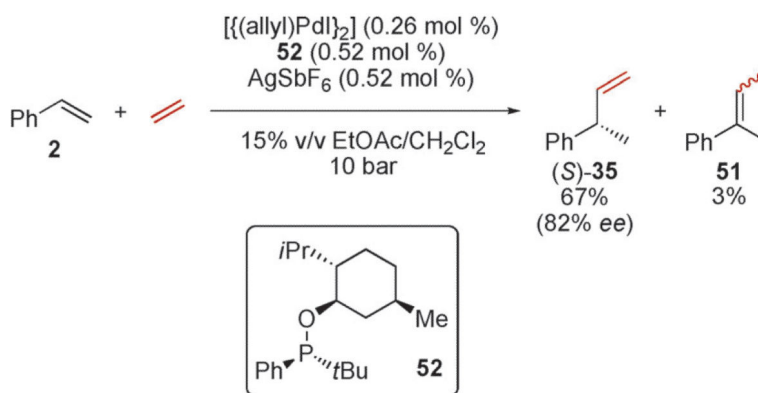
Scheme 16.
The use of menthol-derived phosphonite ligands in palladium-catalyzed asymmetric hydrovinylation reactions.
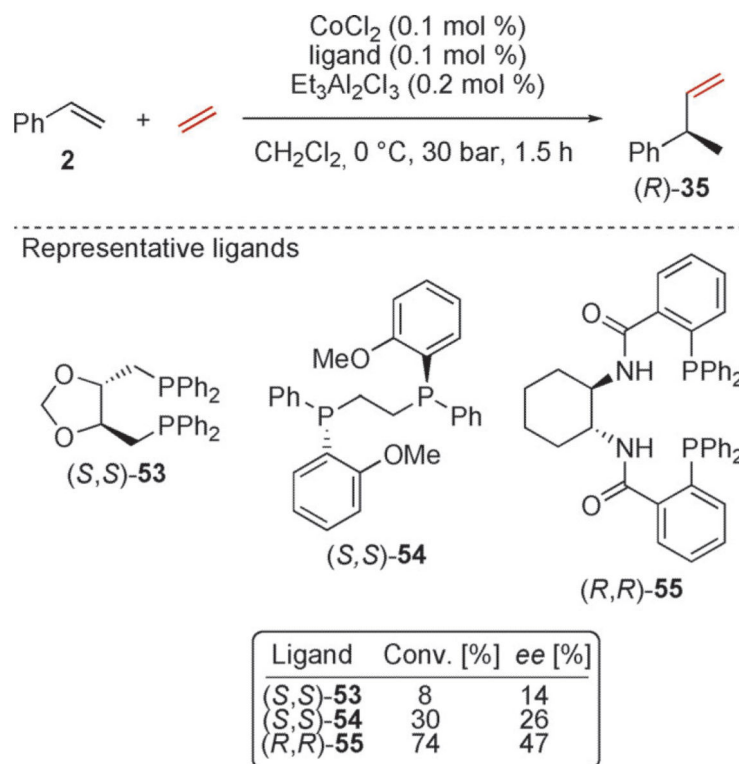
Scheme 17.
Cobalt-catalyzed asymmetric styrene hydrovinylation reactions.
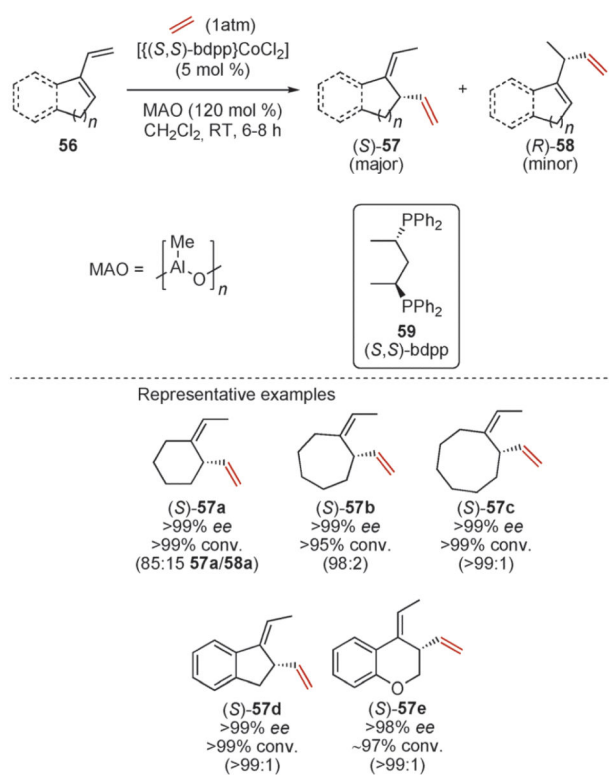
Scheme 18.
Cobalt-catalyzed 1,4-hydrovinylation reactions of vinylcycloalkenes.
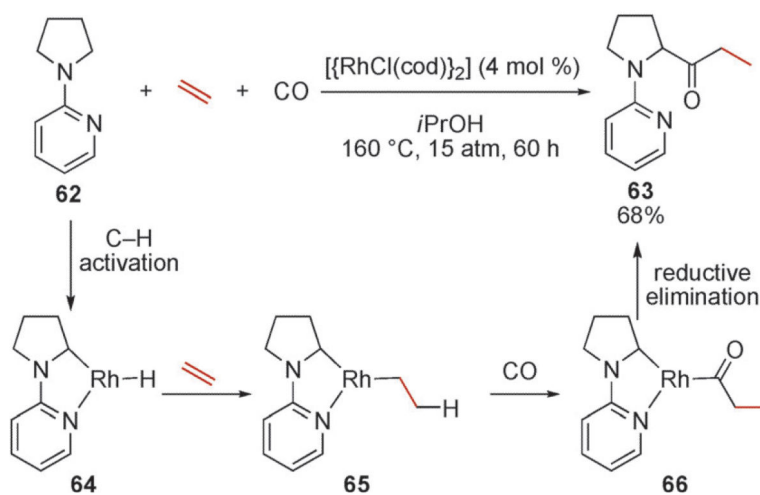
Scheme 19.
The rhodium-catalyzed three-component C_{sp3}–H functionalization of N-(2-*pyridyl*)pyrrolidine using ethylene and carbon monoxide.

Substrate	R	Yield [%]	68/69	69 d.r.
62	H	92	0:100	54:46
67a	6-Me	50	78:22	52:48
67b	4-CO$_2$Me	n.r.	n.a.	n.a.
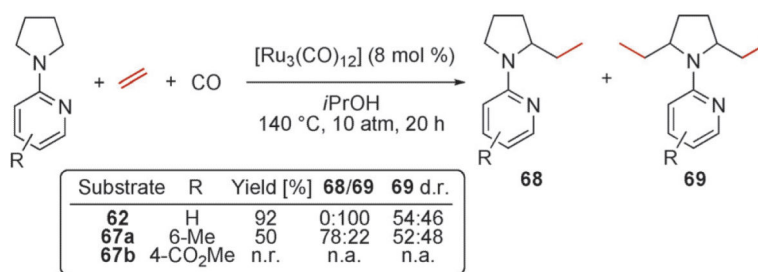
Scheme 20.
Ruthenium-catalyzed C$_{sp3}$–H ethylation reactions and their dependence on directing group functionality.
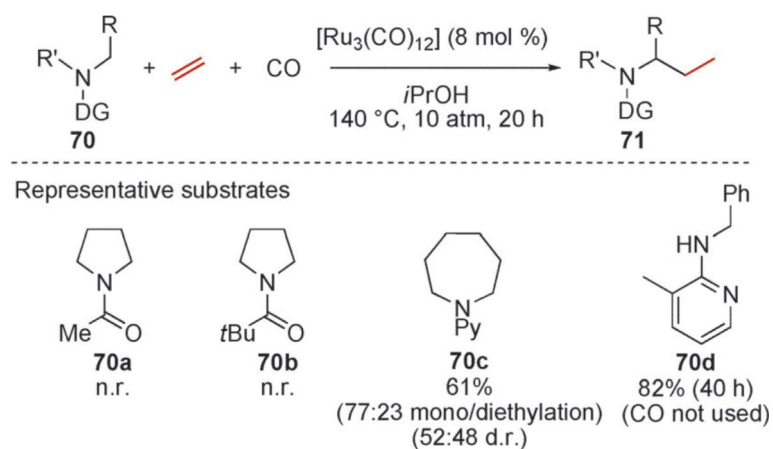
Scheme 21.
Additional substrate scope of directed ruthenium-catalyzed C–H ethylation reactions.
DG=directing group, Py=pyridyl.
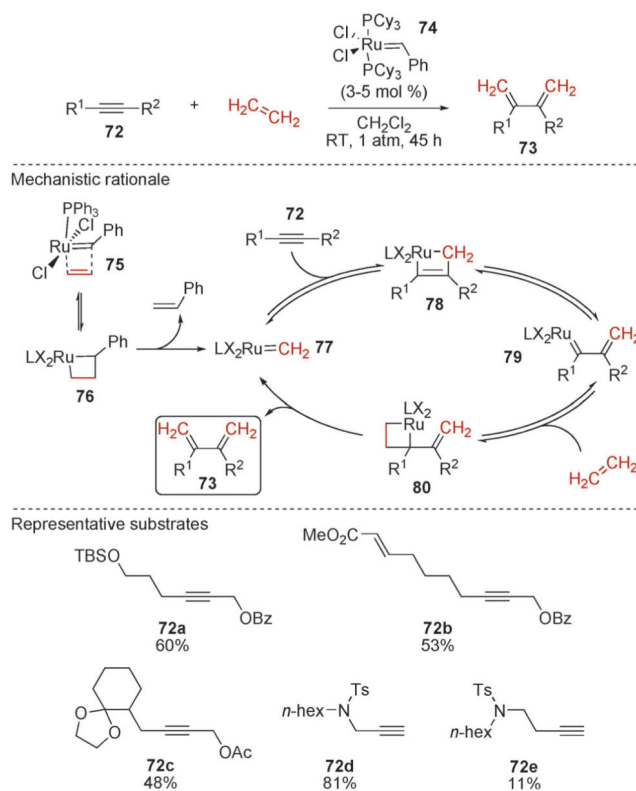
Scheme 22.
Ruthenium-catalyzed enyne metathesis reactions using ethylene as the alkene substrate.
Bz=benzoyl, TBS=tert-butyldimethylsilyl.
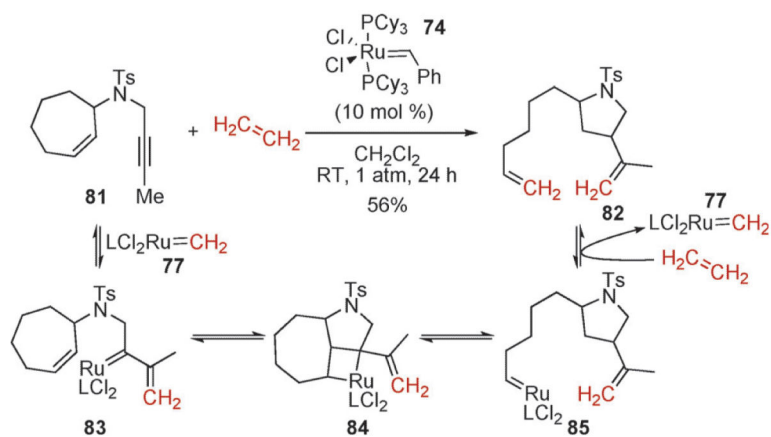
Scheme 23.
Ruthenium-catalyzed ring-closing/ring-opening reactions of alkynes with tethered cyclic alkenes in the presence of ethylene.
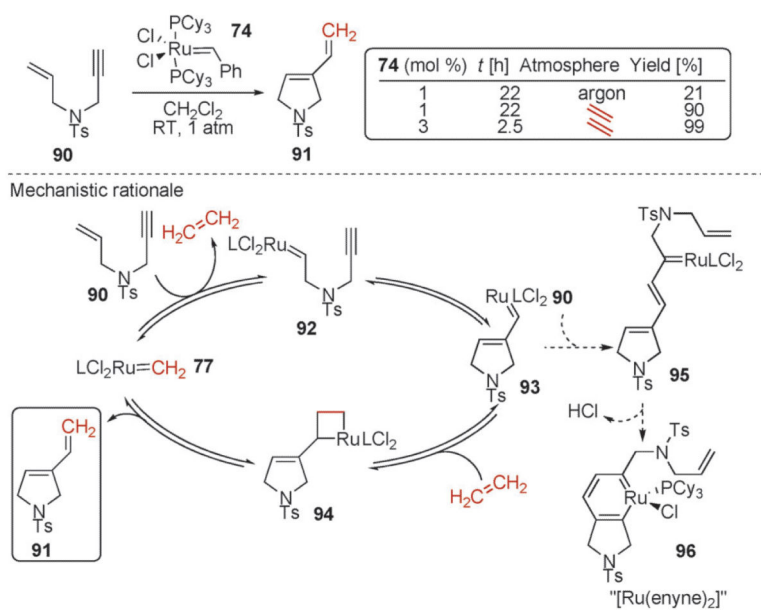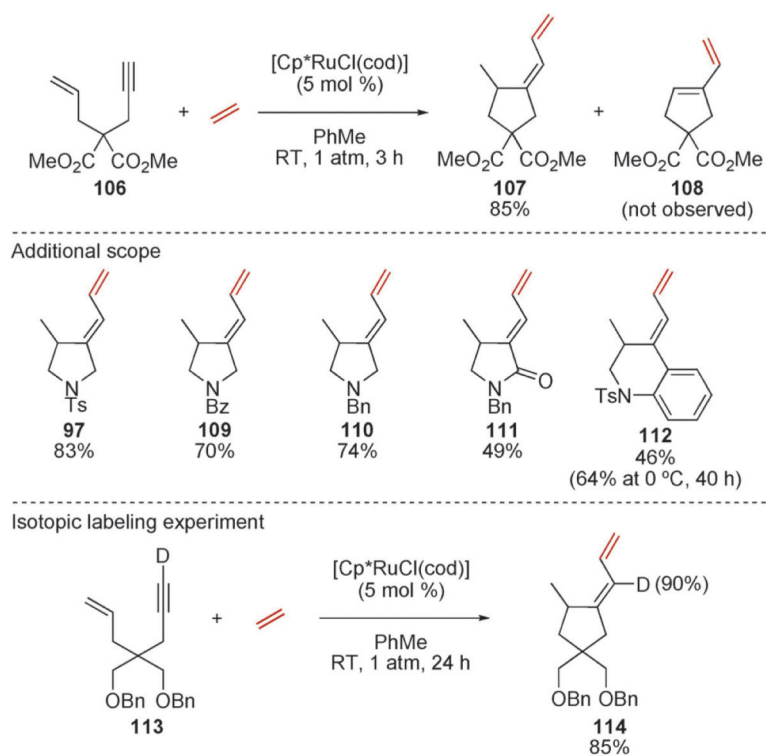
Scheme 24.
An ethylene-mediated ruthenium-catalyzed intramolecular enyne metathesis reaction.
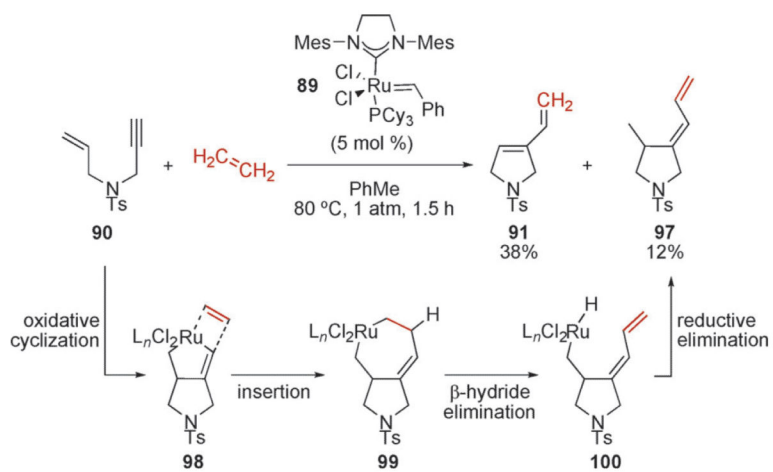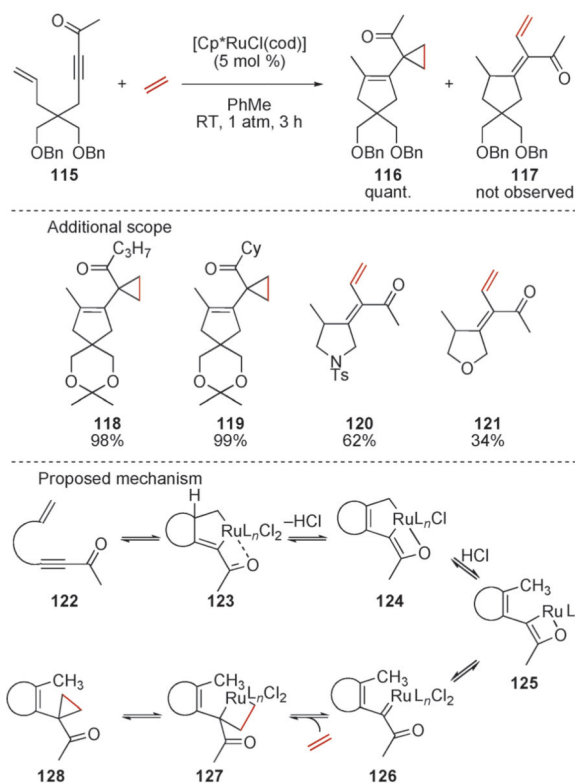
Scheme 25.
Oxidative cyclization of an enyne metathesis susbtrate in the presence of ethylene and Grubbs's second-generation catalyst.
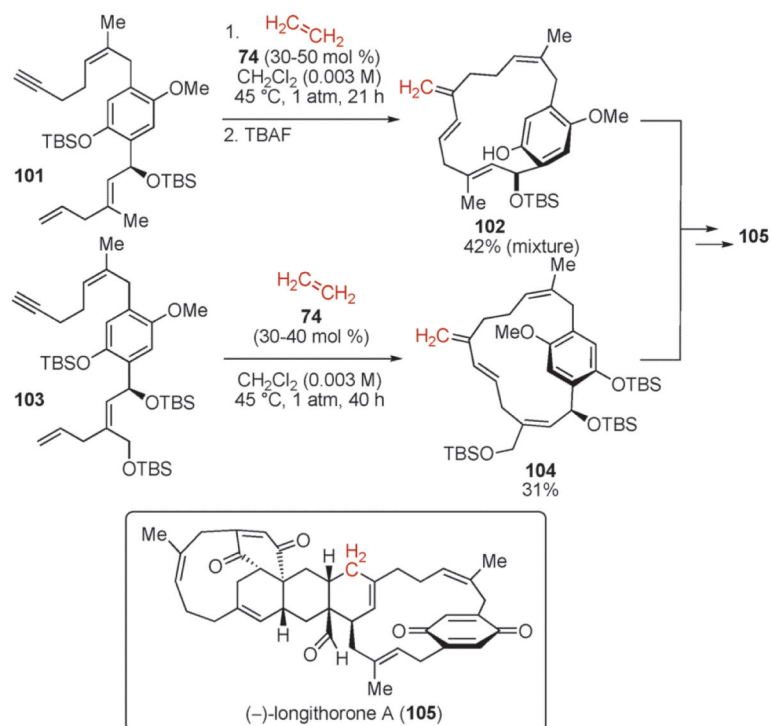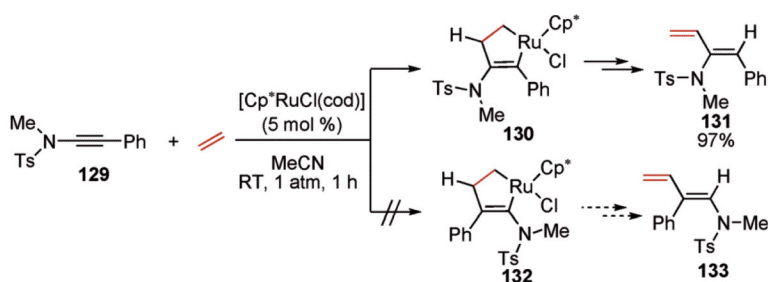
Scheme 26.
Application of ethylene-incorporating ring-closing enyne metathesis reactivity to the total synthesis of (−)-longithorone A. TBAF=tetra-*n*-butylammonium fluoride.
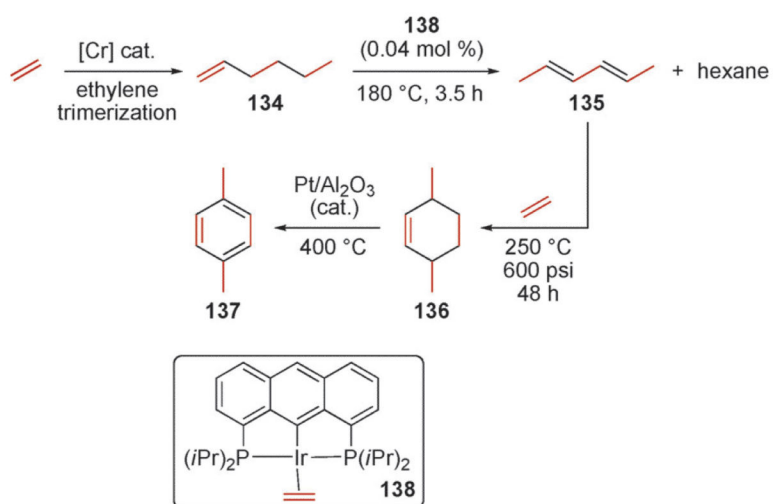
Scheme 27.
Optimization, scope, and mechanistic study of the ruthenium-catalyzed oxidative cyclization/exocyclic diene formation from diterminal 1,6-enynes.

Scheme 28.

The scope and proposed mechanism of the ruthenium(II)-catalyzed tandem cyclopentenation/cyclopropanation reaction of internal alkyne-containing 1,6-enynes.

Scheme 29.
A ruthenium-catalyzed intermolecular coupling reaction of ynamides and ethylene.

Scheme 30.
Brookhart's ethylene-based *p*-xylene synthesis.