CHEMICAL REVIEWS

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Review

Recent Advances in Alkenyl sp^2 C−H and C−F Bond Functionalizations: Scope, Mechanism, and Applications

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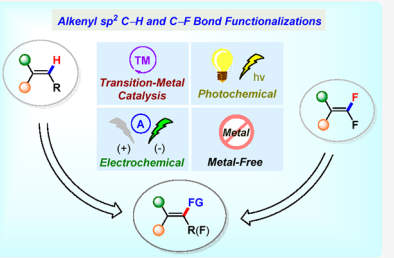
ABSTRACT: Alkenes and their derivatives are featured widely in a variety of natural products, pharmaceuticals, and advanced materials. Significant efforts have been made toward the development of new and practical methods to access this important class of compounds by selectively activating the alkenyl C(sp^2)−H bonds in recent years. In this comprehensive review, we describe the state-of-the-art strategies for the direct functionalization of alkenyl sp^2 C−H and C−F bonds until June 2022. Moreover, metal-free, photoredox, and electrochemical strategies are also covered. For clarity, this review has been divided into two parts; the first part focuses on currently available alkenyl sp^2 C−H functionalization methods using different alkene derivatives as the starting materials, and the second part describes the alkenyl sp^2 C−F bond functionalization using easily accessible *gem*-difluoroalkenes as the starting material. This review includes the scope, limitations, mechanistic studies, stereoselective control (using directing groups as well as metal-migration strategies), and their applications to complex molecule synthesis where appropriate. Overall, this comprehensive review aims to document the considerable advancements, current status, and emerging work by critically summarizing the contributions of researchers working in this fascinating area and is expected to stimulate novel, innovative, and broadly applicable strategies for alkenyl sp^2 C−H and C−F bond functionalizations in the coming years.



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1. INTRODUCTION

Alkenes and their derivatives belong to an important class of compounds in organic chemistry because they are key fragments featured widely in a myriad of pharmaceuticals, bioactive natural products, and advanced functional materials. Furthermore, they can also serve as versatile building blocks in a diverse variety of synthetic transformations. Due to the importance of this class of compounds, numerous conceptually different methods have been developed for the efficient construction of alkenes and their derivatives including cyclic alkenes. Moreover, the stereoselective and intramolecular versions of these methods have also been achieved. Reported methods include the Nobel Prize winning reactions such as the Wittig reaction,[1−3] olefin metathesis,[4−8] and transition-metal catalyzed cross-coupling reactions.[9] While these reactions are extremely efficient and useful, they are still plagued with various problems. For example, the poor atom-economy of the Wittig reaction, poor selectivity control for highly substituted alkenes, as well as disposal problem associated with the phosphine oxide significantly limiting their widespread applications, especially for large production of many value-added alkenes. On the other hand, cross-coupling and olefin metathesis reactions often require the use of expensive transition-metal catalysts and environmentally unfriendly organohalides and/or organometallics. This inevitably leads to the generation of halide wastes and the need to prepare the organometallics. Accordingly, there has been much effort directed toward the development of greener, atom-economical, and practical methods to obtain alkenes and their derivatives starting from simple alkenes or commercially available chemical feedstocks.

An alternative and highly sought-after strategy for the synthesis of value-added alkene molecules is to apply an alkenyl sp^2 C−H activation that can directly functionalize a simple alkene substrate without the preinstallation of an activating group.[10,11] It is often argued that a retrosynthetic scheme based on C−H functionalization is more straightforward and offers higher atom economy. Despite the high alkene sp^2 C−H bond dissociation energy (110 kcal/mol, *cf.* 101 kcal/mol of sp^3 C−H bond dissociation energy),[12] we have witnessed a surge in research activities in the development of new, practical, and broadly applicable methods for the alkenyl sp^2 C−H bond functionalization to access value-added alkenes and their derivatives that traditionally could only be obtained through tedious multistep synthesis.[13−17] Compared to aryl sp^2 C−H activation, the alkenyl C−H functionalization reactions, however, have gained less attention because of its strong π-coordinating ability of C═C double bond to the catalyst that may to some extent inhibit C−H activation process. Remarkably, the alkenyl C−H activation seems to be more sensitive to steric hindrance, and the C−H functionalization of multisubstituted alkenes is more challenging. In addition, the α- *vs* β-C−H bond and the problem associated with *E* and *Z* selectivities are also problems that are prevalent in alkenyl C−H bond functionalizations. Furthermore, the need for selective C−H activation of the different substrates poses additional challenges to overcome.

Similar to alkenyl sp^2 C−H bond, the alkenyl sp^2 C−F bond functionalization of *gem*-difluoroalkenes have also been included in this review as it can be easily synthesized from carbonyl compounds and, in many cases, the C−F bond functionalizations proceed through similar mechanisms with alkenyl sp^2 C−H bond functionalizations. The alkenyl sp^2 C−F bond functionalizations have attracted ever-increasing attention, especially in polymer synthesis. For example, Teflon is readily synthesized *via* the homopolymerization of tetrafluoroethylene (TFE), which is a bulk organofluorine feedstock. The development of robust strategies to selectively functionalize the alkenyl C−F bonds of multisubsituted fluorinated compounds such as *gem*-difluoroalkenes, and their analogues will provide a wider access to many extremely interesting fluorinated building blocks.[18−26] However, the functionalization of alkenyl sp^2 C−F bonds has been considered to be difficult because of their high bond dissociation energies (130.6 kcal/mol for TFE),[12] especially in the presence of weaker C−H or C−X bonds, where X = Cl, Br, *etc.* Nevertheless, many solutions have been successfully established such as the design of metal ligands with steric constraints. It shoud be mentioned that this review focuses on alkenyl sp^2 C−F bond functionalization of *gem*-difluoroalkenes and their analogues, methods of C−X bond functionalization of other *gem*-dihalovinyl systems or aryl halides will not be covered.[27−30]

Over the past several decades, transition metals such as Pd, Rh, Ir, Ru, Cu, Fe, Mn, and Co have been extensively employed to selectively functionalize alkenyl sp^2 C−H and C−F bonds. A variety of different coupling partners such as α,β-unsaturated systems, hypervalent iodine reagents, organometallics, *etc.*, have been widely utilized in these reactions. In this review, we will focus on the latest advances in the development of such new and practical methods for the

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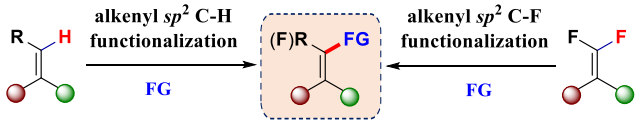
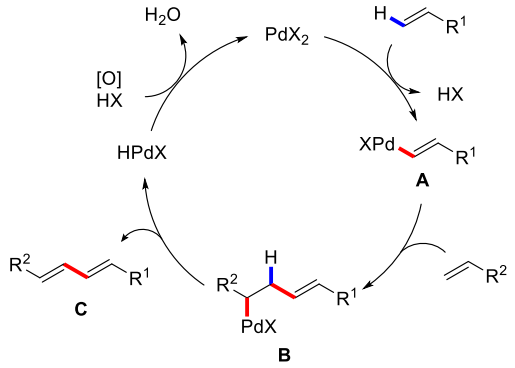
selective transition metal-catalyzed alkenyl sp^2 C−H bond functionalization of alkene substrates and alkenyl sp^2 C−F bond functionalization of *gem*-difluoroalkenes (Scheme 1).

Scheme 1. Alkenyl sp^2 C−H and C−F Bond Functionalizations



The mechanism of alkenyl sp^2 C−H activation by different transition metals has been extensively investigated by many research groups. In this section, we will highlight the general catalytic mechanism scheme for the reactions catalyzed by palladium and rhodium catalysts. For the Pd-catalyzed alkenyl C(sp^2)−H activation, we can draw a generalized catalytic cycle as shown in Scheme 2. Initially, the palladium catalyst activates

Scheme 2. General Mechanism of Palladium-Catalyzed Alkenyl sp^2 C−H Bond Functionalizations

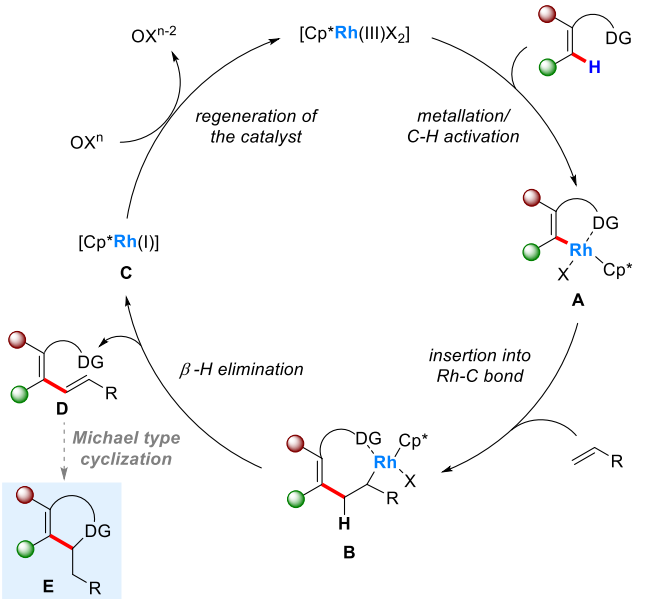


the electron-rich alkene substrate by the generation of vinyl palladium intermediate **A**. Then the incoming electron-deficient alkene coordinates to the intermediate **A**, which follows a migratory insertion into the palladium−C$_{vinyl}$ bond to produce the σ-Pd intermediate **B**. Finally, β-H elimination results in the formation of the expected coupling product **C**, while the oxidants employed in the reaction reactivates the catalyst for the next catalytic cycle. It is important to note that the vinyl palladium species **A** can be either generated by a 1,2-addition process followed by deacetylation or *via* a direct C−H bond activation process. The difference in the reactivities of *Z*- and *E*-1,2-substituted sp^2 C−H bonds of alkenes indicate that direct C−H activation is probably involved in this process.

The generalized mechanism of the directed alkenyl sp^2 C−H activation of the reactions catalyzed by rhodium is depicted in Scheme 3. The rhodium catalyst activates the C−H bond by coordinating to the directing group to form the rhodium−substrate complex **A**, which in turn inserts into the incoming functional groups to form the new C-FG bond **B**. The newly formed complex undergoes β-H elimination to furnish the coupling products **D**. Finally, the active rhodium catalyst is regenerated by the oxidants employed in the reaction.

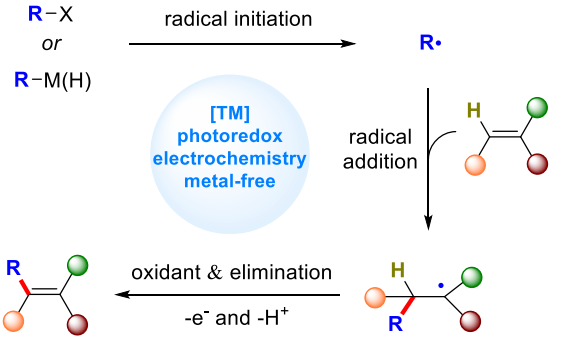
In addition to the common mechanisms proposed for alkenyl C−H bond functionalization by using transition metal catalysts such as palladium and rhodium, another type of alkenyl C−H bond functionalization involves the formation of carbon-centered radicals or heteroatom-centered radicals

Scheme 3. General Mechanism of Rhodium-Catalyzed Directed Alkenyl sp^2 C−H Bond Functionalizations



(Scheme 4). These processes often occur through radical addition to alkene substrates followed by single-electron

Scheme 4. General Mechanism of Alkenyl sp^2 C−H Bond Functionalizations through Radical Processes



transfer (SET) oxidation/elimination under transition-metal catalysis or metal-free conditions. Moreover, the sustainable alkenyl C−H functionalization promoted by photoredox catalysis or electrocatalysis usually involves a radical species. These types of reactions can be carried out in the absence of radical initiators.

Overall, this comprehensive review attempts to describe a panoramic overview of the direct functionalization of alkenyl sp^2 C−H and C−F bonds, with an emphasis on their scope, limitations, and underlying mechanisms. For clarity, this review has been divided into two parts. The first part focuses on alkenyl sp^2 C−H functionalization methods using different alkene derivatives as the starting materials, and we organized this part according to the representative types of olefins used in the reactions, including simple alkenes, aliphatic alkenes containing a directing group, alkenes containing an electron-withdrawing directing group, and alkenes containing a heteroatom. The second part systematically summarizes the alkenyl sp^2 C−F bond functionalization by using easily accessible *gem*-difluoroalkenes as the starting material. In contrast to the alkenyl sp^2 C−H bond functionalization part,

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this section has been categorized according to the coupling partners. In this review, methods published prior to the end of June 2022 are presented. We hope this review can provide a critical, panoramic picture as well as an outlook of this fascinating field and will contribute to inspire continuous research interest and stimulate new breakthroughs in the development of novel and innovative strategies to expand the toolbox of alkenyl sp^2 C−H and C−F bond functionalization reactions, which eventually can drive this fascinating field to a much higher height with more and broader practical applications.

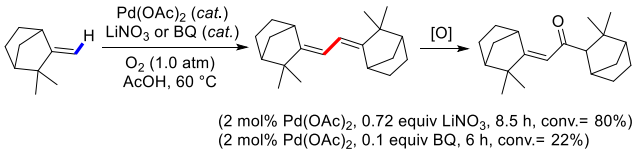
2. ALKENYL C−H BOND FUNCTIONALIZATION OF SIMPLE ALKENES

As mentioned above, alkenes and their derivatives are important compounds in organic synthesis. In this part of the review, we will focus on the development of the synthesis of complex alkenes and their derivatives starting from simple and easily accessible alkenes *via* alkenyl C(sp^2)−H bond functionalization. It is organized based on the coupling reactions involving different types of simple alkenes. Strategies to control the stereochemistries (regio, *E*/*Z*, *etc.*) as well as the intramolecular versions are also included.

2.1. Direct Alkenyl C−H Bond Functionalization of Simple Alkenes

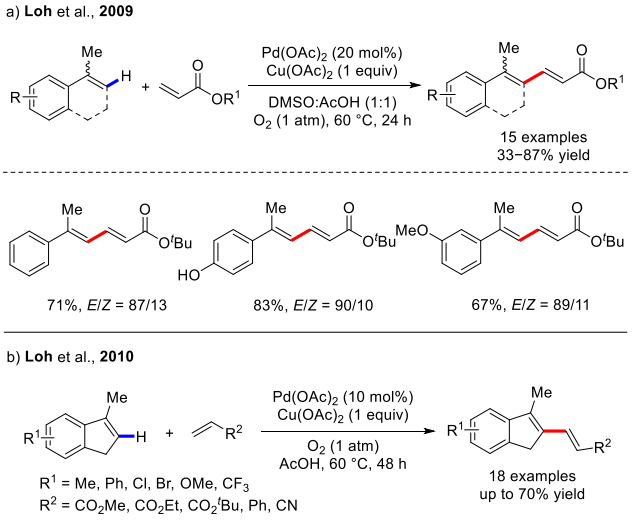
In early 2000, Gusevskaya and co-workers reported a palladium-catalyzed dimerization of camphenes under aerobic oxidative conditions (Scheme 5).[31,32] In AcOH, employing $Pd(OAc)_2$/benzoquinone or $LiNO_3/O_2$ (1.0 atm), the dimerized products were isolated.

Scheme 5. Palladium(II)-Catalyzed Dimerization of Camphenes



Although a cross-coupling reaction between two different simple olefins is synthetically useful, it is significantly more difficult to realize. This is probably due to the difficulty to preferentially activates one alkenyl sp^2 C−H bond over the other. In search of new methods for the synthesis of conjugated dienes that are commonly encountered in numerous natural products and drug candidates with remarkable biological activities,[33,34] the first ever simple alkene−alkene cross-coupling reaction was disclosed by Loh's group in 2009. By exploiting the steric and electronic properties of different alkenes, they successfully established the first cross-coupling of this process by reacting α-substituted styrenes with acrylates (Scheme 6a).[35] The direct cross-coupling reaction between simple alkenes and acrylates could be generally achieved in high efficiency with a catalytic amount of Pd catalyst under typically mild reaction conditions. In the mixture of DMSO/AcOH solvent, employing 20 mol % of $Pd(OAc)_2$ catalyst and 1.0 equiv of $Cu(OAc)_2$ under O_2, various conjugated 1,3-butadienes with different substitution patterns were smoothly synthesized in moderate to good yields (33−87%). Although an exceptional reaction was developed, the reported method has many limitations such as relatively

Scheme 6. Oxidative Cross-Coupling Reactions of 2-Substituted Alkenes with Acrylates



high catalyst loading, low *E*/*Z* regioselectivities, and the need to use α-substituted aryl alkenes, *etc.* In an attempt to render this strategy more general and convenient, Loh and colleagues in 2010 extended to establish a cross-coupling reaction between indenes and various electron-deficient alkenes using $Pd(OAc)_2$ (10 mol %) as the catalyst (Scheme 6b).[36]

Exploring the generality of this strategy, Loh's group further disclosed a general protocol of the palladium-catalyzed cross-coupling reaction of readily available either TIPS-protected allylic or homoallylic alcohol substrates with a broad scope of acrylates, giving rise to a number of synthetically attractive conjugated dienyl alcohols in moderate to high yields with reasonable stereoselectivity. Gratifyingly, the presented strategy could be applied to the assembly of the key C13−C21 fragment of palmerolide A (Scheme 7).[37]

Encouraged by this success, Loh's group substantially extended to disclose a remarkable palladium-catalyzed direct cross-coupling reaction between simple diverse alkenes without an α-substitution and acrylates in the presence of a monoprotected amino acid (MPAA) as the ligand to afford the products with moderate to good *E*/*Z* selectivity (Scheme 8).[38] A broad substrate scope (33 examples) of this transformation was documented with yields of 35−86%. This atom- and step-economical strategy offers a direct method to construct new C−C bonds of synthetically useful dienes from readily available starting materials under benign conditions. It is interesting to note that Loh and co-workers also observed that the reactions with *Z*- and *E*-alkenes gave different results. In contrast to the *E*-alkenes, the *Z*-alkenes generates the products in good yields. On the basis of these results, they proposed that the alkenyl sp^2 C−H activation mechanism is most probably operative in this type of reaction. An alternative mechanism involving 1.2-addition of alkene followed by facile elimination to generate the vinylic palladium was previously proposed as a possible catalytic mechanism. If this is the mechanism, the reaction should proceed similarly irrespective of the geometry of the alkenes.

Mechanistic studies provided further insights into the origins of this process. Later in 2016, Wu and co-workers combined DFT calculation and mass spectrometry to extensively elucidate on the possible mechanism of this Pd(II)/mono-*N*-protected amino acid (MPAA)-catalyzed alkene−alkene

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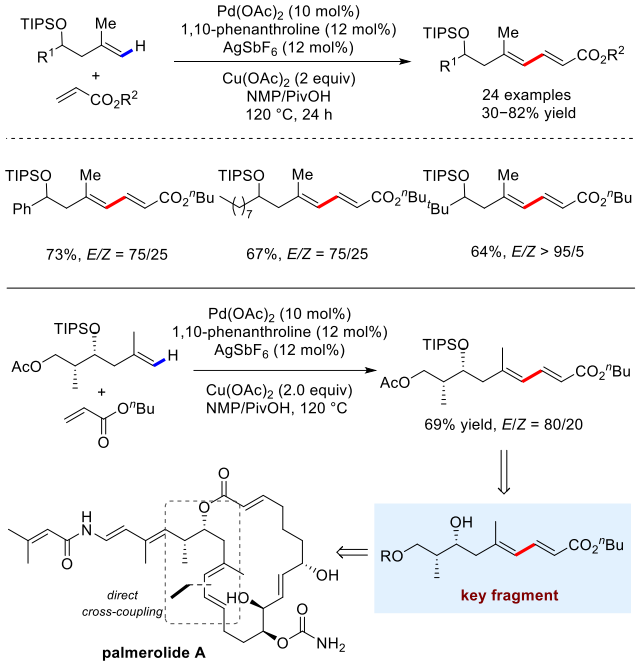
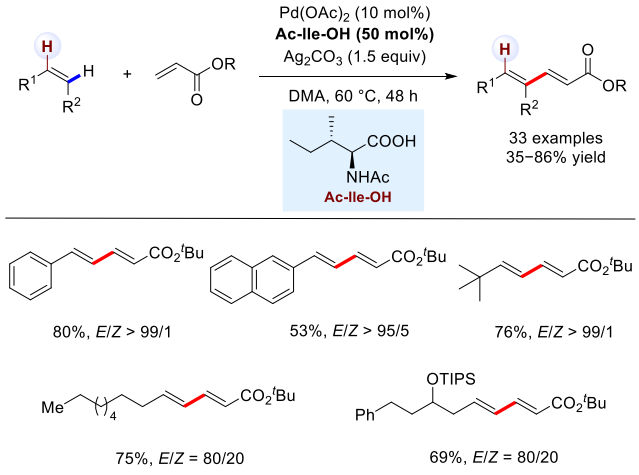
Scheme 7. Palladium(II)-Catalyzed Cross-Coupling of Unactivated Alkenes with Acrylates



Scheme 8. Palladium(II)-Catalyzed Cross-Coupling Reactions of Simple Alkenes with Acrylates

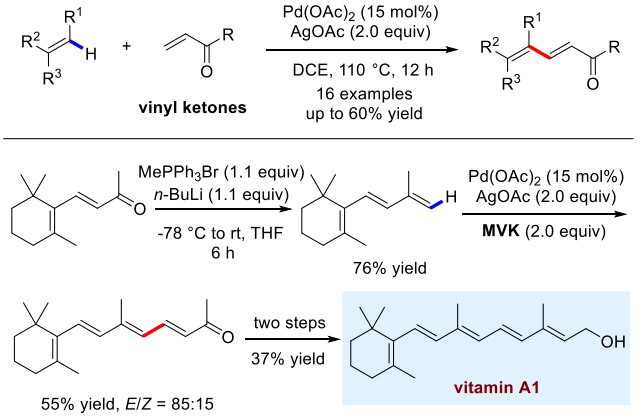


coupling reactions and revealed that the strong binding of MPAA to Pd catalyst and basicity of the *N*-protecting group greatly facilitate the C−H activation step by stabilizing the active palladium catalyst, while the *E*/*Z* selectivity is mainly attributed to the interaction energy between the catalyst and alkene substrates.[39]

Due to the high potential for polymerization, unsaturated ketones such as methyl vinyl ketone (MVK) are rarely employed as the partners in cross-coupling reactions. In 2013, Loh's group introduced a promising approach for the efficient synthesis of conjugated dienyl ketones enabled by palladium(II)-catalyzed cross-coupling reaction of simple alkenes with a series of vinyl ketones (Scheme 9).[40] Of note, the practicality of this strategy was elegantly illustrated by the straightforward synthesis of vitamin A1 and bornelone.

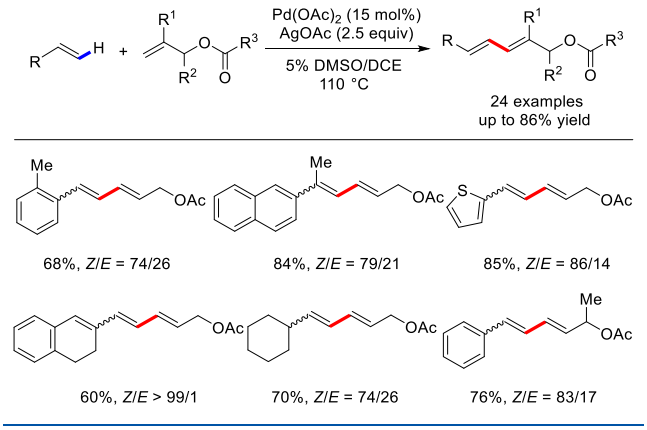
Since these initial reports, extensive studies by various research groups have been carried out to expand this alkene−

Scheme 9. Palladium(II)-Catalyzed Oxidative Cross-Coupling of Alkenes and Vinyl Ketones



alkene coupling reactions. For example, Liu and co-workers in 2012 developed a double vinylic C−H bond functionalization strategy to access diverse conjugated 1,3-dienes using Pd(OAc)$_2$ as the catalyst. The reaction occurred uneventfully with styrenes without an α-substitution as well as a series of unactivated aliphatic alkenes, showcasing an elegant route for the synthesis of 1,3-butadienes (Scheme 10).[41] Nevertheless,

Scheme 10. Palladium(II)-Catalyzed C−H Olefination of Alkenes with Allylic Acetates and Acrylates



this protocol has the disadvantages of having to use 15 mol % of Pd(OAc)$_2$ catalyst as well as 2.5 equiv of AgOAc in order to obtain the coupling products in satisfactory yields.

A more practical and efficient approach for the synthesis of conjugated dienes with low catalyst loading through biomimetic aerobic oxidative cross-coupling of two different C_{vinyl}−H bonds has been developed by the Bäckvall group in 2013 (Scheme 11).[42] They employed only 5 mol % of Pd(OAc)$_2$ with catalytic amounts of electron-transfer mediators such as iron phthalocyanine and *p*-benzoquinone in the presence of O_2 to achieve the synthesis of conjugated dienes with a broad set of alkene substrates.

The palladium-catalyzed oxidative Heck reaction, a synthetically attractive transformation in which an olefinic C−H bond is generally converted into a C−C bond, has widespread applications in modern organic synthesis.[43] However, the overwhelming majority of these protocols require the use of electronically biased olefins such as acrylates or α,β-unsaturated carbonyls in order to achieve high selectivity for the (*E*)-styrenyl products. In 2008, White *et al.* reported an

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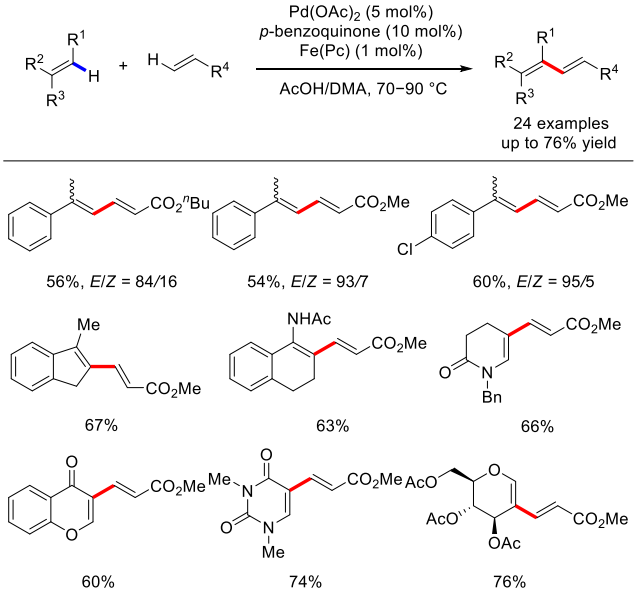
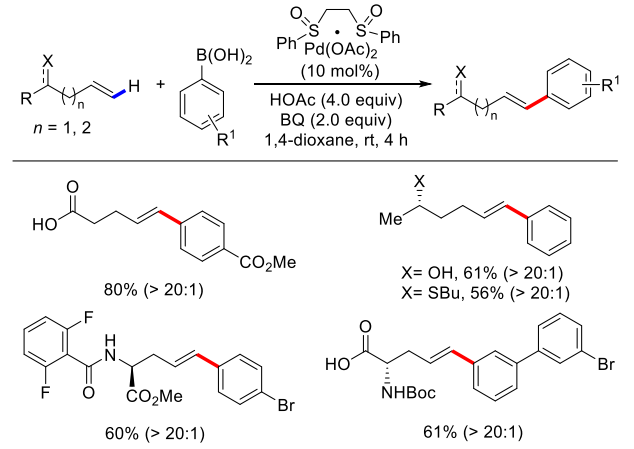
Scheme 11. Biomimetic Aerobic Oxidative Coupling of Simple Alkenes with Various Olefins



efficient substrate chelate-controlled oxidative Heck reaction enabled by a versatile Pd(II)/bis-sulfoxide catalyst that proceeds smoothly with outstanding selectivities for non-resonance biased α-olefins bearing proximal oxygen and nitrogen functionality, thus affording a wide range of coupling products in good yields (Scheme 12).[44]

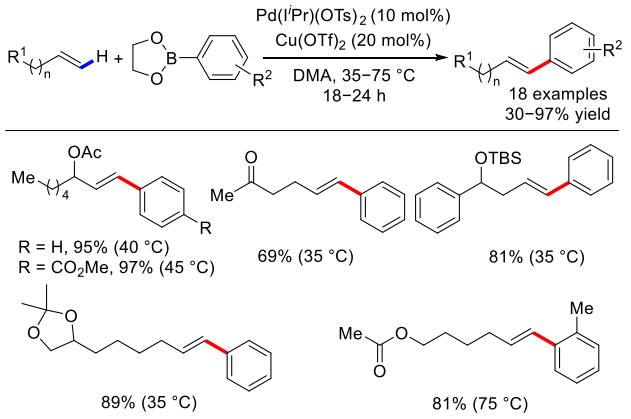
Scheme 12. Intermolecular Substrate Chelate-Controlled Oxidative Heck Reaction



Later in 2010, Sigman *et al.* developed a novel catalyst-controlled oxidative Heck reaction capable of generating a large variety of (*E*)-styrenyl products from electronically nonbiased terminal alkenes with various arylboronic esters (Scheme 13).[45] The high selectivity observed under mild conditions is attributed to the Pd(I^iPr)$(OTs)_2$ catalyst without the need to use base or high temperature. The authors performed preliminary mechanistic investigations, suggesting that the high selectivity may be mainly due to the catalyst's sensitivity to C−H bond strength in the key selectivity-determining β-H elimination step.

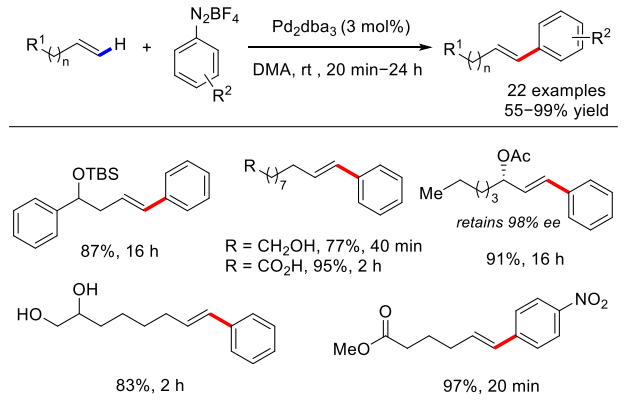
As an extension of this approach, the same group further identified an efficient and simple reaction conditions for the

Scheme 13. Intermolecular Catalyst-Controlled Oxidative Heck Reaction



(*E*)-styrenyl-selective Heck reactions of diverse electronically unbiased terminal olefins bearing a broad range of useful functionalities by using Pd_2dba_3 as the catalyst (Scheme 14).[46]

Scheme 14. Highly (*E*)-Styrenyl-Selective Heck Reactions of Electronically Unbiased Olefins



Interestingly, the highly enantiomerically enriched olefin substrates that may be susceptible to racemization in many cases worked well under the mild conditions with no erosion of enantiomeric excess. Mechanistic investigations demonstrated that the σ-donating feature of DMA solvent is crucial for achieving high selectivity in this process. Meanwhile, Correia and co-workers also achieved a similar regio- and stereoselective substrate-directed arylations of allylamine derivatives with arenediazonium salts.[47] The application of this protocol is also illustrated by a short total synthesis of biologically active naftifine and abamine.

By fine-tuning the steric and electronic factors of alkene substrates, Loh and co-workers were able to establish the divergent synthesis of indenes and α-naphthols *via* an intramolecular rhodium(III)-catalyzed vinylic C−H bond functionalization (Scheme 15).[48] The intramolecular alkene−alkene coupling with acrylates as the internal coupling partners occurred smoothly to generate a series of highly decorated indenes with different substitution patterns in up to 93% yield, while the alkene−enolate coupling exclusively resulted in the formation of α-naphthol derivatives. Detailed mechanistic investigations were also performed, and the results revealed that the reaction occurs *via* the vinylic sp^2 C−H bond functionalization followed by the generation of a five-

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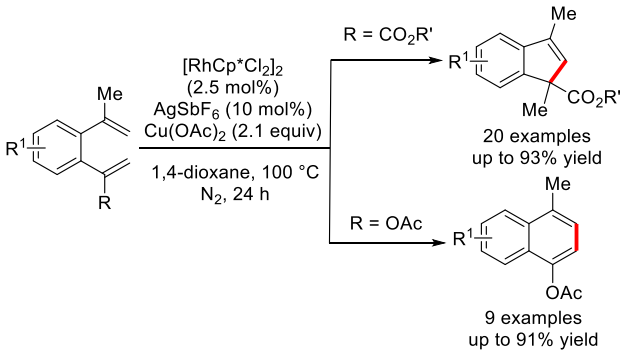
Scheme 15. Divergent Synthesis of Indenes and α-Naphthols *via* Cp*Rh(III)-Catalyzed Intramolecular Alkene−Alkene Coupling

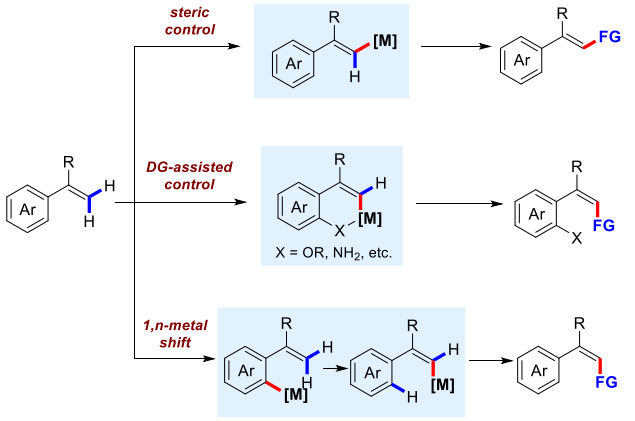


membered intermediate and possibly also a short-lived three-membered intermediate which significantly depends on the coupling alkene functionalities.

2.2. Directed Alkenyl C−H Bond Functionalization of Aromatic Alkenes

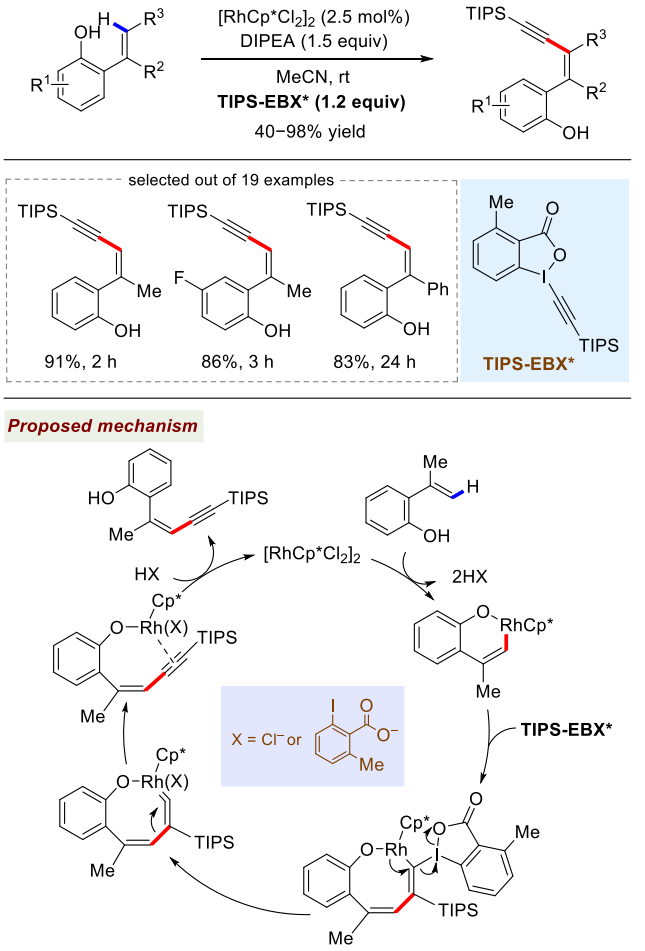
In addition to numerous examples of alkenyl C−H bond functionalizations of simple alkenes discussed above, remarkable efforts have also been devoted toward the chelation-assisted C−H bond functionalization of aromatic alkenes over the years. One of the major challenges in the sp^2 C−H bond of aryl alkenes is to selectively control the sp^2 C−H bond of the alkenes to yield either *E*- or *Z*-product. While it is generally easier to obtain *E*-selective alkenyl metal complexes due to steric effect, method leading to *Z*-selective product are most challenging that usually obtained *via* a chelating group (OH, NH, S, *etc.*). Another appealing approach utilized the 1,*n*-metal migration generated from an aryl halides or aryl metal reagents (Scheme 16).

Scheme 16. General Scheme of Alkenyl C−H Bond Functionalizations of Aromatic Alkenes



In 2015, Nachtsheim and colleagues reported the OH-assisted vinyl C−H alkynylation reaction of 2-vinylphenols with a modified hypervalent iodine(III) reagent (TIPS-EBX*) under rhodium(III) catalysis (Scheme 17).[49] The reactions proceeded smoothly under remarkably mild conditions with high functional group compatibility, excellent chemoselectivity, and exclusive (*Z*)-stereoselectivity, allowing the efficient synthesis of a diverse variety of highly substituted 1,3-enynes in 40−98% yields. The authors proposed that a base-assisted

Scheme 17. Rhodium(III)-Catalyzed OH-Assisted C−H Alkynylation of 2-Vinylphenols with Ethynyl Benziodoxolones and Its Proposed Mechanism



ligand exchange followed by the C−H activation step results in the formation of a rhodacycle intermediate. Subsequent regioselective insertion of the optimized hypervalent iodine-(III) alkyne reagent (TIPS-EBX*) produces the eight-membered rhodacycle species, which further undergoes facile α-elimination and the extrusion of 2-iodo-6-methylbenzoate to give the key rhodium vinylidene complex. Finally, intramolecular concerted 1,2-migration accompanied by a ligand exchange releases the expected C−H alkynylation products and regenerates the rhodium(III) catalyst.

Similarly, Zhang and co-workers carried out the vinylic C−H activation−desymmetrization of 2-vinylphenols with diazabicycles (Scheme 18).[50] The products obtained were trisubstituted olefins with multiple functionalities. Mechanistically, the reaction was suggested to occur *via* alkenyl C−H activation and subsequent alkene insertion to produce the rhodacycle species. Then, β-N elimination occurs to deliver a key ring-opening *trans*-rhodium intermediate, which finally undergoes protonolysis to afford the alkenyl-substituted aminocyclopentenes.

Because of the distinct advantage of easy availability, and the fact that NH_2 moieties indisputably serve as an ideal class of traceless directing groups for the synthesis of heterocyclic scaffolds, free amino functionality (NH_2) has always been identified as one of the most appealing group in the area of alkenyl C(sp^2)−H activation reactions. Indeed, remarkable

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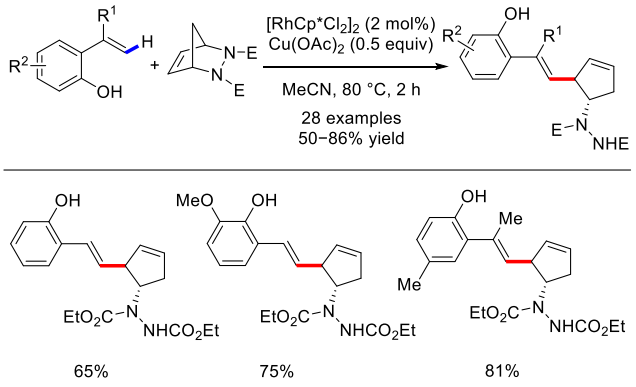
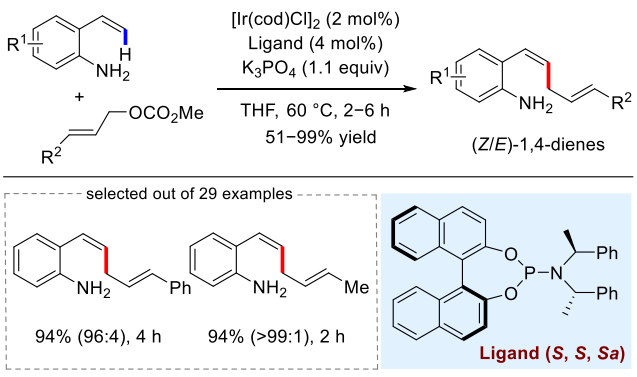
Scheme 18. Rhodium-Catalyzed C−H Activation−Desymmetrization of Diazabicycles with 2-Vinylphenols



endeavors have been devoted toward the development of NH_2-assisted C−H bond functionalizations in recent years. Specifically, You and co-workers in 2009 reported their investigations on the amine-assisted vinylic C−H allylation of 2-aminostyrene derivatives with diverse allylic carbonates under $[Ir(COD)Cl]_2$/Feringa's ligand catalysis, delivering a variety of (*Z*/*E*)-1,4-dienes with the formation of a *cis* double bond, which is complementary to Heck cross-coupling reaction (Scheme 19).[51] This protocol exhibited excellent functional

Scheme 19. Free Amine-Assisted Vinylic C−H Bond Allylation of Styrenes

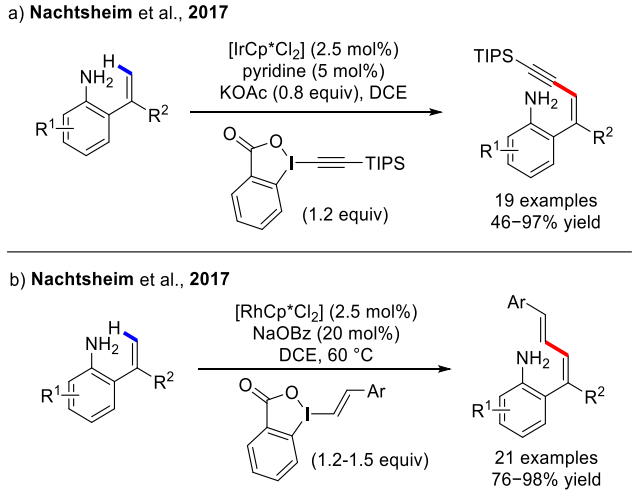


group compatibility to both sides, with the yields ranging from 51% to 99%. The authors also carried out mechanistic studies, and the results suggested that the leaving group of the allyl precursors is crucial for directing the reaction pattern in this case.

Later in 2017, Nachtsheim *et al.* described an effective Ir(III)-catalyzed, free NH_2-directed C−H alkynylations of 2-vinylanilines by using alkynylbenziodoxolones as the efficient electrophilic alkyne transfer reagents, leading to the expedient synthesis of highly desirable 1,3-enynes in excellent yields of up to 97% with exclusive *Z*-stereoselectivity (Scheme 20a).[52] In the same year, they further extended to report the Ir(III)-catalyzed, free NH_2-directed C−H alkenylation of 2-vinylanilines using alkenyl-λ^3-iodanes as the electrophilic alkene-transfer reagents, enabling the synthesis of highly desirable 1,3-dienes in excellent yields (76−98%) with high to perfect (*Z*,*E*) stereoselectivity (Scheme 20b).[53]

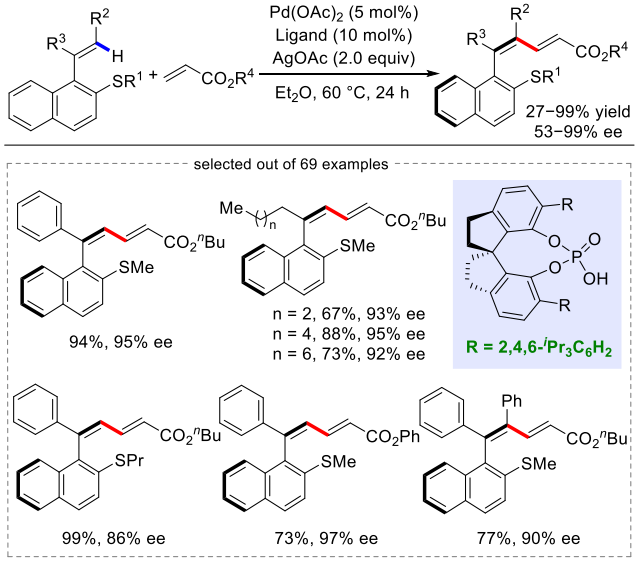
Despite considerable progress in alkenyl C(sp^2)−H functionalizations of styrenes, the direct construction of atropisomeric axially chiral styrenes bearing a conjugated 1,3-

Scheme 20. NH_2-Directed C−H Bond Alkynylation and Alkenylation of 2-Vinylanilines



diene moiety *via* asymmetric alkenyl C−H olefination strategy remains a great long-standing challenge to overcome over the past decades. Very recently, Shi *et al.* reported a highly efficient and atom-economical synthesis of atropisomeric styrenes *via* an enantioselective palladium(II)-catalyzed thioether-directed alkenyl C−H olefination (Scheme 21).[54] The reaction

Scheme 21. Palladium-Catalyzed Thioether-Directed Atroposelective Alkenyl C−H Olefination



occurred through the formation of an *endo*-palladacycle intermediate using chiral spiro-phosphoric acid as the chiral ligand under mild conditions. Notably, this stereospecific strategy features high functional group tolerance, broad substrate scope (69 examples), excellent enantioselectivities (up to 99% ee), and complete *Z*-selectivity control. More importantly, diverse chiral sulfoxide derivatives could be easily obtained by the high diastereoselective oxidation of the resulting axially chiral styrenes, thus providing an alternative handle for the enantioselective synthesis of axial chiral sulfur−olefin ligands, which have been well recognized as efficient and versatile chiral ligands in many catalytic asymmetric synthesis.[55−58] In a very recent report, Xu and co-workers

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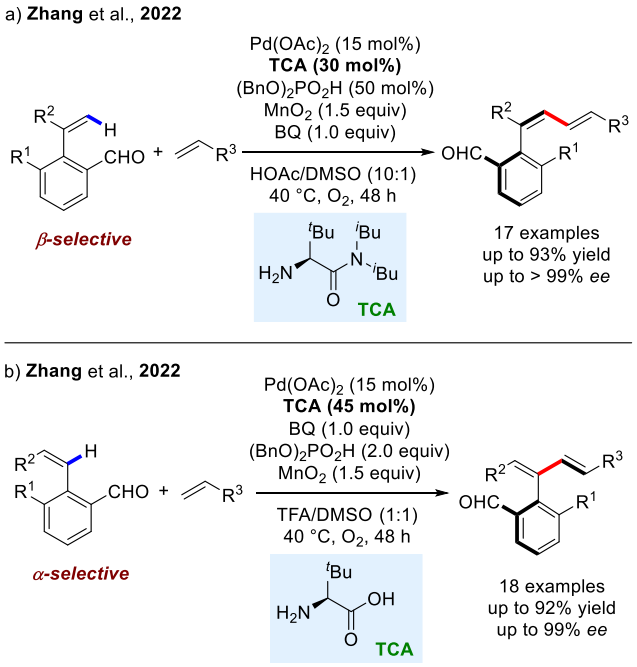
achieved an analogous tosylamine-group-directed transformation in the presence of a chiral tridentate Pybox ligand.[59]

Despite the indisputable advantages of chelating group strategies, the laborious preinstallation and subsequent removal of the directing group sometimes significantly compromise the overall efficiency of the transformations. To address this issue, a large number of transient directing group (TDG) strategies have been devised over the past years.[60−65] Quite recently, by taking advantage of the chiral transient directing group (CTDG) strategy,[66,67] Zhang and co-workers achieved the asymmetric vinylic C−H olefination of 2-vinyl benzaldehydes through a challenging seven-membered *endo*-cyclometalation process. Successfully, an amino acid-derived transient chiral auxiliary was identified in this case (Scheme 22a).[68] A broad

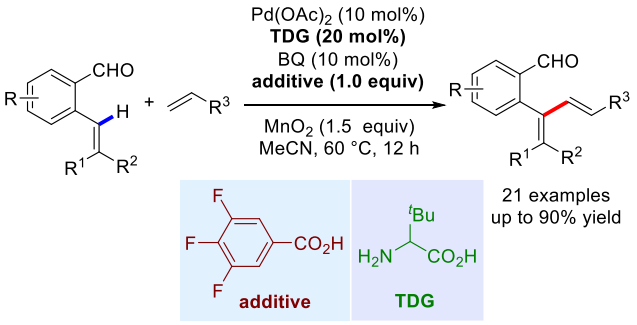
Scheme 22. Synthesis of Axially Chiral Aryl 1,3-Dienes by a Chiral Transient Directing Group



range of 2-vinyl benzaldehydes reacted smoothly with various acrylates and styrenes to afford the corresponding coupling products in high yields (up to 93%) and excellent enantioselectivities (up to >99% *ee*). However, electronically activated alkenes such as vinyl ketones, vinyl sulfones, and acrylamides were proven to be incompatible with the conditions. Unlike this asymmetric coupling reactions where *endo* metallacycles were generated to regioselectively functionalize the vinylic β-C(sp^2)−H bonds of styrene derivatives, the same group expanded to establish the asymmetric α-C(sp^2)−H alkenylations of styrenes using L-*t*-leucine as the transient chiral auxiliary through a six-membered *exo*-cyclopalladation process (Scheme 22b).[69]

Almost simultaneously, Engle and co-workers also reported their exploration of a TDG approach to realize the feasibility of palladium(II)-catalyzed α-C−H olefination of styrenes by the generation of an *exo* alkenyl palladacycle, providing access to diverse 2-aryl-substituted 1,3-dienes with high regio- and *E*/*Z*-selectivity (Scheme 23).[70] In this report, commercially available *tert*-leucine was identified as the optimal transient directing group, and alkenyl aldehydes with different substitution patterns could be readily olefinated to the

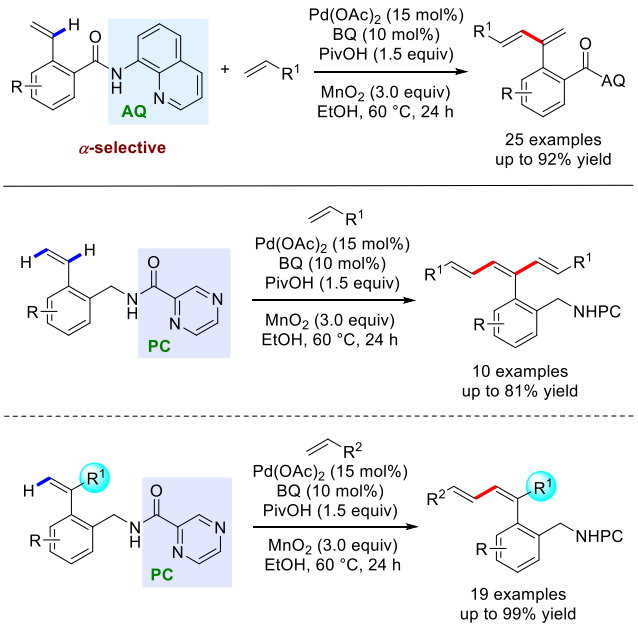
Scheme 23. Pd(II)-Catalyzed Alkenyl C−H Olefination of Aldehydes by a Transient Directing Group



expected coupling products. Notably, unbiased aliphatic alkenes were found to be viable substrates for this transformation, albeit with diminished efficiency. Mechanistic studies including synthesis of two catalytically relevant alkenyl palladacycle complexes and DFT calculations were also carried out to elucidate the plausible mechanism.

Around the same time, Zhang *et al.* investigated the *N*,*N*-bidentate-chelation-assisted α-selective vinylic C−H bond functionalization of styrene derivatives (Scheme 24).[71] The

Scheme 24. Highly Regio- and Stereoselective Vinylic C−H Functionalizations of Styrenes



8-aminoquinoline (AQ) was readily employed as the bidentate directing group of best choice. By the combination of $Pd(OAc)_2$/benzoquinone (BQ), MnO_2 oxidant, and PivOH additive in EtOH at 60 °C, a wide substrate scope (25 examples) of vinylic α-C(sp^2)−H olefination product was documented in satisfactory yields of up to 92%. Interestingly, using 2-pyrazinamide (PC) as the efficacious chelating group, the authors could establish an aerobic approach for α- and β-bis-alkenylations of styrenes under identical conditions. As expected, a series of β-alkenylation products were formed with α-substituted styrenes as substrates.

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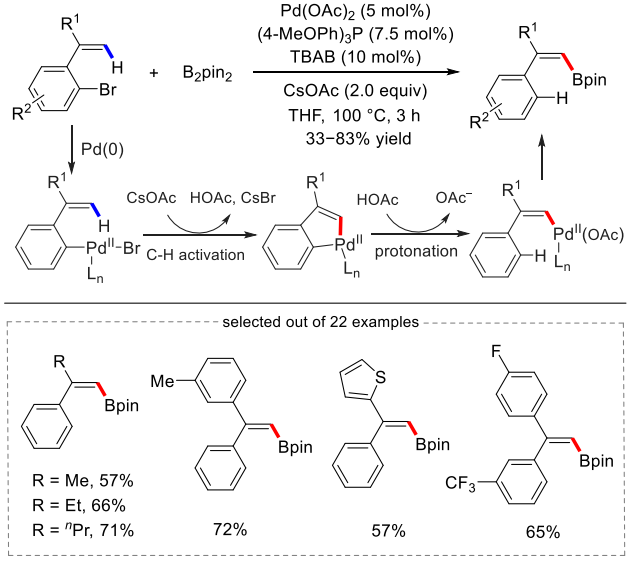
2.3. Migratory Alkenyl C−H Bond Functionalization of Aromatic Alkenes

In addition to the aforementioned chelation-assisted strategy for the activation and further functionalization of styrene olefinic C−H bonds, strategies based on 1,*n*-metal shift allow the direct functionalization of specific distal C−H bonds which may be otherwise difficult to achieve in many cases. Inspired by the seminal work of Larock who illustrated the possible vinyl to aryl palladium 1,4-migration as a reversible process in the migration as a plausible mechanism,[72] the group of Lin and Feng made a significant contribution to the field of migratory alkenyl C−H bond functionalization of aromatic alkenes. In 2016, they elegantly reported the first example of aryl to vinyl 1,4-palladium migration process (Scheme 25).[73] According to

Scheme 25. Alkenyl C−H Bond Borylation *via* Aryl to Vinyl Palladium 1,4-Migration

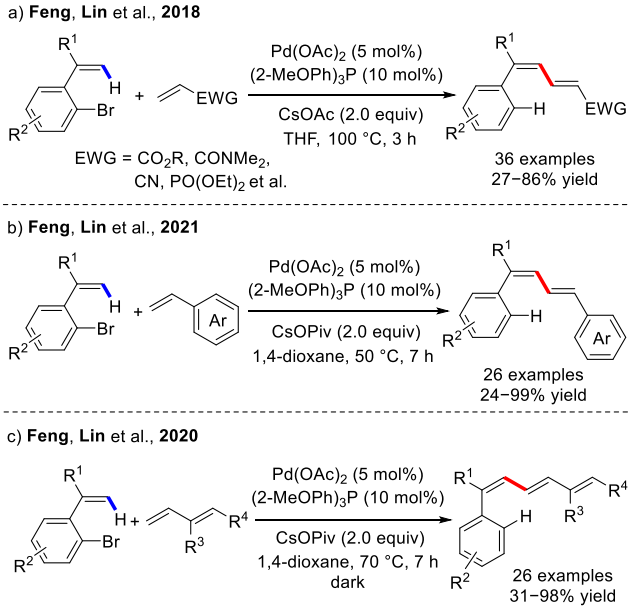


the proposed mechanism, the oxidative addition of aryl bromide to palladium(0) generates the alkenyl palladium(II) intermediate which further reacted with diboron reagents under Miyaura borylation conditions, affording a novel method to the rapid and diverse synthesis of remarkably useful *β*,*β*-disubstituted vinylboronates with broad scope and excellent regioselectivity.

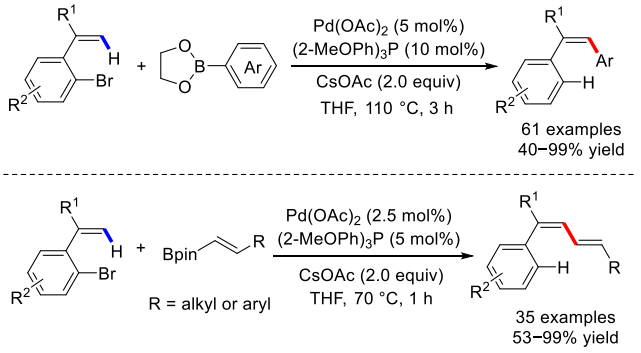
In continuation, Lin, Feng, and co-workers expanded to apply their reliable migration strategy to the highly stereoselective synthesis of conjugated 1,3-butadienes *via* aryl to vinyl palladium 1,4-migration/Heck sequence of 2-bromostyrene substrates with diverse electron-deficient olefins (Scheme 26a),[74] and later styrenes (Scheme 26b).[75] Interestingly, this new methodology could also be applied to efficiently synthesize a series of trisubstituted conjugated 1,3,5-hexatriene derivatives with modest to decent yields (Scheme 26c),[76] which are ubiquitous structures encountered in many natural products and organic functional materials.[77−79]

In 2020, an efficient aryl to vinyl palladium 1,4-migration/Suzuki−Miyaura sequence of 2-bromostyrene substrates with organoboron reagents was also achieved by Lin, Feng, and co-workers (Scheme 27).[80] In this protocol, various phenylboron reagents were tested, and five-membered ethylene glycol-derived boronate esters was found to be the best coupling partner to afford the olefinic C(sp^2)−H arylation products.

Scheme 26. Synthesis of Di- and Trienes *via* Aryl to Vinyl 1,4-Palladium Migration/Heck Sequences



Scheme 27. Suzuki−Miyaura Coupling Enabled by Aryl to Vinyl 1,4-Palladium Migration



The coupling reaction with various commercially available arylethenyl boronates enables the stereospecific synthesis of multisubstituted conjugated 1,3-butadienes. The reaction features easy scalability, extraordinarily broad substrate scope (>90 examples), excellent functional group tolerance, and versatile utility of the corresponding products.

As an extension of this approach, Lin, Feng, and co-workers recently continued this 1,4-palladium migration strategy to accomplish a highly regioselective palladium-catalyzed three-component tandem C−H alkylation/cross-coupling reaction of 2-iodostyrenes with alkyl halides as the electrophile and various easily accessible nucleophiles as the coupling reagents (Scheme 28).[81] The reaction occurs through a cyclopalladation process enabled by the judicious choice of electron-rich 2-pyridone ligand with regiodetermining C−H alkylation of the key aryl-alkenyl-palladacycle species, which was *in situ* captured and identified by NMR and X-ray spectra.

Subsequently, Yu and co-workers illustrated an efficient palladium-catalyzed olefinic C−H bond alkylation of 2-bromostyrenes with cyclobutanols as the coupling partners enabled by a controllable aryl to vinyl 1,4-palladium migration/ring-opening C−C cleavage cascade strategy (Scheme 29).[82] This protocol features excellent regio- and stereoselectivity,

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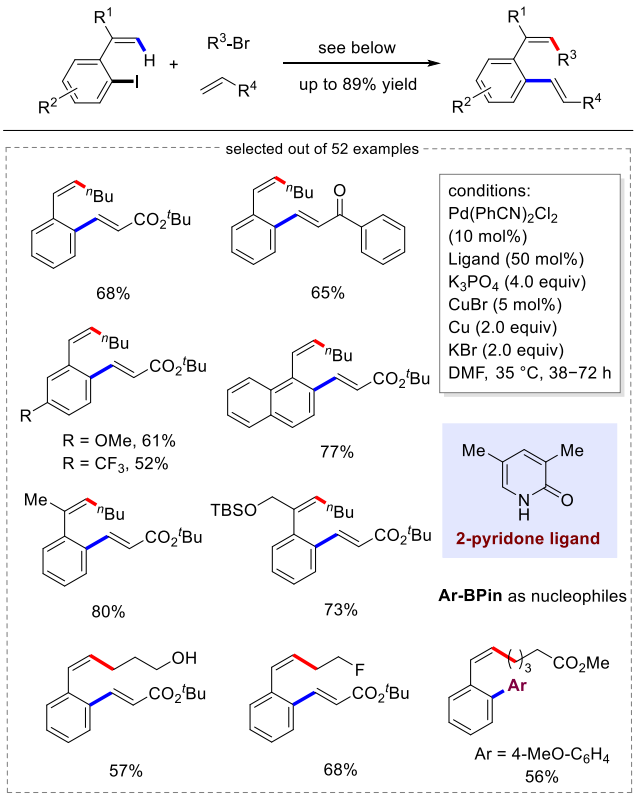
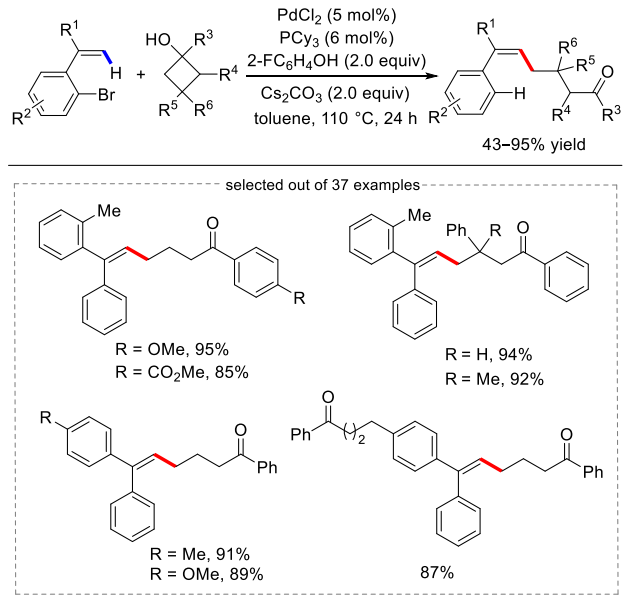
Scheme 28. Regioselective Three-Component Tandem C−H Alkylation/Cross-Coupling Reaction of *ortho*-Iodophenylethylenes



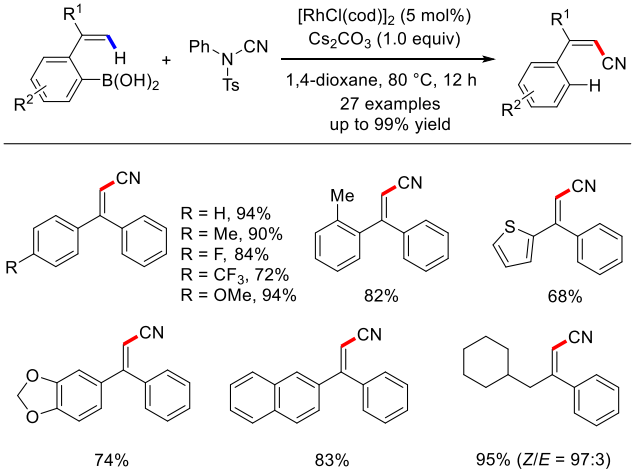
Scheme 29. Alkenyl C−H Bond Alkylation through an Aryl to Vinyl 1,4-Palladium Migration/C−C Cleavage Cascade



wide substrate scope, and high functional group compatibility, providing access to γ-ketone olefins in decent yields (43−95%). Combined mechanistic investigations and DFT calculations demonstrated that the reaction occurs *via* oxidative addition, aryl to vinyl palladium 1,4-migration, ring-opening C−C bond cleavage, and reductive elimination sequences. It should be mentioned that the high efficiency of this protocol is mainly attributed to the thermodynamically favored aryl to vinyl 1,4-palladium migration effectively assisted by the 2-fluorophenol additive.

The Huang group established a stereospecific olefinic C−H cyanation by using *o*-(alkenyl) substituted aryl boronic acids as the substrates combined with easily accessible *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) as the cyanating reagent. The transformation occurred through an aryl to vinyl 1,4-rhodium migration process, giving rise to a diverse variety of *β*,*β*-disubstituted acrylonitriles in up to 99% yield (Scheme 30).[83] The reaction features a broad substrate scope and

Scheme 30. Stereospecific Olefinic C−H Cyanation Enabled by 1,4-Rhodium Migration



excellent functional group tolerance. The proposed mechanism involves the facile formation of an alkenylrhodium intermediate that was readily generated *in situ via* 1,4-rhodium migration from aryl to vinyl, accompanied by an electrophilic cyanation step.

2.4. Annulation of Aromatic Alkenes *via* Alkenyl C−H Bond Functionalization

The annulation processes of styrenes *via* vinylic C−H bond functionalization are especially useful methods because they provide an easy and straightforward access to various polycyclic compounds. Different types of annulation reaction to form pyrans, latones, lactams, as well as diverse spiro rings are covered in this section.

In 2017, Sheykhan, Abbasnia, and their co-workers reported an unprecedented annulation of simple styrenes with readily available electron-deficient maleimides and maleic anhydrides as coupling partners *via* a tandem activation of both aromatic and olefinic C−H bonds in a pseudo-Diels−Alder mode, allowing an economical and convenient synthesis of benzo[*e*]-isoindole-1,3-diones in 63−84% yield (Scheme 31).[84]

In an effort to expand the scope of 1,4-palladium migration strategy, the group of Lin and Feng further established a sequential cross-coupling/annulation of 2-bromostyrene derivatives with internal alkynes, allowing a convenient approach to the synthesis of multisubstituted naphthalenes *via* a controllable aryl to vinyl 1,4-palladium migration process (Scheme 32).[85] Later, they continued to apply this sequential cross-coupling/annulation strategy of 2-bromostyrenes with aromatic bromides to identify a direct approach for the facile synthesis of polycyclic aromatic compounds in yields ranging from 32% to 86% with excellent chemo- and regioselectivity

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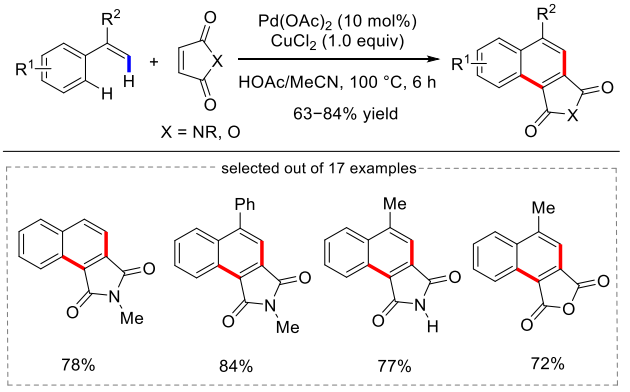
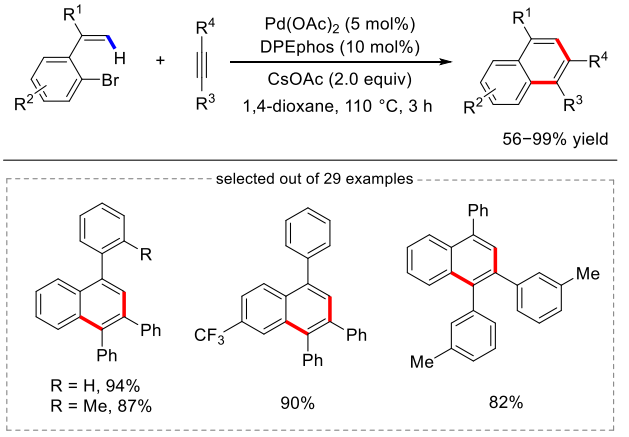
Scheme 31. Synthesis of Benzo[*e*]isoindole-1,3-diones

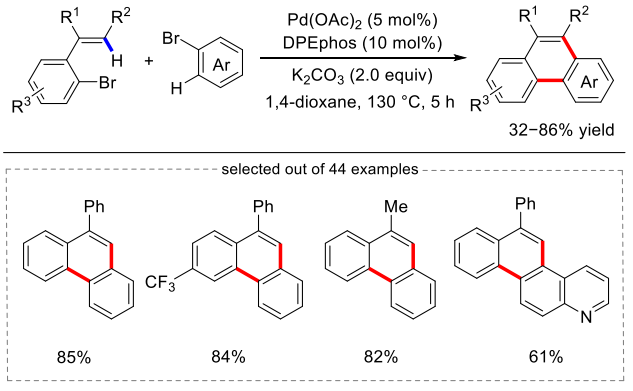


Scheme 32. Synthesis of Naphthalene *via* Benzannulation of (2-Aryl)vinyl Metal Species and Internal Alkynes



(Scheme 33).[86] On the basis of SAESI-MS analysis, a vinyl-coordinated palladacycle species was tentatively proposed as

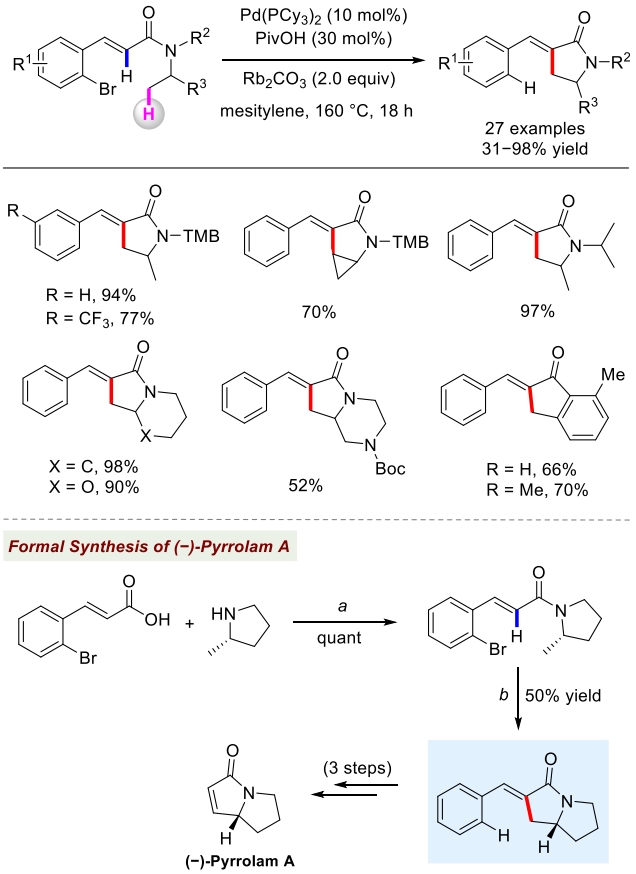
Scheme 33. Sequential Cross-Coupling/Annulation of 2-Bromostyrenes with Aromatic Bromides



the key intermediate for this 1,4-palladium migration and further annulation processes. The authors also performed the kinetic isotope effect (KIE) experiments, and an intermolecular KIE value of 1.68 unambiguously suggests that the alkenyl C–H bond cleavage was probably involved in the rate-determining step in this case.

In 2019, a practical and step-economical approach to construct a diverse range of highly valuable arylidene γ-lactams and indanone derivatives through a palladium(0)-catalyzed intramolecular cascade reaction involving 1,4-palladium migration and subsequent C(sp^3)–H activation has been reported by Baudoin's group (Scheme 34).[87] As a particular

Scheme 34. Synthesis of α-Arylidene γ-Lactams *via* 1,4-Palladium Shift/C(sp^3)–H Activation Strategy



highlight, the applicability of this protocol was demonstrated as a key step with an appreciable 50% yield in the formal synthesis of a pyrrolizidine alkaloid (−)-pyrrolam A.

Phenols are a highly conserved functional group in natural and synthetic chemistry.[88] Strategies to construct heterocycles have also been reported. For examples, methodologies that selectively functionalize a specific C–H bond of phenols can dramatically alter molecular diversity and its function.[89] Particularly, the direct OH-assisted olefinic C–H cyclocarbonylation of 2-vinylphenols could provide an efficient approach for the synthesis of coumarins, which are a ubiquitous class of natural products with a broad variety of biological activities.[90] In this regard, Alper and colleagues in 2012 first illustrated an attractive Pd(II)-catalyzed direct oxidative cyclocarbonylation of 2-vinylphenols with remarkably low pressure of CO (≤100 psi), enabling the preparation of coumarins bearing a diverse array of functional groups in up to 85% yield by using air or 1,4-benzoquinone (BQ) as the terminal oxidant (Scheme 35).[91]

In 2014, Gulías, Mascareñas, and co-workers achieved the rhodium(III)-catalyzed C–H activation/annulation of readily available 2-hydroxystyrenes with CO as the one-carbon coupling partner for the construction of coumarin scaffolds (Scheme 36).[92] Subsequently, the same group further expanded this annulation strategy to large-scale synthesis of

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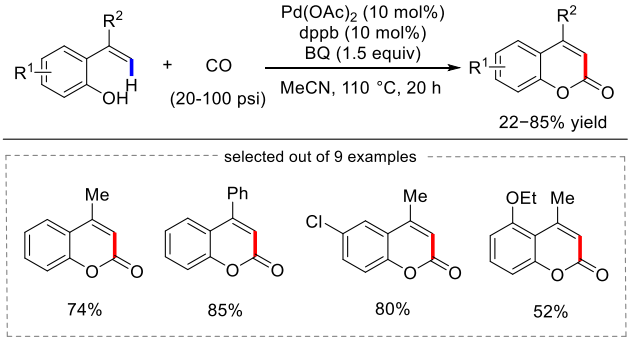
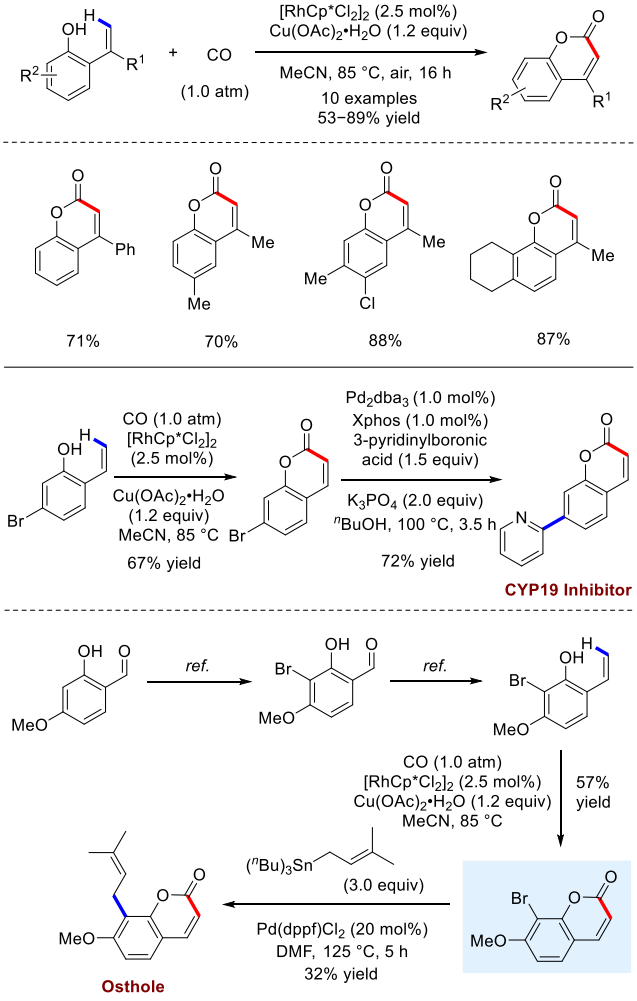
Scheme 35. Palladium(II)-Catalyzed Oxidative Cyclocarbonylation of 2-Vinylphenols



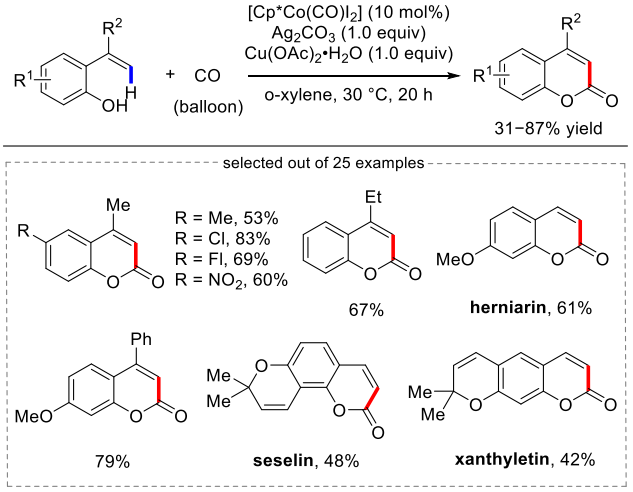
Scheme 36. Synthesis of Coumarins *via* Rhodium(III)-Catalyzed C−H Activation/Annulation



coumarins. The process was straightforward and economical for the assembly of coumarins with different substitution patterns in 53−89% yield. Of note, the utility of this protocol was demonstrated by synthesizing two biologically important coumarin derivatives (Scheme 36).[93]

Shortly after, the Wang research group reported the cyclocarbonylation of 2-alkenylphenols with CO under cost-effective Cp*Co(III) catalysis (Scheme 37).[94] The reaction proceeded under typically mild conditions. Using only balloon pressure CO could achieve high reactivity in this case. The

Scheme 37. Cp*Co(III)-Catalyzed Annulations of 2-Alkenylphenols with CO



utility of this approach is highlighted by a practical gram-scale preparation and the total synthesis of three natural products herniarin, xanthyletin, and seselin.

The direct C−H bond carboxylation reaction using easily accessible, inexpensive, naturally abundant atmospheric CO_2 represents a straightforward method for the atom- and step-economical synthesis of diverse value-added carboxylic acids or their derivatives.[95−100] In 2013, Iwasawa and co-workers described the first example of alkenyl C−H carboxylation of 2-hydroxystyrenes in the presence of 5 mol % of $Pd(OAc)_2$ in diglyme at 100 °C under an atmospheric pressure of CO_2 with Cs_2CO_3 as a base, producing the expected coumarins in high yields (Scheme 38).[101] In this case, the hydroxy group served as an efficacious directing group for the C−H activation step. The authors proposed a plausible reaction mechanism involving the following pathways: the six-membered alkenyl palladium(II) species is readily produced by the chelation-assisted alkenyl C−H bond cleavage of 2-hydroxystyrene with a $Pd(OAc)_2$ catalyst, along with the coordination of another molecule of 2-hydroxystyrene as its cesium salt. The alkenyl palladium(II) species then undergoes a reversible nucleophilic carboxylation process to generate the key palladium carboxylate intermediate, which finally reacts with another molecule of 2-hydroxystyrene as well as the base to deliver the coumarin derivatives with the regeneration of the cyclometalated intermediate.

In 2017, Zhi, Yu, and co-workers realized a transition-metal-free alkenyl C−H bond lactonization of 2-vinylphenols with CO_2 as the ideal one-carbon (C1) source to synthesize highly valuable coumarin derivatives under redox-neutral conditions (Scheme 39a).[102] Later in 2021, the Chen group also reported an analogous cascade radical addition/cyclization reaction of diverse 2-alkenylphenols with readily available CBr_4 as the one-carbon source in the presence of water under photoredox catalysis (Scheme 39b),[103] providing an efficient access to 4-arylcoumarins in a one-pot fashion with a wide substrate scope. Mechanistic investigations confirmed that the reaction should proceed through an oxidizing quenching radical-involving pathway.

The formal [5 + 2] cycloaddition of 2-vinylphenols with diverse alkynes to readily assemble highly appealing benzoxepines in an atom-economical manner was first reported by the Gulías and Mascareñas group in 2014 by using a catalytic

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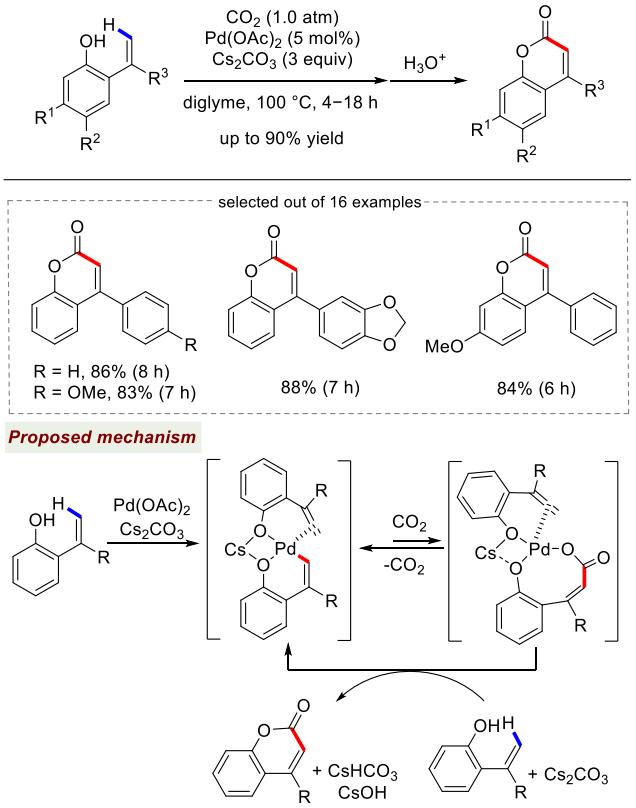
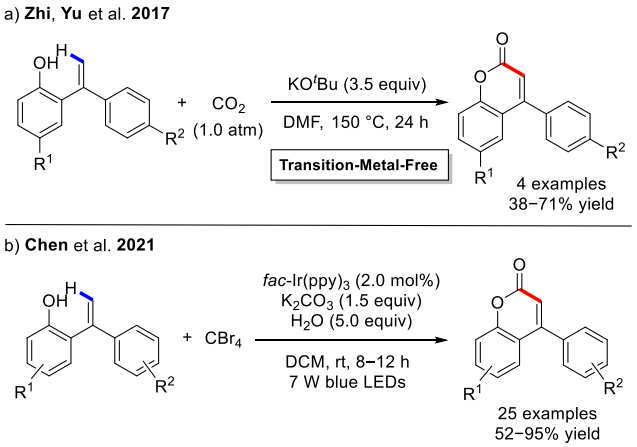
Scheme 38. Pd(II)-Catalyzed Carboxylation of Alkenyl C−H Bonds with CO_2 and Its Proposed Mechanism



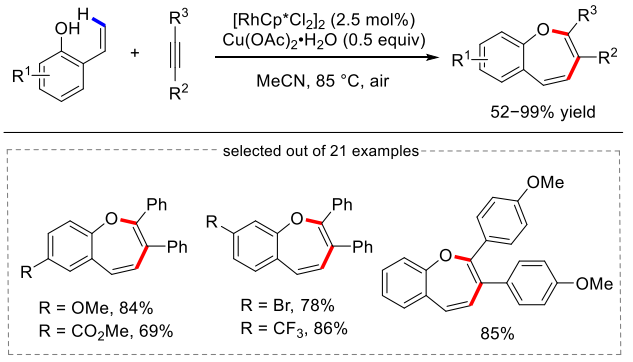
Scheme 39. Direct Alkenyl C−H Carboxylation of 2-Alkenylphenols



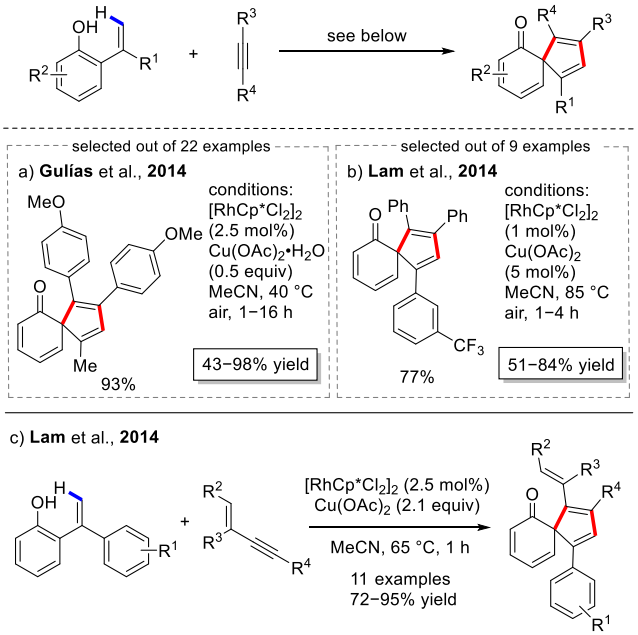
amount of $[RhCp^*Cl_2]_2$ (2.5 mol %) as a catalyst in conjunction with 0.5 equiv of $Cu(OAc)_2{\bullet}H_2O$ as an oxidant. Notably, the reaction accommodated a variety of substituents in the aryl group of vinylphenol substrates (Scheme 40).[92]

The same year, Gulías and Lam independently reported the dearomatizing oxidative annulation reaction of various 2-alkenylphenols with internal alkynes under Rh(III) catalysis, generating the highly functionalized spirocyclic enones with good yields and excellent regioselectivities (Scheme 41a and b).[104,105] Interestingly, conjugated 1,3-enynes were also proved to be viable substrates for the dearomatizing oxidative annulation in Lam's work. As expected, a wide range of spirocyclic products were obtained in high yields (72−95%),

Scheme 40. Synthesis of Benzoxepines *via* Cp*Rh(III)-Catalyzed Formal [5 + 2] Cycloadditions



Scheme 41. Synthesis of Spirocyclic Enones by Rhodium(III)-Catalyzed Dearomatizing Oxidative Annulation



albeit the need to use a superstoichiometric amount of $Cu(OAc)_2$ (2.1 equiv) as the oxidant. The reaction was proposed to proceed *via* the cleavage of alkenyl C−H bond and the dearomatization of the phenol aromatic ring. Recently, Lu and co-workers performed density functional theory calculations to investigate the competing formal [5 + 2] annulation and dearomatizing [3 + 2] annulation pathways, and the results clearly showed the direct reductive elimination of eight-membered rhodacycles is disfavored, and instead the dissociation of the Rh−O bond followed by antarafacial nucleophilic attack is the most favorable pathway for the generation of seven-membered azacyclic and spirocyclic products.[106] In a related report, Gogoi *et al.* also realized a similar transformation under ruthenium(II) catalysis.[107]

More recently, the Ackermann group achieved the elegant synthesis of highly appealing seven-membered benzoxepine derivatives through electro-oxidative rhodium-catalyzed [5 + 2] annulation reactions (Scheme 42).[108] The reaction proceeds *via* dual activation of C−H and O−H bond with molecular hydrogen as the sole byproduct. The expected benzoxepine products were synthesized with a diverse range of

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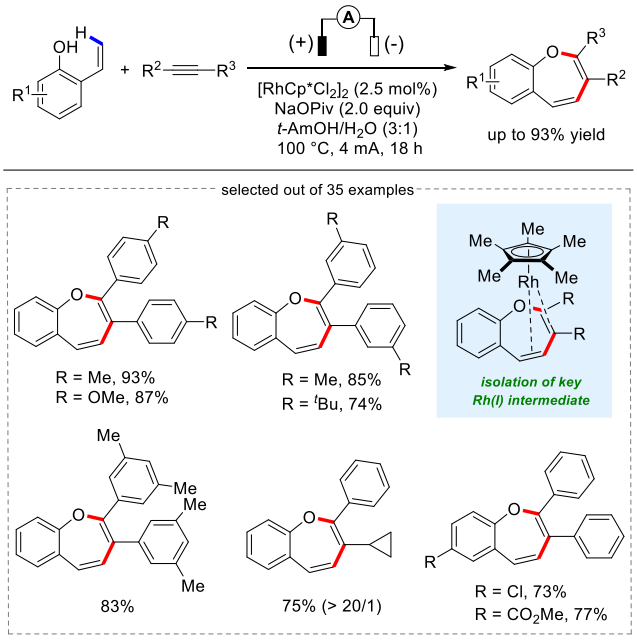
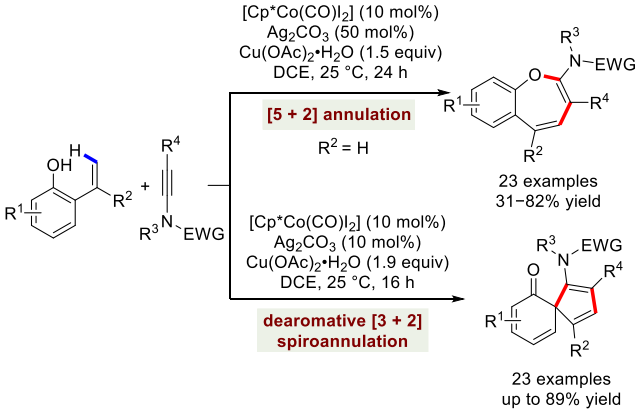
Scheme 42. Electrooxidative Rhodium-Catalyzed [5 + 2] Annulations of 2-Vinylphenol with Alkynes



functional group compatibility. Detailed mechanistic studies were also performed, and monitoring the reaction by NMR spectroscopy clearly revealed that a low-valent rhodium intermediate was likely the catalyst resting state. A key benzoxepine-coordinated rhodium(I) sandwich complex prepared and isolated by the reaction of $Cp^*Rh(OAc)_2$ with the substrates unambiguously provided a solid support for a fast C−H rhodation and a rhodium(III/I) regime in this annulative transformations.

Apart from above-mentioned alkynes and enynes, ynamides as synthetically valuable subgroup of alkynes and versatile building blocks for organic synthesis[109−111] can also couple efficiently with 2-alkenylphenols in a highly regioselective manner. In 2018, Li and colleagues first reported the oxidative [5 + 2] annulation reaction of 2-vinylphenols with ynamides to fabricate valuable 2-aminobenzoxepines under earth-abundant cobalt catalysis *via* C−H/O−H bond functionalizations (Scheme 43).[112] Shortly after, Wang, Li, and their co-workers

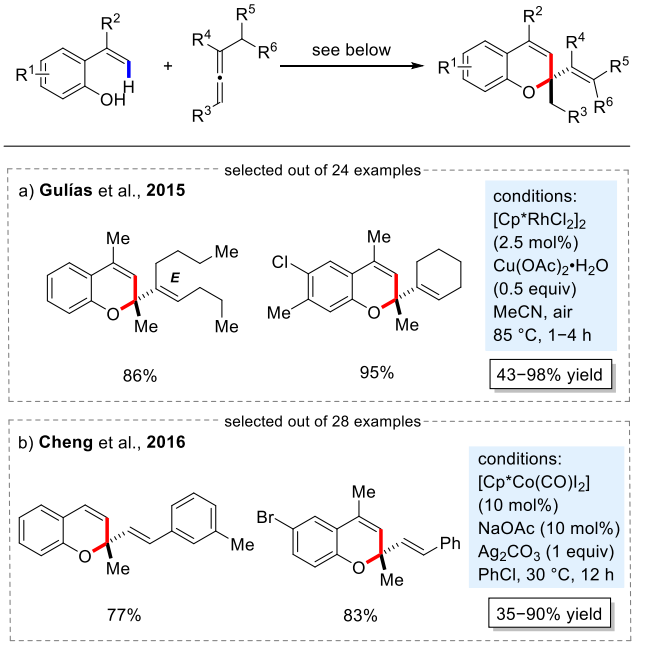
Scheme 43. Cobalt-Catalyzed Oxidative [5 + 2] Annulation and Dearomative [3 + 2] Spiroannulation of 2-Alkenylphenols with Ynamides



extended this method to a formal dearomative [3 + 2] spiroannulation reaction to generate highly decorated spiro-[4,5]decane derivatives bearing a quaternary stereogenic center entirely made of carbons. The reaction worked under especially mild conditions with a broad variety of functional group compatibility (Scheme 43).[113] The coordinating characteristic of the sulfonyl group in the ynamides may determine the regioselectivity of the reaction.

In 2015, the group of Gulías and Mascareñas reported a simple and atom-economical Rh(III)-catalyzed oxidative [5 + 1] annulation of 2-vinylphenols with allenes as one-carbon coupling partners to afford a series of biologically active, six-membered 2,2-disubstituted 2*H*-chromenes, formally involving the cleavage of the C−H and O−H bonds of 2-alkenylphenol substrates (Scheme 44a).[114] Similar to this transformation,

Scheme 44. Synthesis of 2,2-Disubstituted 2*H*-Chromenes *via* Formal [5 + 1] Annulations between 2-Alkenylphenols and Allenes



Cheng and co-workers also realized the present phenolic OH-assisted C−H oxidative annulation reactions by using non-noble $[CoCp^*(CO)I_2]$ as the catalyst under mild conditions (Scheme 44b).[115] This annulative reaction is proposed to proceed *via* the initial alkenyl C−H activation, allene insertion, and an unusual intramolecular regioselective phenoxide addition. The authors argued that the Co−O bond in the π-allylic moiety could have been selectively attacked during the oxidative [5 + 1] annulations to afford the phenoxide intermediate.

Quite recently, Prabhu and co-workers studied the [5 + 1] annulation reactions of 2-alkenylphenols with various maleimides under Rh(III) catalysis in the presence of $Cu(OAc)_2$ (2.0 equiv) as the terminal oxidant, exclusively giving rise to highly functionalized spirocyclic scaffolds bearing an oxygen-containing spiro carbon (Scheme 45).[116]

In contrast to the above results obtained with Rh and Co catalysts which afforded chromene-like coupling products, Gulías and Mascareñas *et al.* demonstrated that 2-alkenylphenols could couple with allenes *via* formal [5 + 2] cyclo-

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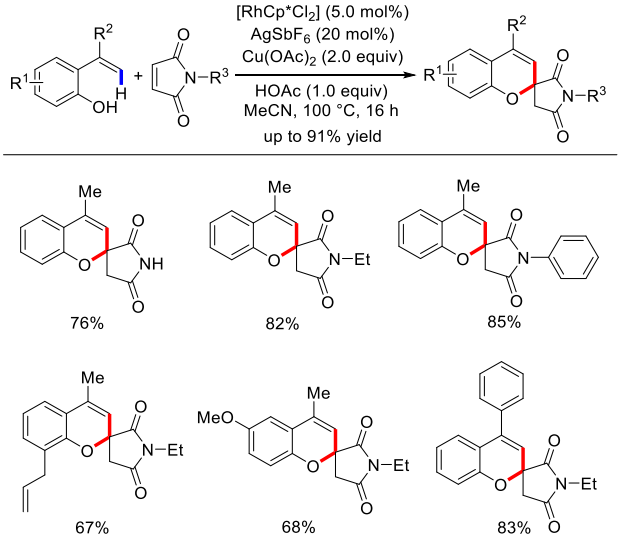
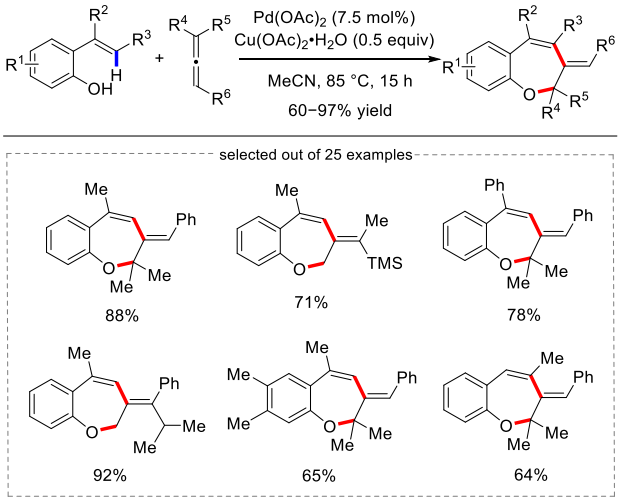
Scheme 45. Rhodium(III)-Catalyzed [5 + 1] Annulation of 2-Alkenylphenols with Maleimides



additions in the presence of $Pd(OAc)_2$ catalyst to produce the seven-membered benzoxepines in decent yields (60−97%) with good regio- and diastereoselectivities (Scheme 46).[117]

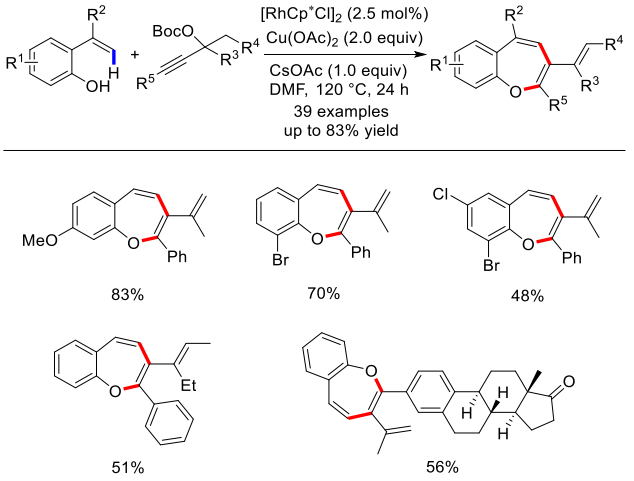
Scheme 46. Palladium(II)-Catalyzed Formal [5 + 2] Annulations of *ortho*-Alkenylphenols with Allenes



Detailed computational studies demonstrated that the different outcome of the reaction by Pd(II) or Cp*Rh(III) catalysts could be ascribed to the geometric requirements associated with their respective square planar or pseudo-octahedral geometries. The square planar geometry of palladium catalyst required in this protocol is generally favored to undergo a reductive elimination process to generate benzoxepine products.

Moreover, propargyl carbonates can also engage in the rhodium(III)-catalyzed oxidative [5 + 2] annulation with various 2-alkenylphenols, exclusively giving the 3-alkenylated benzoxepine derivatives with excellent regioselectivity and high functional group compatibility (Scheme 47).[118] Combined DFT calculations and experimental mechanistic studies clearly revealed the essential role of the traceless assisting OBoc group in controlling the regio- and chemoselectivities of this

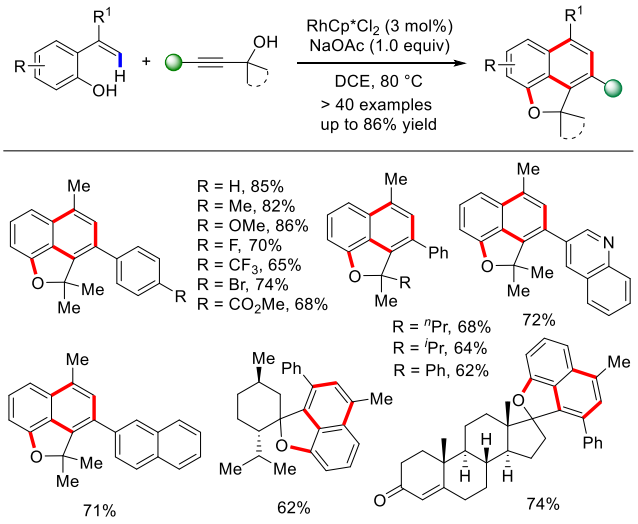
Scheme 47. Rhodium(III)-Catalyzed Oxidative [5 + 2] Annulations of 2-Alkenylphenols with Propargyl Carbonates



transformation in terms of its steric hindrance and good leaving ability.

Unlike the case with propargyl carbonates, Reddy and colleague demonstrated that unprotected propargyl alcohols could couple efficiently with a series of 2-alkenyl phenols to assemble diverse naphthofuran derivatives through a migratory three-point double annulation process (Scheme 48).[119] Under

Scheme 48. Rh(III)-Catalyzed Double Annulation of 2-Alkenylphenols with Unprotected Tertiary Propargyl Alcohols



the optimal conditions, a broad range of fused naphthofurans were documented in reasonable yields up to 86%. Of note, this protocol was also applicable in a more complex setting. It should be mentioned that unsubstituted or disubstituted 2-alkenyl phenols failed to deliver the expected coupling products.

An efficient approach for the concise construction of 2,3-diarylbenzofurans by coupling 2-hydroxystyrenes with iodobenzenes through a C−H activation/oxidation cascade reaction has been reported by Jia and co-workers (Scheme 49).[120] By using this strategy, the overall efficiency of the direct synthesis of natural products decursivine, serotobenine, and

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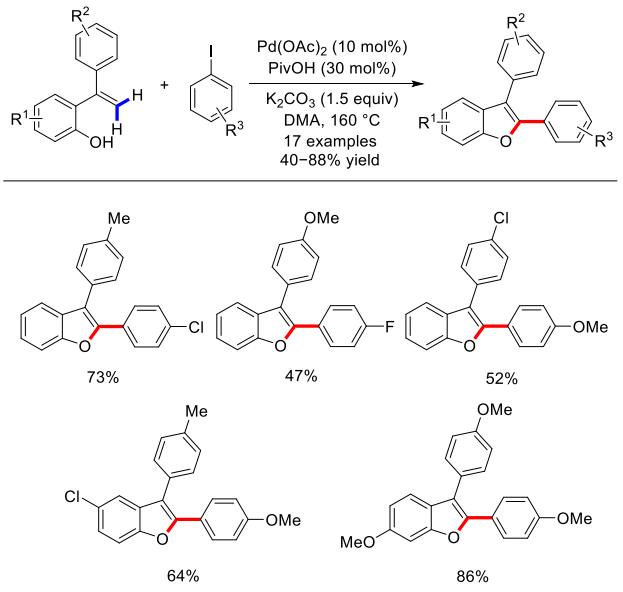
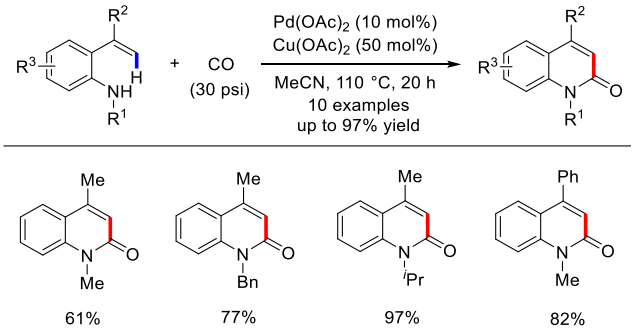
Scheme 49. Synthesis of 2,3-Diarylbenzofurans *via* Alkenyl C−H Activation/Oxidation Tandem Reaction of 2-Hydroxystyrenes with Iodobenzenes



their analogues was greatly improved without the need of protecting group.

Along with their novel strategy to synthesize coumarins *via* the direct oxidative cyclocarbonylation with carbon monoxide,[91] Alper and co-workers extended to disclose an oxidative C−H cyclocarbonylation of various *N*-monosubstituted-2-vinylanilines with CO, providing a general and practical approach for the synthesis of a variety of biologically active 2(1*H*)-quinolinone derivatives in up to 97% yield (Scheme 50).[121]

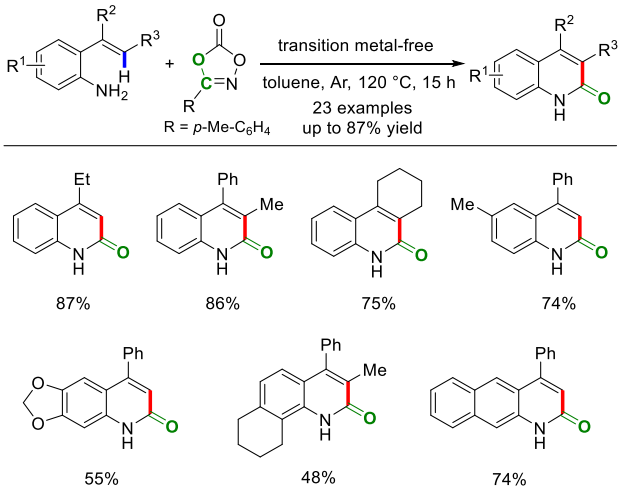
Scheme 50. Palladium(II)-Catalyzed Direct Oxidative Cyclocarbonylation of 2-Vinylanilines with CO



More recently, the impressive example of transition metal-free carbonylative C−H [5 + 1] annulation of 2-alkenylanilines with environmental and user-friendly dioxazolones as the carbonylating reagents was realized by Nan and co-workers (Scheme 51).[122] This protocol allows the rapid synthesis of highly privileged quinolinone derivatives through an unprotected NH_2-assisted olefinic C−H bond functionalizations. A diverse series of value-added products were obtained in appreciable to high yields (35−87%) with excellent functionality tolerance.

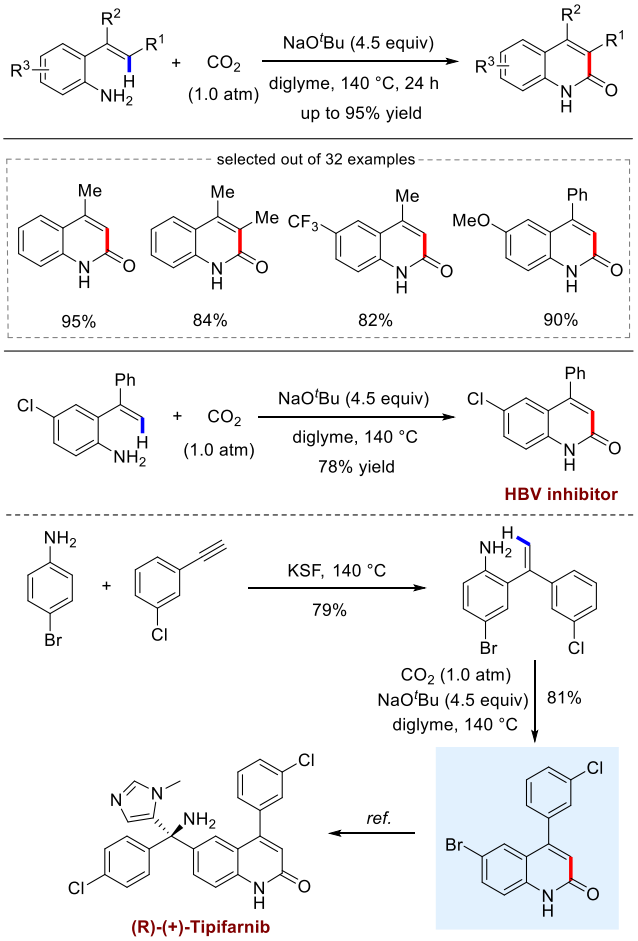
In 2017, Yu and co-workers reported the first example of transition metal-free lactamization reaction of olefinic C−H

Scheme 51. Metal-Free C−H [5 + 1] Carbonylation of 2-Alkenylanilines with Dioxazolones



bonds of unprotected 2-alkenylanilines with nontoxic and readily available carbon dioxide as the ideal carbonyl source in the presence of alkali metal *tert*-butoxides to synthesize electronically and sterically diverse 2-quinolinones in modest to excellent yields (Scheme 52).[123] This efficient and eco-friendly process exhibited a broad substrate scope, high

Scheme 52. Transition-Metal-Free Lactamization of 2-Alkenylanilines with CO_2



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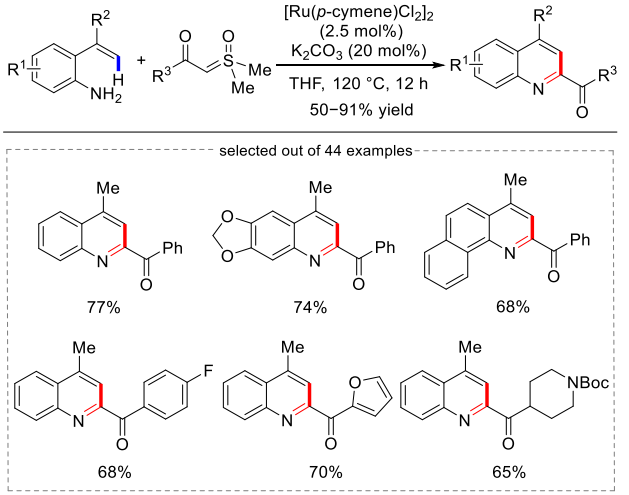
functional group compatibility, and facile scalability, which represents an appealing method for the pharmaceutical industry to the rapid synthesis of drugs and bioactive molecules.

Later in 2019, the group of Ma and Nan disclosed an unprecedented Ru(II)-catalyzed [5 + 1] annulation of 2-alkenylanilines with readily available sulfoxonium ylides as one-carbon coupling partners through the NH_2-assisted olefinic C−H functionalization strategy (Scheme 53).[124] This new

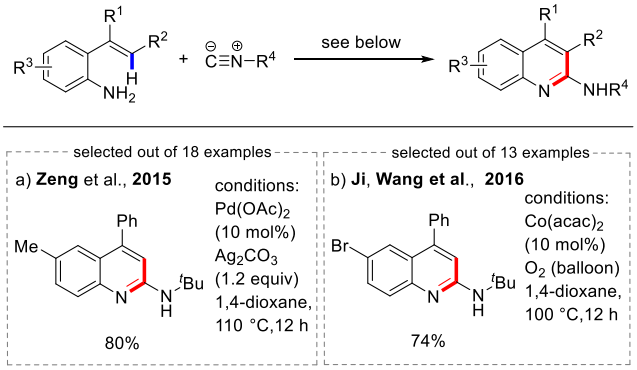
Scheme 53. Ru-Catalyzed Formal [5 + 1] Annulation of Alkenylanilines with Sulfoxonium Ylides



ruthenium-catalyzed annulation reaction employs synthetically ideal free amino functionality as a traceless directing group to assist the vinylic C−H bond functionalizations under aerobic conditions, providing a straightforward construction of 2-acylquinolines, which are widespread in biologically active pharmaceuticals. Quite recently, Yu, Wang, and their cowokers also achieved the same transformation by an operationally simple, photothermomechanochemical approach under iron(II) phthalocyanine catalysis that remarkably obviates the use of any solvent or harsh reaction conditions.[125]

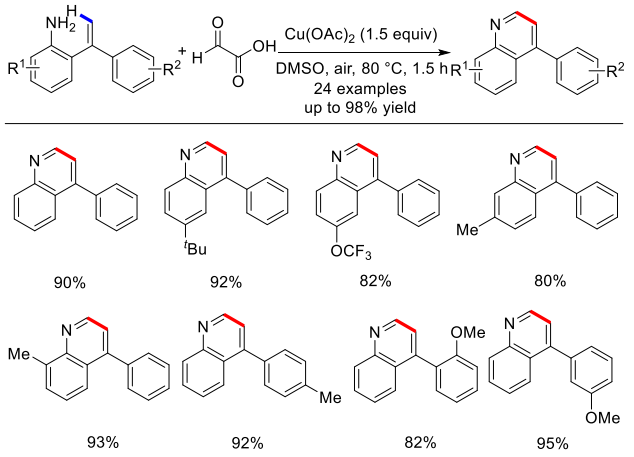
A general palladium-catalyzed oxidative coupling of 2-vinylanilines with isocyanides was achieved by Zeng and co-workers, providing an exceptionally efficient and straightforward approach for the preparation of a variety of highly decorated 2-aminoquinolines (Scheme 54a),[126] which represent an important class of heterocyclic motifs exhibiting a broad range of biological and medicinal activities.[127] Moreover, this isocyanide insertion reaction of 2-vinylanilines was also realized with comparable efficiency by the Ji and Wang group in the presence of cost-effective $Co(acac)_2$ as the catalyst and molecular oxygen as the oxidant (Scheme 54b).[128]

Scheme 54. Rapid Synthesis of 2-Aminoquinolines by Oxidative Isocyanide Insertion with 2-Vinylanilines



Recently, Ding's group reported a Cu(II)-catalyzed [5 + 1] oxidative annulation of free 2-vinylanilines with glyoxylic acid for the synthesis of 4-arylated quinolines (Scheme 55).[129]

Scheme 55. Copper-Mediated Formal [5 + 1] Annulation of 2-Vinylanilines and Glyoxylic Acid



Here, a diverse range of 4-arylated quinolines were synthesized in excellent yields. Of note, the reaction was typically finished within 1.5 h at 80 °C in DMSO. The authors proposed that the Cu(II) catalyst mediated the nucleophilic addition of aniline to the glyoxylic acid to produce an intermediate, which was subsequently dehydrated to generate an imine intermediate. Then, a 6π-electrocyclization of the imine afforded the corresponding 2,3-dihydroquinolines. Further oxidative aromatization and the expulsion of CO_2 resulted in the formation of the desired quinoline products.

In 2017, Mascareñas' group developed an elegant Pd(II)-catalyzed [5 + 2] annulation of *ortho*-alkenylanilides and allenes for the direct synthesis of 2,3-dihydro-1*H*-benzo[*b*]-azepines (Scheme 56).[130] The reaction was highly regio- and diastereoselective, affording the expected products in decent yields. As to the reaction mechanism, preliminary mechanistic studies showed that the C−H activation of the anilides occurred *via* a traditional metalation−deprotonation pathway. Specifically, an initial ligand exchange with the Pd(II) catalyst and the anilide kickstart the reaction to generate the Pd(II) complex intermediate followed by a C−H activation to afford a six-membered palladacycle. Subsequent coordination and regioselective migratory insertion of the allene moiety produced a π-allylic palladacycle. Finally, reductive elimination afforded the corresponding annulation products. Almost at the same time, Zeng and co-workers also achieved this oxidative annulation reactions with excellent yields.[131]

Quite recently, Volla *et al.* established a nonoxidative protocol for the [5 + 1] annulation reaction of 2-alkenylanilides (Scheme 57).[132] The reaction occurred smoothly at room temperature with allenyl acetates under Cp*Rh(III) catalysis, thereafter affording a number of highly functionalized 1,2-dihydroquinolines in excellent yields (76−91%). On the basis of mechanistic studies, the authors

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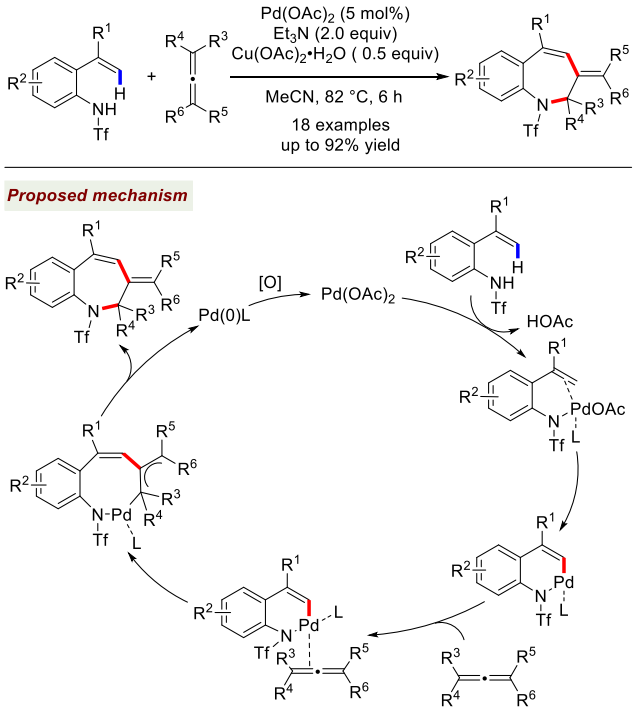
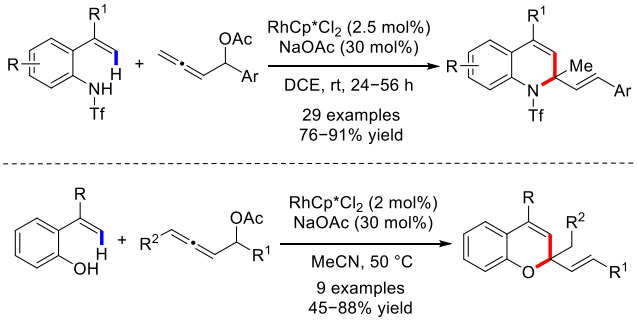
Scheme 56. Pd-Catalyzed Formal [5 + 2] Annulation of *ortho*-Alkenylanilides with Allenes and Its Proposed Mechanism



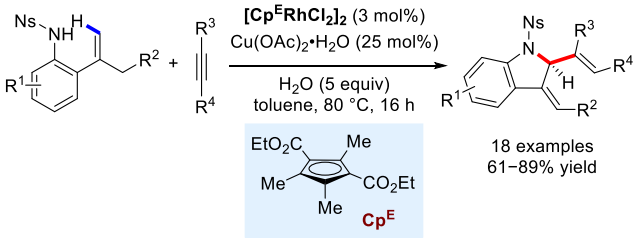
Scheme 57. [5 + 1] Annulation of 2-Alkenylanilides and 2-Alkenylphenols with Allenyl Acetates



tentatively proposed a catalytic cycle involving highly regioselective 2,3-migratory insertion, facile *β*-oxygen elimination, followed by intramolecular nucleophilic cyclization to elucidate the plausible pathway. However, it is worth noting that both 1,3-disubstituted allenes and aliphatic allenes were found to be incompatible with this protocol. Moreover, by slightly modifying the conditions, the authors successfully expanded this [5 + 1] annulation strategy to 2-alkenylphenol substrates. A series of allenyl acetates with different substitution patterns were coupled to deliver the appealing chromene derivatives.

The groups of Gulías and Lam achieved the vinylic C−H activation on 2-alkenylphenols to give oxacyclic or spirocyclic molecules.[92,104] To build on that discovery, they expanded to carry out C−H bond functionalization of styrene-type alkenes to produce 2-substituted indolines. By means of a modified Rh(III) catalyst featuring an electron-deficient η^5-cyclopentadienyl ligand (Cp^E), the coupling reaction of alkynes with 2-alkenyl anilides bearing an Ns group proceeded smoothly in toluene at 80 °C (Scheme 58).[133] By separating

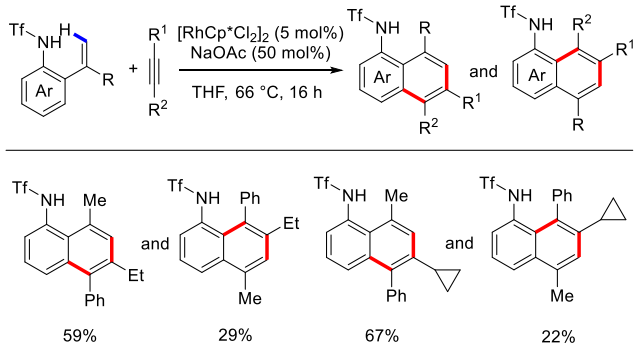
Scheme 58. Synthesis of 2-Substituted Indolines by Rhodium(III)-Catalyzed Annulation of 2-Alkenyl Anilides with Alkynes



out the intermediates and performing deuterium-labeling experiments, it can be concluded that the possible mechanism involves alkenylation of C−H bond to form an intermediate, followed by a 1,5-H shift simultaneously with migration of Rh to afford an intermediate which finally undergoes reductive elimination.

In 2019, the same group also discovered another kind of annulation reaction between alkynes and 2-alkenyl anilides bearing a Tf group (Scheme 59).[134] Apart from obtaining the

Scheme 59. Formation of Unexpected Naphthalene Adducts by Annulation of *ortho*-Alkenyl Anilides with Alkynes



typical naphthylamide product, an unexpected isomer was identified. Mechanistic studies were performed to justify the production of the isomer when the naphthylamide of the alkenyl underwent migration. The results drawn were used in combination with DFT calculations to elucidate the likely mechanism. The C−H bond is activated, then alkyne coordination and insertion occur to produce a seven-membered rhodacycle. The rhodacycle then undergoes reductive elimination to give a Rh-spirocycle that can form two different kinds of cyclopropyl tricyclic intermediates, as supported by computational results. These two different intermediates would then proceed to form their respective products.

However, the oxidative annulation between alkynes and 2-alkenyl anilides by a $Pd(OAc)_2$ catalyst exceptionally produced a rare class of highly appealing nitrogen-containing cyclopentaquinoline derivatives (Scheme 60).[135] Various 2-alkenylanilines with different substitution patterns have proven to be compatible. Mechanistically, this novel transformation undergoes sequential vinylic C−H alkenylation/amination/pyrindination processes in one pot under the same conditions.

The ability to assemble functionalized benzo[*b*]azapines from a chemo- and regioselective [5 + 2] cloaddition of 2-alkenylanilines with propargylic esters is a highly sought-after goal. To this end, Zeng and co-workers established a

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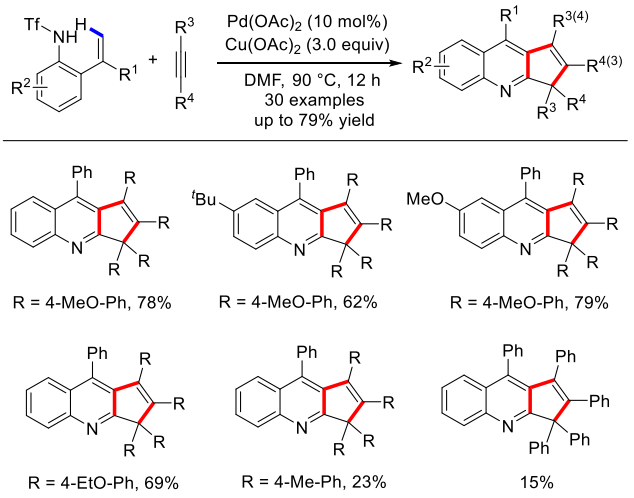
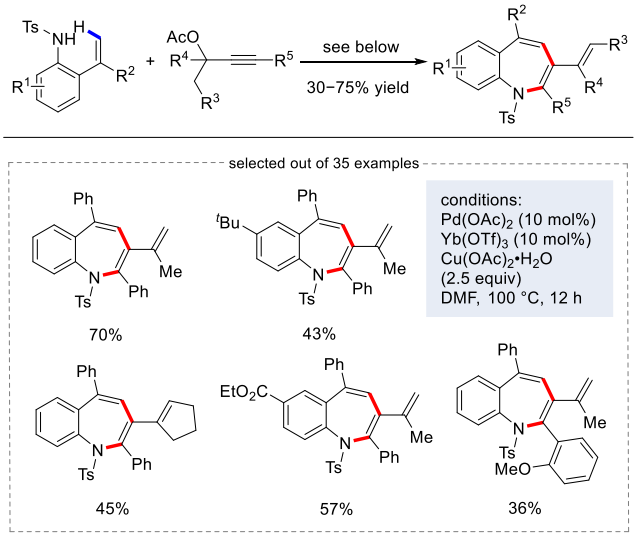
Scheme 60. Synthesis of Cyclopentaquinolines by 2-Vinylanilines with Alkynes



palladium(II)/Lewis acid cocatalyzed annulation protocol to synthesize diverse synthetically valuable benzo[*b*]azapine derivatives by using commercially available 2-alkenylanilines with various propargylic esters (Scheme 61).[136] A broad scope

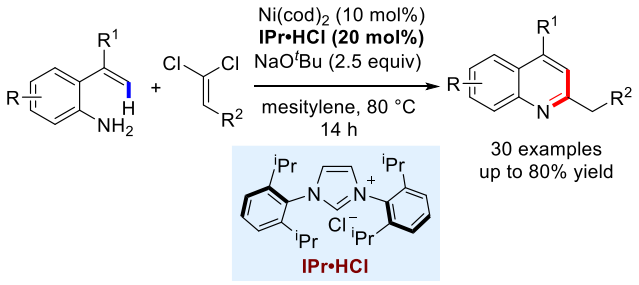
Scheme 61. Oxidative Annulation of 2-Alkenylanilines and Propargylic Esters



of 35 examples of this transformation was presented with yields of 30−75%. Of note, this [5 + 2] annulation protocol was also applicable to the reaction between alkynes and 2-alkenylanilines.

The readily accessible *gem*-dihaloalkenes are versatile synthons which could be used as alkyne precursors for cross-coupling reactions.[27,137] Quite recently, Tian and co-workers employed *gem*-dichloroalkenes for the Ni(0)-catalyzed reaction of 2-vinylanilines to construct polysubstituted quinolines (Scheme 62).[138] By the combination of $Ni(cod)_2$ catalyst, *N*-heterocyclic carbine ligand (IPr•HCl), and NaO^{t}Bu base in mesitylene at 80 °C, a broad scope of 30 examples was documented in yield up to 80%. Notably, *gem*-dichloroalkenes bearing both aryl and alkyl substituents were well tolerated in this case. This reaction can be carried out on a preparative

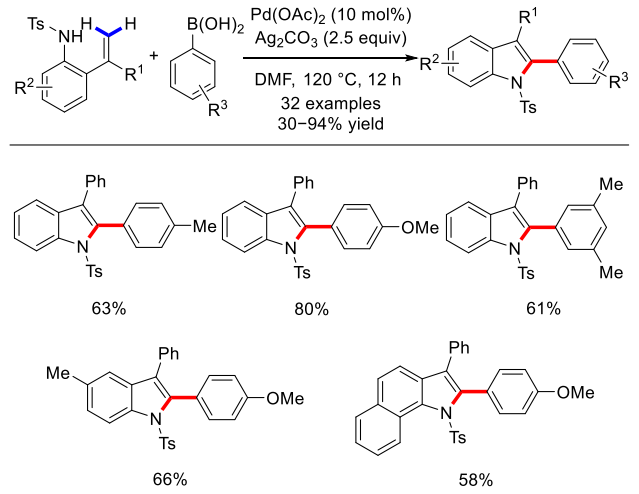
Scheme 62. Nickel-Catalyzed Cascade Reaction of 2-Vinylanilines with *gem*-Dichloroalkenes



scale and was applicable to late-stage derivatization of natural products.

As detailed in Scheme 63, a highly regioselective palladium(II)-catalyzed sequential vinylic C−H bond arylation/intra-

Scheme 63. Sequential C−H Arylation/Amination of 2-Vinylanilines with Arylboronic Acids



molecular amination of Ts-protected 2-vinylanilines with aryl boronic acids under oxidative conditions was reported by Zeng's group in 2018.[139] The scope of this protocol was found to be remarkably broad, delivering an efficient and straightforward platform to access synthetically valuable multifunctionalized indoles.

In 2020, Yi, Zhou, and colleagues reported an unique intramolecular dehydrogenative cross-coupling reaction by taking advantage of a modified Cp*^{Cy}Rh(III) catalyst, resulting in the direct synthesis of highly valuable eight-membered sultam/lactam derivatives with a wide substrate scope and excellent functional group compatibility (Scheme 64).[140] The presented reaction undergoes a redox-neutral pathway to furnish the intramolecular olefinic C−H arylation products with H_2 as the major byproduct.

Besides, the intramolecular vinylic C−H amination of 2-vinyl anilines provide a straightforward and atom-economical approach to construct the privileged indole skeletons. In this regard, a series of conceptually different strategies have been successively established over the past decades. Specifically, Stille and co-workers in 1988 reported the Pd(II)-catalyzed intramolecular cyclization reaction of tosyl-protected 2-alkenylanilines by using *p*-benzoquinone (BQ) as a reoxidant (Scheme 65a).[141] In this case, 10 excess equivalent of lithium

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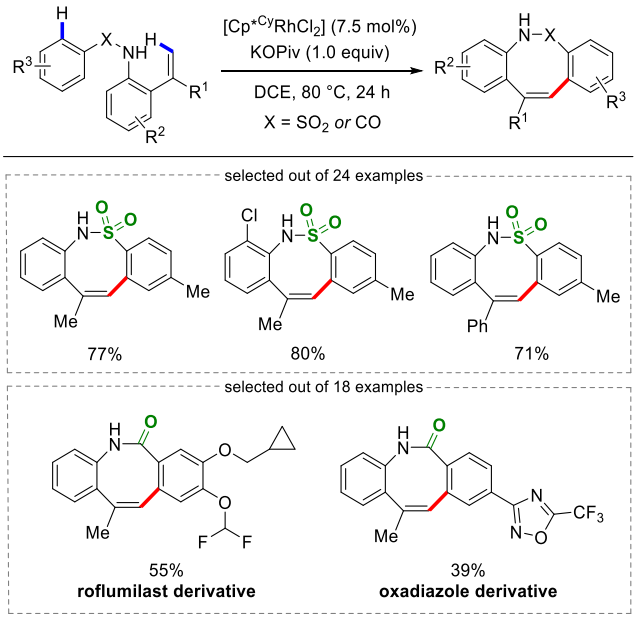
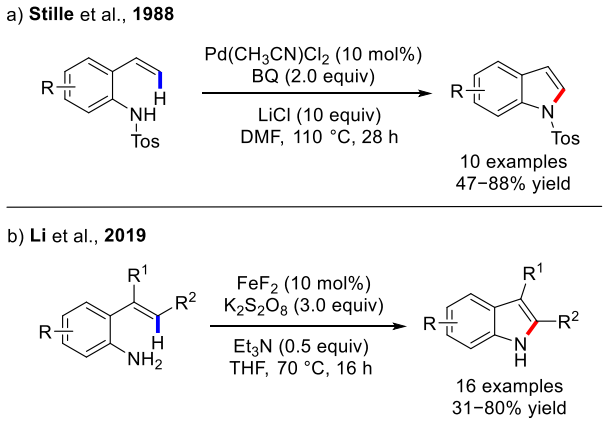
Scheme 64. Intramolecular Dehydrogenative Cross-Couplings for Building Eight-Membered Sultam/Lactam Scaffolds



Scheme 65. Synthesis of Indoles *via* Intramolecular Vinylic C−H Amination of 2-Alkenylanilines

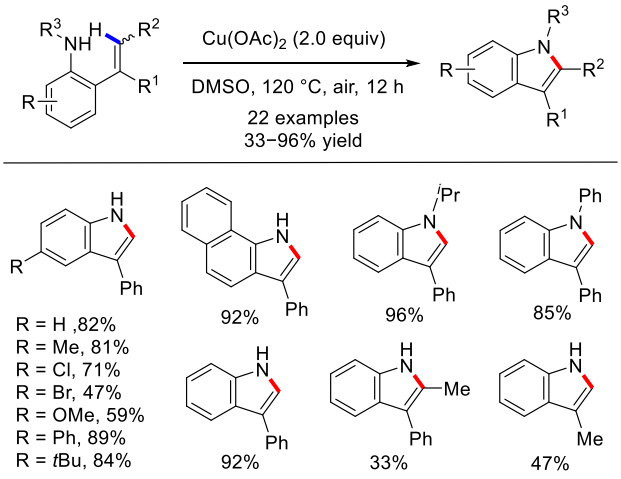


chloride was employed to obtain high efficiency. Recently, the Li group also illustrated an analogous transformation with comparable efficiency with unprotected 2-alkenylanilines as the suitable substrates enabled by a $FeF_2/K_2S_2O_8$ catalytic system (Scheme 65b).[142]

In 2017, Cheng *et al.* accomplished a copper-mediated intramolecular cyclization of various 2-alkenylaniline substrates (Scheme 66).[143] Under the optimal conditions, diverse 2-alkenylanilines bearing a broad range of functionalities could be smoothly converted into the expected products with yields of 33−96%. Remarkably, 2,3-disubstituted indole can be obtained uneventfully, albeit with diminished efficiency. The authors demonstrated the practicality of this protocol by a preparative scale synthesis.

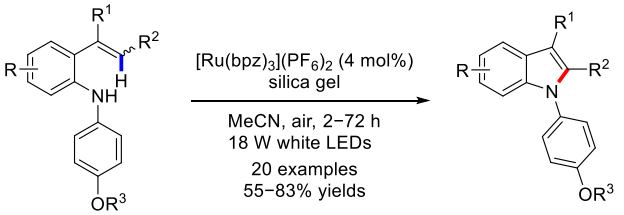
Although these transition metal-based strategies have shown notable features, innovative strategies for the sustainable indole synthesis from 2-alkenylanilines are highly desirable. To this end, a myriad of efficient metal-free methods, including dioxygen-promoted,[144] DDQ-mediated,[145] selenium-catalyzed,[146,147] iodine(III) reagent-mediated,[148−150] as well as NIS-mediated intramolecular aminations[151] have been successively established over the past years. These strategies greatly expanded the toolbox for the expedient synthesis of structurally diverse indole derivatives.

Scheme 66. Synthesis of Indoles by Cu-Mediated Intramolecular Cyclization of 2-Alkenylanilines



With the ever-increasing interests in photoredox catalysis, Zheng *et al.* in 2012 first explored the visible-light-mediated photocatalytic process for the synthesis of *N*-arylindoles by using $[Ru(bpz)_3](PF_6)_2$ as a competent photocatalyst (Scheme 67).[152] In this case, a variety of substrates with different

Scheme 67. Visible-Light-Mediated Synthesis of *N*-Arylindoles



substitution patterns are compatible with the open-air conditions. Nevertheless, a *p*-alkoxyphenyl group on the nitrogen atom is indispensable for the reaction, and no reaction was observed under the same conditions when it was replaced by a phenyl group. It is noteworthy that a broad array of *gem*-disubstituted styryl anilines could undergo a 1,2-carbon shift process to furnish 2,3-disubstituted *N*-arylindoles. Both aryl and alkyl groups can participate in this migratory transformation, and the former one is more preferentially migrated.

Another alternative sustainable strategy to synthesize indoles from 2-alkenylanilines is to employ the electrochemically driven dehydrogenative cyclization process. In this regard, the group of Zha and Wang recently established an iodine-mediated electrochemical protocol of vinylic C−H amination through an ionic process (Scheme 68a).[153] Using Pt plates as both the cathode and the anode in an easy-to-use undivided cell, diverse Ts-protected 2-alkenylanilines bearing different substituents reacted smoothly to afford the expected indoles in yield up to 92%. However, remarkable electronic and steric effects were observed in this case as 7-brominated substrate

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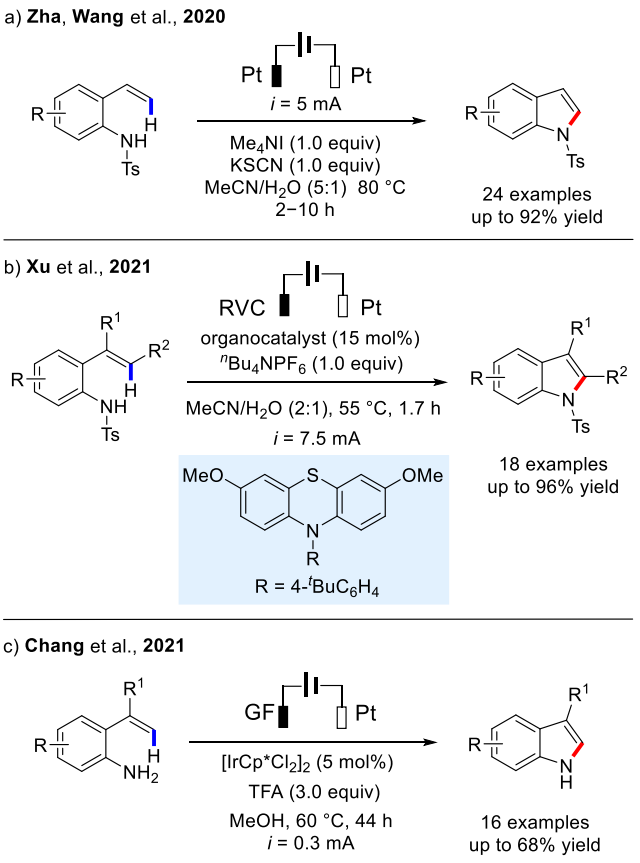
Scheme 68. Synthesis of Indoles through an Electrocatalytic Dehydrogenative Cyclization of 2-Vinylanilides



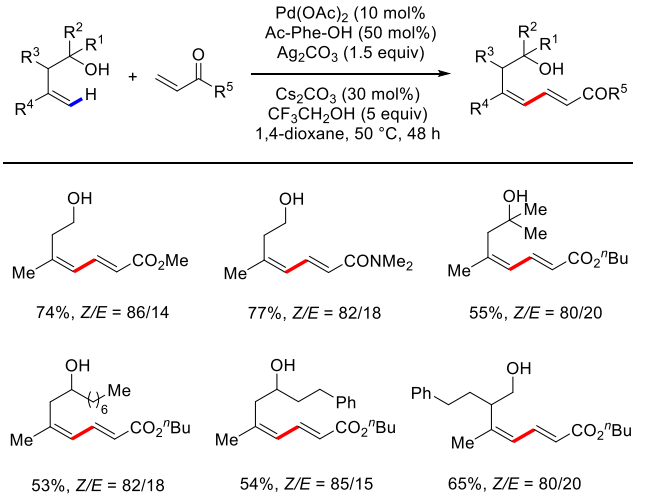
was proven to be incompatible with the electrochemical conditions. Later in 2021, Xu *et al.* disclosed an analogous process carried out in a Schlenk tube equipped with a reticulated vitreous carbon anode (RVC) and a Pt plate cathode in the presence of an organic phenothiazine-based redox catalyst. By virtue of anodic oxidation under metal-free conditions, this protocol produced a variety of 3-substituted and 2,3-disubstituted indoles with H_2 evolution (Scheme 68b)[154] In a related report, Chang and co-workers realized an operationally convenient, Ir(III)-catalyzed dehydrogenative cyclization of unprotected 2-alkenyl anilines under undivided electrolytic conditions. Combined computational studies and electrochemical investigations revealed that the reaction probably proceeds through an electro-oxidation induced reductive elimination pathway (Scheme 68c).[155]

3. ALKENYL C−H BOND FUNCTIONALIZATION OF ALIPHATIC ALKENES CONTAINING A DIRECTING GROUP

After discussing on alkenyl C−H bond functionalization of aryl styrenes, we next turned to focus on the reactions using simple aliphatic terminal alkenes. One of the major challenges in the sp^2 alkenyl C−H bond functionalization of alkenes is the control of the stereochemistries (regio, *E*/*Z*, *etc.*). Similar to the reactions using aryl alkenes, the *E*-selective vinylic C−H bond can be controlled by the steric effect. Similarly, most of the reported *Z*-selective C−H bond functionalizations made use of a directing group. Many different chelating groups forming 5−6 membered metal chelates have been successfully used to give *Z*-selective products. In this part of the review, we will organize the advances according to the types of chelating groups that form 5−6 membered ring chelated intermediates.

Conjugated dienes are found extensively in a variety of pharmaceutically relevant molecules and bioactive natural products and are also important starting materials in organic synthesis. Alkene C−H alkenylation reactions catalyzed by different transition metal catalyst are an atom-economic way to achieve these conjugated dienes. In 2017, Loh's group reported a stereospecific olefination between two alkenes by using a native hydroxyl directing group (Scheme 69).[156] Good *E*/*Z*

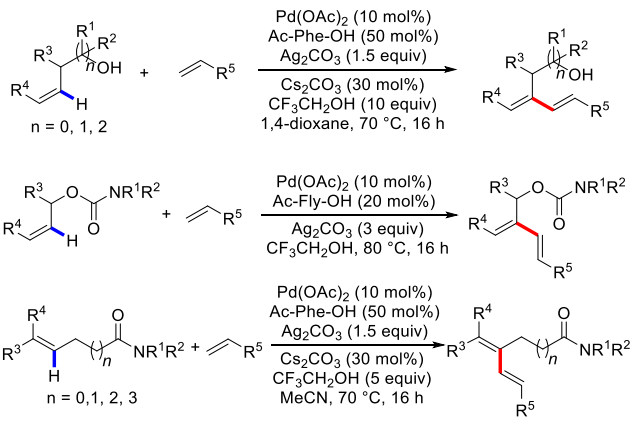
Scheme 69. Oxidative Cross-Coupling Reactions between Homoallylic Alcohols and Alkenes



selectivity was obtained in the products. The hydroxyl group was found to serve as a chelating group not only to guide the activation of alkenyl C−H bonds but to improve on the Z-stereoselectivity in this process.

As an extension of this strategy, Zhong and co-workers later in 2019 also discovered the functionalization of proximal alkenyl C−H bonds of simple aliphatic alkenes (Scheme 70).[157] Monodentate chelation was used for the C−H bond alkenylation, and the reaction was successful with broad substrates containing hydroxyl, carbamate, and amide functional groups. In this work, the proximal C−H alkenyl bond was activated *via* an *o*-monodentate chelation, which occurs through four- to eight-membered *exo*-palladacycles, which is in

Scheme 70. Geminal Group-Directed Alkenyl C−H Olefination



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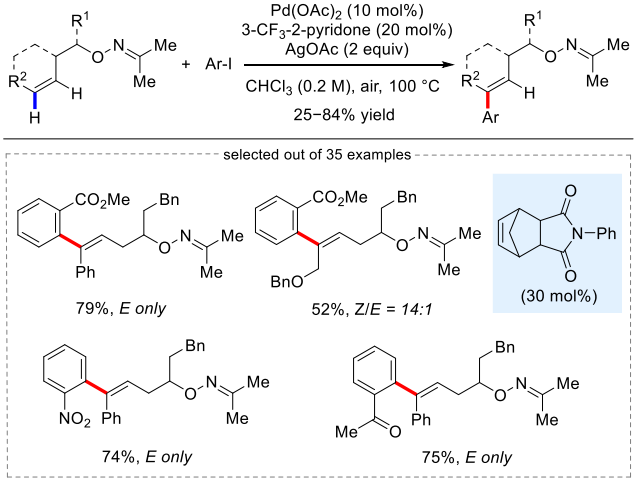
contrast to the *N,N*-bidentate chelation that occurs through a six-membered *endo*-palladacycle as generally proposed in Engle's work. Notably, steroids and ricinoleates are also competent substrates to undergo late-stage functionalizations, which remarkably showcased the capability of this approach.

Almost simultaneously, Dong and co-workers reported a novel approach for the distal-selective alkenyl C−H arylation enabled by palladium/norbornene (NBE) cooperative catalysis (Scheme 71).[158,159] This reaction occurs by activating a

Scheme 71. Distal Olefinic C−H Functionalization *via* Palladium/Norbornene Cooperative Catalysis



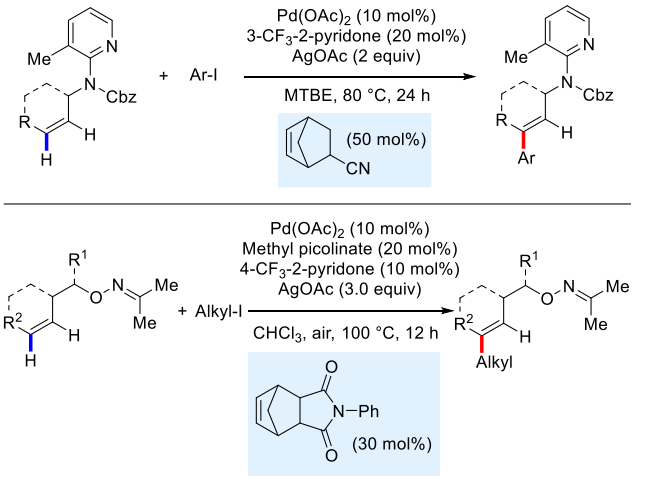
proximal olefinic C−H bond and can be conducted in air with a large variety of *cis*-alkenes, aryl iodides, MeI, and methyl bromoacetate. This reaction is found to process *via* alkenyl sp^2 C−H bond rather than the classical Heck cross-coupling pathway as supported by the detailed mechanistic studies. Mechanistically, the proximal C−H bond of the olefin substrate is activated to form an intermediate, and this process is directed by the easily removable oxime ether directing group. Then, the NBE derivative is inserted into the intermediate, and the oxime ether decoordinates to afford another intermediate which undergoes C−H activation again at the distal position. This results in the formation of a palladacycle, which reacts with ArI to obtain the final product.

The Dong group substantially extended their distal C−H alkenylation through the palladium/norbornene cooperative catalysis strategy to arylate and alkylate the *cis*-olefins by introducing a selective donating group (Scheme 72).[160] The judicious choice of structurally modified norbornene mediator is critical to realize this transformation. The authors successfully demonstrated the arylation of allylamines and primary and secondary derived alcohols.

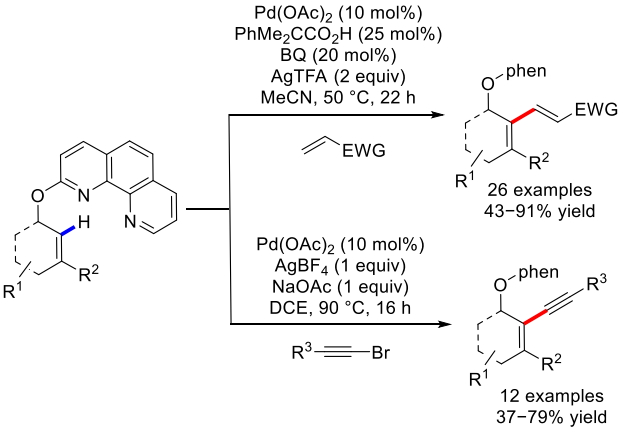
In 2020, Miura and co-workers reported a regioselective palladium(II)-catalyzed phenanthroline-directed vinylic C−H alkenylation of allylic alcohols with electron-deficient alkenes (Scheme 73).[161] In this case, the proximal alkenyl C−H bond was activated over allylic C−O bond with the assistance of a bidentate directing group. Under the same Pd(II)/phenanthroline conditions, the authors utilized alkynyl bromides to alkynylate the allylic alcohols in a regioselective manner.

Lu and Zhao *et al.* reported an oxyacetamide-directed *Z*-type alkenyl C−H functionalization enabled by a Cp*Rh(III) catalyst through a rare *exo*-rhodacyle process (Scheme 74).[162] Multisubstituted alkenes and allenes were synthesized

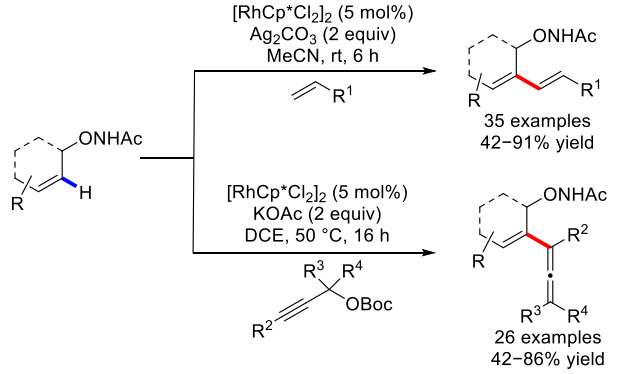
Scheme 72. Palladium/NBE-Catalyzed Distal Alkenyl C−H Arylation and Alkylation of *cis*-Olefins



Scheme 73. Phenanthroline-Directed, Palladium(II)-Catalyzed Regioselective C−H Alkenylation, and Alkynylation of Allylic Alcohols



Scheme 74. Oxyacetamide-Directed Rh(III)-Catalyzed Alkenyl C−H Functionalization of Allylic Alcohols



in modest to excellent yields. With the judicious choice of solvents and base, both alkenes and propargylic carbonates coupling partners reacted well to furnish the corresponding products with high regio- and stereoselectivity. Moreover, unnatural *β*-amino acid can be synthesized using this strategy.

In the same year, Dethe and colleagues extended Loh's strategy[156] and developed a direct Ru-catalyzed method

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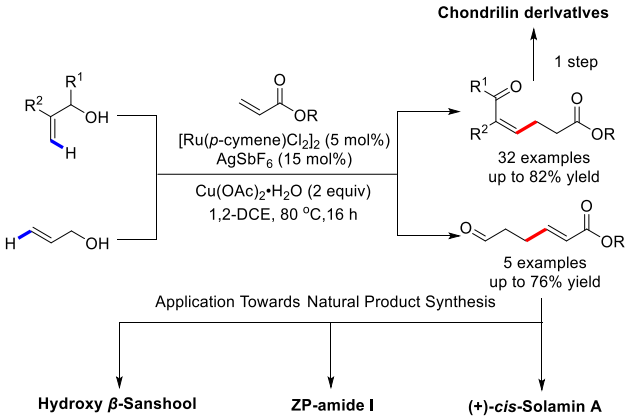
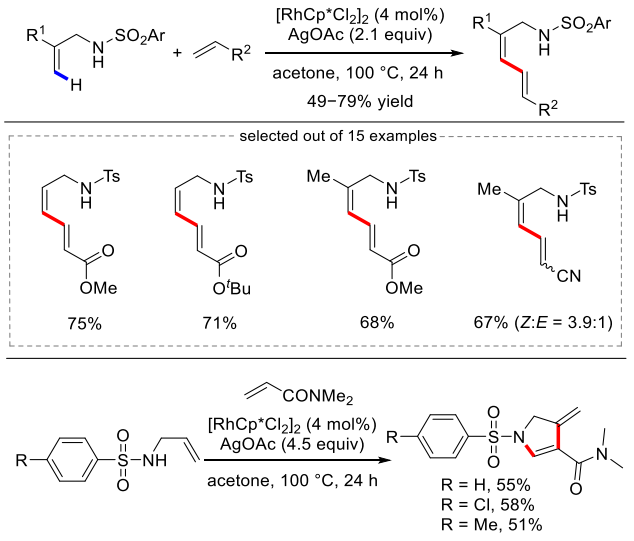
involving an oxidative coupling of allyl alcohols with activated olefins by C(allyl)−H activation of allyl alcohols, providing an efficient and direct access to synthetically useful class of α,β-unsaturated enones (Scheme 75).[163] The authors demonstrated the utility of this method by applying to the synthesis of bioactive natural products such as hydroxy-β-sanshool, ZP-amide I, chondrillin, plakorin, and (+)-*cis*-solamin A.

Scheme 75. Ru(II)-Catalyzed Dehydrogenative Cross-Coupling of Allyl Alcohols with Acrylates

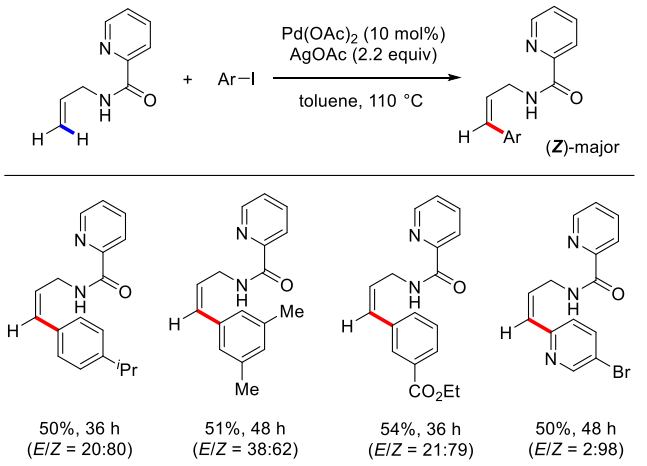


Allylic amines are highly valuable building blocks for the synthesis of various nitrogen-containing molecules. The direct activation of alkenyl C−H bonds of allylic amines also attract tremendous interests in recent years. For example, Li's group in 2013 described a rhodium(III)-catalyzed oxidative vinylic C−H olefination of *N*-sulfonyl allylamines with acrylates and acrylonitriles (Scheme 76).[164] More interestingly, the reaction with electron-deficient *N*,*N*-dimethylacrylamide as the coupling partner exclusively resulted in the formation of 2,3-dihydropyrrole derivatives in modest yields (51−58%). Later on, Babu and co-workers disclosed the bidentate picolinamide-assisted γ-selective C−H arylation of allylamines in the presence of the $Pd(OAc)_2$ catalyst and AgOAc additive to afford a series of *Z*-cinnamylamines with appreciable yields and up to 2:98 *E*/*Z* ratio (Scheme 77).[165]

Scheme 76. Rhodium(III)-Catalyzed Oxidative C−H Olefination of *N*-Allyl Sulfonamides

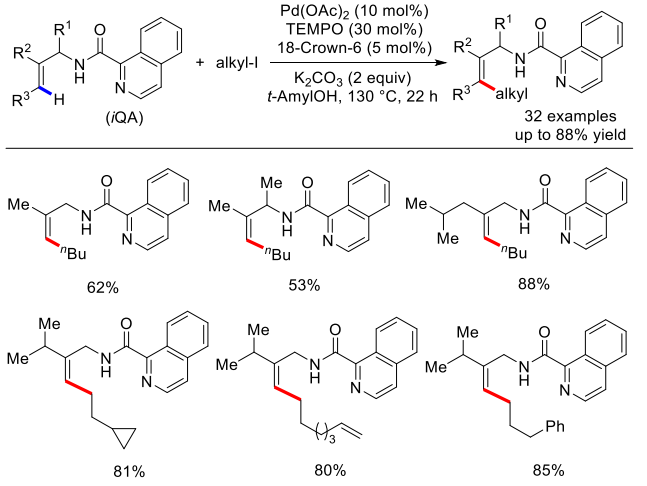


Scheme 77. Pd(II)-Catalyzed Picolinamide-Assisted Construction of *Z*-Cinnamylamines



Additionally, Loh's group also disclosed a general approach for the alkenyl C−H alkylation of allylamines by means of a bidentate isoquinoline-1-carboxamide (*i*QA)-assisted strategy (Scheme 78),[166] providing a general method to selectively produce (*Z*)-tri- and tetra-substituted olefins. Notably, both primary and secondary alkyl iodides reacted well under these conditions.

Scheme 78. Stereospecific Vinylic C−H Alkylation of Allylamines with Alkyl Iodides



Undoubtedly, *C*-vinyl glycosides are a prominent class of carbohydrates widely encountered in many natural products and bioactive molecules.[167−169] Their efficient synthesis is of great importance, and a tremendous synthetic challenge as well.[170−173] More recently, the straightforward and stereoselective synthesis of *C*-vinyl glycosides was disclosed by the He and Chen group through a palladium(II)-catalyzed chelation-assisted C−H glycosylation of unbiased aliphatic alkenes bearing an easily removable isoquinoline-1-carboxamide (*i*QA) auxiliary[166] with glycosyl chlorides (Scheme 79).[174] This strategy can glycosylate both γ and δ C−H bonds

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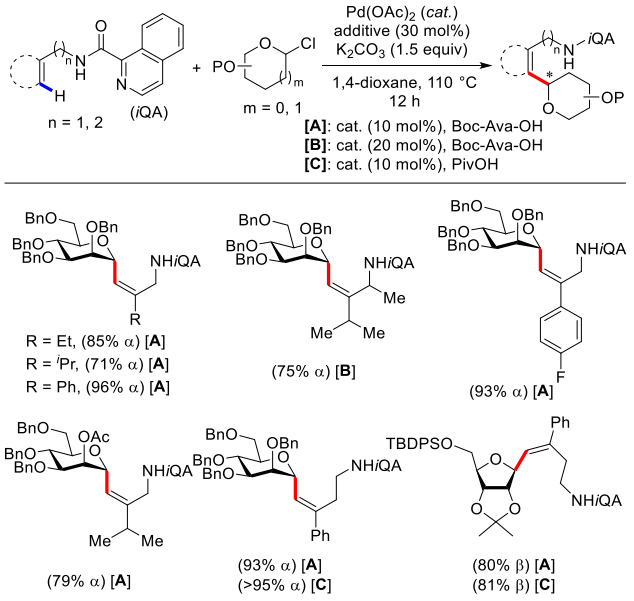
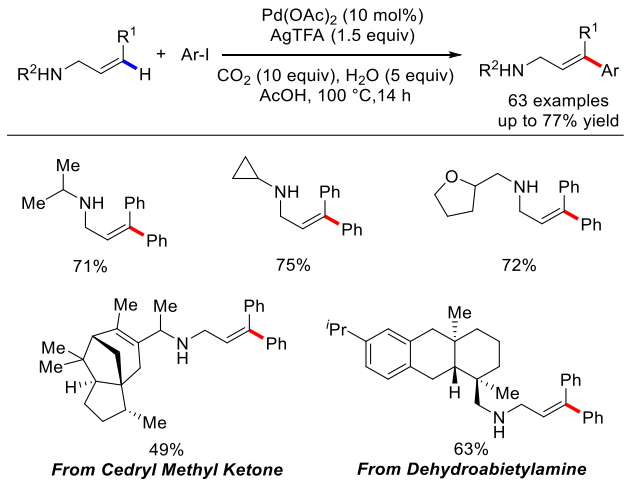
of various readily available alkene substrates in moderate to high yields with excellent regio- and stereoselectivity.

Scheme 79. Stereoselective Synthesis of *C*-Vinyl Glycosides *via* C−H Glycosylation of Aliphatic Alkenes



Moreover, Young's group demonstrated an efficient, simple, and highly selective γ-arylation of unprotected allylamines through a stereo- and regiospecific olefin insertion mechanism (Scheme 80).[175] The authors employed both primary and

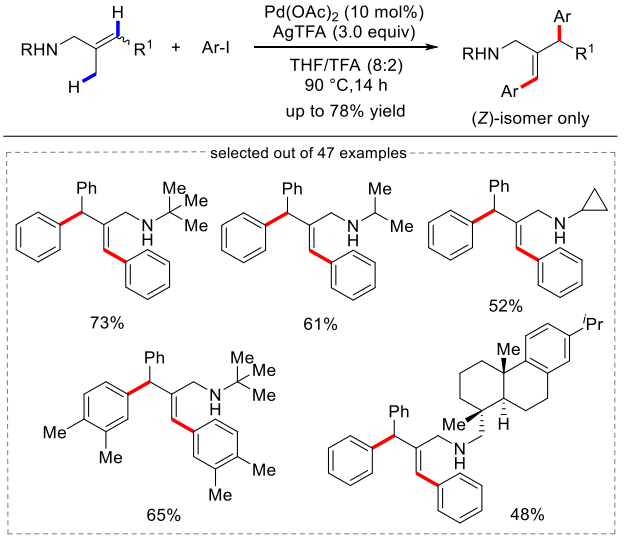
Scheme 80. Regioselective γ-Arylation of Unprotected Allylamines



secondary amines in this transformation. Different functional groups such as ketones, esters, and heterocyclic motifs are compatible with this method, and an extraordinarily broad range of 3,3′-diarylated allylamines were obtained in decent yields.

Following this, the same group extended to report the efficient synthesis of *Z*-selective alkenyl amines by the γ,γ′-diarylation reaction of unprotected β-alkyl allylamines through an interrupted chain walking process (Scheme 81).[176] In this case, they found that the choice of silver salt plays a significant role in arylating the less bulkier secondary and tertiary amines.

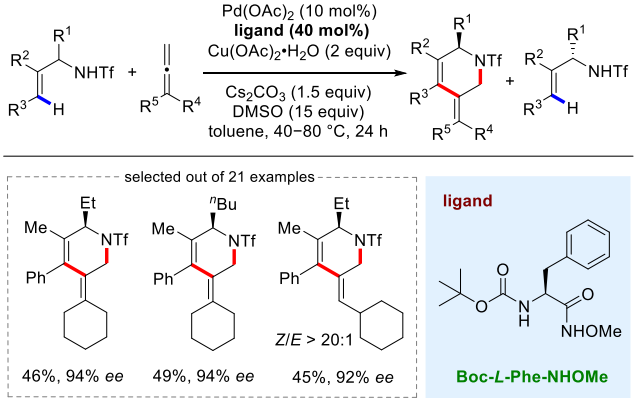
Scheme 81. Pd(II)-Catalyzed γ,γ′-Diarylation of Free Alkenyl Amines



Even the unprotected allyamines could react efficiently in this protocol.

Moreover, Gulias and colleagues disclosed a palladium-catalyzed enantioselective annulation of allyltriflamides with allenes, which relies on an asymmetric alkenyl C−H functionalization step. This protocol allowed an easy and straightforward access to enantioriched allylamines and piperidines with decent stereocontrol in a step- and atom-economical manner (Scheme 82).[177]

Scheme 82. Kinetic Resolution of Allyltriflamides through a Palladium(II)-Catalyzed Vinylic C−H Bond Functionalization with Allenes



In addition to the example of γ-carbonylation[178] and silylation[179] of aliphatic amines (Scheme 83a), Zhao and co-workers also disclosed an example of olefinic δ-C(sp²)−H alkynylation *via* six-membered palladacycles using a readily available oxalyl amide directing group (Scheme 83b).[180] Another notable example of alkenyl δ-C−H bond alkynylation of unbiased alkenes with bromoalkyne was reported by Sarpong and co-workers using a β-carboline amide as inherent directing group (Scheme 83c).[181]

Meanwhile, He and colleagues illustrated an efficient site-selective palladium(II)-catalyzed olefinic δ-C(sp²)−H acetoxylation,[182] and later alkenylation[183] of unactivated cyclic

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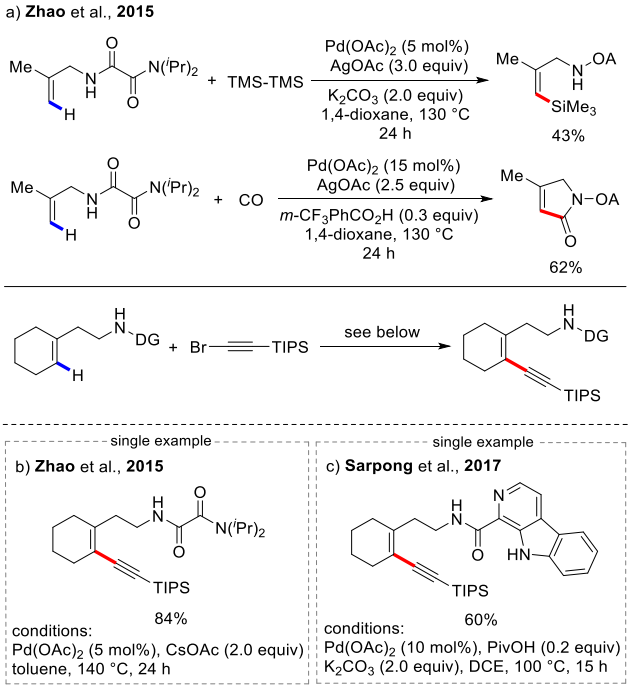
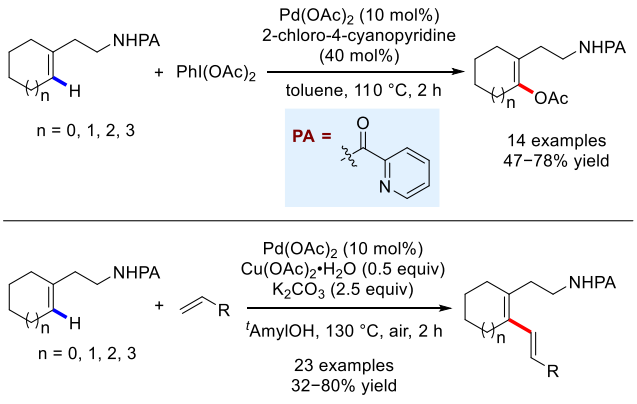
Scheme 83. Various Olefinic C−H Functionalization Reactions of Unbiased Alkenes



alkenes by using picolinamide as a remote bidentate directing group *via* a six-membered palladacycle intermediate (Scheme 84).

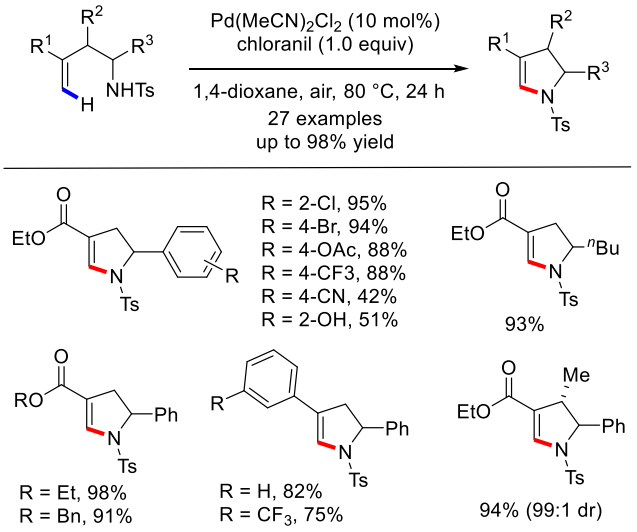
Scheme 84. Palladium-Catalyzed Olefinic δ-C(sp^2)−H Acetoxylation and Alkenylation of Unactivated Cycloalkenes



Apart from the above intermolecular oxidative coupling reactions, Loh's research group in 2017 established an intramolecular approach of vinylic C−H amination for the synthesis of multisubstituted dihydropyrroles (Scheme 85).[184] In this report, the judicious use of chloranil instead of benzoquinone (BQ) greatly facilitated this intramolecular 5-*endo* cyclization to result in the formation of dihydropyrroles. Overall, a broad range of γ,δ-unsaturated tosyl-protected amines delivered the expected products in excellent yields. However, diminished efficiency was observed for electron-rich substituents on the alkene moiety, and long-chain alkyl group completely inhibited this transformation.

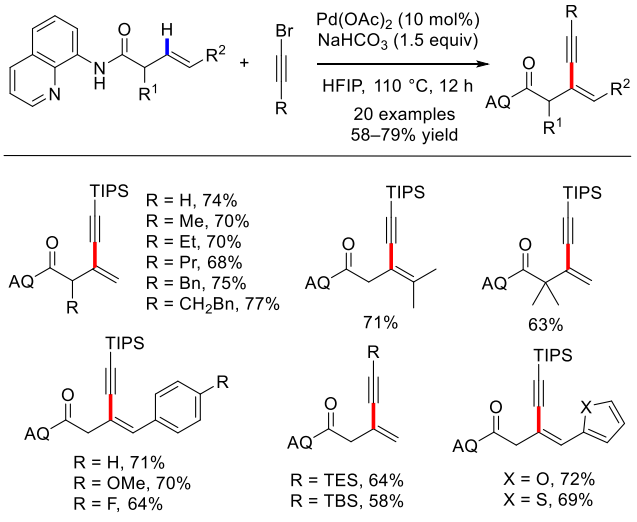
With the assistance of a removable bidentate 8-aminoquinoline auxiliary, Pan and co-workers were able to regioselectively

Scheme 85. Synthesis of Dihydropyrroles *via* Pd(II)-Catalyzed Intramolecular Alkenyl C−H Amination



activate the β-C−H bonds of diverse β,γ-unactivated amides, enabling an expeditious route to a variety of conjugated 1,3-enynes (Scheme 86).[185] Notably, a wide scope with respect to

Scheme 86. Synthesis of 1,3-Enynes *via* Palladium-Catalyzed Vinylic C−H Alkynylation of Alkenes



both terminal and internal unactivated aliphatic alkenes were smoothly coupled with bromoalkynes to generate the alkynylation products with overall high yields (58−79%). Bromoalkynes bearing TIPS, TBS, and TES groups were appropriate coupling partners, while other substituents such as phenylacetylene and methyl propionate were proven to be incompatible with the conditions. On the basis of mechanistic investigations, a plausible catalytic cycle involving Pd(II)/Pd(IV) redox manifold were proposed to elucidate the mechanism.

It is commonly reported that neighboring directing groups of alkenes always resulted in the activation of distal C−H bonds, and this is notably distinct from C−H activation in aryls.[186] However, the activation of proximal C−H bonds in olefin substrates has not been well explored. In 2018, Engle and co-workers elegantly disclosed a landmark work on

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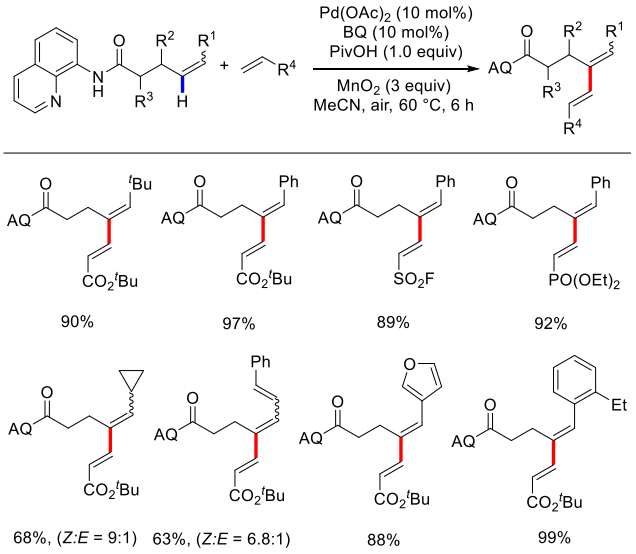
obtaining various highly substituted 1,3-dienes by using $Pd(OAc)_2$ to catalyze the alkenylation of proximal olefinic C−H bonds with a stoichiometric amount of MnO_2 or O_2 and catalytic $Co(OAc)_2$ (Scheme 87).[187] Internal nonconjugated

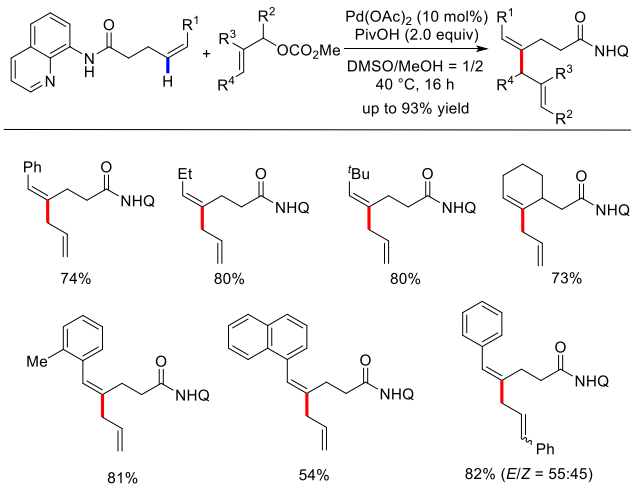
Scheme 87. Synthesis of 1,3-Diene *via* Six-Membered Palladacycles



alkenes reacted well under the typical reaction conditions. Combined experimental and computational investigations confirmed that proximal C−H alkenyl bond activation occurred in this protocol. The structurally well-defined alkenylpalladium(II) dimer was readily isolated and characterized, which can be also used as the catalyst.

Subsequently, Zhong and colleagues disclosed an efficient approach for the synthesis of branched 1,4-dienes through the distal alkenyl C−H allylation of nonconjugated alkenyl amides with allyl carbonates by means of 8-aminoquinoline (AQ) as the bidentate chelating group (Scheme 88).[188] This reaction builds on their previous work in proximal alkenyl C−H functionalization reactions through an *exo*-palladacycle intermediate.[157] Their new protocol employs unactivated *Z*-olefins

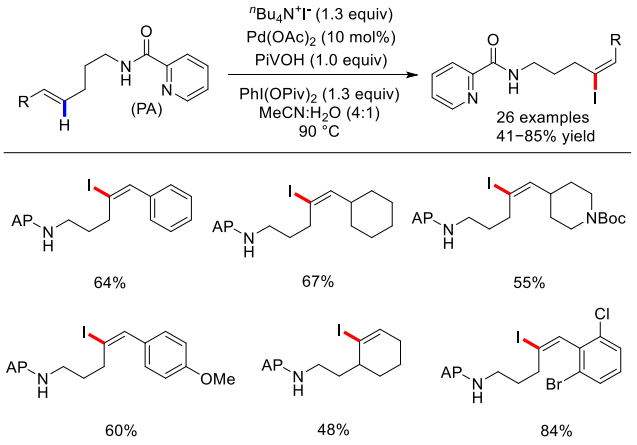
Scheme 88. Synthesis of Branched 1,4-Dienes *via* Bidentate Auxiliary-Directed Alkenyl C−H Allylation



to couple with allyl carbonates under mild and oxidant-free conditions.

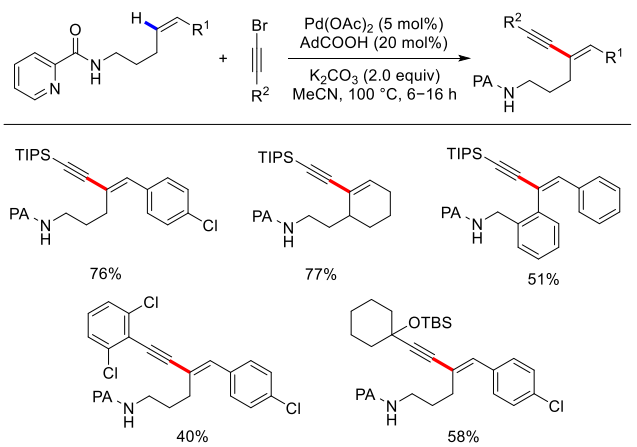
Alkenyl iodides represent a versatile class of building blocks frequently used in organic synthesis,[189−192] which significantly highlights the increasing need for efficient synthesis methods. A straightforward approach to prepare alkenyl iodides would be the direct olefinic C−H iodination of their alkene precursors. In 2019, Carreira and co-workers disclosed an elegant protocol of the regio- and stereoselective Pd(II)-catalyzed C−H iodination of electronically unbiased alkenes bearing the bidentate picolinamide directing group, furnishing the iodination products in yields ranging from 41% to 85% with excellent functional group compatibility (Scheme 89).[193]

Scheme 89. Synthesis of Alkenyl Iodides through the Regioselective Vinylic C−H Iodination of Unactivated Alkenes



As an extension of this approach, the same group later expanded to disclose a palladium-catalyzed remote C−H alkynylation of unactivated alkenes by using bromoalkynes as the alkynylating source (Scheme 90).[194] In this case, readily available picolinamide auxiliary enables the formation of putative 5- and 6-*exo*-metallacycles as key intermediates to produce a series of multisubstituted 1,3-enynes in up to 91% yield with excellent regio- and diastereoselectivity. As a particular highlight, the utility of this strategy has been

Scheme 90. Palladium-Catalyzed C−H Alkynylation of Electronically Unbiased Alkenes



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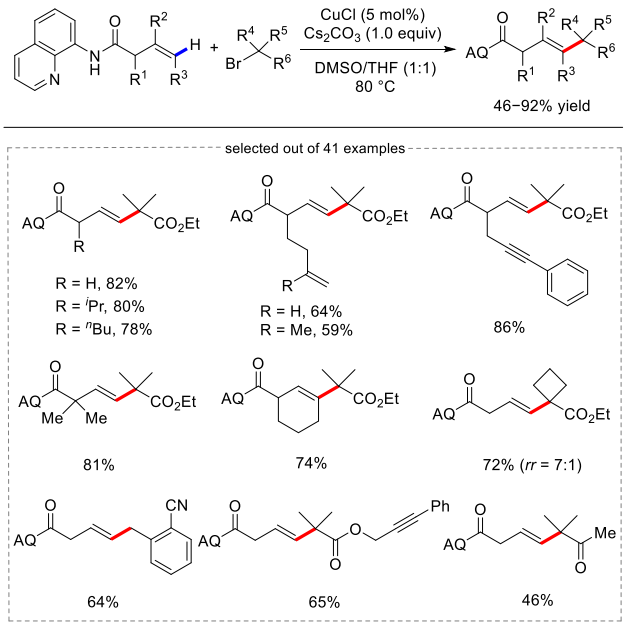
showcased by late-stage modification of biologically important molecules.

Fu, Bi, and co-workers in 2018 successfully achieved a distinctive Cu-catalyzed Heck-type C−H alkylation of unbiased aliphatic alkenes with various alkyl halides by the assistance of a bidentate 8-aminoquinoline (AQ) auxiliary strategy (Scheme 91).[195] Alkene substrates bearing other

Scheme 91. Intermolecular Heck-Type C−H Alkylation of Unactivated Olefins



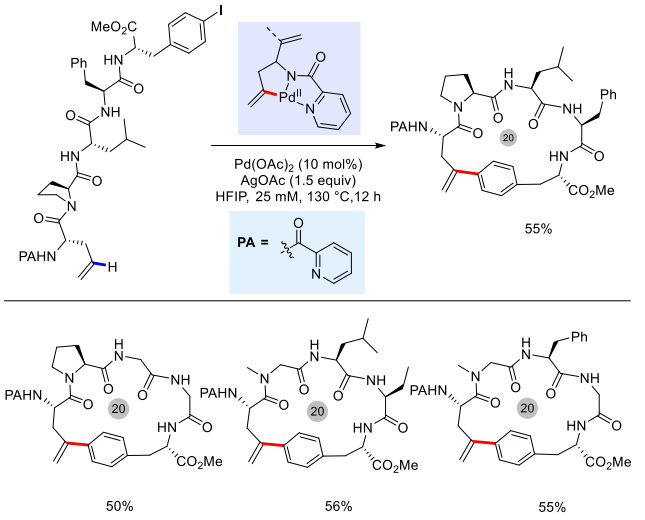
common mono- or bidentate auxiliaries thoroughly failed to furnish the desired products in this transformation. Notably, both 1°, 2°, and 3° alkyl bromides and sterically diverse nonactivated alkenes were tolerated under the conditions to afford the expected products with excellent regio- and stereoselectivity. A wide scope of 41 examples of this transformation was presented with yields of 46−92%. The authors conducted preliminary mechanistic investigations and DFT calculations that clearly indicated a radical pathway involving a concerted H−Br elimination step of a putative conformationally strained Cu(III) intermediate, which is greatly assisted by dimethyl sulfoxide.

Macrocyclic peptides are prevalent in nature and increasingly emerged as fascinating molecular scaffolds to explore the chemical space between small organic molecules and large biologicals for the development of therapeutics and chemical probes to interrogate many complicated biological systems.[196] In 2020, Chen and co-workers disclosed an intramolecular palladium-catalyzed picolinamide-directed alkenyl C−H arylation at the γ and δ positions of *N*-terminal amino acids to the construction of a handful of aryl-alkene-braced macrocyclic peptides from readily accessible precursors, providing the arylated peptide macrocycles in decent yields (Scheme 92).[197]

4. ALKENYL C−H BOND FUNCTIONALIZATION OF ALKENES CONTAINING AN ELECTRON-WITHDRAWING DIRECTING GROUP

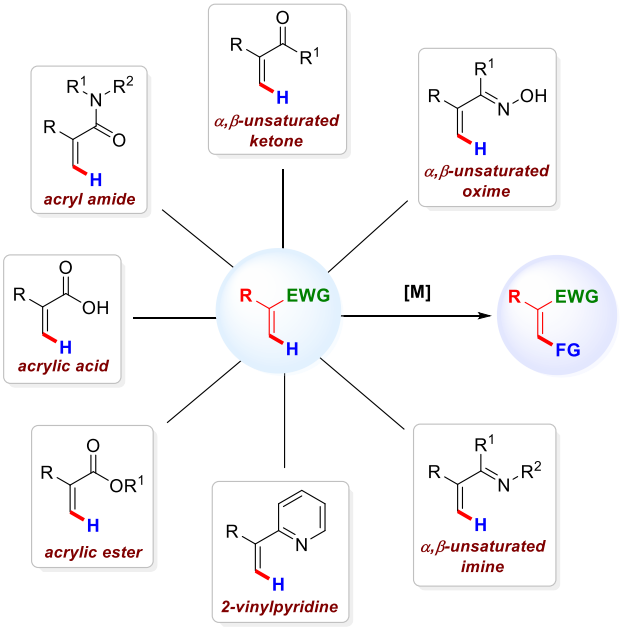
In this section, we will focus on another class of alkene derivatives where the alkenes are attached to an electron-withdrawing groups such as acrylic acids, acrylic esters, acrylic

Scheme 92. Synthesis of Peptide Macrocycles by Intramolecular Alkenyl C−H Arylation



amides, α,β-unsaturated ketones, α,β-unsaturated imines, α,β-unsaturated oximes and their derivatives, as well as 2-vinylpyridines (Scheme 93). These electron-withdrawing

Scheme 93. General Scheme of Alkenyl C−H Bond Functionalization of Alkenes Containing an Electron-Withdrawing Directing Group



groups also serve as directing group to control the stereochemistry of the coupling reactions. In addition, the coupling products contain these versatile functional groups also make them more useful building blocks in organic synthesis.

4.1. Acrylic Acids

Acrylic acids and their derivatives are ubiquitous building blocks in chemical synthesis. Transition metal-catalyzed alkenyl C−H activation of acrylic acids and their derivatives, which allows selectively functionalization of the molecule *via* employing the directing and coordinating groups, has drawn more attention in the last few decades. In C−H activation of

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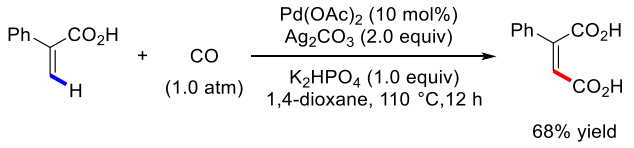
acrylic derivatives, a plethora of reports using rhodium and palladium catalysts have dominated. Nonetheless, this section aims at discussing the alkenyl C(sp^2)−H activation of acrylic derivatives by using different transition-metal catalysts.

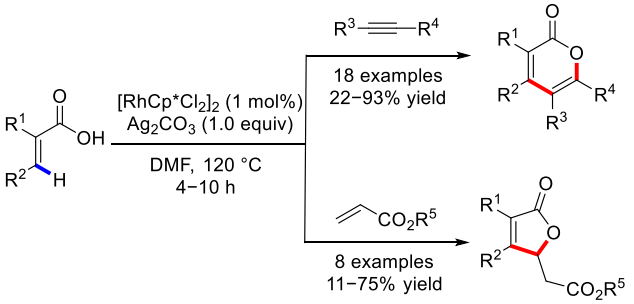
In 2008, Yu's group reported a direct palladium(II)-catalyzed C−H carboxylation by using C−H activation/CO insertion sequences to prepare dicarboxylic acids in modest to excellent yields. Gratifyingly, the alkenyl β-C−H bond of α,β-unsaturated 2-phenylacrylic acid could be carboxylated selectively to afford a *cis*-1,2-dicarboxylic acid in 68% yield (Scheme 94).[198]

Scheme 94. Pd(II)-Catalyzed Vinyl C−H Carboxylation of 2-Phenylacrylic Acid



Pioneering work of Miura and co-workers elegantly elaborated the oxidative vinylic C−H annulation reaction of acrylic acids with diverse alkynes and alkenes by using Cp*Rh(III) catalysts to synthesize various α-pyrones and butenolides (Scheme 95).[199]

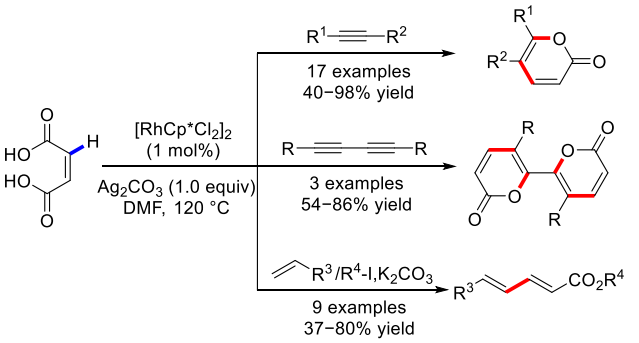
Scheme 95. Oxidative Coupling of Acrylic Acids with Alkynes and Alkenes



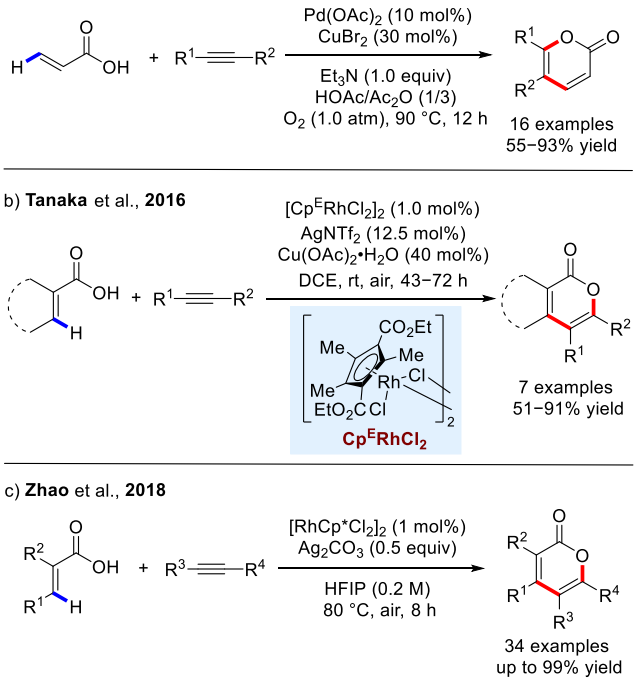
Later in 2013, the same group expanded to report the efficient rhodium(III)-catalyzed decarboxylative and dehydrogenative coupling reaction of commercially available maleic acids with both alkynes and 1,3-diynes to afford a series of multisubstituted α-pyrone derivatives in decent yields (Scheme 96).[200] Moreover, the rhodium catalyst system is also applicable to the reaction with alkenes to exclusively produce dienoic acid derivatives.

Jiang and colleagues reported a practical palladium(II)-catalyzed oxidative [4 + 2] annulation of unsubstituted acrylic acids with diverse internal alkynes by using of O_2 (1 atm) as the oxidant (Scheme 97a).[201] Later in 2016, Tanaka's group also disclosed an analogous oxidative annulation process of acrylic acids with alkynes enabled by an electron-deficient Cp^E rhodium(III) catalyst under mild conditions (Scheme 97b).[202] Following this, Zhao and co-workers also reported the synthesis of α-pyrones *via* oxidative annulation reaction catalyzed by Rh(III) and silver cocatalyst between various substituted acrylic acids and alkynes (Scheme 97c).[203] The protocol accommodated a diverse range of acrylic acids and alkynes, delivering the corresponding α-pyrones in good to

Scheme 96. Decarboxylative and Dehydrogenative Coupling of Maleic Acids with Alkynes and Alkenes



Scheme 97. Oxidative [4 + 2] Annulation Reaction of Acrylic Acids with Alkynes



excellent yields. Impressively, the sorbic acid was also competent substrate for this transformation.

In 2015, Gogoi and co-workers established a general mothod for the preparation of diversely decorated α-pyrone derivatives through a Ru(II)-catalyzed C−H activation/annulation of cinnamic acids with various disubstituted alkynes under cost-effective ruthenium catalysis (Scheme 98).[204] The oxidative annulation reaction features a wide substrate scope and high regioselectivity, affording the expected products in up to 92% yield with low catalyst loading.

Mei and co-workers combined electrochemistry and Ir catalysis to perform alkenyl C−H activation/annulation under oxidative conditions (Scheme 99).[205] This reaction is tolerant toward a broad variety of substrates including complex molecules, giving moderate to excellent yields. The reaction mechanism was investigated in detail. By using stoichiometric reactions, an Ir(I) diene complex was isolated which was hypothesized to be one of the intermediates in the possible catalytic reaction. Further mechanistic experiments were

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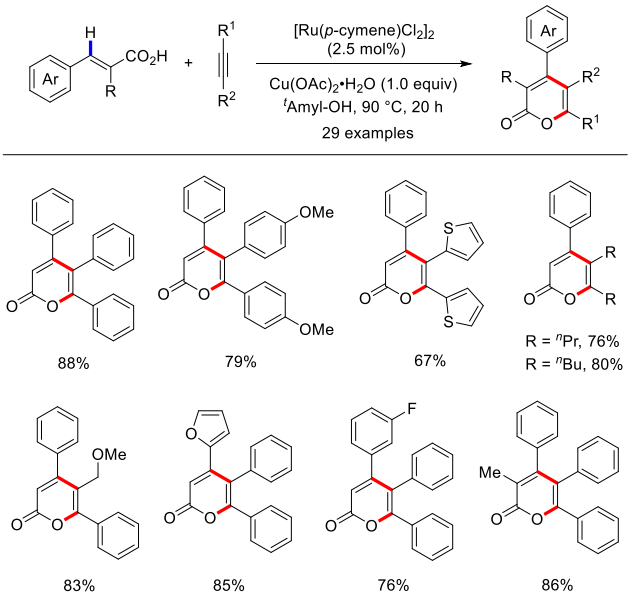
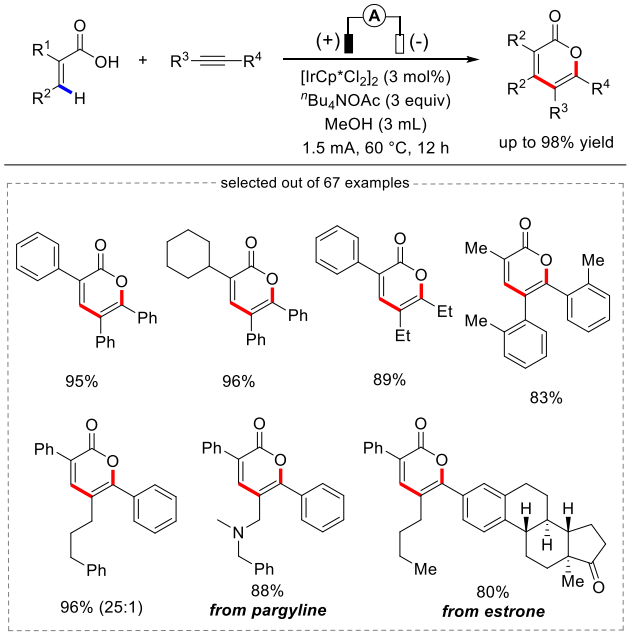
Scheme 98. Synthesis of α-Pyrones *via* Ru(II)-Catalyzed Alkene C−H Bond Functionalization



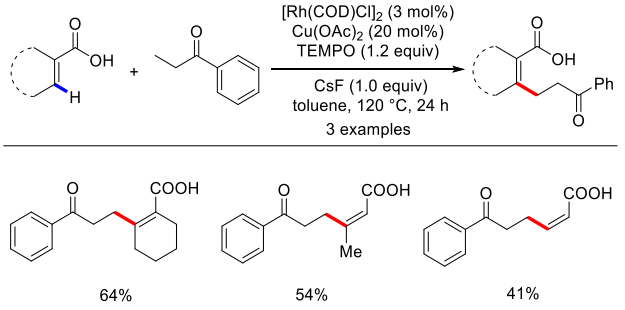
Scheme 99. Cp*Ir(III)-Catalyzed Electrochemical C−H Annulation of Acrylic Acids with Alkynes



performed to prove that common oxidants such as Ag(I) and Cu(II) were not as important as anodic oxidation.

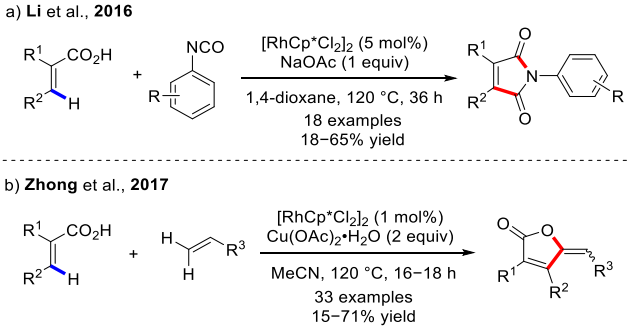
Su and co-workers achieved a novel Rh-catalyzed C−H alkylation of alkenyl carboxylic acids with diverse ketones (Scheme 100).[206] This protocol proceeded *via* the merging of Cu-catalyzed ketone dehydrogenative desaturation process and Rh-catalyzed carboxyl-directed vinyl *ortho*-C−H alkylation. In this case, TEMPO was proved to be essential for the dehydrogenation of ketones as well as the generation of the catalytically active Rh(III)(TEMPO)$_2$L$_n$ catalyst for C−H activation. Besides alkenyl carboxylic acids, the aryl counterparts were also found to be suitable C−H sources for this transformation.

Scheme 100. Carboxyl-Directed C−H Alkylation of Alkenyl Carboxylic Acids



Alkenyl C−H activation and intramolecular cyclization was successfully conducted to generate *N*-arylmaleimide using Rh catalyst by the Li group in 2016 (Scheme 101a),[207] with the

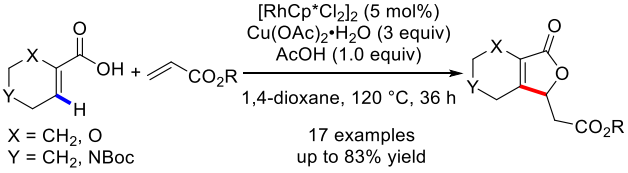
Scheme 101. Rhodium(III)-Catalyzed C−H Activation of Acrylic Acids with Isocyanates and Alkenes



intermediate being an amide. Shortly thereafter, Zhong and coworkers conducted the annulation reaction of substituted acrylic acids with electron-deficient alkenes to produce a broad range of synthetically valuable γ-alkylidenebutenolides (Scheme 101b).[208] Successfully, the reaction could be scaled up to gram scale with only 1 mol % catalyst loading.

In 2017, Zhu's group reported the synthesis of furan-2(5*H*)-ones through the alkenyl C−H activation of cyclo-alkenecarboxylic acids with acrylates in the presence of a Cp*Rh(III) catalyst (Scheme 102).[209] The mechanism involved the

Scheme 102. Synthesis of Furan-2(5*H*)-ones from *cyclo*-Alkenecarboxylic Acids and Acrylates



formation of a seven-membered rhodacycle, followed by hydride elimination and intramolecular cyclization through Michael addition to furnish the desired furan derivatives.

Ackermann's group demonstrated two examples of Rh(III)-catalyzed cross-dehydrogenative alkenylation of acrylic acids bearing various substitution patterns with electron-deficient alkenes *via* electrooxidation (Scheme 103).[210] The expected coupling products were synthesized with chemo- and stereoselectivity *via* environmentally benign oxidative 2-fold C−H activation with H_2 as the sole byproduct.

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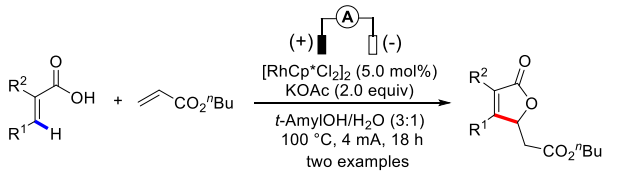
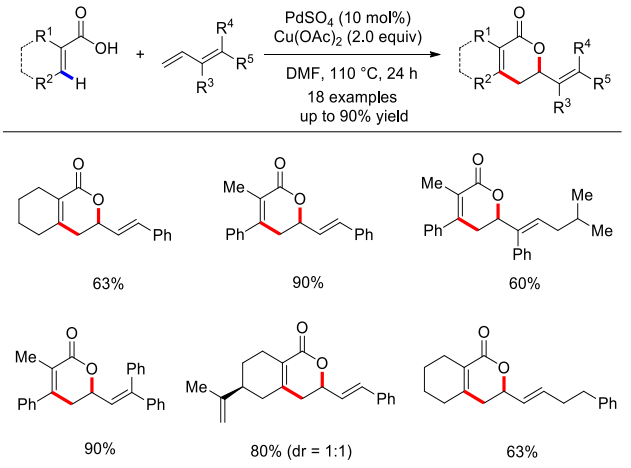
Scheme 103. Rhodium-Catalyzed Electrochemical C−H Alkenylation of Acrylic Acids



The formal [4 + 2] cycloaddition protocol of acrylic acids with various 1,3-dienes was achieved by Zhang and co-workers in 2018 (Scheme 104).[211] The reaction worked uneventfully

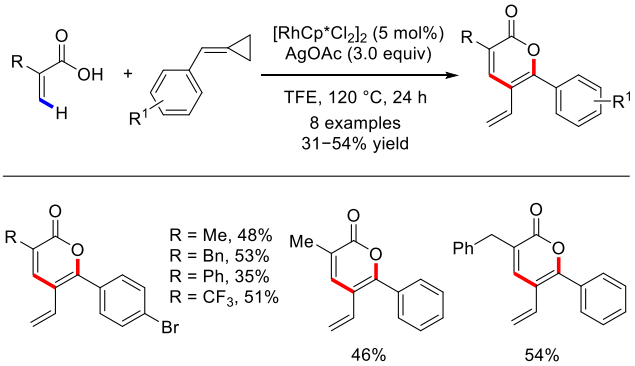
Scheme 104. Palladium-Catalyzed Formal [4 + 2] Cycloaddition of Acrylic Acids with 1,3-Dienes



with 10 mol % $PdSO_4$ as the catalyst in conjunction with stoichiometric $Cu(OAc)_2$ (2.0 equiv) as the oxidant. As a particular highlight, this approach was applicable to the short synthesis of natural product clausamine B.

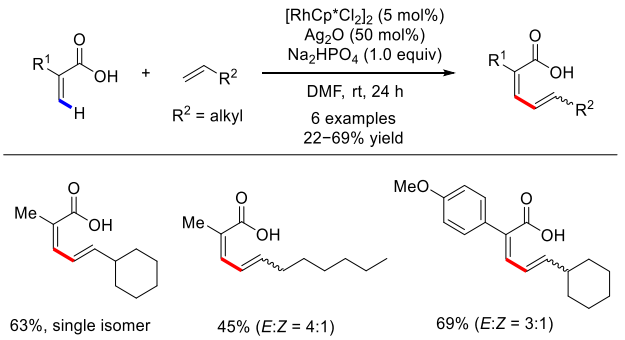
More recently, Jeganmohan and co-workers utilized alkylidenecyclopropanes in the vinylic C−H annulation reactions of acrylic acids under Cp*Rh(III) catalysis (Scheme 105).[212] In this case, acrylic acids with α-substituent reacted uneventfully to produce α-pyrones in moderate yields (31−54%), while β-substituted acrylic acids such as cinnamic acid and crotonic acid were found to be incompatible with this protocol.

Scheme 105. Rhodium(III)-Catalyzed Annulation of Acrylic Acids with Alkylidenecyclopropanes



Despite the remarkable advances in alkenyl C−H olefinations over the past decades, these strategies have been greatly restricted to electronically unbiased alkenes such as acrylates and styrenes. Establishing a general and practical procedure for the vinylic C−H olefination with unbiased alkenes is a long-standing challenge. This can be attributed to the intrinsic poor reactivity as well as the unbiased nature of aliphatic alkenes.[213] In this regard, Jeganmohan *et al.* in 2020 illustrated the Rh^{III}-catalyzed COOH-assisted C−H olefination of diverse α-substituted acrylic acids with unbiased olefins at room temperature (Scheme 106),[214] generating *ortho*-alkenylated

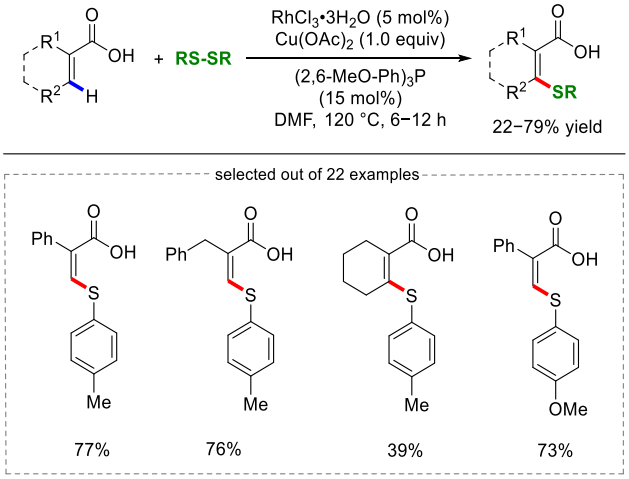
Scheme 106. Rhodium(III)-Catalyzed C−H Olefination of Vinyl Acids with Unactivated Olefins



vinylic acids in modest yields (22−69%). Unfortunately, the reaction conditions were not compatible with simple acrylic acid and β-substituted acrylic acids.

The development of efficient chalcogenylation reactions for the assembly of unsymmetrical diaryl sulfides or diaryl selenides has attracted remarkable attention because of their prevalence in a diverse variety of potent drug candidates, biologically active natural products, and advanced functional materials.[215] In this context, the group of Wang and Ji reported the first example of vinyl C−H thiolation of acrylic acids by using readily available inorganic rhodium salt $RhCl_3 \bullet 3H_2O$ as a catalyst in 2019 (Scheme 107).[216] The efficiency of $RhCl_3 \bullet 3H_2O$ as catalyst was better than that of $[RhCp^*Cl_2]_2$ in this strategy, which produced a series of (*Z*)-alkenyl sulfides exclusively. Of note, the thiolation products could be easily

Scheme 107. Rhodium(III)-Catalyzed C−H Thiolation of Acrylic Acids



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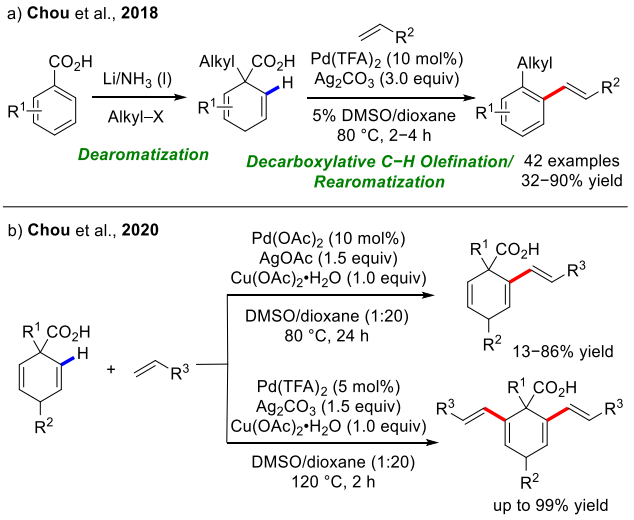
converted into biologically and pharmacologically useful thioflavones.

In 2018, Chou *et al.* established a straightforward method for the rapid synthesis of various *ortho*-alkylated vinylarenes from readily available benzoic acids employing Birch reductive alkylation followed by a tandem decarboxylative C−H olefination/rearomatization sequence (Scheme 108a).[217] Subsequently, the same group further disclosed that proaromatic 1,3-dienes can be synthesized through C−H activation of 1,4-cyclohexadiene by using free carboxylic acid as the directing group (Scheme 108b).[218] Based on the judicious choice of silver salt, direct and sequential bisolefinations of proaromatic 1,3-dienes were also achieved. In this report, the authors carried out kinetic resolution studies to elucidate the mechanism of this process.

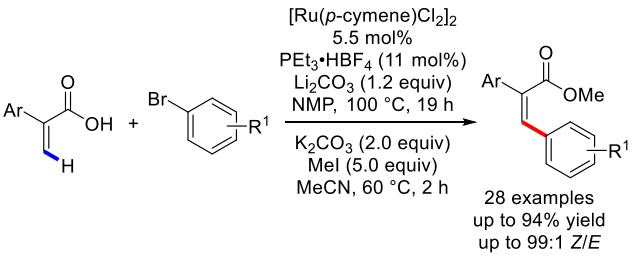
Scheme 108. Palladium-Catalyzed Alkenyl C−H Bond Olefination of Proaromatic Acids



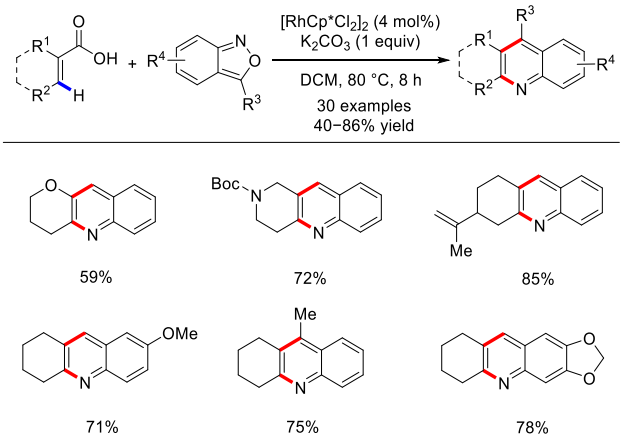
Quite recently, Gooßen *et al.* disclosed the highly *Z*-selective coupling reaction of 2-arylacrylic acids with aryl bromides by the combination of $[Ru(p\text{-cymene})Cl_2]_2$ catalyst, $PEt_3{\bullet}HBF_4$ ligand ,and Li_2CO_3 base in NMP at 100 °C. A broad scope of 28 examples was documented in reasonable yields of up to 94% and (*Z*/*E*)-ratios of up to 99:1. Mechanistic investigations indicated that this carboxylate-directed vinylic C−H arylations probably proceeds *via* a base-assisted cyclometalation process rather than *via* a Heck-type mechanism (Scheme 109).[219]

Gao, Hu, and co-workers established a protocol for the amination/annulation of readily available acrylic acids with anthranils in the presence of a Cp*Rh(III) catalyst (Scheme 110).[220] The carboxylic acid functional group serves as a traceless directing group in this protocol, producing diverse polysubstituted quinolones in modest to excellent yields with H_2O and CO_2 as byproducts.

Scheme 109. Ru(II)-Catalyzed Vinylic C−H Arylation of Acrylic Acids with Aryl Bromides

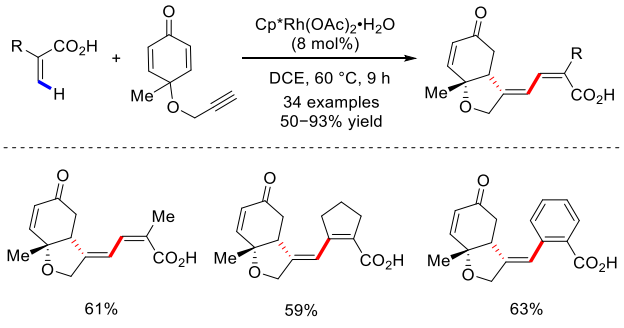


Scheme 110. Rh-Catalyzed C−H Amination/Annulation of Acrylic Acids and Anthranils



The synthesis of conjugated dienes is mostly achieved by the oxidative cross-coupling reaction between two different olefins. In early 2019, Liu's group disclosed a novel redox-neutral method for the synthesis of dienes from acrylic acids and yndienones in the presence of a Rh(III) catalyst (Scheme 111).[221] This reaction is diastereospecific and happens through activation of olefinic C−H bond, alkyne insertion, and Michael addition sequence.

Scheme 111. Synthesis of *cis*-Hydrobenzofuranone *via* Cp*Rh(III)-Catalyzed Coupling of Acrylic Acids and Ynenones



Moreover, Zhang and colleagues elegantly developed an efficient protocol to synthesize cyclopentenones by coupling acrylic acids with commercially available malonates and formaldehyde (Scheme 112).[222] The authors showcased the application of this method by the synthesis of various 5-alkylated cyclopentenones. Using excess malonate and formaldehyde resulted in the formation of multisubstituted cyclopentenones. In continuation of their work on vinylic C−H activation of acrylic acids with formaldehyde, the same group later extended to disclose a Co(III)-catalyzed carboxyl-assisted C−H functionalization of acrylic acids with formaldehyde to produce butenolides in up to 95% yield (Scheme 113).[223] Interestingly, by addition of Na_2CO_3 to the catalytic system, a series of γ-hydroxymethylated butenolides could be obtained in up to 72% yield.

Quite recently, Zhang and co-workers further employed α-diazocarbonyls to couple with acrylic acids under Cp*Rh(III)

https://doi.org/10.1021/acs.chemrev.2c00032
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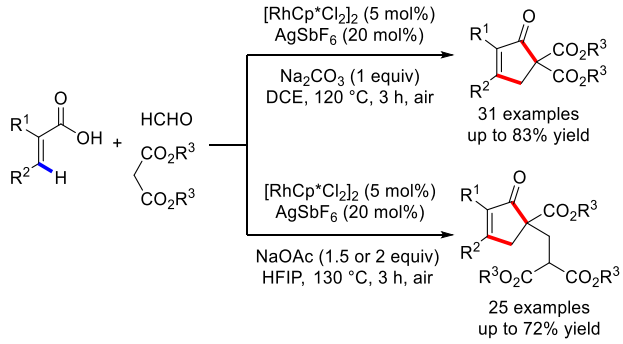
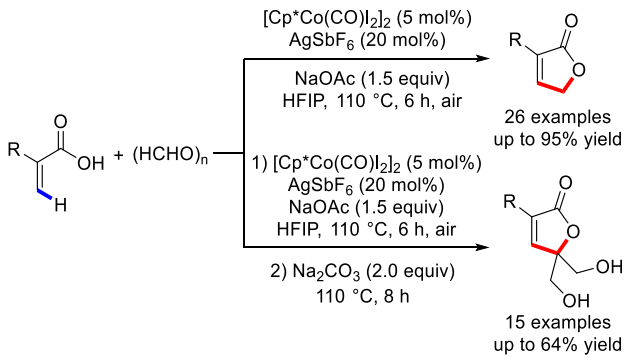
Scheme 112. Synthesis of Cyclopentenones through Rhodium-Catalyzed C−H Annulation of Acrylic Acids with Formaldehyde and Malonates

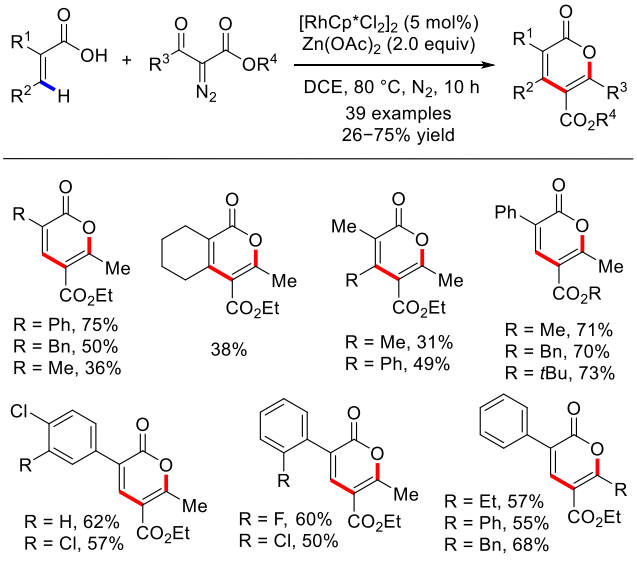


Scheme 113. Synthesis of Butenolides *via* Cobalt-Catalyzed Vinyl C−H Addition to Formaldehyde



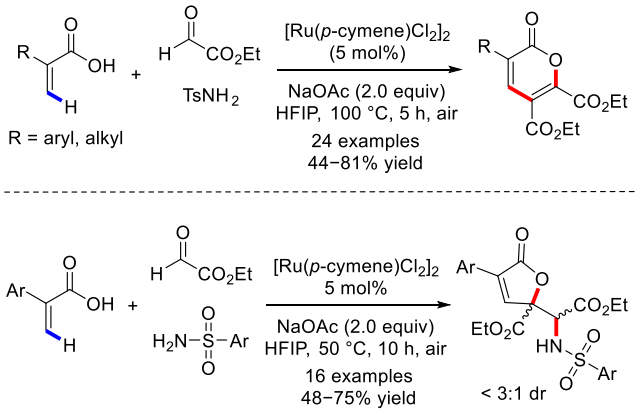
catalysis to synthesize α-pyrones (Scheme 114).[224] Detailed optimization studies revealed that the addition of $Zn(OAc)_2$

Scheme 114. Synthesis of α-Pyrones by Rh-Catalyzed Coupling of Acrylic Acids with α-Diazocarbonyls



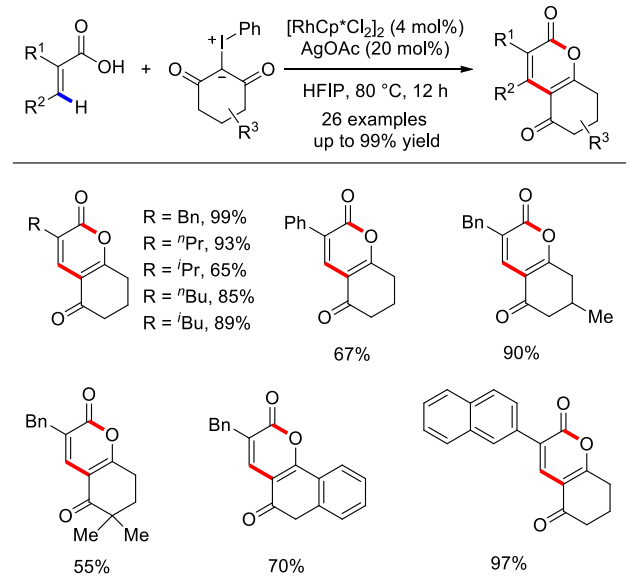
was essential for this transformation, which remarkablely accelerates this carboxyl-directed vinylic C−H annulation process. Electronically diverse acrylic acids reacted smoothly with a variety of α-diazocarbonyl compounds. By slightly elevating the reaction temperature to 90 °C, this protocol also accommodates a series of benzoic acids to afford isocoumarins in modest yields (31−71%). Shortly thereafter, the same group made further efforts to fabricate pyranone derivatives through a Ru(II)-catalyzed three-component cascade reaction of acrylic acids, ethyl glyoxylate, and *p*-toluenesulfonamide (Scheme 115).[225] Notably, an array of butenolides could be readily prepared in high yields under similar catalytic system.

Scheme 115. Ru(II)-Catalyzed Cascade Reaction *via* Vinylic C−H Addition to Glyoxylate



A recent report by Li and co-workers documented a srtaightforward assembly of various cyclic skeletons enabled by rhodium(III) catalysis under redox-neutral conditions (Scheme 116).[226] In this work, readily available hypervalent

Scheme 116. Iodonium Ylides as Carbene Precursors in Cp*Rh(III)-Catalyzed Alkenyl C−H Activation



iodonium ylides were identified as efficient carbene precursors. It should be emphasized that the catalyst loading could be sharply decreased to 0.5 mol % for the preparative-scale synthesis.

Beyond the intermolecular cross-coupling reaction, the Gulías group in 2019 disclosed a general approach to synthesize bicyclic or tricyclic macrocycles containing pyran-2-one or isocoumarin from simple precursors *via* an intramolecular oxidative [4 + 2] annulation of acrylic acids with

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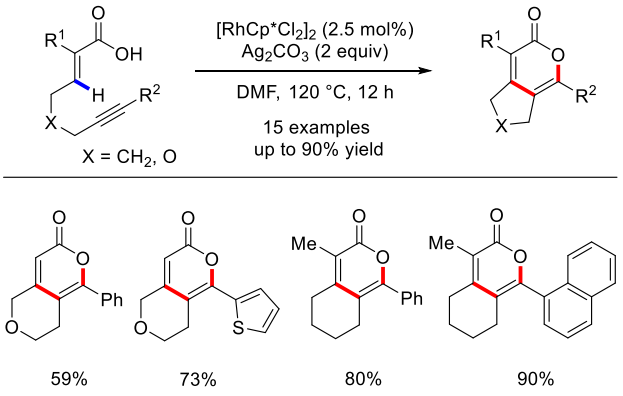
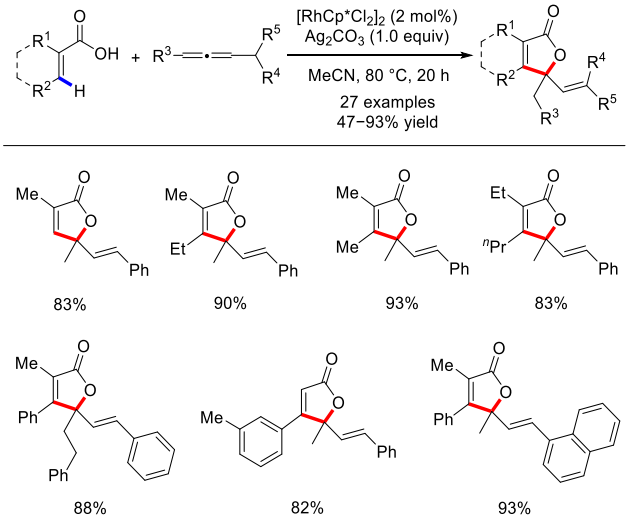
alkynes in the presence of a Cp*Rh(III) catalyst (Scheme 117).[227]

Scheme 117. Cp*Rh(III)-Catalyzed Intramolecular Annulations of Acrylic Acids to Alkynes



The efficient Cp*Rh(III)-catalyzed formal oxidative [4 + 1] annulation of vinylic carboxylic acids with allenes was reported by Cheng and co-workers in 2015 (Scheme 118).[228] Both

Scheme 118. Rh(III)-Catalyzed [4 + 1] Annulation of Vinylic Carboxylic Acids and Allenes



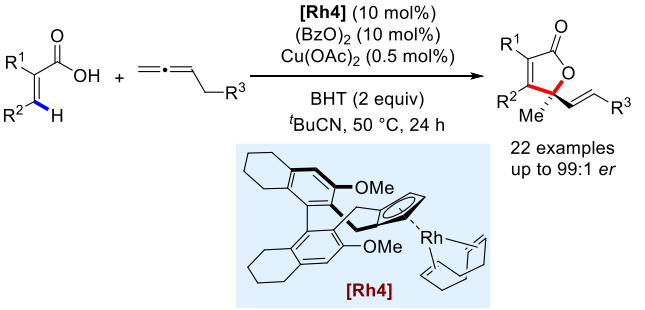
symmetrical and unsymmetrical internal allenes were compatible with the conditions, leading to the synthesis of a variety of bioactive 5-vinyl-substituted 2-furanones in 47−93% yields.

An enantioselective version of this annulation process was later established by Cramer and co-workers in 2020. They were able to enantioselectively activate the alkenyl C−H bonds in acrylic acids with allenes by using a modified Rh(III) catalyst bearing a novel rigid axial chiral cyclopentadienyl (Cp^x) ligand featuring a semisaturated H8-binaphthyl backbone.[229] This enantioselective [4 + 1] annulation process allows the construction of synthetically appealing enantioenriched α,β-unsaturated-γ-lactones in decent yields with enantioselectivity of up to 99% enantiomeric ratio (Scheme 119).[230]

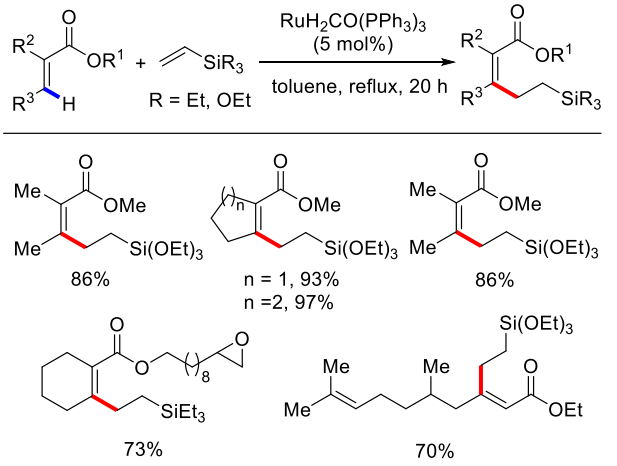
4.2. Acrylic Esters

Early in 1995, Trost's group first disclosed a Ru(0)-catalyzed C−H alkylation of diverse α,β-unsaturated esters with vinylsilanes (Scheme 120).[231] As expected, a wide range of

Scheme 119. Synthesis of Chiral γ-Lactones *via* $Cp^xRh(III)$-Catalyzed C−H Activation of Acrylic Acids with Allenes



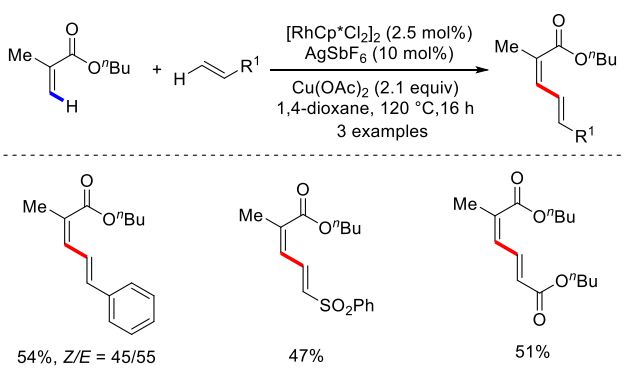
Scheme 120. Ruthenium-Catalyzed Vinylic C−H Alkylation of α,β-Unsaturated Esters



functional groups such as epoxide, alkyl bromide, ketals, and thioketals were tolerated to deliver the alkylation products in decent yields. Ketone and amide moieties are suitable directing groups in this strategy. Notably, this protocol can be applied to functionalize a sugar derivative.

Later, Glorius and colleagues revealed a method of vinylic C−H bond cross-coupling with various directing or activating groups under Cp*Rh(III) catalysis. A variety of 1,1-, 1,2-, and 1,1,2-substituted alkenes reacted uneventfully to give linear 1,3-butadiene products. However, modest yields and poor stereoselectivity were observed with esters as the chelating group (Scheme 121).[232]

Scheme 121. Cp*Rh(III)-Catalyzed Oxidative Vinylic C−H Olefination of Acrylates



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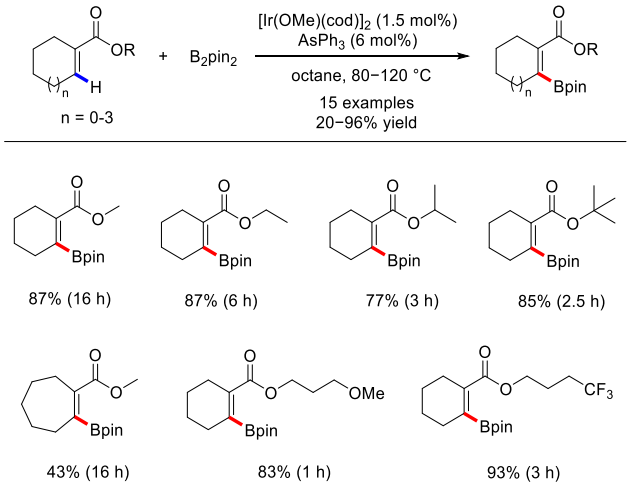
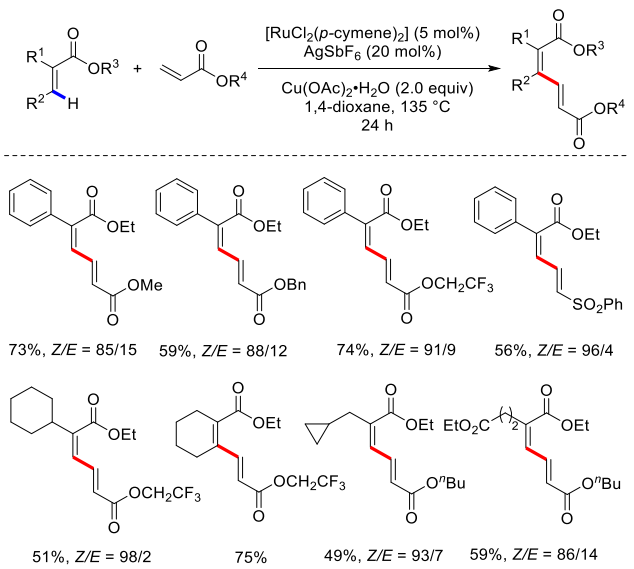
Subsequently, Ishiyama and Ito reported an efficient vinylic C−H borylation of 1-cycloalkenecarboxylates with bis-(pinacolato)diboron catalyzed by an *in situ*-generated Ir complex consisting of $[Ir(OMe)(cod)]_2$ and $AsPh_3$, affording a range of synthetically useful alkenylboronates. A scope of 15 examples of this transformation was documented with yields of 20−96% (Scheme 122).[233]

Scheme 122. Ir(I)-catalyzed Vinylic C−H Borylation of 1-Cycloalkenecarboxylates



There have been some notable contributions on alkene C−H alkenylation reactions to obtain various dienes in the presence of a Ru(II) catalyst. Loh and co-workers were able to stereo- and chemoselectively carry out cross-coupling between two electron-deficient acrylates (Scheme 123).[234] This procedure allows a direct and atom-economical method to obtain functionalized (*Z*,*E*)-muconates and is tolerant toward a large variety of substrates. A diverse array of aliphatic and aryl substituted acrylates can be reacted smoothly to provide moderate to good yields with excellent stereoselectivity. The subtle difference in steric and electronic effect enables the

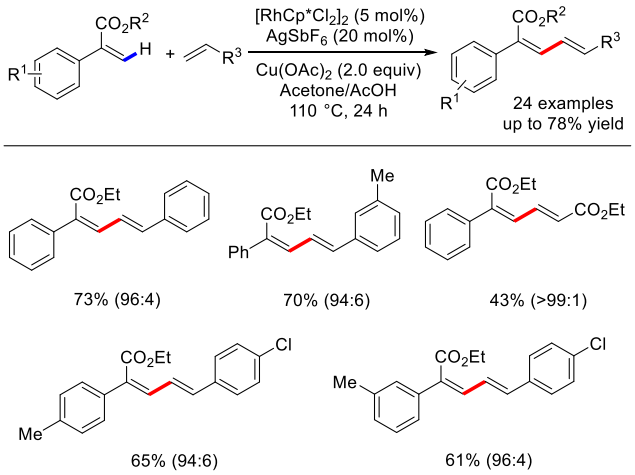
Scheme 123. Ru-Catalyzed Cross-Coupling between Two Electron-Deficient Acrylates



prefential C−H functionalization of α-alkylated acrylates oversimple acrylates and also allows the cross-coupling to proceed.

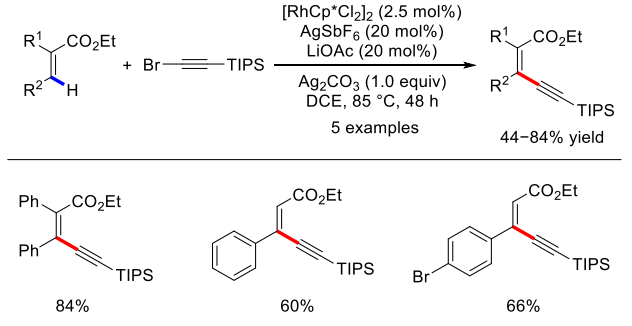
Similarly, Zhang's group also reported an analogous regioselective cross-coupling reaction of acrylates under Cp*Rh(III) catalysis, producing substituted 1,3-butadienes in satisfactory yields with high stereoselectivity (Scheme 124).[235] Notably, a diverse array of styrenes were also found to be competent substrates for this transformation.

Scheme 124. Rhodium(III)-Catalyzed Ester-Directed Olefination of Acrylates



In 2018, Echavarren *et al.* described the vinylic C(sp^2)−H alkynylation of α,β-unsaturated esters with bromoalkynes (inverse-Sonogashira reaction) under rhodium(III) catalysis (Scheme 125).[236] The reaction proceeded smoothly using

Scheme 125. Rhodium(III)-Catalyzed Ester-Directed Alkenyl C−H Alkynylation



synthetically useful ether as the weakly directing group. Of note, the aryl counterparts were also found to be suitable C−H sources for this alkynylation process.

4.3. Acrylic Amides

4.3.1. Arylation. With the success of the alkenyl sp^2 C−H bond functionalization of acrylates, researchers started to trun their attention to acrylic amides.[237] In 2012, Glorius and co-workers reported a novel Cp*Rh(III)-catalyzed dehydrogenative cross-coupling reaction of *N*,*N*-diisopropylmethacrylamides with bromoarenes with a stoichiometric amount of pivalic acid and a catalytic amount of cesium pivalate as additives, leading to the formation of diverse tri- and tetrasubstituted alkenes in moderate yields (27−65%). The

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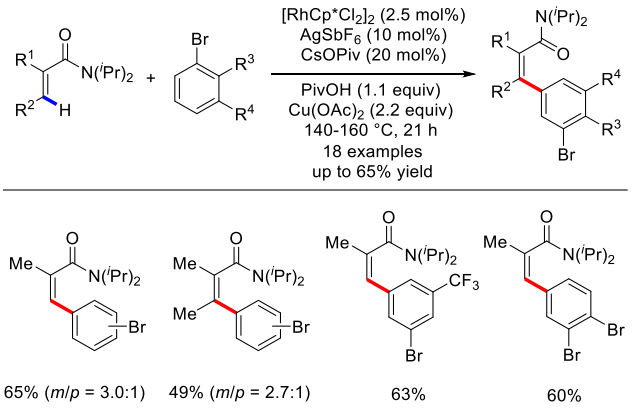
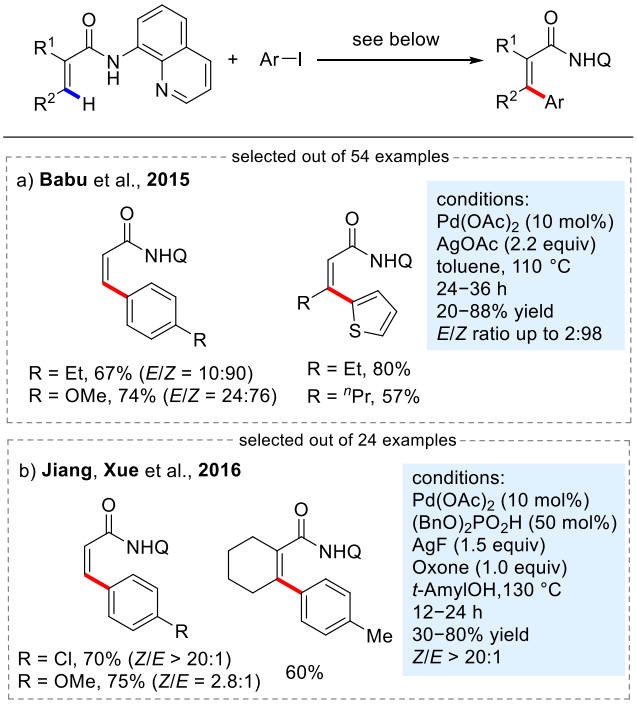
reaction proceeded without any chelate assisting-directing group in arene substrates, thus providing a novel protocol for the highly *Z*-selective synthesis of arene-substituted olefins (Scheme 126).[238]

Scheme 126. Cp*Rh(III)-Catalyzed Dehydrogenative Cross-Coupling of Vinylic Amides with Bromoarenes



The Babu group in 2015 described the synthesis of *β*-arylated acrylamides and *Z*-cinnamamides by using 8-aminoquinoline as the bidentate directing group in the presence of $Pd(OAc)_2$ catalyst (Scheme 127a).[239] The reaction was greatly

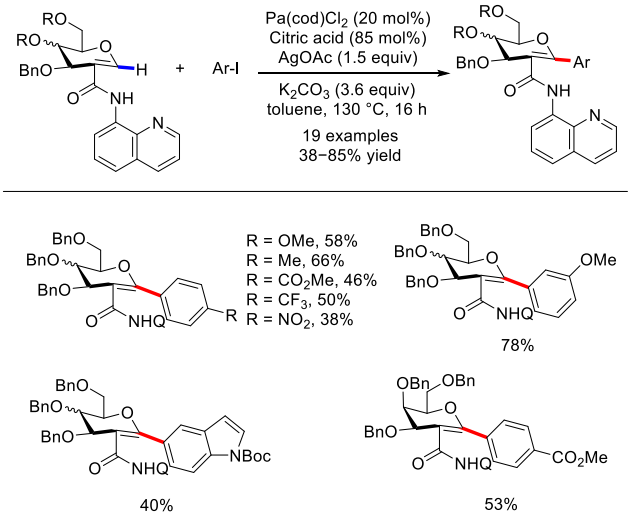
Scheme 127. Palladium-Catalyzed 8-Aminoquinoline-Assisted Vinylic C−H Arylation of Acrylamides



promoted by AgOAc through the directed *Z*-selective C−H activation followed by the *β*-arylation of the vinylic $C(sp^2)$−H bond of *N*-(quinolin-8-yl)acrylamide systems. A broad array of aryl- and heteroaryl iodides bearing different substitution patterns were used as arylating source. The *Z*-selective *β*-arylation of *N*-(quinolin-8-yl)acrylamide systems was elucidated by proposing a plausible mechanism involving the bidentate ligand-assisted, chelation-based C−H functionalization. Subsequently, Jiang *et al.* also achieved a similar 8-aminoquinoline-directed vinylic C−H arylation of acrylamides with 0.5 equiv of $(BnO)_2PO_2H$ as the additive in conjunction with 1.0 equiv of oxone as the oxidant (Scheme 127b).[240]

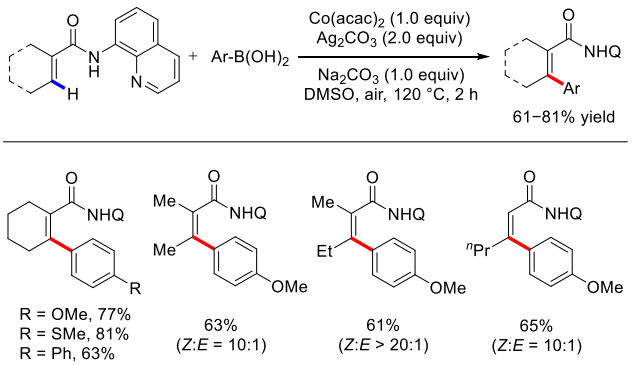
Successfully, Ferry and co-workers demonstrated that the installation of a bidentate 8-aminoquinoline auxiliary at the C2 position of glycals is effective in a Pd(II)-catalyzed alkenyl $C(sp^2)$−H arylation of the anomeric position to access a broad range of unsaturated C-aryl glucosides (Scheme 128).[241] Of note, the application of this novel methodology was showcased by the efficient synthesis of a dapagliflozin analogue.

Scheme 128. Palladium(II)-Catalyzed Vinylic C−H Arylation of the Anomeric Position in Glycosides



In 2016, a novel cobalt-promoted regioselective arylation of alkenyl $C(sp^2)$−H bond of acrylamides with various arylboronic acids has been achieved by using bidentate 8-aminoquinoline as the auxiliary by Zhu and co-workers (Scheme 129),[242] leading to the preparation of the arylated products in decent yields ranging from 61 to 81%.

Scheme 129. Cobalt-Promoted $C(sp^2)$−H Arylation of Acrylamides with Arylboronic Acids



Ackermann and co-workers developed a novel protocol for the sp^2 C−H functionalization by using 1,2,3-triazole as the powerful auxiliary. The authors described the iron-catalyzed C−H arylations of acrylamides in chemo-, site-, and diastereoselective fashion with a broad substrate scope (Scheme 130).[243] This triazole-assisted C−H activation

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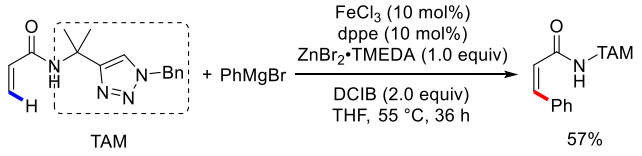
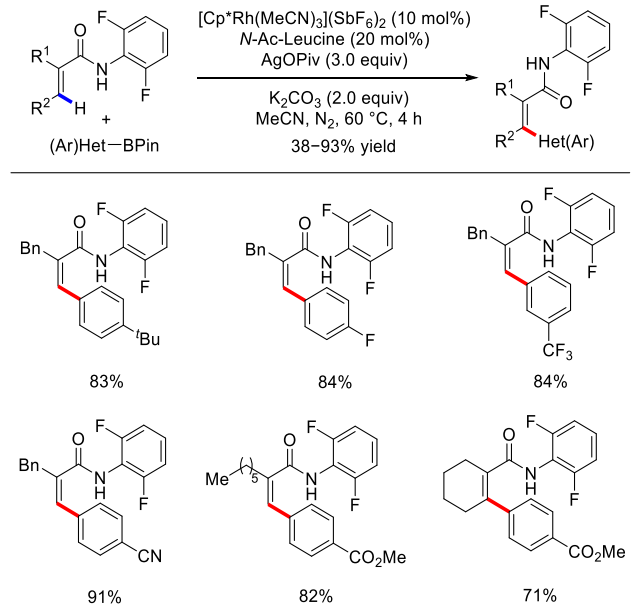
Scheme 130. Iron-Catalyzed Alkenyl C−H Arylation by Triazole Assistance



strategy occurred under remarkably mild reaction conditions, and the triazole auxiliary could be easily removed in a traceless fashion. Notably, this versatile iron-catalyzed system also proved to be applicable for the challenging C(sp^3)−H functionalizations, and proceeds by an organometallic mode of action.

More Recently, Lu and co-workers accomplished the cross-coupling of acrylamides with organoboron reactants by employing $[Cp^*Rh(MeCN)_3]_2(SbF_6)_2$ as the catalyst (Scheme 131).[244] The authors used monoprotected amino acid *N*-Ac-

Scheme 131. Cp*Rh(III)-Catalyzed C−H (Het)arylation of *N*-2,6-Difluoroaryl Acrylamides

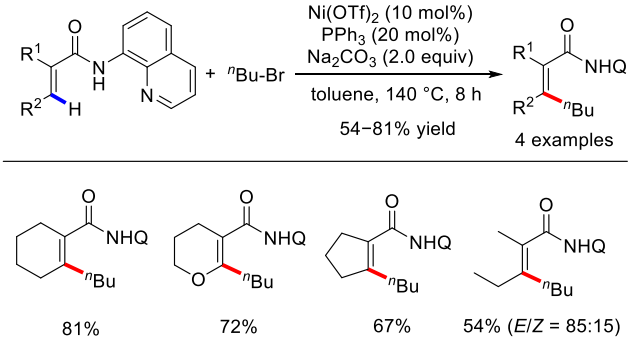


leucine as the ligand for this transformation in MeCN at 60 °C. Silver pivalate and potassium carbonate were used as the oxidant and base, respectively. This reaction proceeds under moderate reaction conditions to afford a broad range of vinyl, aryl, and heterocyclic substituted acrylamides in up to 93% yield.

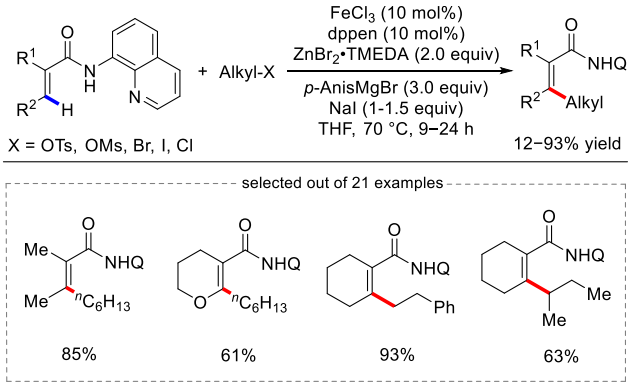
4.3.2. Alkylation. In 2013, the Chatani group reported a bidentate chelation-assisted, nickel-catalyzed C(sp^2)−H alkylation of acrylamides and benzamides with unactivated alkyl halides (Scheme 132).[245] They employed 10 mol % of $Ni(OTf)_2$ as the catalyst and 20 mol % of PPh_3 as the ligand in toluene solvent at 140 °C. The desired alkylated products were synthesized in high yields by using sodium carbonate as a base.

In 2014, Nakamura *et al.* extended their inexpensive and benign iron-catalysis strategy to selectively alkylate C−H bonds of various arene, heteroarene, and alkene molecules (Scheme 133).[246] By taking advantage of the efficient $Fe(acac)_3$/diphosphine catalytic system, a diverse range of primary and secondary alkyl halides, mesylate, and tosylates

Scheme 132. Nickel-Catalyzed Vinyl C−H Alkylation of Acrylamides with *n*-Butyl Bromide



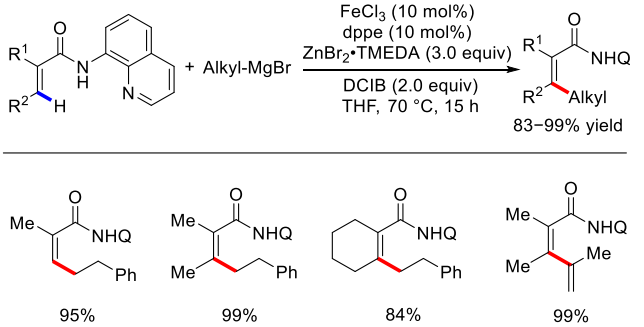
Scheme 133. Iron-Catalyzed Directed C−H Alkylation of Olefinic Carboxamides



alkylated the C−H bonds. ArZnBr was used as a base in this case. The reaction proceeds stereospecifically for alkene substrate. Around the same time, Cook and co-workers also realized an analogous iron-catalyzed C(sp^2)−H alkylation of acrylamides with *n*-butyl bromide in 2-methyltetrahydrofuran (2-MeTHF).[247] The reaction does not require a co-oxidant and proceeds in less than 10 min.

Later, Nakamura and co-workers further reported a stereospecific iron/diphosphine catalyzed C−H alkylation which utilized a bidentate 8-aminoquinoline auxiliary (Scheme 134).[248] Either primary or secondary alkylzinc halide was used as the alkylation source, while a dichloroalkane (DCIB) was screened as an oxidant in this protocol. The authors proposed that the reaction may involve an organoiron(III) species, which selectively activates the alkenyl C−H bond of monosubstituted and unsubstituted acrylamides, to alkylate in a stereoselective

Scheme 134. Iron-Catalyzed Directed C−H Alkylation of Alkenes with Alkylzinc Halides



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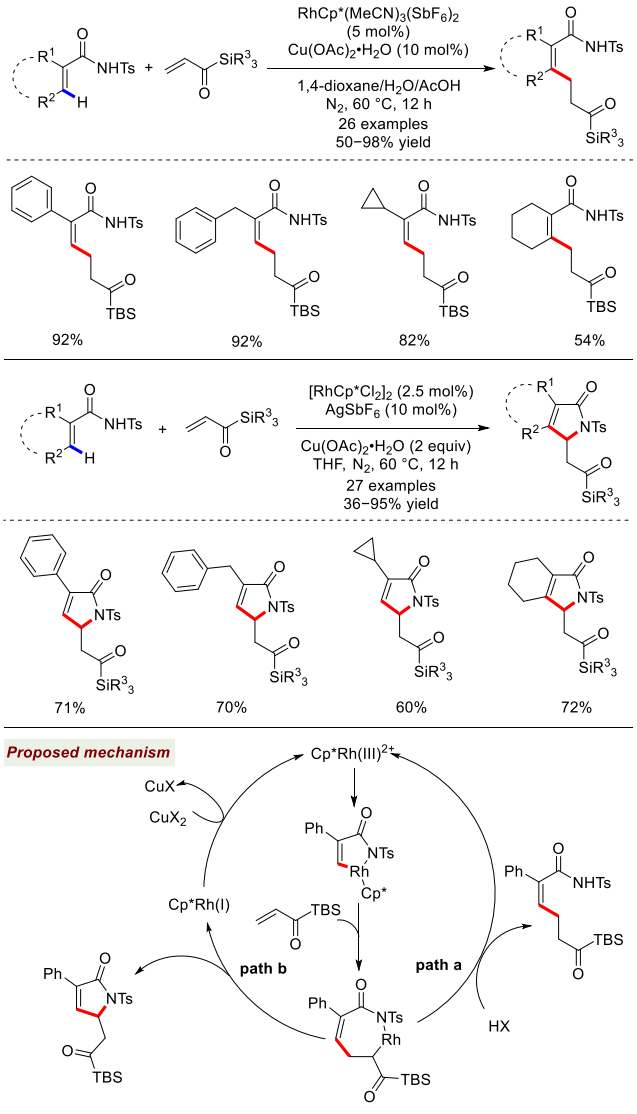
fashion. It should be mentioned that homocoupling of the organometallic reagent and β-hydrogen elimination were not observed in this iron-catalyzed protocol.

Loh and co-workers came up with a substrate-controlled strategy for alkenyl C(sp^2)−H activation reactions. In 2017, they presented an efficient route to synthesize diverse β-alkylated acrylamides and dihydropyrro-2-lones by the activation of alkenyl C−H bonds of *N*-tosyl acrylamides with acrylosilanes as the viable coupling partners under Cp*Rh(III) catalysis (Scheme 135),[249] By slightly modifying the

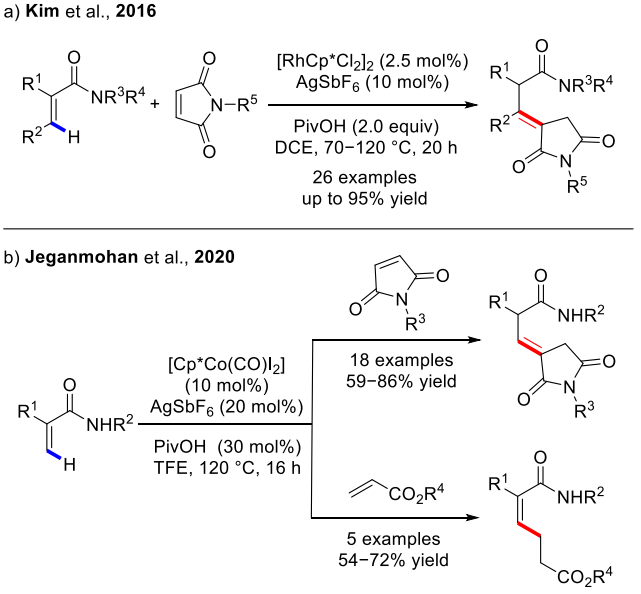
Scheme 135. Rhodium(III)-Catalyzed Switchable C−H Bond Functionalizations of *N*-Tosyl Acrylamides with Acryloylsilanes



conditions, either C−H alkylation or alkenylation products could be obtained in satisfactory yields. The distinct reactivity of acylsilanes is probably attributed to their inherent electronic properties which are distinctive from other carbonyl compounds. On the basis of their mechanistic studies, the authors proposed that the catalytic process may proceed *via* *N*-tosylamide-assisted alkenyl C−H bond cleavage followed by C═C double bond insertion to produce a rhodacycle species. Finally, proto-demetalation occurs under acidic conditions to generate the alkylated products. Alternatively, the annulated products were formed through facile β-H elimination followed by an intramolecular *aza*-Michael reaction.

The rhodium(III)-catalyzed vinylic C−H alkylation and further migration reaction of electron-deficient acrylamides with various maleimides was achieved by Kim's group in 2016 under redox-neutral conditions (Scheme 136a),[250] affording

Scheme 136. Redox-Neutral Coupling of Acrylamides with Activated Alkenes



the biologically important *exo*-cyclized succinimide-containing amides with high regio- and stereoselectivity. Inspired by this precedential work, Jeganmohan *et al.* also established an analogous C−H alkylation of acrylamides with maleimides in the presence of pivalic acid additive to afford olefin-migrated alkylated products under cost-effective Cp*Co(III) catalysis (Scheme 136b).[251] The reaction is compatible with a broad range of substituted acrylamides and maleimides. Under the same conditions, the linear-selective alkylated products were formed with acrylates as the coupling partners.

Besides the above-mentioned activated alkene coupling partners, readily available nitroalkenes could also participate in the alkenyl C−H alkylation of acrylamides. In 2017, Ellman's group disclosed the efficient Cp*Rh(III)-catalyzed alkenyl C−H bond addition to electron-deficient nitroalkenes under redox-neutral conditions (Scheme 137),[252] furnishing the nitro-containing C−H alkylation products in 58−77% yield.

More recently, the highly enantioselective vinylic C−H alkylation of α,β-unsaturated amides with readily available crotonates was elegantly reported by Shibata and colleagues (Scheme 138).[253] The coupling adducts were generally obtained with high yield and ee (up to 99% yield and up to 95% ee) by using a chiral Ir catalyst.

In 2017, López, Mascareñas, and Gulías illustrated an intramolecular Ir(I)-catalyzed functionalization reactions of alkenyl C−H bonds followed by an hydrocarbonation process to construct a diverse number of versatile cyclic systems bearing quaternary stereocenters (Scheme 139).[254] The aryl and heteroaryl counterparts were also found to be suitable C−H sources for this strategy. More interestingly, the cyclic products can be easily transformed to unusual cyclic ketones.

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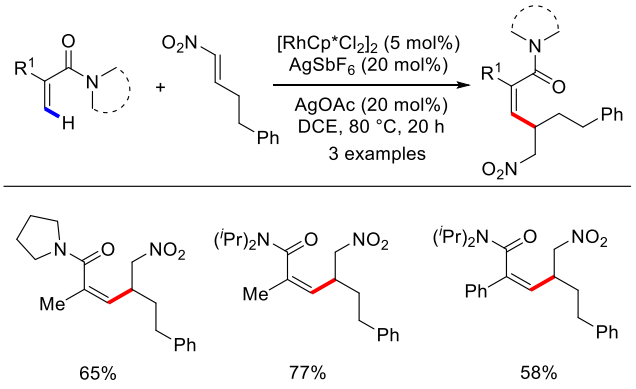
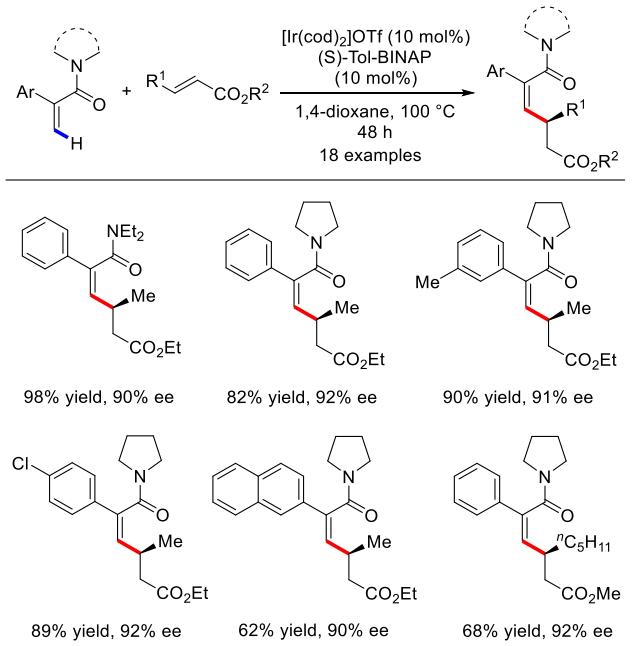
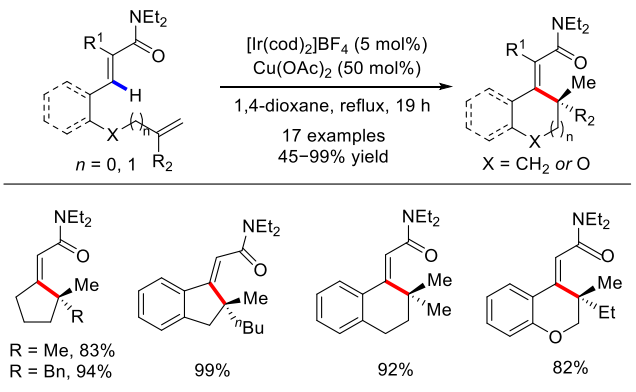
Scheme 137. Cp*Rh(III)-Catalyzed Alkenyl C−H Bond Addition to Nitroalkenes



Scheme 138. Enantioselective Cross-Coupling of α,β-Unsaturated Amides with Crotonate Derivatives



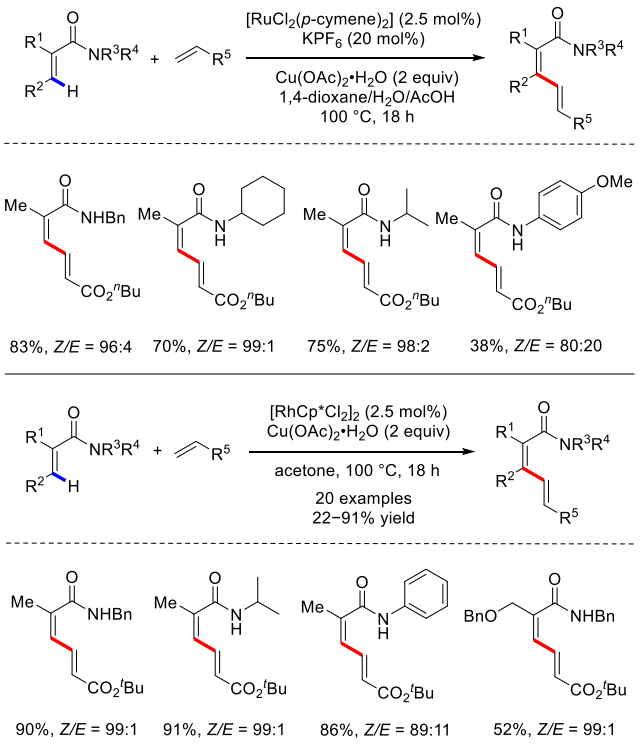
Scheme 139. Enantioselective Iridium(I)-Catalyzed Intramolecular Hydrocarbonation of Alkenes



Mechanistically, the authors proposed that the Ir(I) catalyst first undergoes a C−H activation step with the olefin to form an Ir−H intermediate, followed by a selective *exo*-migratory insertion to generate a cyclic Ir complex. A subsequent C−H reductive elimination generated the expected product.

4.3.3. Alkenylation. In 2012, Loh and co-workers proposed a general method for oxidative cross-coupling acrylamides with diverse electron-deficient olefins (Scheme 140).[255] It is notable that both Ru and Rh were competent

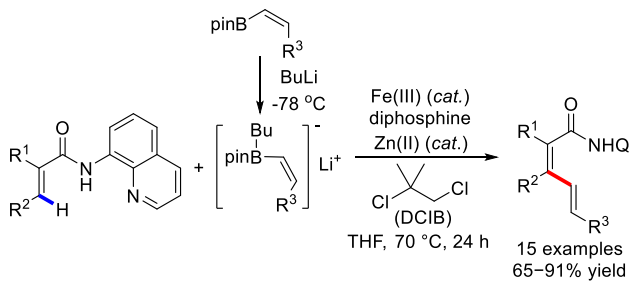
Scheme 140. Ruthenium- and Rhodium-Catalyzed Cross-Coupling of Acrylamides with Alkenes



catalysts for this transformation, generating the corresponding (*Z*,*E*)-dienamides products in high yields with excellent stereoselectivities.

Successfully, Nakamura and co-workers reported an iron-catalyzed alkenylation of olefinic, aromatic, and heteroaromatic substrates under mild oxidative conditions with aryl and alkenyl boron compounds (Scheme 141).[256] The authors argued that the use of zinc(II) salt is essential for this transformation, as it significantly facilitates the transfer of organic group from boron to iron catalyst. The process of alkenyl C−H activation involved the formation a reactive organoiron(III) intermediate in this case.

Scheme 141. Iron-Catalyzed C(sp²)−H Olefination of Alkene Carboxamides with Alkenyl Boronates



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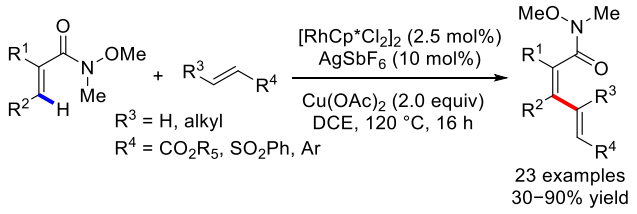
Zhong's group employed Weinreb amide as the directing group for the C−H olefinations of alkenes under Cp*Rh(III) catalysis (Scheme 142).[257] This reaction provided an easy

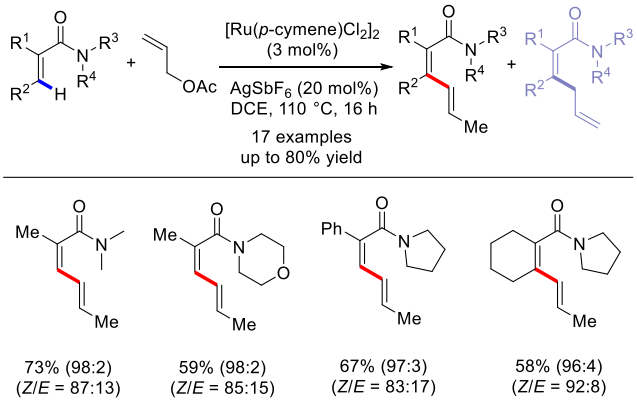
Scheme 142. Rhodium-Catalyzed Weinreb Amide Directed Cross-Coupling between Electron-Deficient Alkenes



route to obtain highly functionalized (*Z*,*E*)-butadienes. Both terminal and internal alkenes were tolerated. It is important to note that the Weinreb amide is easy to synthesize and could be readily converted into other useful functional groups.

As an extension of this strategy, the same group further reported a direct Ru(II)-catalyzed alkenylation of electron-deficient olefins with allyl acetate *via* alkenyl C−H activation (Scheme 143).[258] By employing *N*,*N*-disubstituted amino-

Scheme 143. Ruthenium-Catalyzed C−H Olefination of Electron-Deficient Alkenes with Allyl Acetates

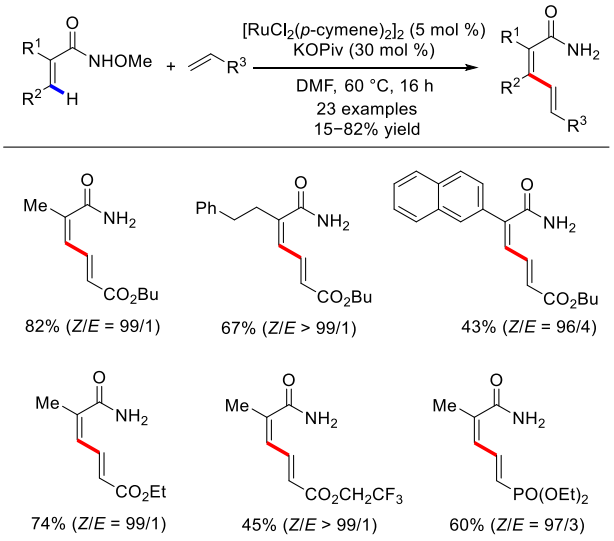


carbonyl as the chelating group, this oxidant-free strategy features high efficiency and decent stereo- and regioselectivities, which unlocks a novel synthetic tool for the synthesis of (2*Z*,4*E*)-butadiene skeletons.

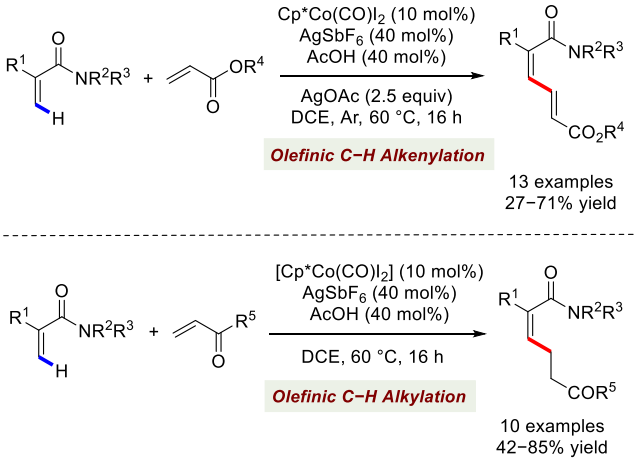
An efficient approach for the oxidant-free cross-coupling reaction of activated alkenes has been established under Ru(II) catalysis by the group of Zhong and Zhang (Scheme 144).[259] With the assistance of the oxidizing directing group CONH(OMe), this strategy presents a benign, direct and efficient approach for the construction of synthetically useful 1,3-butadiene skeletons with excellent *Z*,*E* selectivities.

To exploit the potential of cost-effective cobalt catalysis, the same group further achieved the Cp*Co(III)-catalyzed cross-coupling reactions between electron-deficient alkenes by using readily synthesizable Co(III) complexes [Cp*Co(CO)I$_2$], giving rise to regioselective and stereoselective transformation of a wide variety of *Z*,*E*-dienamides, along with γ-alkenyl ketones by prudent selection of coupling partners (Scheme 145).[260] The carbonyl group character and reaction conditions are responsible for determining the selectivity of the process, which results in the formation of the two kinds of products. Acrylates afforded conjugated dienes *via* β-H elimination,

Scheme 144. Cross-Coupling of Electron-Deficient Alkenes Using an Oxidizing Directing Group



Scheme 145. Cobalt-Catalyzed Olefinic C−H Bond Alkenylation and Alkylation



while α,β-unsaturated ketones produced the C−H alkylated products by proto-demetalation.

Furthermore, the same group also demonstrated the Cp*Ir(III)-catalyzed cross-coupling of electron-deficient olefins by integration of chelation-assisted vinylic C−H alkenylation and transfer hydrogenation, which remarkably obviates the use of a metal oxidant and instead employs a hydrogen acceptor such as chloranil, leading to a highly site- and stereoselective synthesis of (*Z*,*E*)-configurated dienamides in 47−97% yields (Scheme 146).[261]

Tanaka and Shibata found that a highly electron-deficient CpRh(III) complex, bearing two ester moieties on the Cp ring, [Cp^{E}Rh^{III}], could catalyze the aerobic oxidative cross-coupling of substituted acrylamides with both activated and unactivated alkenes (Scheme 147),[262] leading to (2*Z*,4*E*)-dienamides at relatively low temperature (80 °C). The authors employed tertiary, secondary, and primary amide directing groups in this chemistry to obtain the expected products. Through mechanistic studies, the authors revealed that the electron-deficient nature of [Cp^{E}Rh^{III}] complex greatly facilitates the turnover-limiting vinylic C−H bond cleavage of the acrylamides.

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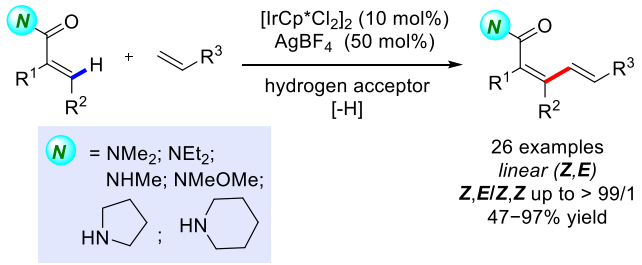
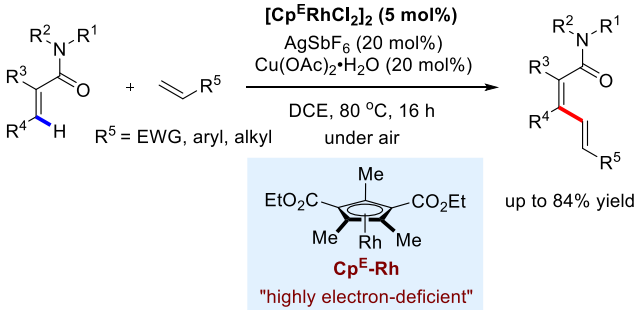
Scheme 146. Iridium(III)-Catalyzed Cross-Coupling Reactions of Alkenes by Hydrogen Transfer

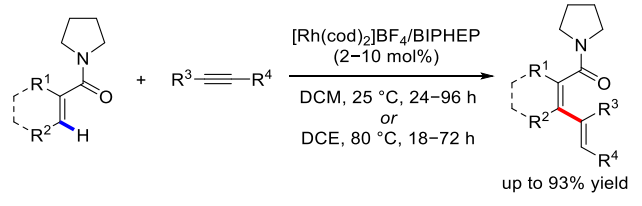


Scheme 147. Electron-Deficient Rh^{III}−Catalyzed Cross-Coupling of Acrylamides with Alkenes



Despite the indisputable advances in this area, chelation-assisted alkene−alkene cross-coupling reactions are predominantly restricted to form (*Z*,*E*)- and (*E*,*E*)-butadienes. Sparse examples were reported on the alkene−alkyne coupling, giving rise to highly valuable (*Z*,*Z*)-butadienes. In 2009, Tanaka and co-workers achieved a regioselective amide-directed alkenylations of olefinic sp^2 C−H bond by using a cationic rhodium(I)/BIPHEP complex (Scheme 148).[263] In this case, the sagacious choice of a 1-pyrrolidinecarbonyl group as the chelating group dramatically accelerates the reaction under especially mild conditions.

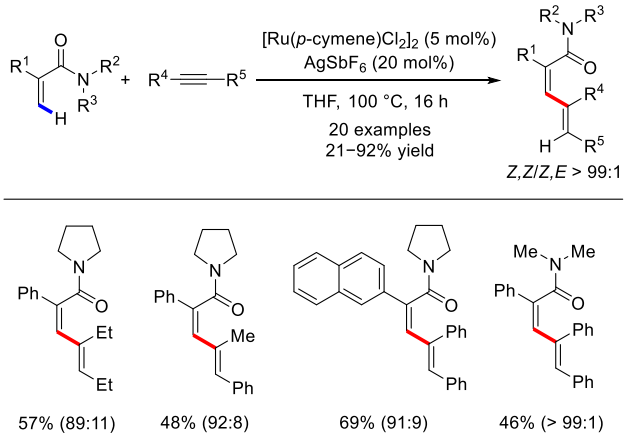
Scheme 148. Cationic Rh(I)/BIPHEP-Catalyzed Amide-Directed C−H Alkenylation



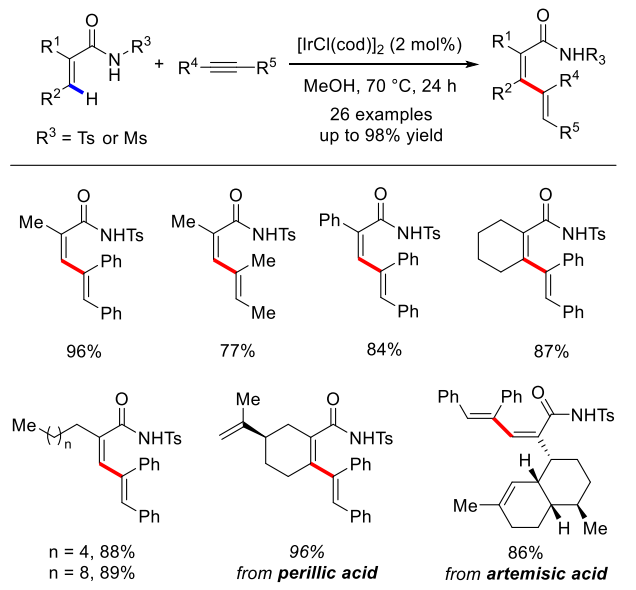
Later in 2017, a highly regio- and stereoselective ruthenium(II)-catalyzed cross-coupling reaction between *α*-substituted acrylamides and internal alkynes *via* directed vinylic C−H bond activation has been realized by the group of Zhang and Zhong (Scheme 149).[264] This atom-economic *syn*-hydrovinylation of alkynes resulted in good efficiency and excellent stereoselectivities under oxidant-free conditions, providing an attractive approach for the synthesis of diverse highly functionalized (2*Z*,4*Z*)-butadienes. *β*-Substituted acrylamides, however, were proven to be incompatible with this protocol.

Subsequently, Zhong's group continued to achieve an iridium-catalyzed alkene−alkyne cross-coupling under ligand- and additive-free conditions (Scheme 150).[265] A broad variety

Scheme 149. Synthesis of (*Z*,*Z*)-Dienamides *via* Ruthenium-Catalyzed Cross-Coupling between Alkenes and Alkynes



Scheme 150. Iridium-Catalyzed Cross-Coupling between Alkenes and Alkynes



of acrylamides could couple with internal alkynes, generating a diverse array of branched (*Z*,*Z*)-butadienes in up to 98% yield with excellent site- and stereoselectivities. As a particular highlight, the synthetic practicality and versatility was demonstrated by late-stage C−H functionalization of biologically active perillic and artemisic acid derived amides.

In 2018, Mascareñas, López, and their co-workers reported an intramolecular Ir(I)-catalyzed carboxamide-assisted C−H olefination *via* the addition of vinylic C(sp^2)−H bonds to the unsaturated moiety of alkynes (Scheme 151),[266] providing a diverse variety of cyclic scaffolds bearing an *exo*-dienyl moiety with well-defined stereochemistry in modest to excellent yields.

The group of Wang and Yu demonstrated the C−H alkenylation through an efficient cost-effective copper-catalyzed reaction of acrylamides with both acyclic and cyclic vinyl boronates in DMSO at 45 °C (Scheme 152).[267] Of note, the substrate scope and functional group tolerance of this method are superior to Pd-catalyzed cross-coupling with vinyl borons.

By means of vinylic C(sp^2)−H activation strategy, the Jeganmohan group developed an aerobic oxidative cross-

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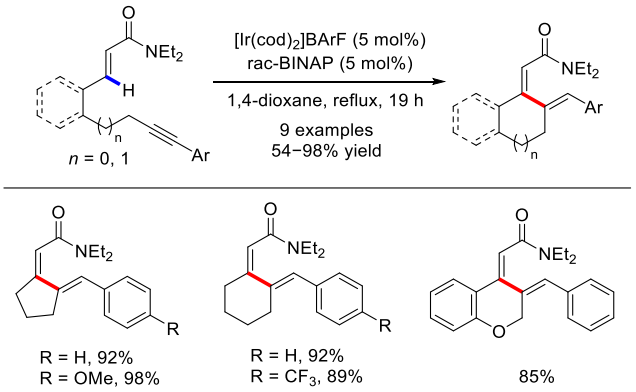
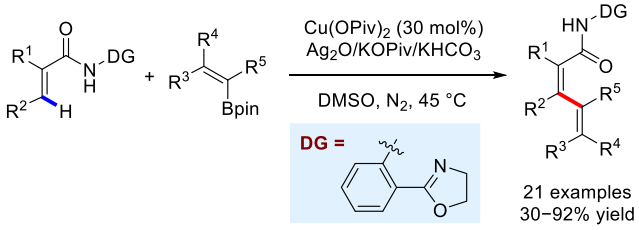
Scheme 151. Intramolecular Hydroalkenylation of Alkynes

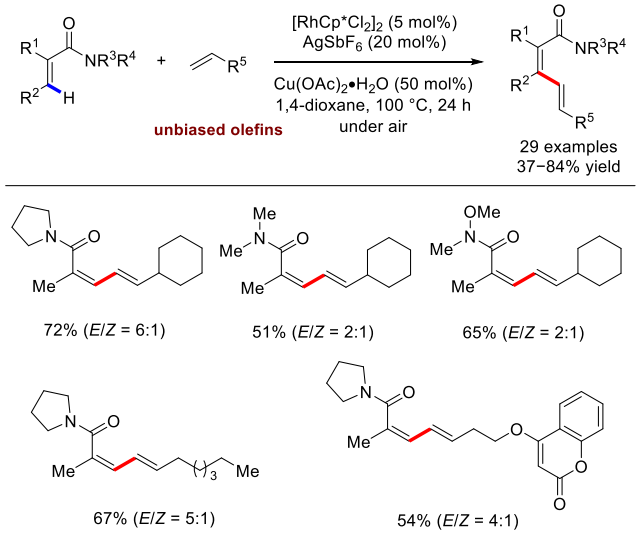


Scheme 152. Cu-Catalyzed C−H Alkenylation of Acrylic Acids with Vinyl Boronates



coupling of acrylamides with unactivated aliphatic alkenes catalyzed by a Cp*Rh(III) catalyst (Scheme 153).[268] The

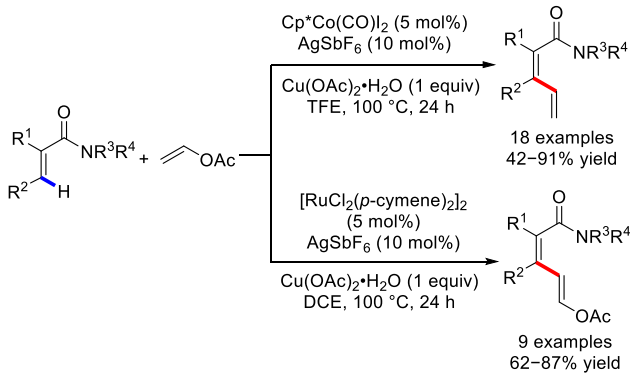
Scheme 153. Cp*Rh(III)-Catalyzed C−H Olefination of Acrylamides with Unbiased Alkenes



authors carried out the reaction in 1,4-dioxane with 5 mol % Rh(III) catalyst, 20 mol % $AgSbF_6$, and $Cu(OAc)_2•H_2O$ at 100 °C to provide diverse synthetically valuable amide-functionalized 1,3-butadienes. The authors tentatively proposed a plausible reaction mechanism involving the chelation-assisted vinylic C−H activation *via* a carboxylate-assisted deprotonation pathway.

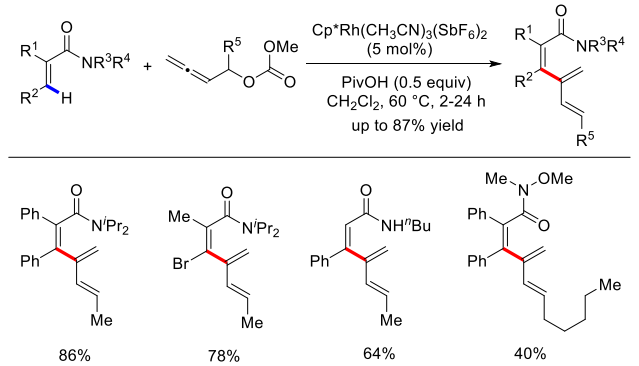
Following this, the same group extended their alkenyl C−H bond functionalization work by disclosing the chemodivergent chelation-directed C−H vinylation and alkenylation of structurally diverse acrylamides with easily accessible vinyl acetates as the coupling partners under Co(III) and Ru(II) catalysis, respectively (Scheme 154).[269]

Scheme 154. Chemodivergent Cross-Coupling of Acrylamides with Vinyl Acetate



In 2013, Glorius and colleagues illustrated a novel and straightforward construction of highly unsaturated [3]-dendralenes by a Cp*Rh(III)-catalyzed alkenyl C−H activation and cross-coupling with allenyl carbinol carbonates (Scheme 155).[270] An assortment of dendralenes with a variety

Scheme 155. Rh(III)-Catalyzed Alkenyl C−H Activation of Acrylamides with Allenyl Carbinol Carbonates



of substitution patterns can be accessed with decent efficiency. The method is highly stereoselective and suited with various directing groups as well as a number of functional groups.

An efficient and stereoselective strategy to produce trifluoromethylated 1,3-butadienes through the vinylic C−H activation of acrylamides with inexpensive 2-bromo-3,3,3-trifluoropropene (BTP) has been developed by Bouillon and Poisson (Scheme 156).[271] Intriguingly, pentafluoroethylated dienes could be also synthesized by the reaction of 2-bromo-3,3,4,4,4-pentafluorobutene with α-aryl-acrylamides under similar conditions.

Macrocycles are essential building blocks in numerous bioactive natural products and pharmaceutically relevant molecules which are especially difficult to synthesize in some cases. Accordingly, it is crucial to develop general and practical strategies for macrocycle synthesis.[272] In 2017, Loh and co-workers elegantly reported the first example of intramolecular oxidative annulation reaction between two activated olefins in the presence of Cp*Rh(III) catalyst. The intramolecular alkene−alkene coupling reaction produced macrolactams

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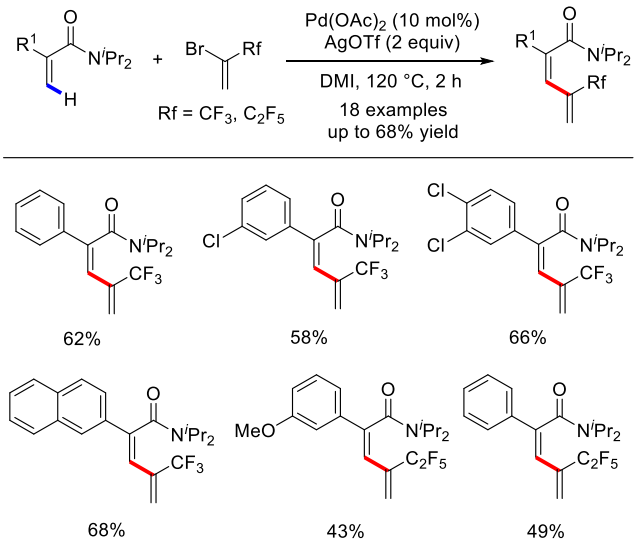
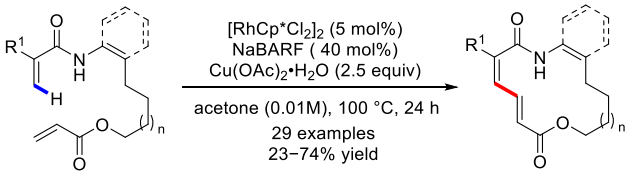
Scheme 156. Rapid Synthesis of 3-Trifluoromethyl-Substituted 1,3-Butadienes *via* Palladium-Catalyzed C−H Bond Functionalization



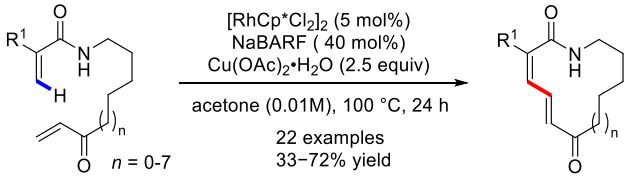
containing a 1,3-conjugated diene moiety with excellent chemo- and stereoselectivity (Scheme 157).[273]

Scheme 157. Macrolide Synthesis *via* Intramolecular Oxidative Cross-Coupling of Alkenes



Later in 2020, Loh's group substantially extended their intramolecular oxidative annulation strategy to α,β-unsaturated ketone fragments and successfully reported an expeditious method for macrolactams synthesis through a Cp*Rh(III)-catalyzed alkene−alkene cross-coupling (Scheme 158).[274] The

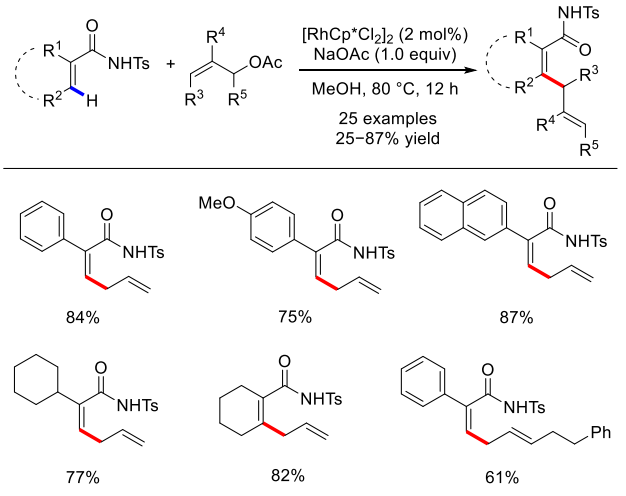
Scheme 158. Macrolactams Synthesis *via* Ring-Closing Alkene−Alkene Cross-Coupling



ring-closing reaction proceeded *via* a Rh(III)-catalyzed vinylic C−H activation process, which opens a new pathway to access diverse macrocyclic molecules of different ring sizes in satisfactory yields (33−72%). Moreover, macrolactams featuring a conjugated 1,3-diene moiety could be easily prepared with high chemoselectivities and *Z,E*-stereoselectivities. The versatile nature of the 1,3-diene moiety was further converted into many useful functional groups, thus allowing the synthesis of many different types of macrocyclics.

4.3.4. Allylation. The allylation reaction is one of the most synthetically useful transformations in organic synthesis because the allyl moieties could be readily converted into many versatile functional groups.[275] In particular, the transition-metal-catalyzed vinylic C−H allylation of readily available starting materials with diverse allylic electrophiles provides a reliable route to incorporate allyl units into organic molecules for the synthesis of skipped 1,4-diene skeletons. For example, Loh's group in 2015 established an elegent synthetic procedure to easily produce 1,4-diene skeletons *via* Cp*Rh-(III)-catalyzed C−H allylation of electron-deficient acrylamides with allyl acetates (Scheme 159).[276] As a consequence

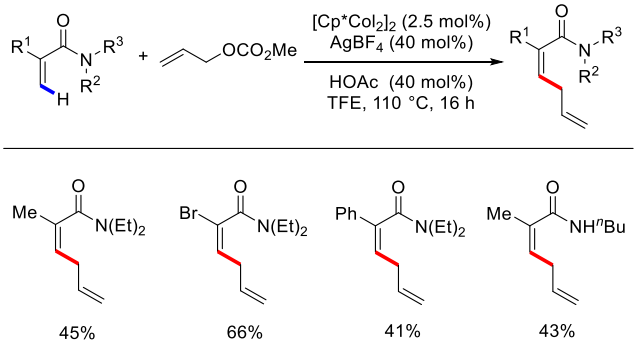
Scheme 159. Cp*Rh(III)-Catalyzed C−H Allylation of Electron-Deficient Alkenes with Allyl Acetates



of using a weakly coordinating group, this reaction provided high yields, and a diverse variety of functional groups were tolerated while maintaining exceptional γ-selectivity.

The same year, Glorius *et al.* disclosed an amide-directed C−H allylation of aromatics, heteroaromatics, and acrylamides with allyl carbonates as reaction partners under cost-effective Cp*Co(III) catalysis (Scheme 160).[277] A number of allyl

Scheme 160. Cobalt(III)-Catalyzed C−H Allylation of Acrylamides with Allyl Carbonates



carbonates can be readily employed to incorporate this synthetically useful functional group, allowing for the construction of skipped 1,4-dienes. Moreover, Kim and co-workers also achieved an analogous transfromation under ruthenium catalysis to generate the allylation products in modest yields.[278]

The highly chemo- and stereoselective Cp*Rh(III)-catalyzed C−H allylation of acrylic acid derivatives with 4-

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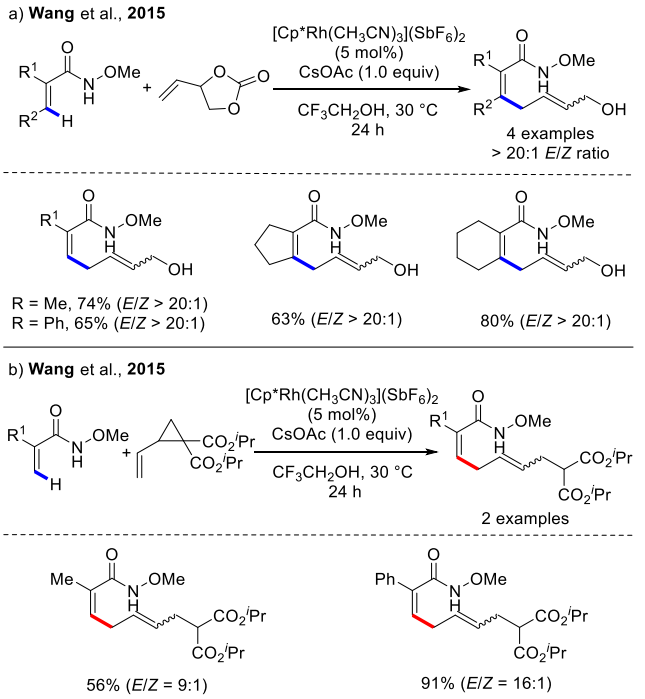
vinyl-1,3-dioxolan-2-ones as coupling partners has been reported by Wang and co-workers (Scheme 161a),[279] allowing

Scheme 161. Cp*Rh(III)-Catalyzed Vinylic C−H Allylation of Acrylamides



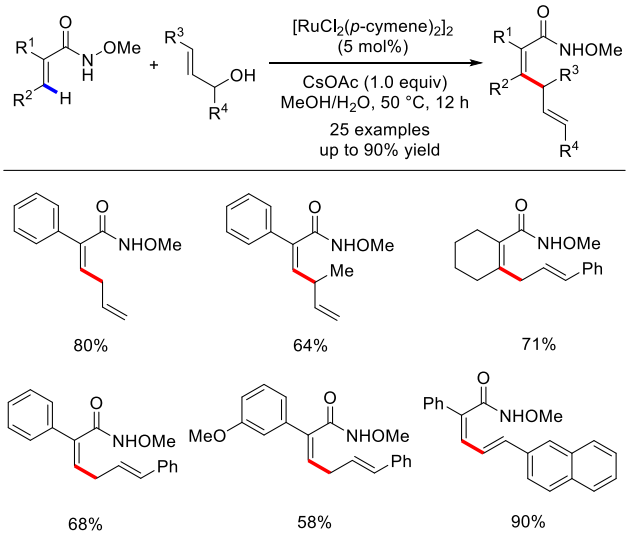
an efficient synthesis of highly functionalized allylic alcohols, which are the most synthetically useful building blocks in organic synthesis.[280] The reaction occurred uneventfully to produce the skipped dienes with remarkable efficiency and excellent E/Z ratios under ambient conditions. Meanwhile, the same group also illustrated the synthesis of 1,4-dienes through a Cp*Rh(III)-catalyzed sequential vinylic C−H activation and C−C activation reaction with vinylcyclopropanes as a versatile coupling partner under identical conditions (Scheme 161b).[281]

The Ji group was able to efficiently synthesize a broad range of skipped 1,4-diene skeletons by a Ru(II)-catalyzed C−H allylation of electronically activated olefins with the assistance of a *N*-methoxycarbamoyl directing group (Scheme 162).[282] This procedure utilizes easily available allyl alcohols to couple with various electron-deficient acrylamides in the presence of inexpensive $[RuCl_2(p\text{-cymene})_2]_2$ catalyst in aqueous solution. A variety of functional groups were tolerated to generate the expected products with excellent regio- and stereoselectivity.

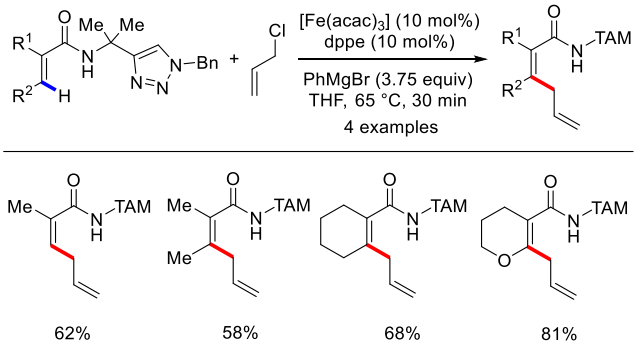
Ackermann's group expanded their sustainable C−H activation strategy to disclose a highly regioselective iron-catalyzed C−H allylation of (hetero) arenes and alkenes with allyl chloride by the assistance of a removable bidentate triazole auxiliary (Scheme 163).[283] This triazole-assisted C−H allylation tolerates with both primary and secondary halides. Notably, the triazole chelating group could be easily removed in a traceless fashion. The authors carried out preliminary mechanistic investigations suggesting that a single-electron-transfer (SET) pathway is probably involved in this process.

In 2019, Zhang and Zhong elaborated an iridium-catalyzed olefinic C−H allylation of acrylamides with diverse conjugated 1,3-dienes, exclusively affording a variety of branched 1,4-diene skeletons (Scheme 164).[284] This atom-economic C−H

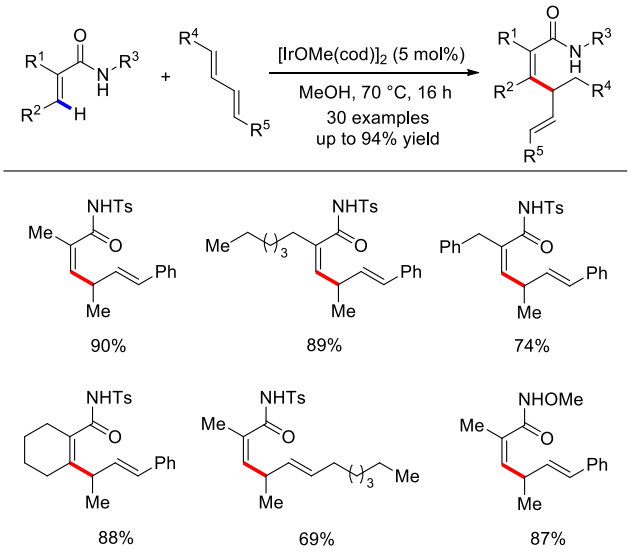
Scheme 162. Ruthenium-Catalyzed C−H Allylation of Acrylamides with Allyl Alcohols



Scheme 163. Iron-Catalyzed Alkenyl C−H Allylation of Acrylamides with Allyl Chloride



Scheme 164. Iridium-Catalyzed Olefinic C−H Bond Allylation of Acrylamides with Conjugated 1,3-Dienes



allylation took place with the assistance of a NH-Ts amide group under additive-and ligand-free conditions. Successfully, they further expanded to carry out this olefinic C−H allylation of NH-Ts acrylamides in water, efficiently affording the

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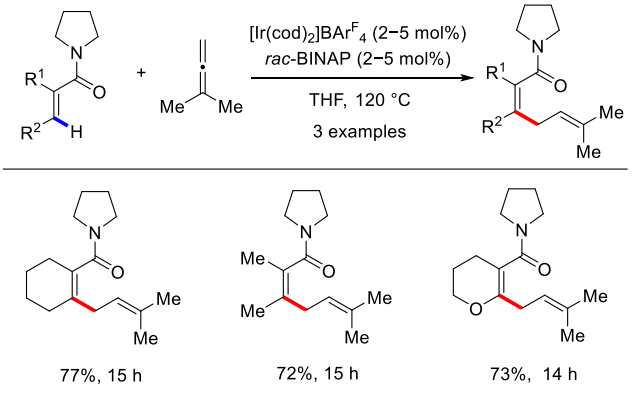
corresponding skipped 1,4-dienes in excellent yields (52−99%).[285]

Moreover, Krische's group in 2009 established a chelation-directed C−H allylation of α,β-unsaturated carboxamides *via* the addition of vinylic C(sp^2)−H bonds to 1,1-dimethylallenes catalyzed by a cationic iridium complex assembled from [Ir(cod)$_2$]BAr$^F_4$ and *rac*-BINAP (Scheme 165),[286] resulting in the adduct products of C−H prenylation in good yields as single isomers.

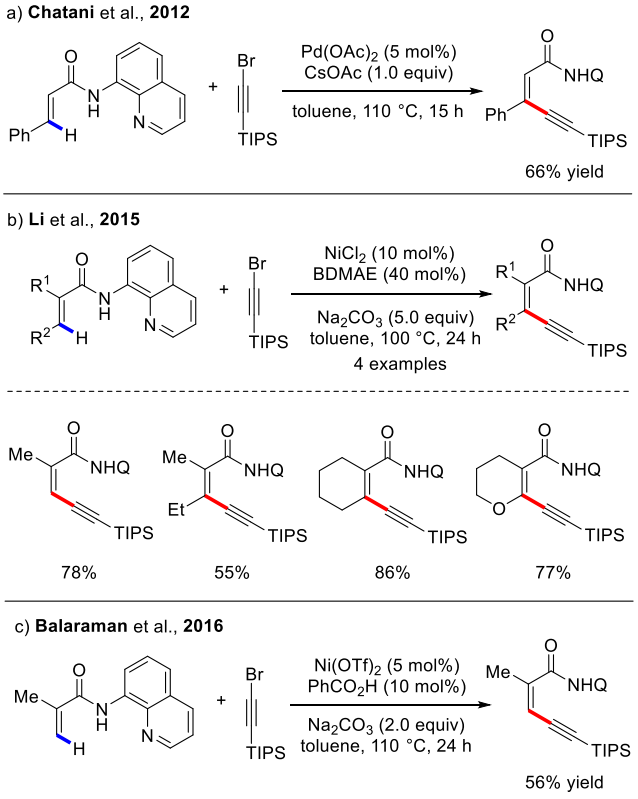
Scheme 165. Iridium-Catalyzed Alkenyl C−H Oxidative Addition−Allene Insertion of α,β-Unsaturated Carboxamides



4.3.5. Alkynylation. Alkyne functional groups are among the most commonly used motifs in a diverse variety of bioactive organic molecules. They can also serve as extremely versatile synthetic building blocks and could be easily converted into other synthetically useful functional groups which dramatically leads to an increase in molecular complexity. It is well-known that the Sonogashira cross-coupling is one of the most robust and powerful strategies for the straightforward synthesis of various functionalized alkynes. Considering the remarkable atom- and step-economy, transition-metal-catalyzed directed C−H alkynylation has been significantly advanced in recent years with the efficacious assistance of a suitable directing group, which greatly enables the rapid and straightforward assembly of diverse alkynes.[287,288]

Over the past decades, a diverse variety of olefinic C−H alkynylations of acrylamides have been realized by different transition metal catalysts, providing concise and efficient methods to highly functionalized conjugated 1,3-enynes. Specifically, the Chatani group described a palladium(II)-catalyzed chelation-assisted C(sp^2)−H alkynylation of aromatic amides by using bidentate 8-aminoquinoline as a removable auxiliary with 1-bromoalkyne (Scheme 166a).[289] Notably, This directed C−H alkynylation is applicable to vinylic C−H bond of α,β-unsaturated amide, allowing the straightforward construction of a conjugated (*Z*)-enyne in 66% yield. Following this bidentate chelation strategy, Li and co-workers subsequently achieved the same vinylic C−H alkynylation by a nonprecious Ni/BDMAE catalyst system (Scheme 166b).[290] In this case, the identified flexible bis(2-dimethylaminoethyl) ether (BDMAE) ligand was crucial to achieve remarkable catalytic efficiency. Furthermore, Balaraman's group later demonstrated that the use of benzoic acid (10 mol %) as a ligand could also achieve comparable

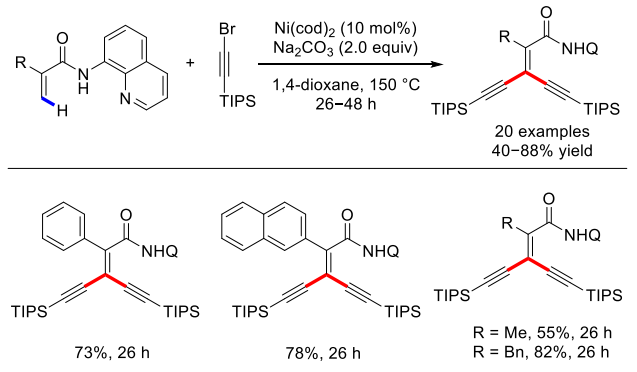
Scheme 166. Palladium- and Nickel-Catalyzed Vinylic C−H Alkynylation of α,β-Unsaturated Amides



reactivity in the Ni(OTf)$_2$-catalyzed olefinic C−H alkynylation reactions (Scheme 166c).[291]

The straightforward protocol for the efficient assembly of *gem*-diethynylethenes would be through a sequential double vinylic C−H activation process. In this regard, Gao's laboratory recently published the first example of nickel-catalyzed 3,3-dialkynylation of 2-aryl acrylamides with 1-bromotriisopropylsilylacetylene (Scheme 167).[292] Of note, the

Scheme 167. Nickel-Catalyzed 3,3-Dialkynylation of 2-Aryl Acrylamides



sagacious choice of bidentate 8-aminoquinoline as the auxiliary was indispensable for this transformation. However, alkynylating reagents, including phenylacetylene, 3-methylbut-1-yne, and *tert*-butyl(ethynyl)dimethylsilane, were all found to be incompatible with the conditions.

Afterward, Ackermann and co-workers published an earth-abundant, environmentally benign iron-catalyzed C−H

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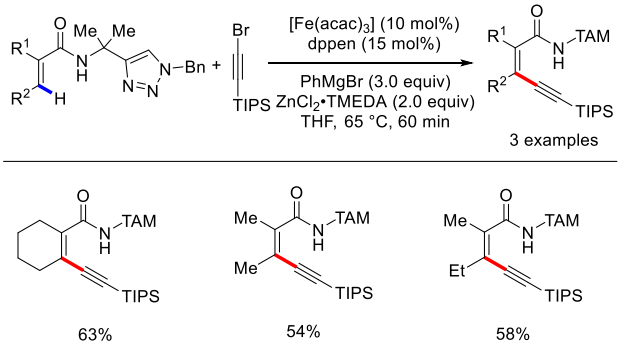
alkynylation of various arenes and heteroarenes enabled by the assistance of a triazole auxiliary (Scheme 168).[293] Of note, the

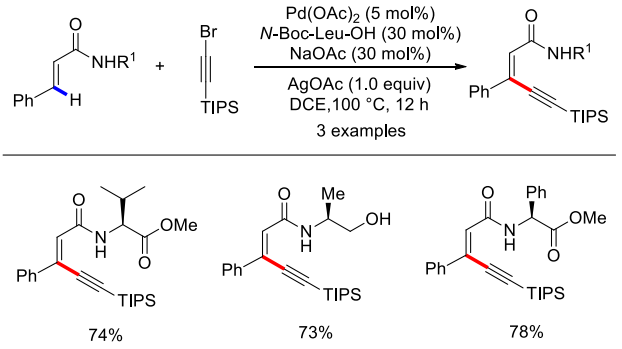
Scheme 168. Iron-Catalyzed Alkenyl C−H Alkynylation of Alkenes through Triazole Assistance



reaction was typically finished within 1.0 h at 65 °C in THF. This sustainable methodology was applicable to α,β-unsaturated amides, furnishing the corresponding 1,3-enynes in modest yields (54−63%).

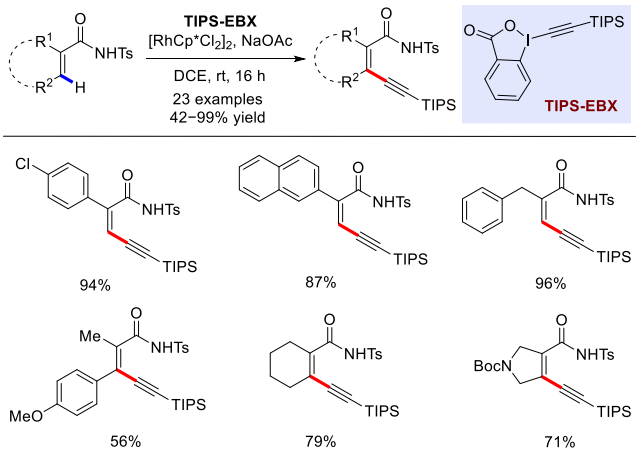
In 2020, the Li group successfully realized a highly regioselective palladium/monoprotected amino acid (MPAA)-catalyzed C−H alkynylation of weak coordination nitrogen functionality including diverse benzylamines, arylethyl amines, and benzedrines. In this report, readily available α,β-unsaturated cinnamamides were also competent substrates to afford the conjugated 1,3-enynes in decent yields (Scheme 169).[294]

Scheme 169. Palladium-Catalyzed Vinylic C−H Alkynylation of Cinnamamides with 1-Bromoalkyne



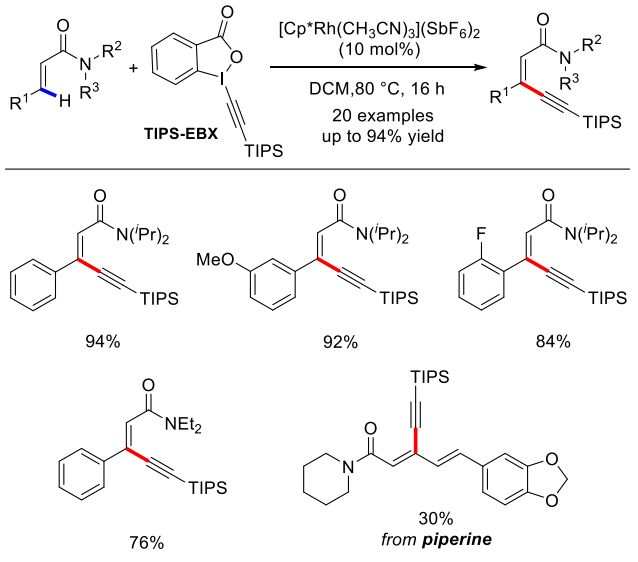
Loh and co-workers continued their research on alkynylation reaction and established an efficient approach for olefinic C−H alkynylation of electron-deficient alkenes with ethynylbenziodoxole (TIPS-EBS) as the alkynylating reagent in the presence of a Cp*Rh(III) catalyst (Scheme 170).[295] Tosyl-imide group was employed as the directing group for this transformation. The weak coordinating ability of this directing group was responsible for the highly efficient and stereospecific C−H alkynylation of olefinic C−H bonds. Operational simplicity, excellent functional group compatibility, as well as especially mild reaction conditions were the key features of this strategy. Hence, this method represented an efficient route for the synthesis of synthetically valuable 1,3-enyne moieties. To showcase the potential of this protocol, the authors derivatized the obtained products into a series of pyridinone and triazole moieties.

Scheme 170. Rhodium(III)-Catalyzed Olefinic C−H Alkynylation of Acrylamides



Almost simultaneously, Glorius and co-workers also established a direct olefinic C−H bond alkynylation of α,β-unsaturated amides with hypervalent iodonium reagents (TIPS-EBS) under Cp*Rh(III) catalysis (Scheme 171).[296]

Scheme 171. Synthesis of Conjugated 1,3-Enynes by Cp*Rh(III)-Catalyzed Alkynylation of Alkenes



This experimentally simple C−H alkynylation reaction occurred smoothly under additive-free conditions, eventually providing an electronically inverted retrosynthetic disconnection of conjugated 1,3-enynes when compared to the classical Sonogashira cross-coupling. Unfortunately, α,β-disubstituted acrylamides precluded alkynylation product formation in this process. Moreover, this protocol could be applied to late-stage C−H alkynylation of natural product piperine, albeit with 30% yield.

In the same year, Li and co-workers illustrated an efficient chelation-assisted C−H alkynylation of a broad range of (hetero) arenes by means of Cp*Rh(III) or Cp*Ir(III) catalysis with hypervalent iodine−alkyne reagents under typically mild conditions (Scheme 172).[297] Olefin substrates were also proved to be compatible in the presence of

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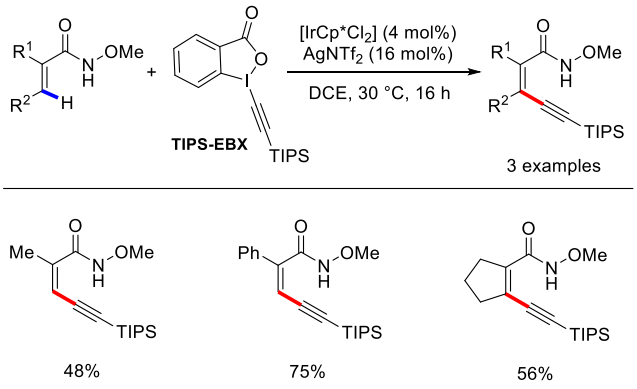
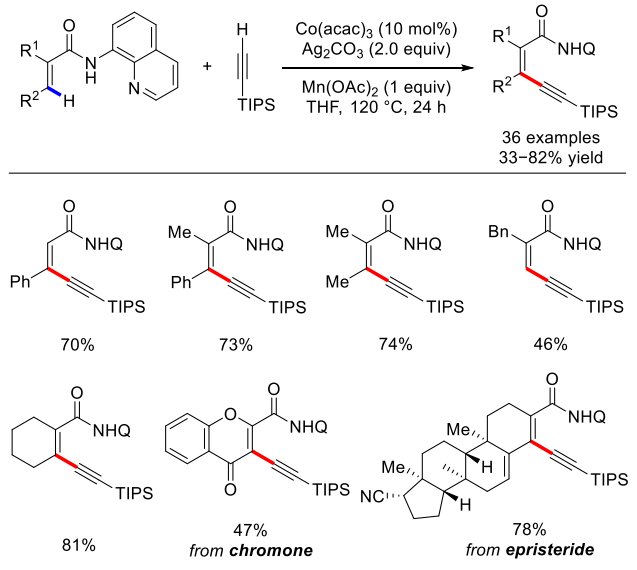
$[IrCp^*Cl_2]_2$ (4 mol %) as a catalyst, enabling the formation of 1,3-enynes in 48−75% yields.

Scheme 172. Cp*Ir(III)-Catalyzed C−H Alkynylation of α,β-Unsaturated Amides



Besides the preactivated alkynylating reagents such as ethynylbenziodoxolones (EBX) and haloalkynes, the use of commercially available terminal alkynes as the alkynylating reagents represents an atom-economical strategy for the C−H alkynylation reactions. In this regard, You and co-workers successfully reported a general and inexpensive $Co(acac)_3$-catalyzed oxidative cross-coupling between a broad range of acrylamides and triisopropylsilylacetylene with the assistance of the bidentate 8-aminoquinoline auxiliary (Scheme 173).[298]

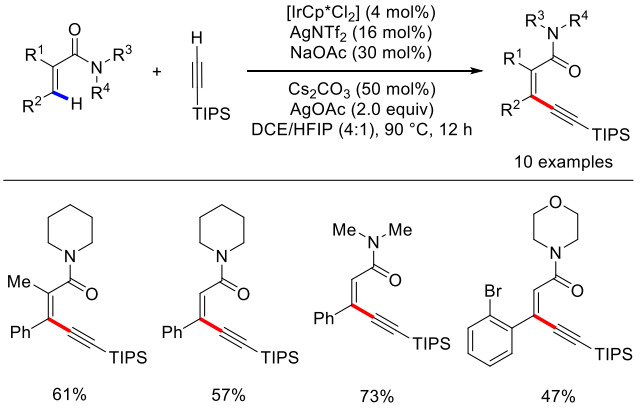
Scheme 173. Co(III)-Catalyzed C−H Alkynylation of Alkenes with Triisopropylsilylacetylene



Notably, a broad scope of 36 examples of this transformation was documentd with yields of 33−82%. Moreover, this protocol was applicable to late-stage alkynylation of a derivative of steroid drug episteride.

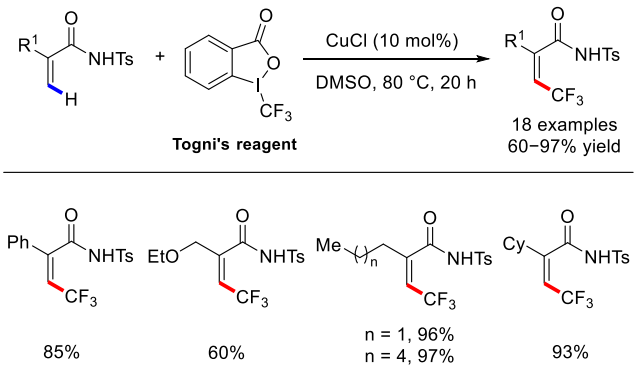
Meanwhile, Li's group elaborated an efficient example of C−H alkynylation of acrylamides by taking advantage of terminal alkynes as the readily available alkynylating reagents under Cp*Ir(III) catalysis (Scheme 174),[299] thus affording a variety of multisubstituted 1,3-enynes with excellent stereoselectivity.

Scheme 174. Cp*Ir(III)-Catalyzed Stereoselective C−H Alkynylation of α,β-Unsaturated Amides



4.3.6. Fluoroalkylation. The incorporation of a fluoroalkyl group into an organic molecule sometimes dramatically enhances its chemical stability, bioavailability, lipophilicity, and so on. Accordingly, remarkable efforts have been devoted toward the development of efficient and straightforward approaches for the synthesis of fluoroalkyl-substituted molecules in past decades. In this context, the direct vinylic C−H trifluoromethylation has drawn significant attentions from synthetic organic chemists.[300] For example, Loh and co-workers in 2013 disclosed an efficient copper-catalyzed olefinic C−H trifluoromethylation of acrylamides with Togni's reagent (Scheme 175).[301] The Ts-protected directing group plays an important role in achieving highly *cis*-selective β-CF_3-functionalized acrylamides in this strategy.

Scheme 175. Chelation-Assisted Copper-Catalyzed Olefinic C−H Trifluoromethylation of Acrylamides



Almost at the same time, Besset's group disclosed a regioselective copper-mediated C−H trifluoromethylation of acrylamides with commercially available Umemoto's reagent (Scheme 176).[302] The reaction occurred in the presence of CuI (1.1 equiv) under acidic conditions, thus resulting in the formation of *Z*-trifluoromethylated α,β-unsaturated amides in 11−69% yield.

Successfully, Tan and Liu reported an elegant transition-metal-free *E*-selective C−H β-trifluoromethylation of α,β-unsaturated carbonyls with Togni's reagent as CF_3 radical precursor (Scheme 177).[303] In this protocol, the authors employed 1.5 equiv of tetrabutylammonium iodide as an initiator activate Togni's reagent to *in situ* generate the highly electrophilic iodine(III) species.[304−306] Interestingly, the

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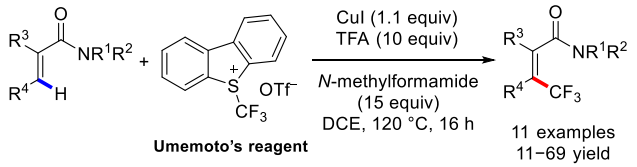
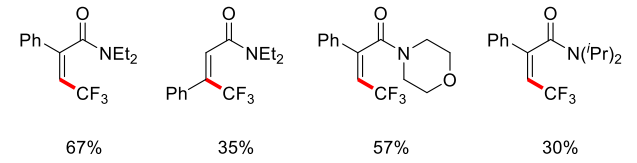
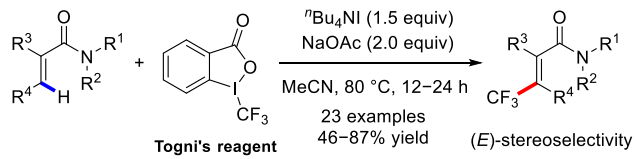
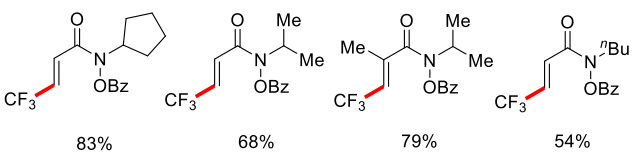
Scheme 176. Copper-Mediated Vinylic C−H Bond Trifluoromethylation of α,β-Unsaturated Amides

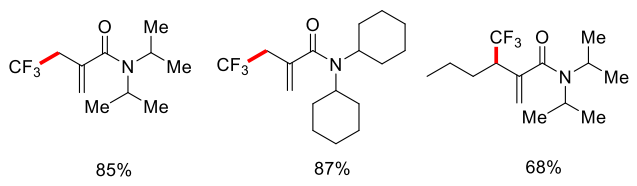




Scheme 177. Transition-Metal-Free Vinylic C−H Trifluoromethylation of α,β-Unsaturated Amides





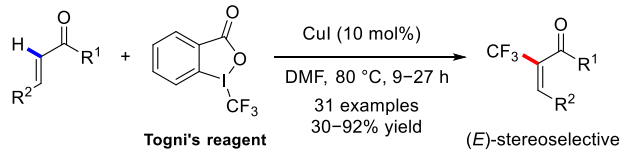


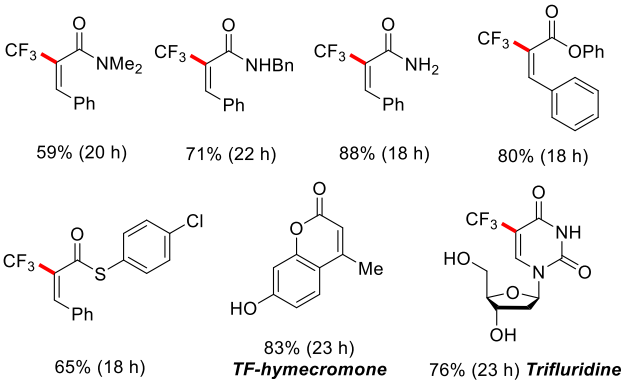
judicious choice of sterically bulky α-alkyl acrylamides could dramatically alter the reaction pattern of this strategy, and exclusively afforded the allylic C−H trifluoromethylated products with high efficiency under identical conditions.

Besides the β-C−H trifluoromethylation of α,β-unsaturated carbonyl compounds, Bi's group in 2014 successfully achieved a highly regioselective copper-catalyzed vinylic C−H α-trifluoromethylation with Togni's reagent (Scheme 178).[307] Likewise, a broad range of alkene substrates including α,β-unsaturated amides, esters, thioesters, as well as enones could engage this transformation to stereospecifically furnish the (*E*)-α-trifluoromethylated products in modest to good yields (30−92%). The authors highlighted the value of this protocol by late-stage vinylic C−H trifluoromethylation of biologically active molecules.

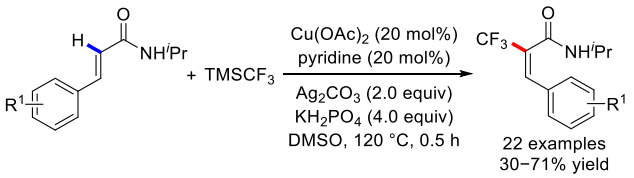
Later, Dai's group also described a regioselective C−H α-trifluoromethylation of α,β-unsaturated acrylamides with readily available, inexpensive Ruppert's reagent ($TMSCF_3$) (Scheme 179).[308] The reaction was typically finished within

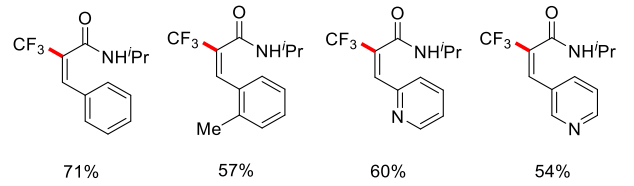
Scheme 178. Copper-Catalyzed Vinylic C−H α-Trifluoromethylation of α,β-Unsaturated Carbonyls





Scheme 179. Copper-Catalyzed α-Selective C−H Trifluoromethylation of Acrylamides with $TMSCF_3$





0.5 h at 120 °C in DMSO. A large variety of β-substituted acrylamide derivatives are well compatible with the conditions, thereafter providing the corresponding (*E*)-trifluoromethylated products in satisfactory yields.

Moreover, Xu and his co-workers expanded their sustainable electrochemical strategy[309] and elaborated the efficient 1,2-hydroxydifluoromethylation and vinylic C−H bond difluoromethylation of various acrylamides by using $CF_2HSO_2NHNHBoc$ as the CF_2H source under electrochemical catalysis. These electricity-powered oxidative olefin functionalizations do not require any metal catalyst or oxidant. The reaction outcome, 1,2-difuntionalization or C−H functionalization reaction, is greatly dictated by the substituents on the amide nitrogen atom of the acrylamides as compared to the reaction conditions. (Scheme 180).[310]

Besset and co-workers reported a straightforward *Z*-selective 2,2,2-trifluoroethylation of acrylamides by Pd-catalyzed alkenyl C−H activation with a fluorinated hypervalent iodine reagent as the CH_2CF_3 source (Scheme 181).[311] Indeed, the reaction occurred smoothly at room temperature under additive-free conditions, enabling the direct synthesis of various *Z*-2,2,2-trifluoroethylated acrylamides in a stereoselective manner.

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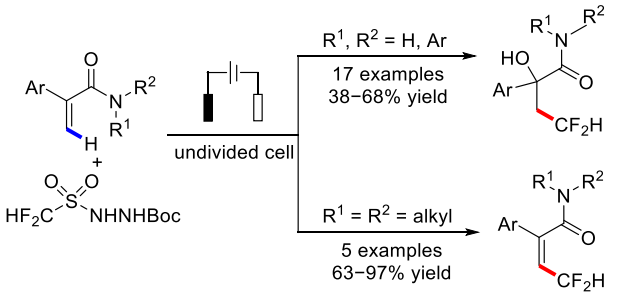
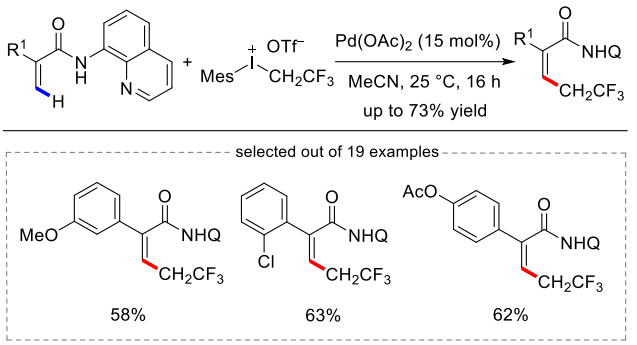
Scheme 180. Electrochemical Difluoromethylation of Electron-Deficient Alkenes



Scheme 181. Palladium(II)-Catalyzed Alkenyl C−H 2,2,2-Trifluoroethylation of Acrylamides at Room Temperature



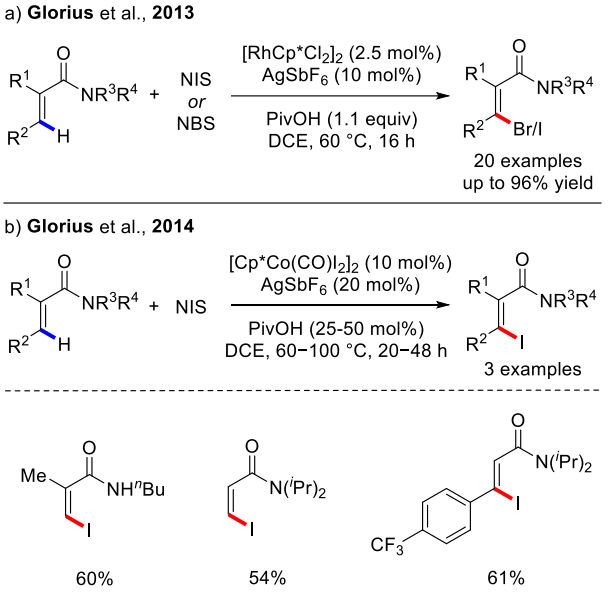
4.3.7. Halogenation. The carbon−halogen bond is one of the central functional groups in organic chemistry. With the ever-increasing efforts devoted toward transition-metal-catalyzed C−H functionalizations, the direct C−H halogenation has also gained considerable momentum in recent years.[312−315] For example, Glorius and co-workers in 2013 demonstrated a remarkable Cp*Rh(III)-catalyzed alkenyl C(sp^2)−H bond halogenation of various α,β-unsaturated amides with readily available *N*-bromosccinimide and *N*-iodosuccinimide to obtain diverse *Z*-haloacrylamide derivatives in DCE at 60 °C (Scheme 182a).[316] Indeed, a large variety of synthetically useful and versatile functional groups are tolerated in this case. Subsequently, they further extended to report the earth-abundant, inexpensive Cp*Co(III)-catalyzed alkenyl C−H iodination of acrylamides to selectively afford the monoiodinated products in modest yields (Scheme 182b).[317]

In 2020, Besset's group disclosed a palladium-catalyzed *Z*-selective chlorination of α,β-unsaturated acrylamides at room temperature with the inexpensive and commercially available *N*-chlorosuccinimide as the chlorinating agent (Scheme 183).[318] 8-Aminoquinoline directing group was readily employed to access a diverse variety of value-added chlorinated olefins as a single *Z* stereoisomer.

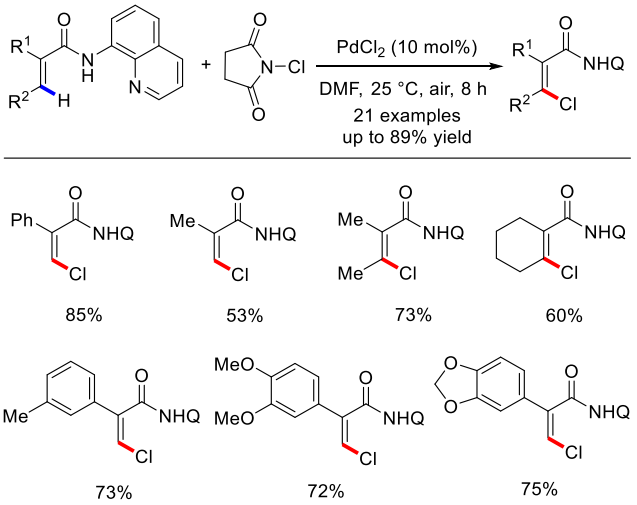
More recently, Morrill *et al.* elaborated a sustainable electrochemical strategy for the highly *Z*-selective C−H chlorination of various acrylamides by taking advantage of $MgCl_2$ as both the chloride source and the electrolyte (Scheme 184).[319] Of note, this protocol obviates the use of transition-metal catalyst and organic oxidant which tolerates a variety of substituted acrylamides, providing an efficient access to an array of synthetically useful *Z*-β-chloroacrylamides in an environmental-friendly manner.

4.3.8. Annulation Reactions. The efficient synthesis of substituted 2-pyridone scaffold is a contemporary field of great

Scheme 182. Synthesis of Haloacrylamides *via* C−H Halogenation of α,β-Unsaturated Acrylamides



Scheme 183. Palladium(II)-Catalyzed Alkenyl C−H Chlorination of Acrylamides



interest because a number of bioactive molecules, pharmaceuticals, and advanced functional materials contain this privileged moiety. Accordingly, remarkable efforts have been devoted toward the construction of 2-pyridone derivatives through the vinylic C−H functionalization over the past decade.[320] Specifically, Li and colleagues in 2010 described a Cp*Rh(III)-catalyzed oxidative cross-coupling of acrylamides with alkynes through C−H/N−H bond functionalizations (Scheme 185a),[321] affording a variety of synthetically valuable 2-pyridones in appreciable to high yields (48−94%). The reaction occurred smoothly by using a low 0.5 mol % catalyst loading of $[RhCp^*Cl_2]_2$ in conjunction with stoichiometric amounts of $Cu(OAc)_2$ (2.2 equiv) as the terminal oxidant. Unfortunately, the use of acrylamides bearing electron-deficient *N*-substituents led to unsatisfactory selectivities, and the β-substituents of the acrylamide substrates showed pronounced effects, furnishing a substituted indole as the major product in this protocol. Additionally, alkyl- and aryl-

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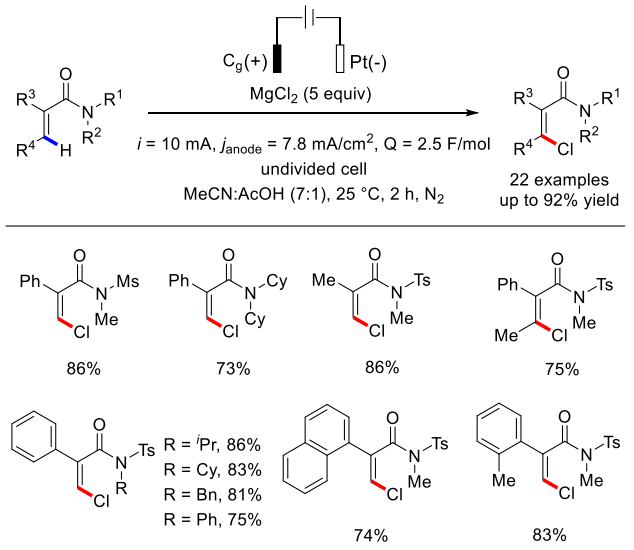
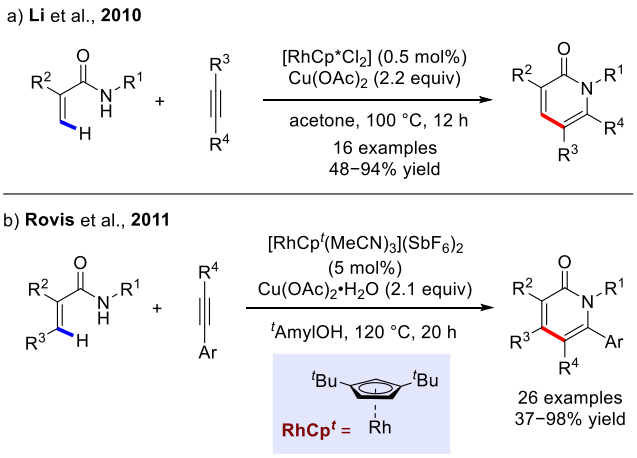
Scheme 184. Electrochemical Oxidative Z-Selective Vinylic C−H Chlorination of Acrylamides



Scheme 185. Oxidative [4 + 2] Annulation Reactions of Acrylamides with Alkynes

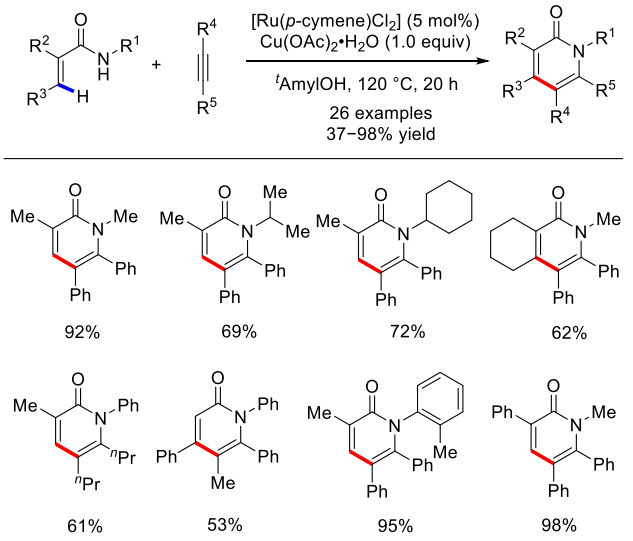


substituted unsymmetrical internal alkynes gave mixed products of regioisomers. Understandably, the ligand is a key element to increase the reactivity and regioselectivity in C−H functionalization reactions. Later in 2011, the Rovis group successfully developed a new ligand, 1,3-di-*tert*-butylcyclopentadienyl (termed Cp^t)[322] that could greatly result in an improved regioselectivity in the alkyne insertion step (Scheme 185b).[323] Internal alkynes with unsymmetrical alkyl and aryl substitution engaged this reaction with good yields and satisfactory regioselectivity.

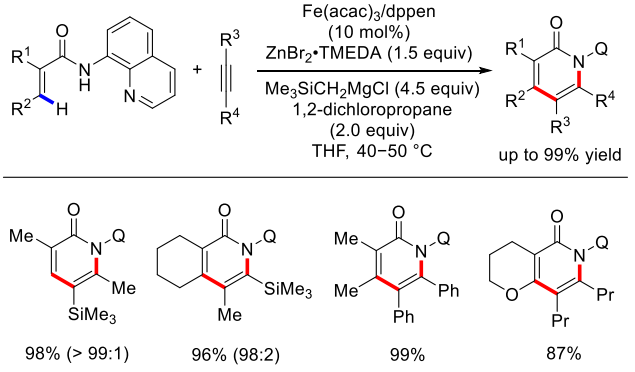
The same year, Ackermann's group disclosed an inexpensive ruthenium-catalyzed oxidative [4 + 2] annulation reactions of alkynes with broad substrate scopes (Scheme 186).[324] Notably, both electron-rich and electron-deficient acrylamides coupled efficiently with diverse unsymmetrically substituted alkynes in this protocol to produce a series of 2-pyridones with remarkably high regioselectivity.

In 2016, Nakamura and Ilies achieved an efficient assembly of 2-pyridones from acrylamides and alkynes enabled by a sustainable iron catalyst under typically mild conditions (Scheme 187).[325] In this report, both acyclic and cyclic alkenes bearing 8-aminoquinoline directing group tolerated

Scheme 186. Oxidative [4 + 2] Annulation Reactions of Acrylamides with Alkynes



Scheme 187. Iron-Catalyzed Cross-Coupling of Amides with Alkynes



smoothly with diverse internal alkynes. A diverse variety of synthetically useful functional groups including alkenyl, allyl, alkynyl, silyl, and thienyl were readily converted, thus showing the robustness of this strategy. More importantly, unsymmetrical internal alkyne produces the 2-pyridones with excellent regioselectivity.

Gratifyingly, transition-metal-catalyzed direct oxidative cyclization reactions of acrylamides with alkynes are not restricted to monoannulation. In 2017, the Sahoo group demonstrated an elegant example of Ru-catalyzed traceless sulfoximine DG-assisted oxidative double annulation of acrylamides with internal alkynes (Scheme 188a).[326] This one-pot protocol was able to assemble four bonds in a naked acrylamide substrate through a single operation, thereafter generating a variety of π-extended pyrido-fused-isoquinolinones which are widely encounter in numerous pharmaceutically relevant molecules and functional materials. Subsequently, the same group expanded this cascade annulation strategy to the annulation of acrylamides with alkynes and naphthoquinone, giving rise to an array of unusual spiro-fused-isoquinolones (Scheme 188b).[327]

Almost simultaneously, Fan and Zhang disclosed a Cp*Rh-catalyzed cascade [4 + 2] annulation/lactonization reaction between acryloyl hydroxamates and ynoates bearing a tertiary propargyl alcohol, which opened a rapid route to assemble γ-

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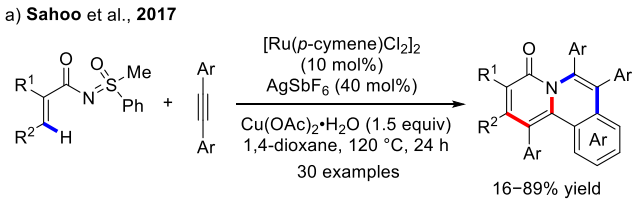
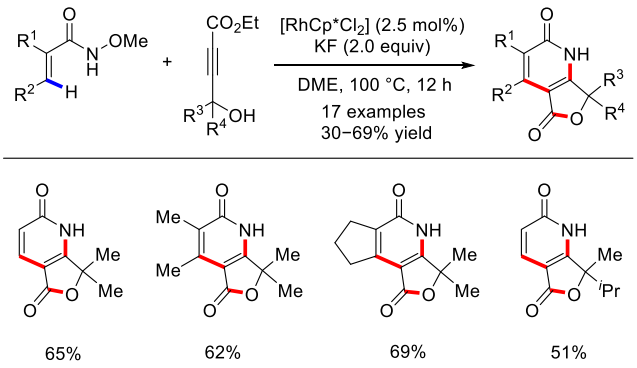
Scheme 188. Ru-Catalyzed Double Annulation of MPS-Enabled Acrylamides with Alkynes



lactone ring-fused pyridones (Scheme 189).[328] This redox-neutral protocol employed readily available starting materials,

Scheme 189. Cp*Rh(III)-Catalyzed Cascade Reactions of Vinylic *N*-Alkoxyamides with 4-Hydroxy-2-alkynoates

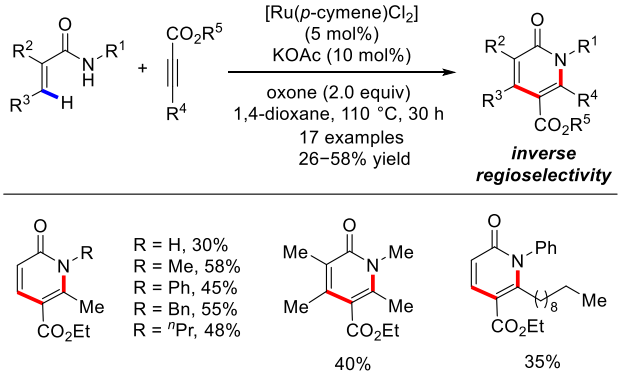


and occurred with high regioselectivity, which was greatly facilitated by the chelation assistance of Cp*Rh(III) catalyst with the hydroxyl group in the ynoates.

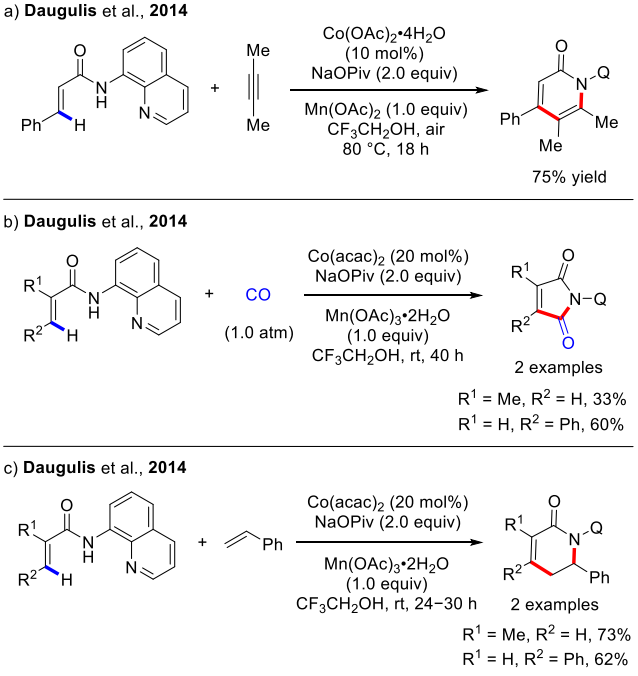
A similar regioselective oxidative annulation of acrylamides with 2-alkynoates through the Ru-catalyzed vinylic C−H activation was established by Mhaske and co-workers in 2019 (Scheme 190).[329] Contrary to the well-known Ru(II)- or Rh(III)-catalyzed annulation protocols, this strategy provided a complete reverse regioselectivity mainly due to the electron-withdrawing nature of the ester group in the 2-alkynoate substrates.

In 2014, Daugulis and colleagues illustrated the cobalt-catalyzed oxidative [4 + 2] annulation of C(sp^2)−H bond by using either picolinamide or aminoquinoline directing groups (Scheme 191a).[330] They used readily available cobalt(II) acetate tetrahydrate catalyst, $Mn(OAc)_2$ cocatalyst in conjunction with atmospheric oxygen as the terminal oxidant. Both internal and external alkynes were tolerated in this protocol. Moreover, the Daugulis group also reported a cobalt-catalyzed carbonylation of aminoquinoline benzamides with carbon monoxide by using atmospheric oxygen as an oxidant in trifluoroethanol solvent at room temperature (Scheme 191b).[331] $Mn(OAc)_3$ was used as an efficient cocatalyst in

Scheme 190. Ru-Catalyzed Regioselective Annulation of Acrylamides with 2-Alkynoates



Scheme 191. Directed Cobalt-Catalyzed Oxidative Annulation Reaction of Vinylic C−H Bonds with Carbon Monoxide, Alkenes, and Alkynes



this process. The corresponding imides were synthesized in good yields from acrylic and benzylic acid derivatives. Shortly after, they substantially extended their 8-aminoquinoline-directed, cobalt-catalyzed sp^2 C−H bond of cinnamic and methacrylic amides with alkenes to produce nitrogen-containing heterocycles (Scheme 191c).[332]

Incorporating fluorine atom into organic molecules is highly valuable because fluorine can provide special characteristics, including increasing the metabolic stability of the molecule and improving the lipophilicity. In 2020, Cramer and co-workers successfully managed to produce 4-fluoro-2-pyridones that are particularly difficult to construct with excellent regioselectivity and efficiency (Scheme 192).[333] This reaction took advantage of alkenic C−H activation, alkynyl triazene insertion, then Lossen rearrangement to afford a key intermediate. Subsequent addition occurs to generate a triazenyl molecule that can be further modified using Wallach reaction to generate the desired product. Additionally, the triazenyl moiety can be modified into fluorinated alkoxy and trifluoromethyl groups.

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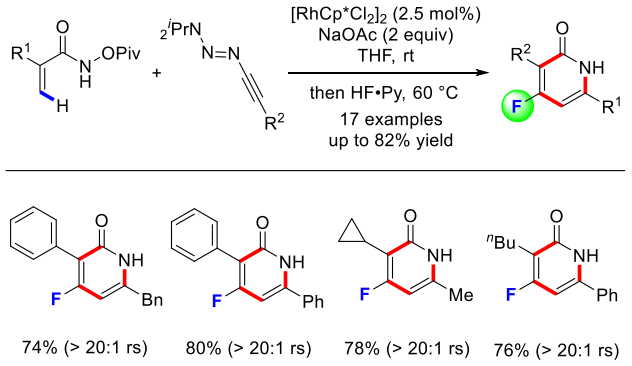
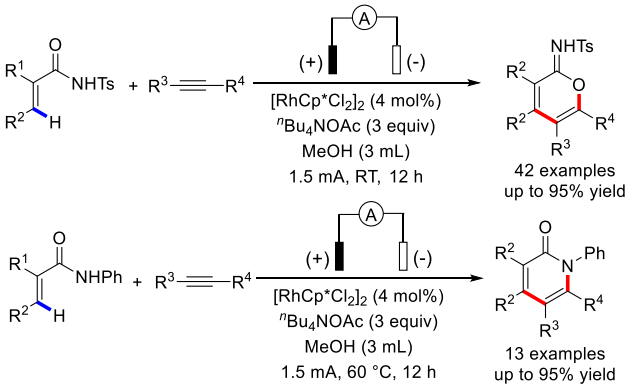
Scheme 192. Regioselective Access to 4-Fluoro-2-pyridones by a Cp*Rh(III)-Catalyzed C−H Activation-Lossen Rearrangement−Wallach Reaction



Mei and co-workers continued on their electrochemical transition metal catalysis strategy[334] and elaborated the synthesis of α-pyridones and α-pyrones *via* electrochemical C−H activation (Scheme 193).[335] In this report, the authors

Scheme 193. Divergent Rh-Catalyzed Electrochemical Vinylic C−H Annulation of Acrylamides with Alkynes

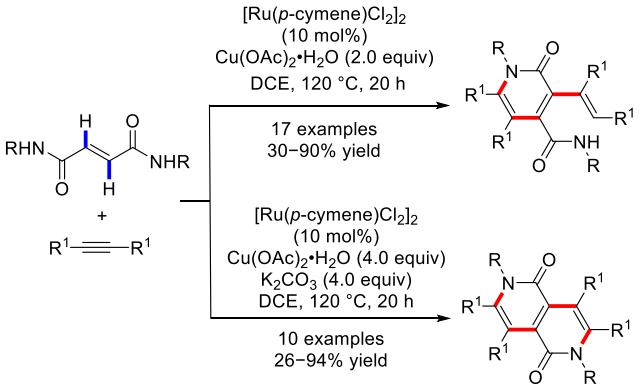


employed a series of acrylamides and alkynes. Depending on the substituents on nitrogen atom and reaction temperature, a variety of structurally diverse α-pyridones and α-pyrones were produced accordingly in excellent yields. It should be mentioned that the undivided electrolytic conditions employed in this protocol ultimately avoided the use of any external oxidant.

Moreover, a notable cascade oxidative vinylic C−H/N−H annulation/alkenylation sequence of fumaramides with various internal alkynes was achieved by means of ruthenium(II) catalysis (Scheme 194).[336] Alkynes bearing a wide range of electron-donating functionalities were well compatible, while electron-withdrawing alkynes furnished the respective product with diminished efficiency. Asymmetric terminal alkynes, however, were found to be incompatible in this protocol. Gratifyingly, in the presence of K_2CO_3 base, the reaction of fumaramides with alkynes proceeded efficiently under identical conditions, giving rise to 2,6-naphthyridine-1,5-diones as the major products.

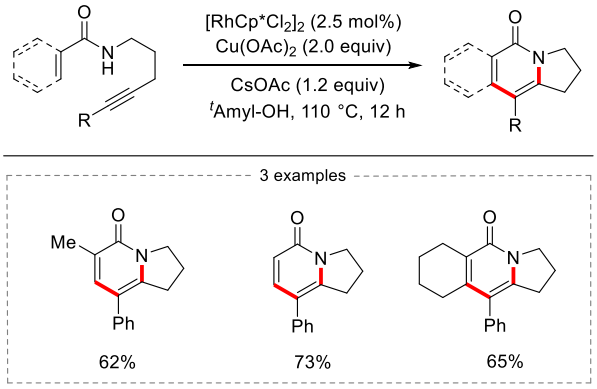
Apart from the intermolecular oxidative annulation reactions, Gulías, Mascareñas, and their co-workers in 2013 achieved a rhodium(III)-catalyzed the formal [4 + 2] annulation of alkyne-tethered acrylamides to readily generate tricyclic indolizinones derivatives with 62−73% yield in an

Scheme 194. Divergent Synthesis of Pyridones and Naphthyridinediones *via* Ru(II)-Catalyzed Double C(sp²)−H of Fumaramides with Alkynes



intramolecular fashion (Scheme 195).[337] The authors performed DFT studies, which suggested that the favored

Scheme 195. Intramolecular Cycloaddition Reaction of Acrylamides and Alkynes



migratory insertion of the alkyne moiety into the resulting rhodacycle generated from the initial C−H activation takes place into the Rh−N instead of the Rh−C bond in this process.

However, this intramolecular protocol requires a super-stoichiometric amounts of $Cu(OAc)_2$ as the external oxidant, leading to the generation of undesired waste. In 2012, the Park group successfully reported an atom-economical oxidizing-directing-group strategy that make use of alkynetethered hydroxamic esters as the substrates, affording diverse hydroxyalkyl-substituted isoquinolones with excellent regioselectivity and broad substrate scope (Scheme 196a).[338] Notably, the utility of this redox-neutral methodology is elegantly demonstrated by the facile total synthesis of phenanthroindolizidine alkaloids using this Cp*Rh(III)-catalyzed C−H activation as the key step. Inspired by this work, Meyer, Cossy, and co-workers later in 2019 further expanded this strategy toward the vinylic C−H functionalization of cyclobutenyl hydroxamates, enabling the rapid synthesis of cyclobuta[*c*]pyridines in decent yields (Scheme 196b).[339]

Another elegant example of intramolecular annulative reaction through the Cp*Rh(III)-catalyzed vinylic C−H activation strategy was disclosed by Meyer and Cossy. They employed a series of ω-alkynyl α-substituted acrylic hydroxamates to undergo macrocyclization to construct a large variety

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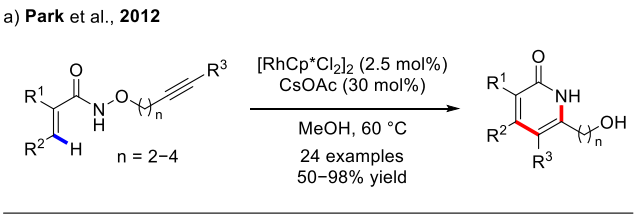
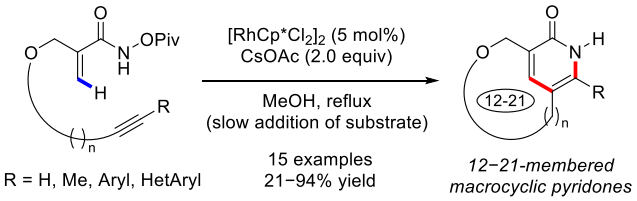
Scheme 196. Rhodium(III)-Catalyzed Intramolecular Annulation of Alkynetethered Hydroxamic Esters



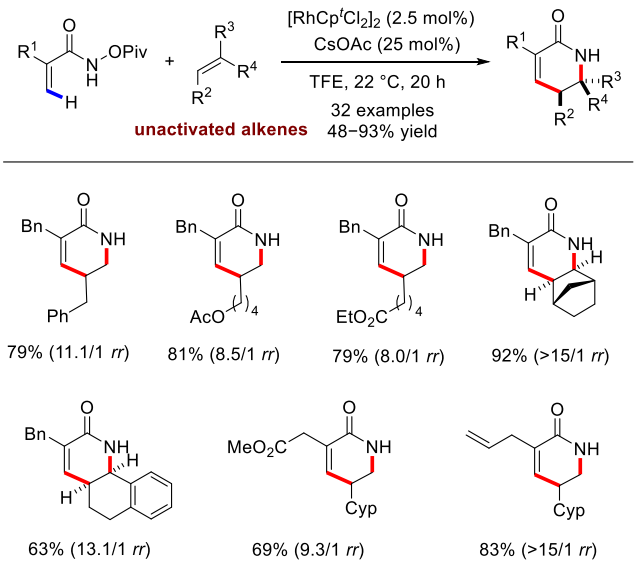
of structurally diverse 12- to 21-membered macrocyclic pyridones. The judicious choice of a *O*-pivaloyl hydroxamate as the effective oxidizing-chelating group was crucial for this strategy to achieve high efficiency (Scheme 197).[340]

Scheme 197. Synthesis of Macrocyclic Pyridones *via* Rh(III)-Catalyzed C−H Activation/Heterocyclization



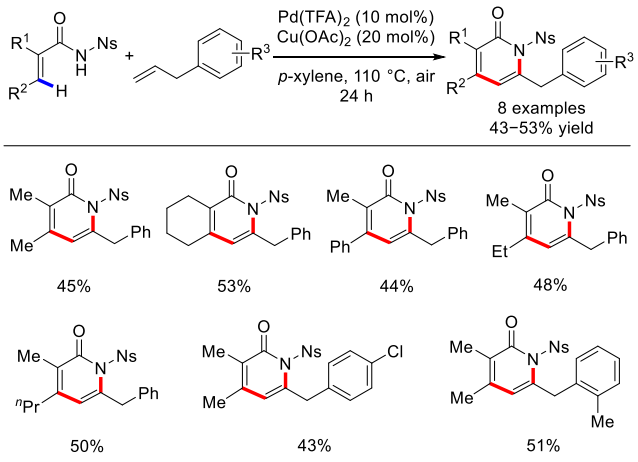
Due to the absence of suitable bias, the vinylic C−H olefination with aliphatic unbiased olefins often suffers from low reactivity and poor regioselectivity.[213] In 2019, Rovis and co-workers examined the formal oxidative [4 + 2] annulation of acrylamides with diverse both terminal and internal unbiased aliphatic alkenes (Scheme 198).[341] The regioselectivity of this reaction was greatly improved by the use of their modified bulky Cp^t ligand (Cp^t = 1,3-di-*tert*-butylcyclopentadienyl) on the Rh^{III} catalyst. A large variety of unprotected *α,β*-unsaturated-*δ*-lactams bearing a diverse array of functional groups were produced with modest to good yields and synthetically satisfactory regio/diastereoselectivity.

Scheme 198. Rh(III)-Catalyzed Oxidative [4 + 2] Annulation of Acrylamides with Unbiased Alkenes



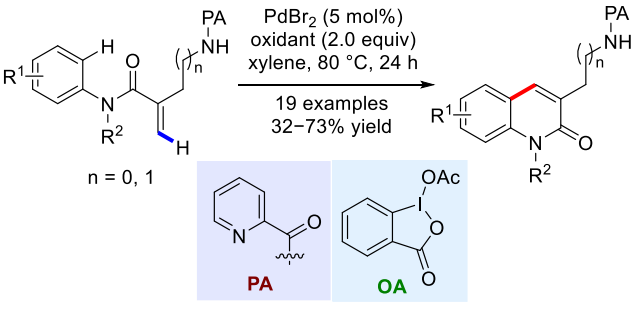
More recently, Wang, Sun, and colleagues elaborated a highly regioselective C−H functionalization/annulation reaction of *N*-sulfonyl acrylamides with unactivated allylbenzenes (Scheme 199).[342] The reaction occurred in the presence of 10 mol % Pd(TFA)$_2$ and 20 mol % Cu(OAc)$_2$ in conjunction with air as the terminal oxidant, which undergoes a C(sp^2)−H allylation/aminopalladation/*β*−H elimination/isomerization sequence, leading to an array of highly functionalized pyridinone derivatives in appreciable yields (43−53%).

Scheme 199. Palladium-Catalyzed Regioselective C−H Functionalization/Annulation of Acrylamides with Allylbenzenes for the Synthesis of Pyridinones



By taking advantage of the picolinamide (PA) directing group, Liu and co-workers were able to construct quinolinone scaffolds through an intramolecular oxidative *endo*-cyclization reaction of vinyl C(sp^2)−H and aryl C(sp^2)−H of *N*-aryl acrylamides (Scheme 200).[343] It is worth noting that the cyclic hypervalent iodine OA(III) is proven to be crucial for the reaction, delivering the expected cyclization product in satisfactory yields. Interestingly, a spiro product was formed for the substrate with incorporation of OMe in this case.

Scheme 200. Pd(II)-Catalyzed Intramolecular C(sp^2)−H/C(sp^2)−H Coupling of *N*-Aryl Acrylamides



Synthesizing *tetra*-substituted carbons are typically difficult in many cases, especially *via* C−H activation. However, Lu and co-workers were able to use *α*-allenols as the coupling partners

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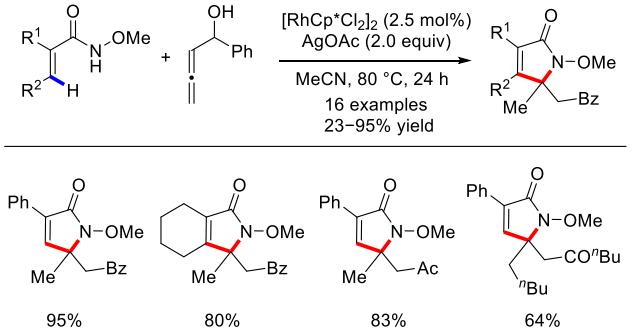
to couple with a γ-lactam containing a tetrasubstituted carbon in the presence of Cp*Rh(III) catalyst (Scheme 201).[344] In

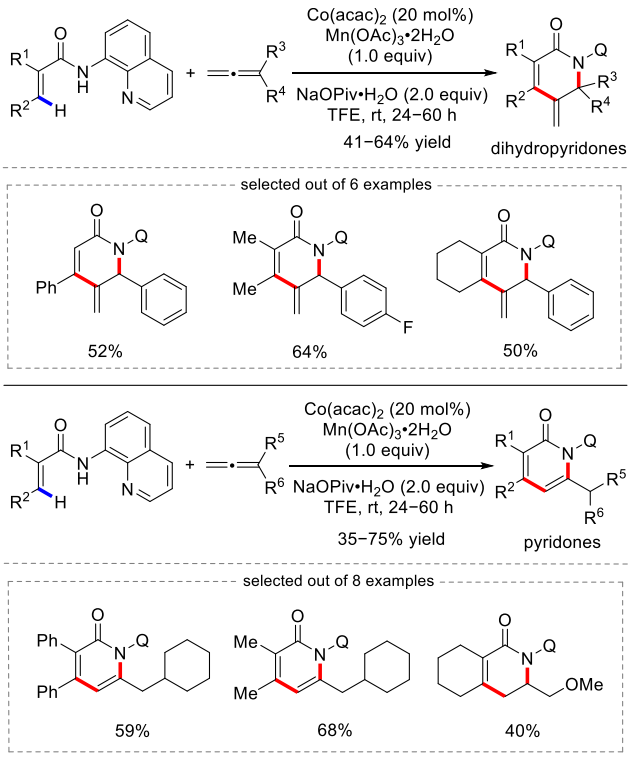
Scheme 201. Regiocontrolled Cross-Coupling of Vinylic Amides with α-Allenols



ensuring chemo- and regioselectivity, the coordination of hydroxyl group in α-allenols was found to be crucial as revealed from the detailed mechanistic studies. This regiocontrolled annulative [4 + 1] protocol provided an efficient route to produce a broad range of 1,5-dihydro-pyrrol-2-ones in synthetically useful yields.

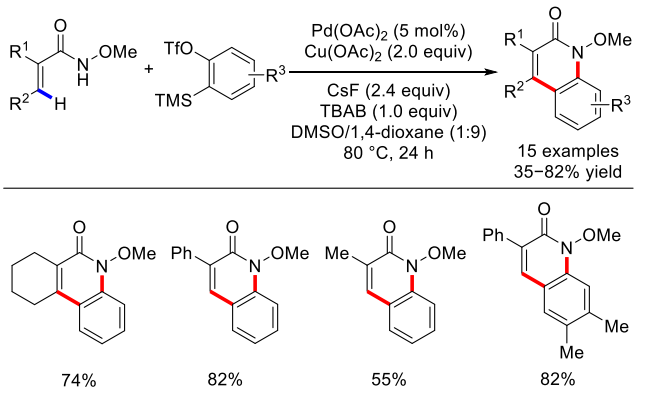
The slight variation of electronic or steric properties of allenes has the potential to alter their reactivity patterns of C−H activation reactions in many cases. For example, Maiti and Volla in 2016 detailed an efficient cobalt-catalyzed heterocyclization of acrylamides with allenes at room temperature (Scheme 202).[345] Here, the reaction of acrylamides with phenylallene and sterical 1,1-dimethylallene by readily available $Co(acac)_2$ smoothly afforded the corresponding dihydropyridone products, while the reaction with cyclohexylallene, methoxyallene, or electron-deficient allenes such as allenyl phosphonate exclusively resulted in the formation of pyridones. The authors argued that the different regioselectivity of the products may be mainly due to the back-donation of lone pair electrons from the oxygen atom of allene substrates.

Scheme 202. Synthesis of Dihydropyridones and Pyridones *via* Cobalt-Catalyzed Alkenyl C−H Activation of Acrylamides with Allenes



Besides the oxidative annulation with alkynes, alkenes, and allenes, Ma and Xu in 2015 successfully achieved an example of Pd(II)-catalyzed oxidative [4 + 2] annulation between acrylamides and arynes (Scheme 203).[346] In this protocol,

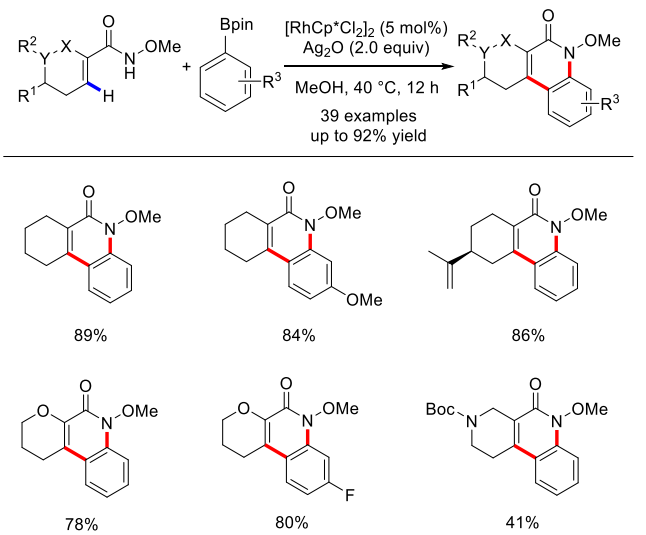
Scheme 203. Synthesis of Quinolinones *via* Palladium-Catalyzed Oxidative Annulation Reaction between Acrylamides and Arynes



the authors made use of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate as the benzyne precursors. Various aryne precursors bearing both electron-rich and electron-deficient groups could smoothly participate in this annulation reaction, producing the corresponding quinolinones in synthetically useful yields.

The Zhu group was able to construct the same scaffolds through an efficient Cp*Rh(III)-catalyzed alkenyl C−H functionalization of *N*-methoxycycloalkene carboxamides with aryl boronic acid pinacol esters (Scheme 204).[347] A variety of *N*-methoxycycloalkene carboxamide derivatives reacted smoothly with diverse aryl boronates in the presence of 5

Scheme 204. Cp*Rh(III)-Catalyzed Cross-Coupling of *N*-Methoxycycloalkene-1-carboxamides with Aryl Boronates



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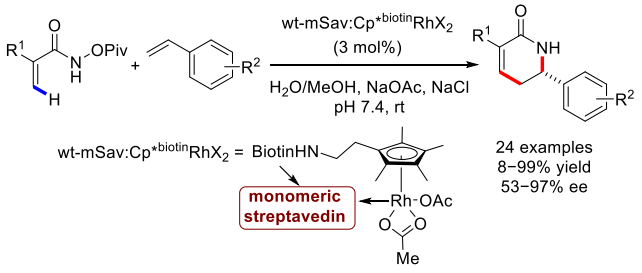
mol % $[RhCp^*Cl_2]_2$ catalyst and 2 equiv of Ag_2O oxidant to furnish the corresponding cycloalkaquinolinones in up to 92% yield. On the basis of detailed mechanistic investigations, the authors revealed that this annulative transformation may occur *via* a dual C−H activation pathway.

Even though asymmetric C−H activation is extremely useful for obtaining chiral compounds, controlling their stereochemistry is an extremely difficult task in some cases.[348−352] Enantioselective C−H functionalization often demands harsh reaction conditions and high temperature that are incompatible with many asymmetric reactions. While the asymmetric C−H activation in the presence of Pd catalyst has gained much traction, catalytic asymmetric C−H activation in aryls have seen advancements due to the development of chiral cyclopentadienyl ligands and chiral acid adducts in past decades. Unfortunately, not much discovery has been done on C−H activation in alkenes.

Lately, an innovative synthetic metalloenzymes (ArMs) system has been established by the Rovis and McNaughton group. This is achieved by inserting a Cp*Rh unit in the mSav active site to asymmetrically produce α,β-unsaturated-δ-lactams, which is done by alkenic C−H activation (Scheme 205).[353] This [4 + 2] annulativeprotocol made use of

Scheme 205. Asymmetric δ-Lactam Synthesis with a Monomeric Streptavidin Artificial Metalloenzyme

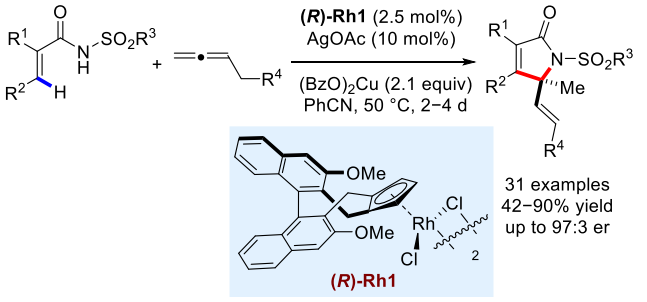


monomeric streptavidin (mSav)-Rh(III) to catalyze the reaction instead of previous mechanisms that use biotin--tetrameric streptavidin (biotin-tSav) that was established by Whitesides[354] and Ward.[355] This new concept is efficient and provides up to 99% yield and enantiomeric excess of 97% under mild and aqueous conditions. Notably, the products can also subsequently be easily converted into enantioenriched piperidines.

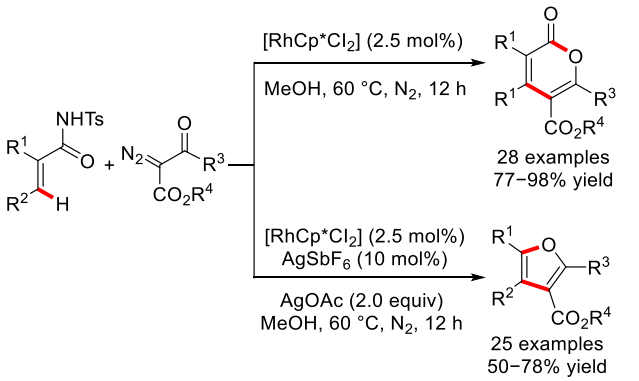
Cramer and co-workers in 2019 revealed another strategy to enantioselectively activate the alkenyl C−H bonds to obtain enantioenriched α,β-unsaturated γ-lactams bearing a quaternary stereocenter by means of a chiral Rh(III) catalyst (Scheme 206).[356] This procedure can be used on a wide variety of acrylamides and allenes to provide an excellent enantioselectivity of up to 97:3 er.

In 2015, Wang *et al.* illustrated the general protocol for the Cp*Rh(III)-catalyzed cyclization reaction of *N*-methoxymethacrylamides and diazo compounds to construct pyridone derivatives.[357] In the following year, Ma and co-workers presented the Cp*Rh(III)-catalyzed cyclization of *N*-tosylacrylamides with diazoacetoacetates to readily construct a series of multisubstituted α-pyrones under redox-neutral conditions (Scheme 207).[358] More interestingly, the reaction between *N*-tosylacrylamides and diazoacetoacetates could also selectively undergo a formal oxidative [2 + 3] cyclization in the presence AgOAc as the oxidant *via* sequential C−H and C−C cleavage

Scheme 206. Synthesis of 2*H*-Pyrrol-2-ones through [4 + 1] Annulation of Acryl Amides and Allenes



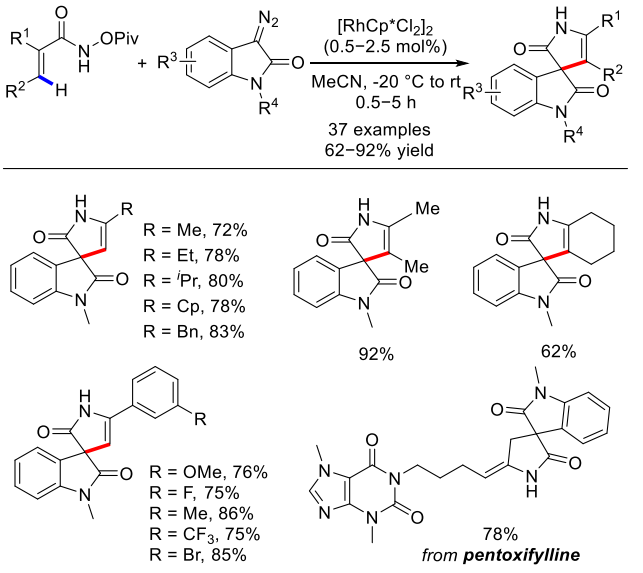
Scheme 207. Rh(III)-Catalyzed Oxidative Cyclization of Acrylamides with Diazo Compounds



to assemble highly functionalized furans. Of note, the authors employed readily available acylsulfonamide as an oxidizing or a traceless directing group in this controllable protocol.

Later in 2019, Dai and co-workers detailed a domino annulation strategy to construct spirooxindole pyrrolones using C−H activation reaction under Cp*Rh(III) catalysis together with Lossen rearrangement (Scheme 208).[359] As a particular highlight, the annulation of *N*-pivaloyloxy benzamides with

Scheme 208. Synthesis of Spirooxindole Pyrrolones by Cp*Rh(III)-Catalyzed Vinylic C−H Activation/Carbene Insertion/Lossen Rearrangement Sequence



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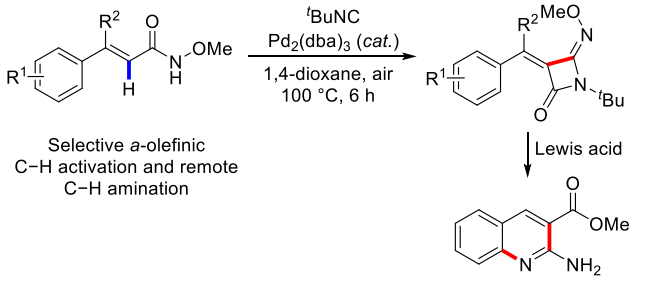
diazo compounds is also demonstrated by late-stage diversification of pentoxifylline, endofolliculina, and pregnenolone. In this report, the vinylic C−H bond is activated to afford an intermediate followed by carbene migratory insertion to generate alkyl rhodium species. Subsequent Lossen rearrangement occurs on this intermediate to generate another intermediate, which then goes through nucleophilic addition and protonation to unambiguously furnish the spirooxindole pyrrolones.

Despite of the remarkable advances on the above-mentioned β-olefinic C−H activation reactions which involves five-membered cyclometalation intermediates, the α-selective alkenyl C(sp^2)−H functionalization of α,β-disubstituted acrylamides has been seldom reported. In 2016, an elegant study by Yu and co-workers elaborated the palladium-catalyzed α-olefinic C−H functionalization of diverse α,β-unsaturated olefins with *t*-BuNC (Scheme 209).[360] By activating of α-olefinic C−H bonds, the synthesis of highly *cis*-stereoselective 4-imino-β-lactam was readily achieved. This protocol tolerated a broad range of heterocycles at the β-position using air as the sole oxidant. Upon the treatment of $BF_3{\bullet}OEt_2$, the obtained products can be easily converted into 2-aminoquinoline derivatives, which are privileged scaffolds widespread in many natural products and pharmaceutically relevant molecules.

Scheme 209. Synthesis of 4-Imino-β-Lactams *via* Pd-Catalyzed α-Selective C−H Functionalization of Olefins



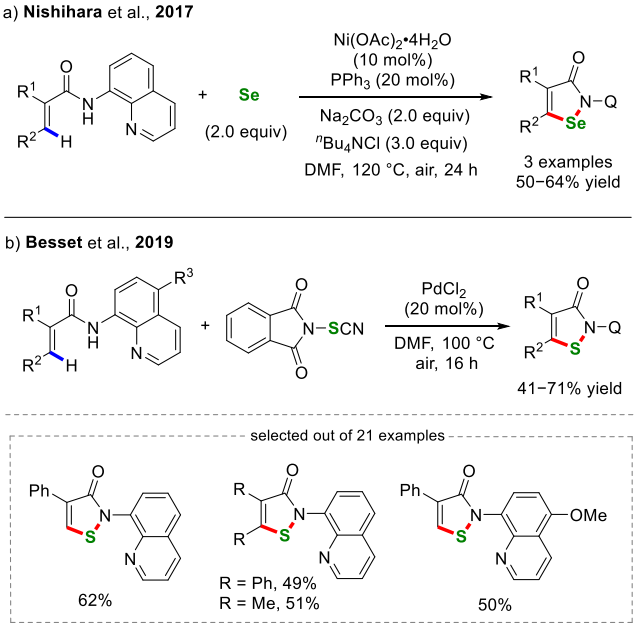
Moreover, the nickel-catalyzed oxidative [4 + 1] annulation of α,β-unsaturated amides bearing the 8-aminoquinoline auxiliary with elemental selenium has been reported by Nishihara and co-workers under aerobic conditions (Scheme 210a),[361] which provides an alternative route to isoselenazolones in synthetically acceptable yields (50−64%). Shortly afterward, Besset's group realized the synthesis of functionalized isothiazolone derivatives from α,β-unsaturated acrylamides and an electrophilic SCN reagent through an aerobic palladium-catalyzed vinylic C−H Bond activation (Scheme 210b).[362]

Nitriles are the key structural unit widely found in numerous organic molecules, and the direct redox-neutral nucleophilic addition to nitriles undoubtedly exhibits a better atom- and step-economy. More recently, Chen and co-workers investigated the inert C−H addition to nitriles and accomplished the Cp*Rh(III)-catalyzed vinylic C(sp^2)−H addition to phenoxyacetonitriles nitriles followed by an annulation sequence, giving rise to a broad set of 1,5-dihydro-2*H*-pyrrol-2-ones in a one-pot manner with decent efficiency (40−81%). Besides acrylamides, the aryl counterparts were also proven to be viable C−H sources in this strategy (Scheme 211).[363]

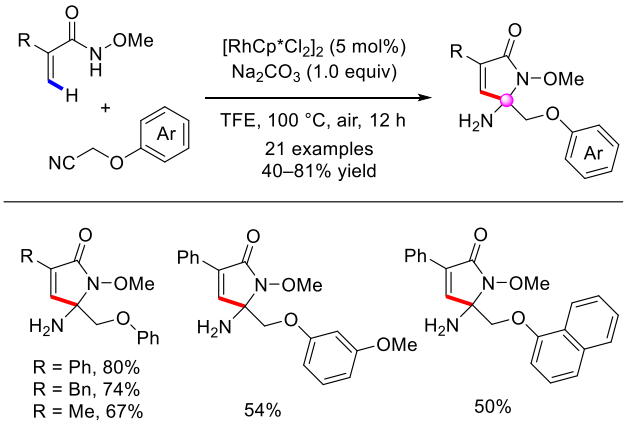
4.3.9. Other Useful Reactions. In 2015, Zhang and co-workers studied the nickel-catalyzed direct vinylic C−H thiolation of alkenes and arenes with diverse diaryl disulfides (Scheme 212).[364] Here, the authors employed 10 mol % $NiCl_2$, 4 equiv of TBAI in conjunction with 2 equiv of sodium carbonate in DMSO at 100 °C to produce alkenyl sulfides and diaryl sulfides in good yields with a broad range of functional group tolerance.

Later in 2018, Wang and Ji disclosed an efficient approach for the vinylic C−H thiolation through the assistance of a weakly coordination *N*-tosylamide group in the presence of 2 mol % $[RhCp^*Cl_2]_2$ catalyst, 50 mol % of silver carbonate, and copper acetate in DMF at 80 °C (Scheme 213).[365] A diverse range of (*Z*)-alkenyl sulfides were synthesized in excellent yields. Notably, this protocol tolerated a large variety of functional groups, and up to 7100 of turnover numbers were obtained for this transformation using as low as 0.01 mol % Cp*Rh(III) catalyst. The authors showcased the applicability of this protocol for the synthesis of (*Z*)-β-alkenyl selenides under identical conditions. Quite recently, Yu and co-workers

Scheme 210. Synthesis of Isoselenazolones and Isothiazolones through Vinylic C−H Activation



Scheme 211. Synthesis of 1,5-Dihydro-2*H*-pyrrol-2-ones by Cp*Rh(III)-Catalyzed Vinylic C(sp^2)−H Addition to Aliphatic Nitriles



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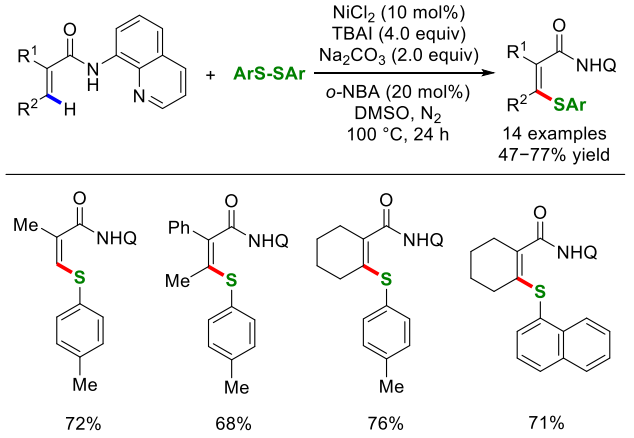
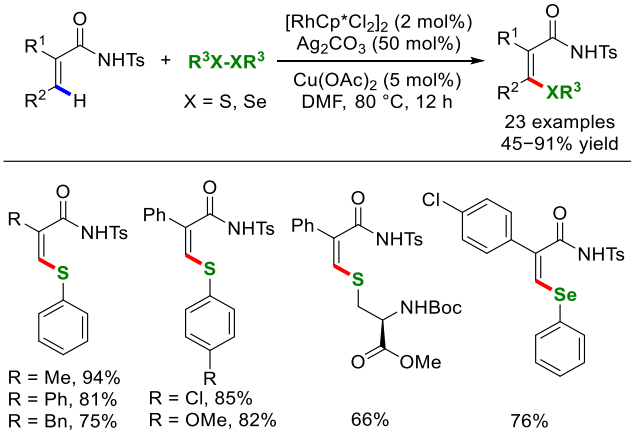
Scheme 212. Nickel-Catalyzed Vinylic C−H Thiolation of Acrylamides



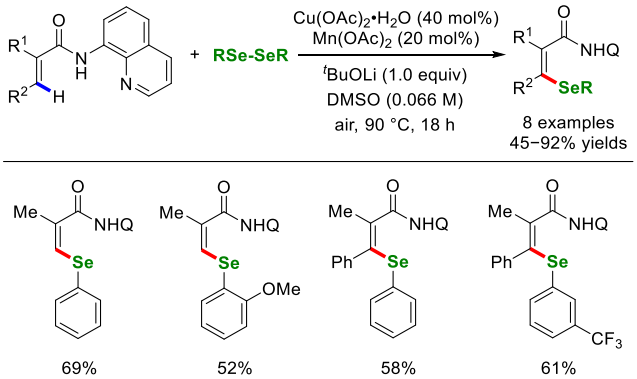
Scheme 213. Cp*Rh(III)-Catalyzed C−H Thiolation of *N*-Tosyl Acrylamides



also achieved an analogous olefinic C−H thiolation of *N*-2,6-difluoroaryl acrylamides with comparable efficiency.[366]

In 2017, the Jana group investigated a dual copper/manganese-catalyzed selenation of both acrylic and benzoic acids by using 8-aminoquinoline auxiliary as the directing group (Scheme 214).[367] In presence of 40 mol % $Cu(OAc)_2 \bullet H_2O$ and 20 mol % $Mn(OAc)_2$ in DMSO at 90 °C, a variety of (*Z*)-vinyl selenides were synthesized in good yields. Lithium *tert*-butoxide was used as a base for this trans-

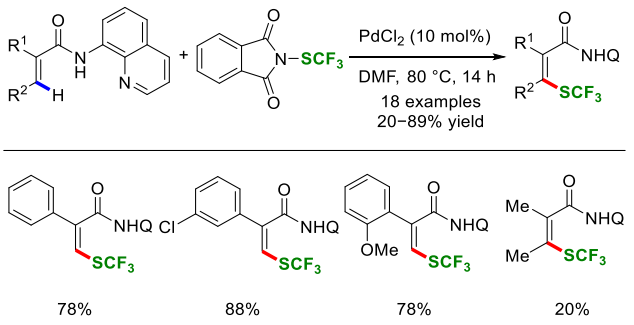
Scheme 214. Copper/Manganese Cocatalyzed Vinylic C−H Selenation of Alkenes



formation while atmospheric oxygen is used as a terminal oxidant.

A highly regioselective Pd-catalyzed chelation-assisted vinylic C−H bond trifluoromethylthiolation of acrylamides bearing the 8-aminoquinoline auxiliary was achieved by Bouillon and Besset in 2017 (Scheme 215).[368] The reaction

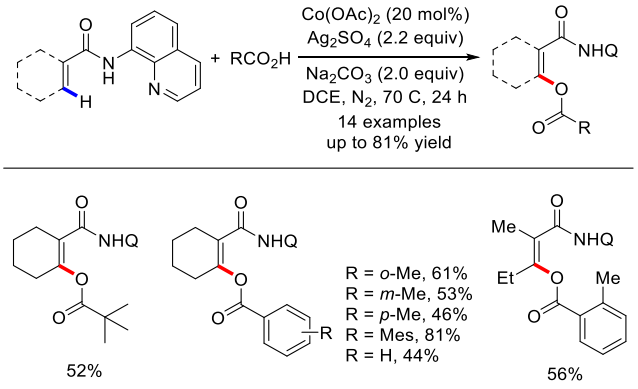
Scheme 215. Pd(II)-Catalyzed Directed Vinylic C−H Trifluoromethylthiolation of Acrylamides



tolerates a diverse array of α,β-unsaturated acrylamides bearing different substitution patterns and affords the corresponding SCF_3-containing alkenes with complete *Z*-selectivity. The authors tentatively proposed a plausible Pd(II)/Pd(IV) catalytic mechanism for this protocol.

In 2018, Zhang *et al.* reported a general oxidative C−H/O−H cross-coupling reaction enabled by a $Co(OAc)_2$ catalyst for the selective vinylic C−H acyloxylation (Scheme 216).[369] 8-

Scheme 216. Cobalt(II)-Catalyzed C−H Acyloxylation of Acrylamides



Aminoquinoline directing group was installed and used as the directing group for the acyloxylation of alkenes and arenes. A wide range of esters were readily synthesized from corresponding acids in the presence of 20 mol % $Co(OAc)_2$, silver sulfate, and sodium carbonate in DCE under N_2 atmosphere at 70 °C. The oxidant silver sulfate, although used in excess, could be recovered back. The recyclable directing group makes this protocol as a robust strategy for the acyloxylation for the alkenyl carboxamides.

Sulfones are an important class of organic molecules which can be served as versatile building blocks in a number of synthetic transformations, including classical Julia olefination and Ramberg−Backlund reaction. The direct functionalization of inert C−H bonds represents an atom- and step-economical strategy to construct structurally diverse sulfones.[370] Recently, a highly stereoselective and straightforward synthesis of (*Z*)-β-

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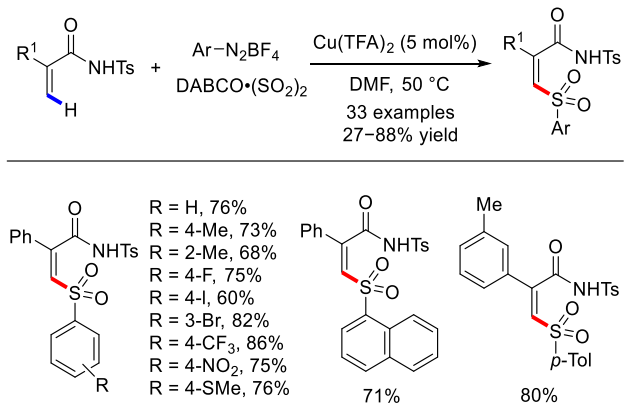
alkenyl sulfones through the copper-catalyzed reaction of *N*-tosyl acrylamides, 1,4-diazabicyclo[2.2.2]octane-sulfur dioxide surrogate in conjunction with aryldiazonium tetrafluoroborates, has been accomplished by Wu and co-workers (Scheme 217).[371] In the presence of copper trifluoroacetate, the vinylic

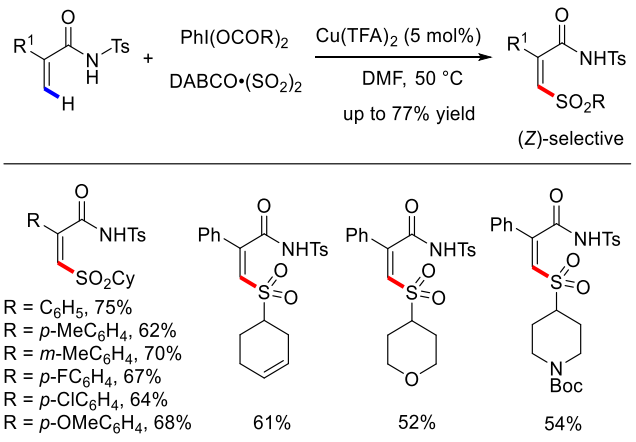
Scheme 217. Copper-Catalyzed C−H Arylsulfonylation of Acrylamides with Sulfur Dioxide



C(sp^2)−H arylsulfonylation of acrylamides with sulfur dioxide (SO_2) as the sulfonyl source proceeds smoothly, leading to diverse (*Z*)-*β*-alkenyl sulfones with excellent regio- and stereoselectivities.

Meanwhile, the Wu group further extended to report the direct C(sp^2)−H alkylsulfonylation of *N*-tosyl acrylamides (Scheme 218).[372] The reaction was conducted in DMF at 50

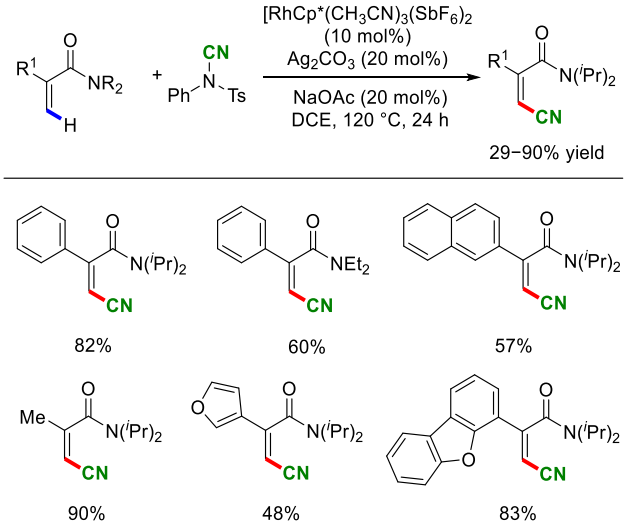
Scheme 218. Copper-Catalyzed Three-Component Decarboxylative Alkylsulfonylation



°C using $Cu(TFA)_2$ as the catalyst. Phenyliodine(III) dicarboxylates were employed as the alkyl radical precursors with *N*-tosyl amidyl group as a weakly coordinating directing group. This copper-catalyzed three-component reaction provided diverse (*Z*)-*β*-alkenyl alkylsulfones in satisfactory yields.

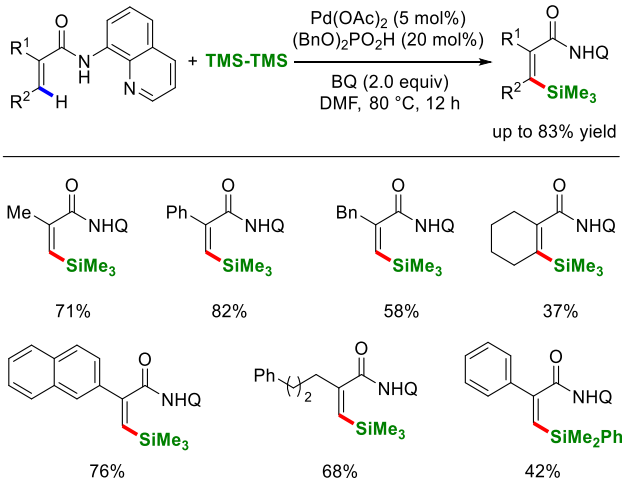
In 2015, Fu's group detailed a practical and highly efficient Cp*Rh(III)-catalyzed vinylic C−H cyanation reaction of various acrylamides and ketoximes with readily prepared, environmental friendly *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) as the cyanation reagent (Scheme 219).[373] The protocol tolerated a variety of synthetically useful functional groups, allowing for the synthesis of versatile alkenyl nitriles in up to 90% yield.

Scheme 219. Rhodium(III)-Catalyzed Vinylic C−H Cyanation of Acrylamides



The direct synthesis of vinylsilanes attracts special attention from synthetic community as they are an important class of valuable building blocks widely used in synthetic chemisty (Hiyama−Denmark coupling, Tamao−Fleming oxidation, *etc.*), polymers, and medicines.[374,375] In 2017, Zhang and coworkers elaborated a stereoselective palladium(II)-catalyzed vinylic C(sp^2)−H silylation of acrylamides with disilanes as the silicon source (Scheme 220).[376] The bidentate 8-aminoquino-

Scheme 220. Pd(II)-Catalyzed Vinylic C−H Silylation of Acrylamides with Disilanes



line amide directing group was readily employed to exclusively produce *Z*-vinylsilanes in synthetically satisfactory yields. Unboubtedly, the use of environmentally benign 1,4-benzoquinone (BQ) as a nonmetal oxidant significantly enables this strategy to be synthetically appealing for the synthesis of *Z*-stereoselective vinylsilanes from readily available starting materials.

The formation of C−O bonds is one of the fundamental reactions in synthetic chemistry. In 2015, Niu and Song

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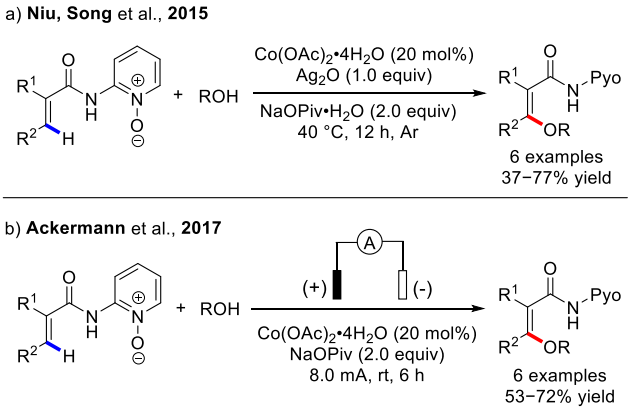
successfully realized an inexpensive, earth-abundant cobalt-catalyzed vinylic C(sp^2)−H alkoxylation of both aromatic and olefinic carboxamides using their 2-aminopyridine-1-oxide as a removable *N,O*-bidentate auxiliary (Scheme 221a).[377] Indeed,

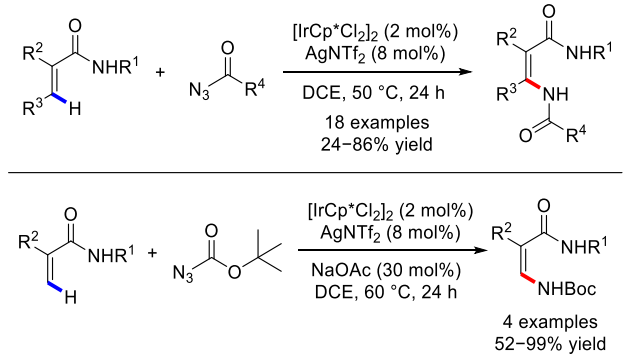
Scheme 221. Direct Alkoxylation of Acrylamides through Vinylic C−H Activation



the reaction worked smoothly under typically mild conditions and tolerated a broad range of both alcohols and amide substrates. Following this, Ackermann's group in 2017 devised an electrochemical cobalt-catalyzed alkenyl C−H alkoxylation of acrylamides, which substantially avoided the use of stoichiometric silver(I) oxidants, providing a sustainable strategy to the synthesis of enolether derivatives (Scheme 221b).[378]

In 2013, Chang *et al.* exploited the Cp*Ir(III)-catalyzed olefinic C−H amidation of *α,β*-unsaturated acrylamides by means of acyl azides as the nitrogen source (Scheme 222).[379]

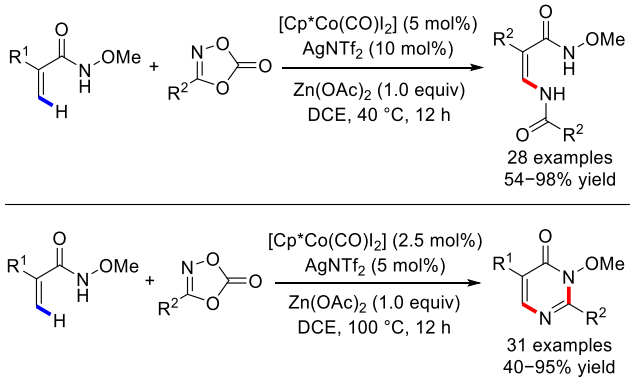
Scheme 222. Ir(III)-Catalyzed Vinylic C−H Amidation of Acrylamides with Acyl Azides and Azidoformates



A broad range of acyl azides bearing various functional groups could readily be employed under mild conditions. This protocol obviates the use of external oxidants and releases N_2 gas as the only byproduct, affording an environmentally benign access to a variety of *Z*-enamides with excellent regio- and stereoselectivity. Subsequently, the same group expanded to report a vinylic C−H amidation with azidoformates as an easily deprotectable amino source, which eventually gives rise to *N*-protected enamines (Scheme 222).[380]

Li's group was able to assemble synthetically useful enamides *via* a cost-effective Cp*Co(III)-catalyzed alkenyl C−H amidation of *N*-methoxy acrylamides with dioxazolones as an amidating reagent (Scheme 223).[381] Interestingly, elevating the reaction temperature to 100 °C, the resulting

Scheme 223. Cp*Co(III)-Catalyzed Amidation of Olefinic C−H Bonds

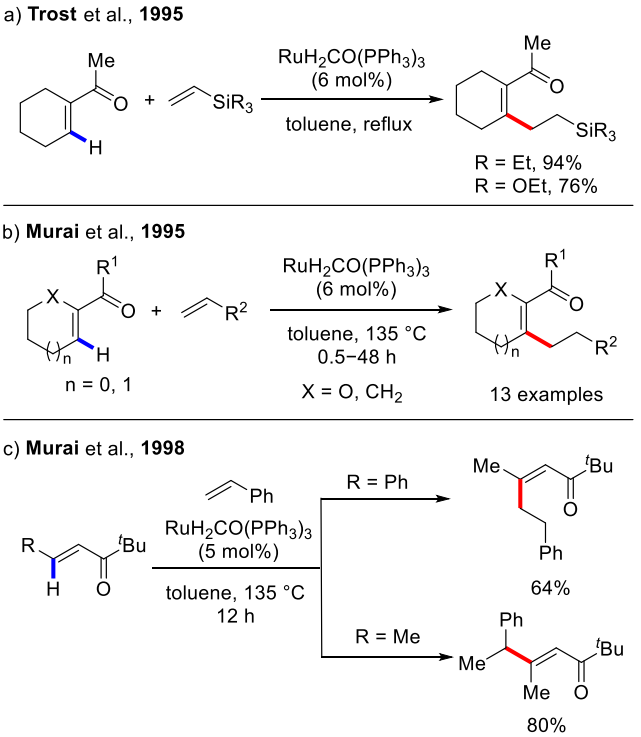


enamides could further undergo a dehydrative cyclization to afford pyrimidones, which can act as a ready directing group for subsequent second aryl C−H amidation to generate diamidated products in high yields.

4.4. *α,β*-Unsaturated Ketones

In 1995, Trost and colleagues first elaborated the Ru(0)-catalyzed alkenyl C−H alkylation of 1-acetylcyclohexene with vinylsilanes, giving rise to the linear products in 94% and 76% yield, respectively (Scheme 224a).[231] Around the same time, Murai's research group also achieved this transformation with a broader olefin scope (Scheme 224b).[382] In this report, both five- and six-membered *α,β*-enones worked well with diverse alkenes such as vinylsilanes, styrenes, and vinylcyclohexane to

Scheme 224. Ru(0)-Catalyzed Vinylic C−H Alkylation of *α,β*-Unsaturated Ketones



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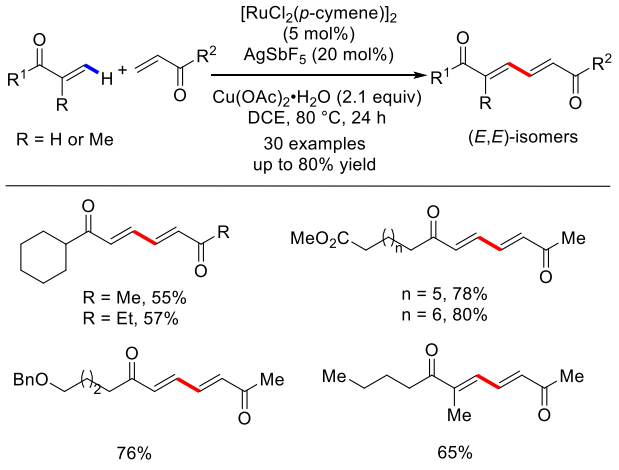
furnish the vinylic C−H alkylation products in 20% to quantitative yields. Later in 1998, Murai and co-workers further expanded to establish a stereodivergent C−H alkylation by using acyclic *α,β*-enones as substrates (Scheme 224c).[383] Specifically, the reaction between phenylsubstituted *trans*-enone and styrene exclusively delivered the linear alkylated product with retention of the olefin geometry, while the methyl-substituted *trans*-enone generated a branched product with inversion of the olefin geometry. The authors tentatively outlined a C−H activation and a hydrometalation pathway to elucidate this discovery.

Vinyl ketones were seldom utilized as coupling partners in cross-coupling reactions due to their potential to undergo homodimerization or polymerization. Quite recently, Dethe *et al.* investigated the viability of direct coupling reactions between two different vinyl ketones. They exploited the cost-effective ruthenium(II) catalysis for the stereoselective oxidative coupling of vinyl ketones (Scheme 225).[384]

Scheme 225. Ruthenium(II)-Catalyzed Stereoselective Oxidative Cross-Coupling of Vinyl Ketones

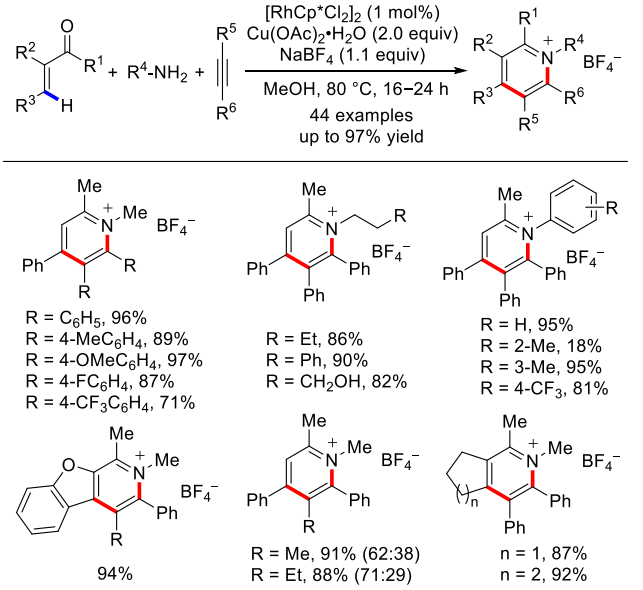


Markedly, a broad range of vinyl ketones were identified as viable substrates in this protocol, giving rise to highly functionalized (*E,E*)-1,6-dioxo-2,4-dienes in appreciable to good yields. Nevertheless, appreciable amounts of homocoupling product were observed in most cases. Moreover, this strategy was applicable to the direct synthesis of some bioactive natural products.

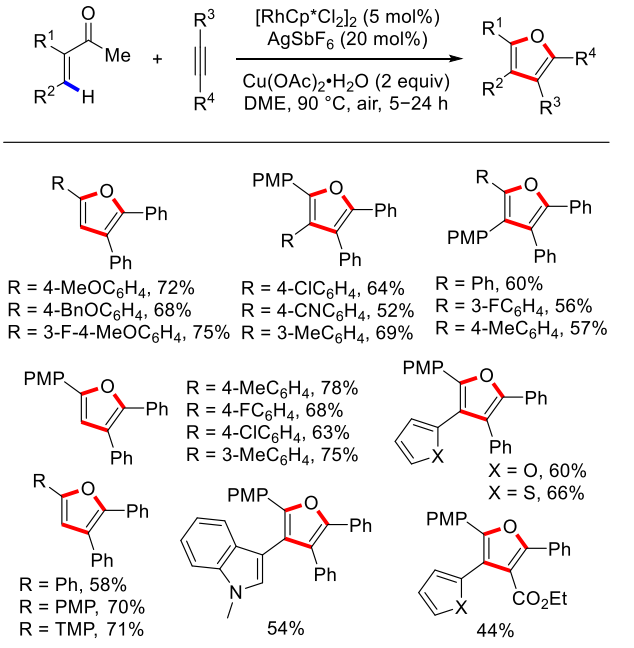
Alkene annulations have been getting more recognition in recent years. Cheng and co-worker disclosed a multicomponent reaction to produce highly substituted pyridinium salts in 2015 (Scheme 226).[385] The authors proposed that the imine was produced *in situ* and underwent oxidative coupling with alkynes to obtain highly substituted pyridinium salts.

You's group elaborated a general method for producing ploysubstituted furans by ketone-directed vinylic C−H annulation of *α,β*-unsaturated ketones with alkynes under synergistic Rh/Cu catalysis (Scheme 227).[386] A series of tri- and tetra-substituted furans can be synthesized through the vinylic C−H activation, followed by [4 + 2] annulation and ring contraction processes. This reaction mechanism is supported by ^{18}O-labeling experiments and intermediate verification reactions. The series of reactions begin when the alkene C−H bond is activated, allowing the alkyne to be inserted and hence forming a seven-membered rhodacycle.

Scheme 226. Synthesis of Pyridinium Salts *via* Rhodium(III)-Catalyzed Alkenyl C−H Activation



Scheme 227. Synthesis of Ploysubstituted Furans *via* Cp*Rh(III)-Catalyzed Alkenyl C−H Activation *α*-Aryl Enones with Alkynes



This process is directed by the ketone group. The intermediate pyrylium salt is then produced *via* reductive elimination to give the [4 + 2] *O*-annulation intermediate. The Rh(I) salt is also produced. The superoxide radical then undergoes nucleophilic attack to give a hydroperoxide intermediate, and then heterolysis of the O−O bond occurs with intramolecular cyclization to give *O*-acylated furanium. The final desired product is then produced *via* hydrolysis.

Following this, the same group further published an efficient synthesis of 1*H*-benzo[*f*]chromene derivatives by the reaction between exocyclic *α,β*-enones and alkynes under Cp*Rh(III) catalysis (Scheme 228).[387] This strategy underwent the formal [4 + 2] vinylic C−H *O*-annulation to afford the active pyrylium

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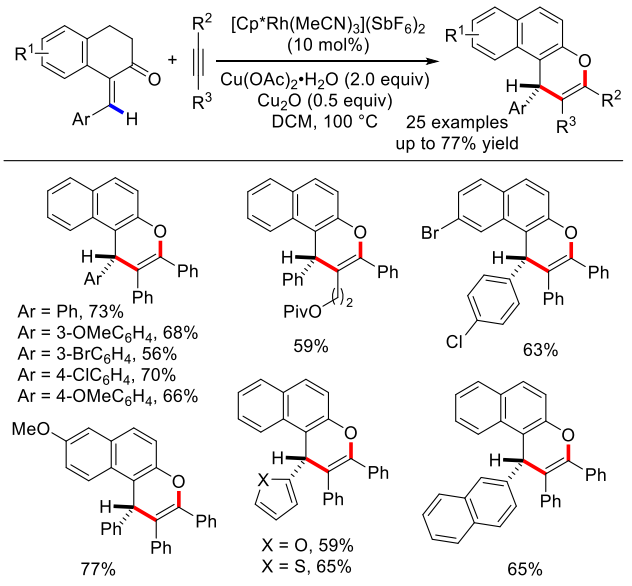
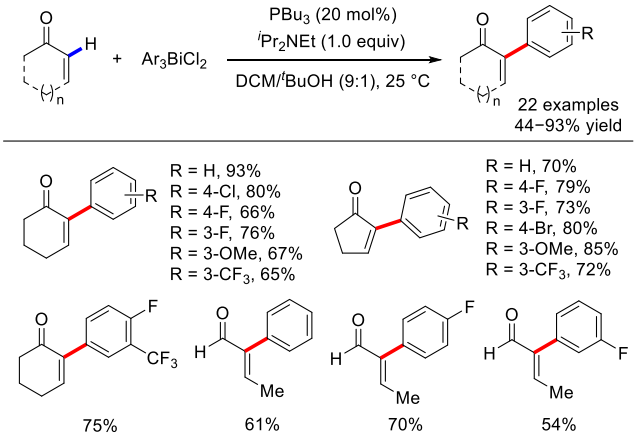
Scheme 228. Cp*Rh(III)-Catalyzed [4 + 2] Vinylic C−H *O*-Annulation of Exocyclic Enones with Alkynes and 1,5-H Shift



salts as the intermediates, which subsequently participated in a base-promoted 1,5-H shift process. By using this protocol, a scope of 25 examples was documented in decent yields.

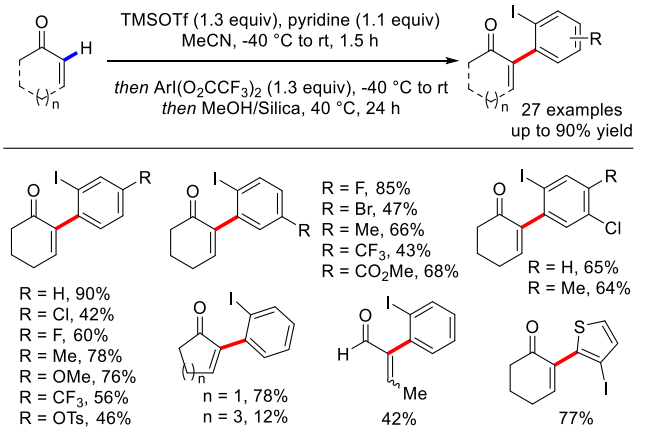
In addition to these annulation reactions, significant advances on the vinylic α-C−H functionalization of α,β-enones has been made over the decades. Specifically, when exposure of cyclic enones or enals to $BiAr_3Cl_2$ and Hunig's base (DIPEA) in the presence of a catalytic amount of tributylphosphine at room temperature, an array of α-arylated enones and enals were smoothly produced in decent yields (44−93%) (Scheme 229).[388]

Scheme 229. Phosphine-Catalyzed α-Arylation of Enones and Enals Using Hypervalent Bismuth Reagents



Recently, Wengryniuk and co-workers established an alternative approach for the synthesis of α-arylated enones through a metal-free alkenyl C−H arylation mediated by hypervalent iodine(III) reagents (Scheme 230).[389] The reaction occurred *via* a novel reductive iodonium Claisen rearrangement of the *in situ*-generated β-pyridinium silyl enol ethers. A broad scope of 27 examples was documented with yield up to 90%. Interestingly, the incorporated arenes

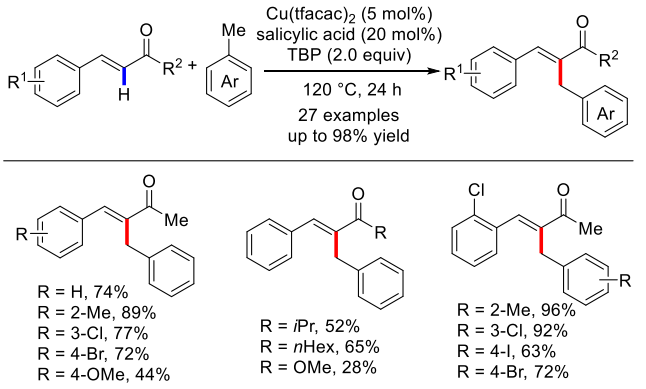
Scheme 230. Metal-Free Vinylic C−H Arylation of Enones Mediated by Hypervalent Iodine Reagents



maintained the synthetically valuable iodine functional handle, enabling further elaboration by traditional cross-coupling reactions.

Huang and collaborators in 2015 developed an efficient method to assemble functionalized α-benzylated enones (Scheme 231).[390] The authors discovered that a reaction

Scheme 231. Copper-Catalyzed Regioselective Alkenyl C−H Benzylation of Enones with Toluenes



between enones and simple toluenes in the presence of $Cu(tfacac)_2$ (tfacac = $CF_3COCHCOCH_3$) catalyst generated a series of α-substituted enones containing different groups. In this report, a broad scope of 27 examples was presented with yield up to 98%. This oxidative coupling protocol made use of di-*tert*-butyl peroxide (TBP) as the oxidant to trigger the generation of benzyl carbon radical. Notably, methyl cinnamate could be also used as the substrate in this case, albeit with a lower yield (28%).

Cho's group elaborated a practical route for the easy preparation of α-trifluoromethylthio-α,β-unsaturated carbonyls in decent yields *via* a highly efficient DABCO-mediated alkenyl C−H trifluoromethylthiolation of diverse α,β-unsaturated carbonyls by using easily available *N*-trifluoromethylthiodibenzenesulfonimide as the SCF_3 source (Scheme 232).[391] Impressively, the reaction occurred smoothly at room temperature and was well compatible with a myriad of α,β-unsaturated esters to afford the corresponding products in satisfactory yields.

An impressive work by Hwang and Ryu uncovered the catalytic carbon insertion into the β-vinyl C−H bond of cyclic

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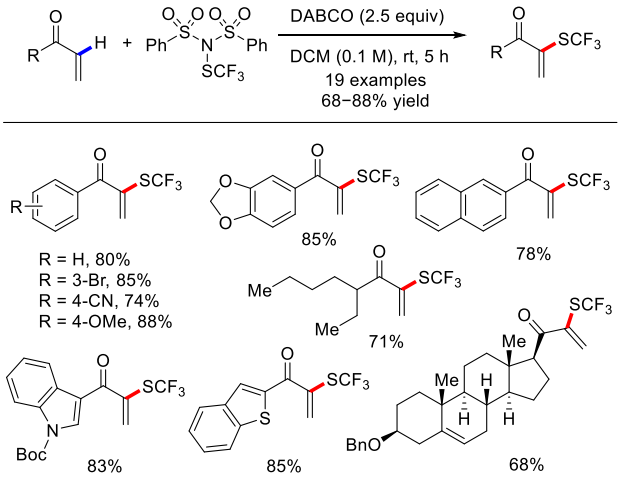
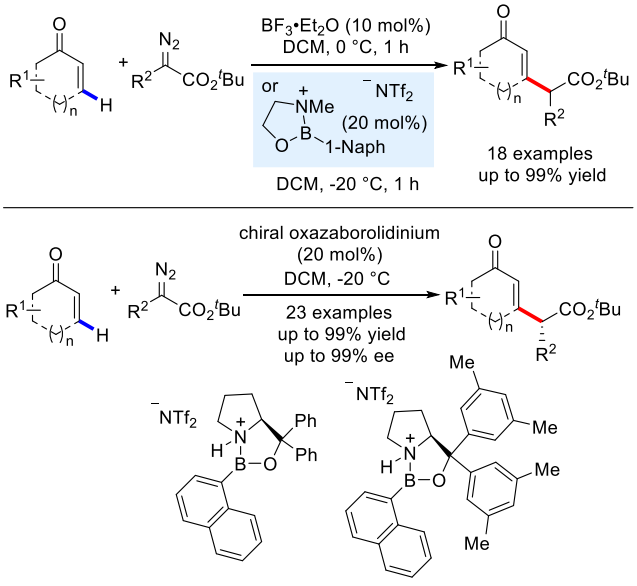
Scheme 232. DABCO-Mediated Electrophilic Alkenyl C−H Trifluoromethylthiolation of α,β-Unsaturated Carbonyl Compounds



enones with diazoacetates as the coupling partner under boron Lewis acid catalysis (Scheme 233).[392] The authors ultilized

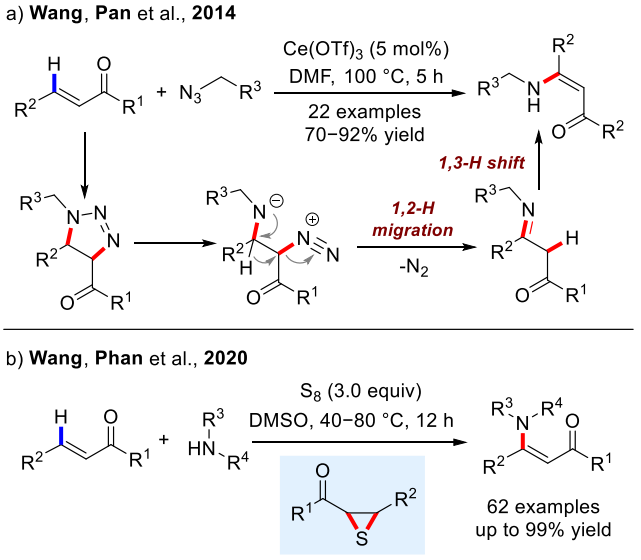
Scheme 233. Catalytic Carbon Insertion into Vinyl β-C−H Bond of Cyclic Enones and Its Enantioselective Version



readily available BF_3•Et_2O or a novel oxazaborolidinium ion as the efficacious catalyst. Meanwhile, the asymmetric version of this process was also achieved by using a chiral oxazaborolidinium ion catalyst (Scheme 233).[393] A variety of enantioenriched β-substituted cyclic enones were obtained in up to 99% yield along with excellent enantiomeric excess (up to 99% ee). As a particular highlight, the potential of this protocol was demonstrated by the formal synthesis of (+)-epijuvabione.

Moreover, Wang, Pan, and their colleagues disclosed a regioselective vinylic C−H amination for the robust synthesis of β-aryl enaminones from chalcones and benzyl azides (Scheme 234a).[394] By means of a catalytic amount of $Ce(OTf)_3$ (5 mol %), the reaction of chalcone with benzyl azides furnished a diverse array of multisubstituted β-aryl enaminones in appreciable to excellent yields with complete *Z*-

Scheme 234. Alkenyl β-C−H Bond Amination of Enaminones

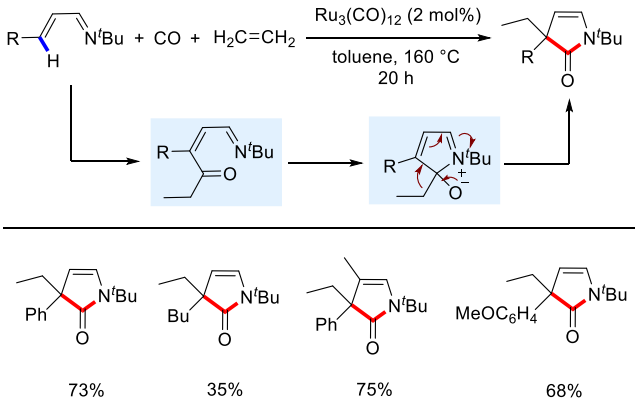


selectivity. The authors rationally speculated that the initial regioselective 1,3-dipolar cycloaddition of chalcone with azides produced the unstable triazoline intermediate, which underwent decomposition to afford a zwitterionic species. Subsequent 1,2-H migration resulted in the formation of the imine intermediate, followed by 1,3-hydrogen shift to afford the β-enaminones. A couple of years later, Phan's group also elaborated a similar synthesis of β-enaminones through trisulfur-radical-anion ($S_3^{\bullet-}$)-triggered alkenyl C−H amination of α,β-unsaturated carbonyls with simple amines (Scheme 234b).[395]

4.5. α,β-Unsaturated Imines

Over the past years, transition-metal-catalyzed alkenyl C−H bond functionalizations of α,β-unsaturated imines has also emerged rapidly as a versatile tool for the synthesis of various complex nitrogen-containing molecules. Early in 2002, pioneering work of Miura and co-workers elegantly elaborated the Ru(0)-catalyzed carbonylation of olefinic C−H bonds of α,β-unsaturated imines with alkenes and carbon monoxide (CO) to synthesize β,γ-unsaturated γ-butyrolactams (Scheme 235).[396] Various aryl and alkyl groups at β-position of the imine substrates reacted uneventfully under the conditions to

Scheme 235. $Ru_3(CO)_{12}$-Catalyzed Reaction of α,β-Unsaturated Imines with CO and Alkenes



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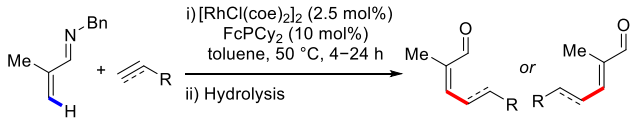
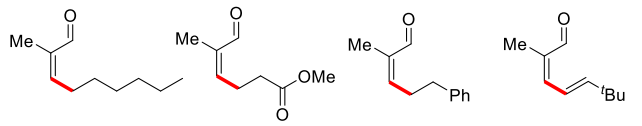
produce the corresponding lactams in appreciable to good yields. The authors tentatively proposed that the reaction occurred *via* the initial formation of ketone derivatives generated by the direct carbonylation at the vinylic β-C−H bond of α,β-unsaturated imines. An intramolecular attack by the imino nitrogen on the carbonyl group followed by a 1,2-shift of the ethyl group then afforded the expected product.

Later, the Ellman group uncovered the rhodium-catalyzed C−C bond formation protocol through a stereoselective alkylation of diverse α,β-unsaturated imines *via* alkenyl C−H activation (Scheme 236).[397] They achieved the highly

Scheme 236. Rh-Catalyzed C−H Bond Alkylation of α,β-Unsaturated Imines

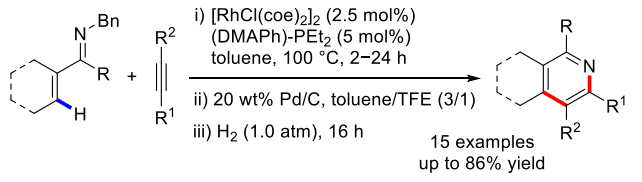


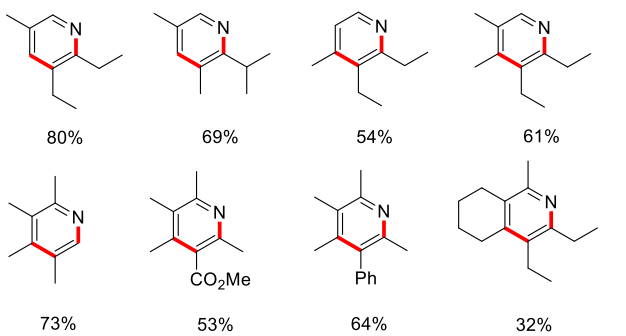


stereoselective synthesis of the tri- and tetrasubstituted α,β-unsaturated imines by means of the electron-donating (dicyclohexylphosphinyl)ferrocene ligand. The *Z*-selective imines could be further hydrolyzed to obtain the β-alkylated α,β-unsaturated aldehydes.

In continuation with their C−H bond functionalization investigations, Ellman's group further elaborated the synthesis of highly substituted pyridines from α,β-unsaturated imines and diverse alkynes *via* alkenyl C−H alkenylation/electrocyclization/aromatization sequence (Scheme 237).[398] In this case, the authors developed new class of ligands and extensively investigated the possible catalytic mechanism of transformation through kinetic simulation studies.

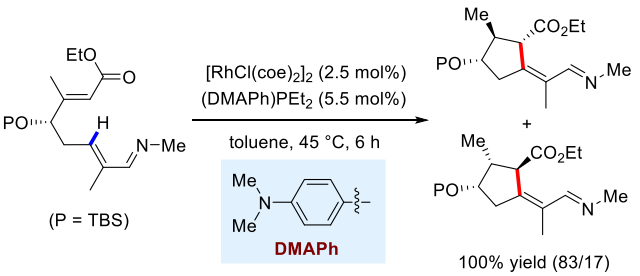
Scheme 237. One-Pot Synthesis of Pyridines from α,β-Unsaturated Imines and Alkynes





Following this, the same group expanded their rhodium-catalyzed olefinic C(sp^2)−H activation strategy for the asymmetric synthesis of (−)-Incarvillateine *via* an intramolecular alkenylation of α,β-unsaturated imines (Scheme 238).[399] By loading 2.5 mol % of the Rh catalysts in

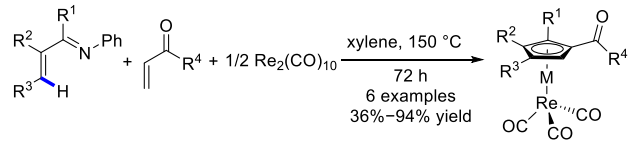
Scheme 238. Asymmetric Synthesis of Fragment of (−)-Incarvillateine

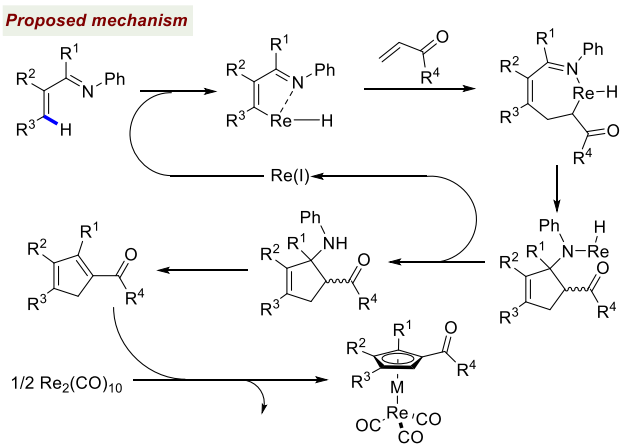


conjunction with employing the mist selective ligand (DMAP)PEt_2, they synthesized the key intermediate with moderate diastereoselectivity.

Subsequently, Kuninobu, Takai, and their colleagues elegantly demonstrated the synthesis of cyclopentadienyl−rhenium complexes through olefinic C−H activation (Scheme 239).[400] The ketimines reacted with α,β-unsaturated carbonyl

Scheme 239. Synthesis of Cyclopentadienyl−Rhenium Complexes from Ketimines, α,β-Unsaturated Carbonyls, and Rhenium Complex





compounds in the presence of a rhenium(0) complex, $Re_2(CO)_{10}$, affording a series of cyclopentadienyl−rhenium complex in 47−94% yield.

Tetrahydropyridines are present in numerous bioactive natural products. Moreover, they are also extremely versatile intermediates for alkene addition reactions to produce privileged piperidine frameworks, which are the most prevalent nitrogen-containing heterocycles widely found in a number of drug molecules.[401,402] As an extension of their continued interest in olefinic C−H activation of α,β-unsaturated imines, the Ellman group in 2012 presented the Rh(I)-catalyzed highly

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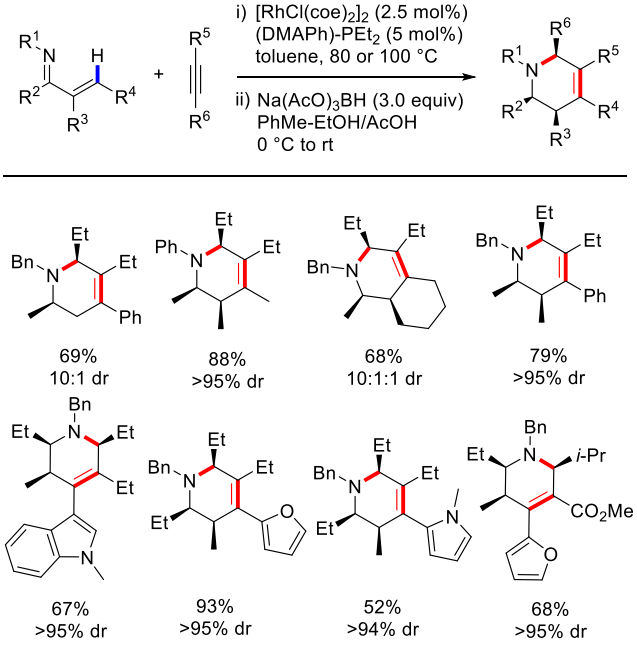
diastereoselective synthesis of tetrahydropyridines (Scheme 240).[403] The established method tolerated a diverse set of

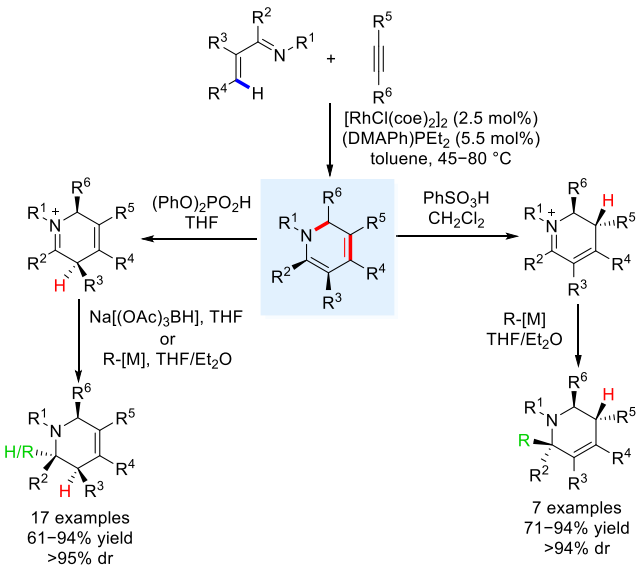
Scheme 240. Rh(I)-Catalyzed Diastereoselective Synthesis of Tetrahydropyridines



internal alkynes bearing alkyl and aryl substituents on the imine-nitrogen to yield multisubstituted piperidine derivatives in 52−95% yield with high diastereoselectivity. The authors rationalized that the observed stereochemical outcome may be due to kinetically controlled protonation followed by face-selective borohydride reduction.

Following this, the Ellman group further elaborated an extraordinary work to synthesize highly diasteroselective piperidine derivatives (Scheme 241).[404] By initial rhodium-catalyzed olefinic C−H activation, they synthesized multi-substituted piperidine derivatives from alkyne and α,β-

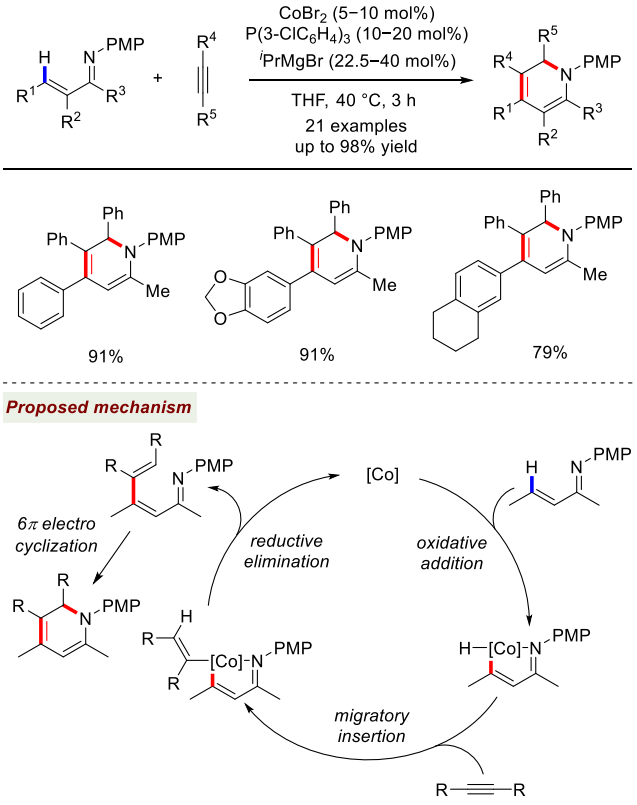
Scheme 241. Synthesis of Substituted Piperidine, Tropane, and 2-Azabicyclo[3.1.0] Systems



unsaturated imines, which were then subjected to distereo- and regioselective protonation under either thermodynamic or kinetic control to provide the distinct iminium ion intermediate. Final nucleophlic additions occurred in an higly diastereoselectve manner.

In 2013, Yoshikai and co-workers illustrated an efficient synthesis of polysubstituted dihydropyridines through an annulative reaction between internal alkynes and α,β-unsaturated imines enabled by a cobalt-triarylphosphine catalyst (Scheme 242).[405] The authors concluded that the

Scheme 242. Cobalt-Catalyzed Annulation of α,β-Unsaturated Imines with Alkynes



reaction involves of the cobalt-mediated olefinic C−H bond alkenylation followed by a 6π electrocyclization process of the resulting azatriene intermediate. By means of this strategy, a variety of polysubstituted piperidines were synthesized in good yields.

Subsequently, the Ellman group expanded their Rh-catalyzed olefinic C−H bond functionalization strategy in combination with electrocyclization to synthesize densely substituted 2-silyl 1,2-dihydropyridines from α,β-unsaturated imines and TMS acetylenes (Scheme 243).[406] The authors treated the piperidine intermediates with acids to produce unstabilized azomethane ylides, which were used to synthesize various nitrogen containing heterocycles. In this case, polysubstituted piperidines, azabicyclo[3.1.0] systems, and tropanes were synthesized from a common intermediate in good to excellent yields with high diastereoselectivity.

Successfully, the same group prepared a robust bench stable Rh catalyst from commercially available $[Rh(cod)Cl]_2$. With the new catalyst, the reaction could be performed outside the glovebox under air atmosphere. The authors synthesized polysubstituted tetrahydropyridines *via* Rh(I)-catalyzed ole-

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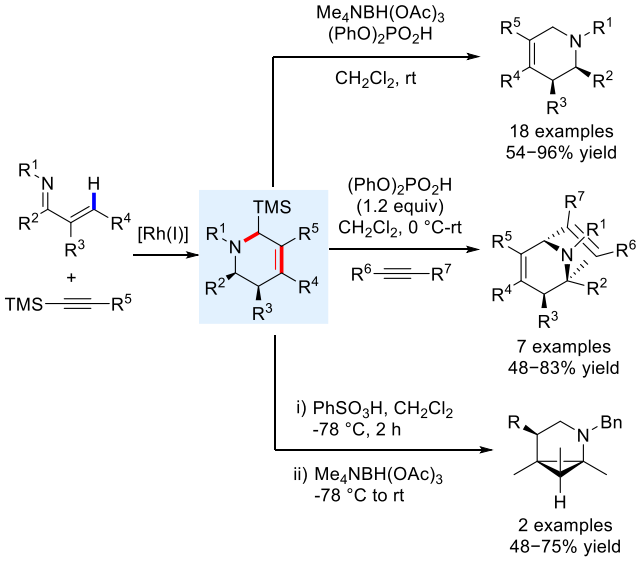
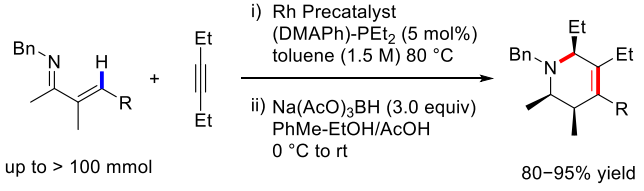
Scheme 243. Synthesis of Substituted Piperidine, Tropane, and 2-Azabicyclo[3.1.0] Systems



finic C−H bond activation/alkenylation/electrocyclization cascade followed by reduction (Scheme 244).[407] The practicality of this method was also demonstrated through a >100 mol scale cascade reaction.

Scheme 244. Synthesis of Multisubstituted Tetrahydropyridines *via* Rh(I)-Catalyzed C−H Bond Functionalization Sequence



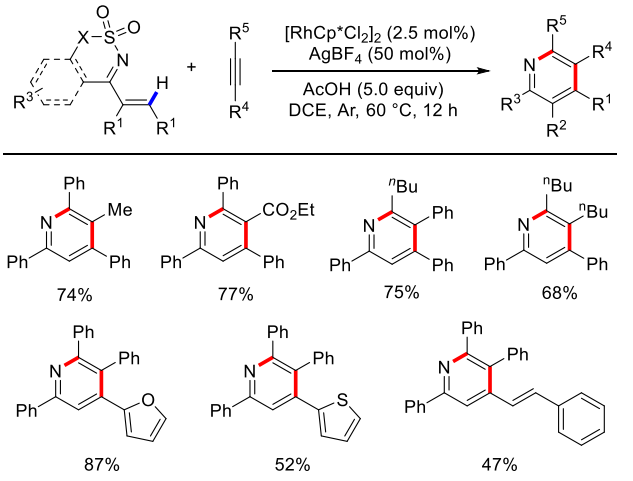
[RhCl(coe)$_2$]$_2$ (0.25 mol%) in the glovebox	[RhCl(cod)]$_2$ (1.0 mol%) on the bench
95% yield	93% yield

A diverse array of highly functionalized pyridines were prepared from a reaction of Cp*Rh(III)-catalyzed alkenyl C−H activation of *N*-sulfonyl ketimines with diverse internal alkynes by Dong's group in 2014 (Scheme 245).[408] The N−S bond of *N*-sulfonyl ketimine substrates served as an internal oxidant for this transformation which involved new C−C/C−N bond formation and S−C/S−N bond cleavage followed by desulfonylation under mild conditions.

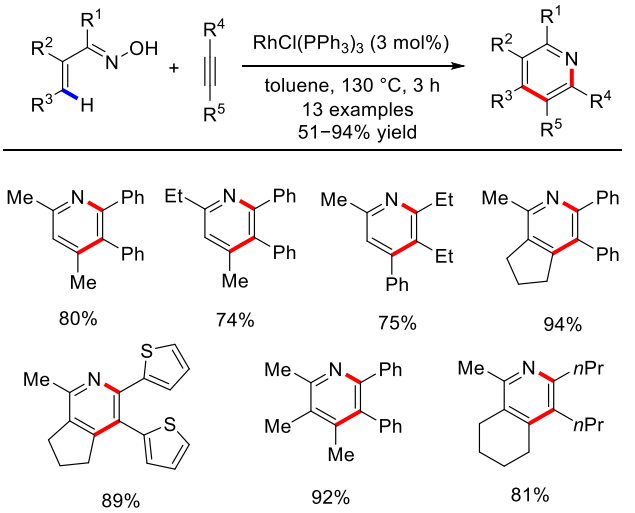
4.6. α,β-Unsaturated Oximes and Derivatives

α,β-Unsaturated oximes are an easily prepared and transformed synthetic scaffolds, which are commonly employed in synthetic organic chemistry.[409,410] Over the decades, remarkable advances have been achieved in the alkenyl C−H functionalizations of α,β-unsaturated oximes and their derivatives. Specifically, Cheng's group in 2008 elegantly illustrated a ketoximes-assisted C−H activation and further intermolecular cyclization of α,β-unsaturated oximes with internal alkynes under RhCl(PPh$_3$)$_3$ catalysis, enabling an efficient route to assemble multisubstituted pyridine scaffolds (Scheme 246).[411] By using this strategy, the same group

Scheme 245. Synthesis of Funtionalized Pyridines from *N*-Sulfonyl Ketimines and Alkynes



Scheme 246. Rh(I)-Catalyzed C−H Annulation of α,β-Unsaturated Ketoximes with Alkynes



subsequently expanded to report a gram-scale synthesis of pentasubstituted pyridines (C2−C6) in a one-pot fashion. However, unsymmetrical alkynes afforded the annulation products with low regioselectivity while requiring high reaction temperature.[412]

Following this, Rovis and co-workers elaborated a similar synthesis of pyridines *via* the Rh(III)-catalyzed reaction of α,β-unsaturated oximes with alkynes under typically benign conditions (Scheme 247a).[413] Notably, it was established that sterically different ligands led to different product selectivities in this protocol. Almost at the same time, Li and Chiba described an analogous transformation for the construction of highly substituted pyridine scaffolds with comparable yields (40−97%) under redox-neutral conditions (Scheme 247b).[414]

Apart from internal alkynes, the group of Bergman and Ellman also employed terminal alkynes as the coupling partner to engage in a Rh(I)-catalyzed one-pot C−H functionalization/electrocyclization/dehydration for the contruction of multisubstituted pyridines with moderate to excellent regioselectivities (Scheme 248).[415] In this protocol, an

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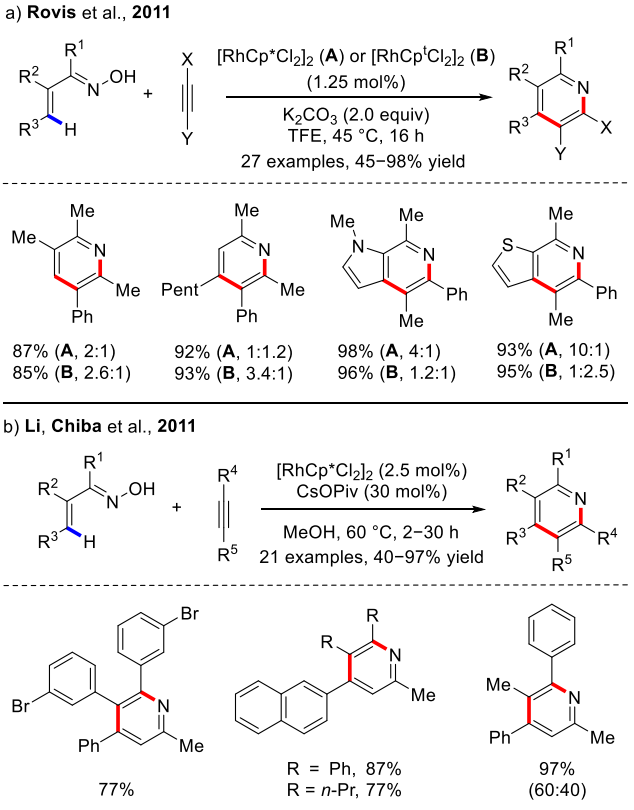
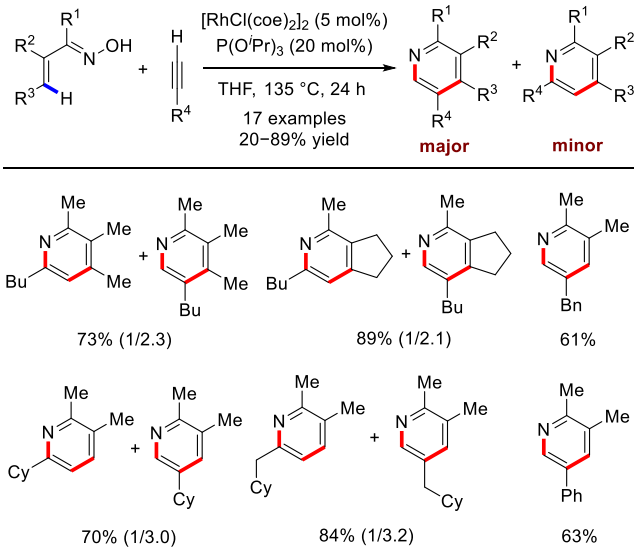
Scheme 247. Rh(III)-Catalyzed Synthesis of Pyridines from α,β-Unsaturated Oximes and Alkynes



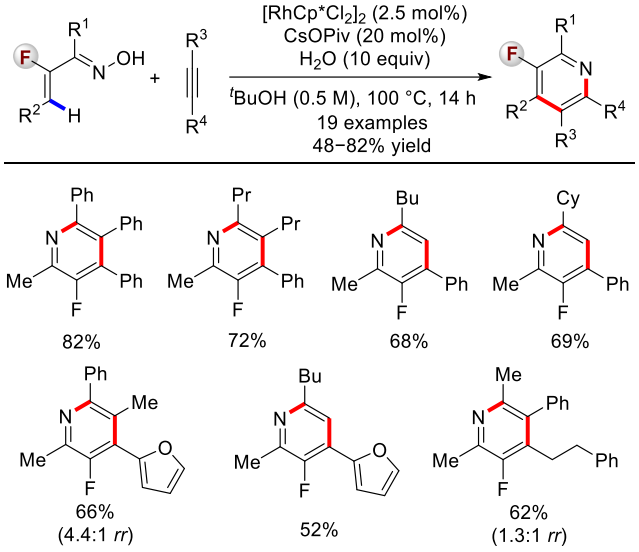
electron-poor phosphite ligand was readily used to prevent the dimerization of the alkynes.

Scheme 248. Synthesis of Substituted Pyridines from α,β-Unsaturated Ketoximes and Terminal Alkynes



Subsequently, Ellman and co-workers extended to demonstrate a novel Cp*Rh(III)-catalyzed C−H activation of α-fluoro-α,β-unsaturated oximes with both internal and terminal alkynes for the synthesis of multisubstituted 3-fluoropyridines (Scheme 249).[416] It was established that structurally diverse oximes bearing aryl, heteroaryl, and alkyl β-substituents were

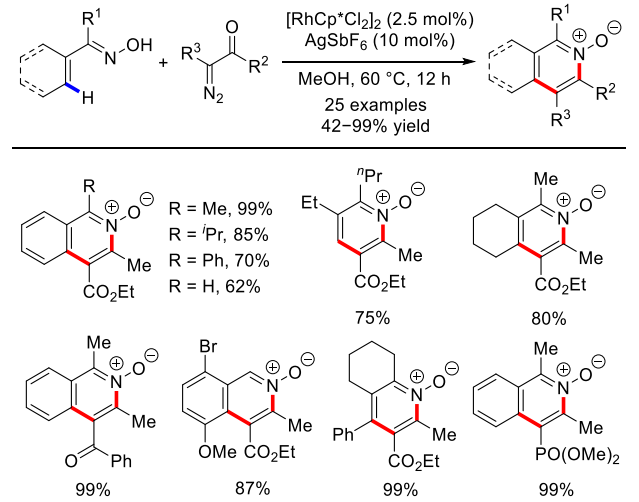
Scheme 249. Cp*Rh(III)-Catalyzed Synthesis of Fluorinated Pyridines



efficacious substrates for this reaction. Notably, terminal alkynes participated in this annulative process, exclusively affording 3-fluoropyridines as a single regioisomer.

Moreover, Glorius and co-workers described an impressive Cp*Rh(III)-catalyzed cyclization reaction between α,β-unsaturated oximes and diazos through the dual activation of both aryl and vinyl C−H bonds, allowing the construction of a series of multisubstituted isoquinolines and pyridine *N*-oxides in high yields (Scheme 250).[417] This annulative strategy incorporated

Scheme 250. Direct Synthesis of Multisubstituted Isoquinoline and Pyridine *N*-Oxides from α,β-Unsaturated Oximes and Diazo Compounds



a tandem C−H activation, ring formation, and condensation steps. The reaction also avoided the need for any external oxidant, while releasing N_2 and H_2O as the byproducts.

Later in 2020, Samanta *et al.* investigated the annulation reaction of unsaturated oxime ethers with fluorinated diazomalonates to construct 2-pyridone derivatives (Scheme 251).[418] Various unsaturated oxime ethers bearing with different substitution patterns were compatible, and a broad scope of 30 examples was documented in yield up to 92%.

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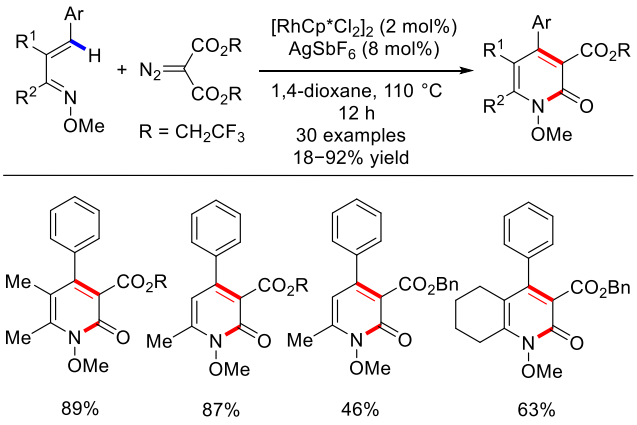
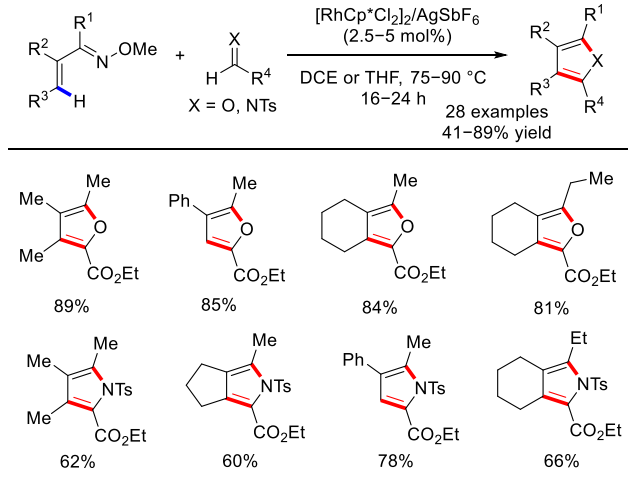
Scheme 251. Synthesis of 2-Pyridones by Rhodium(III)-Catalyzed Annulation of Unsaturated Oxime Ethers with Fluorinated Diazomalonates



Notably, keto-oximes bearing five-, six, seven-, and eight-member rings proceeded uneventfully in this case.

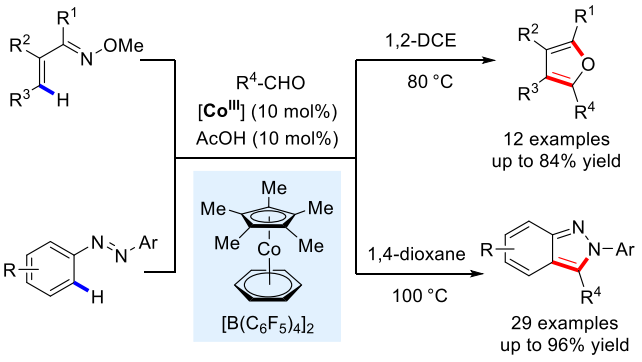
In addition to these annulation examples, Ellman's group also elaborated a novel annulation strategy for the robust assembly of substituted furans and pyrroles. Specifically, the reaction between *O*-methyl *α,β*-unsaturated oximes with both aldehydes and *N*-tosyl imines yields secondary alcohols and amine intermediates, which could readily undergo subsequent cyclization and aromatization to furnish biologically important heterocyclic compounds in modest to excellent yields (Scheme 252).[419]

Scheme 252. Rh(III)-Catalyzed Annulation Reaction for the Synthesis of Substituted Furans and Pyrroles



Encouraged by this work, the same group further identified a novel air-stable cationic Co(III)-catalyst and expanded to evaluate the alkenyl C−H functionalization of *α,β*-unsaturated oxime ethers with aldehydes, followed by a subsequent cyclization and aromatization, providing a cost-effective synthesis of multisubstituted furans in a single step (Scheme 253).[420] Interestingly, only a catalytic amount of AcOH additive was required for achieving high efficiency. This protocol was the first illustration of a Co(III)-catalyzed additions to aldehydes for the synthesis of furans and was compatible with a diverse range of both (hetero)aromatic and aliphatic compounds. Moreover, a diverse array of indazoles

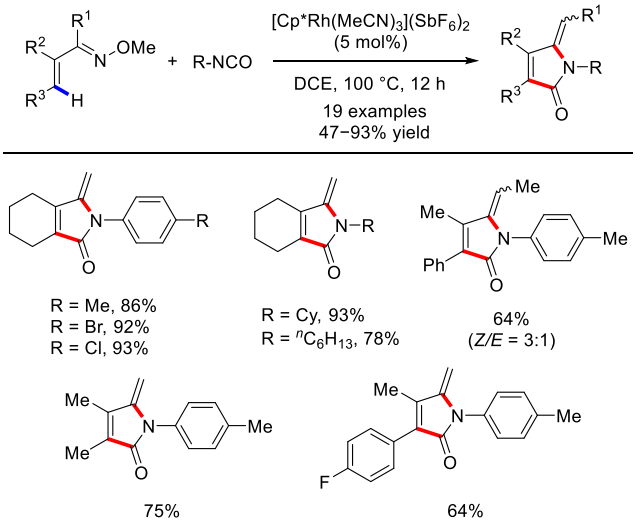
Scheme 253. Co(III)-Catalyzed Synthesis of Furans from *α,β*-Unsaturated Oxime Ethers



can be obtained by this strategy with azobenzenes as the substrates.

The group of Zhou and Li reported a Cp*Rh(III)-catalyzed activation of the alkenyl C−H bond to isocyanates, followed by a subsequent annulation to afford biologically important 5-ylidene pyrrol-2(5*H*)-ones (Scheme 254).[421] The reaction was atom-economic and operated under benign and redox-neutral conditions without the need for any additive, while no environmentally hazardous waste was generated.

Scheme 254. Synthesis of 5-Ylidenepyrrol-2(5*H*)-ones from *α,β*-Unsaturated Oxime Ethers and Isocyanates



More recently, Ravikumar and co-workers also achieved a redox-neutral Cp*Co(III)-catalyzed intermolecular cyclization of *α,β*-unsaturated oxime ethers with internal alkynes (Scheme 255).[422] A variety of multisubstituted pyridines were obtained in decent yields. Remarkably, the strategy exhibited good functional group compatibility and was applicable for late-stage diversification of a bioactive molecule-dehydropregnenolone.

To improve the regioselectivity and substrate scope, the Rovis group in 2013 developed a Cp*Rh(III)-catalyzed complementary approach for pyridine synthesis from *α,β*-unsaturated oxime esters and simple olefins (Scheme 256a).[423] The reaction was found to be highly regioselective and affording a series of multisubstituted pyridines in decent yields when an activated alkene was employed. Mechanistic investigations revealed that the reaction proceeded through a

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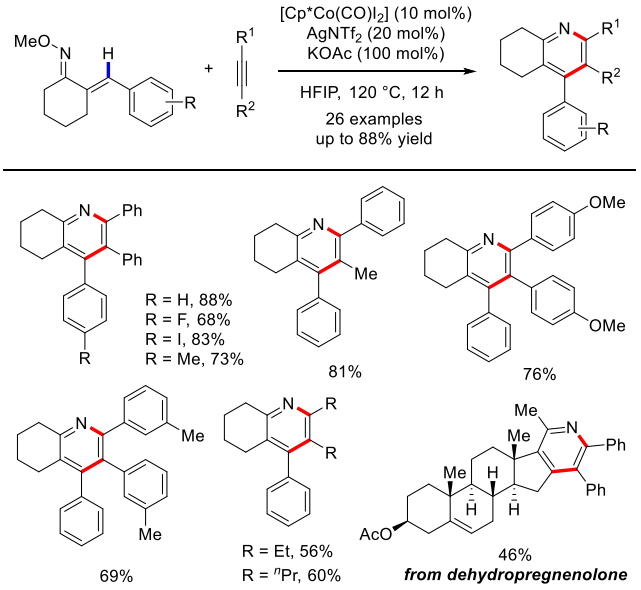
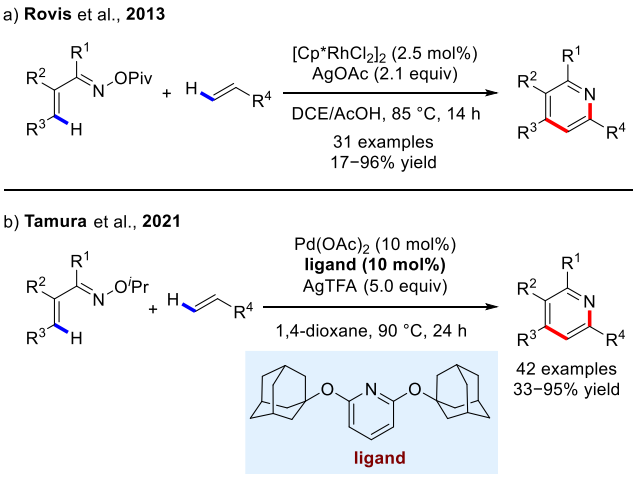
Scheme 255. Redox-Neutral Co(III)-Catalyzed Alkenyl C−H Activation of α,β-Unsaturated Oxime Ethers with Internal Alkynes



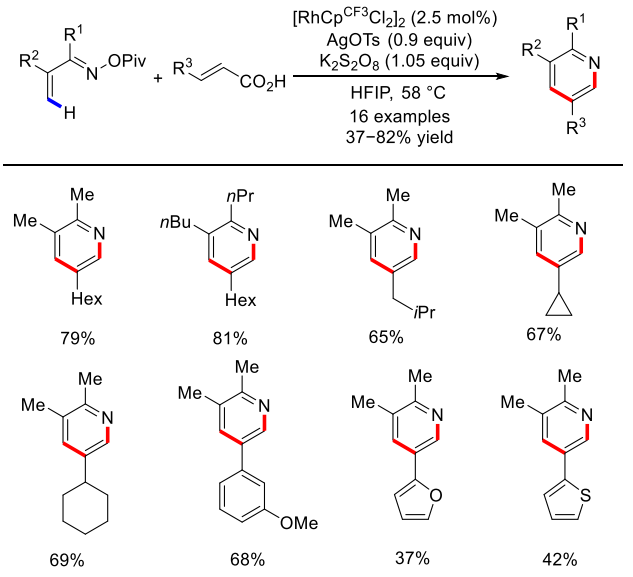
Scheme 256. Regioselective Pyridine Synthesis from α,β-Unsaturated Oxime Esters and Alkenes



reversible C−H activation, followed by the insertion of the olefin, a subsequent C−N bond forming/N−O bond breaking processs afforded the corresponding pyridines. Recently, Tamura's group realized an analogous transformation enabled by Pd(II)-catalyzed vinylic C−H alkenylation of α,β-unsaturated oxime ethers followed by aza-6π-electrocyclization. A sterically hindered pyridine-based ligand was readily identified to facilitate this process (Scheme 256b).[424] Substrates with different degrees of substitution at the alkene moiety furnished the expected products in satisfactory yields (33−95%).

In the following year, the same group further illustrated an efficient decarboxylative cross-coupling of α,β-unsaturated *O*-pivaloyl oximes with unsaturated carboxylic acids to assemble pyridine scaffolds (Scheme 257).[425] The carboxylic acid functioned as a traceless activating group, affording the expected pyridines in good yields and excellent regioselectivity. Further investigations into the mechanism dismissed the

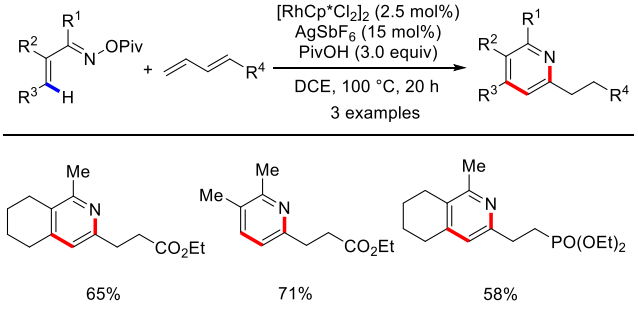
Scheme 257. Decarboxylative Cross-Coupling of α,β-Unsaturated *O*-Pivaloyl Oximes with Unsaturated Carboxylic Acids



picolinic acid intermediate, while a rhodium complex intermediate was isolated, providing clues into the mechanism of the process.

Almost at the same time, Glorius and colleagues elaborated a highly regioselective Cp*Rh(III)-catalyzed C−H activation/cyclization/isomerization approach for the synthesis of multi-substituted pyridines *via* the reaction of α,β-unsaturated oxime esters with 1,3-dienes (Scheme 258).[426] As a particular highlight, the protocol does not require an external oxidant, operated under redox-neutral conditions with a diverse substrate scope.

Scheme 258. Cp*Rh(III)-Catalyzed Pyridine Synthesis from α,β-Unsaturated Oxime Esters with 1,3-Dienes



In 2015, Rovis and co-workers investigated the Rh(III)-catalyzed C−H functionalization of α,β-unsaturated oxime pivalates with 1,1-disubstituted alkenes in an effort to produce 2,3-dihydropyridines. In this report, the oxime pivalates go through a reversible alkenyl C−H insertion with Rh(III) complexes to afford the five-membered rhodacycle. Subsequently, this intermediate readily undergoes irreversible migratory insertion with 1,1-disubstituted alkenes followed by a reductive elimination, affording the desired 2,3-dihydropyridines in 67−92% yield with excellent regioselectivities (Scheme 259).[427] Upon hydrogenation, the corresponding piperidines could be obtained, which are crucial core structures of numerous pharmaceutically relevant molecules.

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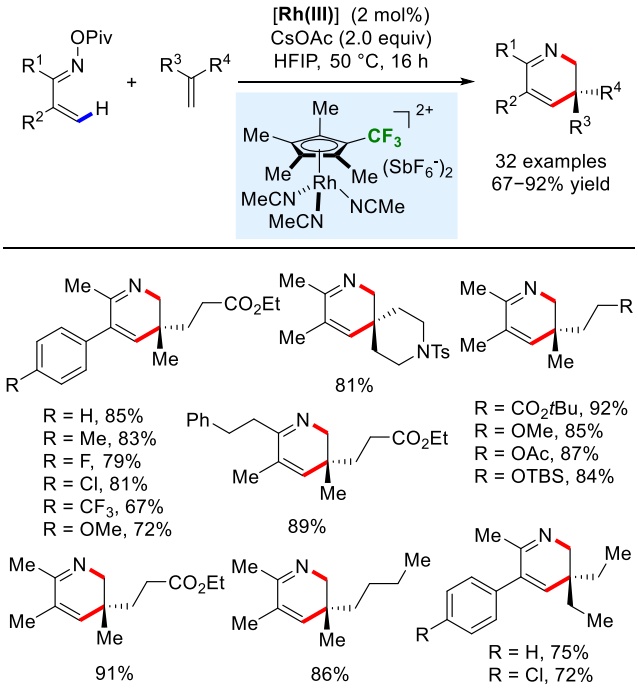
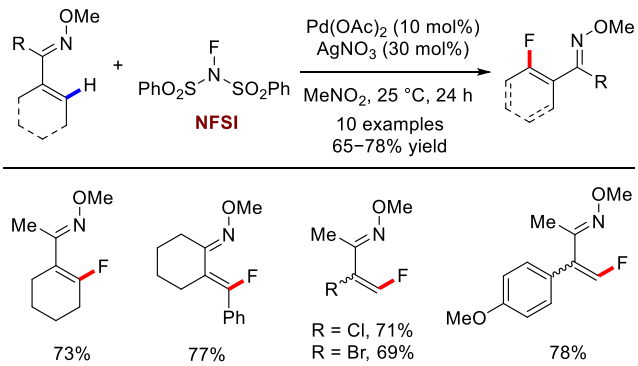
Scheme 259. Direct Synthesis of 2,3-Dihydropyridines through Rh(III)-Catalyzed C−H Functionalization of Unsaturated Oximes



Apart from the annulation examples discussed above, in 2014, Xu and co-workers reported a straightforward fluorination of vinylic C−H bonds by taking advantage of NFSI as the fluorinating agents under benign reaction conditions (ambient conditions in most examples). In the presence of a catalytic amount of inexpensive $AgNO_3$, the alkenyl C(sp^2)−H bonds bearing a diversity of functional groups were selectively fluorinated (Scheme 260).[428] On the basis of their mechanistic

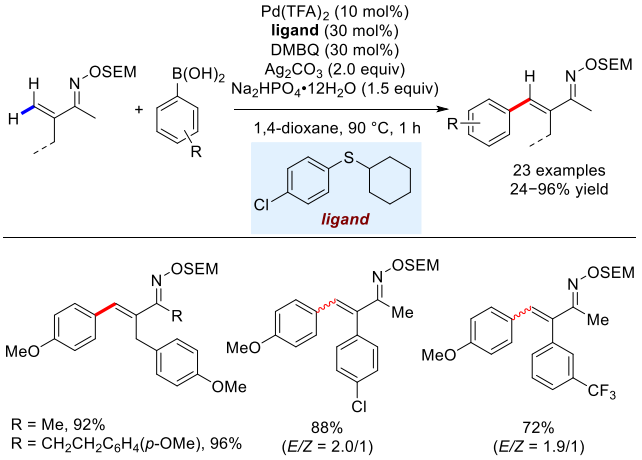
Scheme 260. Nitrate-Mediated Alkenyl C−H Bond Fluorination under Benign Conditions



investigations. the authors tentatively proposed a Pd(II)/Pd(IV) catalytic cycle kickstarted by the formation of the cationic $[Pd(NO_3)]^+$ species. Of note, the aryl counterparts were also found to be suitable C−H sources for this transformation.

Recently, Tamura and co-workers identified a alkyl aryl thioether ligand to enable the palladium(II)-catalyzed electrophilic C−H arylation of α,β-unsaturated *O*-SEM oximes with arylboronic acids (Scheme 261).[429] Varying the structure of the ligand could greatly improve the efficiency of this protocol.

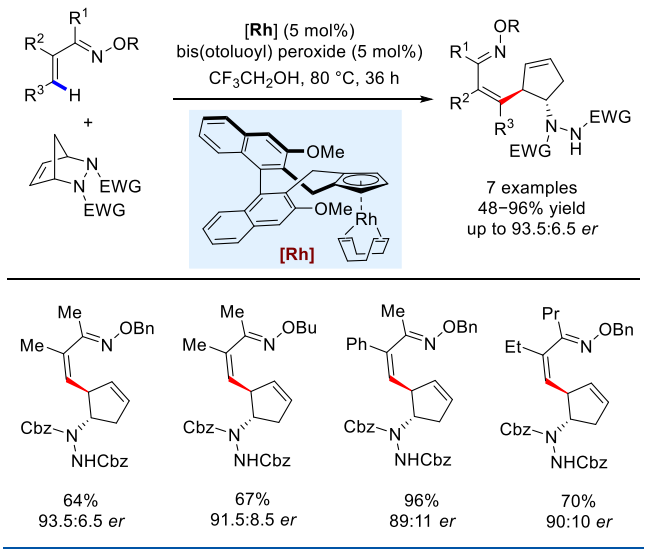
Scheme 261. Pd(II)-Catalyzed C−H Arylation of α,β-Unsaturated *O*-SEM Oximes



The reaction was typically finished within 1 h at 90 °C in 1,4-dioxane, and a wide scope of 23 examples of this transformation was documented with satisfactory yields of 22−96%.

Moreover, Cramer and co-workers expanded their chiral Cp*Rh(III) catalysis strategy and illustrated the first enantioselective alkenyl C−H activation/ring-opening between various α,β-unsaturated oxime ethers and 2,3-diazabicyclo[2.2.1]hept-5-enes, enabling an efficient access to chiral cyclopentenylamines in decent yields and high enantioselectivities (Scheme 262).[430]

Scheme 262. Cp*Rh(III)-Catalyzed Enantioselective C−H Activation/Ring-Opening to Synthesize Chiral Cyclopentenylamines



4.7. 2-Vinylpyridines

In the early days of alkenyl C−H bond activation of 2-vinylpyridines, Murai and co-workers in 1998 first investigated the Ru(0)-catalyzed C−H carbonylation of alkenes. Reacting 2-vinylpyridines with carbon monoxide and ethene in a catalytic amount of $Ru_3(CO)_{12}$ catalyst afforded propionylation at the alkenyl C−H bond in these 2-pyridylalkenes (Scheme 263).[431] The carbonylation took place regioselectively at the γ-position with respect to the nitrogen on the

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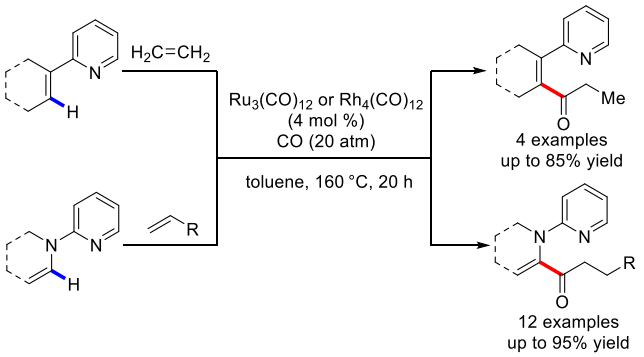
Scheme 263. $Ru_3(CO)_{12}$-Catalyzed Carbonylation of C(sp^2)−H Bond of 2-Vinylpyridines



pyridine ring. Remarkably, this method can also be applied to *N*-(2-pyridyl)enamines, whereby the alkenyl moiety is segregated from the pyridine by an sp^3-nitrogen, generating the corresponding ethyl ketones as the product. Moreover, $Rh_4(CO)_{12}$ also exhibited excellent catalytic activity for the reactions of *N*-(2-pyridyl)enamines with a diverse array of alkenes.

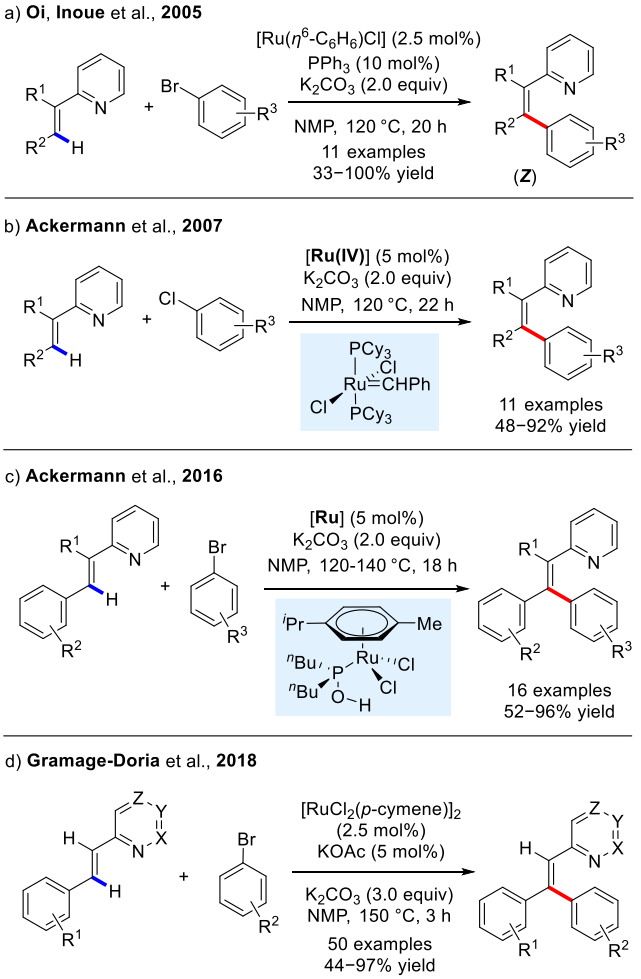
In 2005, the group of Oi and Inoue disclosed the regio- and stereoselective alkenyl C−H arylation reaction of 2-vinylpyridines with aryl bromides catalyzed by specific Ru(II)−phosphine complexes, delivering a series of *β*-arylated (*Z*)-2-alkenylpyridines with the aryl moiety *cis* to the pyridyl group, which is in sharp contrast to the $Pd(OAc)_2$-catalyzed Mizoroki−Heck coupling reaction (Scheme 264a).[432] Later in 2007, Ackermann's group developed an efficacious diastereoselective Ru(IV) carbene-catalyzed arylation of the vinylic C(sp^2)−H bonds of 2-vinylpyridines with aryl chlorides (Scheme 264b).[433] Of note, the direct arylation−hydrosilylation sequence was also presented in this report.

A couple of years later, the same group further extended to elaborate a chemo-, site-, and diastereoselective C−H functionalization of alkenes enabled by the well-defined air- and moisture-stable ruthenium(II) complexes bearing a trivalent phosphinous acid (PA) ligand (Scheme 264c).[434] Detailed mechanistic investigation revealed that a C−X bond breaking occurred *via* a single-electron transfer (SET) process, and proof of a phosphinic acid-assisted C−H ruthenation step was also reported. Following this, Gramage-Doria's group in 2018 also illustrated an analogous Ru(II)-catalyzed olefinic C(sp^2)−H bond (hetero)arylation by making use of diazines as the directing groups (Scheme 264d).[435]

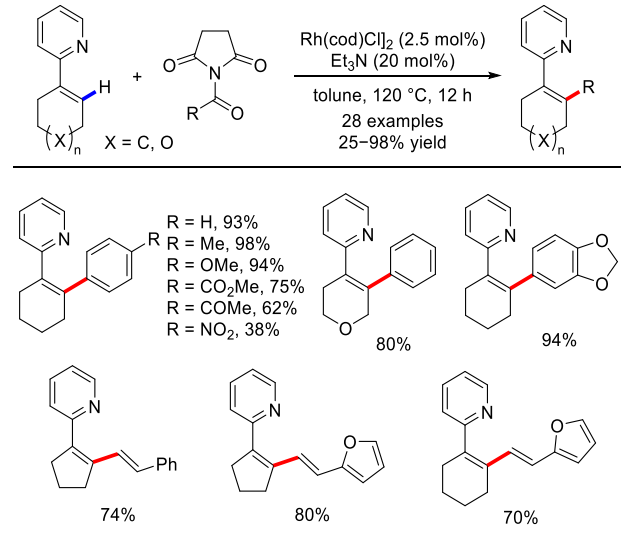
Afterward, Wang and co-workers achieved an efficient $[Rh(cod)Cl]_2$-catalyzed 2-pyridyl group-assisted alkenyl C-(sp^2)−H functionalization reaction with aroyl- or acrylamides, giving rise to a series of arylated or alkenylated olefins in satisfactory yields with good functional group compatibility (Scheme 265).[436]

Kuninobu, Takai, and their co-workers reported on a recatalyzed insertion of *α,β*-unsaturated carbonyls, alkynes, and aldehydes into alkenyl C(sp^2)−H bonds to produce *γ,δ*-unsaturated carbonyl compounds, dienes, and allyl silyl ethers, respectively (Scheme 266).[437] The reaction kickstarted with a vinylic C−H activation, further insertion of the unsaturated compounds to form the new Re−C bond, and a final reductive elimination (or transmetalation for aldehydes) to yield the expected products.

Scheme 264. Ru-Catalyzed Vinylic C(sp^2)−H Bond Arylation of 2-Vinylpyridines



Scheme 265. Rh-Catalyzed Vinylic C(sp^2)−H Bond Functionalization with Aroyl- and Acrylamides



In a related study, Wang and co-workers elaborated a cost-effective Mn(I)-catalyzed nucleophilic addition of chemically inactive alkenyl C(sp^2)−H bonds to aldehydes (Scheme 267).[438] The strategy exhibited a broad scope of substrates

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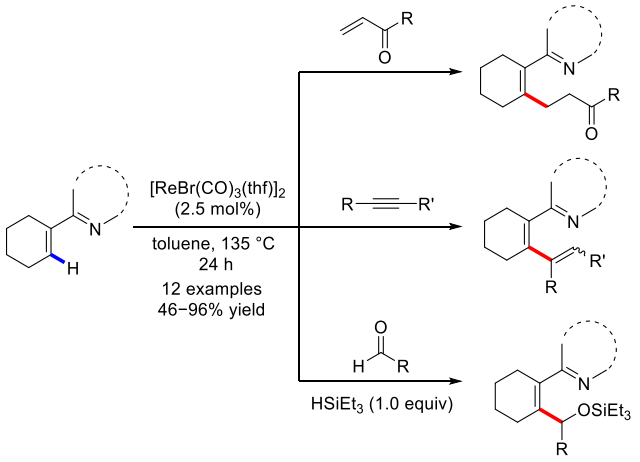
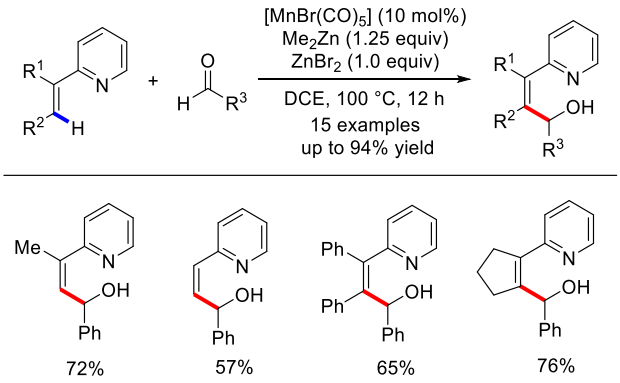
Scheme 266. Re-catalyzed Insertion of Unsaturated Molecules into Olefinic C−H Bonds



Scheme 267. Mn(I)-Catalyzed Nucleophilic Addition of Alkenyl C(sp^2)−H Bonds to Aldehydes



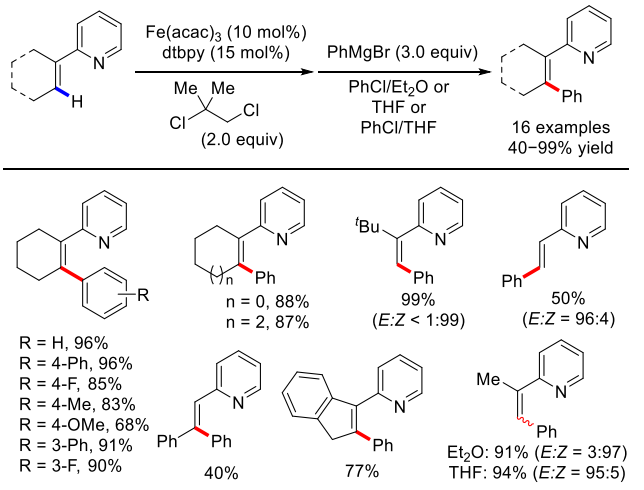
with excellent regio- and stereoselectivity. Detailed mechanistic investigation revealed a plausible mechanistic pathway of the reaction.

Nakamura and co-workers achieved an impressive iron-catalyzed stereospecific alkenyl C(sp^2)−H bond functionalization with Grignard reagents for the synthesis of substituted alkenes (Scheme 268).[439] The reaction between aryl magnesium compounds and 2-vinylpyridines resulted in a stereospecific substitution at the C−H bond *syn* to directing group. The transformation operated with ease and without isomerization of the alkene product. Mechanistic studies suggested that the strategy was consistent with a Fe-catalyzed C−H bond activation instead of a Mizoroki−Heck reaction.

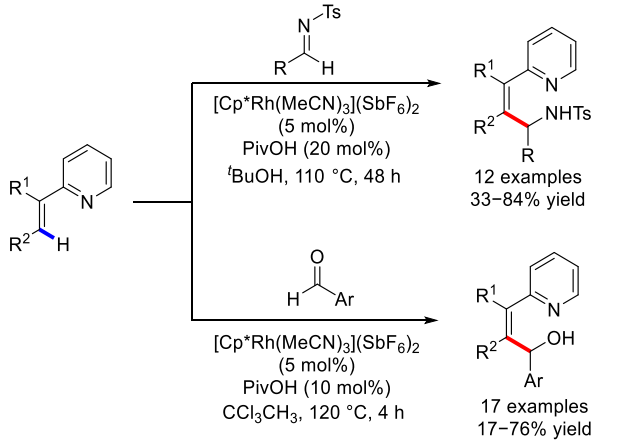
One year later, Shi's group uncovered a convenient approach of Cp*Rh(III)-catalyzed alkenyl C(sp^2)−H addition to both *N*-sulfonylaldimines and aryl aldehydes, eventually allowing an efficacious and atom-economical strategy to access a diverse array of allyl amines and allyl alcohols in decent yields (Scheme 269).[440]

Expanding their alkenyl C−H activation strategy, Loh's group in 2012 established a general approach for the alkenyl C−H sulfonylation of α-methyl vinylpyridines with sulfonyl chlorides (Scheme 270).[441] Various aryl sulfonyl chlorides were moderately efficient, giving rise to the expected products in reasonable yield (54−71%). Notably, aliphatic sulfonyl chloride was also a competent substrate for this transformation, albeit with diminished efficiency (25%). The authors

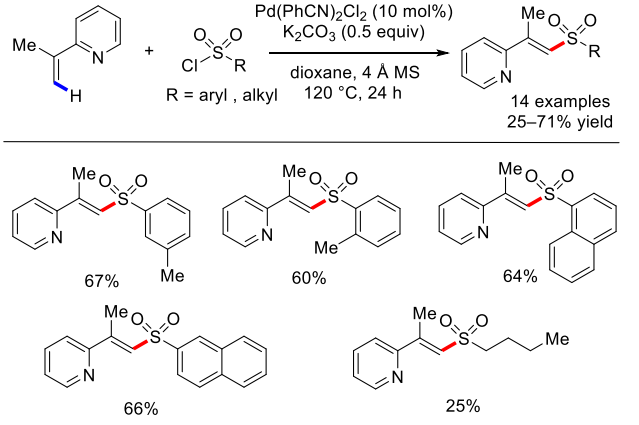
Scheme 268. Fe(III)-Catalyzed Stereospecific Alkenyl C(sp^2)−H Functionalization with Grignard Reagents



Scheme 269. Cp*Rh(III)-Catalyzed Alkenyl C(sp^2)−H Addition to *N*-Sulfonylaldimines and Aldehydes



Scheme 270. Palladium(II)-Catalyzed Alkenyl C−H Bond Sulfonylation



tentatively proposed a plausible Pd(II)/Pd(IV) catalytic cycle to elucidate the possible mechanism of this reaction.

Moreover, Yu and colleagues in 2016 presented a directed Cp*Rh(III)-catalyzed C(sp^2)−H Michael addition to CF_3-substituted α,β-unsaturated ketones (Scheme 271).[442] Both aromatic and alkene substrates bearing a chelating group

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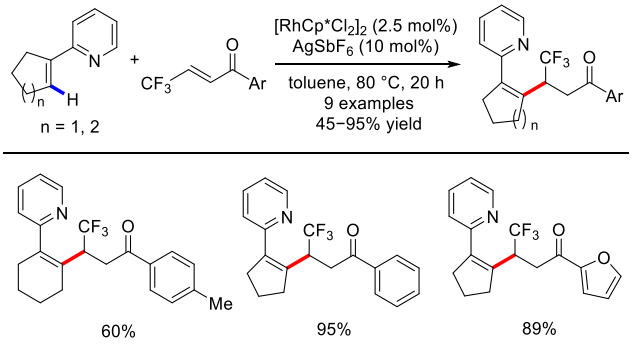
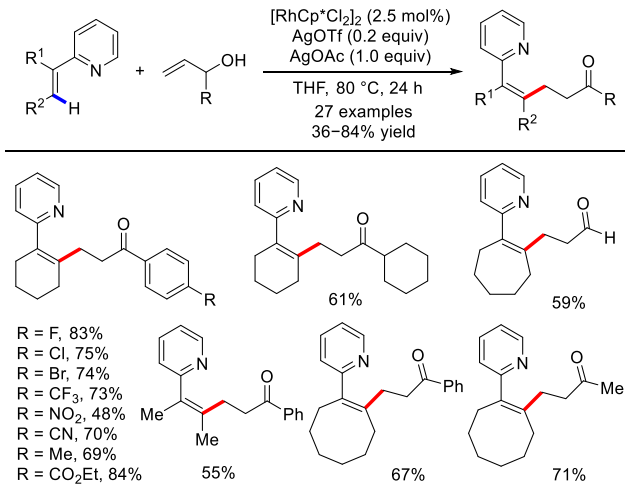
Scheme 271. Cp*Rh(III)-Catalyzed Alkenyl C(sp^2)−H Michael Additions to β-Trifluoromethyl α,β-Unsaturated Ketones



reacted smoothly with a wide range of β-trifluoromethyl-α,β-unsaturated ketones to deliver the respective products in an atom-economical manner with decent yields.

Furthermore, Wang's group elaborated the synthesis of β-alkenyl carbonyls through a Cp*Rh(III)-catalyzed oxidative coupling of 2-vinylpyridines with readily available allylic alcohols (Scheme 272).[443] A series of allylic alcohols coupled

Scheme 272. Cp*Rh(III)-Catalyzed C−H Oxidative Coupling of 2-Vinylpyridines with Allylic Alcohols

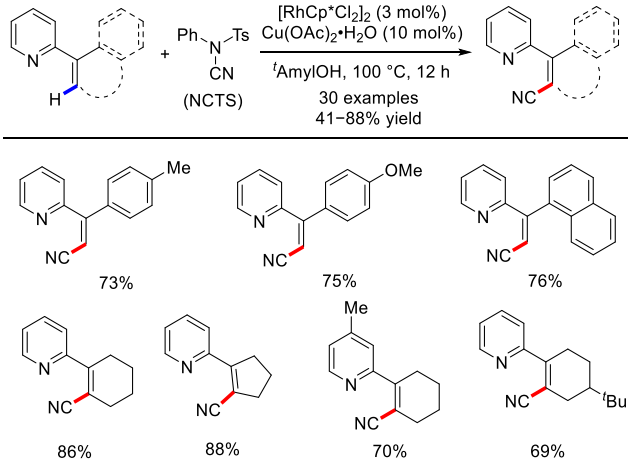


effectively to afford the corresponding products in modest to good yields. Markedly, allylic alcohols reacted specifically at the γ-position, while alkenylpyridines reacted at the *cis*-β-position in this case.

α,β-Unsaturated nitriles are one of the most common scaffolds embedded in pharmaceutically relevant molecules and bioactive natural products. Anbarasan's group in 2015 established an efficacious and regioselective Cp*Rh(III)-catalyzed alkenyl C−H cyanation by exploiting environmentally friendly *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) as the cyanating agent (Scheme 273).[444] This strategy exhibited high functional group compatibility and enabled the construction of a diverse variety of substituted acrylonitriles in decent yields (41−88%). As a particular highlight, the authors showcased the practicality of this strategy by the synthesis of a chlorpheniramine-based antagonist.

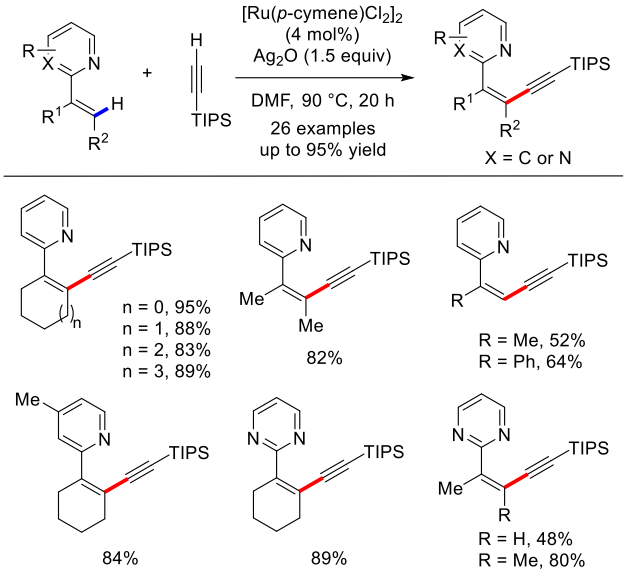
Quite recently, Wang's group initiated their investigations to exploit the ruthenium(II)-catalyzed oxidative coupling reaction of 2-vinylpyridines with triisopropylsilylacetylene. In this

Scheme 273. Cp*Rh(III)-Catalyzed Alkenyl C(sp^2)−H Cyanation of Alkenes



report, silver oxide (Ag_2O) was proven to be indispensable for achieving high efficiency. Gratifyingly, both 2-pyridyl and 2-pyrimidyl were competent directing groups for this strategy, enabling the synthesis of highly functionalized 3-enyne products in good yields with excellent *Z*-selectivity (Scheme 274).[445]

Scheme 274. Ru-Catalyzed Cross-Coupling Reaction of Alkenes with Triisopropylsilylacetylene



5. ALKENYL C−H BOND FUNCTIONALIZATION OF ALKENES CONTAINING A HETEROATOM

In this section of the review, we will summarize the work related to alkenyl sp^2 C−H bond of diverse 2-heteroatom substituted alkenes (Scheme 275). In most of these cases, there can serve as enolate equivalents or latent protecting groups for the corresponding atom. The use of photoredox and electrochemical strategies to carry out C−H bond functionalization of alkenes bearing a 2-heteroatom substituted auxiliary have recently gained ever-increasing popularity. Metal-free systems have also emerged in recent years which may provide greener approaches for C−H functionalization of alkenes and

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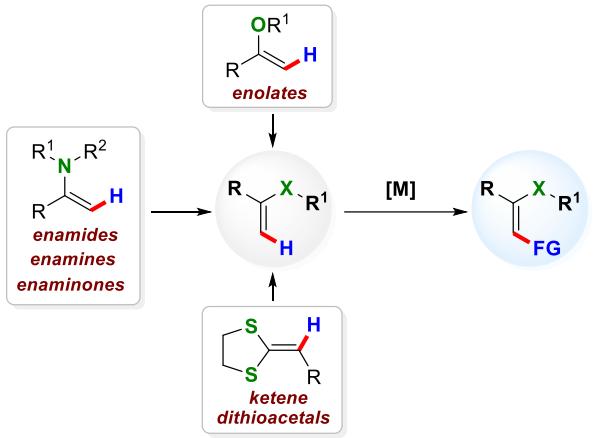
Scheme 275. General Scheme of Alkenyl C−H Bond Functionalizations of Alkenes Containing a Heteroatom Directing Group



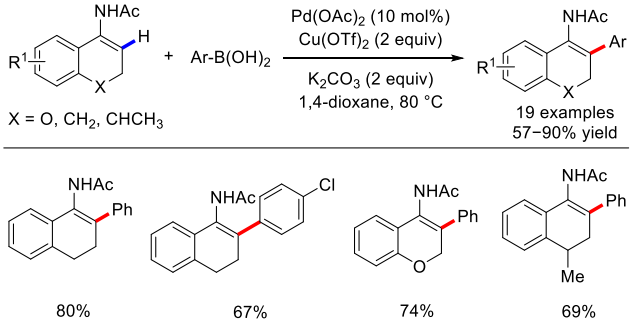
their derivatives. Moreover, the use temporary chiral amines to *in situ* generate enamides, enamines, and their equivalents provides novel opportunities for the asymmetric C−H bond functionalizations with coupling partners containing pro-chiral centers.

5.1. Enamides

Enamides are extremely important synthetic building blocks because they are stable enolate equivalents and can be used to couple with a wide variety of electrophiles.[446] Furthermore, they can be easily converted into amines including chiral amines *via* asymmetric hydrogenation. As a consequence, there have been many methods developed for the preparation of this important class of compounds. Among these established methods, the selective alkenyl C−H bond functionalization of simple and easily accessible enamides provides one of the most direct and practical methods to access highly functionalized enamides.[447,448] In this part of the review, we summarized the comprehensive advances on the alkenyl C−H bond functionalizations of enamides. Metal catalysis, photoredox, as well as electrochemical strategies will be included.

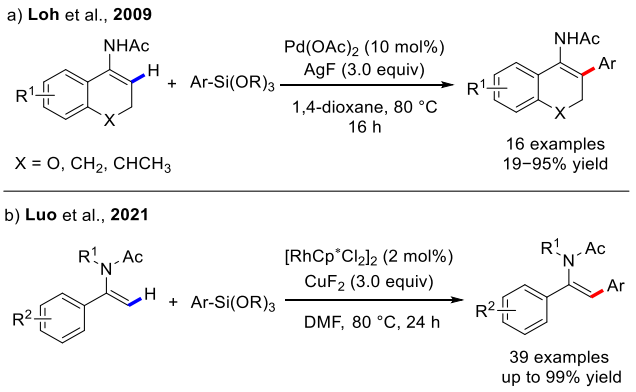
5.1.1. Arylation. The first β-C(sp^2)−H arylation of enamides was investigated by Loh and co-workers in 2009. They reported an unprecedented arylation of cyclic enamides with various arylboronic acids through a C−H activation reaction enabled by Pd(OAc)$_2$ catalyst (Scheme 276).[449] A diverse number of arylboronic acids bearing both electron-donating and electron-withdrawing groups undergo a smooth cross-coupling to yield the arylated products in modest to good yields, while electron-withdrawing groups, such as CO_2R, COR, CN, NO_2, *etc.*, on the cyclic enamides were not scrutinized. Due to excessive oxidation, *N*-(2-arylnaphthalen-1-yl)acetamides were also observed as byproducts when X was methylene.

Scheme 276. Pd(II)-Catalyzed Vinylic C−H Arylation of Cyclic Enamides



Subsequently, the same group extended to establish a palladium(II)-catalyzed C−H arylation of cyclic enamides by using environmentally friendly arylsilanes as the coupling reagents, producing the corresponding 2-arylated enamides in 19−95% yield (Scheme 277a).[450] In this silicon-based strategy,

Scheme 277. Vinylic C−H Arylation of Enamides with Arylsilanes



AgF was employed as both an oxidant and a desilyl reagent. However, this strategy was found to be incompatible with acyclic enamides. To address this issue, Luo and co-workers very recently successfully developed an efficient Cp*Rh(III) catalysis system to realize the highly stereoselective direct β-C(sp^2)−H bond arylation of acyclic enamides with electronically and sterically (hetro)arylsilanes by the judicious utilization of copper(II) fluoride as the efficacious sliane activator and catalyst reoxidant (Scheme 277b).[451]

During the course of their investigations, Loh and co-workers also achieved a novel Pd(II)-catalyzed C(sp^2)−C(sp^2) dehydrogenative cross-coupling reaction for the β-C−H arylation of enamides by employing simple arenes in the reaction (Scheme 278a).[452] This process delivered the corresponding enamides with excellent *Z*-selectivity. Notably, this protocol accommodates a wide diversity of functional groups such as F, Cl, OMe, CF_3, COMe, and CO_2Me. Electron-rich arenes (such as toluene and diphenyl ether) and halobenzenes produced the corresponding *para*-, *meta*-, and *ortho*-regioisomers. Highly electron-deficient arenes such as methyl benzoate and benzotrifluoride predominantly afforded *meta*-isomers, while the *ortho*-isomers were not obtained in the reaction. In addition, a double arylation done in sequence *via* the monoarylated product was also investigated. When employing trifluoroacetic acid in replacement of acetic acid, the expected tetrasubstituted enamides were obtained in decent yields. Later in 2016, Piersanti and co-workers expanded Loh's strategy and detailed an efficient Pd(II)-catalyzed cross-dehydrogenative coupling between methyl *N*-phthaloyl dehydroalanine esters and diverse simple arenes (Scheme 278b).[453]

Diaryliodonium salts were identified as practical aryl sources in the copper(II)-catalyzed olfinic C−H arylation of cyclic

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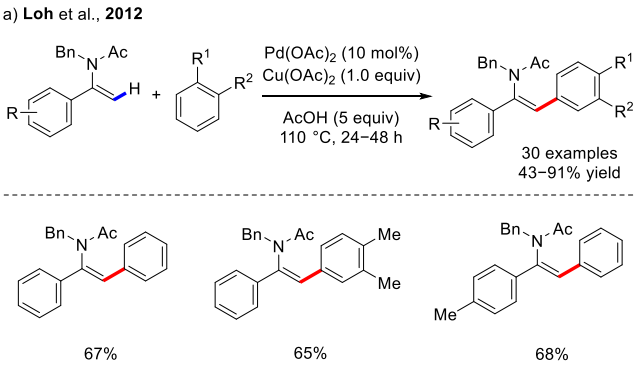
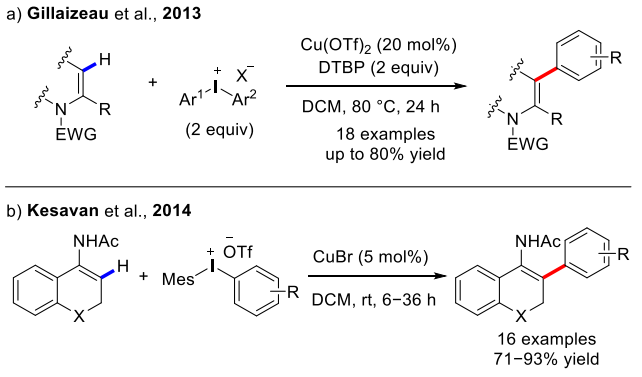
Scheme 278. Pd(II)-Catalyzed Alkenyl C−H Arylation of Enamides with Simple Arenes



enamides (Scheme 279a).[454] This process exhibited excellent functional group tolerance. Various sterically hindered diary-

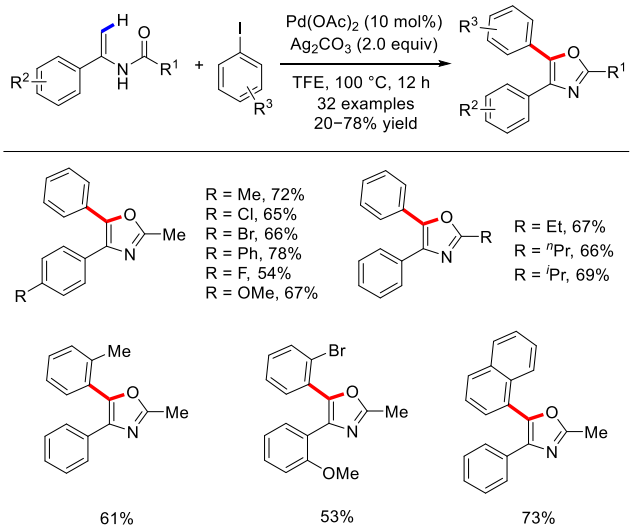
Scheme 279. Copper-Catalyzed Vinylic C−H Arylation of Enamides with Diaryliodonium Salts



liodonium salts, however, gave lower reactivity, and the expected products were not obtained. One year later, Kesavan's group also reported an efficient Cu(I)-catalyzed C−H arylation of cyclic enamides with diaryliodonium salts. Of note, this reaction was conducted at room temperature without any base or additive, featuring a wide substrate scope with good to excellent yields (Scheme 279b).[455]

In 2017, Zhang and co-workers elaborated a general approach for the synthesis of multisubstituted oxazoles by the tandem oxidative cyclization of acyclic enamides with aryl iodides (Scheme 280).[456] The reaction occurred *via* the amide-directed vinylic C−H arylation followed by a silver-mediated oxidative cyclization sequence, thus allowing the rapid assembly of 2,4,5-trisubstituted oxazoles from readily available

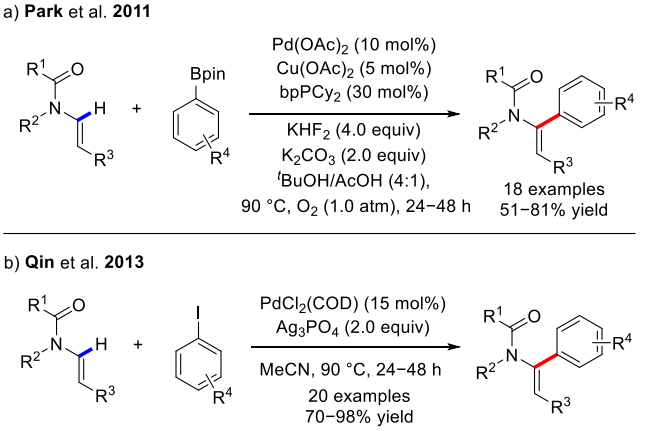
Scheme 280. Synthesis of Substituted Oxazoles *via* Pd-Catalyzed Cascade Oxidative Cyclization of Enamides



starting materials. As a particular highlight, the authors showcased the potential of this protocol by the straightforward construction of the core skeleton of a nonsteroidal anti-inflammatory drug aristoxazole.

Apart from β-selective alkenyl C(sp^2)−H arylation of enamides, Park's group in 2011 successfully developed a palladium(II)-catalyzed α-C−H arylation of *N*-substituted enamides with arylboronic acids under oxidative Heck cross-coupling conditions, enabling the stereoselective synthesis of β-substituted β-amidoacrylate derivatives in moderate to high yields (Scheme 281a).[457] Subsequently, Qin and co-workers

Scheme 281. Pd(II)-Catalyzed Vinylic α-C−H Arylation of Enamides



expanded this strategy to report an efficient α-C(sp^2)−H arylation of *N*-substituted enamides with aryl iodides under a $PdCl_2(COD)/Ag_3PO_4$ catalytic system. The scope of both enamides and aryl iodides were found to be broad and not sensitive to electronic and steric factors (Scheme 281b).[458]

Moreover, Loh's group continued their alkenyl C−H activation strategy onto enamide, and described the intramolecular palladium(II)-catalyzed C−H arylation of *N*-protected enamides *via* a *6-endo* Heck cyclization process, providing a robust access to substituted 1,2-dihydroisoquinoline derivatives (Scheme 282).[459] By the combination of

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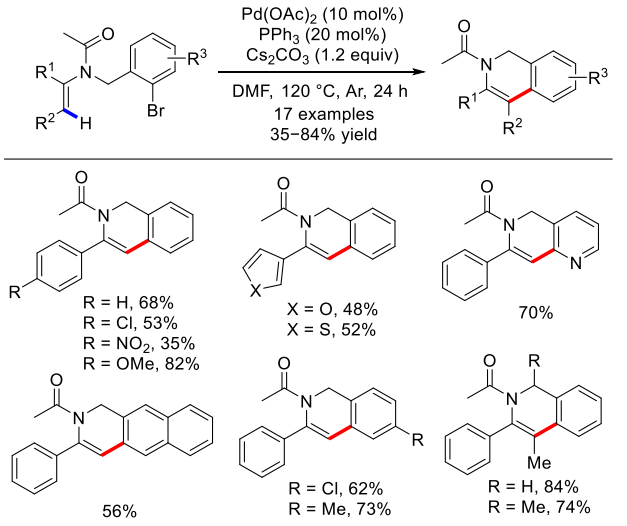
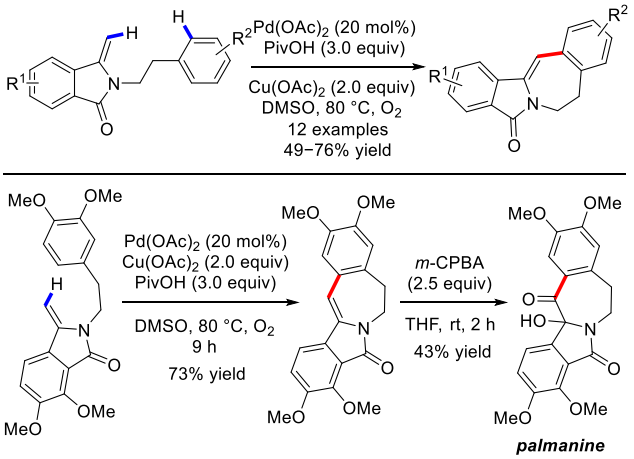
Scheme 282. Palladium(II)-Catalyzed Intramolecular Vinylic C−H Arylation of Enamides



$Pd(OAc)_2$ catalyst, PPh_3 ligand and Cs_2CO_3 base in DMF at 120 °C, a scope of 17 examples of this reaction was documented in reasonable yields of 35−84%. Notably, various nitrogen-containing products such as 1,1′-disubstituted ethylenes, 2-azabicyclo[3,3,0]octadienes, as well as 5/5/6-membered pyrroloisoindolone derivatives can be obtained through a rare *β*-N−Pd elimination process by fine-tuning the phosphine ligands and bases.

Afterward, the group of Tong and Wang elaborated an efficient and straightforward synthesis of 2,3-dihydro-1*H*-benzo[*d*]azepine, a seven-membered heterocyclic core embedded in 7,8-dihydro-5*H*-benzo[4,5]-azepino[2,1-*a*]isoindol-5-one *via* the Pd(II)-catalyzed intramolecular cross-dehydrogenative coupling of both aryl and vinyl C−H bonds (Scheme 283).[460] The authors showcased the practicality of this

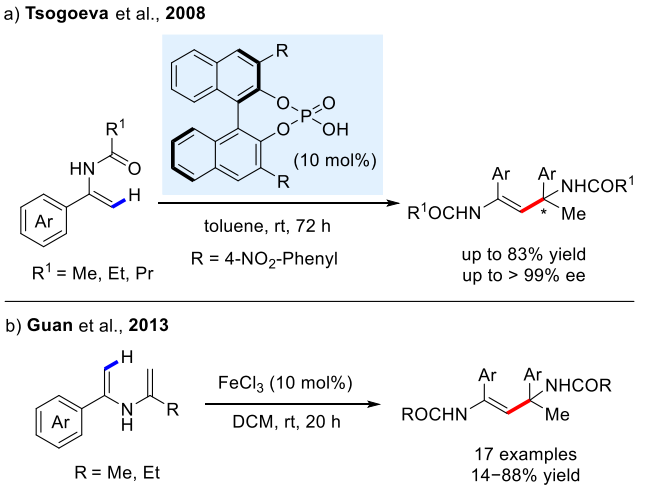
Scheme 283. Synthesis of *N*-Heterocyclic Scaffolds *via* Pd(II)-Catalyzed Dehydrogenative Cross-Coupling



protocol by the total synthesis of aporhoeadane alkaloids, including palmanine, chilenamine, and lennoxamine, by using this strategy as the key step.

5.1.2. Alkylation. Kobayashi's group in 2004 discovered that enamides could be employed as nucleophiles to couple with a series of electrophiles in the presence of strong Lewis or Brønsted acids, and the cross-coupling products of enamides were eventually obtained.[461−463] Inspired by this work, Tsogoeva's group investigated a chiral Brønsted acid-catalyzed stereoselective reaction of enamides to form alkylated enamides bearing a chiral quaternary carbon center (Scheme 284a).[464] Later in 2013, Guan and co-workers reported the

Scheme 284. Self-Condensation of Enamides for the Synthesis of Enamido-Substituted Nitrogen-Containing Quaternary Carbon Centers

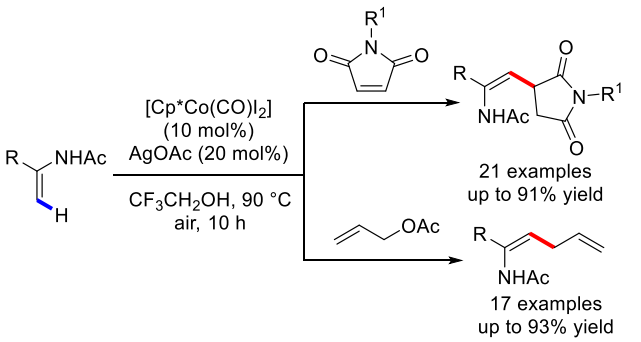


Fe(III)-catalyzed self-condensation of various enamides, putting forward a novel and practical approach for the assembly of nitrogen-containing quaternary carbon centers (Scheme 284b).[465] Of note, the reaction was typically performed at room temperature, and a scope of 17 examples of this transformation was presented with acceptable yields.

Transition metal-catalyzed alkenyl C(sp^2)−H alkylation through an enamide-directing group is an effective strategy for producing the alkylated enamides. In 2017, Zhang's research group reported a Cp*Co(III)-catalyzed olefinic C(sp^2)−H alkylation of enamides with maleimides. This reaction could be accomplished with the allylated *Z*-enamides formed exclusively (Scheme 285).[466] Notably, allyl acetates were also viable coupling partners under the conditions to afford the allylation products.

Recently, tremendous efforts have been directed toward the radical-type C−H alkylation of enamides. For example, Loh's group in 2016 investigated the alkenyl C−H alkylation of enamides with *α*-bromo carbonyl compounds through a radical

Scheme 285. Cobalt(III)-Catalyzed Cross-Coupling of Enamides with Maleimides/Allyl Acetates



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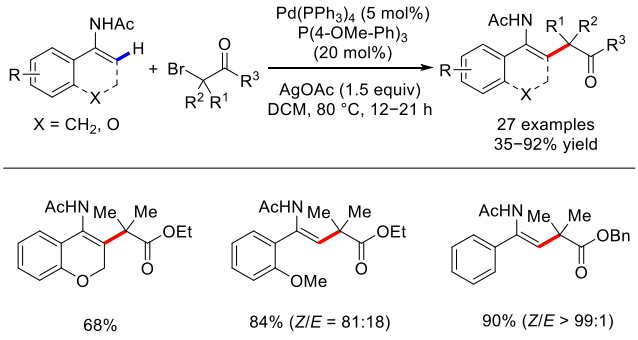
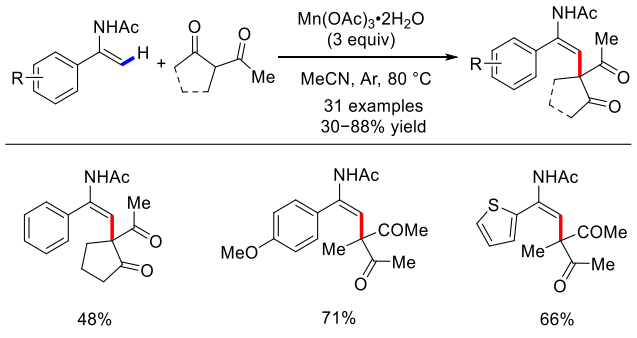
pathway. Under the optimal reaction conditions, a handful of enamides coupled efficiently with α-bromo carbonyls to deliver the expected alkylation products in high yields (Scheme 286).[467]

Scheme 286. Cross-Coupling of Enamides with Sterically Hindered α-Bromocarbonyls



1,3-Dicarbonyl compounds could also be used as alkyl radicals to couple with enamides. In 2004, an efficient Mn(III)-mediated oxidative CDC reaction between acyclic enamides and 1,3-dicarbonyl compounds was reported by Li's group. In the presence of $Mn(OAc)_2 \bullet 2H_2O$, a broad scope of 31 examples was presented in reasonable yields of 30−88% (Scheme 287).[468]

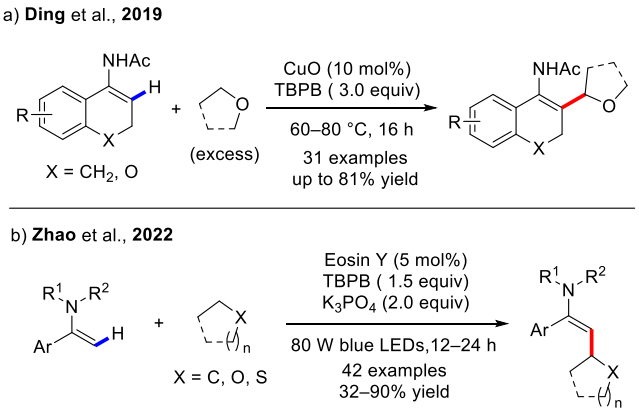
Scheme 287. Direct Oxidative Coupling of Enamides and 1,3-Dicarbonyl Compounds



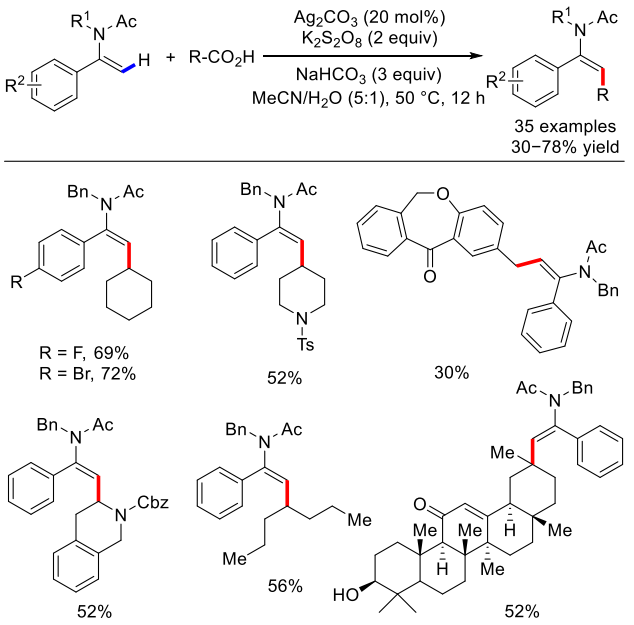
Moreover, ether compounds have also been exploited as alkyl radical precursors in the presence of excess amounts of oxidants. Specifically, Ding *et al.* in 2019 accomplished a Cu-catalyzed oxidative cross-dehydrogenative coupling (CDC) reaction of cyclic enamides with ethers, yielding the desired alkylated enamides in good yields (Scheme 288a).[469] Quite recently, Zhao and co-workers also achieved an analogous transformation under photoredox catalysis. In this report, nonexpensive and nonpoisonous eosin Y was employed as the photocatalyst. A broad range of ethers, thioethers, or even simple alkanes were all competent coupling partners in this metal-free protocol (Scheme 288b).[470]

It is established that readily available alkyl carboxylic acids are extensively exploited as $C(sp^3)$-radical precursors *via* a single-electron transfer (SET) and decarboxylation pathway. In continuation with their investigations of β-$C(sp^2)$−H functionalization of enamides, Loh and co-workers successfully reported a direct Ag(I)-catalyzed decarboxylative β-$C(sp^2)$−H alkylation of enamides with commercially available alkyl carboxylic acids as alkylating reagents (Scheme 289).[471] By

Scheme 288. Alkenyl C−H Alkylation of Enamides with Ethers or Alkenes



Scheme 289. Ag(I)-Catalyzed Decarboxylative Cross-Coupling of Enamides with Unactivated Aliphatic Carboxylic Acids



the combination of Ag_2CO_3 catalyst, $K_2S_2O_8$ oxidant and $NaHCO_3$ base in $MeCN/H_2O$ at 50 °C, a broad array of enamides bearing various synthetically useful functional groups alkylated in reasonable yields of 30−78%.

Moreover, Loh's group also developed a visible-light-promoted, *fac*-$Ir(ppy)_3$-catalyzed decarboxylative C−H alkylation of enamides with activated alkyl carboxylic acids, alkyl *N*-hydroxyphthalimide esters (NHPI-esters). Under the optimized conditions, a broad diversity of enamides could be smoothly alkylated in this process, giving rise to the functionalized enamides in 53−91% yields. Notably, *N*-hydroxyphthalimide esters bearing primary, secondary, and even tertiary alkyl groups were all found to be viable substrates in this case (Scheme 290).[472] Quite recently, Chen and co-workers expanded to realize a similar visible-light-promoted decarboxylative alkylation under simple transition metal- and photocatalyst-free conditions.[473]

In 2019, Xiao's research group expanded their visible-light photoredox catalysis,[474] and reported an example of $Ir(4\text{-}Fppy)_2(bpy)PF_6$-catalyzed deaminative approach for the

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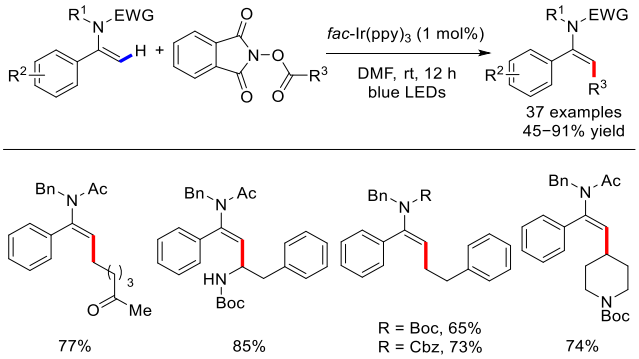
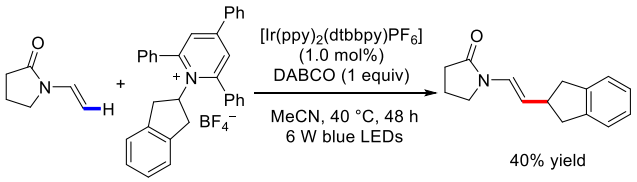
Scheme 290. Photoredox-Catalyzed C−H Alkylation of Enamides with *N*-Hydroxyphthalimide Esters



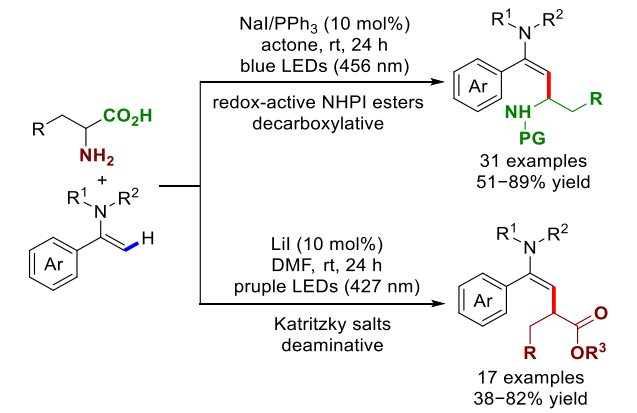
alkenyl C−H alkylation of enamide by making use of easily prepared Katritzky salts as the alkylating reagent, affording an alkylated enamide in 40% yield (Scheme 291).[475]

Scheme 291. Photoredox-Catalyzed Deaminative C−H Alkylation of Enamides with Katritzky Salts



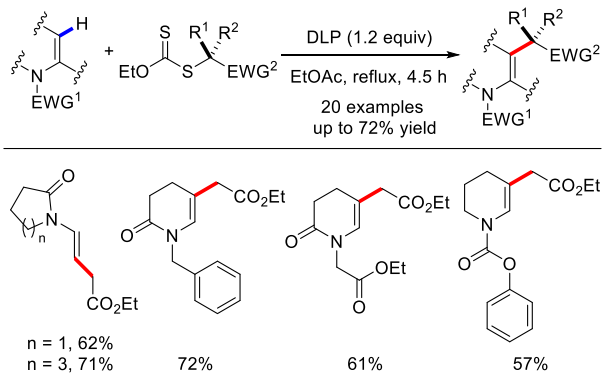
The use of rare and expensive iridium photocatalyst undoubtedly raises remarkable concerns about the sustainability and economics of this protocol. To this end, Fu's group in 2021 expanded this visible-light-induced deaminative alkylation of enamides with a large variety of Katritzky's *N*-alkylpyridinium salts of amino acids in the presence of 10 mol % LiI under purple LED irradiation conditions (Scheme 292).[476] Gratifyingly, this transition metal-free strategy is also compatible with redox-active NHPI-esters to generate the decarboxylative alkylation products by using a combination of NaI (10 mol %) and PPh_3 (10 mol %) in acetone. Both primary, secondary, and even tertiary unactivated alkyl carboxylic acids could participate in this stereoselective alkylation with modest to high yields (38−82%).

Scheme 292. Visible-Light-Induced Iodine-Anion-Catalyzed Decarboxylative/Deaminative Vinylic C−H Alkylation of Enamides



In 2020, Gillaizeau's group successfully applied xanthate-based radical chemistry to describe an efficient olefinic β-C−H alkylation of nonaromatic enamides with readily biodegradable lauroyl peroxide (DLP) as the radical initiator (Scheme 293).[477] This approach features a broad substrate scope and

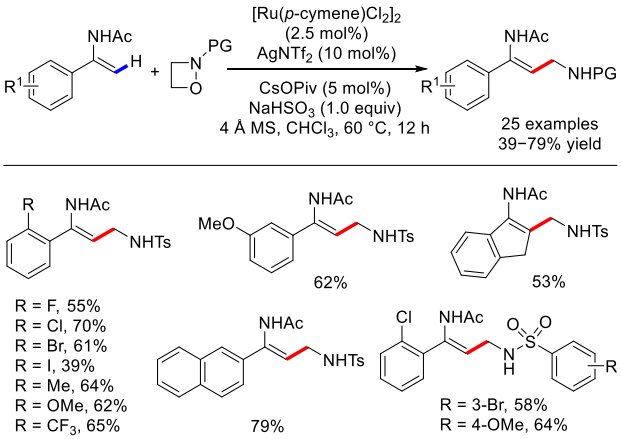
Scheme 293. Vinylic C(sp^2)−H Alkylation of Enamides Using Xanthate Chemistry



excellent functional group tolerance, thus leading to the expedient synthesis of a broad array of synthetically appealing γ-amino-β,γ-unsaturated acyl scaffolds in satisfactory yields.

Around the same time, Hu and co-workers employed 1,2-oxazetidines as the formaldimine precursors to participate in a novel Ru(II)-catalyzed regioselective alkenyl C−H aminomethylation of enamides through a ring-opening strategy (Scheme 294).[478] Notably, the corresponding aminomethy-

Scheme 294. Ru-Catalyzed C−H Aminomethylation of Enamides with 1,2-Oxazetidines



lated enamides could be readily converted into value-added nitrogen-containing scaffolds, which remarkably renders this protocol more synthetically useful for the synthesis of highly functionalized enamides.

Apart from the above-mentioned examples using a preinstalled directing group for the vinylic C−H bond functionalizations, the use of transient directing groups allows for a transient ligand to be used, potentially in catalytic quantities, thus without the need for preinstallation or subsequent removal steps.[479,480] In this regard, Dong's group in 2017 elegantly devised a novel *in situ* installed enamide-directing strategy for the synthesis of α-alkylated ketones enabled by a cationic iridium catalyst (Scheme 295),[481]

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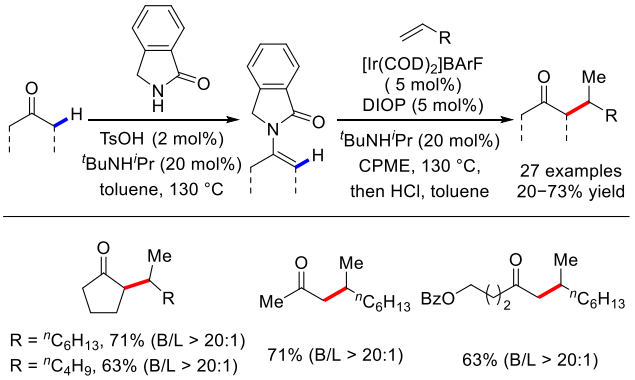
affording the branched-selective products which are extremely valuable building blocks but are nontrivial to obtain by conventional methods.[482]

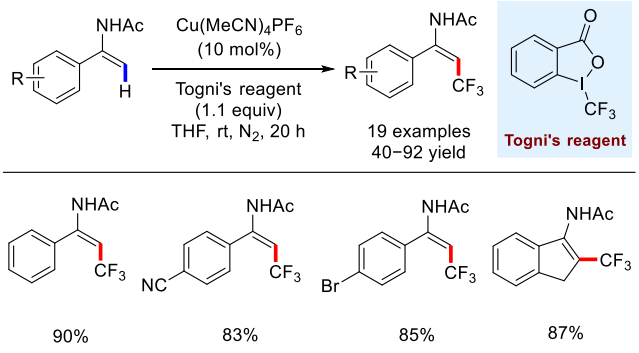
Scheme 295. Branched-Selective Ketone α-Alkylation *via* an Enamide Directing Strategy



5.1.3. Fluoroalkylation. Fluoroalkyl compounds have received elevated attention in the last 10 years because of their peculiar biological activities. In this context, the alkenyl C−H fluoroalkylation of enamides has been extensively investigated as an appealing strategy to obtain structurally diverse fluoroalkylated enamides.[483]

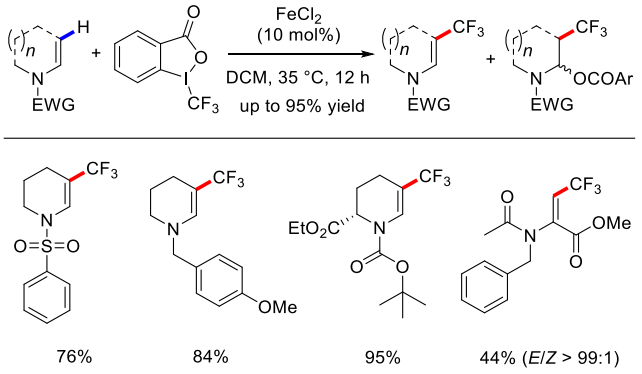
In particular, Togni's reagent has been widely utilized as the trifluoromethylation reagent in numerous C−H bond functionalization reactions.[484] In 2012, Loh's group disclosed an efficient and straightforward β-C(sp^2)−H trifluoromethylation of enamides catalyzed by a Cu(I) species (Scheme 296).[485] A large number of enamides with different substitution patterns were subjected to the optimized conditions, yielding the trifluoromethylated enamides in modest to good yields.

Scheme 296. Copper-Catalyzed Olefinic C−H Trifluoromethylation of Enamides



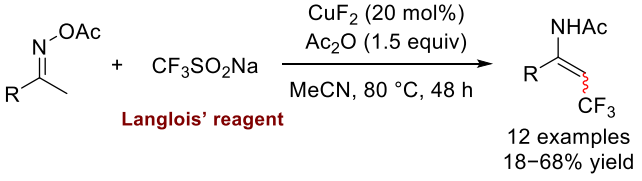
Contrastingly, radical oxidative cross-coupling could also offer a powerful strategy for the olefinic β-C−H trifluoromethylation of enamides. In this regard, Gillaizeau and coworkers in 2015 elaborated an efficient Fe(II)-catalyzed direct C3-trifluoromethylation of enamides with Togni's reagent through a radical pathway. The desired trifluoromethylated products were obtained in 31−95% yields (Scheme 297).[486] By decreasing the reaction time to 2 h, it was established that the oxotrifluoromethylated byproduct was detected in 55% yield. However, the deprotonation product was not formed when using methanol as the solvent instead.

Scheme 297. Fe-Catalyzed C−H Trifluoromethylation of Enamides



In 2017, Selander's group utilized inexpensive and air-stable Langlois' reagent (CF_3SO_2Na) as the radical fluoroalkyl source for the redox-economical synthesis of β-trifluoromethylated enamides *via* a Cu(II)-catalyzed reaction with oxime acetates (Scheme 298).[487]

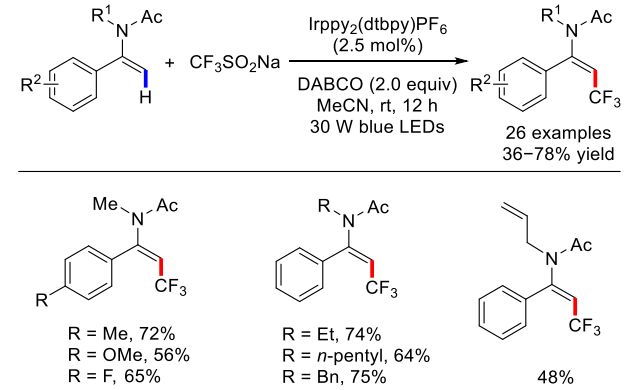
Scheme 298. Synthesis of Trifluoromethylated Enamides with Langlois' Reagent



Very recently, the group of Chen and Yang illustrated a convenient visible-light-promoted approach for the vinylic β-C−H trifluoromethylation of enamides with Langlois' reagent as the CF_3 radical source (Scheme 299).[488] An array of trifluoromethylated enamides were produced in modest to high yields with good *E*-selectivity under typically mild conditions.

The direct C−H difluoromethylation of enamides could also be realized under photoredox catalysis. In 2019, Loh and coworkers disclosed a direct Ir(ppy)$_3$-catalyzed β-C(sp^2)−H difluoromethylation of both cyclic and acyclic enamides by making use of a difluoromethylating reagent [PPh_3CF_2H]Br

Scheme 299. Visible-Light-Promoted Olefinic C−H Trifluoromethylation of Enamides with Langlois' Reagent



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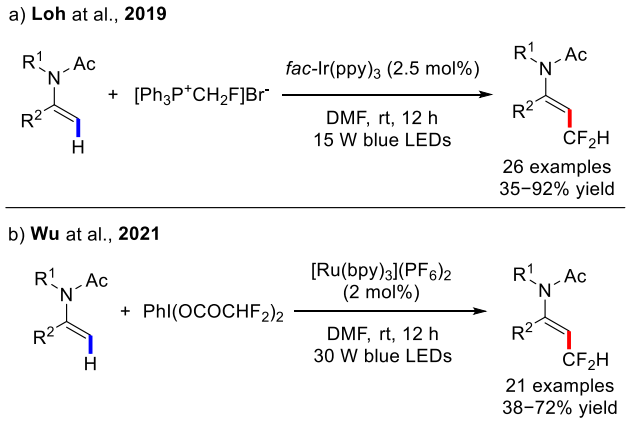
promoted by visible-light (Scheme 300a).[489] A large variety of β-difluoromethylated enamides bearing various synthetically

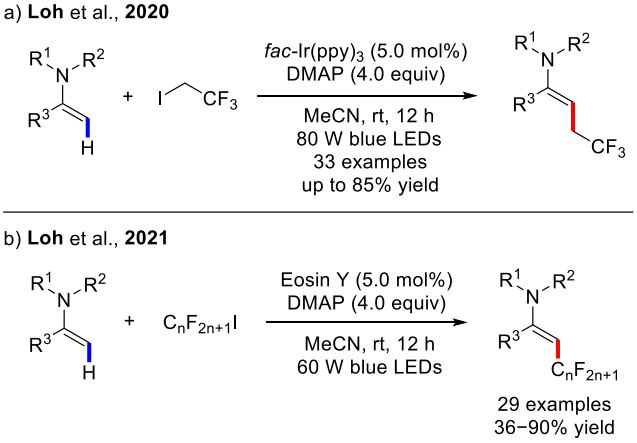
Scheme 300. Difluoromethylation of Enamides *via* Photoredox Catalysis



useful functional groups were obtained in moderate to excellent yields (35−91%). Following this, Wu's group later employed easily accessible hypervalent iodine(III) [bis-(difluoroacetoxy)iodo]benzene reagents to engage this photoredox-catalyzed process to generate a broad range of (*E*)-β-difluoromethylated enamides (Scheme 300b).[490]

Loh and co-workers further achieved a photoredox-catalyzed β-C(sp^2)−H trifluoroethylation of enamides with commercially available 2,2,2-trifluoroethyl iodide, thus allowing a robust and efficacious synthetic route to various pharmaceutically pivotal β-trifluoroethylated enamides with excellent regio- and stereoselectivities (Scheme 301a).[491] Subsequently, the

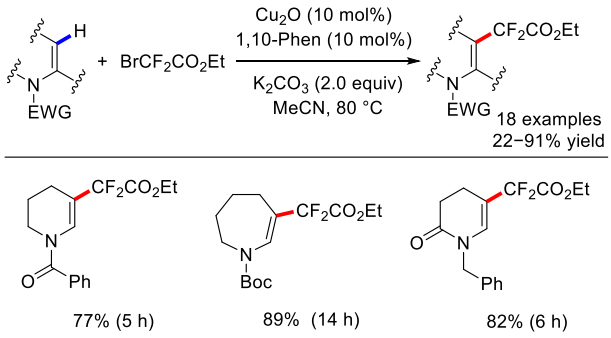
Scheme 301. Visible-Light-Induced Vinylic C−H Trifluoroethylation and Perfluoroalkylation of Enamides



same group further described a metal-free visible-light-induced stereoselective alkenyl C(sp^2)−H perfluoroalkylation of structurally diverse enamides with perfluoroalkyl iodides in the presence of organic dye eosin Y as the photocatalyst, giving rise to a sustainable and environmentally benign approach to the synthesis of perfluoroalkyl-containing enamides (Scheme 301b).[492]

Commercially available fluoroalkyl halides have been extensively employed as fluoroalkyl radical sources under transition-metal-catalyzed reaction conditions. The copper-based catalytic system has been established as an effective approach for the β-C(sp^2)−H functionalization of enamides. In the very first report of its kind, Gillaizeau's group disclosed a Cu(I)-catalyzed alkenyl C−H fluoroalkylation of enamides using $BrCF_2CO_2Et$ (Scheme 302).[493] On the basis of

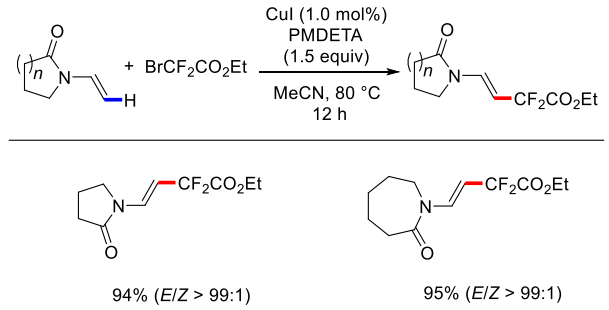
Scheme 302. Copper-Catalyzed Olefinic C−H Difluoroacetylation of Enamides



mechanistic studies, it was established that the fluorinated enamide was obtained in a comparable yield when one equivalent of TEMPO was added. More recently, the same group further achieved a similar (fluoro)alkylation under iron catalysis.[494]

In 2017, an easily accessible Cu(I)-catalyzed β-C(sp^2)−H fluoroalkylation of enamides with fluoroalkyl halides *via* a radical addition/oxidation/deprotonation sequence was reported by Wang's group (Scheme 303).[495]

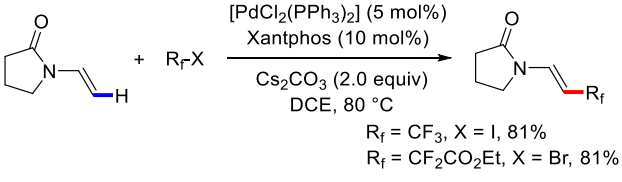
Scheme 303. Copper-Catalyzed Vinylic C−H Difluoroalkylations and Perfluoroalkylations of Alkenes



The palladium(II)-catalyzed Heck-type fluoroalkylation of enamides and simple alkenes with fluoroalkyl halides was investigated by Zhang's group (Scheme 304).[496,497] In the majority of the examples, the β-fluoroalkylated derivatives were obtained in excellent yields.

Moreover, β-C(sp^2)−H fluoroalkylation of enamides promoted by visible-light *via* photocatalysis was also

Scheme 304. Palladium-Catalyzed Heck-Type C−H Difluoroalkylation of Alkenes



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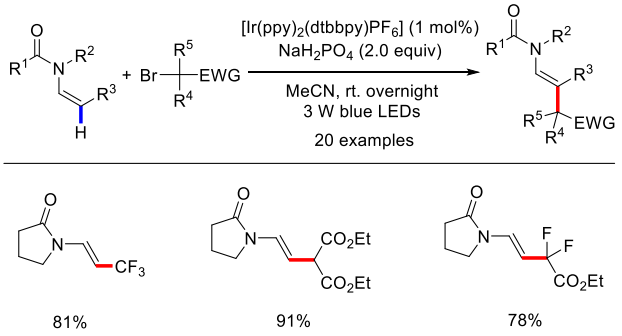
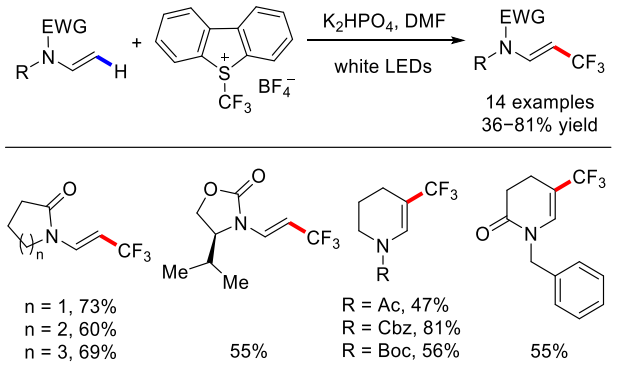
established. In 2012, Yu's group detailed a radical C−H alkylation of enamides promoted by visible-light by taking advantage of $[Ir(ppy)_2(dtbbpy)PF_6]$ as a photocatalyst. In this approach, electron-withdrawing groups bearing halides were utilized as the alkylating radical agents to generate the desired products in decent yields (Scheme 305).[498] Remarkably, CF_3SO_2Cl was also a competent trifluoromethyl radical source, affording the desired trifluoromethylated enamide in 81% yield.

Scheme 305. Direct Vinylic C−H Functionalization of Enamides Using Visible-Light Photoredox Catalysis



In 2016, Yu's group extended to investigate the vinylic β-C−H trifluoromethylation of enamides promoted by visible-light in the absence of any photocatalyst. By making use of Umemoto's reagent as the trifluoromethylating reagent, the desired trifluoromethylated enamides were produced in modest to good yields (Scheme 306).[499]

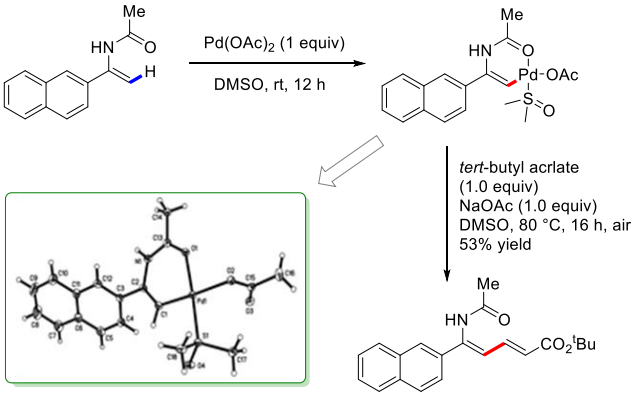
Scheme 306. Visible-Light-Promoted and Photocatalyst-Free Trifluoromethylation of Enamides



5.1.4. Olefination. The direct alkenyl β-C(sp^2)−H olefination of enamides can be readily achieved through a vinylic C−H activation strategy. In 2011, Loh's group reported the first example of Pd(II)-catalyzed oxidative cross-coupling reaction of structurally diverse enamides with acylates by using molecular oxygen as the terminal oxidant. The X-ray structure of the cyclic vinylpalladium(II) complex was obtained, suggesting that C−H activation was most probably involved in the mechanism (Scheme 307).[500]

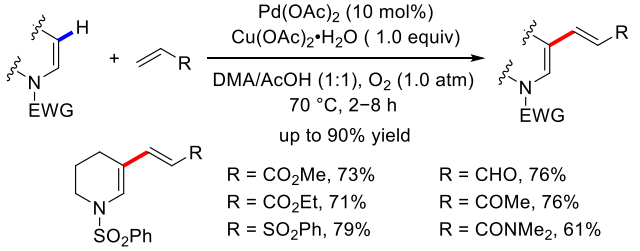
Later, Gillaizeau's group devised a mild and effective strategy for the β-C−H olefination of nonaromatic enamides *via* a Pd(II)-catalyzed alkenyl C−H activation process (Scheme 308).[501] This work exhibited a wide substrate scope of both

Scheme 307. Synthesis and Characterization of a Cyclic Vinylpalladium(II) Complex



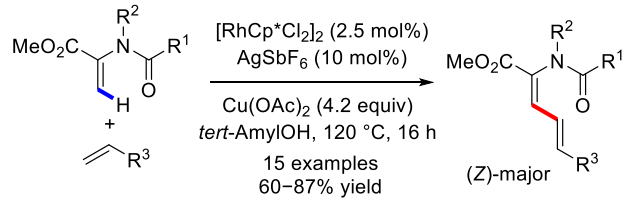
nonaromatic cyclic enamides and electronically activated alkenes.

Scheme 308. Pd(II)-Catalyzed Direct C−H Olefination of Nonaromatic Enamides



Rhodium complex was also proved to be an efficient catalyst for the β-C−H alkenylation of enamides. Glorius and co-workers used $[RhCp^*Cl_2]_2$ and $AgSbF_6$ along with $Cu(OAc)_2$ as the oxidant. They demonstrated a Cp*Rh(III)-catalytic system for the alkenylation of enamides with terminal olefins (Scheme 309).[502] However, simple enamides were found to be

Scheme 309. Cp*Rh(III)-Catalyzed Oxidative Vinylic C−H Olefination of Enamides



inappropriate for this process. Ester-substituted enamides presented an appropriate electronic disposition, which underwent a smooth transformation with olefins to afford the *Z*-isomers as major products.

In 2018, Dong's group presented a Cp*Rh(III)-catalyzed amide directing group-assisted C−H alkenylation between oxindoles and activated olefins, thus allowing an atom-economical and straightforward strategy to construct valuable and multipurpose functionalized *N*-(2*E*,4*Z*)-butadiene substituted oxindoles (Scheme 310).[503] Oxindoles functioned well as a directing-group was utilized extensively in this protocol.

5.1.5. Alkynylation. In a similar fashion, nitrogen-containing conjugated enynes could be readily acquired by

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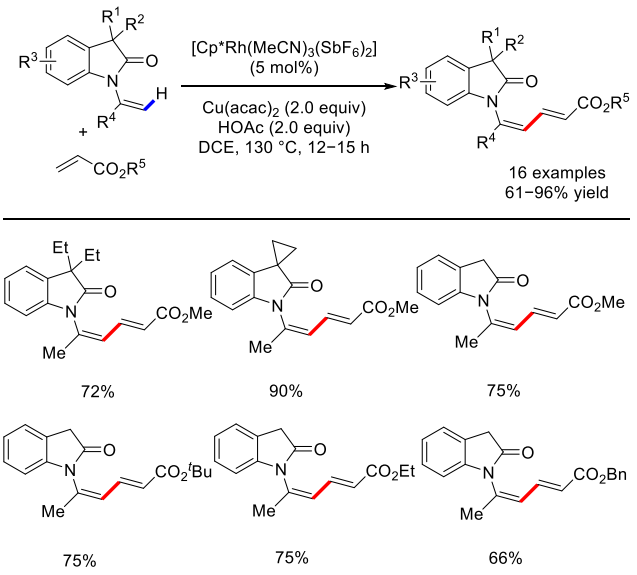
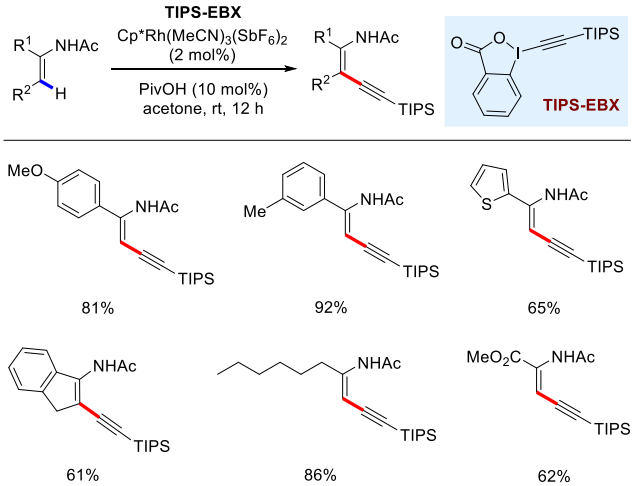
Scheme 310. Cp*Rh(III)-Catalyzed Alkenylation of Oxindoles and Olefins to Synthesize *N*-(2*E*,4*Z*)-Butadiene Substituted Oxindoles



the β-C(sp^2)−H alkynylation of enamides. Since the early 2010s, Loh's group reported an effective Cp*Rh(III)-catalyzed olefinic β-C−H alkynylation of enamides by using an alkynyliodonium(III) reagent (TIPS-EBS) for the stereospecific configuration of synthetically practical *Z*-enynamides under extremely benign conditions (Scheme 311).[504] This

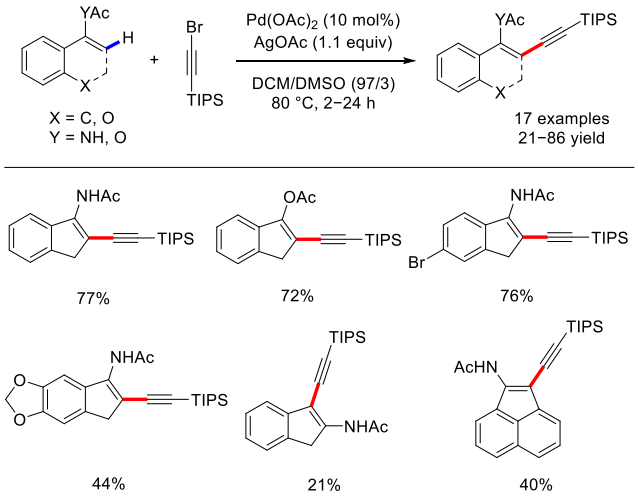
Scheme 311. Rhodium(III)-Catalyzed Olefinic C−H Alkynylation of Enamides



catalytic system portrayed an excellent tolerance of various functional groups. The process was well tolerated, with aryl-substituted enamides bearing electron-rich groups (Me, OMe, Ph, *N*-piperidyl), electron- deficient groups (CF_3, CN, SO_2Me, COMe) as well as halogen groups (F, Cl, Br). In addition, both naphthyl-substituted and heterocyclic enamides reacted smoothly in this transformation. Remarkably, nonaromatic enamides also gave the alkynylated products in excellent yields, and ester-substituted enamides reacted smoothly in this process.

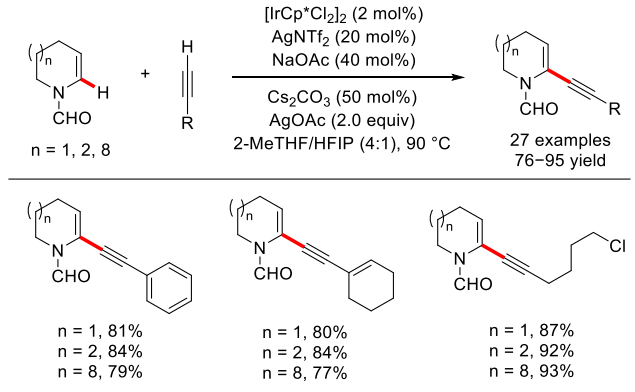
On the basis of the six-membered palladacycle complex, Loh and co-workers further established an efficient Pd(II)-catalyzed C−H alkynylation of cyclic enamides on the C3-position with readily available alkynyl bromides (Scheme 312).[505] Of note, DMSO was necessarily added as a ligand to stabilize the transition state in this process.

Scheme 312. Palladium-Catalyzed C−H Alkynylation of Enamides with Alkynyl Bromides



A couple of years later, Beng and co-workers described an atom-economical Cp*Ir(III)-catalyzed dehydrogenative vinylic β-C(sp^2)−H alkynylation of cyclic nonaromatic eneformamides with diverse terminal alkynes (Scheme 313).[506] The

Scheme 313. Iridium-Catalyzed α-C−H Alkynylation of Cyclic Nonaromatic Eneformamides



versatility of the corresponding α-alkynyl eneformamides renders this protocol synthetically appealing for the synthesis of azapolycyclic architectures and relevant saturated cyclic amines.

5.1.6. Carbonylation. Carbonyl compounds are crucial intermediates in synthetic organic chemistry, and a large number of robust strategies for the incorporation of this functional group into synthetically useful organic molecules have been reported over the decades.[507] Lately, numerous investigations have been focused on the alkenyl C−H carbonylation of enamides catalyzed by transition metals, and a handful of acylating agents are utilized for the incorporation of carbonyl groups.

Direct carbonylation reactions with CO have been and will continue to be a hot research topic in the fertile field of C−H functionalization reactions. In this regard, Guan and co-

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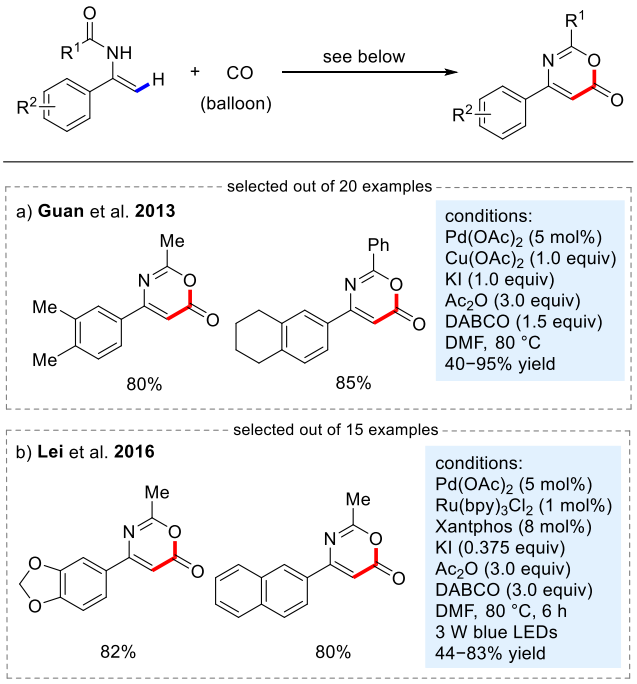
workers in 2013 reported a Pd(II)-catalyzed vinylic C−H carbonylation of acyclic enamides with atomospheric pressure of CO in the presence of KI and Ac_2O as additives (Scheme 314a).[508] Afterward, Lei's group also achieved this oxidative

Scheme 314. Oxidative Alkenyl C−H Carbonylation of Enamides with Carbon Monoxide

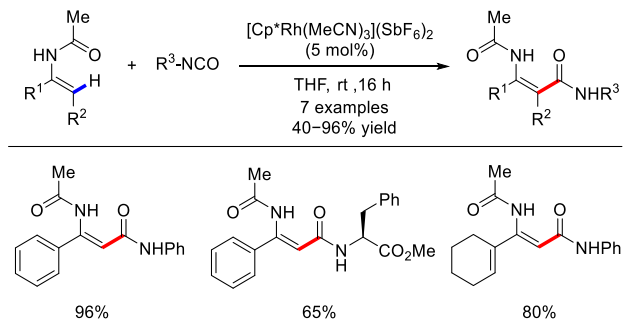


alkenyl C−H carbonylation by combination of photoredox and palladium catalysis in conjunction with molecular oxygen as the terminal oxidant, which remarkably obviated the use of stoichiometric amounts of $Cu(OAc)_2$, thus providing an environmentally friendly approach for the rapid synthesis of 1,3-oxazin-6-ones in 44−83% yields (Scheme 314b).[509]

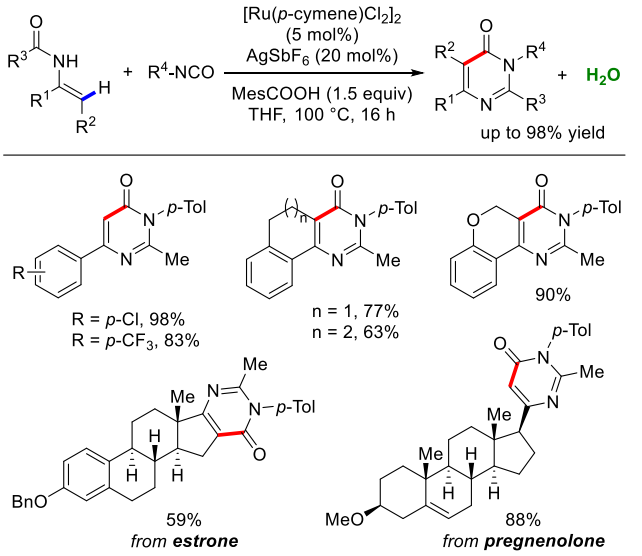
In 2011, Bergman, Ellman, and co-workers investigated a vinylic C−H activation strategy through a Cp*Rh(III)-catalyzed amidation of enamides with isocyanates. Under the standard conditions, the expected enaminone products were obtained in satisfactory yields (Scheme 315).[510]

Later, Loh and colleagues were able to establish a practical and environmentally friendly approach for the straightforward construction of pyrimidin-4-ones through an efficient Ru(II)-catalyzed heteroannulation between enamides and isocyanates (Scheme 316).[511] This strategy proceeded with a diverse

Scheme 315. Rh(III)-Catalyzed Alkenyl C−H Amidation of Enamides with Isocyanates



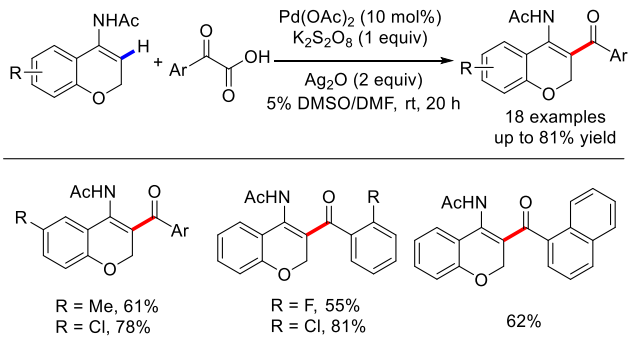
Scheme 316. Synthesis of Pyrimidin-4-ones through a Ruthenium-Catalyzed Heteroannulation between Enamides and Isocyanates



substrate scope and excellent functional group compatibility, only releasing water as an innocuous waste. Of note, the authors demonstrated the feasibility of this strategy by late-stage modification of biologically active natural products.

The group of Guo and Duan illustrated a Pd(II)-catalyzed alkenyl C−H functionalization approach *via* a decarboxylative acylation of cyclic enamides with various α-oxocarboxylic acids as the efficacious acylating agents under typically mild conditions, allowing a practical and efficient method for the preparation of acylated enamides from readily available starting materials. (Scheme 317).[512]

Scheme 317. Palladium-Catalyzed Decarboxylative Acylation of Enamides with α-Oxocarboxylic Acids



Liang and co-workers achieved a palladium(II)-catalyzed chelation-assisted β-C(sp^2)−H carboxamidation of acyclic enamides through the incorporation of isocyanides. This strategy portrayed excellent functional group compatibility, yielding the corresponding enaminone products in modest yields. (Scheme 318).[513]

Moreover, the sustainable iron-catalyzed alkenyl β-C−H carbonylation of enamides was also investigated through a carbonyl radical pathway. In 2014, Loh's group reported the C−H alkoxycarbonylation of acyclic enamides with carbazates enabled by an iron(II)phthalocyanine [Fe(Pc)] catalyst in conjunction with *tert*-butyl hydroperoxide (TBHP) as an

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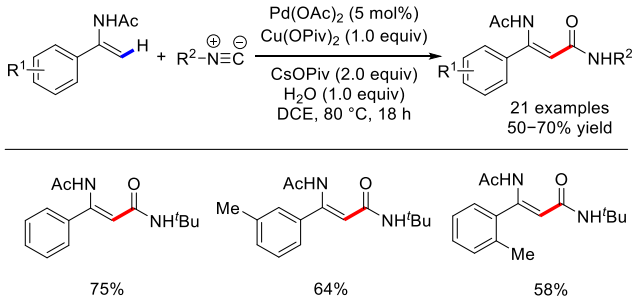
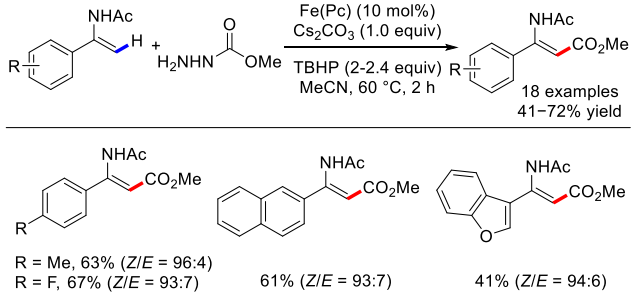
Scheme 318. Synthesis of *N*-Acyl Enamine Amides *via* Pd(II)-Catalyzed C−H Carboxamidation of Enamides with Isocyanides



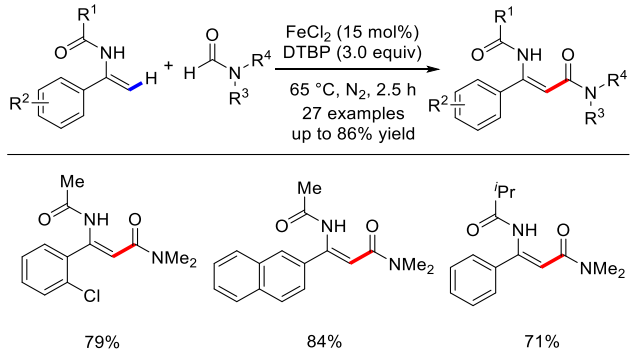
oxidant, generating the enaminone products in modest yields (Scheme 319).[514]

Scheme 319. Iron-Catalyzed C−H Alkoxycarbonylation of Enamides with Carbazates



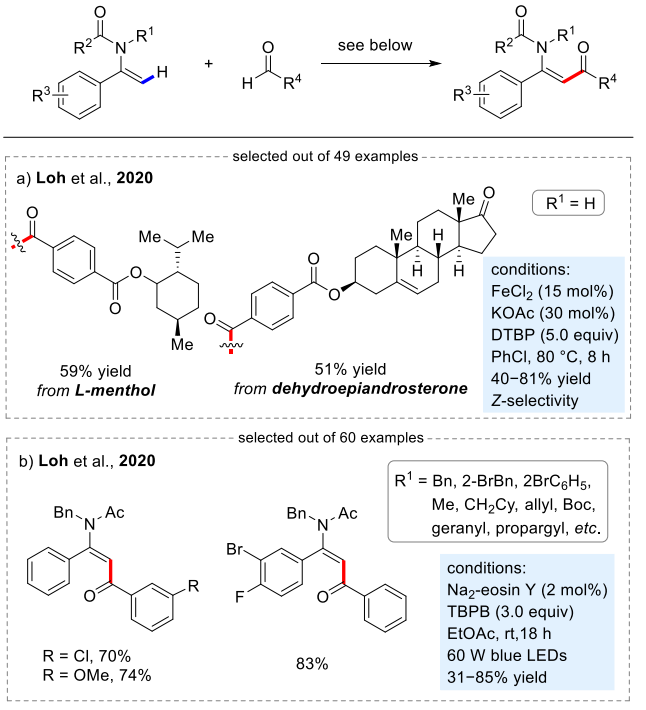
Enlightened by this work, Loh and co-workers continued to investigate the Fe(II)-catalyzed C−H carbonylation of enamides and reported the dehydrogenative cross-coupling reactions between acyclic enamides and formamides (Scheme 320).[515] This protocol gave rise to various carbamoylated enamides with complete *Z*-selectivities.

Scheme 320. Iron-Catalyzed C−H Carbamoylation of Enamides with Formamides



Subsequently, the same group further reported an efficient dehydrogenative carbonylation of enamides with simple aldehydes enabled by an iron catalyst to deliver a diverse series of synthetically valuable β-ketoenamides with excellent stereoselectivity and good functional group tolerance. Notably, this approach was applicable to late-stage diversification of biologically active natural products (Scheme 321a).[516] Meanwhile, Loh and co-workers also achieved this transformation

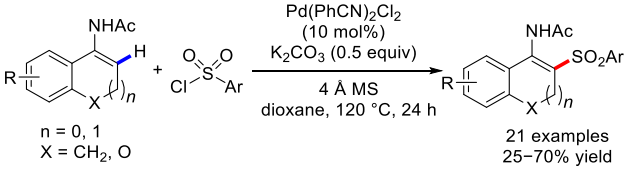
Scheme 321. Synthesis of β-Ketoenamides *via* Olefinic C−H Carbonylation of Enamides with Aldehydes



through a sustainable and environmentally friendly transition-metal-free photoredox catalysis, affording the β-ketoenamides in 35−91% yields. (Scheme 321b).[517]

5.1.7. Sulfonylation. β-Amido sulfones serve as crucial scaffolds widespread in a variety of pharmaceutically relevant compounds and bioactive natural products. The development of efficient strategies for the synthesis of β-amidovinyl sulfones is highly sought after. Among the established methods, the direct alkenyl C−H sulfonylation of enamides offers a rapid route to acquire β-amidovinyl sulfones. In this regard, Loh's group in 2013 reported a Pd(II)-catalyzed alkenyl C−H sulfonylation of cyclic enamides with commercially available sulfonyl chlorides (Scheme 322).[441] A handful of structurally diverse arylsulfonyl chlorides were studied under the optimized conditions, and the expected coupling products were formed in modest yields.

Scheme 322. Palladium-Catalyzed Alkenyl C−H Bond Sulfonylation of Enamides



By making use of $Ir(ppy)_2(dtbbpy)PF_6$ as a photoredox catalyst, Yu's group in 2013 described a similar C−H sulfonylation of acyclic enamides promoted by visible light through a radical mechanism. The process features a broad substrate scope of both enamides and sulfonyl chlorides, yielding a series of β-amidovinyl sulfones in 65−99% yields (Scheme 323).[518]

In 2018, the oxidative cross-coupling synthesis of β-amino sulfones from sodium sulfinates and enamides through a metal-

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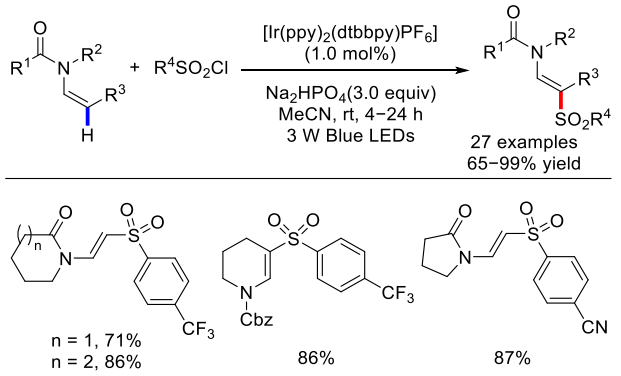
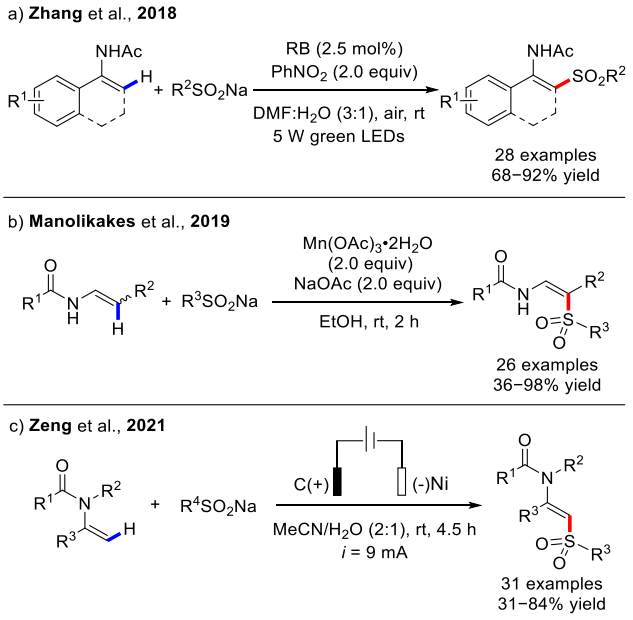
Scheme 323. Photoredox-Catalyzed Alkenyl C−H Bond Sulfonylation of Enamides



free, visible-light promoted approach was reported by Zhang's group (Scheme 324a).[519] This process utilized a cost-effective,

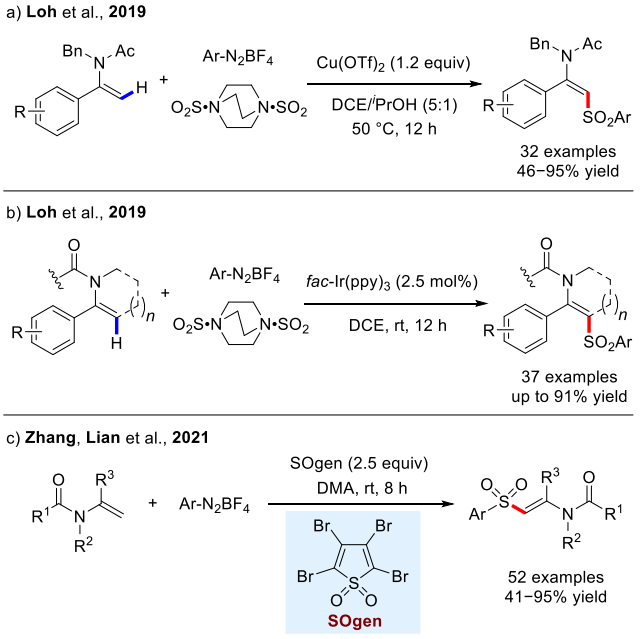
Scheme 324. Direct Alkenyl C−H Sulfonylation of Enamides with Sodium Sulfinates



readily available organic dye Rose Bengal (RB) as the photoredox catalyst in combination with nitrobenzene or atmospheric oxygen as the oxidant. The scope of enamides was found to be broad and not sensitive to electronic and steric factors. The desired sulfonylated enamides were obtained in high yields (68−92%). Subsequently, Manolikakes' group also realized the C−H sulfonylation of acyclic enamides with comparable efficiency through a manganese(III) acetate-mediated radical process (Scheme 324b).[520] More recently, Zeng and co-workers further achieved a sustainable electrochemical sulfonylation of acyclic enamides under metal- and oxidant-free conditions (Scheme 324c).[521]

The direct incorporation of sulfur dioxide (SO_2) has been used as an appealing approach for the construction of sulfonyl derivatives.[522] In 2019, Loh and colleagues elaborated a copper-mediated three-component coupling reaction between acyclic enamides, aryldiazonium tetrafluoroborates, and 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO) for the synthesis of β-arylsulfonylated enamides (Scheme 325a).[523] In

Scheme 325. Alkenyl C−H Sulfonylation of Enamides with DABSO and SOgen



the same year, they also invesitgated this vinylic C−H arylsulfonylation of enamides under $Ir(ppy)_3$ catalysis in the absence of blue LEDs irradiation (Scheme 325b).[524] This process occurred under benign conditions, giving rise to the corresponding β-amidovinyl sulfones in up to 91% yield. More recently, Zhang and Lian further established a transition-metal- and base-free strategy for the arylsulfonylation of enamides by using a cheap and bench-stable SO_2 surrogate (tetrabromothiophene *S*,*S*-dioxide, SOgen),[525] which could ex situ generate SO_2 gas in a controlled and predictable manner (Scheme 325c).[526]

5.1.8. Phosphorylation. Phosphorus is one of the most abundant elements in the earth's crust which plays an indispensable role in the growth of living organisms.[527] Accordingly, it is crucial to establish robust strategies for the synthesis of structurally diverse phosphorus-containing compounds (especially β-phosphorylated enamides) because of their widespread applications in synthetic chemistry. The groups of Zhang and Zou independently described the Mn(III)-mediated oxidative CDC reaction of acyclic enamides with *H*-phosphonates or *H*-phosphine oxides. Specifically, Zhang's group demonstrated the synthesis by means of $Mn(acac)_3$ as the oxidant in conjunction with toluene as the solvent without the use of any base in the reaction. The protocol exhibited a diverse scope of substrate with excellent *Z*-selectivity (Scheme 326a).[528] On the other hand, Zou's group discovered that $Mn(OAc)_3$ could provide comparable efficiency in the presence of K_2CO_3 in methanol. The reaction was typically finished within 0.5 h at room temperature, affording β-phosphorylated enamides as *E*/*Z*-configurations mixtures with the *E*-isomers formed predominantly (Scheme 326b).[529] Quite recently, Xu *et al.* accomplished an analogous Mn(III)-promoted C−H phosphorylation of tertiary acyclic enamides with comparable efficiency (Scheme 326c).[530]

Apart from these radical-based processes, the group of Zhang and Ma in 2018 established an efficient Pd(II)-catalyzed $C(sp^2)$−H functionalization protocol for the direct phosphorylation of enamides with high chemo- and stereoselectivity

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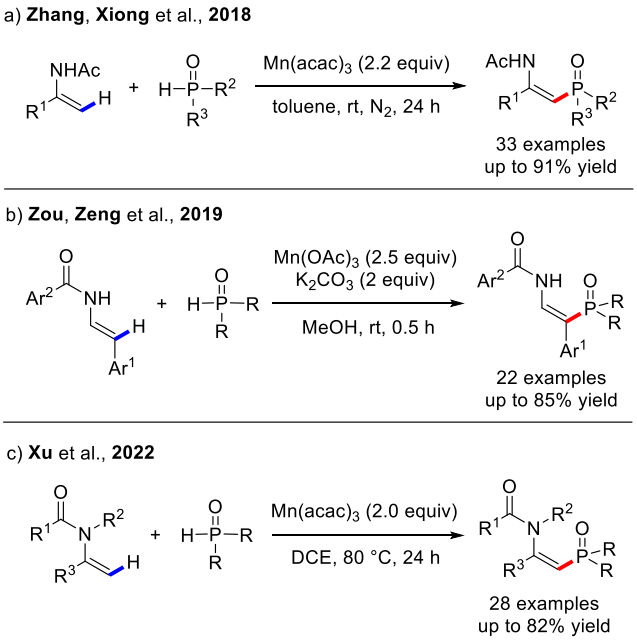
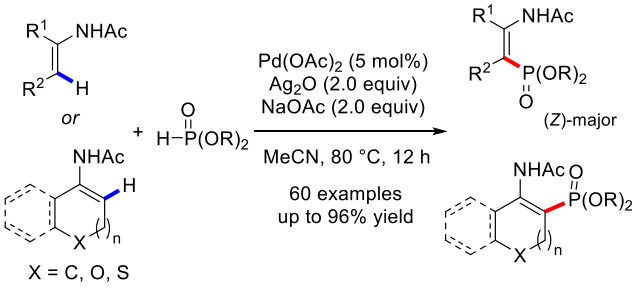
Scheme 326. Manganese(III)-Mediated Olefinic C−H Phosphorylation of Enamides



(Scheme 327).[531] An extraordinarily broad scope of 60 examples was documented in yield up to 96%. Both cyclic

Scheme 327. Palladium(II)-Catalyzed Vinylic C−H Phosphorylation of Enamides

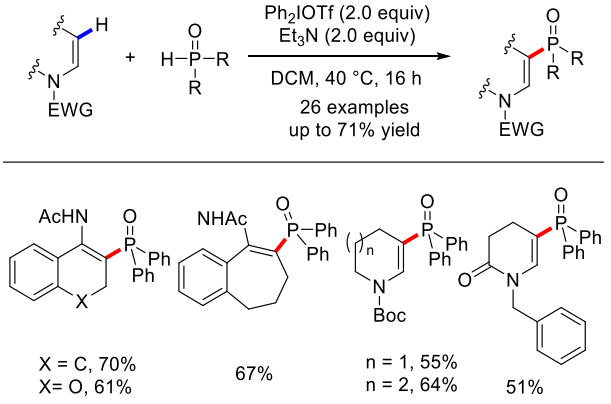


and acyclic enamides with different substitution patterns were well tolerated. Notably, this protocol was applicable to late-stage modification of bioactive natural products such as pregnenolone and prasterone derivatives.

Later, Gillaizeau's group devised an alternative approach for the direct C−H phosphorylation of enamides by using diphenyliodonium salt combined with Et_3N as the efficacious radical initiator under transition-metal-free conditions (Scheme 328).[532] Based on their mechanistic studies, the authors proposed a tentative catalytic mechanism involing a single-electron-transfer process initiated by the electron donor−acceptor (EDA) complex between Et_3N and diphenyliodonium salts.

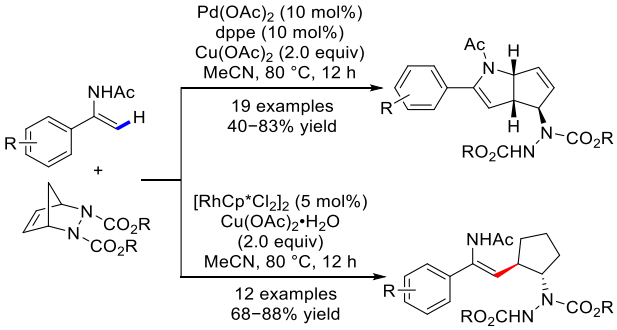
5.1.9. Annulation Reaction. The outstanding step-economy of annulation reactions makes it highly sought after for the assembly of diverse complex polycyclics in organic synthesis. Diazabicycle olefins are versatile synthons for the synthesis of highly functionalized cyclopentenes with extensive structural diversity. In 2017, John and Radhakrishnan reported the Pd(II)-catalyzed oxidative annulation of acyclic enamides with strained diazabicyclics *via* tandem ring-opening and ring-

Scheme 328. Diphenyliodonium Ion/Et_3N Promoted C−H Phosphorylation of Enamides



closing sequences (Scheme 329),[533] thereafter enabling the stereoelective synthesis of multisubstituted cyclopentene fused

Scheme 329. Synthesis of Cyclopentene Fused 2-Pyrrolines *via* Pd-Catalyzed Oxidative Annulation of Enamides with Diazabicyclics



2-pyrrolines in moderate to high yields. By making use of $[RhCp^*Cl_2]_2$ as the catalyst, a broad array of *trans*-disubstituted cyclopentenes could be obtained through a ring-opening desymmetrization process.

More recently, the formal oxidative annulation between enamides and maleimides was established by Luo's group through an efficient manganese(II) acetate-promoted dehydrative dehydroaromatizing [4 + 2] cycloaddition, providing access to a broad series of highly valuable pyrrolo[3,4-*c*]-pyridine derivatives (Scheme 330).[534] Various substituted maleimides were suitable coupling parters for this transformation. NH-free maleimide, however, was proven to be much less efficient (17%). Of note, alkylenamides failed to deliver the expected product in this case. Interestingly, the target product exhibited typical aggregation-induced emission (AIE) characteristics, which remarkably expand the potential application of these pyrrolo[3,4-*c*]-pyridine derivatives.

Pioneering work of Fagnou, Stuart, and their co-workers revealed an efficient pyrrole synthesis utilizing enamides with diverse internal alkynes under cationic Cp*Rh(III) catalysis. In 2010, they expanded their rhodium(III) catalysis strategy to disclose the vinylic C−H bond functionalization of enamides for the expedient synthesis of multisubstituted pyrroles (Scheme 331).[535] Easily prepared $[Cp^*Rh(MeCN)_3][SbF_6]_2$ was readily employed as the efficacious catalyst to achieve this transformation. The reaction occurred smoothly in the presence of a catalytic amount of $Cu(OAc)_2 \bullet H_2O$ (20 mol

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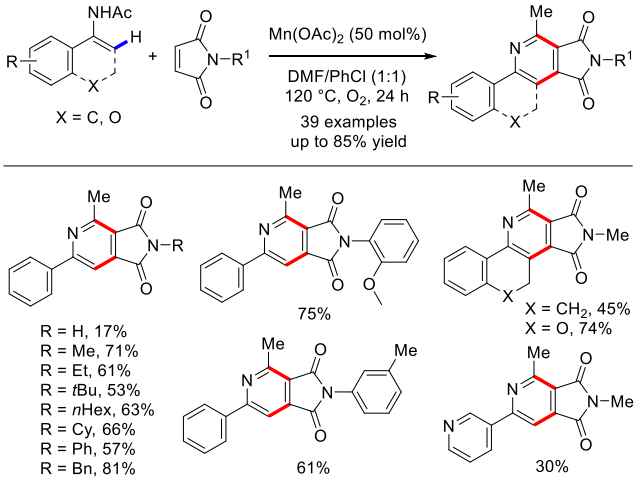
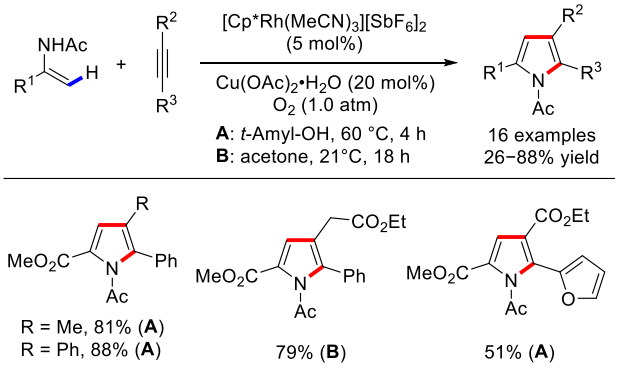
Scheme 330. $Mn(OAc)_2$-Promoted Formal [4 + 2] Cycloaddition of Enamides with Maleimides



Scheme 331. Rhodium(III)-Catalyzed Vinylic C−H Functionalization of Enamides with Alkynes



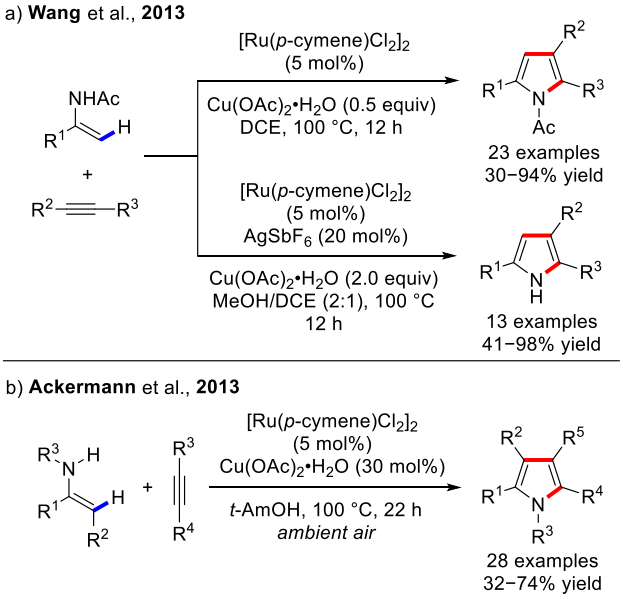
%) in conjunction with molecular oxygen as the terminal oxidant. Notably, both symmetrical and unsymmetrical internal alkynes were tolerated to deliver the corresponding pyrroles with excellent regioselectivities.

Later in 2013, the groups of Wang[536] and Ackermann[537] independently disclosed the inexpensive ruthenium(II)-catalyzed oxidative annulation reaction of enamides with internal alkynes to construct substituted pyrroles *via* C−H/N−H bond functionalizations (Scheme 332). In Ackermann's report, they employed a catalytic amount of $Cu(OAc)_2 \bullet H_2O$ (30 mol %) under an ambient atmosphere of air as the terminal oxidant. Interestingly, *N*-unsubstituted pyrroles could be produced directly with the addition of $AgSbF_6$ and MeOH as illustrated in Wang's work.

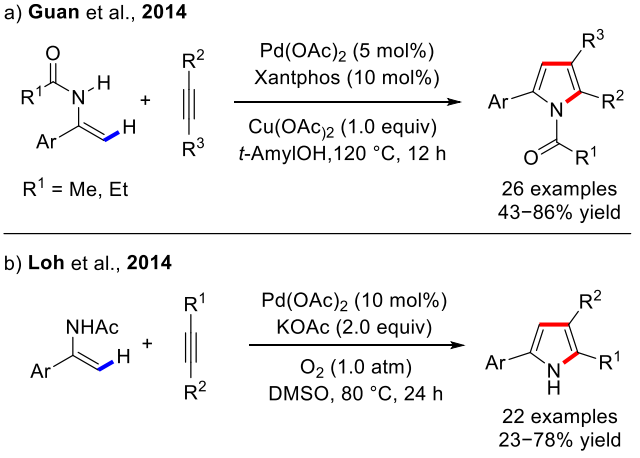
In 2014, Guan and colleagues elaborated the synthesis of *N*-substituted pyrroles enabled by a palladium(II)-catalyzed annulative reaction of enamides with a diverse array of internal alkynes (Scheme 333a).[538] Around the same time, Loh's group also achieved an analogous pyrrole synthesis in synthetically useful yields using molecular oxygen as an oxidant for the palladium catalyst regeneration (Scheme 333b).[539] However, poor regioselectivities were observed with unsymmetrical internal alkynes as the annulation partners in this protocol.

However, when employing electron-deficient internal alkynes as coupling partners, the annulation reaction of enamides could be carried out under copper-promoted conditions, which undoubtedly provided a cost-effective strategy for the expeditious synthesis of NH-free pyrroles (Scheme 334).[540]

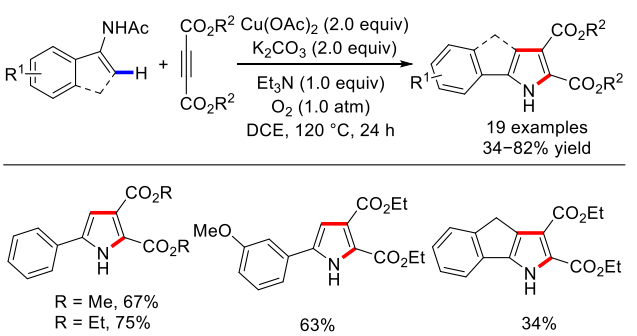
Scheme 332. Ruthenium-Catalyzed Pyrrole Synthesis *via* Oxidative Annulation of Enamides with Alkynes



Scheme 333. Synthesis of Substituted Pyrroles *via* Pd(II)-Catalyzed Oxidative Annulation of Enamides with Internal Alkynes



Scheme 334. Synthesis of Substituted Pyrroles *via* Copper-Promoted Oxidative Annulation of Enamides and Alkynes



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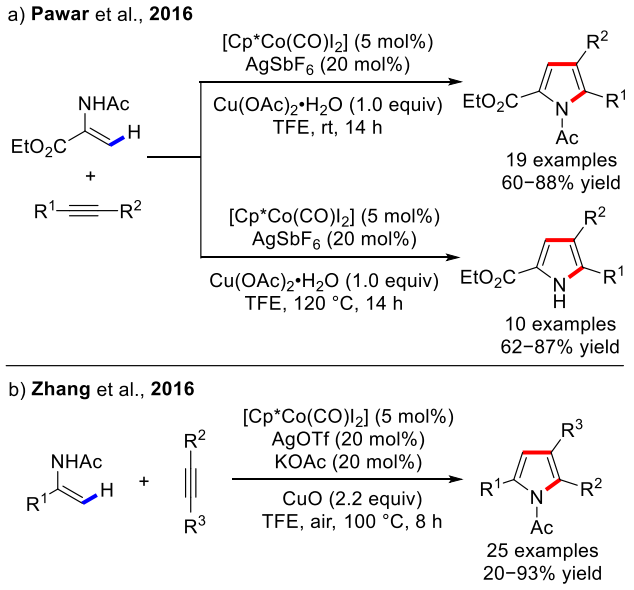
Pawar's group later illustrated an efficient earth-abundant, environmentally benign Cp*Co(III)-catalyzed pyrrole synthesis from enamides and alkynes (Scheme 335a).[541] The

Scheme 335. Synthesis of Substituted Pyrroles *via* Cp*Co(III)-Catalyzed [3 + 2] Annulation of Enamides and Alkynes

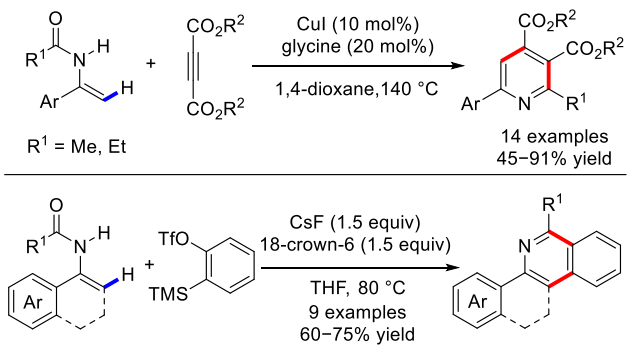


reaction occurred smoothly at room temperature, resulting in the formation of *N*-acetyl pyrroles in high yields (60−88%). In this protocol, a broad range of *N*-unsubstituted pyrroles can also be formed at elevated temperature. In the same year, Zhang and co-workers also achieved this cobalt-catalyzed formal oxidative [3 + 2] annulation in the presence of CuO as an oxidant (Scheme 335b).[542]

Apart from the formation of five-membered pyrrole derivatives,[540] Guan and co-workers demonstrated that the copper-catalyzed oxidative annulation of enamides with electron-deficient internal alkynes could also deliver substituted pyridines (Scheme 336).[543] More interestingly, this reliable strategy can extend to couple with aryne precursors for the facile assembly of multisubstituted isoquinoline derivatives under metal-free reaction conditions.

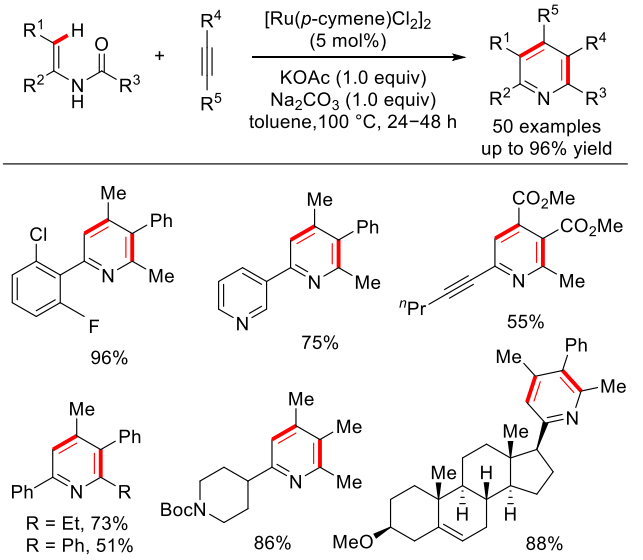
In 2015, Wang's group devised an economic approach for the convenient and regioselective assembly of multisubstituted pyridines through the formal dehydrative [4 + 2] cycloaddition

Scheme 336. Formal Dehydrative [4 + 2] Cycloaddition of Enamides with Electron-Deficient Internal Alkynes



of acyclic enamides with a broad array of internal alkynes under ruthenium catalysis (Scheme 337).[544] Unsymmetric

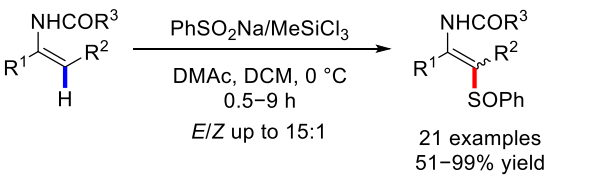
Scheme 337. Ru-Catalyzed Formal Dehydrative [4 + 2] Cycloaddition of Enamides and Alkynes



internal alkynes participated well in this cyclization reaction, exclusively generating a single regioisomer. When employing diynes as coupling partners, multisubstituted bipyridines could also be produced by this methodology under slightly modified conditions. Combined mechanistic studies and DFT calculations clearly demonstrated that this dehydrative cycloaddition reaction probably occurred through a concerted metalation deprotonation (CMD) process.

5.1.10. Other Useful Reactions. In 2014, Sun's group devised a rapid route for the synthesis of *β*-sulfinyl enamides *via* a direct alkenyl C−H sulfinylation of enamides with the sulfinylative agent (PhSOCl), which is conveniently generated *in situ* from $PhSO_2Na$ and $MeSiCl_3$ (Scheme 338).[545] The presence of DMAc served as a Lewis base in this process.

Scheme 338. Direct Synthesis of *N*-Protected-*β*-Sulfinylenamines *via* *C*-Sulfinylation of Enamides and Enecarbamates



The Ag(I)-mediated oxidative C−H sulfenylation of enamides with disulfides for the synthesis of *β*-sulfenylated enamides was illustrated by Yang, Deng, and their co-workers in 2014 (Scheme 339).[546] Gratifyingly, this approach was applicable to the C−H selenation of enamides with diaryl diselenide, albeit in a 28% yield.

Zhang's group investigated a Cp*Rh(III) and Ag(I) cocatalyzed alkenyl C−H acetoxylation of enamides by utilizing $Cu(OAc)_2•H_2O$ as both acetoxylating reagent and oxidant. The process was highly stereoselective, exclusively giving rise to *Z*-configuration products in modest yields

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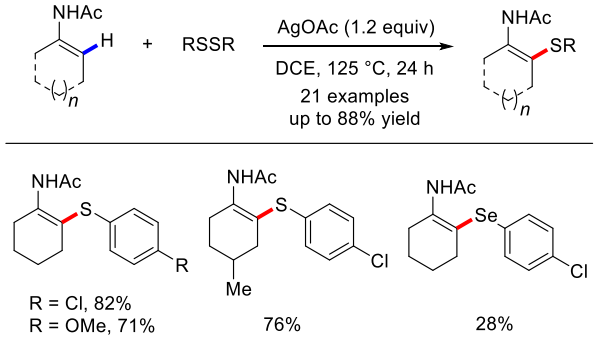
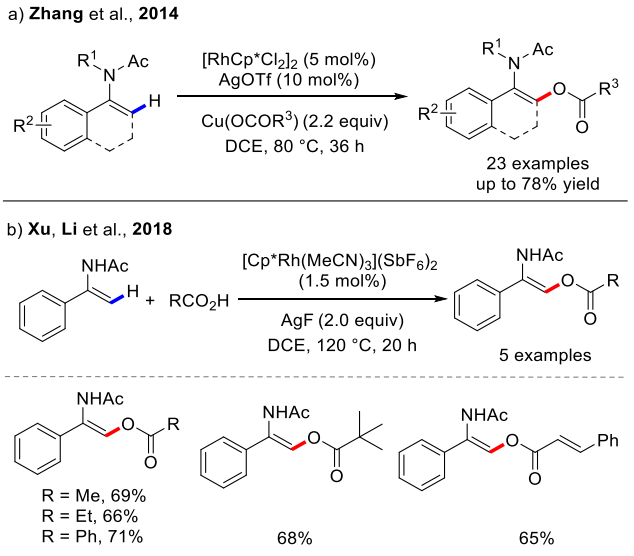
Scheme 339. Silver-Mediated C−H Sulfenylation of Enamides with Disulfides



(Scheme 340a).[547] Later, Xu and colleagues also achieved an efficient alkenyl C−H acyloxylation of enamides with simple carboxylic acids enabled by a cationic Rh(III) catalyst (Scheme 340b).[548]

Scheme 340. Cp*Rh(III)-Catalyzed Vinylic C−H Acetoxylation of Enamides

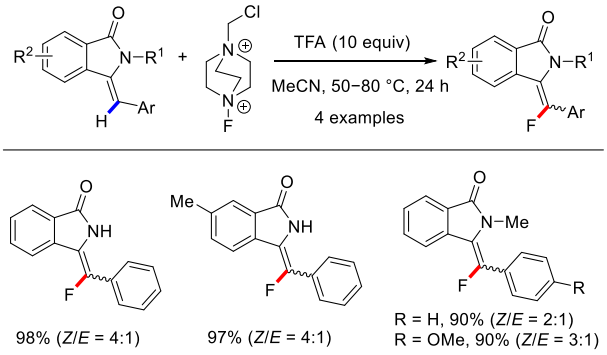


In addition, Prakash's group illustrated a direct olefinic C−H fluorination of enamides with commercially available Selectfluor as the fluorinating reagent under Brønsted acidic conditions, affording a series of hitherto unknown fluoro-containing olefins in excellent yields (Scheme 341).[549]

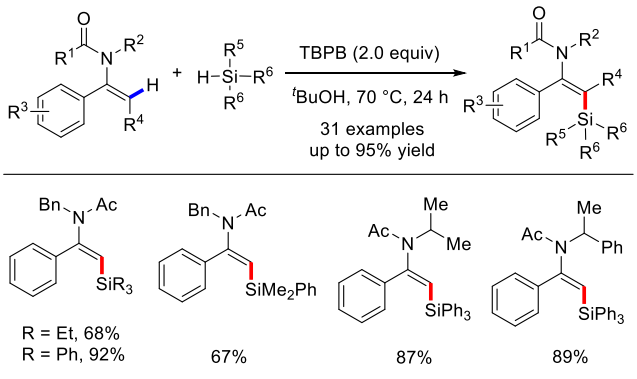
Xu and co-workers were able to synthesize highly useful vinylsilanes through an efficient and sustainable transition-metal-free dehydrogenative silylation of various enamides with simple silanes (Scheme 342).[550] This reaction proceeded smoothly in the presence of *tert*-butyl peroxybenzoate (TBPB) to trigger the formation of silyl radical. The authors highlighted the potential of this protocol by the derivatization of the corresponding vinylsilanes into a variety of value-added complex molecules.

In a recent report, Zeng's group divised a robust and green approach for the metal-free C−H thiocyanation of enamides with easily accessible NH_4SCN to assemble a diverse array of (*E*)-*β*-thiocyanoenamides with high regio- and stereoselectivities (Scheme 343).[551]

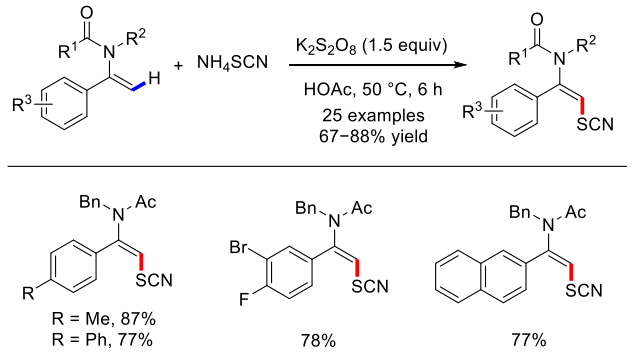
Scheme 341. Direct Olefinic C(sp^2)−H Fluorination of Enamides



Scheme 342. Synthesis of Vinylsilanes *via* Metal-Free Dehydrogenative Silylation of Enamides



Scheme 343. Regio- and Stereoselective Olefinic C−H Thiocyanation of Enamides with NH_4SCN



5.2. Enaminones

β-Keto enamines, or generally known as enaminones, contain unique electronic effects in its core structure, an electron-donating amino group and an electron-withdrawing carbonyl on either end of the C=C double bond. In addition, enaminones possess interesting properties and are versatile building blocks in organic synthesis. The application of enaminones bearing different substitution patterns on the nitrogen of the amino group were extensively investigated. Despite the extensive studies on this topic, *N*,*N*-disubstituted enaminones,such as *N*,*N*-dimethyl enaminones, were not similarly scrutinized. In contrast to other conventional enaminones, *N*,*N*-dimethyl enaminones present a highly polarized C=C double bond due to the neighboring electron-donating amino group and electron-withdrawing

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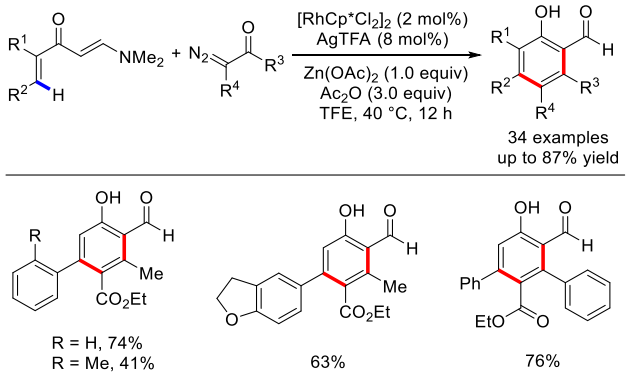
carbonyl, which consequently result in a higher electron density at the α-carbon as compared to the amino group. In addition, the *N*,*N*-dimethyl moiety functions as a better leaving group in contrast to other enaminones, thus allowing a number of transformations to be carried out with ease. As such, there have been a ever-increasing interest dedicated toward the study of *N*,*N*-dimethyl enaminones in recent years.

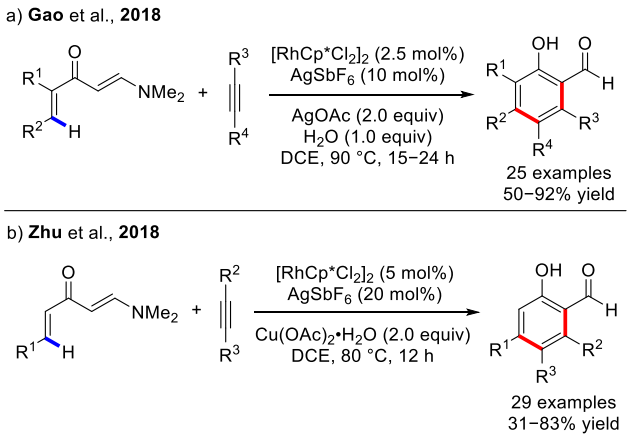
In 2018, Loh and co-workers reported a Cp*Rh(III)-catalyzed regioselective [4 + 2] cycloaddition of enaminones with α-diazo-β-ketoesters, allowing the construction of a series of highly functionalized salicylaldehydes with good functional group compatibility (Scheme 344).[552] In this case, alkenyl C−H bond functionalization/cyclization cascade reaction and subsequent rearomatization gave rise to the corresponding products in a single step under benign conditions. The scope of the reaction was broad, both with regard to the enaminones and the α-diazo-β-ketoesters.

Scheme 344. Synthesis of Salicylaldehydes through Regioselective [4 + 2] Cycloadditions of Enaminones with Diazocarbonyls



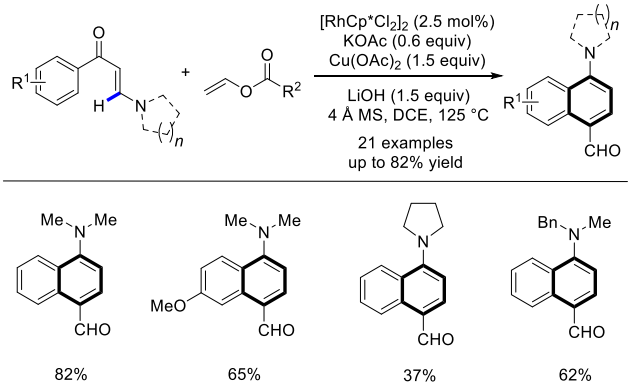
In the same year, the groups of Gao[553] and Zhu[554] independently published the efficient and straightforward assembly of multisubstituted salicylaldehyde derivatives through an enaminone-directed regioselective C−H [4 + 2] annulation of vinyl enaminones with diverse alkynes under Cp*Rh(III) catalysis (Scheme 345).

Scheme 345. Synthesis of Salicylaldehydes through Regioselective [4 + 2] Annulations of Enaminones with Alkynes



A Cp*Rh(III)-catalyzed C−H [5 + 1] annulation strategy for the construction of polyaromatic rings from enaminones was developed by Loh's group (Scheme 346).[555] The reaction featured a wide functional group tolerance and offered a novel route to synthesize polycyclic aromatic compounds bearing amino and formyl substituents. On the basis of mechanistic studies, the authors proposed that the active Rh(III) catalyst activated the *ortho*-position of the phenyl ring through a weak keto-coordination to yield an intermediate. Subsequent coordination and migratory insertion of the olefin gave a rhodacycle intermediate,which then underwent a β-hydride elimination to give another immediate. Upon rotation of the C−C bond, another C−H activation step promoted by the pivalate group formed another Rh(III) complex. Reductive elimination of this complex afforded a six-membered cyclic intermediate. The amino group and rhodium complex was subsequently removed,and upon condensation of the carbonyl formed an iminium ion intermediate. Lastly, hydrolysis and aromatization of the iminium ion generated the desired product.

Scheme 346. Cp*Rh(III)-Catalyzed [5 + 1] Annulation of Enaminones with Vinyl Esters



Subsequently, Loh and co-workers continued to present the Rh^{III}-catalyzed formal oxidative [3 + 3] annulation of easily prepared enaminones with electron-deficient acrylates through alkenyl C−H activation and subsequent intramolecular aminolysis cyclization (Scheme 347),[556] allowing an efficient and practical access to highly functionalized *N*-substituted 2-pyridones in up to 91% yield with good functional group compatibility.

More recently, Guo and colleagues were able to assemble multisubstituted pyridines through an efficient [4 + 2] annulation of enaminones with diverse α,β-unsaturated ketoxime acetates (Scheme 348).[557] In the presence of $FeCl_2$ (10 mol %), the annulation reaction proceeded uneventfully, and a broad scope of 49 examples of the desired products was documented in appreciable yields of up to 87%. Of note, the reaction could be performed in the a Vaportec flow reactor, which definitely allowed for a substantial shortening of the reaction time, furnishing the annulation products in comparable yields. Preliminary mechanistic investigations were carried out which revealed that $FeCl_2$ may play as a Lewis acid to activate the α,β-unsaturated ketoxime acetates for the subsequent nucleophilic addition in this case.

The reaction of enaminones with diverse α-diazoketones could produce *NH*-free pyrroles. In 2013, Reddy and co-workers described the synthesis of trisubstituted pyrroles

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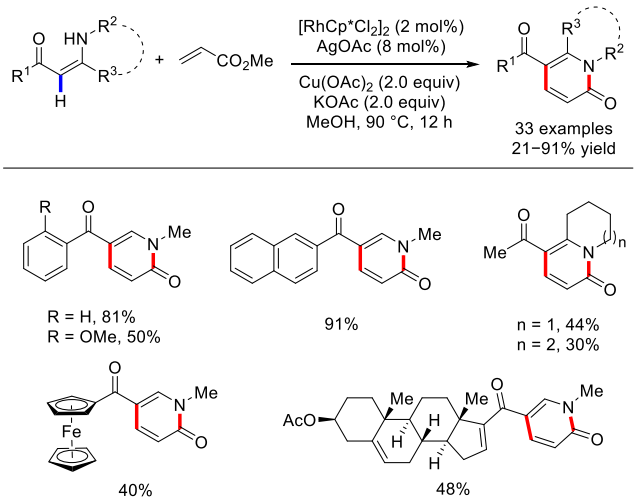
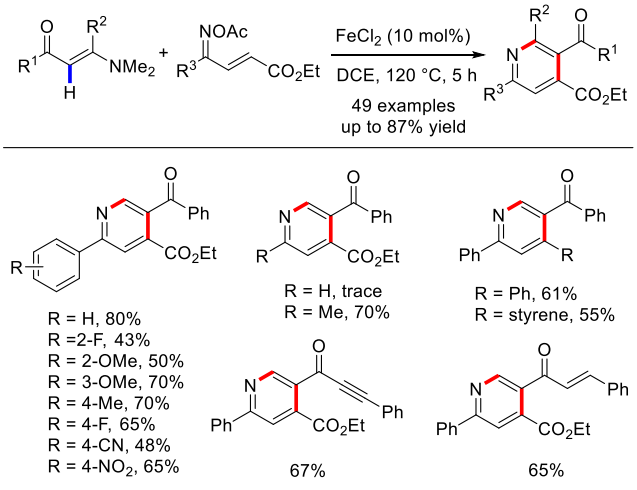
Scheme 347. Synthesis of 2-Pyridones through Rh^{III}-Catalyzed Formal Oxidative [3 + 3] Annulation of Enaminones with Acrylates

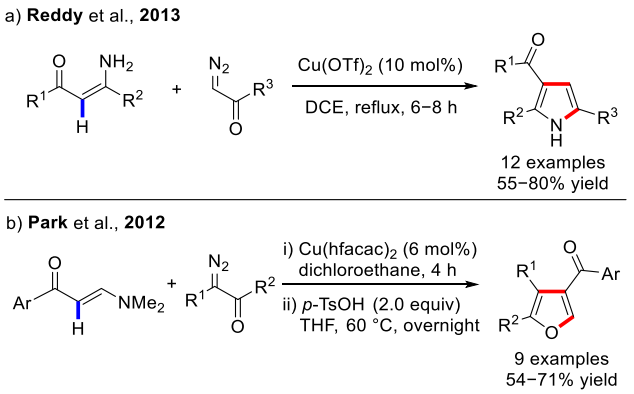


Scheme 348. Synthesis of Pyridines through Fe(II)-Catalyzed [4 + 2] Annulation of Enaminones with α,β-Unsaturated Ketoxime Acetates



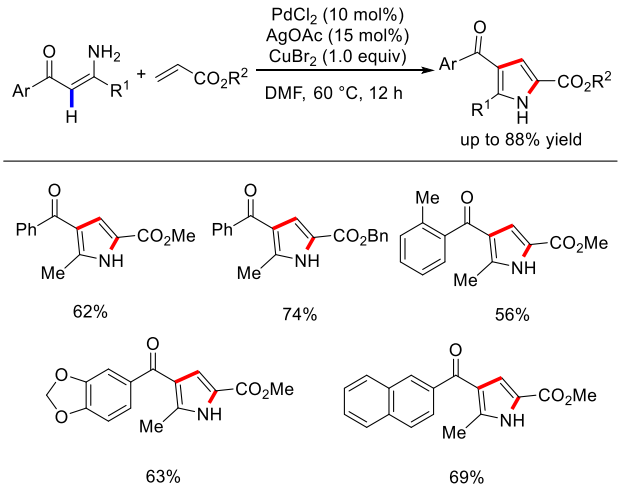
through the cross-coupling reaction of α-diazoketones with β-enaminoketones by using $Cu(OTf)_2$ (10 mol %) as the catalyst (Scheme 349a).[558] Gratifyingly, Park's group demonstrated that the copper-catalyzed [3 + 2] cycloaddition of *N*,*N*-dimethyl enaminones with diazoketones exclusively afforded 2-amino-2,3-dihydrofurans, which could be readily converted into highly functionalized furans in the presence of *p*-toluenesulfonic acid (Scheme 349b).[559]

Scheme 349. Synthesis of Multisubstituted Furans and Pyrroles with Enaminones with α-Diazoketones



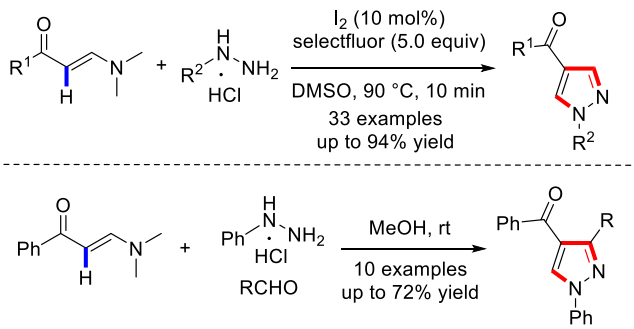
The group of Liu and Wan recently illustrated a Pd(II)-catalyzed annulation between enaminones and activated olefins for the construction of *NH*-free pyrroles (Scheme 350).[560] The three $C(sp^2)$–H bonds were activated in the reaction to yield the corresponding pyrroles with good functional group tolerance. Evolution of H_2 gas from the reaction was also detected. Upon generation of the active Pd(II) catalyst, C–H activation of enaminones with the catalyst gave a Pd(II) complex. Subsequently, a 1,2-migratory insertion of the olefin to the Pd(II) complex formed a palladacycle, which readily underwent β-H elimination to yield a dienamine intermediate. Dehydrogenative *C*-, *N*-palladation followed by a reductive elimination afforded the corresponding pyrroles. More recently, the same group further reported the construction of pyrazoles *via* a metal-free [2 + 2 + 1] annulation reaction of enaminones with hydrazines (Scheme 351).[561]

Scheme 350. Pd-Catalyzed Triple-Fold C–H Activation with Enaminones and Alkenes



Apart from the above-mentioned heterocycles, Cacchi and colleagues accomplished the rapid synthesis of multisubstituted indoles by the copper-catalyzed intramolecular oxidative cyclization of *N*-aryl enaminones (Scheme 352a).[562] Later on, the group of Chang and Yu also published an analogous

Scheme 351. Synthesis of Pyrazoles *via* Metal-Free [2 + 2 + 1] Annulation of Enaminones with Hydrazines



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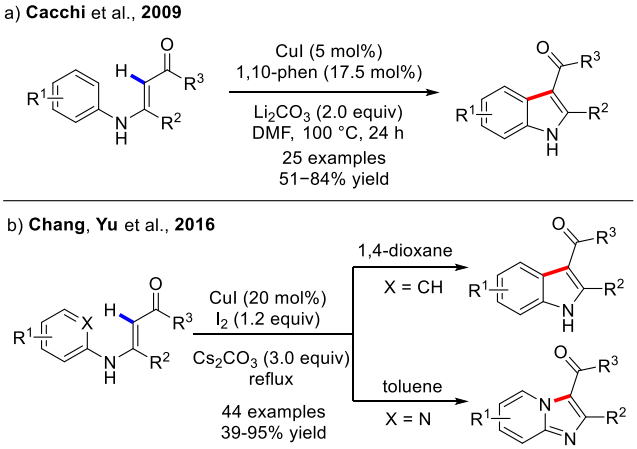
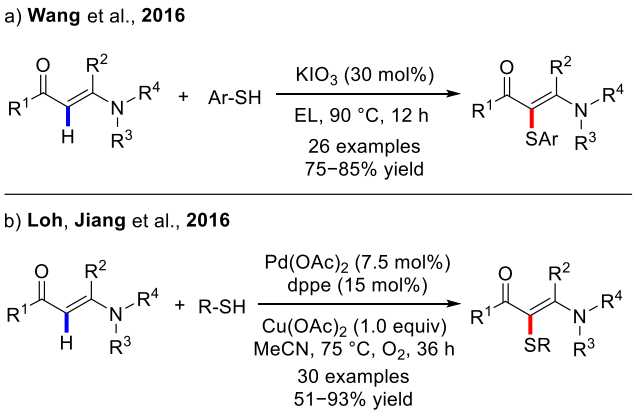
Scheme 352. Cu-Catalyzed Intramolecular Oxidative Cyclization of Enaminones



transformation by means of a CuI/I_2 system (Scheme 352b).[563] Remarkably, the protocol could afford a diverse range of imidazo[1,2-*a*]pyridines in decent yields.

The direct alkenyl C−H sulfenylation of enaminones represents a straightforward approach to the synthesis of polyfunctionalized aminothioalkenes. In 2016, Wan *et al.* reported a metal-free aerobic coupling of enaminones with thiophenols in the presence of a catalytic amount of KIO_3 as an efficacious hypervalent iodate catalyst (Scheme 353a).[564] The

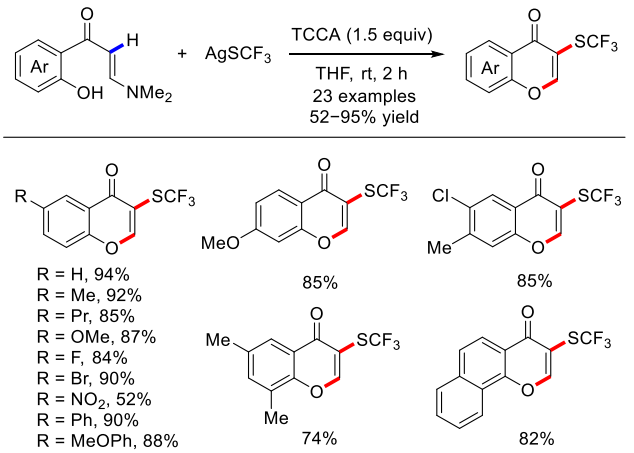
Scheme 353. Synthesis of Polyfunctionalized Alkenes through KIO_3-Catalyzed Aerobic Cross-Coupling of Enaminones with Thiophenols



sustainable biobased ethyl lactate (EL) was employed as a green solvent in this protocol to furnish the expected aminothioalkenes in excellent yields (75−85%). Alternatively, Loh and co-workers performed a similar transformation enabled by a $Pd(OAc)_2$/dppe catalytic system (Scheme 353b).[565]

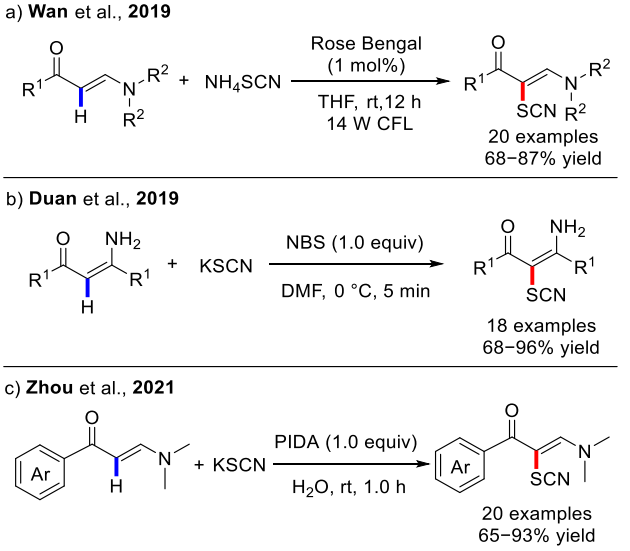
The incorporation of a SCF_3 group into organic molecules will substantially enhance their biological activities. By using readily accessible $AgSCF_3$ and trichloroisocyanuric acid (TCCA) to *in situ* generate the electrophilic trifluoromethylthio radical, Yang and co-workers were able to assemble a diverse range of SCF_3-contaning chromones from *o*-hydroxyarylenaminones. A scope of 23 examples of this transformation was presented with yields of 52−95% (Scheme 354).[566] More recently, a similar trifluoromethylselenolation (CF_3Se) of *ortho*-hydroxyarylenaminones was achieved under photoredox catalysis.[567]

Scheme 354. Synthesis of 3-((Trifluoromethyl)thio)-4*H*-chromen-4-one from *o*-Hydroxyarylenaminones and $AgSCF_3$



Additionally, Wan *et al.* described the metal-free C−H thiocyanation of enaminones with NH_4SCN as the thiocyano source under the visible-light irradiation of a 14 W compact fluorescent lamp (CFL) with Rose Bengal as the nonmetal photocatalyst (Scheme 355a).[568] In the same year, the groups

Scheme 355. Synthesis of SCN-Containing Enaminones *via* Olefinic C−H Thiocyanation



of Duan[569] and Zhou[570] independently elaborated the efficient synthesis of SCN-containing enaminones under mild *N*-bromosuccinimide (NBS)- and iodobenzene diacetate (PIDA)-mediated conditions (Scheme 355b,c). Meanwhile, the olefinic C−H thiocyanation of *o*-hydroxyarylenaminones was also achieved, affording a large variety of biologically important 3-thiocyanato-4*H*-chromen-4-ones[568,570,571]

In 2018, Yan and co-workers developed an efficient iron-based approach to prepare diverse polysubstituted thiazoles from readily available enaminones and elemental sulfur. In this case, the C−S bond is formed with sulfur powder through the

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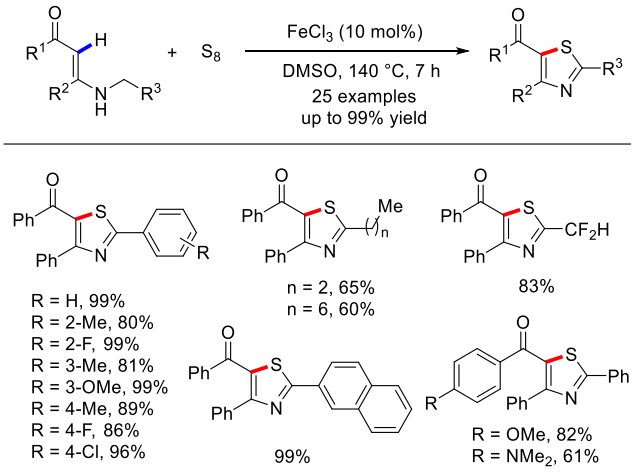
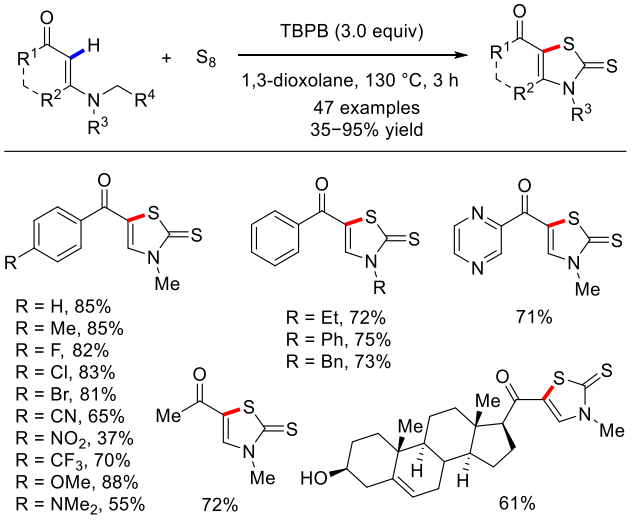
direct functionalization of C(sp^2)/C(sp^3)−H bonds (Scheme 356).[572] Both electron-rich and electron-deficient functional groups were compatible with the reaction, affording the products in excellent yields.

Scheme 356. Synthesis of Thiazoles from Enaminones and Elemental Sulfur through the Vinylic C−H Functionalization/C−S Bond Formation



Quite recently, Fu and co-workers described the use of similar starting materials to perform an unprecedented TBPB-promoted oxidative cyclization for the synthesis of structurally diverse five-membered thiazole-2-thiones (Scheme 357).[573]

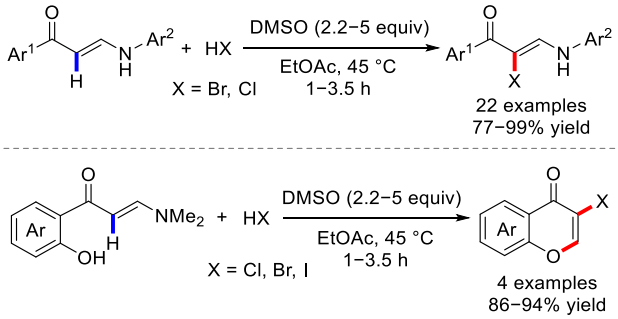
Scheme 357. TBPB-Promoted Oxidative Cascade Cyclization of Enaminones with Elemental Sulfur



This strategy undergoes C(sp^2)−H/C(sp^3)−H bond sulfuration of enaminones between the alkenyl and *N*-alkyl moieties along with a subsequent C(sp^3)−H bond thiocarbonylation, leading to the highly appealing synthesis of thiazole-2-thiones in modest to excellent yields with a broad substrate scope.

The Maddani group demonstrated a metal-free alkenyl C−H halogenation of *N*-aryl enaminones by using a readily available and inexpensive DMSO-halo acid combination strategy under typically mild conditions (Scheme 358).[574] The scope of enaminones was found to be broad and not sensitive to electronic and steric factors. Interestingly, this protocol was

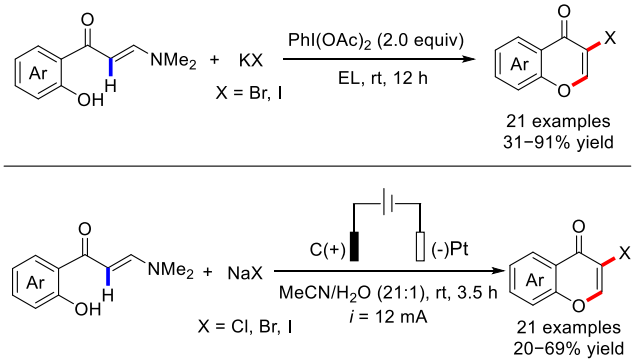
Scheme 358. Transition Metal-Free Oxidative Olefinic C−H Halogenation of *N*-Aryl Enaminones



applicable to *o*-hydroxyarylenaminone substrates, furnishing the halogenated chromenones in excellent yields.

In a subsequent report, Liu and colleagues described the facile synthesis of 3-halochromones with simple KX (X = Br, I) salts as a halogen source in the presence of PhI(OAc)$_2$ oxidant (Scheme 359).[575] Instead of a radical-based pathway, control

Scheme 359. Synthesis of 3-Halochromones from 2-Hydroxylphenyl Enaminones and Metal Halides



experiments definitely indicated that this protocol proceeded through an electrophilic halogenation involving the formation of a halogenium intermediate. Shortly thereafter, the same group extended to establish the electrochemical method for this transformation with sodium halide (NaX, X = Cl, Br, I) as the halogen source (Scheme 359).[576]

In an effort to forge C−O bond, Loh and co-workers in 2018 disclosed an efficient alkenyl C−H acyloxylation of enaminones with PhI(OAc)$_2$ under transition-metal-free conditions (Scheme 360).[577] This transformation occurred smoothly at room temperature to deliver a diverse array of (*E*)-vinyl acetates in yields ranging from 45% to 91%.

Meanwhile, Wan's group employed aroyl peroxide as *O*-centered free-radical precursor and accomplished the catalyst-free synthesis of both 3-acyloxyl chromones and *α*-acyloxyl enaminones through a radical-involved pathway under extremely mild conditions (Scheme 361).[578]

The group of Yang and Chen in 2017 elaborated a direct synthesis of 3-CF_2/CF_3-containing chromone derivatives by the reaction of *o*-hydroxyphenylenaminones with $BrCF_2COOEt$ or Ph_2SCF_3OTf under visible-light photoredox catalysis (Scheme 362a).[579] The reaction was conducted under irradiation of white LEDs (18 W) at room temperature to give the corresponding products in 51−88% and 32−75% yield, respectively. Around the same time, Zhang and co-workers

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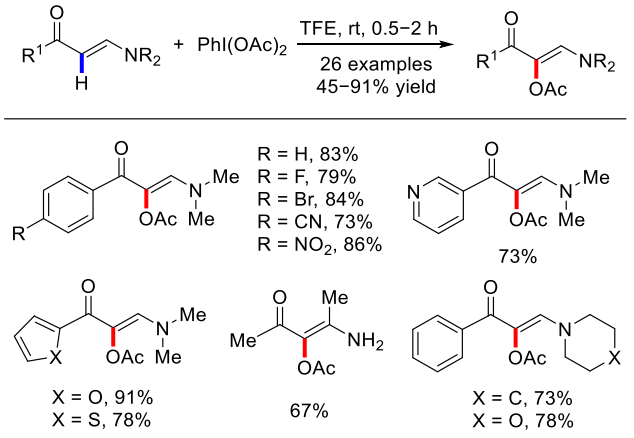
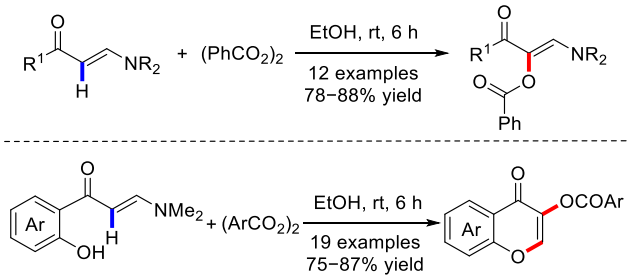
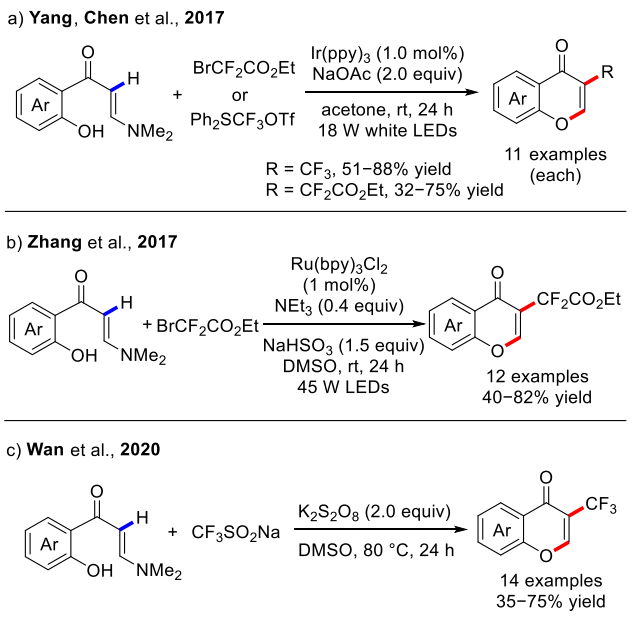
Scheme 360. Site-Selective C−H Acyloxylation of Enaminones with Phenyliodine(III) Diacetate



Scheme 361. Synthesis of Acyloxyl Enaminones and Chromones *via* Free-Radical C−H Acyloxylation



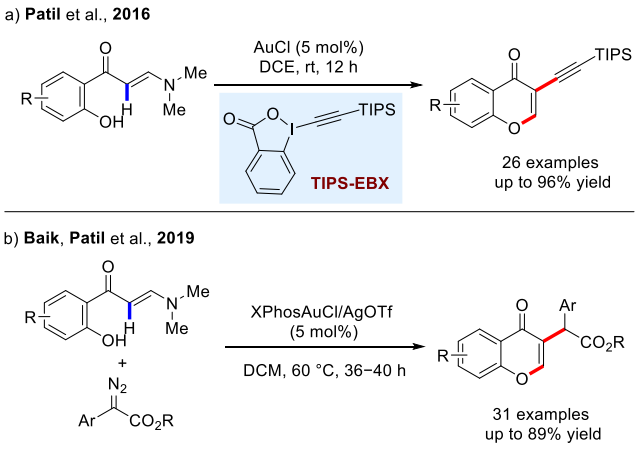
Scheme 362. Direct Synthesis of 3-CF_2/CF_3-Containing Chromones from 2-Hydroxylphenyl Enaminones



performed a similar transformation for the synthesis of 3-CF_2-containing chromones using inexpensive $Ru(bpy)_3Cl_2$ as the photocatalyst (Scheme 362b).[580] Afterward, Wan's laboratory utilized Langlois' reagent (CF_3SO_2Na) as the trifluoromethyl radical source and accomplished the metal-free synthesis of 3-CF_3-containing chromones in the presence of $K_2S_2O_8$ as the oxidant (Scheme 362c).[581]

Moreover, the Patil group explored the reaction of *o*-hydroxyphenylenaminones with TIPS-EBX reagent in the presence of AuCl as a catalyst, leading to a diverse array of 3-alkynyl chromones (Scheme 363a).[582] Afterward, they

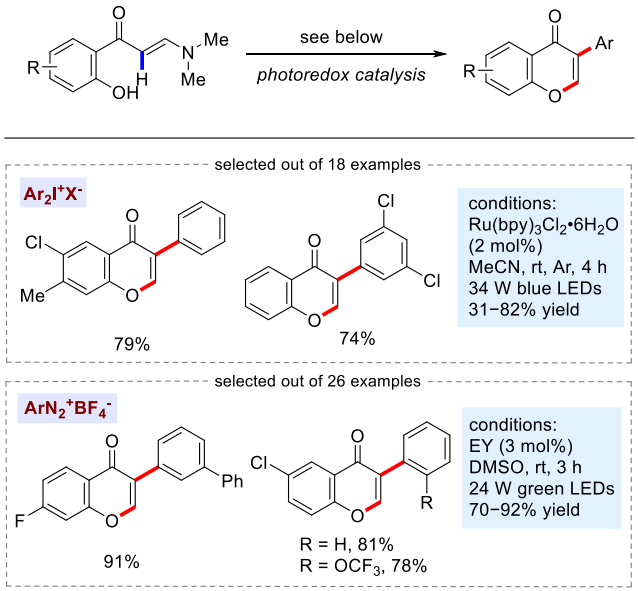
Scheme 363. Synthesis of 3-Substituted Chromones *via* Gold-Catalyzed *o*-Hydroxyarylenaminones with TIPS-EBX Reagent and Diazo Compounds



extended to investigate the reaction between *o*-hydroxyarylenaminones and diazo compounds under gold catalysis, affording a series of 3-alkylated chromones in up to 89% yield (Scheme 363b).[583] Detailed experimental and computational studies revealed a plausible pathway involving the OH-group assisted C−H bond alkylation of enaminones.

In 2020, the group of Iaroshenko and Mkrtchyan was able to synthesize isoflavones through a consecutive cascade arylation between *o*-hydroxyarylenaminones and *in situ* generated aryl radicals under photoredox catalysis (Scheme 364).[584] In this report, the authors employed diaryliodonium and diazonium salts as the aryl radical precursors. The photo-Meerwein arylation reaction of aryldiazonium tetrafluoroborates proceeded with eosin Y as a photocatalyst under irradiation of

Scheme 364. Visible-Light-Mediated Arylation of *ortho*-Hydroxyarylenaminones



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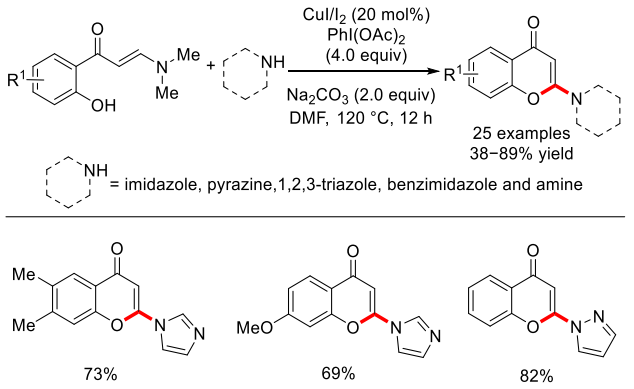
green LEDs, while the arylation process by diaryliodonium triflates underwent smoothly at room temperature in the presence of $Ru(bpy)_3Cl_2•6H_2O$ under irradiation of blue LEDs.

The same year, Liu and co-workers illustrated a highly regioselective β-C(sp^2)−H activation of enaminones with various nitrogen heterocycles for the construction of 2-nitrogenated chromones (Scheme 365).[585] This strategy

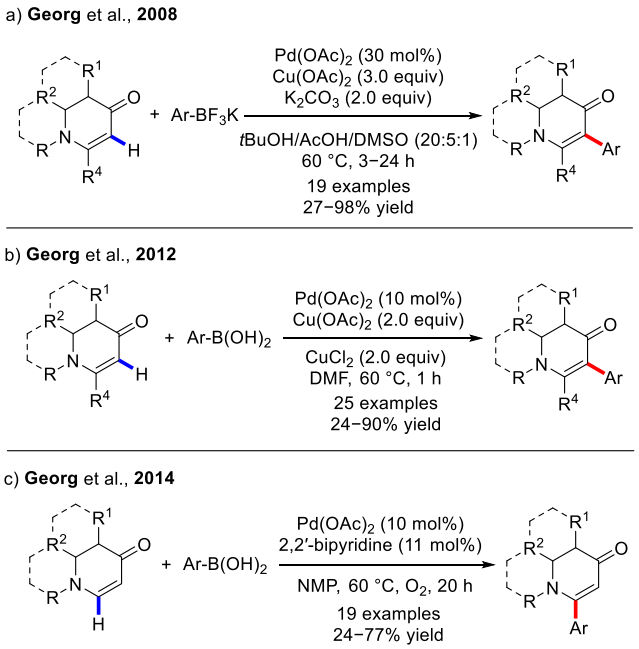
Scheme 365. Copper-Catalyzed β-C(sp^2)−H *N*-Heteroarylation of Enaminones



unveiled a novel approach to access useful heterocyclic structures. The reaction was promoted by molecular iodine, which gave a 3-iodochromone intermediate and HI. In the presence of the oxidant $PhI(OAc)_2$, molecular iodine was regenerated from HI. The 3-iodochromone intermediate was subsequently activated by the Cu(II) species to form a complex which was subjected to nucleophilic attack by the nitrogen heterocycles to form a Michael intermediate. The elimination of HI with the assistance of a base afforded the 2-nitrogenated chromones.

Cyclic six-membered enaminones, also known as 2,3-dihydropyrid-4(1*H*)-ones, are versatile and synthetically useful intermediates that demonstrate unique biological properties and could undergo a series of transformations to afford various biologically active piperidine-containing molecules. As such, the vinylic C−H functionalization of nonaromatic, cyclic enaminones has been extensively investigated over the past years. Specifically, Georg's group in 2008 presented the first example of Pd(II)-catalyzed lakenyl C−H arylation of 2,3-dihydropyrid-4(1*H*)-ones with aryltrifluoroborates, giving rise to an efficient approach for the assembly of 3-arylpiperidines, which are a privileged structure and prevalent scaffold in numerous natural products (Scheme 366a).[586] Although an elegant reaction has been developed, the protocol suffers from a relatively high catalyst loading (30 mol %). To circumvent this issue, Georg *et al.* expanded to establish a new strategy that accommodates readily available boronic acids as the coupling partner in the presence of 10 mol % $Pd(OAc)_2$ (Scheme 366b).[587] The reaction was typically finished within 1 h at 60 °C in DMF. The authors claimed that this significant improvement can be attributed to the addition of stoichiometric copper(II) salts, which can greatly facilitate the delivery of the aryl group to the Pd(II) catalyst center through the facile formation of arylcopper species, thereafter significantly increasing the efficiency of the transmetalation process. Later in 2014, the same group further accomplished a highly regioselective C−H arylation at the C6 position of cyclic

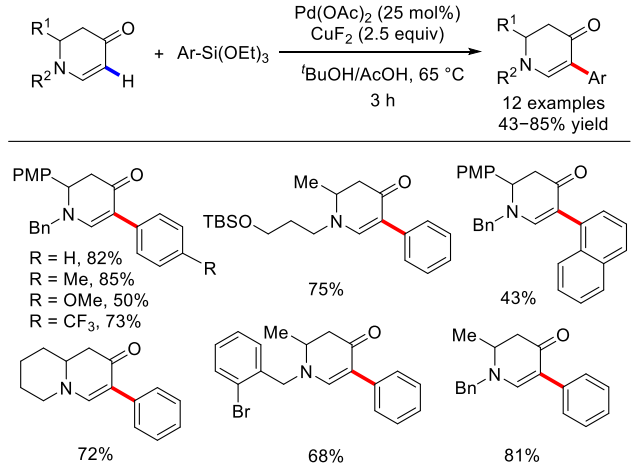
Scheme 366. Palladium(II)-Catalyzed C−H Arylation of Cyclic Enaminones with Organoboron Reagents



enaminones enabled by a Pd(II)/bpy catalytic system with molecular oxygen as the sole oxidant (Scheme 366c).[588]

Meanwhile, Georg and co-workers also investigated the alkenyl C−H Hiyama cross-coupling of enaminones with organosilicon reagents (Scheme 367).[589] By taking advantage

Scheme 367. Palladium(II)-Catalyzed C−H Arylation of Cyclic Enaminones with Organosilicon Reagents



of copper(II) fluoride (CuF_2) as both sliane activator and reoxidant, the coupling reaction between 2,3-dihydropyrid-4(1*H*)-ones and aryltriethoxysilanes occurred smoothly to afford C5-arylated enaminones. Gratifyingly, Denmark's reagent such as dimethylphenylsilanol can also participate without the need to use extra fluoride activator. Soon after, the authors further reported the C−H arylation of cyclic enaminones with aryl iodides (Scheme 368).[590]

Moreover, Georg and colleagues also investigated the palladium(II)-catalyzed C−H olefination of cyclic enaminones with both primary and secondary electron-deficient alkenes (Scheme 369a).[591] By using a combination of $Cu(OAc)_2$ (2.0

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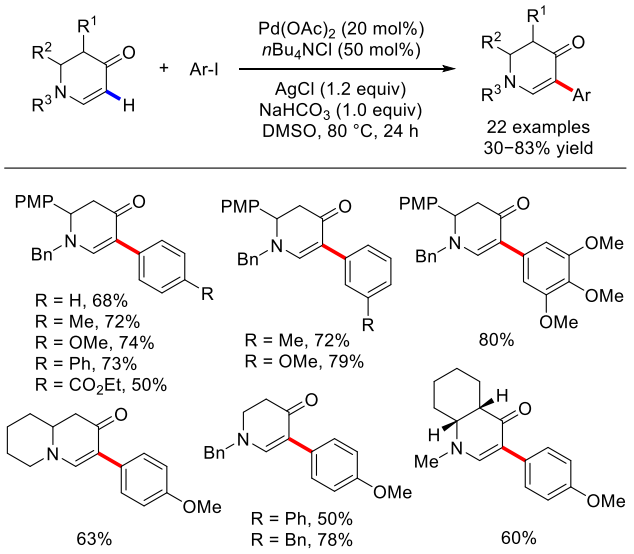
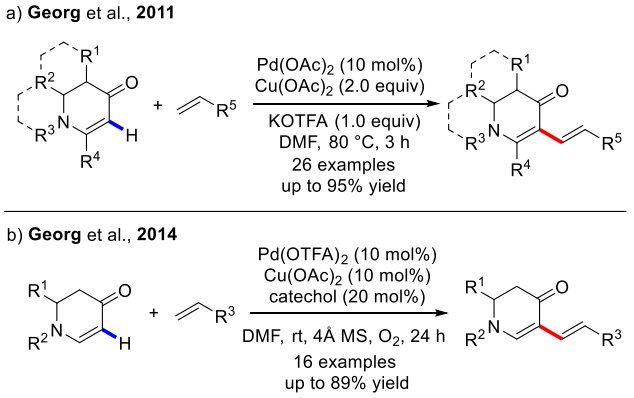
Scheme 368. Palladium(II)-Catalyzed C−H Arylation of Cyclic Enaminones with Aryl Iodides



Scheme 369. Pd(II)-Catalyzed C−H Olefination of Cyclic Enaminones



equiv) and KOTFA (1.0 equiv) in DMF at 80 °C, the reaction occurred smoothly, and excellent conversion was observed for most substrates. Later in 2014, the authors expanded this alkenylation to establish the biomimetic strategy of aerobic C−H olefination of enaminones at room temperature (Scheme 369b).[592]

5.3. Enamines

Arguably, enamines have long been used as extremely versatile building blocks for the synthesis of a variety of nitrogen-containing molecules[593,594] and also play a prominent role in the field of organocatalysis.[595] Considering the unique property of enamines, the alkenyl C(sp^2)−H functionalization of readily available enamines has drawn considerable attention from the synthetic community, and a myriad of efficient and straightforward methodologies have been established over the decades for the purpose of streamlining synthetic routes to fabricate highly functionalized enamines. Specifically, the group of Zhao and Du in 2012 reported an efficient transition-metal-free C−H acyloxylation of enamines with carboxylic acids by means of iodosobenzene (PhIO) as the oxidant, exclusively furnishing a diverse array of β-acyloxy enamines that can be readily converted into oxazole derivatives (Scheme 370).[596] The protocol was proposed to take place through the *in situ* generation of $PhI(OCOR)_2$, followed by the facile β-acyloxylation of enamines.

Scheme 370. PhIO-Mediated β-C−H Acyloxylation of Enamines with Carboxylic Acids

Subsequently, the same group further developed a coupling reaction between structurally diverse enamines and electron-deficient amines by using a TBAI/TBHP oxidative system, enabling an efficient assembly of synthetically appealing diaminoalkenes in decent yields (37−95%) (Scheme 371).[597]

Scheme 371. TBAI/TBHP-Mediated Oxidative Coupling of Enamines with Electron-Deficient Amines

This oxidative C(sp^2)−N bond formation reaction may involve the formation of tetra-*n*-butylammonium iodite from TBAI and TBHP, which then undergoes an electrophilic addition process by enamines to generate the adduct species. Subsequent nucleophilical substitution reaction with amines affords the corresponding imines which further isomerized into the thermodynamically more stable diaminoalkene derivatives.

In the following year, the group of Wang and Fan disclosed an efficient metal-free oxidative cross-coupling of enamines with *N*-protected propargyl amines by taking advantage of a $PhIO/Bu_4NI$-mediated system (Scheme 372).[598] A scope of 22 examples of this transformation was presented with yield up to 87%. In this report, tetrabutylammonium iodide (Bu_4NI) serves as an activator of PhIO. Interestingly, the resulting oxidative coupling products can undergo a copper(II)-mediated electrophilic cyclization process to afford structurally

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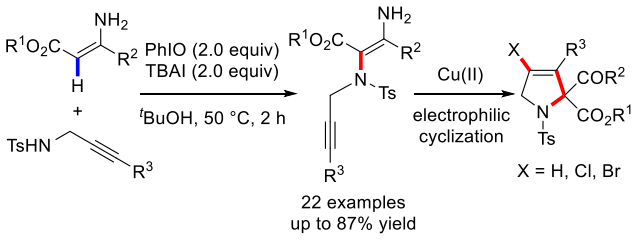
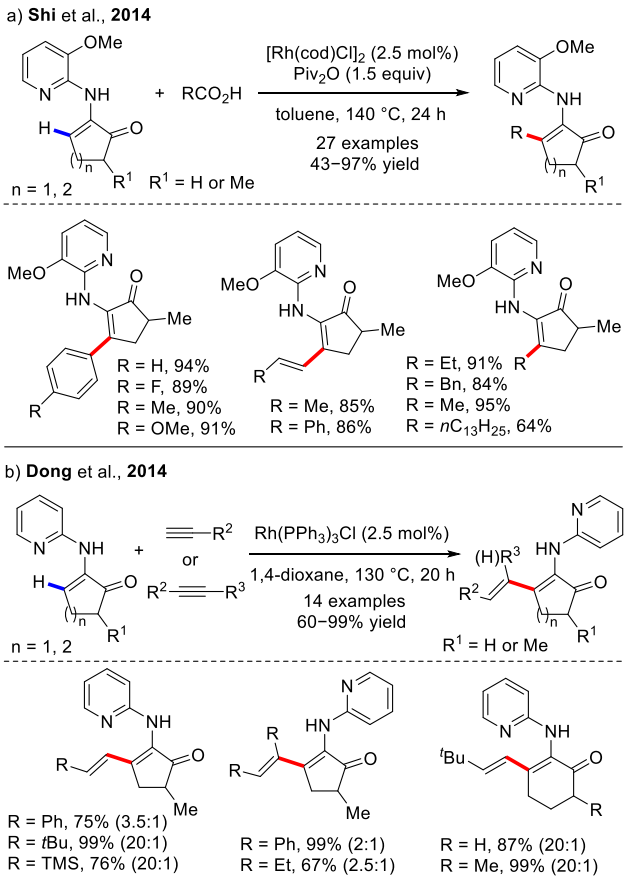
Scheme 372. Iodine(III)-Mediated Cross-Coupling of Enamines with Propargyl Amines and Subsequent Cyclization to Multisubstituted 3-Pyrrolines



diverse multisubstituted 3-pyrrolines, which are recognized as a key substructure in many pharmaceutically relevant molecules.

The group of Sun and Shi in 2014 published the Rh-catalyzed hydrogen-bonding assisted alkenyl β-C−H functionalization of both five- and six-membered cyclic enamines with carboxylic acids by means of 3-methoxy-2-pyridinyl amino group as the directing group (Scheme 373a).[599] A broad range

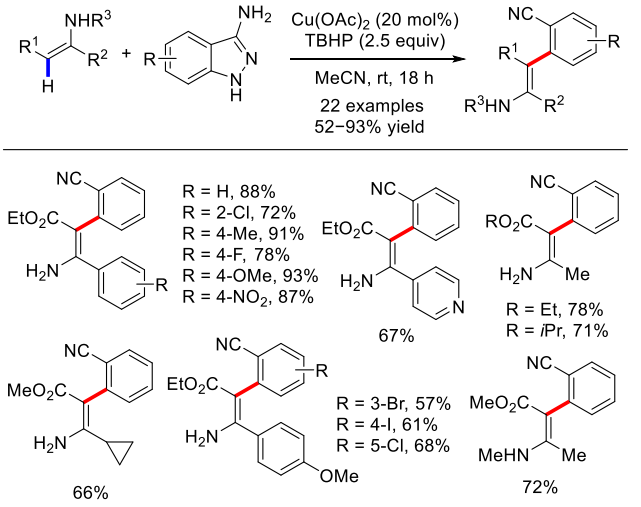
Scheme 373. Rh-Catalyzed Cross-Coupling of Cyclic Enamines with Carboxylic Acids or Alkynes



of aryl, alkenyl carboxylic acids as well as aliphatic acids are all competent coupling partners for this decarbonylative reaction. Of note, the directing group can be easily removed by the treatment with TsOH in aqueous media, offering an alternative approach to highly functionalized cyclic 1,2-diketones. Almost at the same time, Dong and colleagues made use of a similar strategy to the synthesis of β-alkenylated α-enamino-ketones *via* enamine-directed vinyl C−H/alkyne couplings (Scheme 373b).[600]

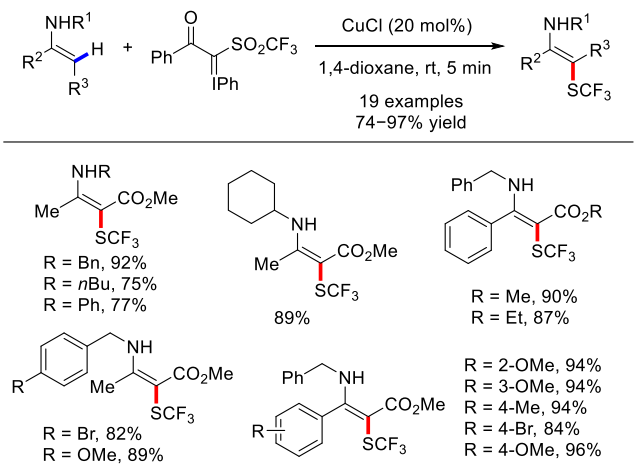
Several years later, Song and colleagues successfully established a general denitrogenative C−H arylation of enamines with 3-aminoindazoles as the arylating agents *via* the C−N bond cleavage, providing a series of arylated enamines in good yields (Scheme 374).[601] Mechanistically, the authors proposed that a benzonitrile radical may be probably involved in this C−H arylation process.

Scheme 374. Copper-Catalyzed Alkenyl C−H Arylation of Enamines with 3-Aminoindazoles



The introduction of a trifluoromethylthio group (CF_3S-) into enamines through vinylic C−H cleavage has been also explored. In 2013, Shibata's group elaborately designed a novel and shelf-stable electrophilic trifluoromethylthiolation reagent, that is, trifluoromethanesulfonyl hypervalent iodonium ylide. A variety of trifluoromethylthiolated enamines were nicely obtained in excellent yields (74−97%) in the presence of a catalytic amount of CuCl (20 mol %) (Scheme 375).[602] The reaction was typically finished within 5 min at room temperature in 1,4-dioxane. The scope was impressive as indoles and β-keto esters were also suitable substrates in this case, furnishing the trifluoromethylthiolated products in high yields. From a mechanistic point of view, the authors suggested that the *in situ* reduction of trifluoromethanesulfonyl group by

Scheme 375. Copper-Catalyzed Vinylic C−H Bond Trifluoromethylthiolation of Enamines



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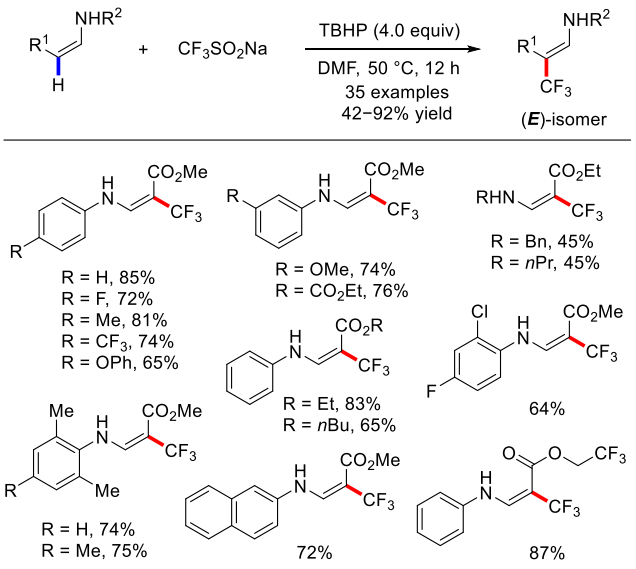
an intramolecular rearrangement process gives rise to the CF_3S group, which is identified as the key step in this protocol.

Later in 2017, Jiang and Wu established a general protocol for the cross-coupling of enamines with Langlois' reagent (Scheme 376).[603] A series of enamines can couple efficiently

Scheme 376. Synthesis of β-Trifluoromethylated Enamines with Langlois' Reagent



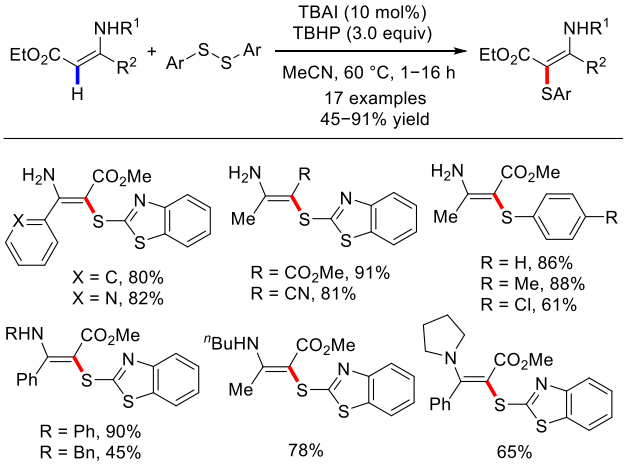
with CF_3SO_2Na by using TBHP as both initiator and oxidant under transition-metal-free conditions, giving rise to a facile synthesis of β-trifluoromethylated enamines in moderate to excellent yields (42−92%) with exclusive *E*-configuration.

Vinyl sulfides are privileged and extremely important scaffolds that are widespread in a series of biologically active natural products and pharmaceutically relevant molecules. In 2016, the Du group found that the reaction of enamines with diaryl disulfides could afford a broad array of α-thioenamines in appreciable yields (45−91%) by using a catalytic amount of tetrabutylammonium iodide (10 mol %) in combination with 3.0 equiv of *tert*-butyl hydroperoxide (TBHP) (Scheme 377).[604] This metal-free TBAI/TBHP oxidative system also enables the formation of C−Se bonds for the synthesis of α-selenylated enamines, albeit with relatively low yields (28−42%).

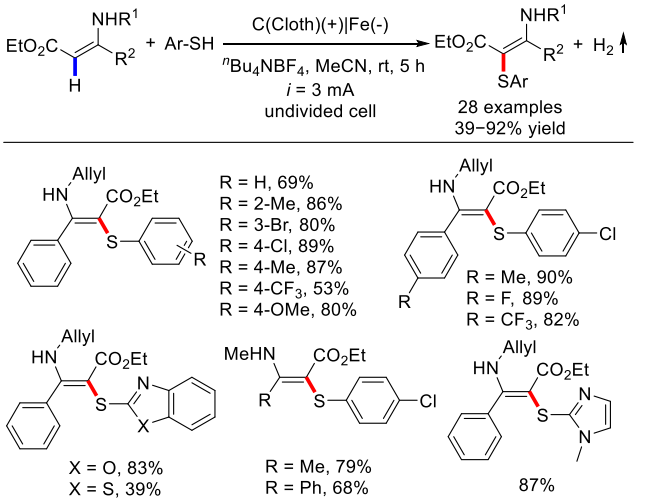
Afterward, Lei and co-workers illustrated a rare example of electrochemical oxidative C−H/S−H coupling to forge the C−S bond, providing a sustainable, atom-economical, and environmentally friendly approach for the synthesis of vinyl sulfides with H_2 as the only byproduct (Scheme 378).[605] A broad range of enamines and thiophenols could be readily converted under electrochemical oxidative conditions, significantly obviating the use of external oxidants. A plausible mechanism involving the generation of a thiyl radical was tentatively proposed to elucidate this C−S formation process. More recently, Li and Xie followed this work in an attempt to expand the substrate scopes of this electrochemical protocol by employing a modified conditions with a carbon felt anode and a nickel plate cathode as the electrode materials.[606]

Subsequently, Wu's group presented a general and highly efficient strategy for the vinylic β-C−H phosphorylation of enamines enabled by cost-effective cobaloxime catalysis under visible-light irradiation with hydrogen evolution (Scheme

Scheme 377. TBAI/TBHP-Mediated Oxidative Coupling of Enamines with Disulfides



Scheme 378. Electrochemical Oxidative Cross-Coupling of Enamines with Thiophenols



379).[607] The reaction occurred under especially mild conditions and exhibited excellent functional group tolerance for both enamines and *H*-phosphine oxides, providing a concise route to a series of β-phosphinoyl products in 52−99% yield with modest *Z*-selectivity. On the basis of experimental and spectroscopic investigations, a reductive quenching pathway of cobaloxime catalyst to generate phosphinoyl radical was proposed to elucidate the mechanism.

In a recent report, Hashmi, Tian, and their co-workers reported the use of enamines as substrates to couple with hypervalent iodine(III) reagents under gold catalysis, in which a series of tetrasubstituted conjugated 1,3-enynes were obtained in a regioselective manner (Scheme 380).[608] Mechanistically, the Au(I) species **I** was initially produced under the typical conditions, which then undergoes oxidative addition with hypervalent iodine reagent to afford the alkynyl Au(III) intermediate **II**. Subsequent alkenyl C−H functionalization of enamines with alkynyl Au(III) species **III** followed by a facile reductive elimination process would release the corresponding 1,3-enynes and simultaneously regenerate the Au(I) catalyst.

A diverse array of highly functionalized naphthalene derivatives were readily prepared by the group of Wei from

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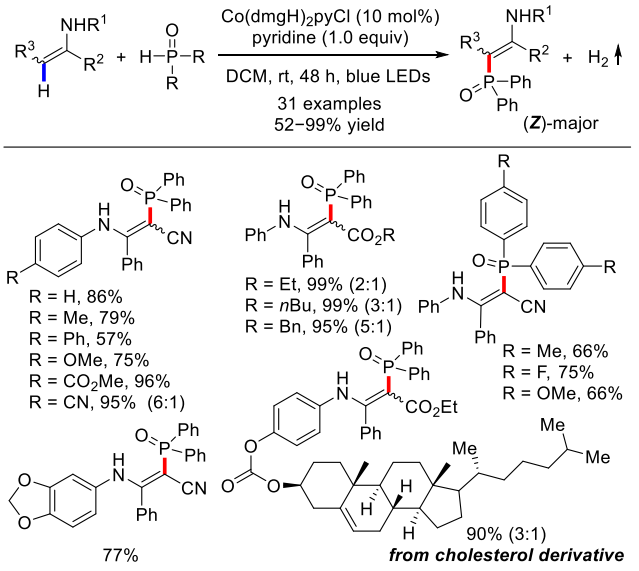
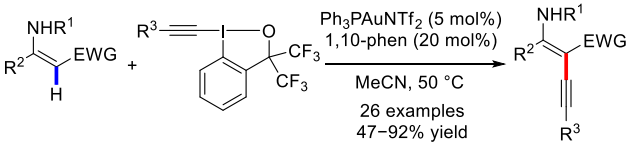
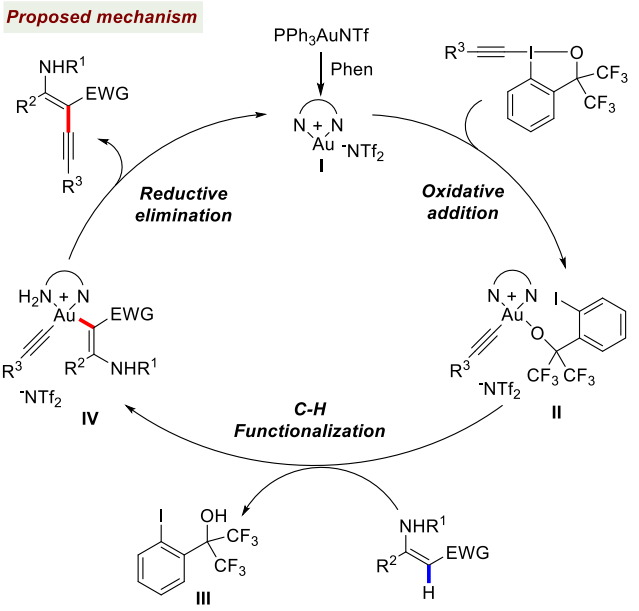
Scheme 379. Direct Alkenyl C−H Phosphorylation of Enamines Enabled by Cobaloxime Catalysis



Scheme 380. Synthesis of Tetrasubstituted 1,3-Enynes by Gold-Catalyzed C−H Alkynylation of Enamines

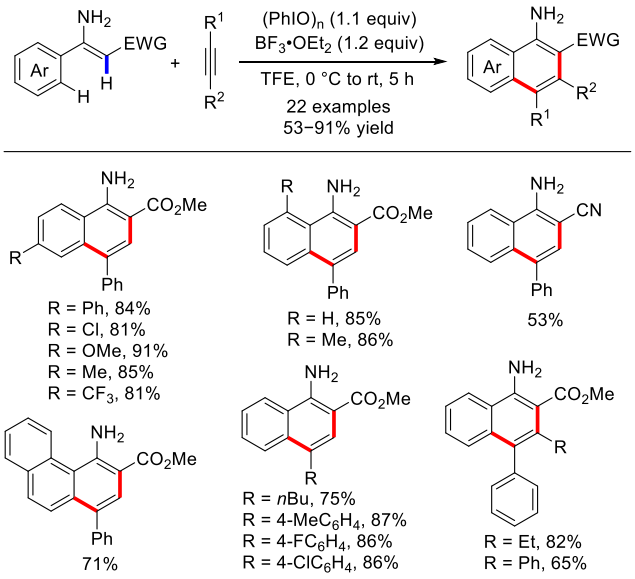




readily available enamines and alkynes *via* a general, practical, and efficient iodine(III)-mediated oxidative benzannulation strategy (Scheme 381).[609] This metal-free protocol features a wide substrate scope and especially mild conditions. In this case, the nucleophilic attack of alkyne on the iodine(III) species generated from the reaction of enamine with PhIO was crucial for subsequent intramolecular electrophilic benzannulation process.

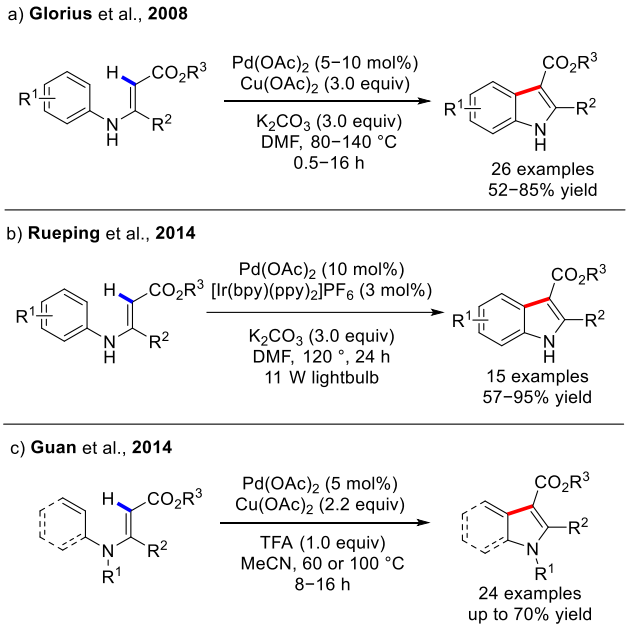
Glorius and co-workers in 2008 took the lead in realizing a direct and broadly applicable approach for the efficient

Scheme 381. Synthesis of Polysubstituted Naphthalene Derivatives *via* Iodine(III)-Mediated Benzannulation of Enamines with Alkynes



synthesis of 2,3-disubstituted NH-free indoles through the palladium-catalyzed intramolecular oxidative cyclization of *N*-aryl enamines, which can be readily prepared from commercially available aniline derivatives (Scheme 382a).[610]

Scheme 382. Synthesis of Indoles and Pyrroles *via* Pd-Catalyzed Intramolecular Oxidative Cyclization of *N*-Aryl Enamines



Initial mechanistic studies unambiguously favored a σ-bond-metathesis or deprotonation pathway for this transformation. Later in 2011, they continued to uncover the details of this dehydrogenative cross-coupling reaction.[611] In the aftermath of this work, the Rueping group achieved a similar transformation enabled by the synergistic palladium and photoredox catalysis while obviating the use of stoichiometric $Cu(OAc)_2$ as the oxidant (Scheme 382b).[612] Around the same time, Guan's

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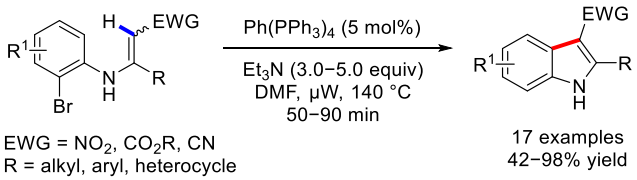
group carried out the intramolecular oxidative cyclization of tertiary enaminations in an effort to prepare various multisubstituted pyrroles and indoles in decent yields with a stoichiometric amount of TFA as an additive (Scheme 382c).[613]

Moreover, Kurth and co-workers in 2013 described the intramolecular coupling of *o*-bromoaniline-based *N*-aryl *β*-nitroenamines by the combination of $Pd(PPh_3)_4$ catalyst and Et_3N additive, offering an efficient route to access 3-nitroindoles in decent yields with excellent regioselectivity (Scheme 383).[614] It is noteworthy that the reaction occurs

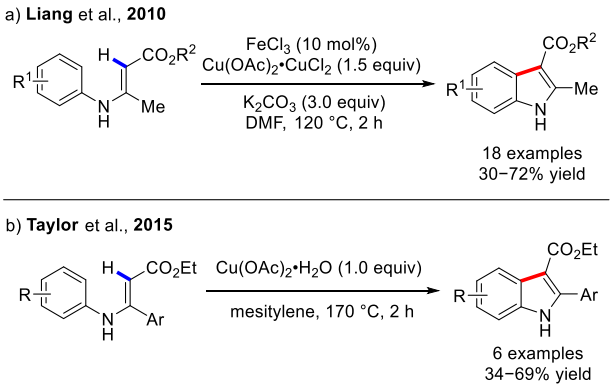
Scheme 383. Microwave-Assisted Pd-Catalyzed Indole Synthesis from *N*-Aryl Enamines



under microwave irradiation conditions. Moreover, a variety of 3-carboalkoxy- and 3-cyanoindoles can be obtained by this microwave-assisted protocol.

By taking advantage of environmentally benign, sustainable, and inexpensive iron catalyst combined with a highly active $Cu(OAc)_2{\bullet}CuCl_2$ as the oxidant, Liang and colleagues were able to prepare a series of multisubstituted indoles in synthetically satisfactory yields (Scheme 384a).[615] The

Scheme 384. Sustainable Synthesis of Indoles *via* Oxidative Cyclization of *N*-Aryl Enamines

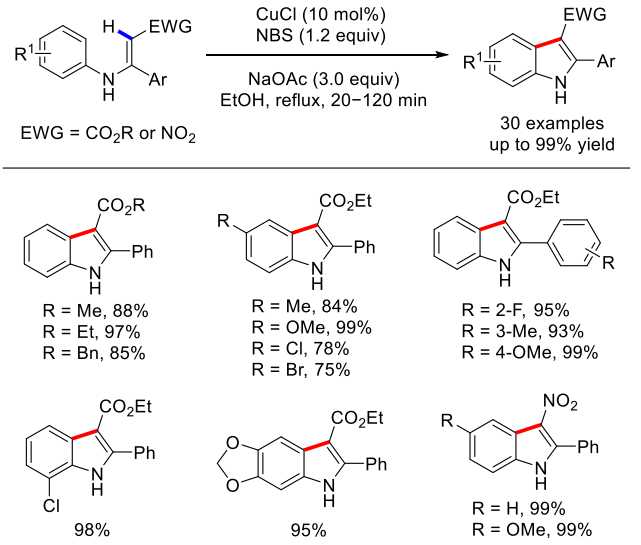


generated iron and copper bimetallic chelate species by the coordination of the *N*-atom and the C=C bond was assumed to greatly enhance the activity of the enoate intermediate in this protocol. Later in 2015, Taylor and co-workers performed analogous investigations by their Cu(II)-mediated protocol at relatively high temperature (Scheme 384b).[616]

Subsequently, Zhang *et al.* achieved an efficient one-pot synthesis of 2,3-disubstituted indoles through a facile oxidative cyclization reaction of *N*-aryl enamines by a combination of CuCl, *N*-bromosuccinimide (NBS), and NaOAc, leading to the corresponding polysubstituted indoles in up to 99% yield (Scheme 385).[617]

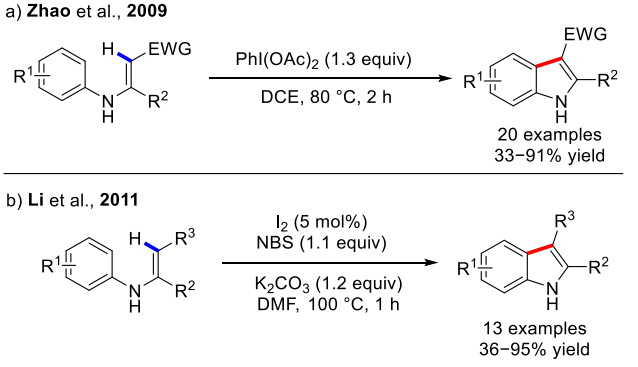
However, it should be noted that the intramolecular cyclization of *N*-aryl enamines for indole synthesis can be performed under transition-metal-free conditions. For instance,

Scheme 385. CuCl/NBS Mediated Oxidative Cyclization of *N*-Aryl Enamines



Zhao and co-workers in 2009 expanded their PIDA-mediated strategy and established a novel metal-free approach for indoles synthesis from *N*-aryl enamines in the presence of phenyliodine(III) diacetate (PIDA) (Scheme 386a).[618] The

Scheme 386. Metal-Free Indole Synthesis *via* Oxidative Cyclization of *N*-Aryl Enamines



mechanism of this process was not investigated in detail, but the authors suggested an intramolecular SN_2'-type cyclization pathway to elucidate the formation of indoles. Shortly afterward, Li and co-workers found that *N*-aryl enamines could also undergo an intramolecular oxidative cyclization process to produce a series of functionalized indoles by using a I_2/NBS catalytic system. A scope of 13 examples of this transformation was presented with yields of 36−95% (Scheme 386b).[619]

The merging of photoredox catalysis with Co catalysis opened new avenues on the route toward the synthesis of indoles from enamines. In 2016, Wu and colleagues accomplished an elegant synergistic iridium/cobalt-catalyzed strategy for indole synthesis by the intramolecular dehydrogenative annulation of *N*-aryl enamines under visible-light irradiation (Scheme 387a).[620] Using $Ir(ppy)_3$ as the photosensitizer and $Co(dmgH)_2(4\text{-}CO_2Mepy)Cl$ as the cobaloxime catalyst, a series of *N*-aryl enamines can be readily converted into the expected indoles under ambient conditions with H_2 as the only byproduct, with 23 examples documented in yields of

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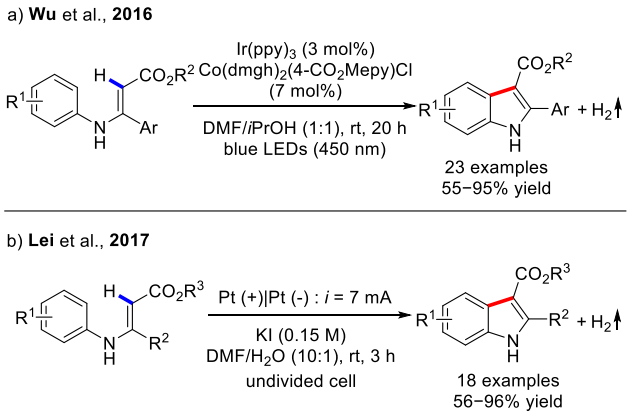
Scheme 387. Synthesis of Indoles by Intramolecular Dehydrogenative Cyclization of *N*-Aryl Enamines

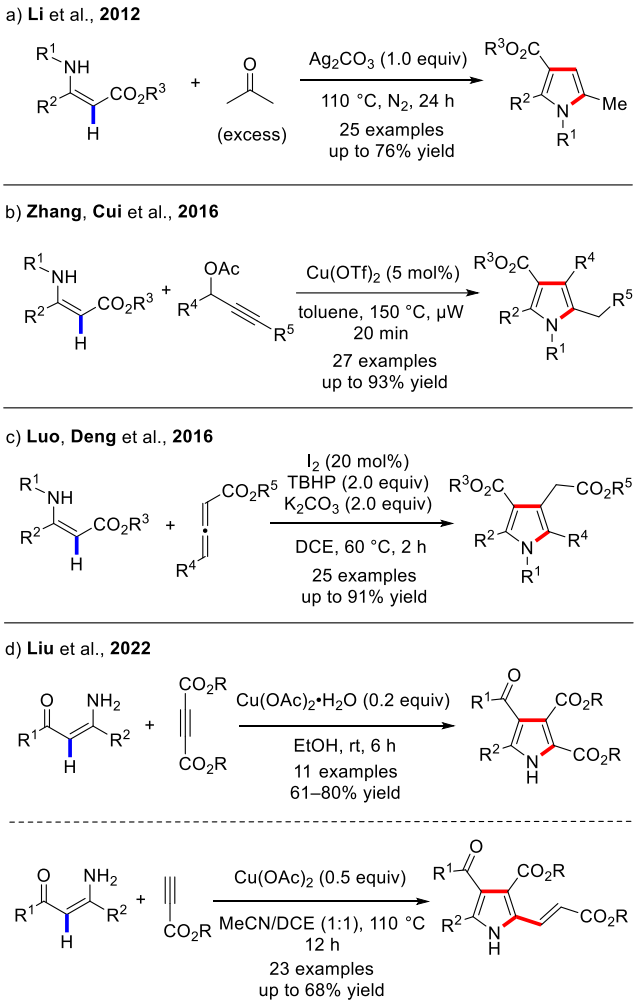


55–95%. Combined spectroscopic and electrochemical investigations indicated that this formal dehydrogenative annulation protocol proceeds through a visible-light-catalyzed oxidation of *N*-aryl enamines, followed by an intramolecular radical addition process. One year later, Lei's group also achieved the same transformation in the presence of KI under electrochemical conditions (Scheme 387b).[621]

Moreover, substituted pyrrole synthesis has been also realized from enamine starting materials. In 2012, Li and colleagues elaborated a general approach to access tetrasubstituted pyrroles by the dehydrogenative cross-coupling between enamines and acetone with 1.0 equiv of silver carbonate as an oxidant (Scheme 388a).[622] Later, the group of Zhang and Cui discovered that enamines reacted smoothly with propargyl acetates through a copper-catalyzed cascade propargylation/alkyne azacyclization/isomerization sequence to produce fully substituted pyrroles in up to 93% yield (Scheme 388b).[623] The reaction was carried out in toluene at 150 °C under microwave irradiation. Soon after, Luo, Deng, and their colleagues obtained a similar transformation with allenes as the coupling partner by the combination of KI, TBHP, and K_2CO_3 in DCE solvent (Scheme 388c).[624] A plausible mechanism was discussed, and the reaction may proceed *via* a tandem Michael addition/oxidative annulation pathway. More recently, Liu *et al.* established the copper-mediated annulation of enaminones with internal dialkyl ethylenedicarboxylates at room temperature, giving rise to diverse 2,3-dicarboxylate-functionalized pyrroles in high yields (61–80%). Interestingly, a broad array of 2-vinyl pyrroles could be synthesized when employing terminal propiolates as coupling partners under modified conditions (Scheme 388d).[625]

Meanwhile, efficient and practical synthetic strategies for the homo- and heterocoupling of enamines have been also established for the synthesis of structurally diverse pyrroles in recent years. Specifically, Guan and co-workers in 2016 elaborated a robust approach for the synthesis of a large variety of multisubstituted NH-pyrroles by a $K_2S_2O_8$-mediated oxidative homocyclization of enamines (Scheme 389a).[626] The same group further expanded to describe a novel Cu-catalyzed tandem oxidative cyclization/1,2-amino migration of enamines, affording aminomethylsubstituted pyrroles in good yields (Scheme 389b).[627] An optimized set of conditions consisted of substrate solutions in MeCN in the presence of $Cu(TFA)_2$ catalyst, AgOAc additive, and O_2 oxidant. One year

Scheme 388. Direct Synthesis of Multisubstituted Pyrroles from Enamines



later, Chen and colleagues elaborated the synthesis of unsymmetrically multisubstituted pyrroles *via* copper-catalyzed aerobic dimerization (Scheme 389c).[628] Subsequently, they continued to report the synthesis of symmetric fully substituted pyrrole derivatives from enamines by an electrochemical-oxidation-induced annulation process (Scheme 389d).[629] Meanwhile, Roy, Sarkar, and their co-workers described a similar approach for multisubstituted NH-pyrrole synthesis under electrochemical conditions. Notably, with trifluoroethanol (TFE) as a unique additive, this electrochemical strategy also enables the heterocoupling of aryl- and alkylsubstituted enamines to afford a series of tetrasubstituted NH pyrroles in comparable yields. Combined experimental and theoretical studies were also performed to elucidate the "magic effect" of TFE additive in promoting this heterocoupling reactions (Scheme 389e).[630]

Apart from the above-described examples for pyrrole synthesis, the group of Li and Gao in 2015 developed a novel method for the convenient synthesis of diverse multisubstituted *trans*-2,3-dihydropyrroles from enamines and chalcones *via* an iodine-promoted, one-pot cascade Michael/cyclization sequence, affording the products in modest to excellent yields (Scheme 390).[631]

In the course of their investigations on the intramolecular cyclization of enamines for indole synthesis,[610] Glorius and co-

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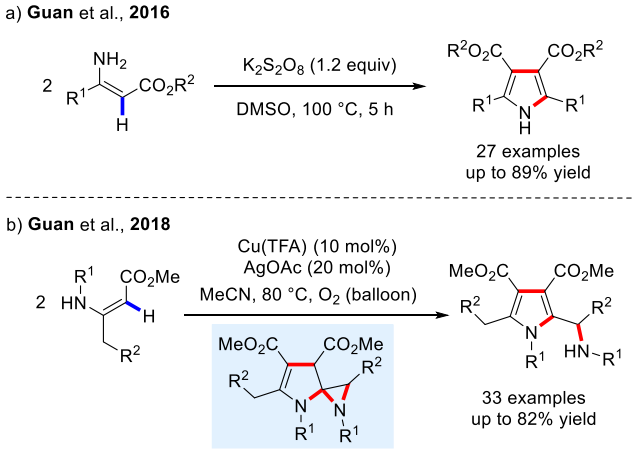
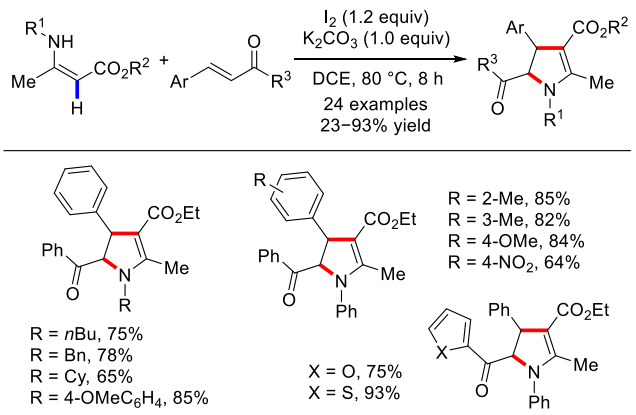
Scheme 389. Synthesis of Multisubstituted Pyrroles *via* Oxidative Cyclization of Enamines

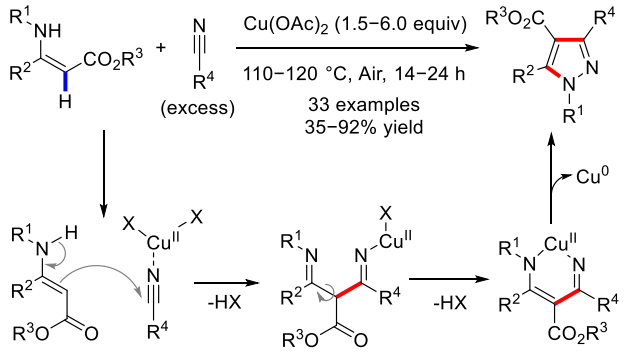


Scheme 390. Rapid Synthesis of Multisubstituted 2,3-Dihydropyrroles from β-Enamine Esters



workers found that the use of acetonitrile as the solvent instead of DMF exclusively resulted in the formation of tetrasubstituted pyrazoles (Scheme 391).[632] The reaction proceeded

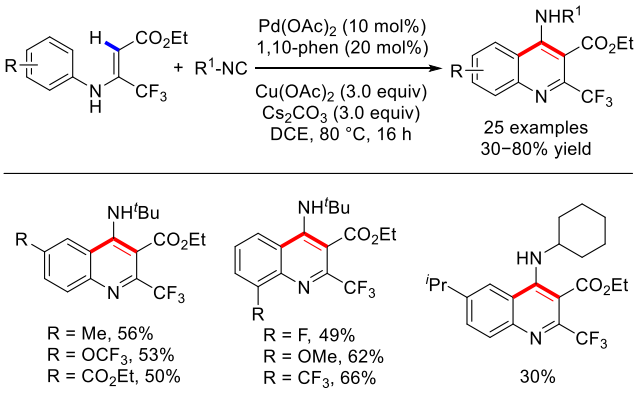
Scheme 391. Synthesis of Tetrasubstituted Pyrazoles from Enamines and Nitriles



involving an oxidative N–N bond formation in the presence of copper acetate as both a Lewis acid activator and as an oxidant. Mechanistically, the nitrile substrate is nicely activated by the copper(II) Lewis acid, greatly facilitating the addition of the nucleophilic enamines. Subsequent loss of HOAc results in the formation a 1,3-bisimine. After rotation around the former *Z* double bond followed by elimination of another HOAx, a Cu^{II}-chelate species was produced. Finally, reductive elimination furnishes the desired pyrazoles and releases copper(0) simultaneously.

Ding's group in 2015 published the efficient palladium-catalyzed intermolecular cyclization reaction of various *N*-aryl enamines with isocyanides as versatile C1 building blocks through both aromatic and olefinic C(sp^2)–H bonds cleavage (Scheme 392).[633] By using a combination of $Pd(OAc)_2$

Scheme 392. Pd-Catalyzed Intermolecular Oxidative Cyclization of Enamines with Isocyanides



catalyst and 1,10-phen ligand, a series of highly valuable 4-aminoquinolines were produced in decent yields (30–80%). This cascade oxidative cyclization protocol was proposed to undergo sp^2C–H bonds activation of enamines, isocyanides migratory insertion, and reductive elimination sequences.

Quinoxalines, also known as benzo[*a*]pyrazines, are an extremely important class of nitrogen-containing heterocyclic scaffolds widespread in numerous natural products and drug candidates with remarkable biological activities.[634−636] As such, tremendous efforts have been made for the preparation of quinoxalines from *N*-aryl enamines. Specifically, Zhang and colleagues in 2014 reported that *N*-aryl enamines could react with nitromethane through an oxidative tandem nitrosation/cyclization sequence enabled by the KI/TBHP catalytic

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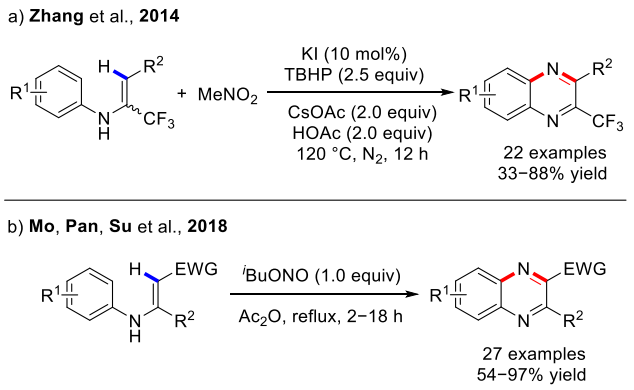
system, furnishing the metal-free synthesis of 3-trifluoromethylquinoxalines in a single step with high efficiency (Scheme 393a).[637] In a related synthesis, Mo, Pan, Su, and their co-

Scheme 393. Synthesis of Quinoxalines through Alkenyl C−H Functionalization of *N*-Aryl Enamines



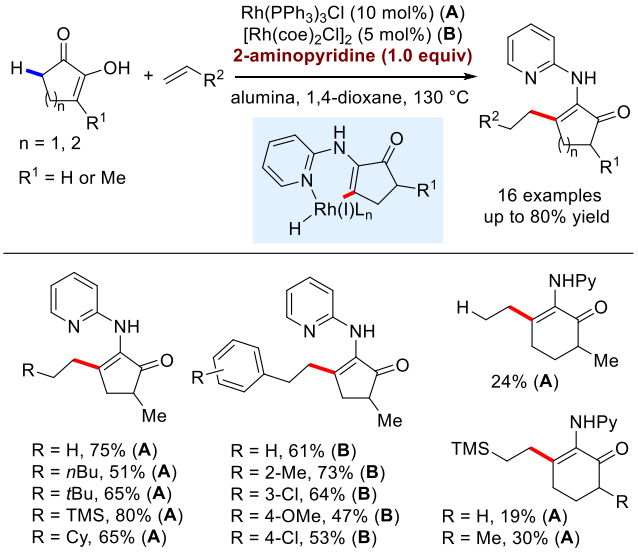
workers utilized readily available *iso*-butyl nitrite (IBN) as a novel nitrogen reagent to construct C−N bonds and reported on a reaction between *N*-aryl enamines and IBN in the presence of Ac_2O (Scheme 393b).[638] This process presumably involved the generation of the key β-imino oxime ester intermediate and subsequent 6πe-azacyclization.

In addition to the examples discussed above, in which enamines were used directly as the starting materials for the reaction, there are a few processes employing the combination of simple ketones or aldehydes with suitable directing groups to *in situ* generate enamines. Such carbonyl-involved synergistic transition-metal/enamine catalysis would unambiguously convert the ketone sp^3 αC−H bonds to sp^2 bonds, thus significantly enhancing the reactivity toward oxidative addition by a low-valent transition metal. Although the overall reaction of this strategy is the α-C−H transformation of ketones, the inherent catalytic mechanism involves the enamine vinylic C−H functionalization step.[639−644]

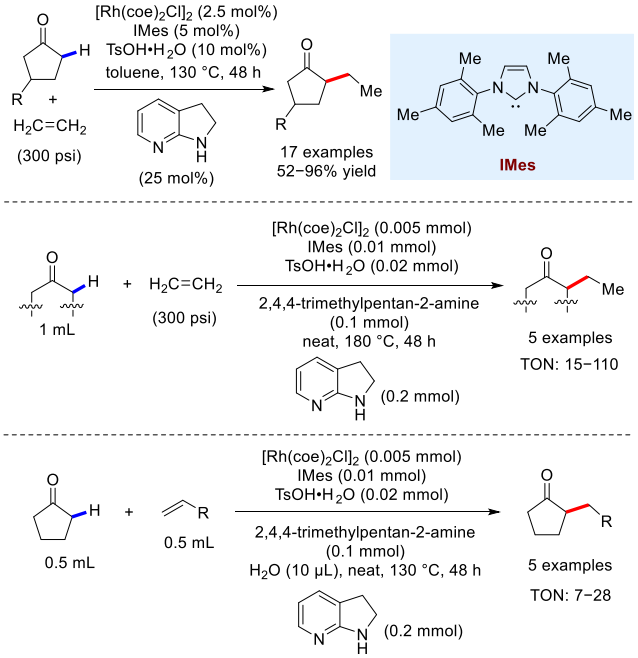
In demonstrating the proof of concept,[645] Dong and coworkers pioneered to explore the feasibility of such a dual activation strategy and successfully accomplished an unprecedented Rh-catalyzed α-C−H alkylation of cyclic 1,2-diketones by using terminal olefins as the alkylating agents (Scheme 394).[646] In this ketone α-alkylation protocol, a stoichiometric amount of 2-aminopyridine was employed as the efficacious *in situ* installed directing group. A wide range of simple olefins including aliphatic, aromatic olefins, and even ethylene gas were compatible with the conditions, exclusively affording the linear alkylation products.

In 2014, Dong's group elegantly disclosed a distinctive and regioselective α-alkylation of cyclopentanones with simple olefins (Scheme 395).[647] In this report, readily available 7-azaindoline was identified as the optimal bifunctional aminocatalyst. Using the combination of $[Rh(coe)_2Cl]_2$ catalyst (2.5 mol %), *N*-heterocyclic carbene (NHC) ligand (IMes, 5 mol %), 7-azaindoline (25 mol %), and TsOH•H_2O additive (10 mol %) in toluene, a range of 3-substituted cyclopentanones coupled regioselectively with ethylene at the less-hindered position under both pH and redox-neutral conditions, delivering the products in decent yields with moderate diastereoselectivity. Notably, other cyclic, acyclic ketones as well as terminal α-olefins were also compatible substrates

Scheme 394. Rh(I)-Catalyzed C−H Bond Alkylation of Enamines Generated from 1,2-Diketones



Scheme 395. Regioselective α-Alkylation of Ketones with Olefins *via* Rh-Enamine Cooperative Catalysis



under slightly modified conditions, albeit with modest efficiency.

Inspired by Córdova's seminal work of palladium and enamine cooperative catalysis to obtain α-allylic alkylation of ketones with allylic acetates,[648,649] Lei, Luo, and colleagues in 2014 elaborated an efficient oxidative α-C−H alkylation of regular ketones with allylarenes enabled by synergistic nucleophilic enamine activation and Pd-catalyzed allylic C−H functionalization (Scheme 396).[650] However, this Pd/proline cocatalyzed oxidative coupling protocol was limited to allylarenes, and, furthermore, the asymmetric version of this process did not furnish the enantioselective products.

Later in 2015, Dong and Lim continued to describe a complementary protocol for the intramolecular Conia-ene-type

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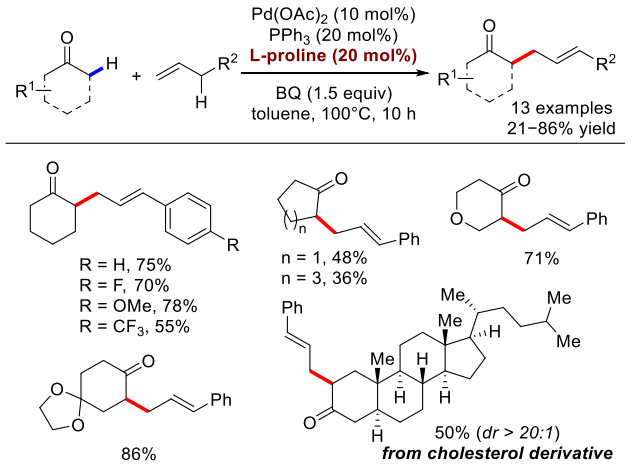
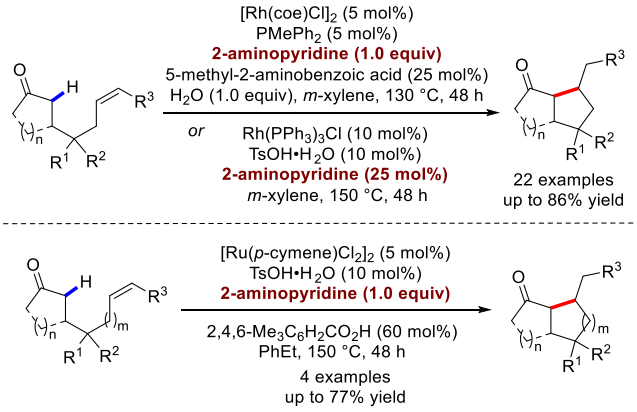
Scheme 396. Oxidative Coupling of Allylarenes with Unactivated Ketones *via* Synergistic Pd/Enamine Catalysis



ketone α-C−H alkylation with olefins by taking advantage of a similar dual-activation strategy (Scheme 397).[651] Likewise, a

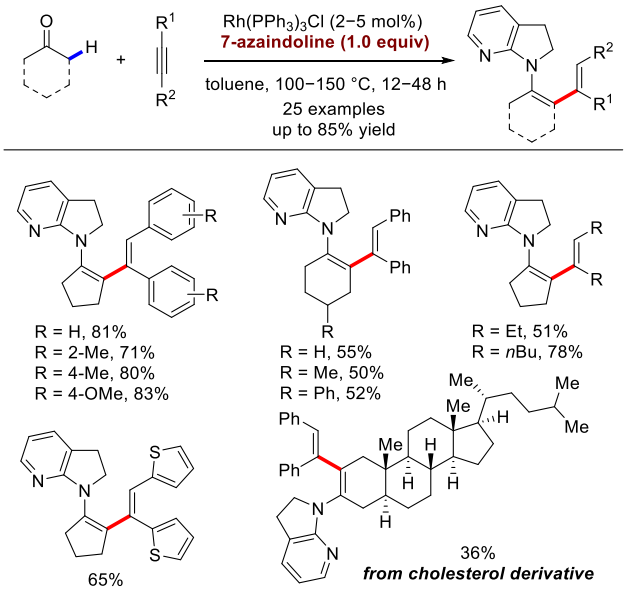
Scheme 397. Rh- and Ru-Catalyzed Intramolecular Ketone α-Alkylation *via* Dual Activation



stoichiometric amount of 2-aminopyridine was identified as the bifunctional aminocatalyst. The authors found that the rhodium catalyst system was recognized to be more efficient for the generation of five-membered rings, whereas a ruthenium-based catalyst was discovered to furnish the six-membered ring products.

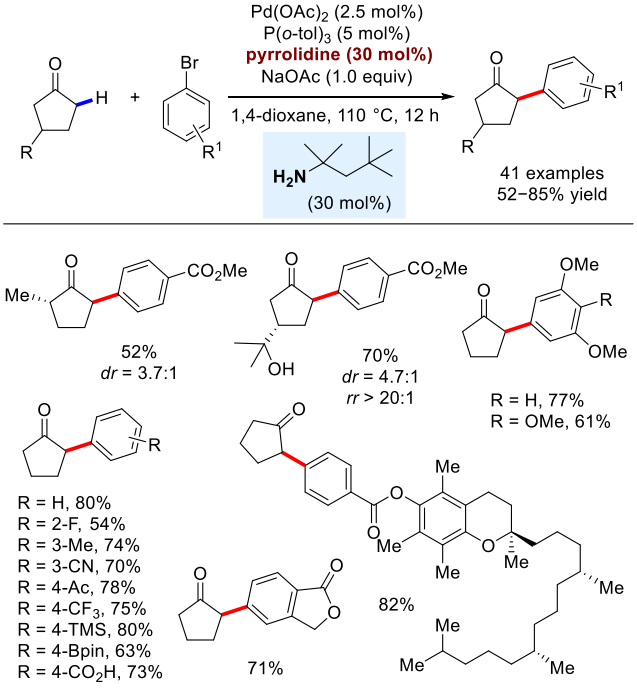
Almost at the same time, Dong and colleagues also devised an amino/Rh cooperative catalysis protocol for the α-C−H alkenylation of regular ketones with various internal alkynes by the combination of Wilkinson's catalyst and bifunctional 7-azaindoline aminocatalyst, enabling the controllable synthesis of thermodynamically stable α,β-enones and kinetically favored β,γ-enones with decent yields (Scheme 398).[652] Gratifyingly, a broad range of functionalities were compatible, and excellent *E*-selectivity was observed. Moreover, a series of control, kinetic monitoring, and deuteriumlabeling experiments were performed to investigate the catalytic mechanism of this process. Mechanistically, the reaction may involve a sequence of the insertion of the rhodium(I) species into the *in situ* formed enamine vinyl C−H bond, subsequent alkyne coordination, Rh−H migratory insertion, and reductive elimination.

Scheme 398. Rhodium-Catalyzed α-Alkenylation of Ketones with Internal Alkynes



Furthermore, Dong and co-workers also elaborated a palladium and enamine cooperative catalysis approach for the direct α-C−H monoarylation of cyclopentanones with aryl bromides (Scheme 399).[653] Both aminocatalyst and $Pd(OAc)_2$

Scheme 399. Direct α-Arylation of Cyclopentanones by Palladium/Enamine Cooperative Catalysis



proved to be indispensable for achieving high efficiency. Of note, no coordinating moiety on the aminocatalyst was required in this reaction, which is quite different from that of synergistic Rh/enamine catalysis.

A couple of months later, a general procedure for the enantioselective α-arylative desymmetrization reaction of cyclohexanones by the combination of $Pd(OAc)_2/PPh_3$ and

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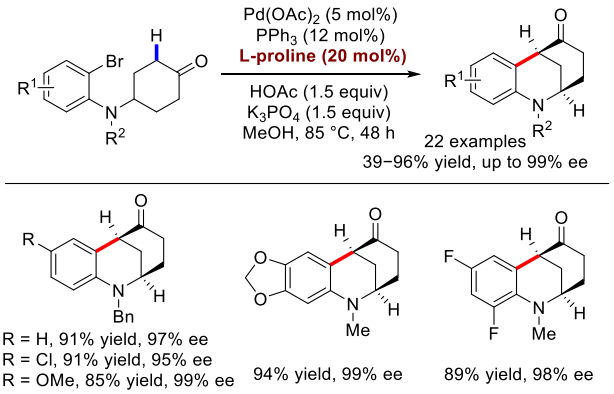
(L)-proline catalysis was presented by Jia and colleagues, unexpectedly giving rise to a diverse array of chiral bridged morphan derivatives bearing α-carbonyl tertiary stereocenters (Scheme 400).[654] Stochiometric amount of K_3PO_4 base and

Scheme 400. Synergistic Pd/(L)-Proline Catalyzed Enantioselective α-Arylative Desymmetrization of Cyclohexanones

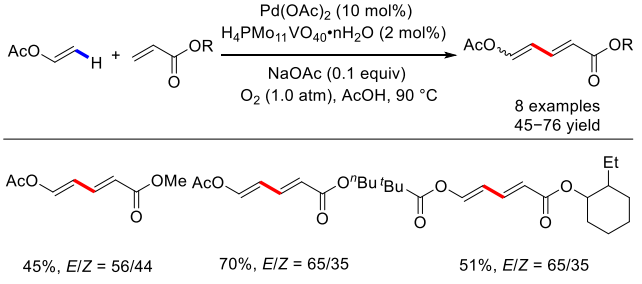


HOAc additive were required for the reaction. A broad scope of 22 examples of this reaction was documented with yields of 39–96% and excellent enantiomeric excesses (up to 99%).

5.4. Enolates

5.4.1. Enol Acetates. Early in 2004, the Ishi group first investigated the $Pd(OAc)_2$/HPMoV catalyzed aerobic oxidative cross-coupling of vinyl carboxylates with acrylates using O_2 as the sole oxidant in acetic acid, affording the conjugated 1,3-dienes in 45–76% yields (Scheme 401).[655]

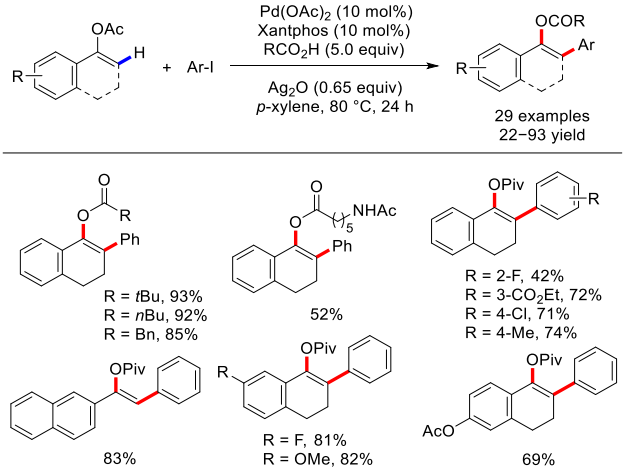
Scheme 401. $Pd(OAc)_2$/HPMoV-Catalyzed Oxidative Cross-Coupling of Vinyl Carboxylates with Acrylates



Later in 2015, Loh and co-workers explored the intermolecular reaction of vinylacetates with various aryl iodides in the presence of a superstoichiometric amount of carboxylic acids (Scheme 402).[656] Contrast to the direct olefinic C–H arylation, this protocol underwent a three-component oxyarylation of vinylacetates with the retention of C=C bonds, leading to the difunctionalized vinyl esters in modest to excellent yields.

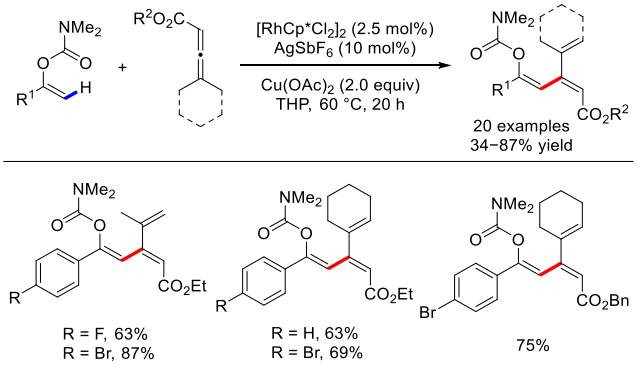
5.4.2. Enol Carbamates. Enol carbamates have been long well-recognized as key structural motifs of numerous biologically relevant pharmaceuticals and also served as versatile synthons for a series of transformations.[657] As a consequence, the vinylic C–H functionalization of enol carbamates has been extensively investigated in recent years. Specifically, Fu's group in 2014 roported the Cp*Rh(III)-catalyzed C–H activation of enol carbamates with allenes to afford highly unsaturated

Scheme 402. Palladium(II)-Catalyzed Intermolecular Oxyarylation of Vinylacetates



conjugated alkenes with excellent regioselectivity (Scheme 403).[658] The produced olefins could be easily converted into

Scheme 403. Synthesis of Conjugated Olefins through Rh(III)-Catalyzed C–H Activation of Enol Carbamates with Allenes



synthetically important cyclic skeletons through an intramolecular transesterification or Diels–Alder reaction, which definitely renders this protocol highly appealing in organic synthesis.

The same year, Glorius and co-workers described a vinylic C–H alkenylation of enol carbamates with a series of activated olefins under Cp*Rh(III) catalysis (Scheme 404).[659] Notably, both cyclic and acyclic enol-carbamates were compatible with the conditions. More interestingly, bis-protected estrone derivative only afforded the vinylic C–H olefination product, thus providing an efficient strategy for the highly regioselective functionalization of ketone-containing molecules.

Successfully, Zhang, Zhong, and co-workers presented an inexpensive ruthenium(II)-catalyzed alkenyl C–H olefination of enol carbamates, affording a diverse array of linear (*Z*,*E*)-configured butadiene skeletons in modest to high yields (Scheme 405).[660] In this report, the valuable branched (*Z*,*Z*)-butadienes could also be obtained by the regio- and stereoselective atom-economic *syn*-hydrovinylation of enol-carbamates with internal alkynes under oxidant-free conditions.

Moreover, Kim's group presented a Cp*Rh(III)-catalyzed regioselective vinylic C–H allylation of enol carbamates with 4-vinyl-1,3-dioxolan-2-ones and allylic carbonates to furnish a

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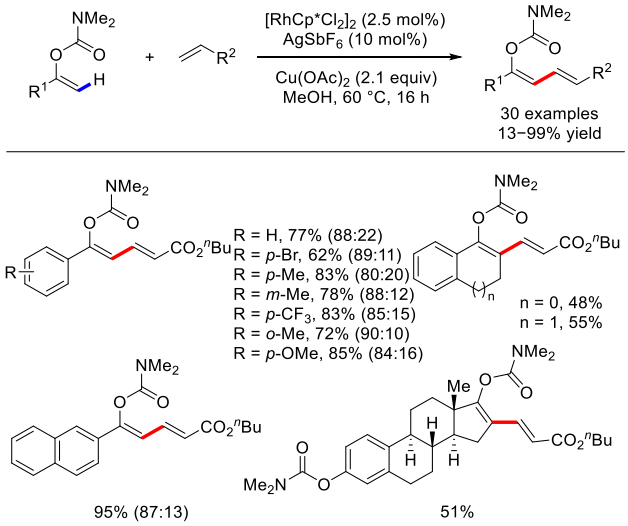
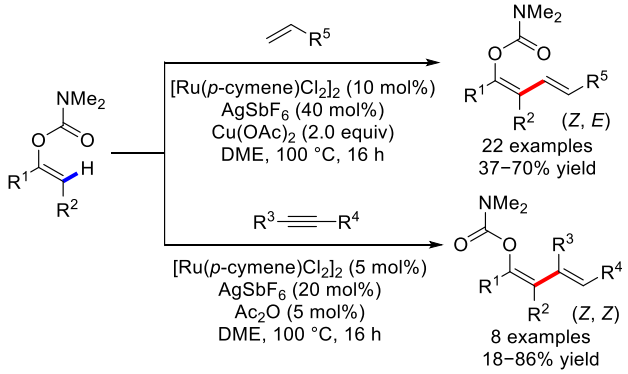
Scheme 404. Cp*Rh(III)-Catalyzed C−H Olefination of Enol Carbamates with Activated Alkenes

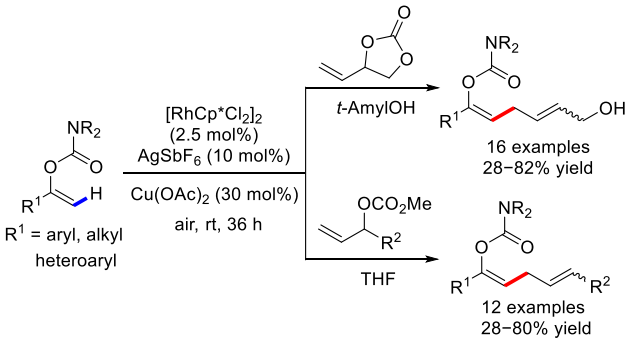


Scheme 405. Ru-Catalyzed Olefinic C−H Alkenylation of Enol Carbamates



diverse array of allylic alcohols and terminal allylated products, respectively (Scheme 406).[661] The authors demonstrated that

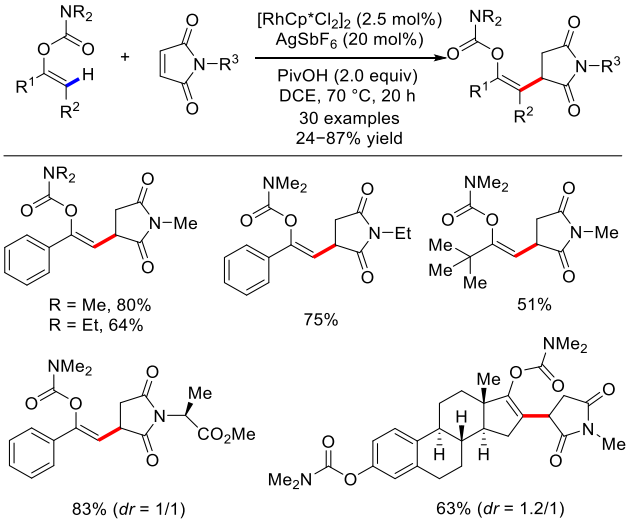
Scheme 406. Rh(III)-Catalyzed Vinylic C−H Allylation of Enol Carbamates with Allylic Carbonates



the efficacious assistance of a carbamoyl directing group enables a highly efficient synthesis of synthetically useful allylated enol carbamates. In addition, the same group also described the alkenyl C−H alkylation of enol carbamates with maleimides under rhodium(III) catalysis (Scheme 407).[662]

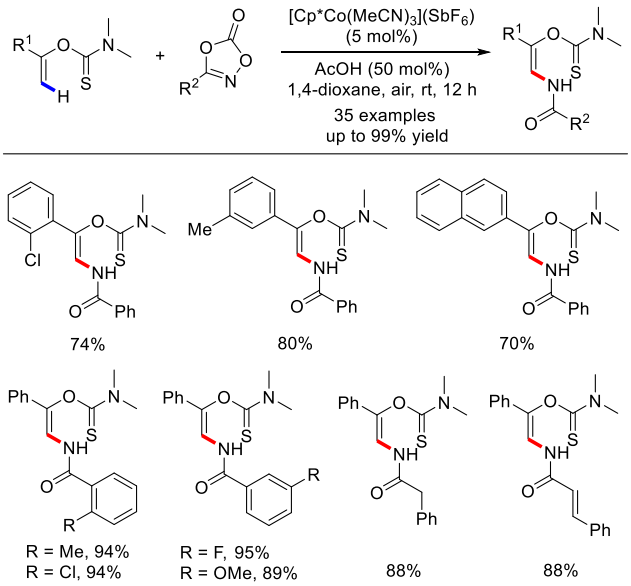
More recently, Niu's group reported the regioselective thiocarbamate-directed vinylic C−H amidation of alkenes with

Scheme 407. Rh(III)-Catalyzed Vinylic C−H Alkylation of Enol Carbamates with Maleimides



dioxazolones enabled by earth-abundant and cost-effective Cp*Co(III) catalysis under especially mild conditions, exclusively giving rise to a broad array of (*Z*)-selective enamines in up to 99% yield with excellent functional group compatibility (Scheme 408).[663]

Scheme 408. Thiocarbamate-Directed Cp*Co(III)-Catalyzed Olefinic C−H Amidation



5.4.3. Enol Phosphates. Enol phosphates often serve as a versatile alternative to the corresponding halides and triflates to engage in the transition-metal-catalyzed coupling reactions because of their high stability and ready availability. Despite the remarkable achievements in phosphorus-containing groups assisted C−H activation reactions,[664] the direct alkenyl C(sp^2)−H functionalization of enol phosphates is extremely difficult to achieve. To address this issue, Loh and co-workers expanded their olefinic C−H functionalization strategy and reported in 2015 the unprecedented example of Cp*Rh(III)-catalyzed coupling reactions of enol phosphates with a broad array of activated alkenes, alkynes as well as allenes, leading to

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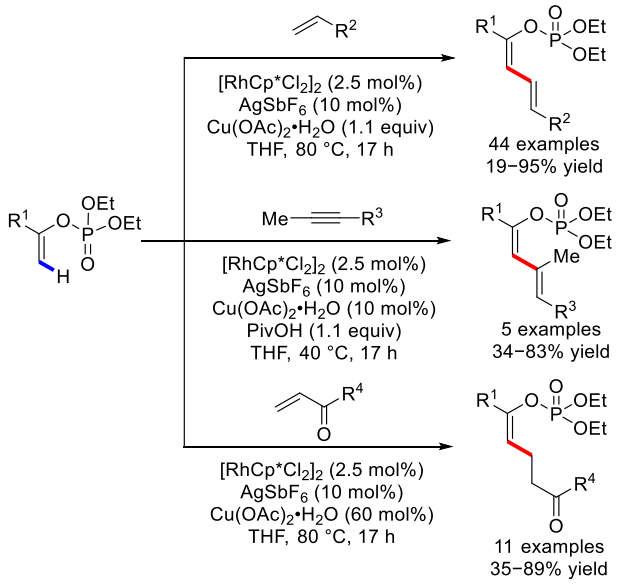
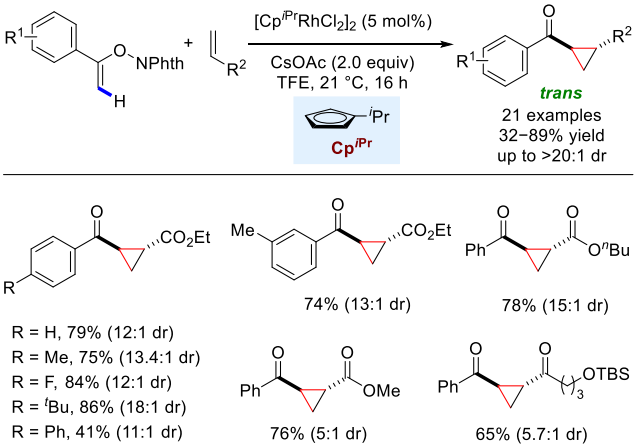
the synthesis of a series of synthetically valuable alkenylated and hydroalkenylated enol phosphates with good regio- and stereoselectivity (Scheme 409).[665]

Scheme 409. Cp*Rh(III)-Catalyzed C−H Alkenylation and Hydroalkenylation of Enol Phosphates



5.4.4. *N*-Enoxyphthalimides. Cyclopropanes are reasonably widespread in numerous biologically related pharmaceuticals and natural products,[666,667] but their stereoselective synthesis remains challenging, especially through the C−H functionalization strategy. In 2014, Rovis and co-workers accomplished a novel Rh(III)-catalyzed cyclopropanation reaction of *N*-enoxyphthalimides with electron-deficient alkenes, producing a diverse array of *trans*-1,2-disubstituted cyclopropanes with modest stereocontrol (Scheme 410).[668] In

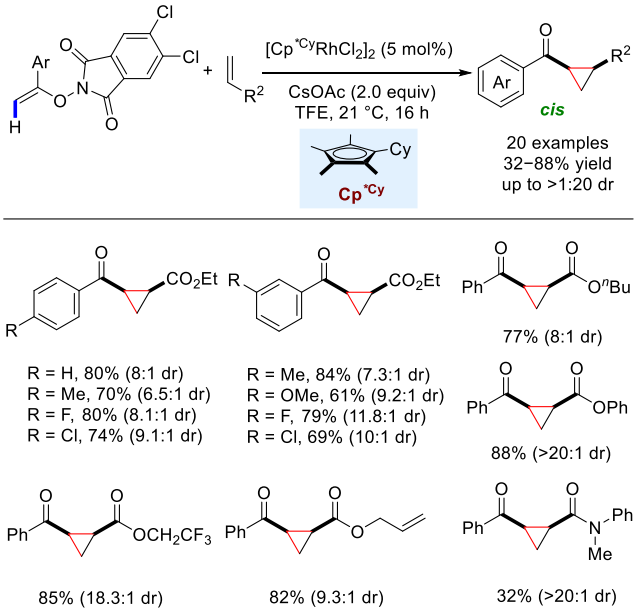
Scheme 410. Rh(III)-Catalyzed Diastereoselective [2 + 1] Annulation of *N*-Enoxyphthalimides and Alkenes



this report, the authors elegantly designed a new monosubstituted isopropylcyclopentadienyl ligand ($Cp^{i\text{-}Pr}$) on the Rh(III) catalyst, which significantly improves the catalytic efficiency and diastereoselectivity of this transformation. The protocol was proposed to occur *via* the irreversible activation of vinylic C−H bond followed by two migratory insertion steps including across the electron-deficient olefin to generate the σ-alkylrhodium(III) species and subsequent intramolecular carborhodation through a 3-*exo*-trig cyclization process.

The development of stereodivergent transformation is definitely of great interest as it enables funneling of a given reaction pathway toward one stereochemical product or another by slightly modifying the reaction parameters. By judicious modulation of the stereoelectronic properties of Rh(III) catalyst and alkene substrates, Rovis and co-workers were able to switch the diastereoselectivity of this $Cp^{X}Rh(III)$-catalyzed cyclopropanation methodology from their *trans*-diastereomers to the corresponding *cis*-congeners (Scheme 411).[669] The authors systematically screened 4,5-dichloro-

Scheme 411. Rh(III)-Catalyzed *cis*-Cyclopropanation of *N*-Enoxyphthalimides and Alkenes



substituted phthalimides together with a cyclohexyl-Cp-ligated Rh(III) catalyst as the best combination to synthesize a variety of *cis*-cyclopropane scaffolds in decent yields (32−88%) and high diastereoselectivities (up to >20:1 dr).

The cyclopropanation of allylic alcohols is especially difficult to achieve by the well-established Simmons−Smith and diazo decomposition reactions. The Rovis group continued their rhodium(III)-catalyzed cyclopropanation of *N*-enoxyphthalimides with alkenes and expanded to report a diastereoselective [2 + 1] annulation of allylic alcohols with *N*-enoxyphthalimides. This transformation was greatly promoted by the electron-deficient trifluoromethyl-*tetra*-methyl-cyclopentadienyl (Cp^{CF3}) ligand, yielding the cyclopropanation products which are not accessible by other routes (Scheme 412).[670] Of note, both *trans*- and *cis*-1,2-disubstituted primary allylic alcohols were compatible with this stereospecific protocol. Mechanistic studies demonstrated that the pendant hydroxyl group is indispensable for both reactivity and diastereocontrol. The diastereoselectivity of this transformation probably arises from an intermediate generated from the ring-opening acylation of allylic alcohol. Meanwhile, Rovis and co-worker also achieved a similar cyclopropanation protocol for *N*-enoxyphthalimides and unbiased olefins under modified conditions.[671]

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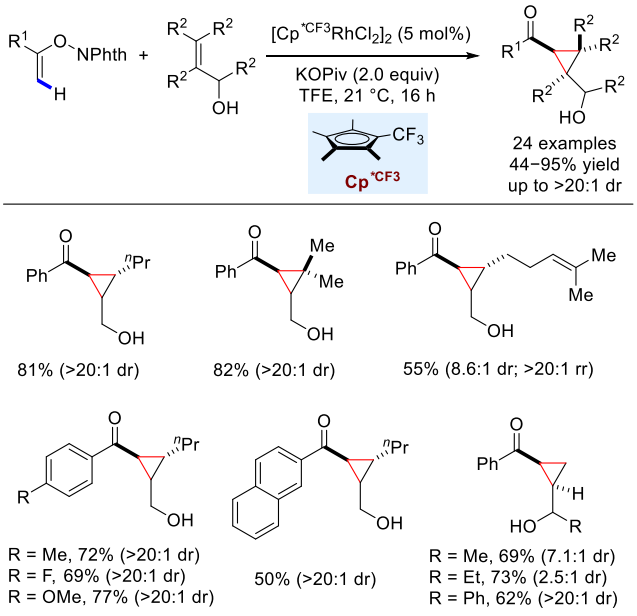
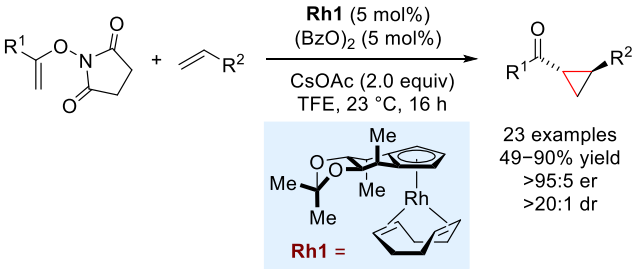
Scheme 412. Rh(III)-Catalyzed Cyclopropanation of *N*-Enoxyphthalimides with Allylic Alcohols



The enantioselective and diastereoselective Rovis cyclopropanation of electron-deficient alkenes with *N*-enoxysuccinimides was accomplished by Cramer's group through a chiral cyclopentadienyl Rh(III)-catalyzed olefinic C−H bond functionalization (Scheme 413).[672] The reaction occurred

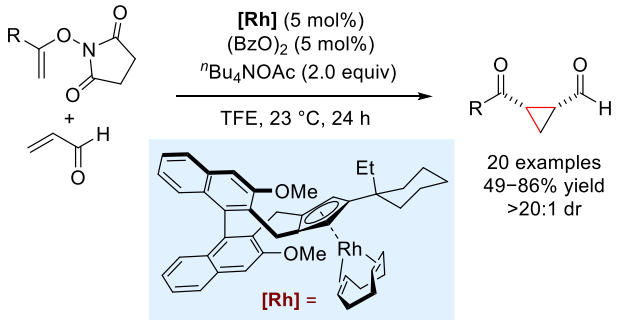
Scheme 413. Chiral Cyclopentadienyl Rh^{III}-Catalyzed Enantioselective Cyclopropanation of Electron-Deficient Olefins



uneventfully under typically mild and open-flask conditions, yielding diverse chiral cyclopropane products in 49−90% yields with decent stereocontrol. The authors highlighted the potential of this strategy by using this protocol as a key step for the synthesis of oxylipin family of natural products and inhibitor UPC-648.

More recently, Cramer *et al.* made further efforts to report the cyclopropanation of *N*-enoxysuccinimides with acrolein enabled by a tailored Cp^{x}Rh^{III}-catalyzed vinylic C−H functionalization to obtain diverse disubstituted *cis*-cyclopropanes in good enantio- and diastereoselectivity (Scheme 414).[673] In this report, the bulky ethylcyclohexyl group as C4 substituent of the second-generation Cp^{x} ligand greatly enforced the *cis*-selectivity of the cyclopropanation event. More interestingly, upon treatment with primary amines under Cp*Ir(III) catalysis, the resulting dicarbonyl *cis*-cyclopropanes could undergo an iterative aminative transfer hydrogen process to afford an exquisite set of rigid saturated 3-azabicyclo[3.1.0]-

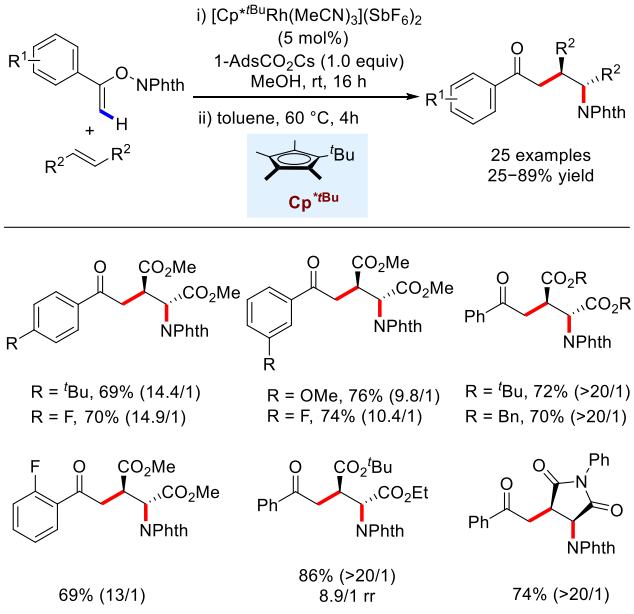
Scheme 414. Cp^{x}Rh^{III}-Catalyzed *cis*-Cyclopropanation of Enoxysuccinimides with Acrolein



hexanes, which are extremely important motifs widespread in biologically active compounds.

Apart form the formation of cyclopropane adducts, the reaction of *N*-enoxyphthalimides with alkenes could also undergo *syn*-carboamination to generate the alkene difunctionalization products. In this regard, Rovis and co-workers elaborated an unprecedented Rh(III)-catalyzed intermolecular *syn*-carboamination of 1,2-disubstituted alkenes initiated by an alkenyl C−H activation event that employs *N*-enoxyphthalimides as the bifunctional source of both carbon- and nitrogen-based functionalities (Scheme 415),[674] thereafter allowing the

Scheme 415. Rh(III)-Catalysed *syn*-Carboamination of Internal Alkenes



stereospecific formation of one C−C bond and one C−N bond across an alkene in one step. Of note, the use of sterically hindered *tert*-butyl-tetramethyl-cyclopentadienyl ligand (Cp*^{tBu}) dramatically alters the inherent chemoselectivity and enables the formation of the *syn*-carboamination with excellent diastereoselectivity. Key to the success of this protocol is the judicious choice of methanol as a solvent which could significantly promote the phthalimide group to undergo an *in situ* ring-opening process.

Moreover, Cramer and co-workers continued their elegant enantioselective Cp^{x}Rh^{III}-catalyzed alkenyl C−H activation strategy and further illustrated the intermolecular asymmetric

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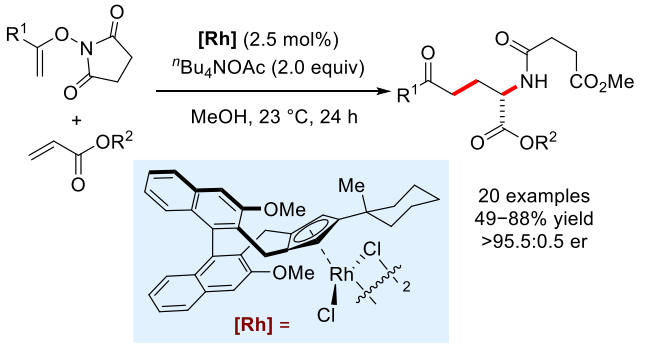
carboamination of electron-deficient acrylates with *N*-enoxysuccinimides at ambient temperature (Scheme 416).[675] A

Scheme 416. Enantioselective Cp^{x}Rh(III)-Catalyzed Carboaminations of Acrylates



fine-tailored sterically bulky chiral Cp^x ligand was proven to be essential for ensuring high reactivity and enabling the reaction toward the intermolecular carboamination process, yielding a diverse array of enantioenriched non-natural α-amino esters in 49−88% yields and excellent enantiomeric ratios of >99.5:0.5.

5.5. Ketene Dithioacetals

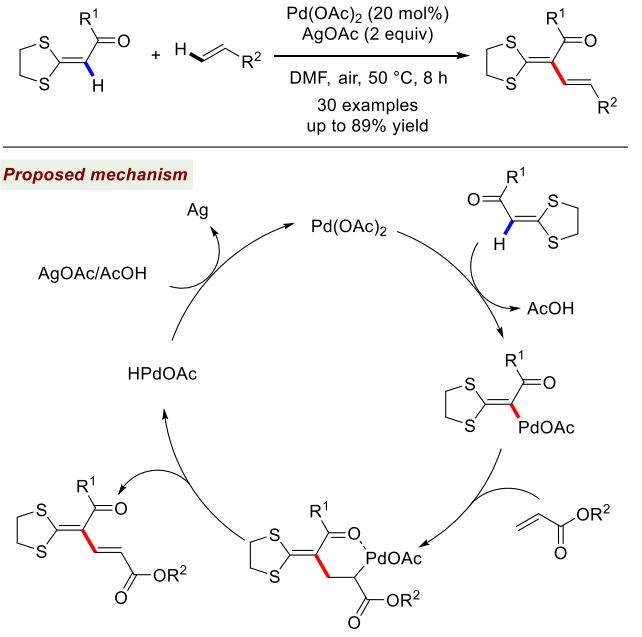
Ketene dithioacetals are highly valuable intermediates and versatile synthons which have found widespread applications in the synthesis of diverse functional organic molecules.[676] The direct α-functionalization of ketene dithioacetals through alkenyl C(sp^2)−H bond functionalization provides a robust tool for the synthesis of highly functionalized ketene dithioacetal derivatives. In 2010, the Yu group first reported a highly regioselective coupling reaction between terminal alkenes and diverse α-oxoketene dithioacetals to synthesize a wide range of functionalized 1,3-butadienes in the presence of $Pd(OAc)_2$ (20 mol %) catalyst (Scheme 417).[677] Further condensation of the corresponding 1,3-butadienes by diamines gave rise to biologically active bicyclic pyridones.

The same group further expanded this Pd(II)-catalyzed alkenyl C(sp^2)−H olefination to α-cyanoketene dithioacetal substrates (Scheme 418).[678] A diverse range of electron-deficient alkenes reacted well to yield the highly functionalized linear 1,3-butadienes with air as the terminal oxidant, while styrene derivatives underwent the oxidative cross-coupling to give both linear and branched 1,3-butadienes using AgOAc as the oxidant. Interestingly, various unbaised cyclic and internal linear alkene substrates both coupled smoothly in the presence of a catalytic amount of benzoquinone (BQ) in air, generating the skipped 1,4-butadienes.

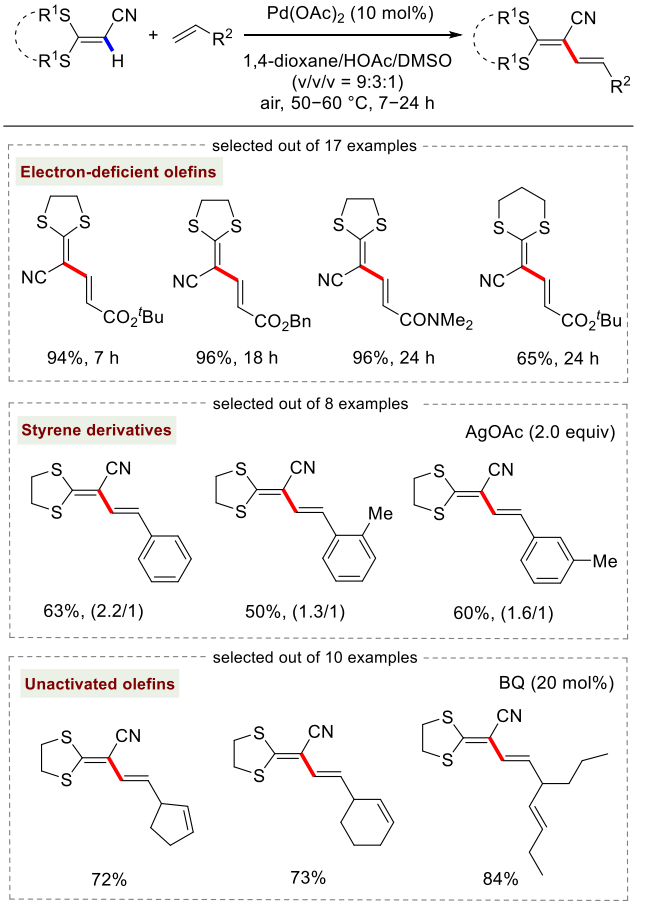
Later, Li's group also achieved the vinylic α-olefination of ketene dithioacetals with a broad array of styrenes under visible-light photoredox catalysis and external oxidant-free conditions with H_2 gas as the only byproduct (Scheme 419).[679] This atom-economical protocol employed 5 mol % of Mes-Acr$^+$ClO$_4^-$ as the photocatalyst in conjunction with 15 mol % of Co(dmgH)$_2$PyCl as a proton-reduction catalyst, yielding a diverse variety of multisubstituted 1,3-dienes in modest to excellent yields.

Moreover, Yu's group demonstrated a palladium(II)-catalyzed oxidative C−H bond allylation of α-oxoketene dithioacetals with a series of allyl carbonates (Scheme 420).[680] This methodology allows a concise route to diverse

Scheme 417. Palladium(II)-Catalyzed Oxidative Cross-Coupling of α-Oxoketene Dithioacetals with Alkenes and Its Proposed Mechanism



Scheme 418. Pd-Catalyzed Oxidative Cross-Coupling of α-Cyanoketene Dithioacetals with Olefins



highly functionalized skipped 1,4-butadienes in modest to good yields (35−75%).

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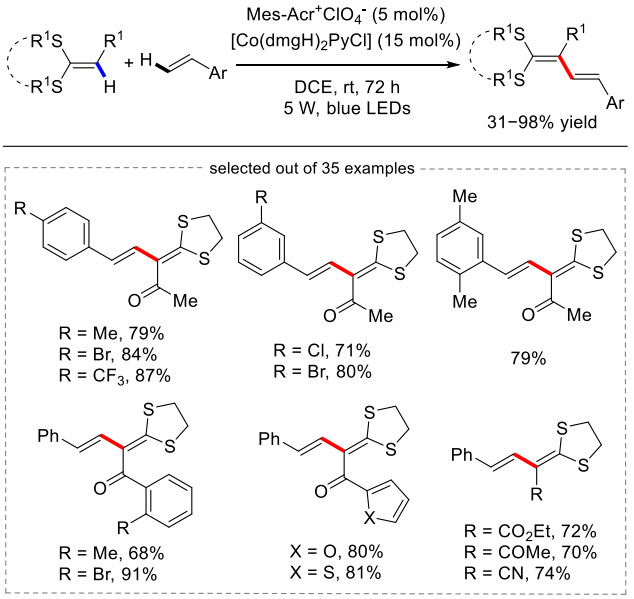
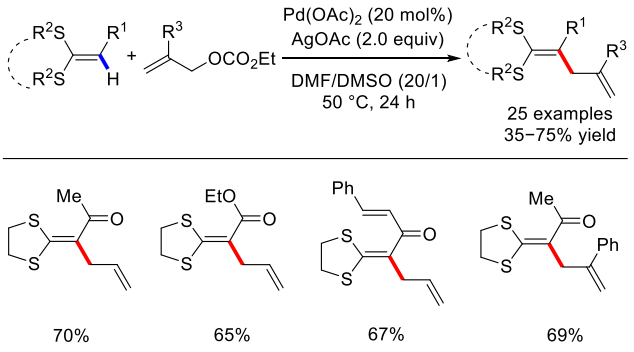
Scheme 419. Visible-Light Photoredox-Catalyzed C−H Olefination of Ketene Dithioacetal with Styrenes



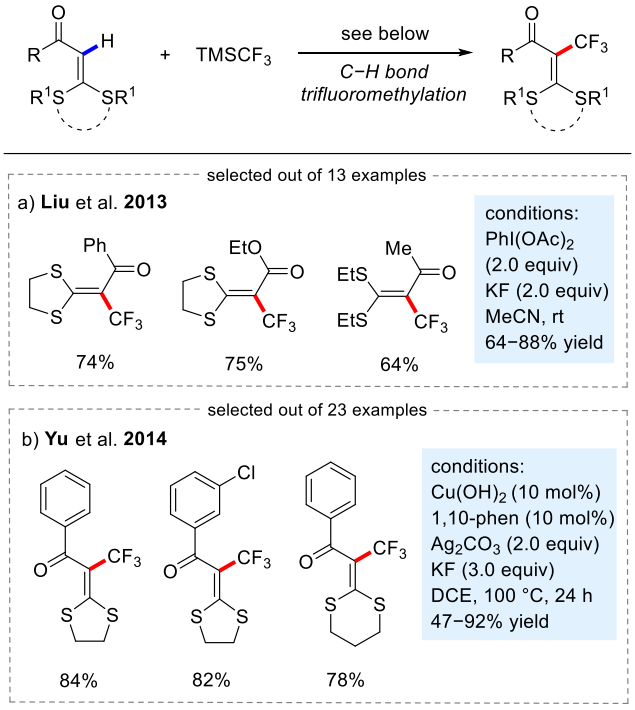
Scheme 420. Oxidative C−H Allylation of Ketene Dithioacetals with Allyl Carbonates



In 2013, Liu and co-workers described a direct C(sp^2)−H trifluoromethylation of ketene dithioacetals by using PhI^+CF_3 as the trifluoromethyl source, which is readily generated *in situ* by simply mixing $PhI(OAc)_2$, $TMSCF_3$, and KF (Scheme 421a).[681] The reaction could proceed smoothly at room temperature under metal-free conditions, delivering the trifluoromethyled ketene dithioacetals in moderate to good yields. Following this, the Yu group also introduced an efficient copper-catalyzed alkenyl C(sp^2)−H trifluoromethylation of α-oxoketene dithioacetals by using $Cu(OH)_2$ as the catalyst in combination with $TMSCF_3$ as the trifluoromethylating agent (Scheme 421b).[682] Both cyclic and acyclic dithioalkyl α-oxoketene acetals were viable substrates in this strategy, and various synthetically useful substituents were well tolerated The authors performed detailed mechanistic studies, which clearly demonstrated that the olefinic C−H bond cleavage was not involved in the rate-determining step, and a radical-involved catalytic mechanism is tentatively proposed on the basis of a TEMPO-quenching experiment of the trifluoromethylation reaction.

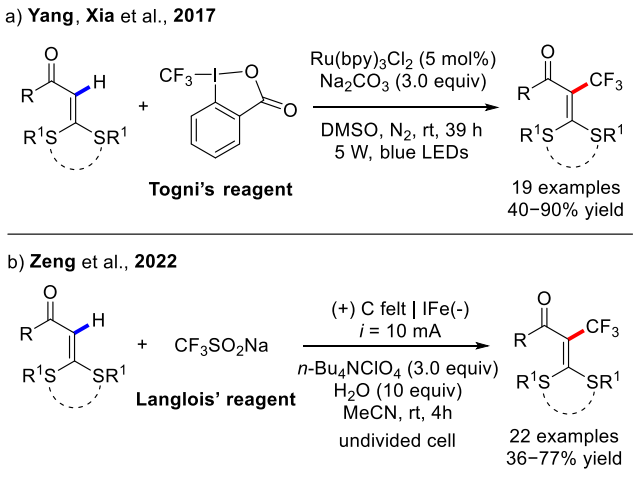
Besides, the sustainable C−H trifluoromethylation of α-oxoketene dithioacetals was later realized by employing $Ru(bpy)_3Cl_2$ as the photocatalyst and Togni's reagent as the trifluoromethylating reagent under visible-light photoredox

Scheme 421. α-Trifluoromethylation of Ketene Dithioacetals with $TMSCF_3$



catalysis (Scheme 422a).[683] Very recently, Zeng *et al.* achieved a similar transformation with cheap and bench-stable

Scheme 422. Photoredox Catalysis and Electrochemical Oxidative Trifluoromethylation of α-Oxoketene Ketene Dithioacetals



CF_3SO_2Na (Langlois' reagent) as the trifluoromethyl radical source, affording an array of trifluoromethylated α-oxoketene dithioacetals in modest yields (Scheme 422b).[684]

The palladium(II)-catalyzed C−H difluoroalkylation of ketene dithioacetals with bromodifluoroacetates was reported by Wang, Zhu, and co-workers (Scheme 423),[685] which enables the rapid synthesis of a class of CF_2-containing *tetra*-substituted ketene dithioacetals in decent yields with high functional group compatibility and wide substrate scope. Due to the unique structural properties of α-oxoketene dithioacetals, the authors proposed an alternative Pd(0)/Pd(I) catalytic

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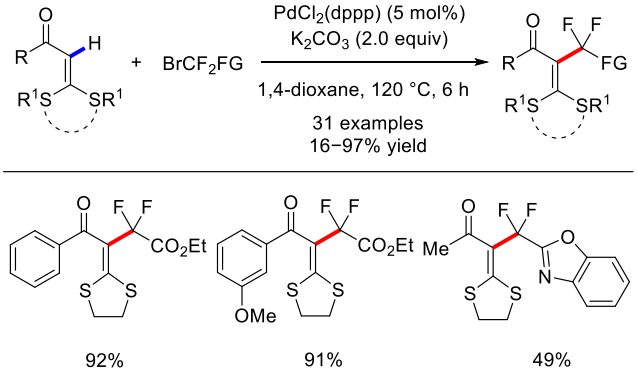
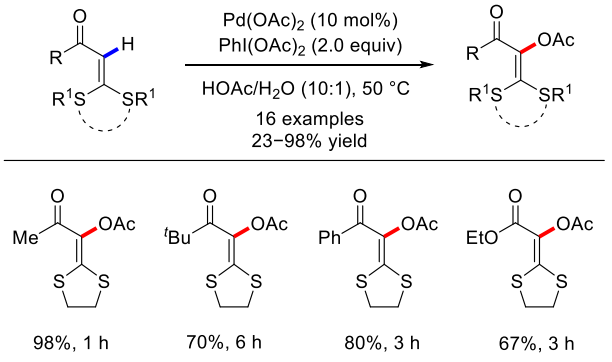
Scheme 423. Pd-Catalyzed C−H Difluoroalkylation of Ketene Dithioacetals with Bromodifluoroacetates



cycle involving two single-electron transfer (SET) processes in this transformation.

The formation of C−O bonds is one of the fundamental transformations in synthetic organic chemistry. As a consequence, a myriad of synthetically useful methods have been extensively established to forge diverse C−O bonds.[686] The formation of C−O bonds through the activation of inert C−H bonds has particularly aroused much interests in the past few years.[687,688] In 2014, Wang, Liu, and co-workers reported a highly regioselective palladium-catalyzed C(sp^2)−H acyloxylation between various ketene dithioacetals and carboxylic acids by utilizing PhI(OAc)$_2$ as an oxidant, delivering a large variety of functionalized vinyl esters with good efficiency and excellent functional group tolerance (Scheme 424).[689]

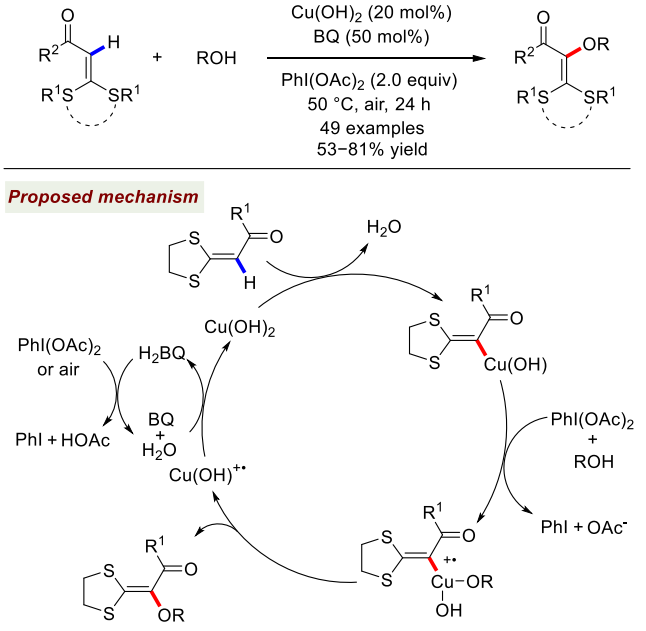
Scheme 424. Palladium-Catalyzed Vinylic C−H Bond Acetoxylation of Ketene Dithioacetals



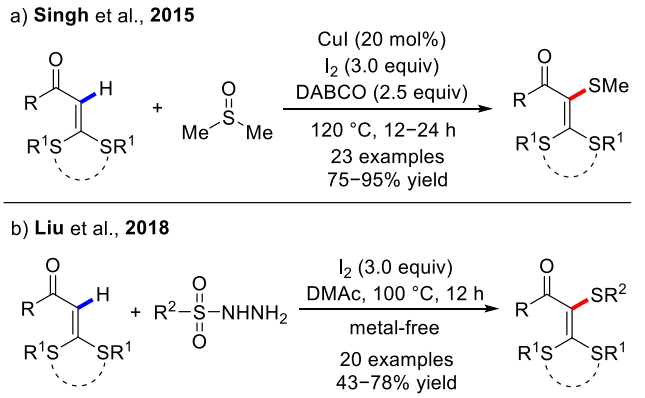
Additionally, the Yu group also demonstrated a Cu(II)-promoted C−H alkoxylation of α-oxoketene dithioacetals with alcohols by means of a combination of PhI(OAc)$_2$ and benzoquinone as the oxidants (Scheme 425).[690] A broad range of alkoxylated ketene dithioacetals were produced with good yields (53−81%). Primary mechanism investigations were carried out. Based on a series of control and kinetic isotope effect (KIE) experiments, a plausible reaction mechanism involving a single-electron-transfer (SET) process was tentatively proposed.

The C−S bond formation reactions of ketene dithioacetals through the direct alkenyl C(sp^2)−H bond functionalization were also realized by Singh and co-workers in 2015 (Scheme 426a).[691] This operationally simple one-pot reaction proceeded smoothly in the presence of iodine and a copper(I) salt with readily available dimethyl sulfoxide (DMSO) as both the

Scheme 425. Copper-Promoted C−H Alkoxylation of Ketene Dithioacetals and Its Proposed Mechanism



Scheme 426. Vinyl C−H Sulfenylation/Alkyl Thiolation of Ketene Dithioacetals



thiomethyl source and solvent, leading to the synthesis of polythiolated alkenes in high yields (75−95%). Later, Liu and co-workers further reported a practical alkenyl C−H sulfenylation/alkyl thiolation reaction of ketene dithioacetals under transition-metal-free conditions (Scheme 426b).[692]

Organic thiocyanates are versatile synthetic intermediates in the synthesis of many important pharmaceuticals and other sulfur-containing organic compounds.[693] In 2017, Wang and Xu presented the first transition-metal-free C−H thiocyanation reaction of ketene dithioacetals by using *in situ* generated *N*-thiocyanatosuccinimide (NTS) as the thiocyanation reagent in the presence of *N*-chlorosuccinimide (NCS) and NH_4SCN under ambient conditions (Scheme 427).[694] The methodology accommodated a wide range of olefin substrates to afford SCN-containing ketene dithioacetals with excellent yields. More importantly, the SCN group in the resulting products could be readily converted into diverse sulfur-containing groups, such as $-SCF_3$ and thiotetrazole, thus rendering the strategy potentially useful for the discovery of new drug candidates.

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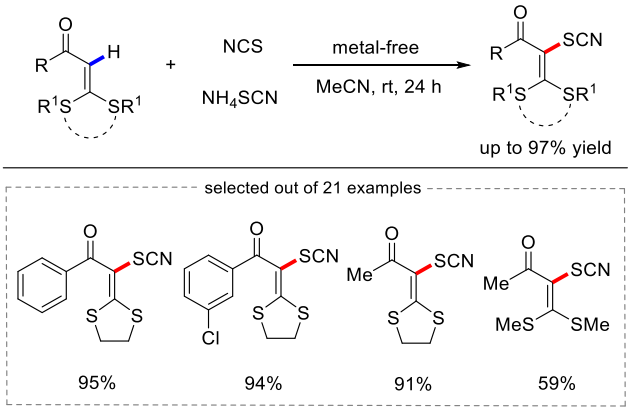
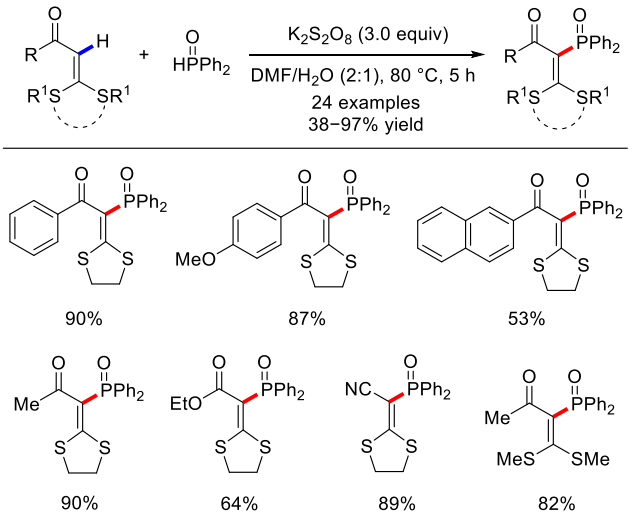
Scheme 427. Transition-Metal-Free Alkenyl C−H Bond Thiocyanation of Ketene Dithioacetals



Apart from the oxidative C−O, C−S cross-couplings, the direct alkenyl C−H phosphorylation of ketene dithioacetals for the construction of C−P bonds was also efficiently achieved under metal-free or $AgNO_3$-mediated conditions (Scheme 428).[695] Gratifyingly, both *H*-phosphonates and *H*-phosphine

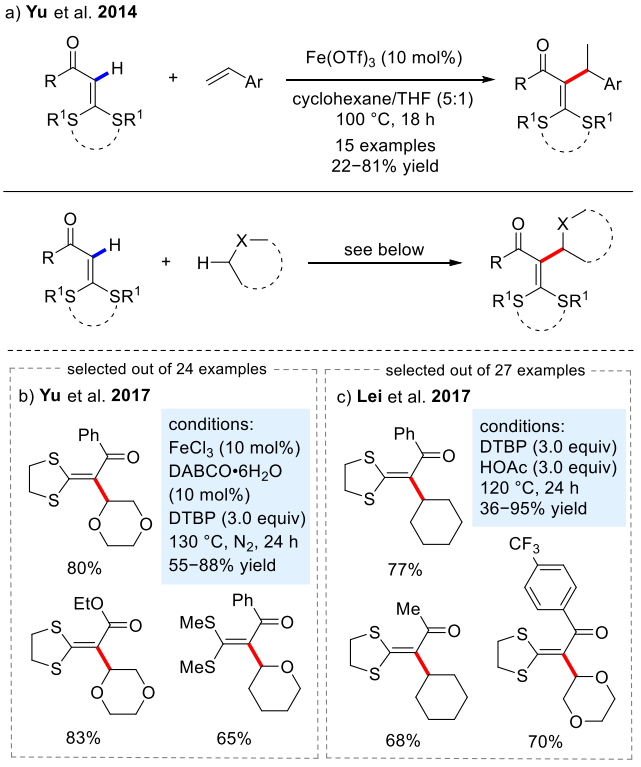
Scheme 428. Transition-Metal-Free Alkenyl C−H Bond Phosphorylation of Ketene Dithioacetals



oxides were compatible in this reaction, with yields ranging from 38% to 97% with good regioselectivity. Further elaboration of the resulting phosphorylated products with hydrazine hydrate could provide an alternative method for the synthesis of phosphorylated pyrazole derivative. The authors performed kinetic isotope effect (KIE) study to gain more insights, and the results clearly suggested that the rupture of the vinylic C−H bond should not be involved in the turnover-limiting step. Radical trapping experiments indicated that a radical pathway might be probably involved in this process.

Yu and co-workers successfully developed an iron-catalyzed C−H alkylation of *α*-oxoketene dithioacetals by using styrenes as the alkylating reagents, providing a variety of functionalized ketene dithioacetal derivatives in modest to high yields (Scheme 429a).[696] Later, Yu and Lei independently described the direct oxidative C−H alkylation of ketene dithioacetals with simple ethers and toluene derivatives using di-*tert*-butyl peroxide (DTBP) as the terminal oxidant (Scheme

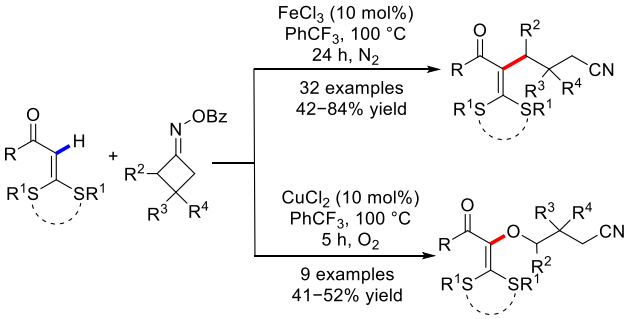
Scheme 429. Direct C−H Bond Alkylation of Ketene Dithioacetals



429b,c).[697,698] However, a catalytic amount of $FeCl_3$ (10 mol %) and DABCO•6H_2O (10 mol %) were both indispensable in Yu's strategy in order to obtain high yields (55−88%).

Subsequently, Yu's group further disclosed another example of iron-catalyzed olefinic C−H alkylation of *α*-oxoketene dithioacetals with various cyclobutanone oxime esters *via* a ring-opening radical C−C bond cleavage strategy under redox-neutral conditions (Scheme 430).[699] Interestingly, the C−H

Scheme 430. Direct C−H Alkylation and Alkoxylation of Ketene Dithioacetals



alkoxylation of *α*-oxoketene dithioacetals could be also achieved when conducting the reaction under an O_2 atmosphere in the presence of $CuCl_2$ as the catalyst.

Moreover, Yu and co-workers extended their investigations to illustrate an efficient visible-light-induced alkenyl C(sp^2)−H arylation of *S*,*S*-functionalized internal alkenes, that is, *α*-oxoketene dithioacetals, using aryldiazonium salts (ArN_2BF_4) as the coupling partners in conjunction with Ru(bpy)$_3$Cl$_2$•6H_2O as the photosensitizer at ambient temperature (Scheme 431),[700] offering an environmentally friendly

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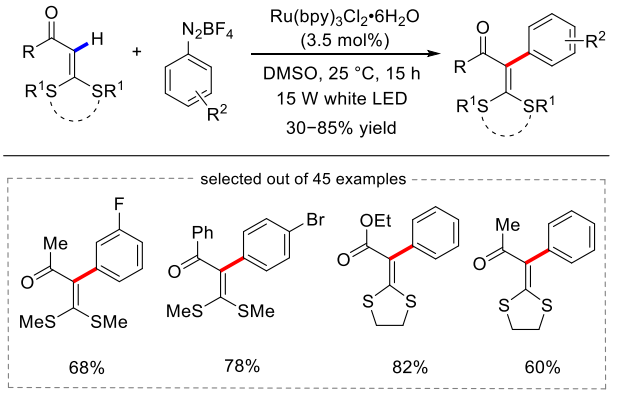
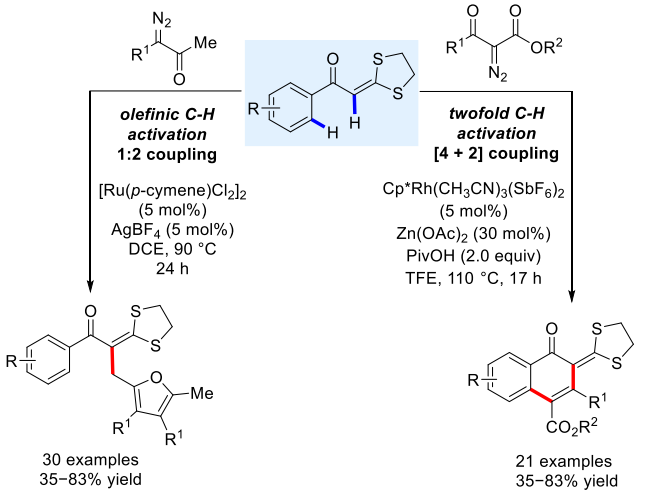
strategy to synthesize all-carbon tetrasubstituted alkenes including anticancer drug tamoxifen.

Scheme 431. Photoredox-Catalyzed C−H Arylation of Ketene Dithioacetals



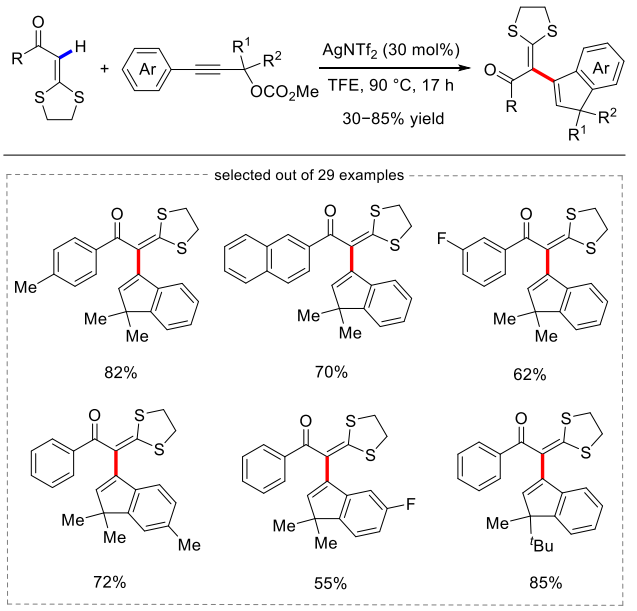
One year later, Li and co-workers disclosed an efficient chemodivergent cross-coupling reaction of α-oxoketene dithioacetals with diazo compounds by the catalyst-controlled alkenyl C−H activation/functionalization (Scheme 432).[701]

Scheme 432. Ruthenium- and Rhodium-Catalyzed Chemodivergent Couplings of Ketene Dithioacetals and α-Diazo Ketones



The ruthenium(II)-catalyzed C−H activation exclusively occurred at the α-position of ketene dithioacetals and 1:2 coupling with α-diazoketoesters where dimerized carbene was identified as a key intermediate, leading to the formation of C−H furfurylation products. In contrast, the Cp*Rh(III)-catalyzed C−H activation of α-benzoylketene dithioacetals occurred *via* both aryl and alkenyl C−H bond cleavage to produce the [4 + 2] annulation naphthalenone derivatives. In a subsequent manuscript, the same group further described the example of silver-catalyzed vinylic C−H bond functionalization of α-oxoketene dithioacetals with tertiary propargylic carbonates through a cascade nucleophilic addition and intramolecular Friedel−Crafts alkylation process (Scheme 433).[702] This novel protocol features a broad substrate scope, operational simplicity, and simple reaction conditions, providing a powerful method to the synthesis of various

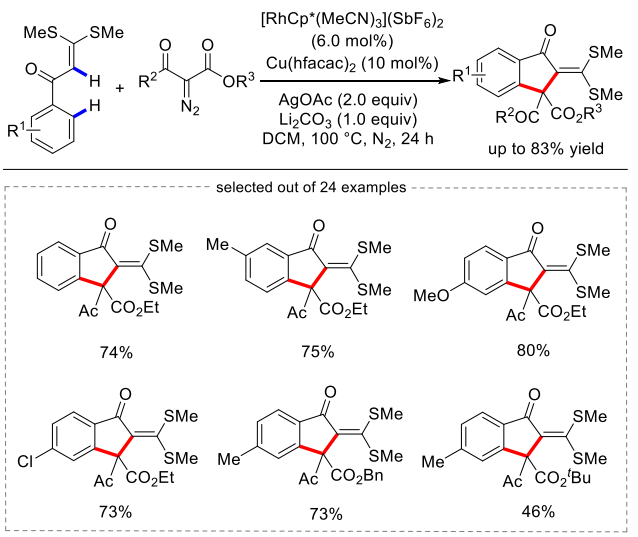
Scheme 433. Ag(I)-Catalyzed Tandem Nucleophilic Addition and Friedel−Crafts Alkylation between Ketene Dithioacetals and Propargyl Carbonates



functionalized indenes with moderate to good yields (30−85%).

More recently, Xiao and colleagues demonstrated that the annulative coupling reaction of α-aroyl ketene dithioacetals with diazo compounds under Cp*Rh(III) catalysis *via* aryl and alkenyl C−H bond functionalizations exclusively furnish the highly functionalized indanone derivatives bearing an all-carbon quaternary stereocenter at the β-position (Scheme 434),[703] which is quite different from that of [4 + 2] annulation to afford naphthalenone derivatives as demonstrated in Li's work.[702]

Scheme 434. Synthesis of β-Quaternary Indanones *via* Alkenyl C−H Activation



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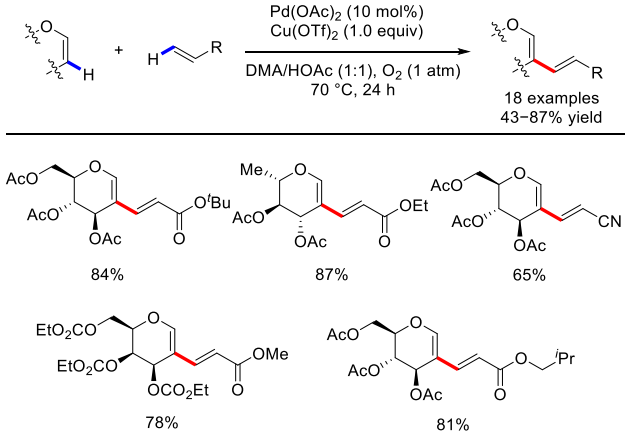
6. MISCELLANEOUS ALKENYL C−H BOND FUNCTIONALIZATIONS

In 2011, Liu and co-workers achieved a Pd(II)-catalyzed cross-coupling between glycals and activated olefins under benign conditions (Scheme 435).[704] This strategy provides a convenient access to C2-functionalized glycals, which are conventional intermediates in natural products and biologically important structures. The substrate scope features a variety of sugars, protecting groups, and substituents on the olefins. The desired products were obtained in decent yields with excellent *E*-selectivity.

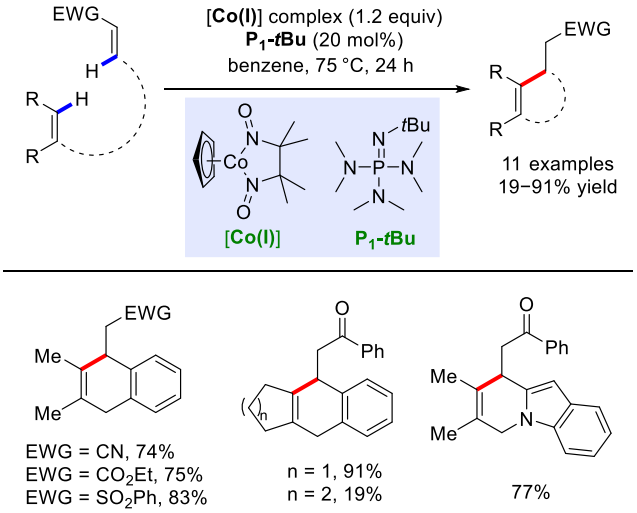
Scheme 435. Palladium(II)-Catalyzed Cross-Coupling of Glycals with Activated Olefins



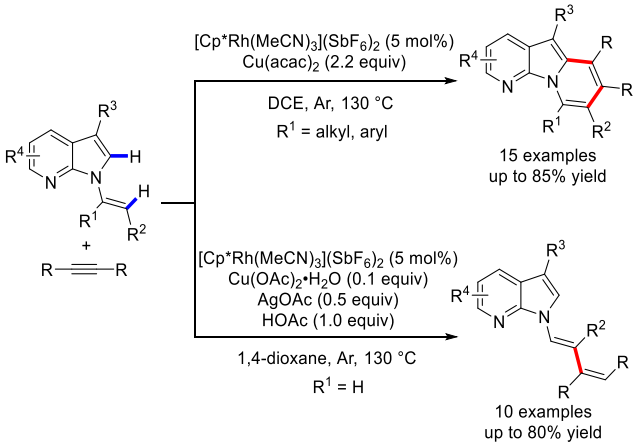
Toste, Bergman, and their co-workers developed a straightforward one-pot Co(I)-catalyzed C−H functionalization and Michael addition of alkenes to synthesize the corresponding cyclic tetraalkyl-substituted, γ,δ-unsaturated compounds in good to excellent yields (Scheme 436).[705] The postulated intermediates in the proposed mechanism were characterized. The catalytic turnover for the base and active catalyst was also documented in this investigation.

Later, Dong's research group illustrated an efficacious Cp*Rh(III)-catalyzed alkenyl C(sp^2)−H of 7-azaindoles with internal alkynes to stereoselectively construct dienes and polycyclic heteroaromatic ring products (Scheme 437).[706] This groundbreaking method was significantly influenced by the reaction conditions and the substituents on the vinylic moiety.

Scheme 436. Cobalt-Dinitrosyl Mediated Vinylic C−H Functionalization Reaction

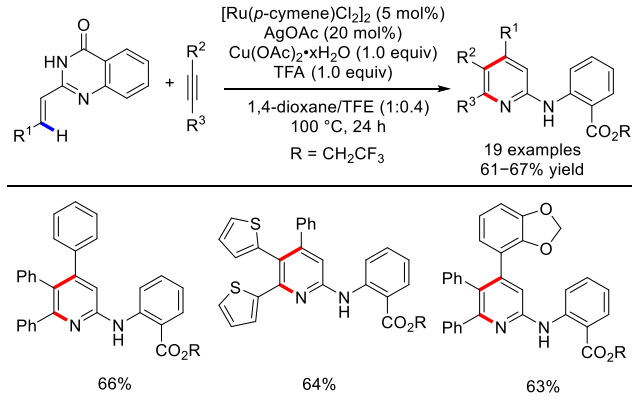


Scheme 437. Cp*Rh(III)-Catalyzed Vinylic C(sp^2)−H of 7-Azaindoles with Alkynes



Almost at the same time, Cook's group elaborated a direct synthesis of 2-aminopyridines by a Ru(II)-catalyzed alkenyl C−H functionalization followed by an amide alcoholysis (Scheme 438).[707] This strategy featured a highly chemo- and regioselective synthesis of the pyridine ring due to a site-specific C−H activation of the substrates. An array of multisubstituted 2-aminopyridines were obtained in decent yields. Mechanistic investigations shed light on the key oxidative C−H activation/cyclization processes.

Scheme 438. Ru(II)-Catalyzed C−H Functionalization for the Synthesis of 2-Aminopyridines



In the following year, Zhu and colleagues illustrated a Cp*Rh(III)-catalyzed olefinic C−H functionalization for the cross-coupling of oxadiazoles with alkynes for the construction of 2-acylamino and 2-amino pyridines derivatives which are crucial heterocyclic core structures for many natural products and pharmaceuticals containing a reactive functional group. By alternating the solvent, selective protection/deprotection of amino groups can be achieved. Notably, the reaction features exceptional functional group tolerance, excellent yields, and regioselectivity (Scheme 439).[708]

Meanwhile, the same group also disclosed a fascinating associative covalent relay process through a Cp*Rh(III)-

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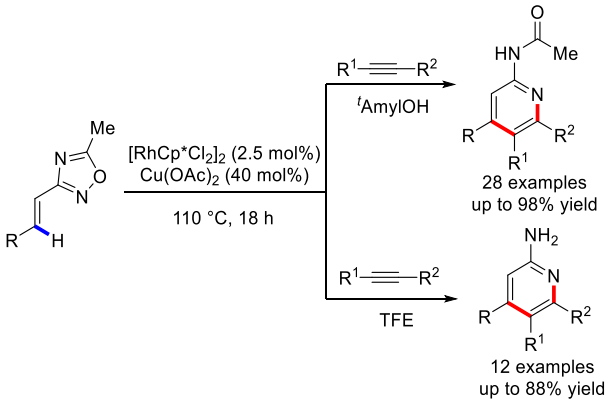
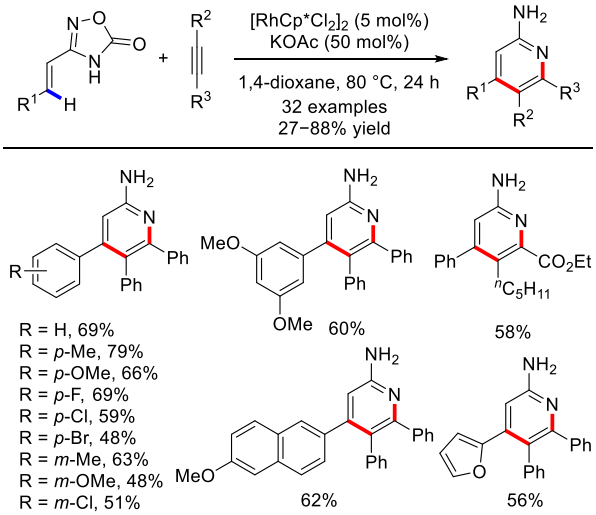
Scheme 439. Rhodium(III)-Catalyzed Cross-Coupling of Oxadiazoles with Alkynes



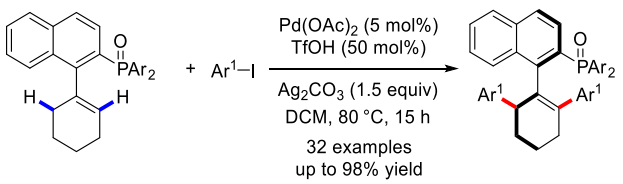
catalyzed oxadiazolone-directed olefinic C−H cross-coupling with alkynes, providing an efficient access to structurally diverse 2-aminepyridines (Scheme 440).[709] Although the mechanism was justified by previous works, the proposed relay formalism in this report provided a mechanistic conceptual framework for investigations.

Scheme 440. Rhodium(III)-Catalyzed Oxadiazolone-Directed Olefinic C−H Cross-Coupling with Alkynes



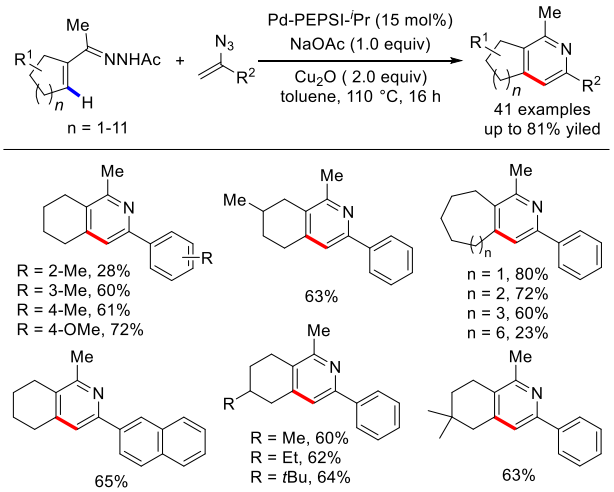
Yang's group in 2019 elaborated a palladium(II)-catalyzed Mizoroki−Heck type reaction to construct a diverse of mono- or diaryl-substituted phosphine liagnds with excellent yields and diastereoselectivity (Scheme 441).[710] Mechanistic investigations suggested that this P═O directed protocol goes through a cationic Heck reaction promoted by the Ag salt.

Scheme 441. Pd(II)-Catalyzed Mizoroki−Heck Type Reaction to Synthesize Phosphine Ligands



Recently, an innovative approach for producing cycloalkeno-[*c*]-fused pyridines has been established by Jiang, Zhang, and their co-workers (Scheme 442).[711] By coupling *N*-acetyl

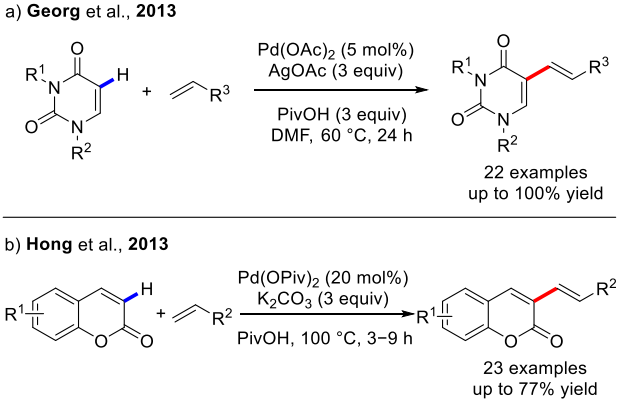
Scheme 442. Pd-Catalyzed Alkenyl C−H Activation and Cyclization of *N*-Acetyl Hydrazones of Acylcycloalkenes with Vinyl Azides



hydrazones bearing medium to large cycloalkenes with vinyl azides, a variety of regioselective fused pyridines can be obtained. A broad scope of 41 examples was presented in up to 81% yield.

Heterocyclic alkenes are an important class of feedstocks and synthetic valuable synthons for the synthesis of biologically important heterocyclic scaffolds. Remarkable advances on the direct vinylic C−H functionalization of heterocyclic alkenes have been made over the decades.[712] For selected examples, Georg's group used uracils as alkene substrates to couple with acrylates or similarly electron-deficient olefins (Scheme 443a).[713] $Pd(OAc)_2$/AgOAc was the best catalyst/oxidant

Scheme 443. Selected Examples of Vinylic C−H Bond Olefination of Heterocyclic Alkenes



combination for this reaction. Of note, the additive was essential to improve the efficiency of reaction, and PivOH was found to be the best choice. Moreover, Hong *et al.* reported the coupling of coumarin with acrylates and styrenes, where $Pd(OPiv)_2$ was used as the catalyst precursor with 1 atm of O_2 as the oxidant. The reaction was regioselective and occurred at the C3-position of coumarins (Scheme 443b).[714]

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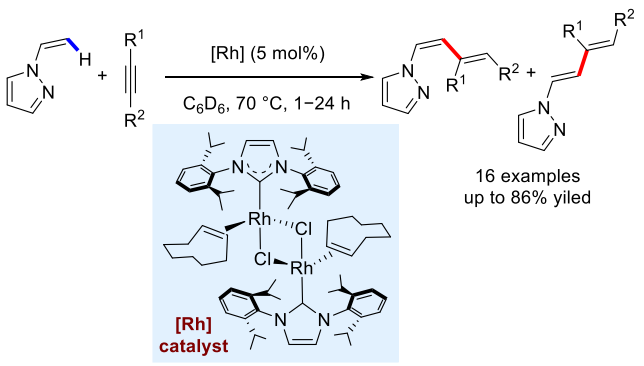
The group of Castarlenas and Oro disclosed the first example of cross-coupling between *N*-vinylpyrazoles and alkynes *via* directed vinylic C−H activation, resulting in the formation of Markovnikov-selective butadienyl pyrazoles in decent yields with moderate to good regioselectivities (Scheme 444).[715] The reaction occurred smoothly in the presence of

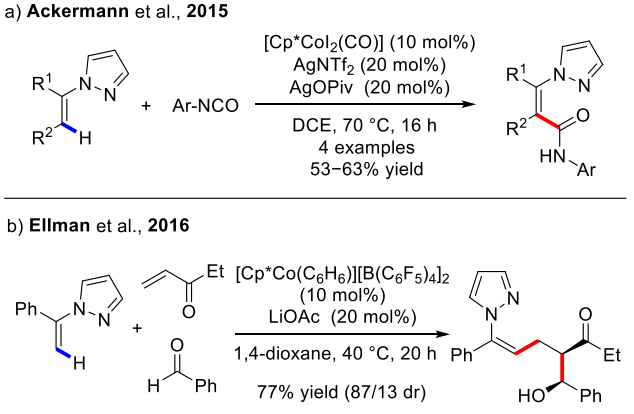
Scheme 444. Rh-Catalyzed Cross-Coupling between *N*-Vinylpyrazoles and Alkynes



rhodium catalyst bearing a carbene and *cis*-cyclooctene ligand, which is crucial for this hydrovinylation of the electron-rich nitrogenated alkenes. Notably, this protocol allows the rapid synthesis of diverse conjugated acyclic trienes through a cascade alkyne dimerization and hydrovinylation sequence in a one-pot fashion.

Later, Ackermann's group illustrated a Cp*Co(III)-catalyzed reaction of *N*-vinylpyrazoles with isocyanates, affording the vinylic C−H aminocarbonylation products in moderate yields (Scheme 445a).[716] Subsequently, Ellman and co-workers

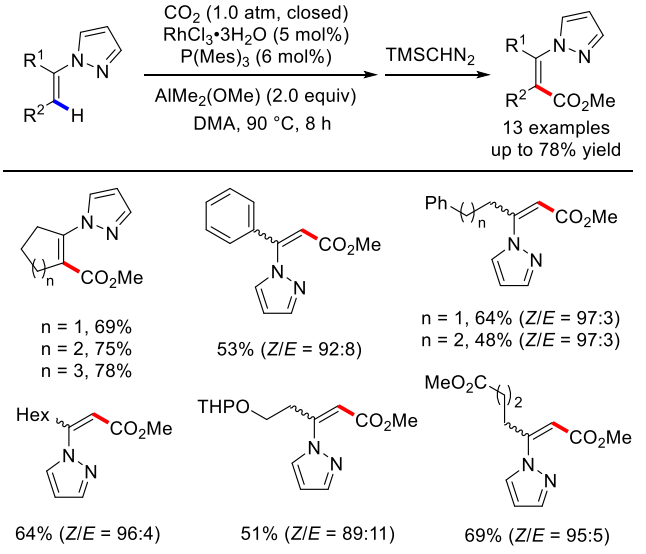
Scheme 445. Cp*Co(III)-Catalyzed Alkenyl C−H Bond Functionalization of *N*-Vinylpyrazoles



demonstrated a highly efficient, stereoselective C(sp^2)−H bond addition across activated alkenes and polarized π-bonds (Scheme 445b).[717] In this report, both aromatic and alkenyl C−H bonds can undergo this three-component addition cascade. Notably, enones, aldehydes, as well as *N*-tertbutanesulfinyl imines are all compatible with this protocol.

Recently, Iwasawa *et al.* achieved the Rh(III)-catalyzed alkenyl C−H carboxylation of alkenylpyrazoles (Scheme 446).[718] By the combination of $RhCl_3•3H_2O$ catalyst, trimesitylphosphine ligand, and $AlMe_2(OMe)$ additive in DMA at 80 °C, the alkenyl C−H bonds of both cyclic and

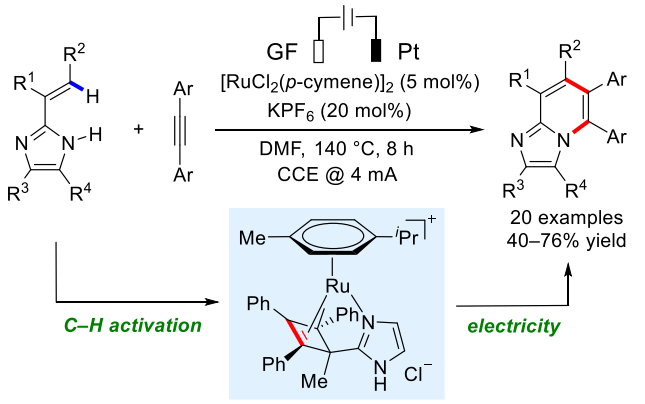
Scheme 446. Rhodium(III)-Catalyzed Alkenyl C−H Carboxylation of *N*-Vinylpyrazoles



acyclic alkenylpyrazoles was smoothly carboxylated in decent yields under CO_2 atmosphere. Notably, the carboxylation reaction proceeded smoothly on a preparative scale even with a decreased catalyst loading (1.0 mol %) at lower reaction temperature.

Moreover, Ackermann and colleagues expanded to employ imidazole as the directing group and established a general protocol for the Ru(II)-catalyzed electrochemical dehydrogenative annulation reaction of alkenyl imidazoles with internal alkynes, leading to the formation of a variety of bridgehead *N*-fused [5,6]-bicyclic heteroarenes (Scheme 447).[719] In this

Scheme 447. Ru(II)-Catalyzed Electrochemical Dehydrogenative Annulation of Alkenyl Imidazoles with Internal Alkynes



report, the authors identified the unprecedented azaruthenabicyclo[3.2.0]heptadienes as key intermediates, which were unambiguously characterized by X-ray analysis. It is noteworthy that this ruthenaelectro-catalyzed dehydrogenative C−H/N−H annulation protocol was not restricted to alkenyl imidazoles, a broad array of 2-arylimidazoles could be smoothly annulated with both symmetrical and unsymmetrical internal alkynes under modified conditions. Deatiled mechanistic investigations are suggestive of an oxidation-induced

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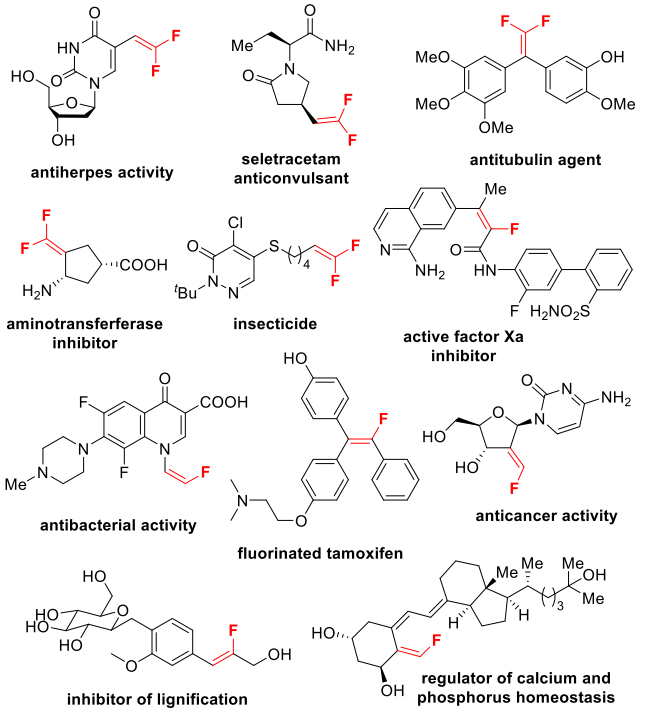
reductive elimination pathway within a ruthenium(II/III) manifold.

7. ALKENYL C−F BOND FUNCTIONALIZATION OF *GEM*-DIFLUOROALKENES

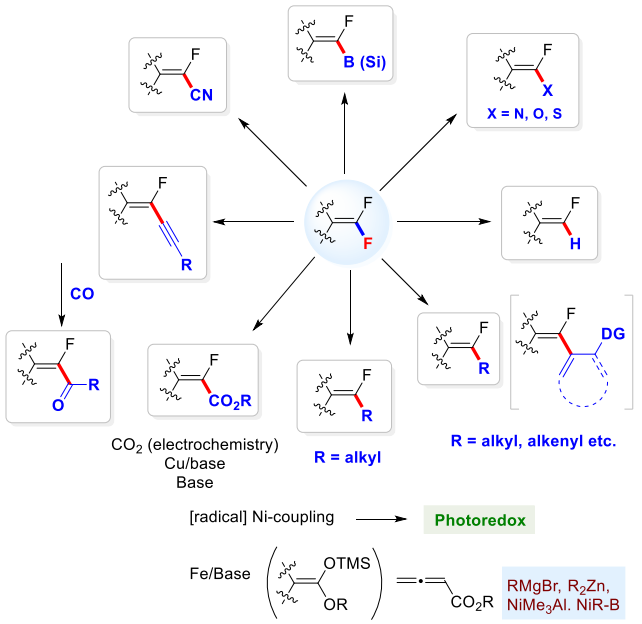
Fluoroalkenes represent an extremely important class of privileged structural motifs, which have found widespread applications in pharmaceutical and material sciences (Scheme 448).[720−727] For example, tetrafluorinated ethylene (TFE) has been used as the monomer for the synthesis of Teflon. The ability to access various α-fluoroalkenes will certainly facilitate the development of novel drugs and functional materials. Accordingly, there have been much effort directed toward the development of novel synthetic methods to obtain this class of compounds, including the reactions using fluorinating reagents with vinylic halides or metals. However, most of the reported protocols suffer from the need to use preactivation substrates or nonreadily available starting materials, low regio- or stereoselectivity, as well as poor functional group compatibility due to the use of sensitive reagents.

Scheme 448. Representative Examples of Mono- and Difluorovinyl-Containing Bioactive Molecules



Indeed, *gem*-difluoroalkenes are synthetically valuable fluorinated scaffolds frequently encountered in numerous biologically active pharmaceuticals and agrochemicals. The judicious use of readily prepared *gem*-difluoroalkenes as starting materials to generate alkenyl fluorinated metal complexes through alkenyl C−F functionalization or as electrophiles offers a highly efficient and operationally simple approach for the incorporation of α-fluoroalkenyl motifs onto structurally diverse organic molecules. As a consequence, the cleavage, activation, and further functionalization of the alkenyl C(sp^2)−F bond of *gem*-difluoroalkenes have received considerable attention in recent years.[18−26] In this section, we systematically summarized the recent advances on the alkenyl sp^2 C−F bond functionalization methods mainly focusing on the use of readily available *gem*-difluoroalkenes as starting materials. Moreover, polyfluoroalkenes such as tetrafluoroethylene (TFE) and its analogues will also be covered. In contrast to alkenyl sp^2 C−H bond functionalization part, we will organize this section according to the cross-coupling partners (Scheme 449).

Scheme 449. General Scheme of Alkenyl C−F Bond Functionalizations of *gem*-Difluoroalkenes



7.1. C−H Bond Formation

Monofluoroalkenes are versatile fluorinated building blocks with widespread applications in medicinal chemistry and material sciences, which can also be used as an important fluorinated synthon for further synthetic transformations.[728] Hydrodefluorination (HDF) generally provides the simplest synthetic transformation of C−F bonds,[729] and the hydrodefluorination of *gem*-difluoroalkenes allows the straightforward synthesis of monofluoroalkenes. Early in 1979, Burton's group first reported the reduction of *gem*-difluoroalkenes in the presence of commercially available sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al) as the efficacious reductant, yielding the β-fluoroalkenes in high yields with up to 93:7 stereoselectivity (Scheme 450a).[730] Following this, Wu and Cao in 2015 also reported a general and efficient method for the selective hydrodefluorination of *gem*-difluoroalkenes by utilizing Red-Al as the reducing agent without the use of any base and catalyst under mild conditions (Scheme 450b).[731] A large variety of monofluoroalkenes were synthesized in modest to excellent yields with decent *E*-selectivity.

By treatment of 3,3-difluoro allylic alcohols with methyllithium followed by reduction with $LiAlH_4$, Tellier and coworkers were able to synthesize a series of monofluoroalkenyl alcohols in a stereoselective manner (Scheme 451a).[732,733] Later, Paquin's group successfully achieved a synthetic route to *trans*-β-fluorostyrenes from (*Z*)-1-aryl-2-fluoro-1-(trimethylsilyl)ethenes by employing $LiBEt_3H$ as the reductant followed by a stereospecific removal of the silyl group in the presence of water and TBAF (Scheme 451b).[734]

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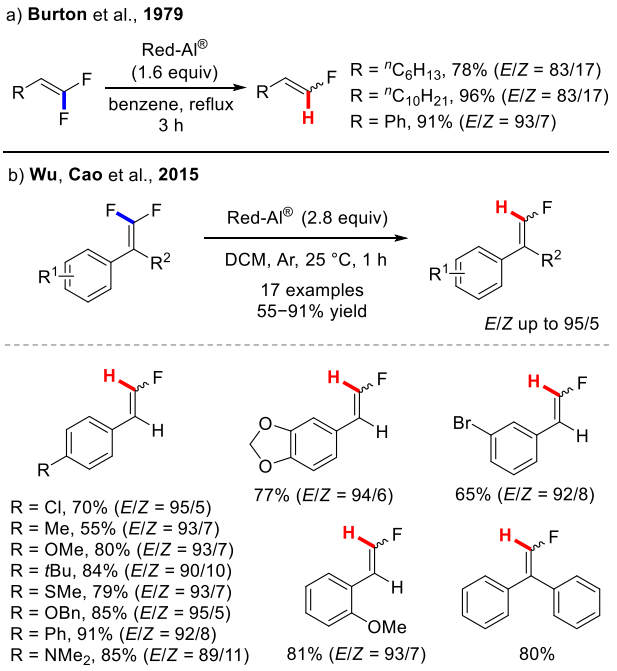
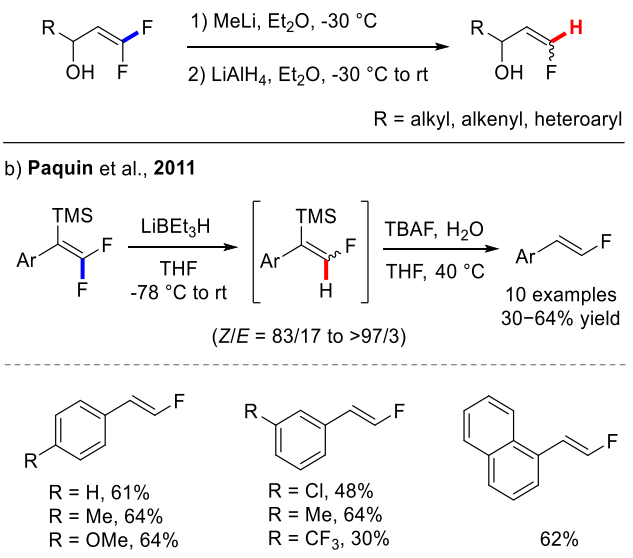
Scheme 450. Synthesis of Monofluoroalkenes through Hydrodefluorination of *gem*-Difluoroalkenes



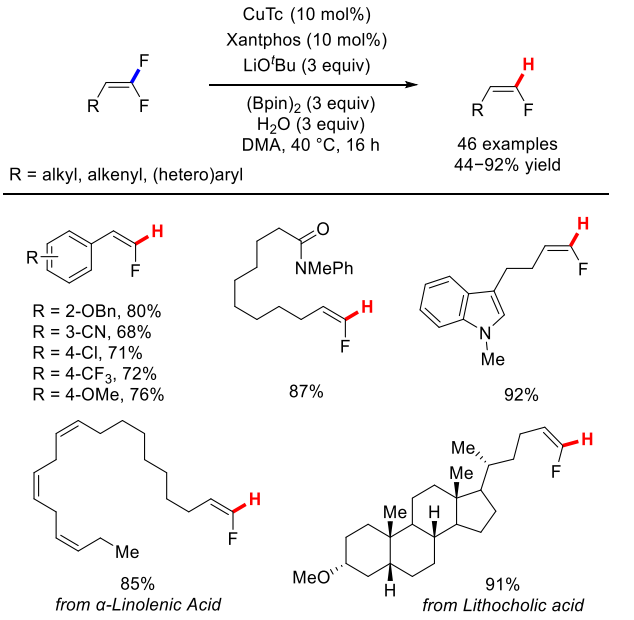
Scheme 451. Synthesis of Monofluoroalkenes through Selective Reduction of *gem*-Difluoroalkenes



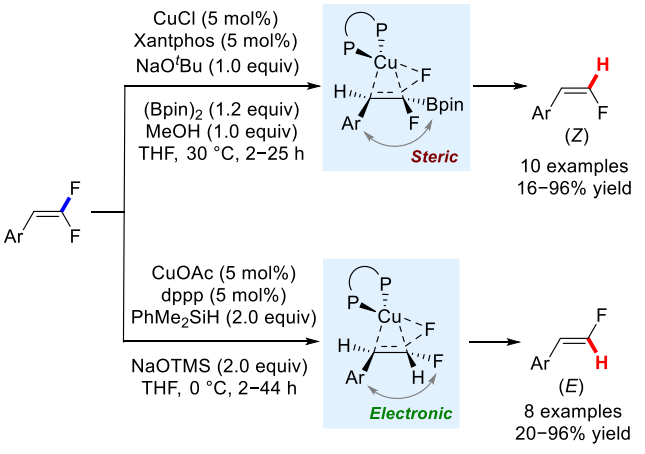
By means of water as the proton source, *gem*-difluoroalkenes can undergo a stereoselective and regioselective copper-catalyzed hydrodefluorination reaction through vinylic C−F activation to form a diverse array of di- and trisubstituted *Z*-fluoroalkenes (Scheme 452).[735] A wide range of substrates tolerated in this strategy, including aliphatic, aromatic, *α,β*-unsaturated, and substituted *gem*-difluoroalkenes. More importantly, a series of *gem*-difluoroalkenes derivatived from natural products were also able to react smoothly under the mild conditions to generate the corresponding late-stage diversification products in excellent yields.

Around the same time, Ito and co-workers achieved a stereodivergent hydrodefluorination reaction of *gem*-difluoroalkenes (Scheme 453).[736] This method steroselectively afforded both (*Z*)- or (*E*)-terminal monofluoroalkenes from

Scheme 452. Synthesis of *Z*-Monofluoroalkenes *via* Hydrodefluorination of *gem*-Difluoroalkenes



Scheme 453. Copper-Catalyzed Stereodivergent Hydrodefluorination of *gem*-Difluoroalkenes



the same starting material. In the presence of $(Bpin)_2$, *Z*-product was formed after deborylation due to the specific conformation of key intermediate that avoids steric repulsion between the bulky Bpin and aryl group. In contrast, the use of copper(I)/hydrosilane catalytic system exclusively afforded an array of *E*-monofluoroalkenes due to the electronic repulsion between F and aryl group in the elimination transition state of copper(I)-hydride adducts.

Several years later, Tsui's group described a highly stereoselective palladium-catalyzed hydrodefluorination reaction of tetrasubstituted *gem*-difluoroalkenes using dimethylphenylsilane (Me_2PhSiH) as the "H source" (Scheme 454).[737] A series of trisubstituted terminal (*E*)-monofluoroalkenes can be obtained in 52−99% yields with excellent *E*/*Z* selectivity (>99:1). The stereocontrol of this reaction was proposed to be

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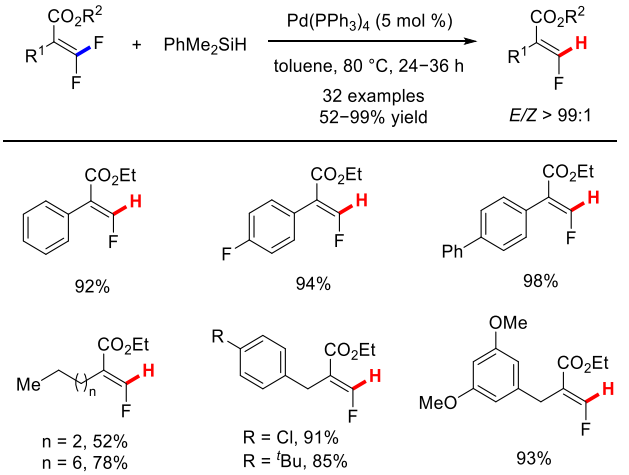
Scheme 454. Pd-Catalyzed Hydrodefluorination of Tetrasubstituted *gem*-Difluoroalkenes



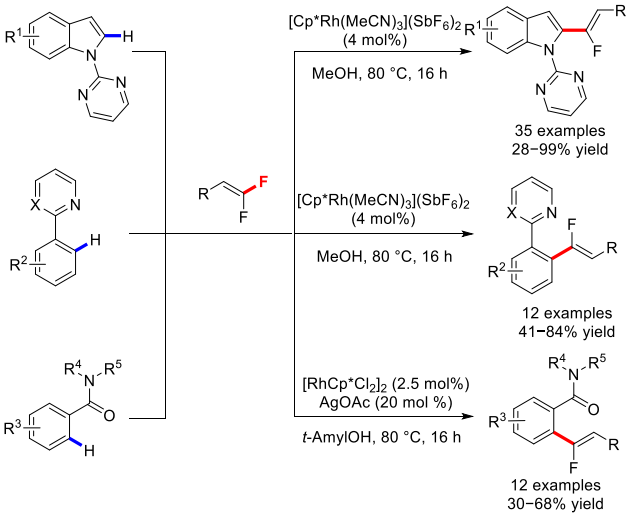
influenced by the ester-directing C−F bond oxidative addition step in the catalytic mechanism.

7.2. C−C Bond Formation

7.2.1. C−H-/C−F Functionalization Reaction. As mentioned above, fluoroalkenes are important core structures which are widely found in medicinal molecules. Nevertheless, the synthetic pathway to this class of compounds is very sparse, and previous strategies often suffer from poor atom economy or harsh reaction conditions. By using appropriate directing groups, *gem*-difluoroalkenes can readily engage in transition metal-catalyzed C−F/C−H functionalization reactions, thus providing an efficient route to monofluoroarylalkenes. Various transition-metal catalysts have been used to realize this C−C bond coupling reaction *via* alkenyl C−F activation in recent years.

Seminal example of such process was first disclosed by Loh's group in 2015. They pioneered an impressive Cp*Rh(III)-catalyzed C−H/C−F activation for the synthesis of (hetero)-arylated monofluoroalkenes (Scheme 455).[738] Exploiting the abundant nature of *gem*-difluoroalkenes as electrophiles, this strategy presented a highly effective and convenient way to

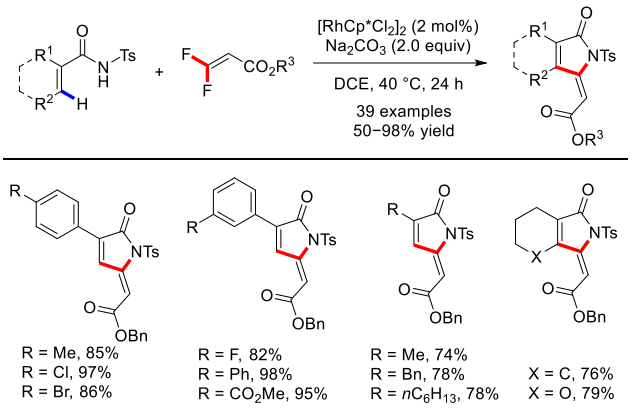
Scheme 455. Synthesis of Monofluoroalkenes through Cp*Rh(III)-Catalyzed C−H/C−F Activation



introduce α-fluoroalkenyl moieties onto (hetero)aryls without the presence of an oxidant. In addition, the use of an alcoholic solvent and the generation of HF in the reaction was established to be advantageous toward the outcome of the reaction, suggesting the likelihood of a hydrogen-bonding interaction during the cleavage of the C−F bond.

Following this, Loh's group extended to report the [4 + 1] annulation of acrylamides and *gem*-difluoroacrylates to produce 5-methylene-1*H*-pyrrol-2(5*H*)-one derivatives through a Cp*Rh(III)-catalyzed alkenyl C−H activation combined with 2-fold C−F bond cleavage (Scheme 456).[739] This stereo-

Scheme 456. Cp*Rh(III)-Catalyzed [4 + 1] Annulation of Acrylamides with *gem*-Difluoroacrylates



specific strategy was similar to the formal dehydrogenative alkylidene carbene insertion reaction. To identify the key intermediate of this process, the authors performed control experiments. By reacting acrylamide with *gem*-difluoroacrylate in the presence of $[RhCp^*(MeCN)_3](SbF_6)_2$ catalyst and NaOAc, the expected annulation product was produced along with an acyclic monofluoroacrylate. By elevating the reaction temperature to 80 °C, the acyclic monofluoroacrylate was readily converted into the annulation product, which clearly confirmed that this protocol should undergo a stepwise quasinucleophilic displacement route. In the same year, Wang and co-workers also achieved a similar heteroannulation reaction by using a combination of Rh(III) and Ag(I) in a relay catalysis process.[740] The OTs group was used instead of the CO_2R group, which allowed further synthetic transformations *via* traditional cross-coupling reactions.

The direct synthesis of fluorinated heterocycles was achieved by Wang's group with 2,2-difluorovinyl tosylate as starting material through a Cp*Rh(III)-catalyzed C(sp^2)−H functionalization of arenes and alkenes (Scheme 457).[741] In this process, *N*-substituted benzamides can be coupled efficiently with 2,2-difluorovinyl tosylate to produce a range of fluorinated quinoline-1(2*H*)-ones. Interestingly, reactions between an alcohol and *N*-OPiv benzamides gave *gem*-difluorinated dihydroisoquinolin-1(2*H*)-ones, while reactions with *N*-OMe benzamides afforded acyclic monofluorinated alkenes, which could be further cyclized in the presence of a Brønsted acid (H_2SO_4) to produce 4-fluoroisoquinolin-1(2*H*)-ones. Both reactions involved a seven-membered rhodacycle species as the key intermediate.

Subsequently, Loh and colleagues further demonstrated that *N*-pyrimidylindoles undergoing C−H alkylation with α,α-difluorovinyl tosylate in the presence of Cp*Rh(III) catalyst

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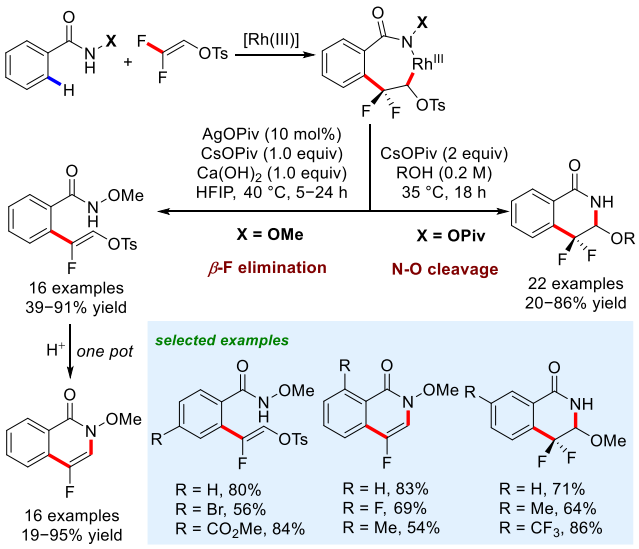
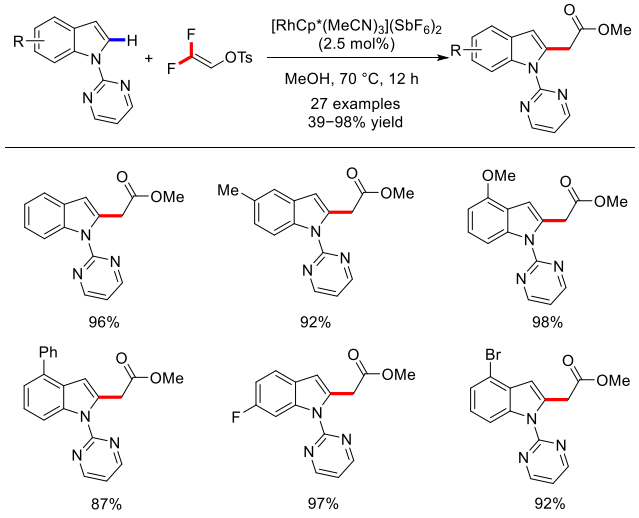
Scheme 457. Synthesis of Fluorinated Heterocycles *via* Rhodium-Catalyzed Coupling of Benzamides with 2,2-Difluorovinyl Tosylate



produced a broad range of C2 alkylated indoles (Scheme 458).[742] In this case, the tosyl difluorinated enol ether acted as an unconventional substitute for an acetate building block.

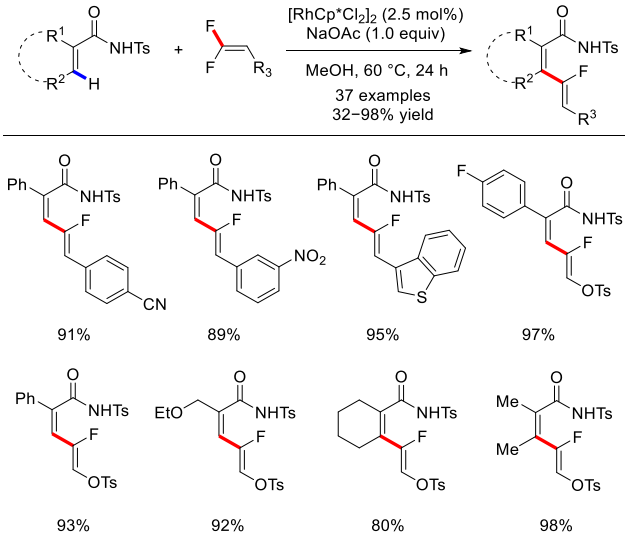
Scheme 458. Rh(III)-Catalyzed Alkylation of Indoles and α,α-Difluorovinyl Tosylate



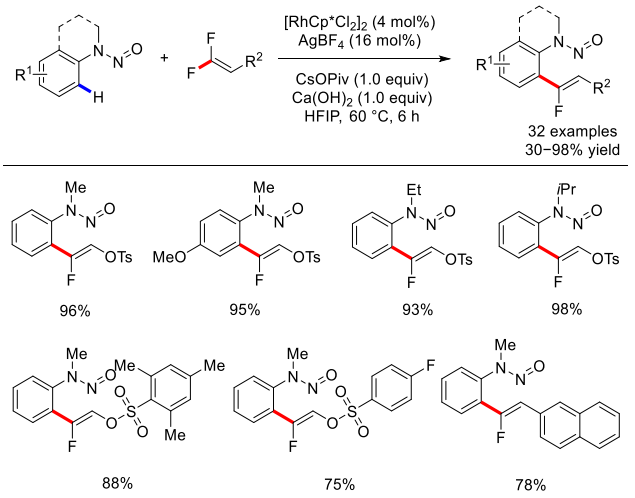
Moreover, Loh and co-workers investigated the Cp*Rh(III)-catalyzed defluorinative C−H vinylation of acrylamides with *gem*-difluoroolefins in order to construct of a variety of 2-fluoro-1,3-dienes (Scheme 459).[743] An initial alkenyl C(sp^2)−H bond activation, accompanied by nucleophilic addition and β-fluoride elimination, gave the coupling products in decent yields with exceptional stereocontrol. Mechanistic studies illustrated that due to the peculiar effects of the fluorine substituent, the reactivity of this transformation was not observed for analogues containing heavier halide atoms.

However, *N*-nitrosoanilines and 2,2-difluorovinyl tosylates undergo regio- and stereoselective α-fluoroalkenylation under Cp*Rh(III) catalysis to give *ortho*-substituted products in basic conditions (Scheme 460).[744] An array of *Z*-monofluoroalkenes

Scheme 459. Cp*Rh(III)-Catalyzed Defluorinative C−H Vinylation of Acrylamides with *gem*-Difluoroalkenes



Scheme 460. Rh(III)-Catalyzed α-Fluoroalkenylation of *N*-Nitrosoanilines with 2,2-Difluorovinyl Tosylates



were obtained in modest to excellent yields *via* chelation-assisted C−H bond activation, migratory insertion, and β-F elimination. In this report, the nitrosoaniline directing group was also able to give *ortho*-substituted products in high regioselectivity. Many of such reactions involve Ca^{2+} additives but the potential role of this cation was not mentioned. However, it is possible that the high affinity of Ca^{2+} for F^- makes it easier to remove the fluoride ion from the reaction, facilitate β−F elimination, and regenerate the active Cp*Rh-(III) catalyst.

Generally, the use of native directing group sometimes substantially increases the overall efficiency of the reaction as it remarkably avoids the preinstallation and subsequent removal of the auxiliary. Recently, Peng and colleagues made use of the quinazolinone ring as the inherent coordinating group to produce a broad array of 2-(*o*-monofluoroalkenylaryl)-quinazolinones by means of 2,2-difluorovinyl tosylate as the monofluoroolefin synthon (Scheme 461).[745]

Fu and Xiao *et al.* reported the Cp*Rh(III)-catalyzed C−H activation of 1-arylpyrazoles and further cross-coupling with methyl trifluoroacrylate for the straightforward synthesis of *E*-

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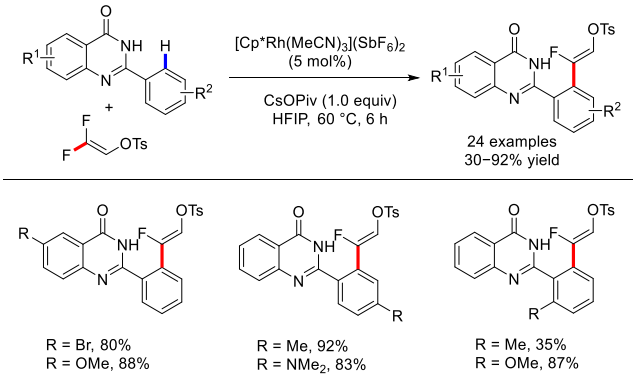
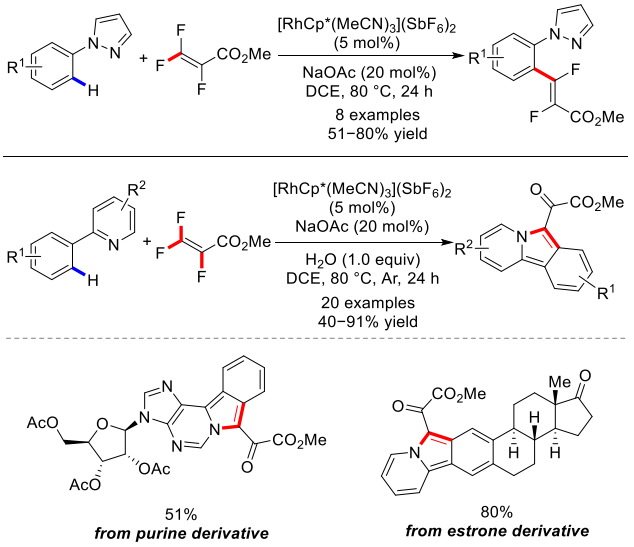
Scheme 461. Rh-Catalyzed C−H α-Fluoroalkenylation of 2-Arylquinazolinones with 2,2-Difluorovinyl Tosylate



monofluoroalkenes (Scheme 462).[746] Notably, complex heterocycles can be obtained by this strategy as the reaction

Scheme 462. Cp*Rh(III)-Catalyzed C−H Activation of 1-Arylpyrazoles with Methyl Trifluoroacrylate

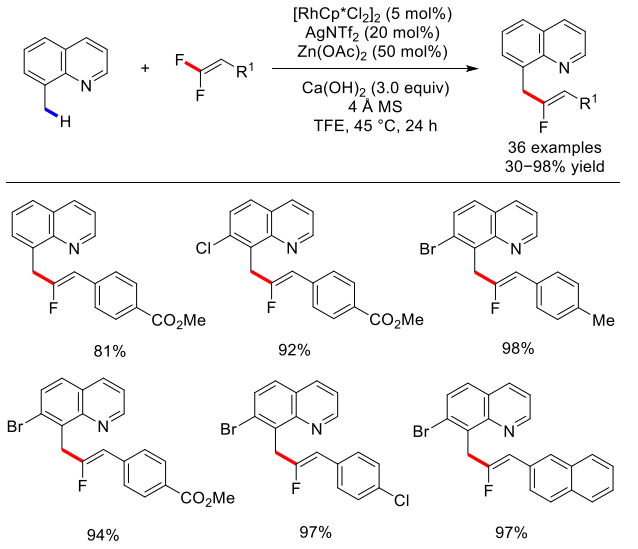


between β-carboxymethyl α,α-difluoroalkene and 2-phenylpyridines afforded a broad range of benzoindolizines by removing three F atoms in a single step. This protocol can be applied to complex bioactive molecules such as purine and estrone derivatives to give the corresponding products in 51% and 80% yield, respectively.

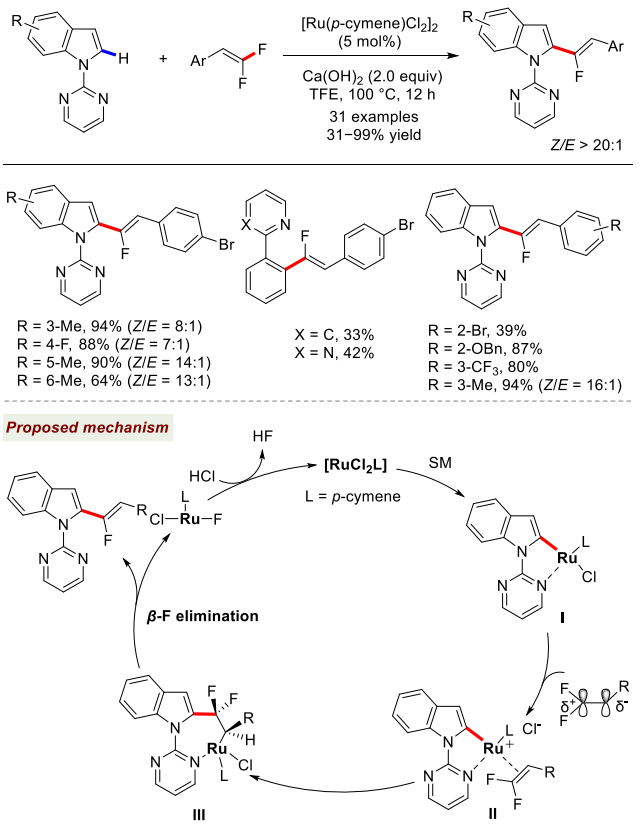
In addition, Li's group successfully developed the Cp*Rh(III)-catalyzed benzylic C(sp^3)−H fluoroalkenylation of 8-methylquinoline derivatives with *gem*-difluoroalkenes under redox-neutral conditions (Scheme 463).[747] The mechanism is similar to the other reactions in this section and likewise gave *Z*-monofluoroalkenes in high regio- and stereoselectivity.

Ru catalysts can be also used to couple *gem*-difluoroalkenes with indoles at the C2 position assisted by a 2-pyrimidinyl directing group (Scheme 464).[748] The reaction is redox-neutral and uses both C−H bond activation and C−F bond cleavage to produce a variety of 1,2-diarylsubstituted monofluoroalkenes with high stereo- and regioselectivities and *Z*-monofluoroalkenes as the major product. In this α-fluoroalkenylation reaction, the 2-pyridyl and 2-pyrimidnyl groups were essential to achieve excellent selectivity.

Scheme 463. Rh(III)-Catalyzed Fluoroalkenylation of 8-Methylquinolines with *gem*-Difluoroalkenes



Scheme 464. Ru(II)-Catalyzed α-Fluoroalkenylation of Arenes *via* C−H Activation and C−F Cleavage



Mechanistically, the Ru(II) catalyst undergoes cyclometalation with *N*-pyrimidinylindole to give a five-membered metalacyclic intermediate **I**. *gem*-Difluoroalkene then coordinates to the intermediate to form a Ru−C(alkyl) complex **II**, which then regioselectively undergoes migratory insertion to afford a seven-membered Ru complex **III**. The electronic structure of the *gem*-difluoroalkene controls the migratory insertion reaction, by having the nucleophilic aryl group add to the electrophilic fluorinated position. The Ru is added to the β-

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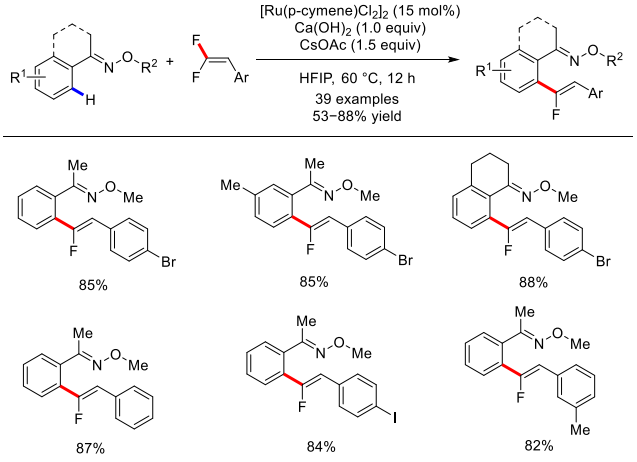
position relative to F as a result of this reaction. This intermediate then selectively undergoes β-F elimination through a *syn*-coplanar transition state to give the product and Ru(II) fluoride. Finally, anion exchange can be performed with a chloride to regenerate the Ru(II) catalyst.

Ji's group illustrated a general and efficient example of α-fluoroalkenylation of oxime ethers with various *gem*-difluorostyrenes through a Ru(II)-catalyzed C−H/C−F bond cleavage strategy (Scheme 465).[749] Remarkably, the alkenyl

Scheme 465. Ru(II)-Catalyzed α-Fluoroalkenylation of Oxime Ethers with *gem*-Difluorostyrenes



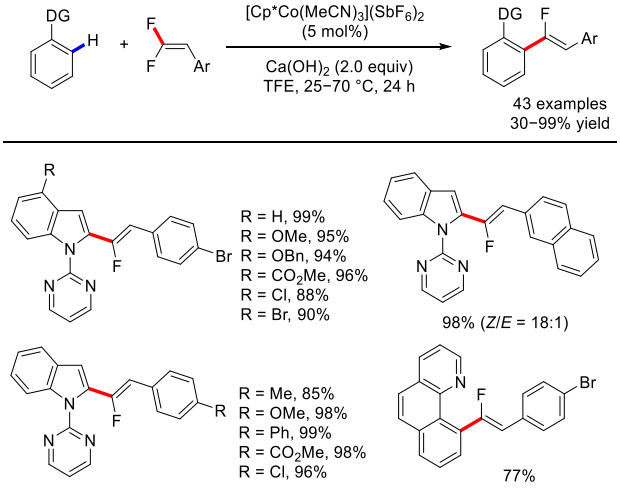
moiety in the resulting products existed exclusively in the *Z*-configuration. This method worked with a variety of substrates along with good tolerance of functional groups. The proposed mechanism was ascertained through the identification of a cycloruthenated intermediate. The *O*-methyl oximyl-directing group can be removed with ease to acquire α-fluoroalkenylated acetophenones.

Coupling reactions between *gem*-difluoroalkenes and substituted indoles *via* the sustainable cobalt-catalyzed chelation-assisted C−H/C−F functionalizations are also accessible. Li and co-workers in 2016 described the first example of Cp*Co(III)-catalyzed α-fluoroalkenylation of diverse (hetero) arenes with *gem*-difluorostyrenes under redox-neutral conditions (Scheme 466).[750] The reaction proceeded smoothly to furnish a series of 1,2-diaryl-substituted monofluoroalkenes in moderate to good yields with excellent *Z*-selectivity.

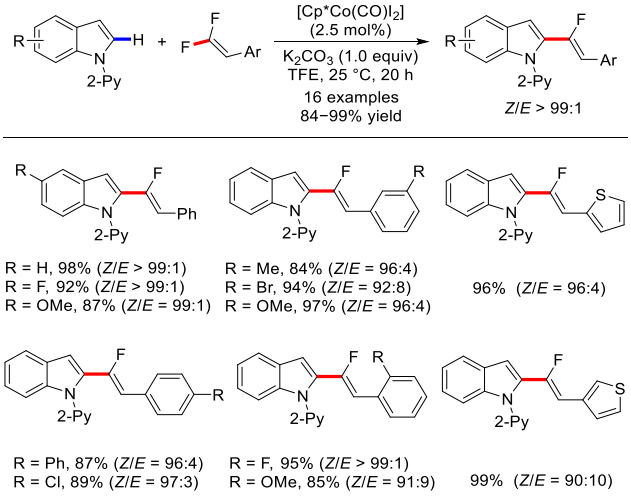
Subsequently, Ackermann's group elaborate an efficient room-temperature C−F/C−H functionalization reactions enabled by user-friendly Cp*Co(CO)I_2 catalyst, affording an array of monofluorinated heteroarenes in excellent yields (84−99%) with high diastereoselectivity (Scheme 467).[751] This alkenylative reaction occurred under exceedingly mild conditions *via syn* Co−F elimination to produce the corresponding *Z*-fluoroalkenes. Extensive mechanistic studies suggested a fast cleavage of the C−F bond involved in this process.

The Cp*Co(III)-catalyzed alkenyl C−H functionalization of biologically active 6-arylpurine derivatives accompanied by selective olefinic C−F bond cleavage of *gem*-difluoroalkenes was reported by Yoshino and Matsunaga (Scheme 468).[752] Such reactions employed the purine moiety as a native directing group for the C−H activation process to generate a range of monofluoroalkenes with satisfactory *Z*-selectivity.

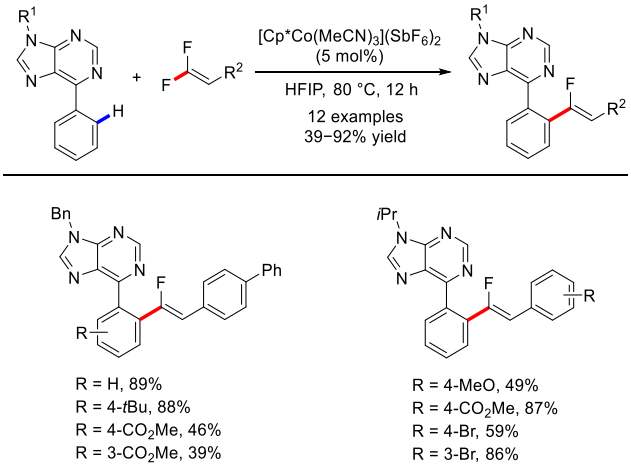
Scheme 466. Co(III)-Catalyzed α-Fluoroalkenylation of Heteroarenes with *gem*-Difluorostyrenes



Scheme 467. Room-Temperature Co(III)-Catalyzed C−H/C−F Bond Functionalizations of Indoles with *gem*-Difluoroalkenes



Scheme 468. Co(III)-Catalyzed α-Fluoroalkenylation of 6-Arylpurines with *gem*-Difluoroalkenes



Loh and colleagues further explored the use of less toxic Mn catalysts to perform C−H bond activation/C−F bond cleavage

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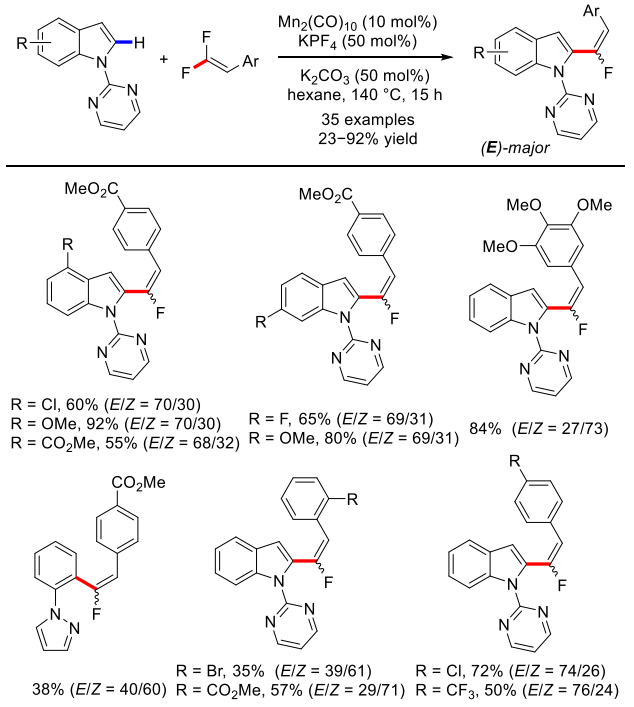
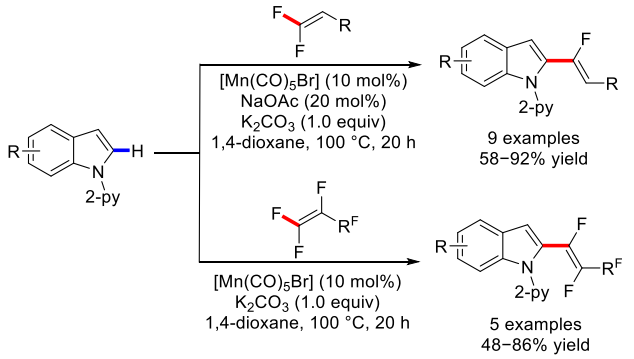
reactions (Scheme 469).[753] However, unlike previous reactions, this protocol produces the thermodynamically unfavorable *E*-monofluoroalkene as the major product, without the need of any additional oxidants. This is probably due to the selective *β*-defluorination from the key intermediate. Despite this, reactions involving 1-phenyl-pyrazole delivered *Z*-monofluoroalkenes, and sterically hindered *gem*-difluoroalkenes similarly gave the *Z*-products.

Meanwhile, the C−H/C−F functionalization of *gem*-difluoroalkenes and perfluoroalkenes were also performed by using a commercially available $Mn(CO)_5Br$ catalyst to produce monofluorinated and polyfluorinated alkenes, respectively (Scheme 470).[754] These reactions occurred with high chemo-, positional-, and diastereoselectivity. In this case, the 2-pyridyl auxiliary could be easily removed by the treatment with NaSPh and MeOTf, affording free (*NH*)-indoles.

Scheme 469. Synthesis of Monofluoroalkenes *via* Mn-Catalyzed C−H Activation and C−F Cleavage

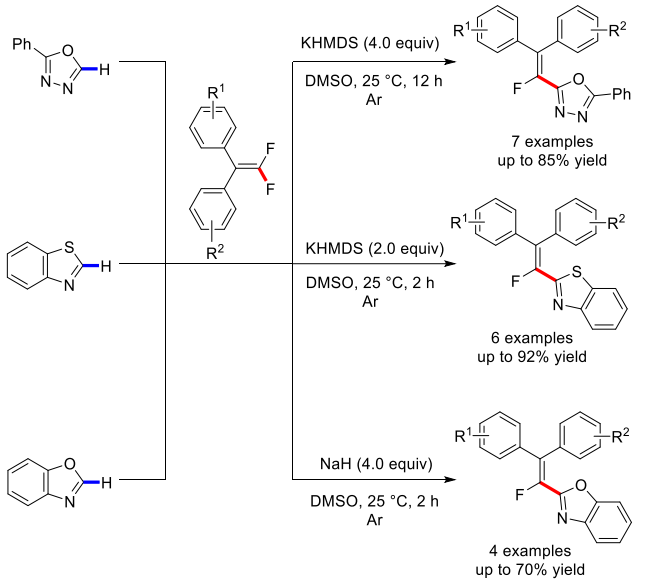


Scheme 470. Mn(I)-Catalyzed C−H/C−F Activation of (Hetero) Arenes with *gem*-Difluoroalkenes and Perfluoroalkenes



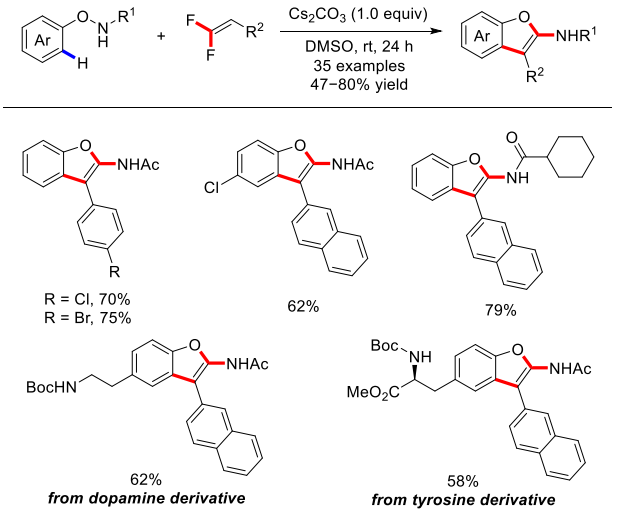
In 2015, Cao *et al.* reported a straightforward metal-free C−H *α*-fluorovinylation of azole heterocycles, including 2-phenyl-1,3,4-oxadiazole, benzothiazole, and benzoxazole with diverse *gem*-difluoroalkenes through a room-temperature nucleophilic vinylic substitution (S_NV) with the assistance of KHMDS or NaH (Scheme 471).[755]

Scheme 471. Base-Mediated *α*-Fluoroalkenylation of Azole Heterocycles with *gem*-Difluoroalkenes



In a recent report, Zhou and Yi *et al.* illustrated an effective and metal-free [3 + 2] annulation reaction of *N*-phenoxy amides with *gem*-difluoroalkenes through a Cs_2CO_3-promoted tandem [3,3]-sigmatropic rearrangement, providing a straightforward approach to assemble a variety of 2-aminobenzofurans in a one-pot reaction (Scheme 472).[756] In this case, the reaction proceeded through the cleavage of multiple bonds involving C−H, O−N, and two C−F bonds. The utility of this strategy was hightlighted by the application of the on-DNA

Scheme 472. Cs_2CO_3-Mediated [3 + 2] Annulation of *N*-Phenoxy Amides with *gem*-Difluoroalkenes



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synthesis as well as the products' applicability as potential anticancer agents.

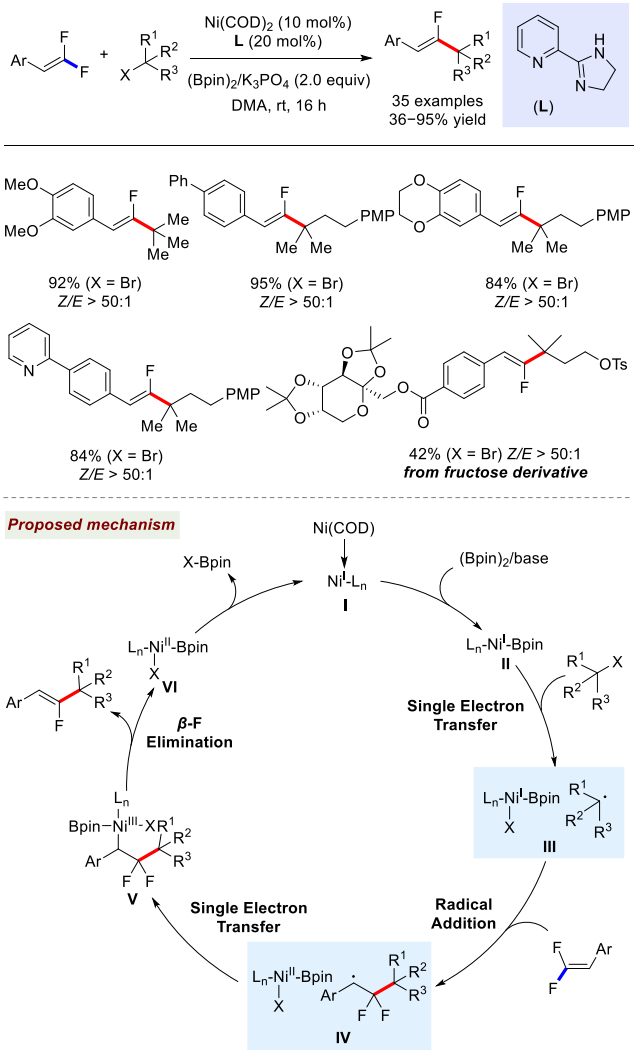
7.2.2. Alkylation. Sterically hindered secondary and tertiary alkyl halides engage in the nickel-catalyzed $C(sp^2)-C(sp^3)$ defluorinative reductive cross-coupling with *gem*-difluoroalkenes to produce monofluoroalkenylated products *via* selective C−F bond cleavage (Scheme 473).[757] A range of functional groups tolerated in this reaction to generate the expected products with excellent *Z*-stereoselectivity. Mechanistically, $Ni(COD)_2$ is first transformed into the active Ni(I)-L_n complex **I**, which then undergoes borylation to form $L_nNi(I)$-Bpin species **II**. With a single electron transfer (SET) to an alkyl halide, a caged alkyl radical/Ni(II) intermediate **III** was produced. Then, radical addition of the intermediate onto *gem*-difluoroalkene occurs regioselectively at the difluorinated position to give a caged complex **IV**, which then undergoes another SET to form a key Ni(III) species **V**, which subsequently undergoes *β*-F elimination to give *Z*-monofluoroalkene and a Ni(III) compound **VI**. Further reduction regenerated the active Ni(I) catalyst. This reaction displays excellent *Z*-stereoselectivity because the steric crush is minimized during the *β*-F elimination step.

A variety of monofluoroalkenes can be readily formed at room temperature by Zn(0)-mediated decarboxylative defluoroalkylation of *gem*-difluoroalkenes with *N*-hydroxyphthalimide (NHPI) esters as the alkyl radical precursors (Scheme 474).[758] The reactions could be scaled up and gave the products with great *Z*-stereoselectivity. Mechanistically, Zn(0) first undergoes SET to the NHP ester to produce a radical anion, which then fragments into a stabilized NHP anion and *O*-based carboxyl radical. The radical further undergoes decarboxylation to afford the thermodynamically preferred alkyl radical (R•), which subsequently undergoes attack to the *gem*-difluoroalkene to furnish a difluorinated radical intermediate. Another SET reduction by Zn^+ occurs again to generate a *β*,*β*-difluorinated anion, then *β*-F elimination occurs using the conformationally favorable anticoplanar pathway to give the *Z*-monofluoroalkenes. Very recently, a similar defluorinative alkylation was also achieved under photoredox catalysis.[759]

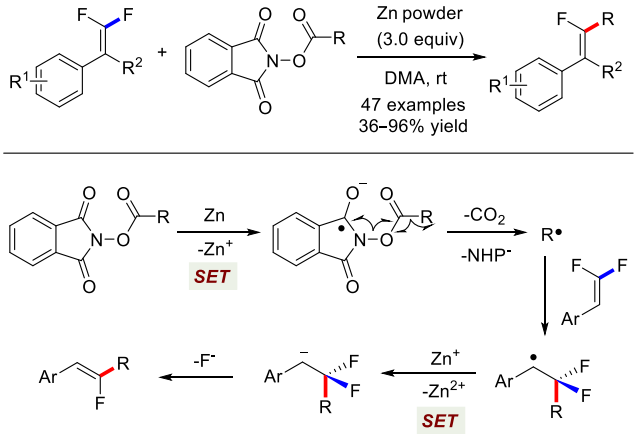
Interestingly, the Fe catalyst can also facilitate the cross-coupling reaction of *gem*-difluoroalkenes with several unactivated and heteroatom substituted alkenes *via* hydrogen atom transfer (HAT) reaction. This allows a small group of structurally diverse alkylated monofluoroalkenes to be synthesized with great *Z*-selectivity (Scheme 475).[760]

A distinctive and efficient method of reductive coupling between *gem*-difluoroalkenes and unactivated alkyl bromides using Ni catalyst is able to regioselectively and stereoselectively furnish a series of *α*-benzylfluoroalkenes (Scheme 476).[761] A large variety of functionalized monofluoroalkenes could be synthesized *via* a characteristic catalytic mechanism involving alkyl-Ni chain migration and defluorinative cross-coupling. This reaction occurs *via* oxidative addition of C−Br bond to Ni(0) to form a Ni(II) species **II**, which then undergoes single-electron reduction by Mn(0) and subsequent chain migration to generate Ni(I) **V** with a Ni−C bond at the stabilized benzylic position. *gem*-Difluoroalkene coordinates to the complex to form a Ni(I) intermediate **VI**. The intermediate is then subjected to regioselective migratory insertion, producing the alkyl-Ni(I) adduct **VII**. Finally, *β*-F elimination occurs to produce the coupling monofluoroalkenes accom-

Scheme 473. Nickel-Catalyzed Defluorinative Reductive Cross-Coupling of Secondary and Tertiary Alkyl Halides with *gem*-Difluoroalkenes



Scheme 474. Zinc-Mediated Decarboxylative Defluoroalkylation of *gem*-Difluoroalkenes



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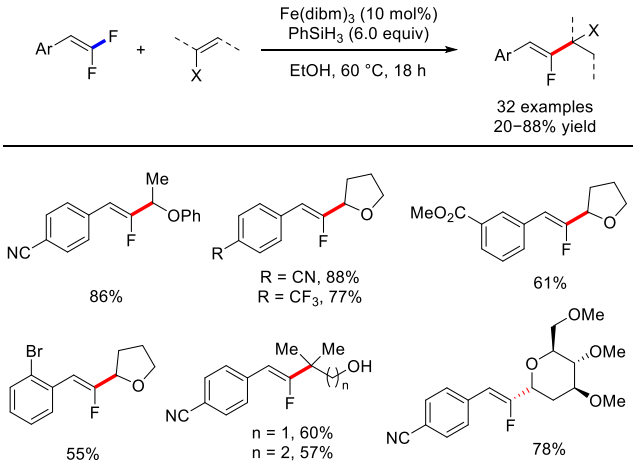
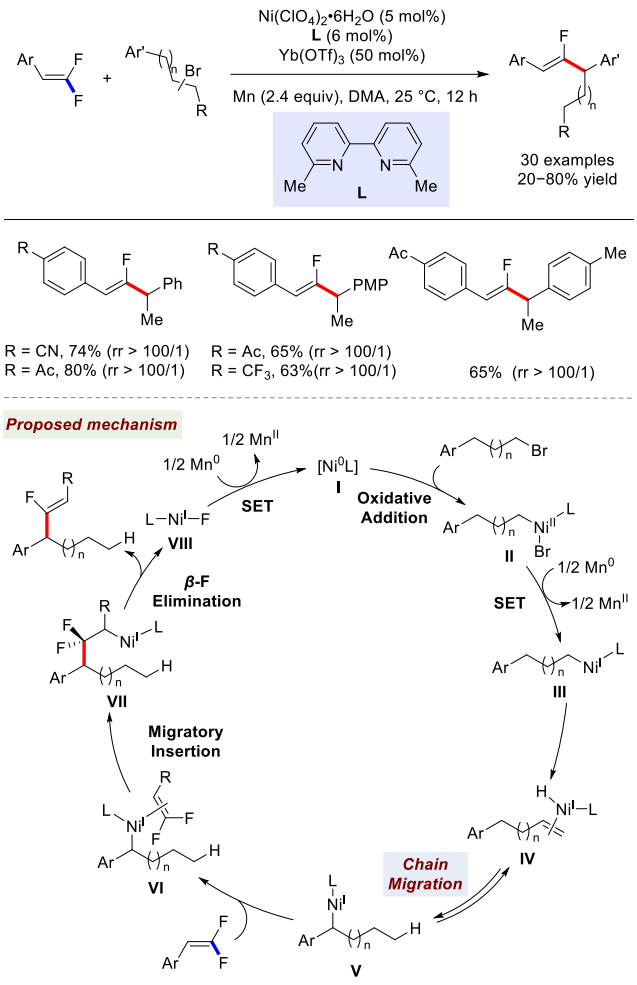
Chem. Rev. 2022, 122, 17479−17646

Scheme 475. Iron-Catalyzed Defluorinative Cross-Coupling of Alkenes with *gem*-Difluoroalkenes



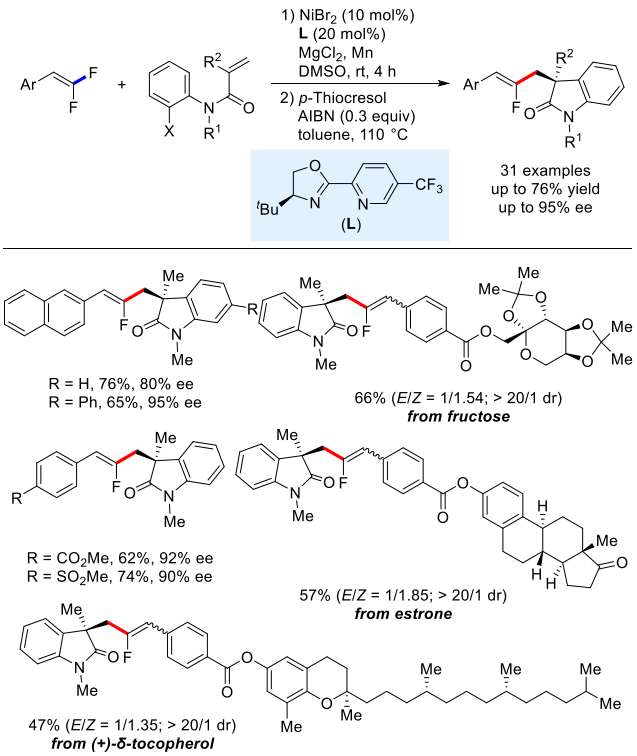
Scheme 476. Ni(II)-Catalyzed Reductive Coupling of Alkyl Bromides with *gem*-Difluoroalkenes and Its Proposed Mechanism



panied by the Ni(I)-F species **VIII**, which undergoes further reduction by Mn(0) to regenerate the active Ni(0) catalyst.

Synthetically useful chiral 3,3-disubstituted oxindoles bearing a monofluoroalkenyl moiety can be obtained *via* an efficient Ni-catalyzed enantioselective reductive monofluoroalkenylation between aryl bromides and *gem*-difluoroalkenes (Scheme 477).[762] The reaction occurred smoothly at room temperature, affording the products in decent yields with 85−

Scheme 477. Nickel(II)-Catalyzed Enantioselective Reductive Monofluoroalkenylation of Aryl Bromides with *gem*-Difluoroalkenes



95% enantiomeric excess. The chelating Pfaltz-type ligand was used to regulate the enantioselectivity of this transformation. Of note, this protocol was applicable to the manipulation of biologically active molecules.

In 2019, Terada's research group reported a novel organocatalytic nucleophilic substitution reaction between *gem*-difluoroalkenes and ketene silyl acetals (Scheme 478).[763] The reaction occurred under especially benign conditions by the use of phosphazene P4-*t*Bu as an organobase catalyst to afford a series of monofluoroalkenes bearing an alkoxycarbonylmethyl group in excellent yields and *Z*-selectivities.

In the same year, Li's group accomplished a highly regio- and stereoselective method for the synthesis of fluorinated 1,4-enynes bearing an all-carbon quarternary center at the propargylic position (Scheme 479).[764] The strategy proceeded through an alkynylenolate intermediate followed by a nucleophilic addition and subsequent β-F elimination. Notably, this protocol accommodated broad substrate scope and functional groups under mild reaction conditions. The resulting products can be further converted into other synthetic useful intermediates. Moreover, this strategy can be applied toward the rapid synthesis of various α-alkenyl allenoates by exploiting 3,3-disubstituted allenoates.

Transition metal-catalyzed alkenyl C−F bond alkylation of *gem*-difluoroalkenes with organometallic reagents such as Grignard reagents, organozinc reagents, and organoaluminum reagents have been well documented in recent years. In 2014, Cao *et al.* reported a novel ligand-free Kumada−Tamao−Corriu cross-coupling of *gem*-di- and monofluoroalkenes with alkyl/aryl magnesium halides enabled by palladium- and

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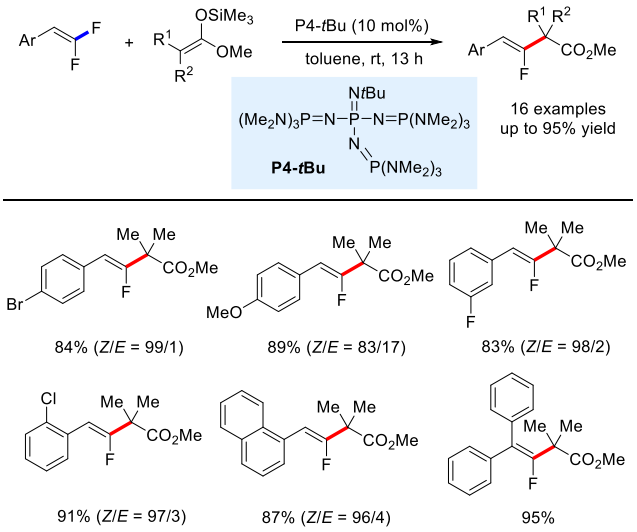
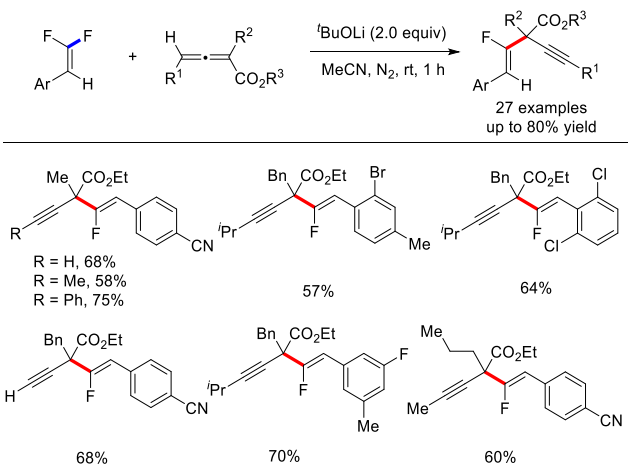
Scheme 478. Phosphazene P4-*t*Bu-Catalyzed Nucleophilic Substitution of *gem*-Difluoroalkenes with Ketene Silyl Acetals

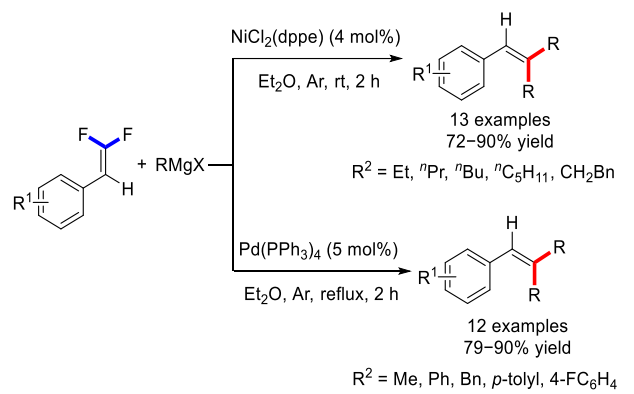


Scheme 479. Regio- and Stereoselective Synthesis of Fluorinated 1,4-Enynes



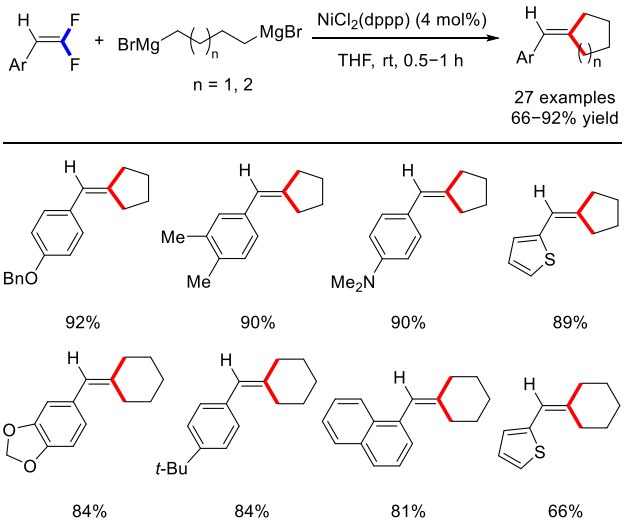
nickel-based catalytic systems, giving rise to dicross- or monocross-coupled products in high yields (Scheme 480).[765] Later, the same group further expanded to report the Ni(II)-

Scheme 480. Kumada−Tamao−Corriu Cross-Coupling Reaction of *gem*-Difluoroalkenes with Grignard Reagents



catalyzed Kumada-type double cross-coupling between *gem*-difluoroalkenes and 1,4- or 1,5- Grignard reagents (Scheme 481).[766] The protocol occurred smoothly under especially

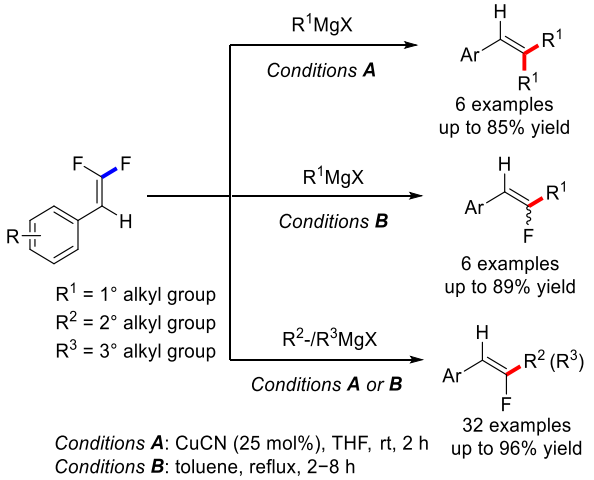
Scheme 481. Ni(II)-Catalyzed Kumada-Type Double Cross-Coupling of *gem*-Difluoroalkenes with Di-Grignard Reagents



ambient conditions to furnish a diverse array of synthetically appealing exocyclic trisubstituted alkenes which are frequently encountered in numerous pharmaceutically relevant compounds and important organic materials.[767]

Subsequently, Cao and colleagues continued their research on a powerful Cu(I)-catalyzed or metal-free cross-coupling of *gem*-difluoroolefins with Grignard reagents (Scheme 482).[768]

Scheme 482. Cu(I)-Catalyzed/Transition Metal-Free Cross-Coupling of *gem*-Difluoroalkenes with Grignard Reagents



Interestingly, the tertiary and secondary C−F bond alkylation of *gem*-difluoroalkenes progressed with ease in the presence of CuCN catalyst or under catalyst-free conditions, yielding the alkylated fluoroalkenes in satisfactory yields with excellent *Z*-selectivity.

Besides these trisubstituted *gem*-difluoroalkenes for the stereoselective synthesis of monofluorostyrenes by steric control, Tsui and colleagues established a chelation-controlled

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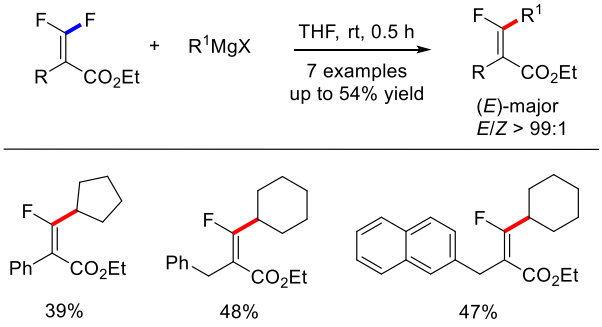
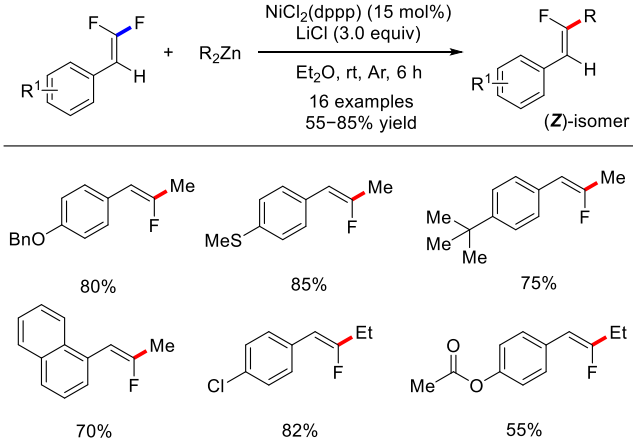
alkenyl C−F bond functionalization of tetrasubstituted *gem*-difluoroalkenes with Grignard reagents under transition metal-free catalysis, giving rise to stereodefined tetrasubstituted (*E*)-monofluoroalkenes in moderate yields (Scheme 483).[769]

Scheme 483. Selective C−F Bond Functionalization of Tetrasubstituted of *gem*-Difluoroalkenes with Grignard Reagents



Moreover, Cao's group was able to prepare alkylated monofluoroalkenes by reacting organozinc reagents with *gem*-difluoroalkenes through a nickel-catalyzed cross-coupling reaction (Scheme 484).[770] In this report, LiCl is used to

Scheme 484. Nickel-Catalyzed Cross-Coupling of Organozinc Reagents with *gem*-Difluoroalkenes

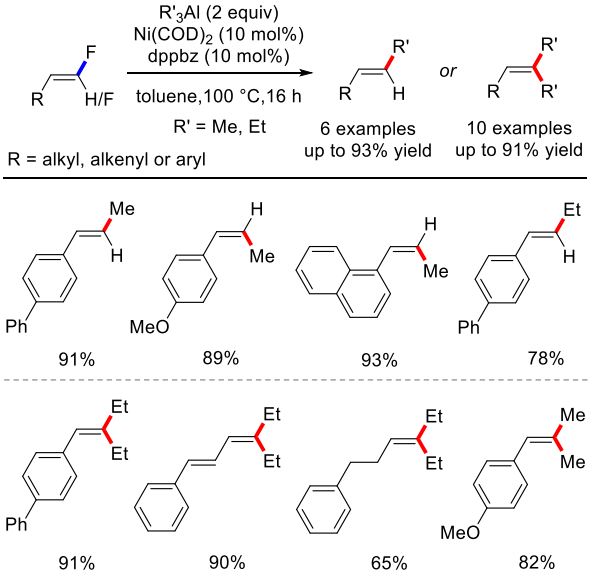


facilitate the reaction, and mild reaction conditions are sufficient to selectively synthesize diverse *Z*-monofluoroalkenes in appreciable yields.

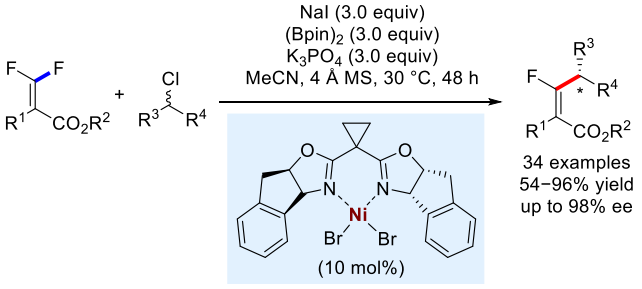
In a recent report by the group of Liu and Ma, an efficient defluorinative alkylation of aryl and vinyl C(sp^2)−F bond has been accomplished under nickel catalysis with trialkylaluminum reagents as the alkyl source (Scheme 485).[771] Of note, a wide range of vinyl monofluorides and vinyl *gem*-difluorides were successfully alkylated in the presence $Ni(COD)_2$ and dppbz.

Sparse examples have been reported involving the formation of monofluoroalkenes bearing a chiral carbon center. More recently, Shi *et al.* presented the first asymmetric reductive defluorinative cross-coupling between *gem*-difluoroalkenes and racemic benzyl electrophiles by means of B_2pin_2 as a stoichiometric nonmetallic reductant under nickel catalysis (Scheme 486).[772] In this strategy, a diverse range of monofluoroalkenes bearing a stereogenic allylic center was

Scheme 485. Ni-Catalyzed Defluorinative Alkylation with Trialkylaluminum Reagents



Scheme 486. Enantioselective Nickel-Catalyzed Reductive Defluorinative Cross-Coupling of *gem*-Difluoroalkenes and Carbon Electrophiles



obtained in 54−96% yield. Mechanistic studies demonstrated that a radical-involved pathway may be operative in this stereo- and enantioselective protocol, and the ester group in *gem*-difluoroalkenes may greatly facilitate the C−F bond cleavage through oxidative addition to a chiral nickel complex.

In another instance, Liao and colleagues realized a highly enantioselective nucleophilic addition of fluorinated enolates to *gem*-difluoroalkenes under copper catalysis with their sulfoxide phosphine (SOP) as a ligand, leading to fabricate a wide range of structurally diverse chiral vicinal difluorides bearing a tertiary fluorinated carbon center in moderate to good yields and high *Z*/*E*-selectivity together with excellent enantioselectivity (Scheme 487).[773] Different types of acetates and acetamides were tolerated with the mild conditions. It should be pointed out, however, that a slight detrimental effect on stereocontrol was found in some amide substrates.

7.2.3. Alkenylation and Allylation. Hydroalkenylation of *gem*-difluoroalkenes and alkynes can also be catalyzed by Ni to produce 2-fluoro-1,3-dienes (Scheme 488).[774] By using a combination of $Ni(COD)_2$, PCy_3, BEt_3, LiO^iPr, and ZrF_4, the products can be obtained in up to 89% yield. The combination of BEt_3 and LiO^iPr acted as a hydride source, while ZrF_4 helped to increase yields as a cocatalyst. Mechanistically, the oxidative cyclization of *gem*-difluoroalkene and alkyne in the presence of Ni(0) results in the regioselective formation of the

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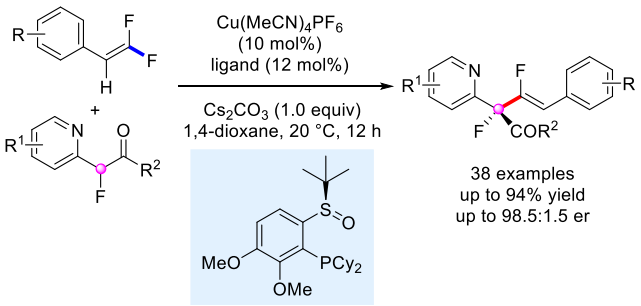
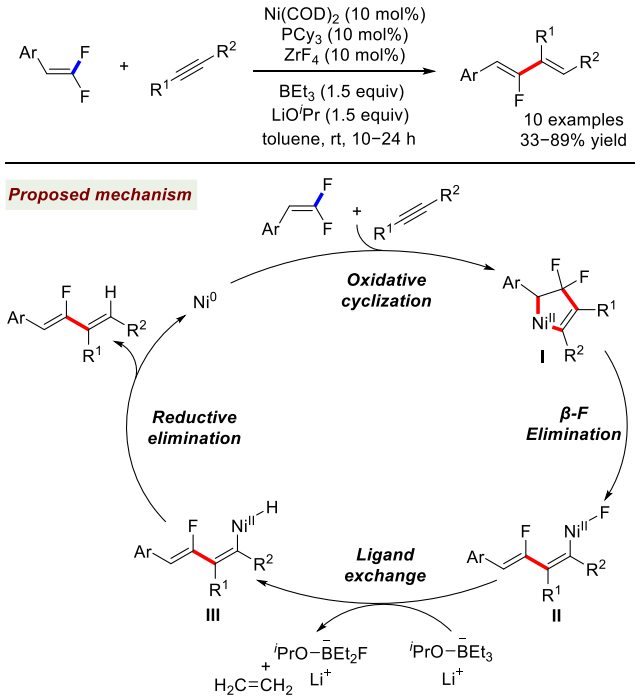
Scheme 487. Synthesis of Chiral Vicinal Difluorides through Enantioselective Cu-Catalyzed Nucleophilic Addition of Fluorinated Reagents



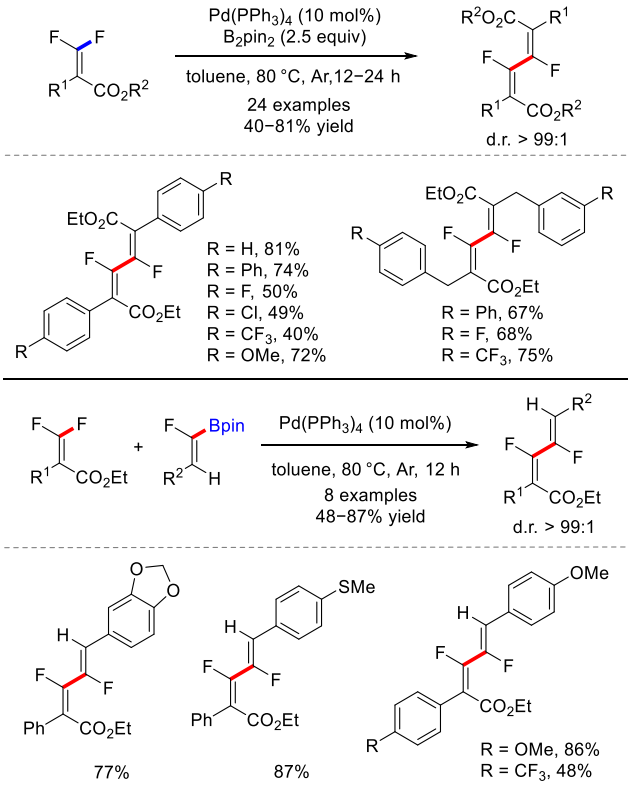
Scheme 488. Nickel-Catalyzed Hydroalkenylation of *gem*-Difluoroalkenes and Alkynes



β,β-difluorinated nickelacyclopentene intermediate **I**. The new metal−carbon bond is placed *β* with respect to F, similar to the previous migratory insertion reactions. Subsequent *β*-F elimination occurs to produce vinylnickel fluoride **II** containing a *Z*-fluoroalkene. The vinylnickel fluoride **II** then reacts with BEt_3 and LiO^iPr to form vinylnickel hydride **III**, which experiences reductive elimination to release the 2-fluoro-1,3-dienes and regenerate the active Ni(0) catalyst.

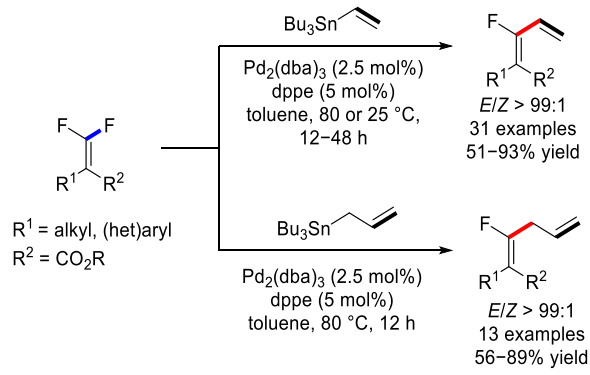
Quite recently, Tsui's group illustrated a highly diastereoselective Pd(0)-catalyzed 2-fold Miyaura borylation/Suzuki−Miyaura cross-coupling of C−F bonds for the direct preparation of stereodefined difluorinated 1,3-dienes (Scheme 489).[775] In this report, a diverse array of symmetrical 1,3-dienes bearing a vicinal difluoro fragment were produced exclusively as a single diastereomer from the corresponding tetrasubstituted *gem*-difluoroalkenes. Interestingly, a series of unsymmetrical difluorinated 1,3-dienes can also be obtained through the Pd(0)-catalyzed cross-couling of *gem*-difluoroalkenes with borylated monofluoroalkenes.

Scheme 489. Synthesis of Difluorinated 1,3-Dienes *via* Pd-Catalyzed C−F Activation of Tetrasubstituted *gem*-Difluoroalkenes



Moreover, the same group also expanded to report a Pd(0)-catalyzed stereoselective C−F bond vinylation and allylation of tetrasubstituted *gem*-difluoroalkenes for the synthesis of synthetically useful monofluorinated 1,3- and skipped 1,4-dienes in high yields and excellent diastereoselectivities (Scheme 490).[776] Unlike the widely used $Pd(PPh_3)_4$, the

Scheme 490. Pd(0)-Catalyzed Stereoselective C−F Bond Vinylation and Allylation of Tetrasubstituted *gem*-Difluoroalkenes



catalytic system incorporated a Pd(0) and dppe as the ligand was illustrated for Stille-type cross-coupling between *gem*-difluoroolefins and vinyl- or allyltin reagents.

7.2.4. Arylation. Early in 1991, Heitz and Knebelkamp pioneered to report the first example of Pd-catalyzed defluorinative cross-coupling between 1,1-difluoroethylene and aryl iodides (Scheme 491a).[777] In this work, the migratory

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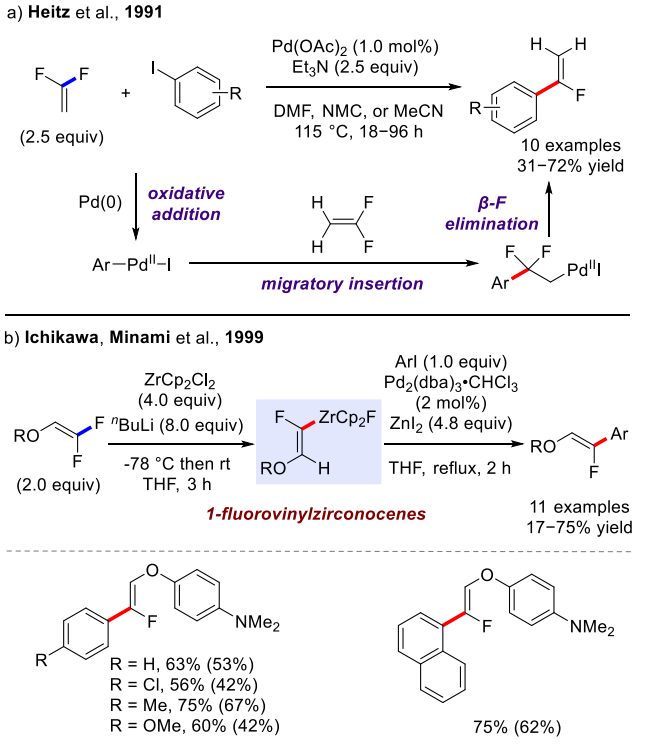
Scheme 491. Synthesis of Fluorostyrenes *via* Vinylic C−F Activation of Fluoroolefins with Aryl Iodides

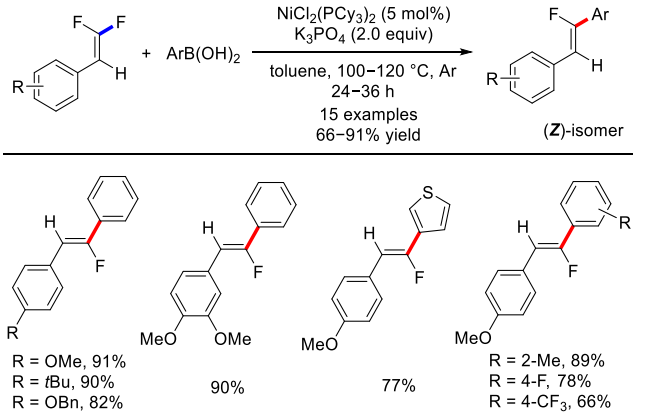


insertion of 1,1-difluoroethylene into C−Pd bonds of arylpalladium(II) iodides generated by initial oxidative addition proceeds smoothly to afford the β,β-difluorinated phenethylpalladium(II) complex, which subsequently undergoes a facile β-F elimination to furnish α-fluorostyrenes. A couple of years later, the group of Ichikawa and Minami further discovered that the treatment of 1,1-difluoro-1-ethylenes with a low-valent zirconocene reagent ($ZrCp_2$) generated the thermostable 1-fluorovinylzirconocenes *via* a vinylic C−F bond cleavage, which engaged in palladium-catalyzed coupling reaction with aryl iodides in a one-pot operation to afford arylated fluoroethylenes in acceptable yields (Scheme 491b).[778]

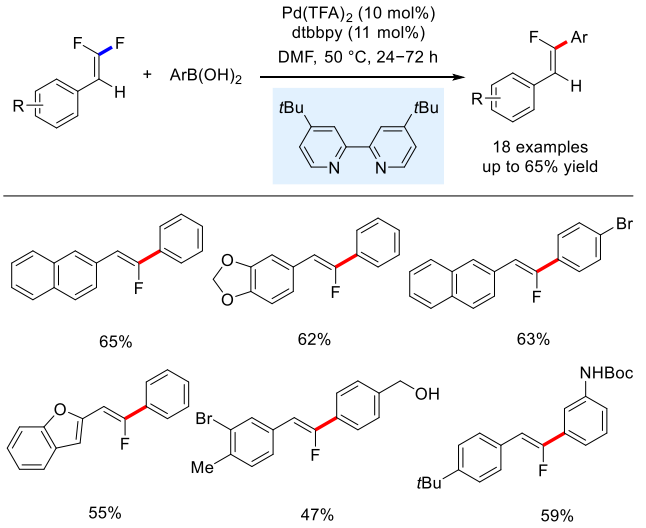
The Suzuki−Miyaura coupling is one of the most dominant strategies for the construction of C−C bonds in modern synthetic chemistry. The defluorinative Suzuki−Miyaura type cross-coupling of *gem*-difluoroalkenes with boronic acids through alkenyl C−F activation gives rise to monofluoro-substituted olefins. In 2015, Cao's group first reported the stereoselective Ni-catalyzed Suzuki-type cross-coupling between *gem*-difluoroalkenes and a series of arylboronic acids (Scheme 492).[779] In the presence of $NiCl_2(PCy_3)_2$ (5 mol %) and K_3PO_4, a number of *Z*-monofluorostilbenes were produced in good yields with exceptional regioselectivity. The authors tentatively proposed a plausible mechanism that proceeds through the oxidative addition of the alkenyl C−F bond accompanied by cross-coupling with arylboronic acids.

Another opportunity for the defluorinative Suzuki−Miyaura cross-coupling of *gem*-difluoroalkenes with arylboronic acids has been established by Toste and co-workers (Scheme 493).[780] Overall, this redox-neutral protocol features a broad functional group scope, which conveniently proceeds *via* a β-F elimination process to yield the products with excellent diastereoselectivity (≥50:1). The utility of this strategy was

Scheme 492. Nickel-Catalyzed Suzuki−Miyaura Type Cross-Coupling of *gem*-Difluoroalkenes with Arylboronic Acids



Scheme 493. Pd(II)-Catalyzed Defluorinative Suzuki−Miyaura Cross-Coupling of *gem*-Difluoroalkenes with Arylboronic Acids



highlighted in the rapid synthesis of a Gleevec analogue by utilizing a monofluorostilbene to function as an amide isostere.

Recently, Tsui's group established a conceptually similar approach to prepare a series of tetrasubstituted (*E*)-monofluoroalkenes (Scheme 494).[781] Detailed DFT calculations suggested that the reaction proceeds through a formal [4 + 1] cycloaddition pathway accompanied by a 1,5-sigmatropic fluoride migration, which is promoted through the chelation of the ester-substituent group to the Pd-catalyst. The mechanism also justified the low C−F bond strength for its successive cleavage (slow step) and the stereoselectivity control. Mechanistically, the C−F activation readily generates a vinylpalladium(II) fluoride intermediate. which subsequently participates in a transmetalation effortlessly with arylboronic acids without the need for an external base.

Shen and colleagues found that the combination of lithium organoborates with zinc bromide ($ZnBr_2$) readily *in situ* generated a highly reactive lithium aryl zincate species, which significantly facilitates transmetalating the aryl group from boron to nickel catalyst.[782] Continuing this approach, they applied readily available "ate-type" aryl pinacol boronates for the ready assembly of *Z*-selective monofluoroalkenes from *gem*-

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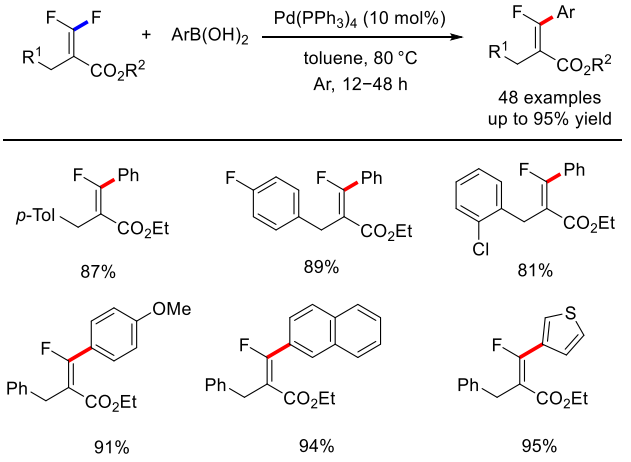
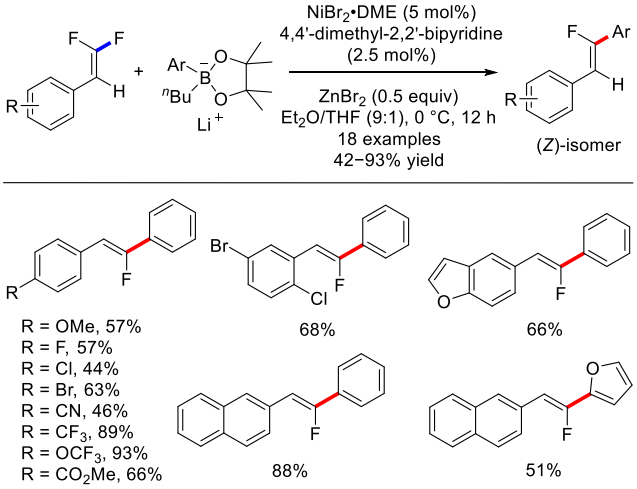
Scheme 494. Pd-Catalyzed Suzuki−Miyaura Coupling of *gem*-Difluoroalkenes with Arylboronic Acids



difluoroalkenes in the presence of a catalytic amount of $ZnBr_2$ (Scheme 495).[783]

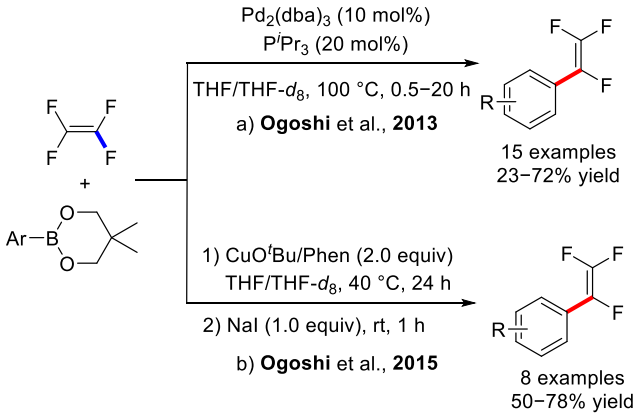
Scheme 495. Ni-Catalyzed Defluorinative Coupling of *gem*-Difluoroalkenes with Lithium Organoborates



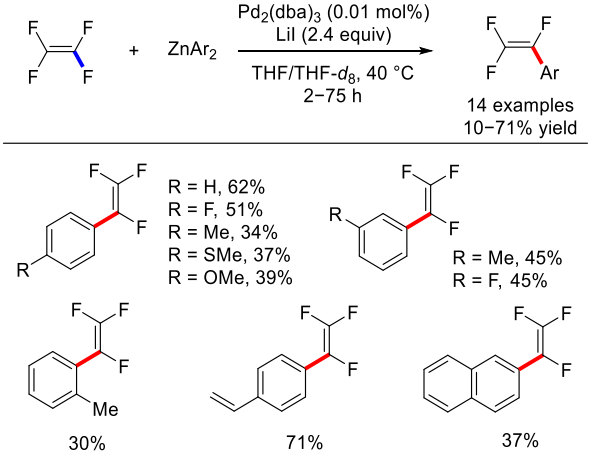
Readily available tetrafluoroethylene (TFE) is an economical bulk organofluorine feedstock for the mass production of commonly used poly(tetrafluoroethylene) and copolymers. In 2013, Ogoshi and co-workers achieved a defluorinative Suzuki−Miyaura type coupling of tetrafluoroethylene with arylboronates under Pd-catalyzed base-free conditions (Scheme 496a).[784] The reaction took place smoothly through the formation of the key palladium(II) fluoride intermediate without the use of a Lewis acid additive to facilitate the oxidative addition of a vinylic C−F bond to Pd(0) catalyst. Later, they successfully expanded to elaborate the efficient synthesis trifluorostyrenes *via* a facile β-F elimination of the 2-aryl-1,1,2,2-tetrafluoroethylcopper intermediate which is *in situ* generated from arylboronates, copper *tert*-butoxide, and tetrafluoroethylene (TFE) with 1,10-phenanthroline as a ligand (Scheme 496b).[785]

In 2011, Ogoshi and colleagues also reported the palladium-catalyzed C−F bond monoarylation of TFE with *in situ*-prepared arylzinc agents, affording a variety of α,β,β-trifluorostyrenes in synthetically satisfactory yields (Scheme 497).[786] This strategy employs lithium iodide as a Lewis acid to facilitate the oxidative addition of a vinylic C−F bond to Pd(0) even at room temperature, thereafter generating a well-defined trifluorovinylpalladium(II) iodide species, which was readily isolated and unambiguously determined by X-ray diffraction.

Scheme 496. Synthesis of Trifluorostyrene Derivatives from Tetrafluoroethylene and Arylboron Reagents



Scheme 497. Pd-Catalyzed C−F Bond Arylation of Tetrafluoroethylene (TFE) with Arylzinc Reagents



Moreover, Ishihara's group reported the examples of C−F bond arylation of readily available benzyl 2,3,3-trifluoroacrylate with various arylmagnesium bromides (Scheme 498).[787] The reaction occurred smoothly at −78 °C in the presence of CuBr (13 mol %) as the catalyst, delivering a variety of α,β-difluoroacrylates in up to 90% yield with high *Z*-selectivity. Both alkyl- and alkenylmagnesium halides were compatible with this protocol to afford the corresponding defluorinative products.

7.2.5. Alkynylation. The fluorinated conjugated enynes represent an important class of synthetically useful building blocks in organic synthesis. In 2014, Cao *et al.* first disclosed a benign and practical strategy for the stereoselective synthesis of fluorinated conjugated enynes by reacting readily available *gem*-difluoroalkenes with terminal alkynes in the presence of ^{n}BuLi and K_3PO_4 (Scheme 499).[788] This Sonogashira-type defluorinative cross-coupling afforded a series of conjugated β-fluoroenynes in up to 93% yield with high *E*-selectivity.

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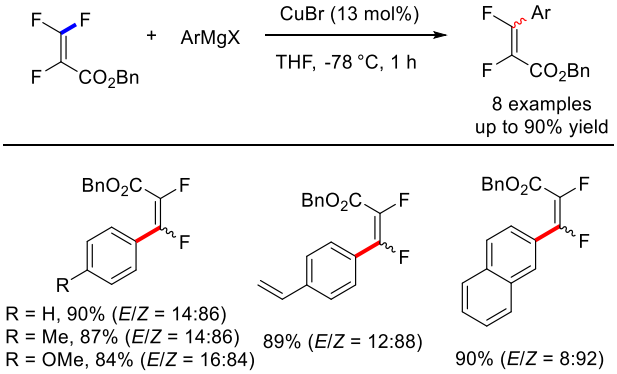
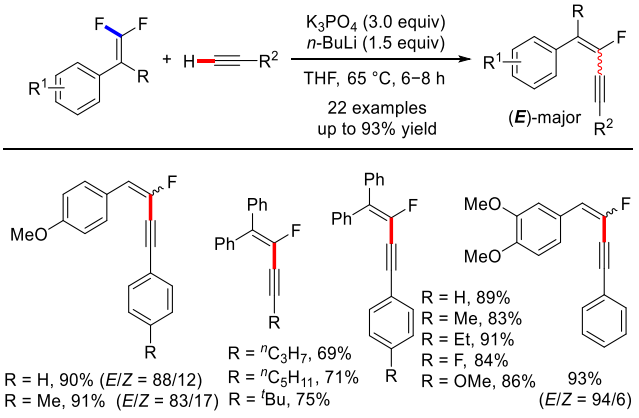
Scheme 498. Copper-Catalyzed C−F Bond Arylation of *gem*-Difluoroalkenes with Grignard Reagents

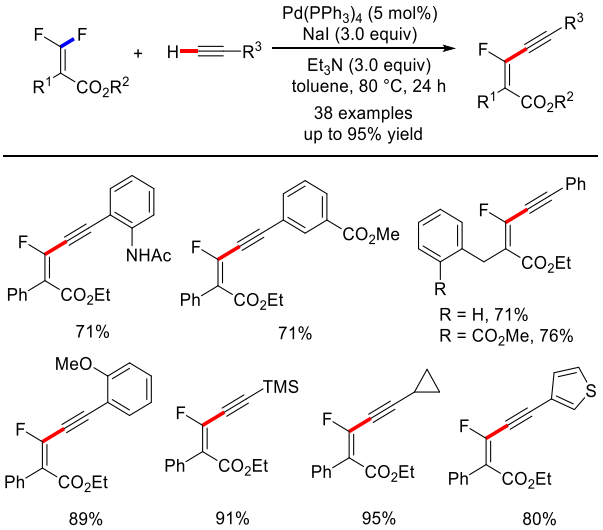


Scheme 499. Synthesis of *β*-Fluoroenynes by Reaction of *gem*-Difluoroalkenes with Terminal Alkynes



In a related report, Tsui and co-workers illustrated an impressive stereoselective Pd-catalyzed C−F alkynylation of tetrasubstituted *gem*-difluoroalkenes with diverse terminal alkynes (Scheme 500).[789] This defluorinative Sonogashira-type coupling enables the efficient synthesis of a broad series of conjugated tetrasubstituted monofluoroenynes with a definited stereochemistry. The high stereoselectivity of this protocol

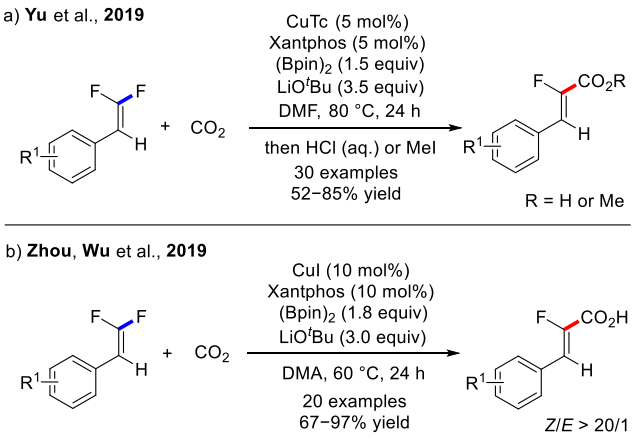
Scheme 500. Pd(0)-Catalyzed C−F Alkynylation of Tetrasubstituted *gem*-Difluoroalkenes with Alkynes



could be rationalized by the chelation-assisted oxidative addition of the Pd catalyst to the alkenyl C−F bond. The key intermediate, a monofluorovinyl Pd(II) species, was readily isolated alongside with an X-ray crystal structure as proof for the proposed mechanism.

7.2.6. Carboxylation. *α*-Fluoroacrylic acid derivatives are versatile motifs widespread in many pharmaceutically relevant molecules.[790] Consequently, remarkable attention has been devoted toward the development of efficient and practical methods for the rapid synthesis of *α*-fluoroacrylic acids. In this regard, Yu's group in 2019 synthesized a diverse array of *α*-fluoroacrylic acids through the selective alkenyl C−F carboxylation of *gem*-difluororoalkenes with an atmospheric pressure of CO_2 by a copper(I)/diboron catalytic system (Scheme 501a).[791] This formal *ipso* monocarboxylation of C−

Scheme 501. Stereoselective Defluorinative C−F Bond Carboxylation of *gem*-Difluoroalkenes with CO_2



F bonds can be performed *via* telescoping synthesis to stereoselectively afford the (*Z*)-product. Intriguingly, the challenging *gem*-difluorodienes were also compatible with this protocol. Later, detailed theoretical calculations were carried out by Shi's group,[792] and the results clearly revealed that the reaction proceeds successively *via* the migratory insertion of difluoroalkene into the Cu(I)-B intermediate, *syn* *β*-F elimination, transmetalation, and rate-determining carboxylation steps. The regioselectivity of this reaction is rationalized by the migration insertion step. Almost simultaneously, the group of Zhou and Wu also established a similar approach for the stereoselective alkenyl C−F bond carboxylation (Scheme 501b).[793] Due to the use of stoichiometric bis(pinacolatodiboron) as a nonmetallic reductant, a large number of synthetically useful functionalities were compatible under the conditions. More challenging *gem*-difluorodienes engaged in this C−F carboxylation strategy to furnish conjugated *α*-fluorocarboxylic acids in decent yields with high *Z*-selectivity. Impressively, the less reactive (*E*)-fluorostyrenes delivered the corresponding cinnamic acids with the retension of stereochemistry ($E/Z > 20/1$), while no reaction occurred when the corresponding (*Z*)-isomers were employed. This reveals that a *trans*-*β*-F elimination may be operative in this process.

The group of Wu and Zhou extended to disclose a green and sustainable strategy for the straightforward construction of *α*-fluoroacrylic acids through the electrochemical defluorinative C−F carboxylation of *gem*-difluoroalkenes with CO_2 (Scheme

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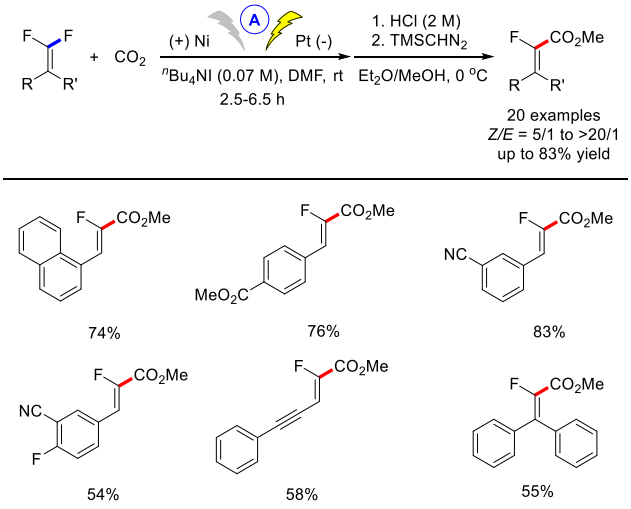
502).[794] Utlizing a Pt plate as the cathode and an inexpensive Ni plate as the anode in an easy-to-use undivided cell, the

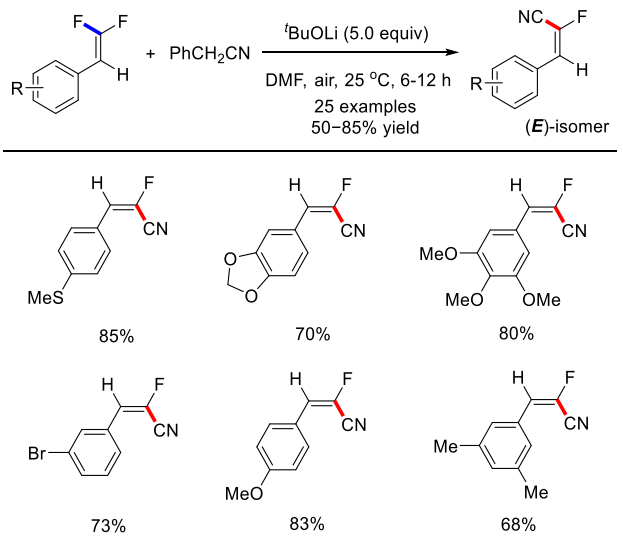
Scheme 502. Electrochemical Defluorinative C−F Carboxylation of *gem*-Difluoroalkenes with CO_2



reaction progressed with ease under typically ambient conditions in the absence of any exorbitant transition-metal catalysts, ligands, external base, or reductant. A series of α-fluoroacrylic acids were obtained in 35−83% yield with up to 20:1 Z/E ratio. The authors performed a cyclic voltammetry experiment and tentatively proposed an unorthodox process involving single-electron reduction, reaction with CO_2, single-electron reduction, and β-F elimination.

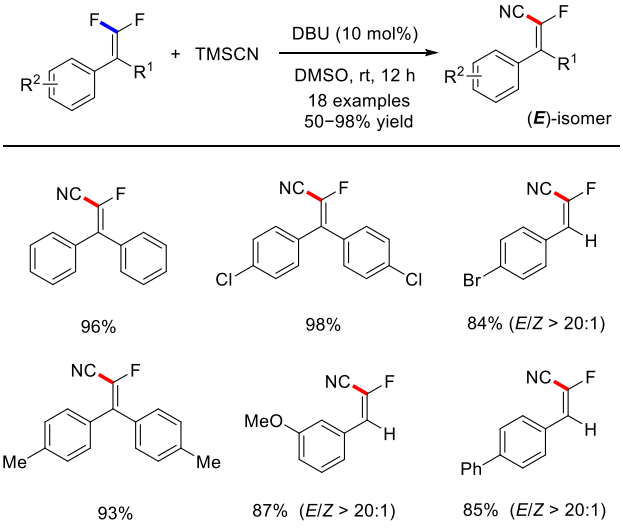
7.2.7. Other Useful Reactions. In 2016, Cao's group disclosed a stereoselective C−F bond cyanation of *gem*-difluoroolefins with readily available benzyl nitriles as the environmentally benign cyanating agent (Scheme 503).[795] The reaction operated under a copper-free system and ambient conditions. A series of synthetically versatile monofluorinated alkenyl nitriles were prepared in yields ranging from 50% to 85% with excellent stereoselectivity. A plausible catalytic mechanism was proposed involving the oxidation of the C−H bond, cleavage of the C−CN bond, and subsequent nucleophilic vinylic substitution (S_NV) to afford the expected products.

Scheme 503. Stereoselective C−F Bond Cyanation of *gem*-Difluoroolefins with Benzyl Nitriles



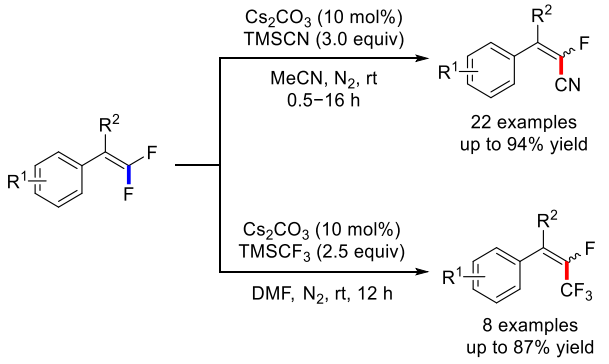
Later, He's group also demonstrated the synthesis of α-fluoroacrylonitriles through a transition metal-free organocatalytic C−F bond cyanation of *gem*-difluoroolefins with TMSCN. In the presence of a catalytic amount of DBU, the *gem*-difluoroalkenes participated in a nucleophilic addition-β-elimination reaction to generate the α-fluoroacrylonitriles in satisfactory yields with exceptional Z/E stereoselectivity (Scheme 504).[796]

Scheme 504. Organocatalytic C−F Bond Cyanation of *gem*-Difluoroolefins with TMSCN



Around the same time, Deng *et al.* reported the feasible strategy for the nucleophilic substitution of *gem*-difluoroalkenes with trimethylsilyl nucleophiles (Scheme 505).[797] In this

Scheme 505. Nucleophilic Substitution of *gem*-Difluoroalkenes with TMSNu



case, a catalytic amount of Cs_2CO_3 (10 mol %) was used as a promoter to maintain a high concentration of the nucleophilic anions, which was proposed to kickstart the catalytic cycle. This strategy enables the construction of diverse highly functionalized monofluoroalkenes bearing a cyano or trifluoromethyl group with modest to excellent stereoselectivities.

More recently, Wu and colleagues continued their carbonylation strategy[798] and presented an unprecedented Pd/Cu synergistic system for the formal defluorinative carbonylative

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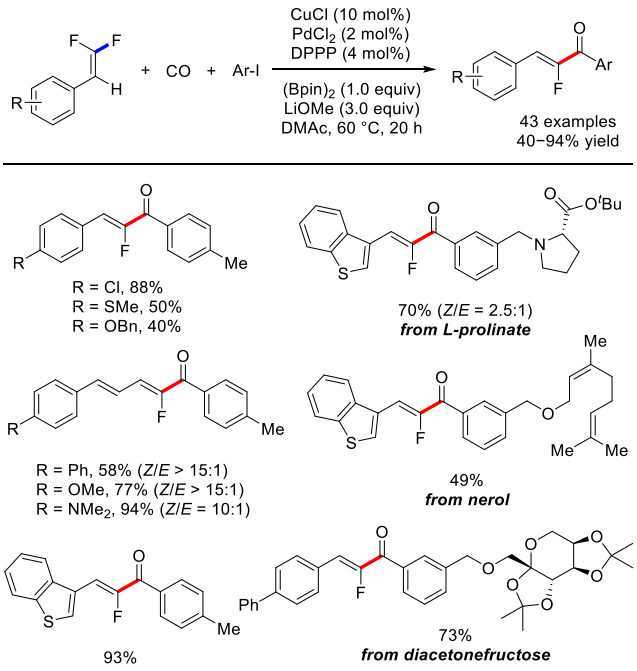
coupling reaction between *gem*-difluoroalkenes and aryl iodides, providing an efficient access to a variety of α-fluorochalcones under benign conditions in appreciable yields with excellent *Z*-selectivity (Scheme 506).[799] Preliminary mechanistic experiments suggested that the transmetalation of the alkyl-Pd(II)I complex and CuBpin species was a crucial step for the catalytic cycle.

Scheme 506. Pd/Cu-Catalyzed Formal Defluorinative Carbonylative Coupling of *gem*-Difluoroalkenes with Aryl Iodides

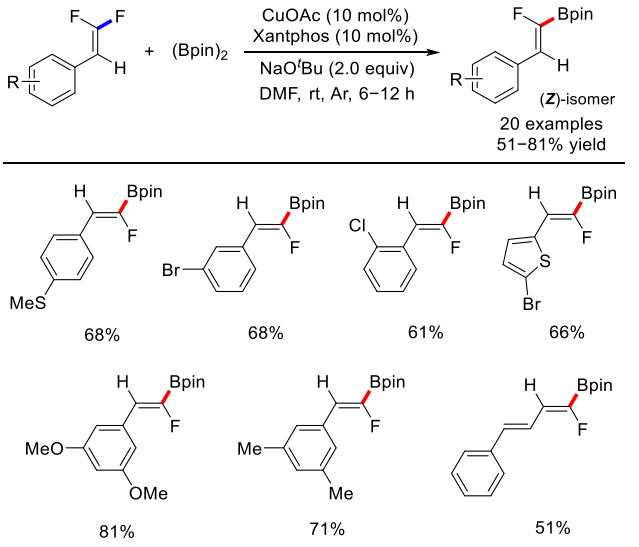


7.3. C–Het Bond Formation

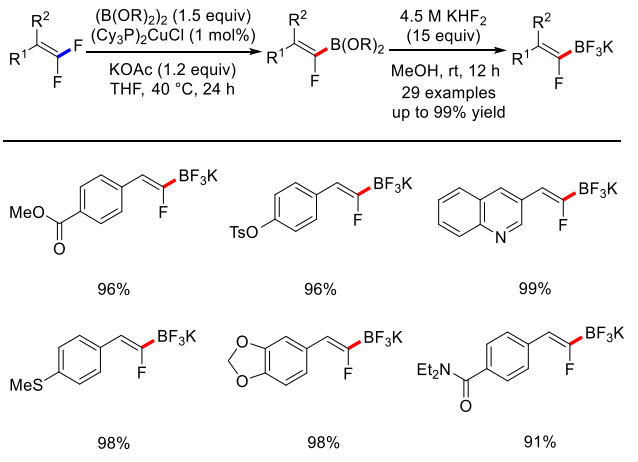
7.3.1. Borylation and Silylation. Organoboron- and organosilicon-based reagents are widely used in organic synthesis and drug discovery. Accordingly, there have been considerable efforts toward the development of broadly applicable methods to prepare this extremely important class of compounds. The direct alkenyl C–F bond functionalization of *gem*-difluoroalkenes undoubtedly offers a practical and unique tool for the synthesis of fluorinated alkenyl borons and silanes, which could also act as versatile building blocks for further elaborations to synthesize value-added complex molecules.[25] In 2017, Cao and colleagues continued their C–F bond functionalization strategy and described the first example of copper-catalyzed stereoselective C–F bond borylation of *gem*-difluoroalkenes with bis(pinacolato)diboron (B_2pin_2) in the presence of NaO^{t}Bu base and Xantphos ligand at room temperature, enabling a convenient synthesis of structurally diverse (*Z*)-fluorinated alkenylboronic pinacol esters in 51–81% yields (Scheme 507).[800]

Meanwhile, the research group of Niwa, Ogoshi, and Hosoya also established a straightforward approach to fabricate a series of borylated fluoroalkenes *via* the copper-catalyzed regioselective monodefluoroborylation of diverse polyfluoroalkene substrates, including (difluorovinyl) arenes, (trifluorovinyl) arenes, tetrafluoroethylene (TFE), and trifluoromethylated monofluoroalkenes (Scheme 508).[801] The type of boron reagent used in the reaction depends on the electronic

Scheme 507. Cu-Catalyzed Stereoselective Borylation of *gem*-Difluoroalkenes with Bis(pinacolato)diboron



Scheme 508. Copper-Catalyzed Regioselective Monodefluoroborylation of Polyfluoroalkenes



character of *gem*-difluoroalkenes. Substrates bearing an electron-deficient aryl group made use of $(Bpin)_2$ as coupling partners, while those with electron-rich aryl group employed $(Bnep)_2$. The resulting (fluoroalkenyl)-boronic esters could be readily converted into the corresponding potassium trifluoroborate salts by the treatment with KHF_2 in MeOH.

Subsequently, Ito's group employed a Cu(I)/Xantphos catalytic system for the defluoroborylation of aliphatic *gem*-difluoroalkenes by means of $(Bpin)_2$ as the borylating reagent in conjunction with KO^{t}Bu as the base (Scheme 509).[802] α-Boryl-α-fluoroalkenes were synthesized with high *Z*-stereoselectivity, which can be isolated after converting into corresponding trifluoroborates. On the basis of preliminary DFT calculations, the authors proposed a plausible mechanism for this process. Initially, Cu(I) alkoxide is formed from CuCl, the ligand, and KO^{t}Bu, which then reacts with $(Bpin)_2$ to produce a boryl-Cu(I) intermediate. An alkyl-Cu(I) species is then produced *via* a four-centered reaction between the key boryl-Cu(I) intermediate and *gem*-difluoroalkenes, which subsequently undergoes β-F elimination to give the (*Z*)-defluoroborylated products accompanied by the release of copper(I) fluoride. Finally, CuF reacts with diboron and

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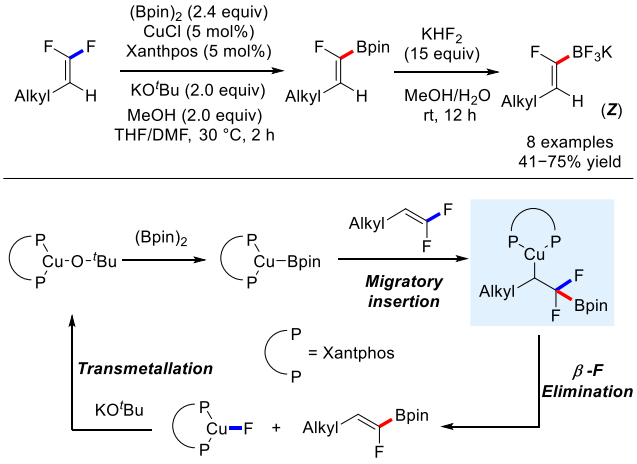
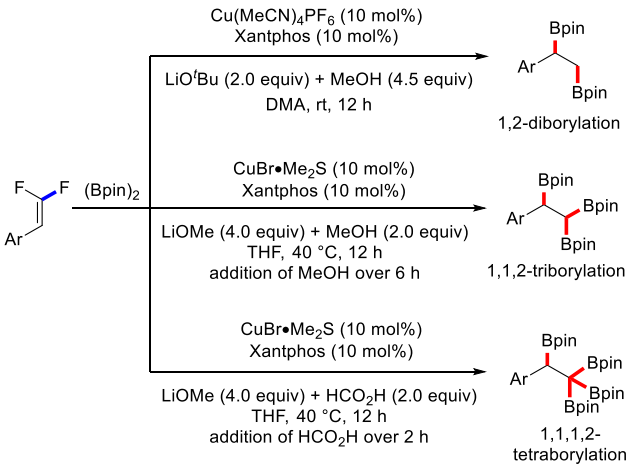
Scheme 509. Cu(I)-Catalyzed Defluoroborylation of Aliphatic *gem*-Difluoroalkenes



KO^{t}Bu to reform the transmetalated active boryl-Cu(I) intermediate.

The chemoselective polyborylation reaction of *gem*-difluoroalkenes with $(Bpin)_2$ is greatly facilitated by Cu(I) catalyst *via* dual alkenyl C−F bond activation (Scheme 510).[803] By slightly

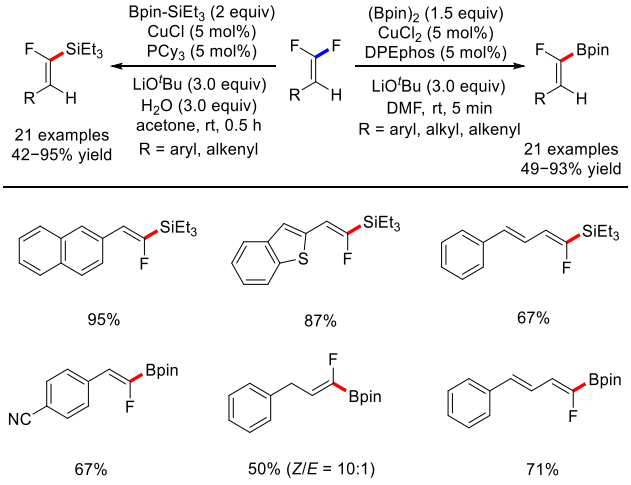
Scheme 510. Highly Tunable Copper-Catalyzed Multiborylation of *gem*-Difluoroalkenes



adjusting the type of Cu salts, additives, and solvents, together with the reaction temperature, a large variety of multiborylated compounds, including 1,2-alkyldiboronates, 1,1,2-alkyltriboronates, and 1,1,1,2-alkyltetraboronates, can be selectively produced. Notably, Xantphos was kept as the ligand in all three C−F borylation reactions. The borylated products could subsequently be further functionalized and serve as helpful starting materials.

Cu catalysts with different oxidation states, ligands, and additives can also be used to catalyze the defluorinative borylation and silylation of *gem*-difluoroalkenes (Scheme 511).[804] Using $CuCl_2$ together with DPEphos will promote C−F bond borylation, while employing the $CuCl/PCy_3$ catalytic system will promote C−F bond silylation. In this report, aliphatic *gem*-difluoroalkenes was not compatible with this protocol to undergo defluorinative silylation. In contrast, the defluorinative borylation of aliphatic *gem*-difluoroalkenes

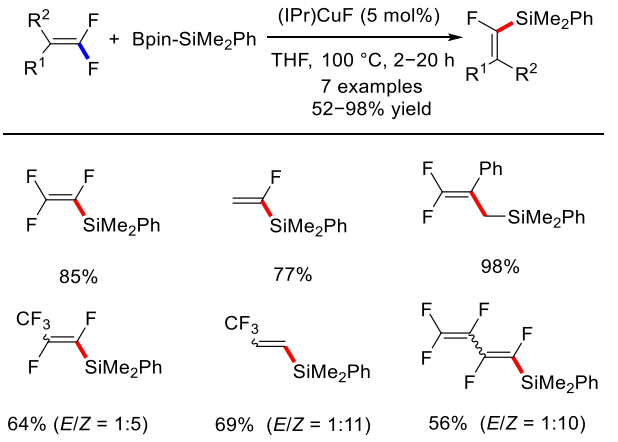
Scheme 511. Cu(I)/Cu(II)-Catalyzed Defluorinative Borylation and Silylation of *gem*-Difluoroalkenes



occurred smoothly to afford monofluoroalkenyl boronic esters in 50% yield.

Silylated fluoroolefins could be served as synthetically important building blocks for the synthesis of bioactive natural products and pharmaceuticals. Using the (IPr)CuF catalyst, Ogoshi's group was able to perform the C−F bond defluorosilylation of diverse substrates including *gem*-difluoroalkenes, tetrafluoroethylene (TFE), and other polyfluoroalkenes with silylborane reagent, affording a variety of fluorinated vinylsilanes (Scheme 512).[805] The obtained

Scheme 512. Synthsis of Fluorinated Vinylsilanes *via* Copper-Catalyzed C−F Bond Defluorosilylation of Polyfluoroalkenes with Silylborane Reagent



(trifluorovinyl)phenyldimethylsilanes can react with iodobenzene in a copper-mediated cross-coupling reaction to produce α,β,β-trifluorostyrene. Mechanistic studies illustrated that this defluorosilylation process proceeded through the 1,2-addition of a silylcopper species to the polyfluoroalkene followed by a facile selective β-F elimination which is greatly facilitated by the *in situ* generated Lewis acidic F−Bpin.

Generally, it is difficult to selectively defluorosilylate and convert a highly stable fluoroolefin into the corresponding silylated fluoroalkenes. In 2019, Shi's group developed a convenient and economical approach for the defluorosilylation of fluoroalkenes with silylboronates to assemble a series of

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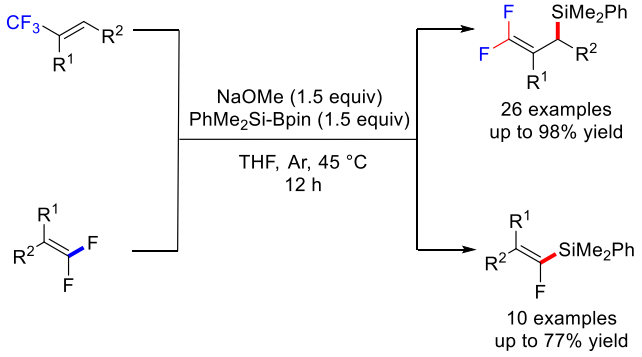
silylated fluoroolefins under transition metal- and ligand-free conditions (Scheme 513).[806] The reaction occurred in the

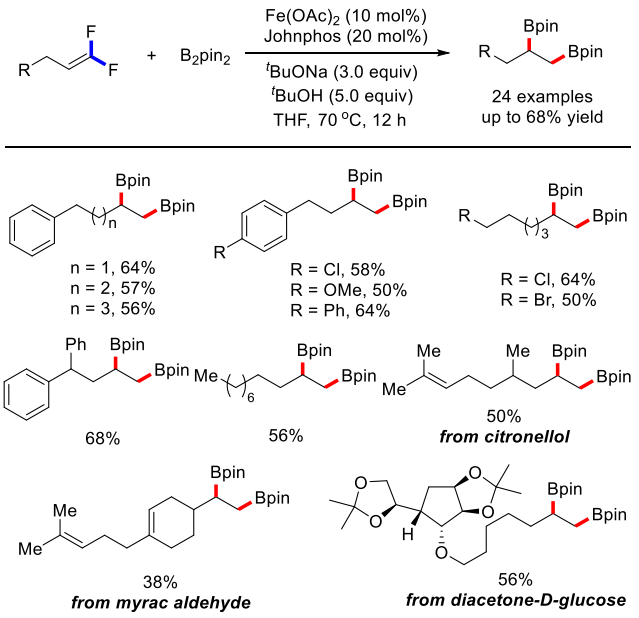
Scheme 513. Metal-Free Defluorosilylation of Fluoroalkenes with Silylboronates



presence of NaOMe and tolerated a broad range of substrate scope. DFT calculations were performed and illustrated that transient silyl anion complex participated in an S_N2' or S_N^v substitution type process, which accounts for this alkoxy base-promoted defluorosilylation.

In 2021, the group of Zhu and Feng uncovered the example of Fe(II)-catalyzed defluoroborylation of diverse unactivated *gem*-difluoroalkenes, *gem*-dichloroalkenes, and *gem*-dibromoalkenes, affording the corresponding 1,2-bis(boryl)-alkanes in modest to good yields (Scheme 514).[807] This strategy featured

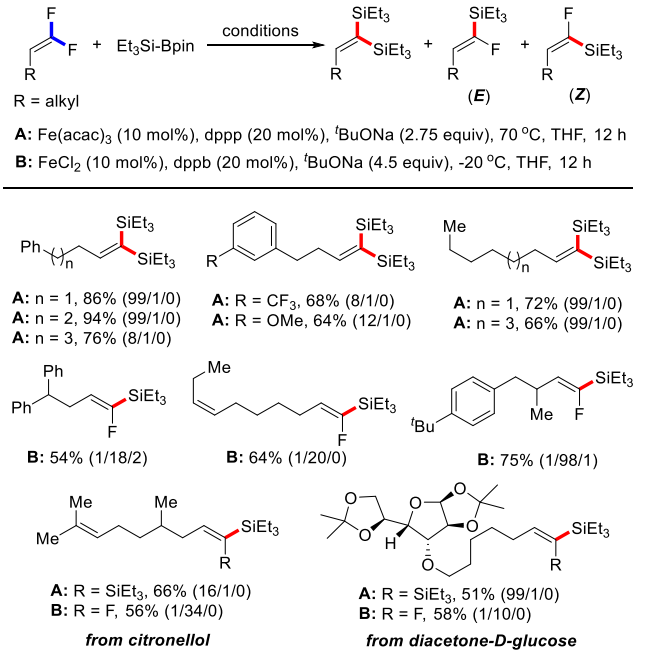
Scheme 514. Synthesis of 1,2-Bis(boryl)alkanes *via* Defluoroborylation of *gem*-Dihaloalkenes



high regioselectivity, a wide substrate scope, and excellent funational group compatibility. Initial mechanistic experiments suggested a double β-F elimination involved in the mechanism, and 1,1-diborylated olefins could have been possible intermediates in this transformation.

The same group continued to describe the regio- and stereoselective defluorosilylation of unbiased aliphatic *gem*-difluoroalkenes *via* iron-catalyzed controllable C−F bond cleavage (Scheme 515).[808] By slightly adjusting the conditions,

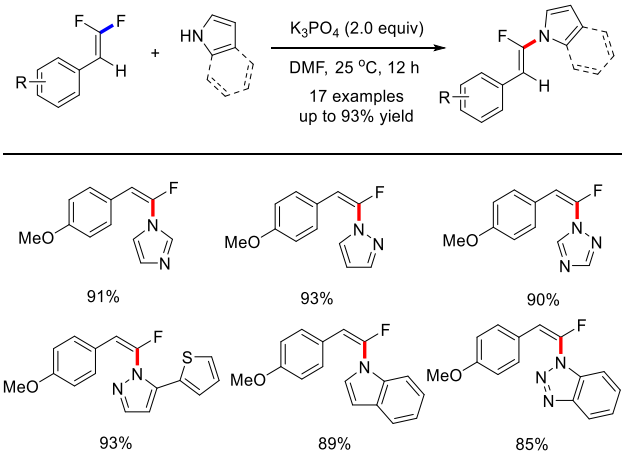
Scheme 515. Regio- and Stereoselective Iron-Catalyzed Controllable Defluorosilylation of Unactivated *gem*-Difluoroalkenes



a diverse array of *gem*-disilylated and (*E*)-silylated alkenes were readily prepared in high yields. Combined experimental and DFT calculation studies demonstrated that the chemoselectivity of disilylation might undergo a thermodynamically favored process through an insertion/elimination/addition mechanism.

7.3.2. Miscellaneous. In 2014, Cao's group illustrated a versatile transition-metal-free approach for the formation of C−N bonds through a vinylic nucleophilic substitution reaction (S_NV) of (2,2-difluorovinyl) arenes with a large variety of nitrogen-based heterocycles under basic and relatively benign conditions (Scheme 516).[809] This Ullmann-type transformation occurred uneventfully in the presence of K_3PO_4 under ambient conditions, yielding the (*E*)-*N*-*α*-fluorovinyl derivatives of azoles in decent yields with high stereocontrol.

Scheme 516. Synthesis of *N*-(*α*-Fluorovinyl)azoles from *gem*-Difluoroalkenes and Azoles



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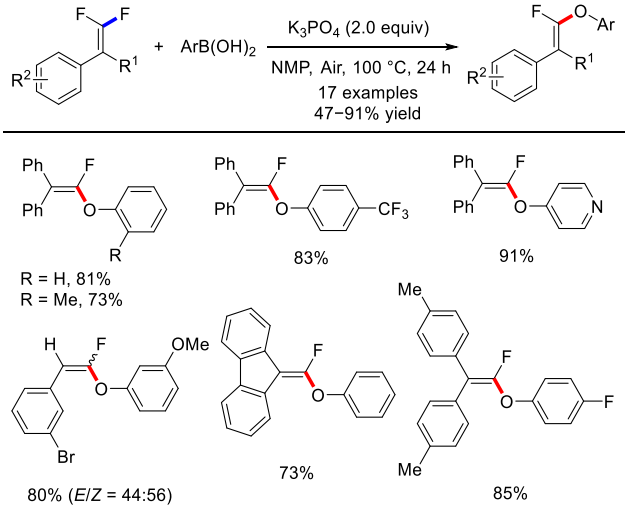
Subsequently, the same group continued to report a unique three-component reaction in an effort to synthesize fluorovinyl aryl ethers from *gem*-difluoroalkenes, arylboronic acids, and oxygen under catalyst-free conditions (Scheme 517).[810]

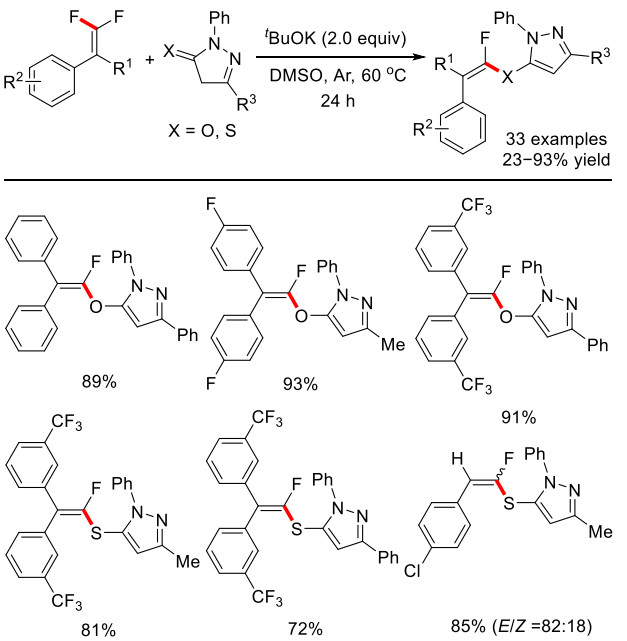
Scheme 517. Synthesis of Fluorovinyl Aryl Ethers from *gem*-Difluoroalkenes, Arylboronic Acids, and Oxygen



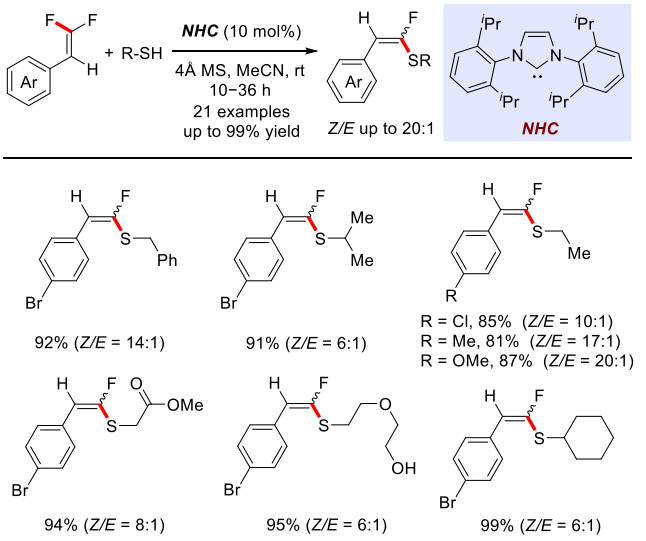
In 2016, Cao's group further described a practical and benign strategy for the efficient synthesis of fluorovinyl pyrazolyl ethers and thioethers *via* the coupling reaction between aryl substituted *gem*-difluoroalkenes and pyrazolin-5-ones or pyrazolin-5-thiones in the presence of an alkoxy base (Scheme 518).[811]

Successfully, the group of Du and He disclosed the *N*-heterocyclic carbene-catalyzed stereoselective synthesis of alkenyl C−S bond formation reaction. Under a catalytic amount of the stable carbene, a variety of thiols participated in this base-free nucleophilic substitution reaction with *gem*-difluoroalkenes to afford the corresponding α-fluorovinyl thioethers in up to 99% yield with excellent *Z*-selectivity (Scheme 519).[812]

Scheme 518. Efficient Synthesis of Fluorovinyl Pyrazolyl(thio)ethers from *gem*-Difluoroalkenes with Pyrazolin-5-ones(thiones)

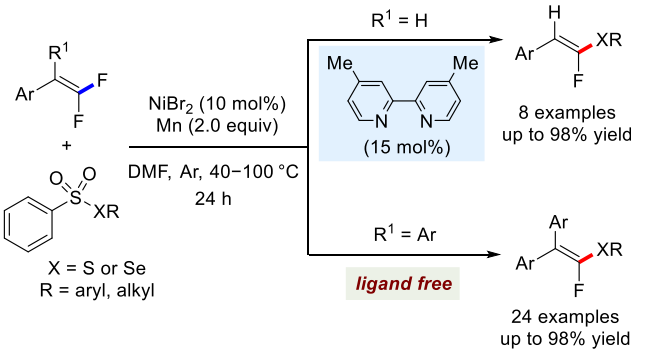


Scheme 519. NHC-Catalyzed Stereoselective Synthesis of α-Fluorovinyl Thioethers



Moreover, Ji and co-workers elaborated a defluorinative reductive cross-coupling reaction between *gem*-difluoroolefins and thiosulfonates/selenosulfonates under nickel catalysis, enabling the synthesis of thiolated or selenylated monofluoroalkenes through the regioselective cleavage of the vinylic C−F bond. Of note, this protocol features highly accessible substrates, benign reaction conditions, and excellent *E*-selectivity (Scheme 520).[813]

Scheme 520. Ni-Catalyzed Defluorinative Reductive Cross-Coupling Reaction of *gem*-Difluoroalkenes and Thiosulfonate/Selenosulfonate



An efficient approach for the preparation of diverse synthetically valuable α-fluoro-β-arylalkenyl sulfones from *gem*-difluoroalkenes and sodium sulfinates in the absence of any transition metal or base has been reported by Shi's group (Scheme 521).[814] The protocol demonstrated a wide functional group tolerance with excellent stereoselectivity. Remarkably, this strategy can also be used for late-stage transformation of value-added complex compounds such as drugs and natural products.

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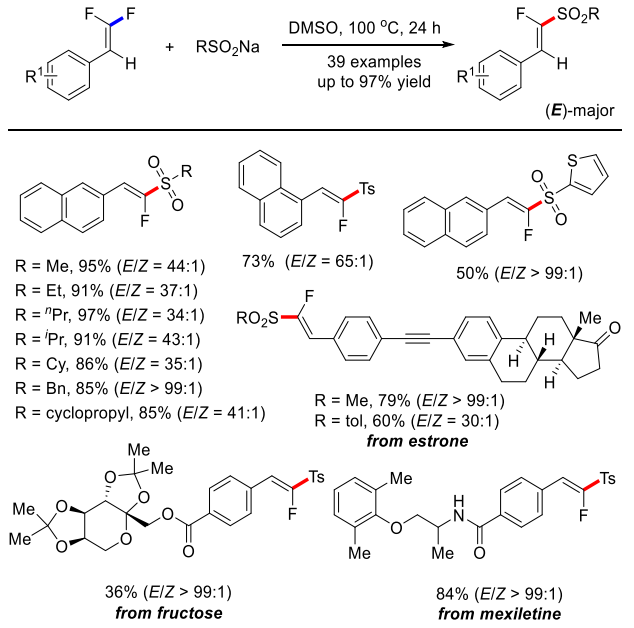
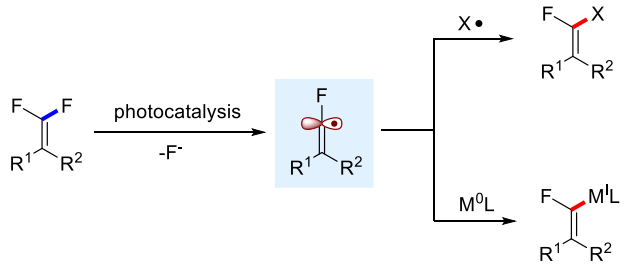
Scheme 521. Direct Synthesis of α-Fluoro-β-arylalkenyl Sulfones from *gem*-Difluoroalkenes with Sodium Sulfinates



7.4. Photoredox Catalysis

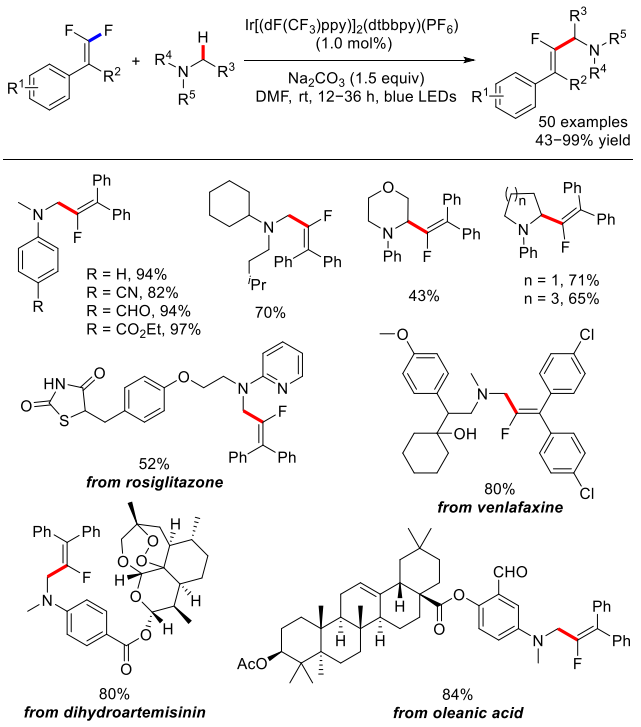
Along with the ever-increasing efforts in photoredox chemistry over the past decade, a large number of novel and straightforward strategies have emerged which greatly enriched the alkenyl C−F bond functionalizations of *gem*-difluoroalkenes under visible-light-induced catalysis or visible-light redox/transition-metal synergistic catalysis to incorporate various fluorine-containing moieties into organic molecules.[815] Under photoredox conditions, *gem*-difluoroalkenes can be easily irradiated to undergo C−F bond cleavage, thus generating a monofluoroalkenyl radical through a SET process. The reaction can be quenched by another radical to furnish the coupling products. This radical can be formed by the oxidized photoredox catalyst or by a transition metal-based cocatalyst. Alternatively, the metalated complex can be readily transformed into many synthetically appealing moieties by further coupling with other organic electrophiles (Scheme 522).

Scheme 522. Visible-Light-Promoted C−F Bond Activation of *gem*-Difluoroalkenes



In 2016, Hashmi's group first initiated the C−F bond functionalization of *gem*-difluoroalkenes by photoredox catalysis (Scheme 523).[816] They elaborately realized an unprecedented radical−radical cross-coupling between α-aminoalkyl radicals and monofluoroalkenyl radicals generated from *gem*-difluoroalkenes, producing a large variety of tetrasubstituted monofluoroalkenes in good yields. The elegant

Scheme 523. Visible-Light-Promoted Defluorinative C(sp³)−H Monofluoroalkenylation of Tertiary Amines with *gem*-Difluoroalkenes



late-stage diversification of top-selling drugs (rosiglitazone, citalopram, and venlafaxine, *etc.*) and bioactive natural products (oleanic acid, androsterone, and dihydroartemisinin) significantly illustrated the synthetic potential of this radical-involved strategy. More recently, a similar stereoselective C−F bond functionalization of *gem*-difluoroalkenes was also achieved by Li's group through a chelation-assisted, nickel- and photoredox-catalyzed strategy.[817]

Similarly, Zhou and co-workers presented the direct synthesis of fluorinated tetrahydropyridines and bridged azabicyclo[3.m.1] frameworks which are less accessible by other methods *via* an unprecedented photocatalytic dehydrogenative/defluorinative cross-coupling approach from both acyclic and cyclic tertiary amines with α-trifluoromethyl alkenes, followed by an intramolecular defluorinative C−H functionalization (Scheme 524a).[818] Subsequently, the same group further accomplished the construction of biologically important fluorinated benzo[*a*]quinolizidines and dihydrobenzoxepines from dihydroisoquinoline acetic acids (Scheme 524b)[819] and *o*-hydroxyphenylacetic acids (Scheme 524c)[820] through a radical-based decarboxylative/defluorinative cross-coupling under visible light photocatalysis. It must be noted that the combination of bifunctional nucleophiles with α-trifluoromethyl alkenes involving the consecutive two C−F bond cleavage strategy was successively reported by the groups of Ichikawa[821−823] and Zhang[824,825] under base- or transition-metal-mediated conditions.

Loh and co-workers in 2018 established a practical photoredox-catalyzed defluorinative trifluoromethylation of α-trifluoromethyl alkenes and *gem*-difluoroalkenes (Scheme 525).[826] The reactions progressed effectively through the addition of air-stable Langlois' reagent as the trifluoromethyl radical source, followed by a β-fluoride elimination to give the

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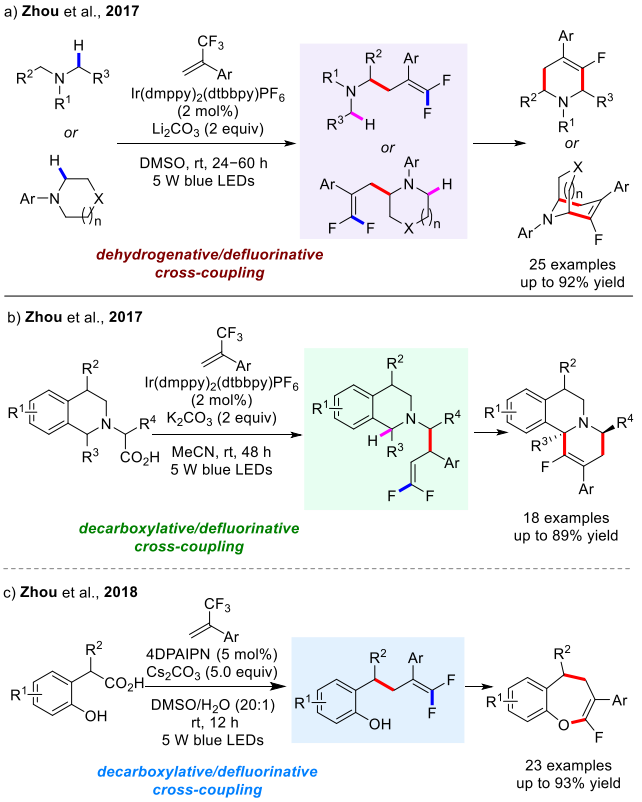
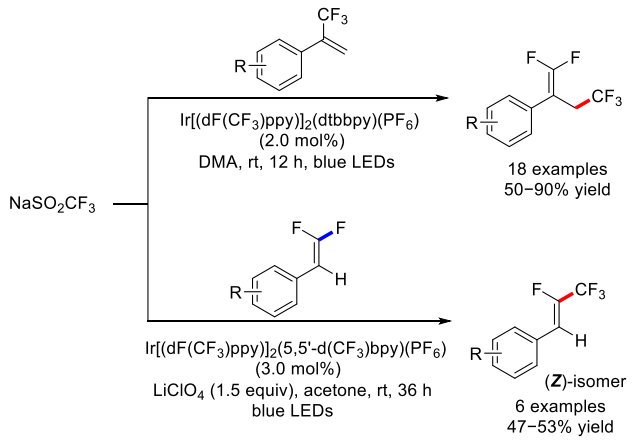
Scheme 524. Visible Light-Mediated Double C−F Bond Activation of α-Trifluoromethyl Alkenes



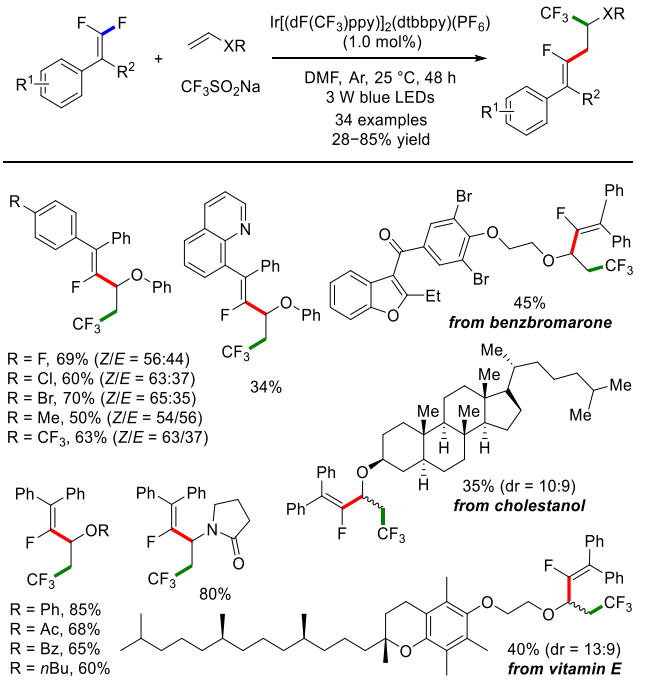
Scheme 525. Photoredox-Catalyzed Defluorinative Trifluoromethylation of α-Trifluoromethyl Alkenes and *gem*-Difluoroalkenes



corresponding multifluorinated olefins in modest yields with excellent stereoselectivity.

The visible-light-promoted vicinal trifluoromethylation and monofluoroalkenylation of alkenes through a radical−radical cross-coupling process has been developed by Wang and collaborators. This redox-neutral protocol employed *gem*-difluoroalkenes and Langlois' reagent as the radical sources, enabling a mild and step-economical route to incorporate two privileged fluorinated moieties into simple alkenes in one step. The utility of this strategy is highlighted by late-stage diversification of pharmaceutically relevant compounds (Scheme 526).[827]

Scheme 526. Visible-Light-Induced Defluorinative Trifluoromethylation and Monofluoroalkenylation of Simple Alkenes



Visible light can also be used to carry out photocatalytic decarboxylation of *N*-protected α-amino acids with *gem*-difluoroalkenes at room temperature, producing a diverse array of α-amino monofluoroalkenes which should find widespread applications in pharmacology and material chemistry (Scheme 527).[828] In this case, this reaction begins when the photocatalyst Ir(III) is irradiated to produce an excited *Ir(III). As this is a strong oxidizing agent, the excited *Ir(III) readily removes an electron from the deprotonated *N*-Boc proline, followed by decarboxylation to generate a transient α-aminoalkyl radical **I** accompanied by the formation of Ir(II). Ir(II) then causes *gem*-difluoroalkene to undergo reduction and form a radical anion, which subsequently undergoes decomposition by losing F^- to produce a monofluoroalkenyl radical **II** while regenerating the Ir(III) photocatalyst *via* SET. Finally, radicals **II** and **I** undergo cross-coupling with each other to form the decarboxylative monofluoroalkenylation product.

Inspired by this work, An and Li *et al.* reported a general and practical monofluoroalkenylation of unactivated carboxylic acids through an efficient photoredox catalytic decarboxylation in the presence of 2,4,5,6-tetra(9*H*-carbazol-9-yl) isophthalonitrile (4CzIPN) as the organic photocatalyst (Scheme 528).[829] This strategy circumvents the exploitation of presynthesized redox-active esters and high-powered light sources, allowing a benign method for the straightforward decarboxylative cross-coupling of unactivated carboxylic acids. In addition, this strategy caters for the exceptional and gruelling late-stage monofluoroalkenylation of complex molecules such as bioactive ramipril, gemfibrozil, dehydroabietic acid, enoxolone, as well as the sugar-derivative cyclic α-oxy acid.

In the same year, Feng's group reported the efficient C−F bond carboxylation of *gem*-difluoroalkenes through photoredox/palladium dual catalysis (Scheme 529).[830] In this metallaphotoredox C−F activation reactions, electronically

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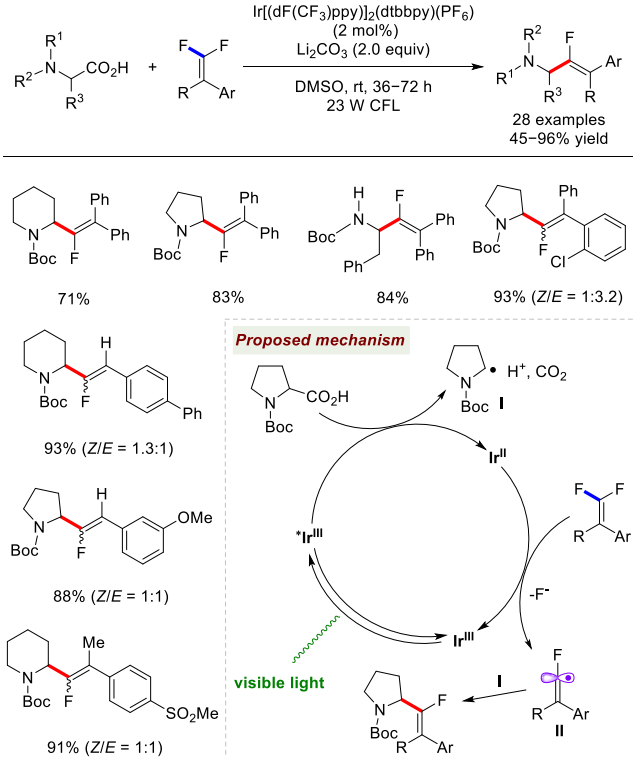
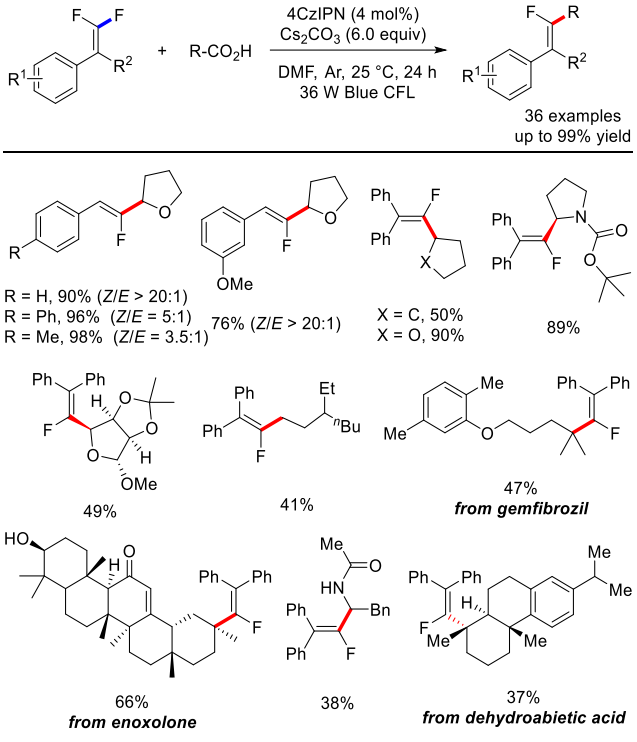
Scheme 527. Photocatalytic Decarboxylation of *N*-Protected *α*-Amino Acids with *gem*-Difluoroalkenes

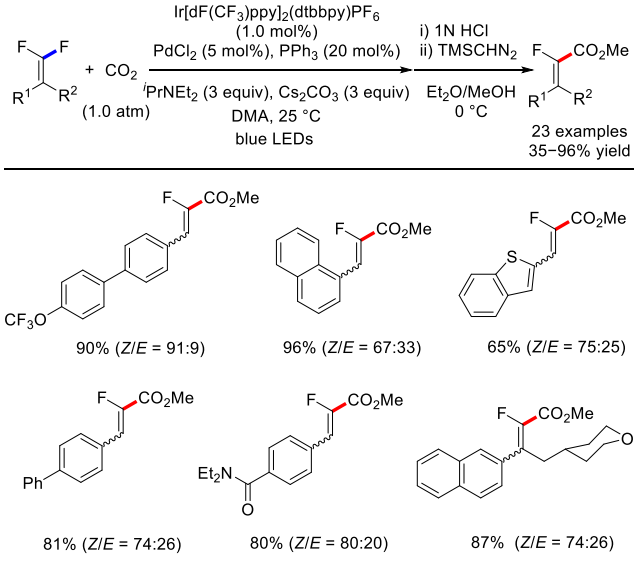


Scheme 528. Photoredox Catalytic Decarboxylative Monofluoroalkenylation of *gem*-Difluoroalkenes with Carboxylic Acids



diverse substituted *gem*-difluoroalkenes can efficiently undergo C−F carboxylation with an inert CO_2 electrophile to form a large variety of value-added *α*-fluoroacrylic acids, which then undergoes further esterification to produce the respective methyl esters.

Scheme 529. Selective Defluorinative Carboxylation of *gem*-Difluoroalkenes by Photoredox/Palladium Dual Catalysis



Defluorinative monofluoroalkenylation can also be achieved *via* cooperative photoredox and hydrogen-atom-transfer (HAT) catalysis (Scheme 530).[831] This reaction allows the cross-coupling of diverse amines, ethers, and thioethers to regioselectively form monofluoroalkenes with different *α*-heteroatom substituents. Mechanistically, the photocatalyst is initially irradiated with a blue LED to produce the excited redox active Ir(III)*, which then oxidizes quinuclidine to form the Ir(II) complex and the radical cation **I**. The Ir(II) catalyst then provides one electron to the *gem*-difluoroalkene, then loses F^- to produce the radical **II** and regenerate the photocatalyst. At the same time, the oxidized quinuclidine radical cation **I** undergoes HAT with amine to form the *α*-aminoalkyl radical **III**. Finally, the two radicals **II** and **III** heterodimerize to form the defluorinative monofluoroalkenylation product. By the synergetic merger of photoredox and bromine-based hydrogen atom transfer catalysis, quite recently, Deng and colleagues achieved a similar transformation under batch and continuous-flow conditions with a broad range of C−H patterns, including ethers, amides, and aliphatic aldehydes.[832]

The group of Sun and Zhou presented the C−F bond alkylation of *gem*-difluoroalkenes under visible-light-promoted conditions with readily prepared 4-alkyl-1,4-dihydropyridines (DHPs, also known as Hantzsch esters) as the alkyl radical precursors (Scheme 531).[833] A broad range of primary, secondary, and even tertiary 4-alkyl substituted DHPs were all compatible with this photoredox strategy to afford alkyl substituted monofluoroalkenes in 26−95% yield.

Quite recently, Wang *et al.* elaborated a practical strategy for the defluorinative monofluoroalkenylation of alkyl bromides through a silyl radical-mediated halogen abstraction process under visible-light photoredox catalysis (Scheme 532).[834] Mechanistic studies suggested that the products were selectively formed through the coupling of aliphatic radicals and fluoroalkenyl radicals. Halogen abstraction promoted by the presence of silyl radicals allowed the strategy to be applied for the monofluoroalkenylation of a wide diversity of alkyl and

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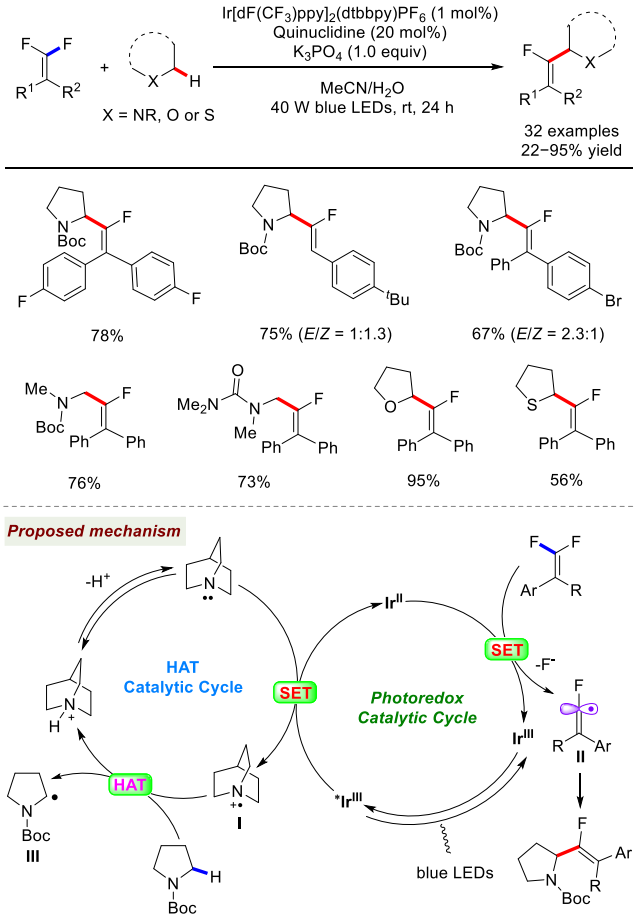
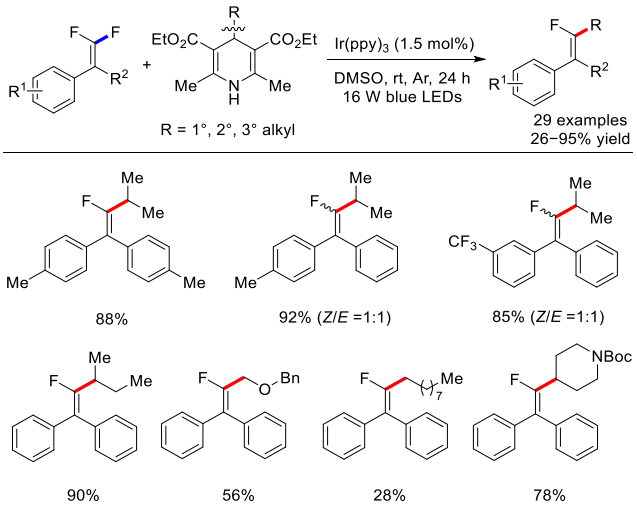
Scheme 530. Defluorinative Monofluoroalkenylation *via* Cooperative Visible-Light Photoredox and Hydrogen-Atom-Transfer (HAT) Catalysis



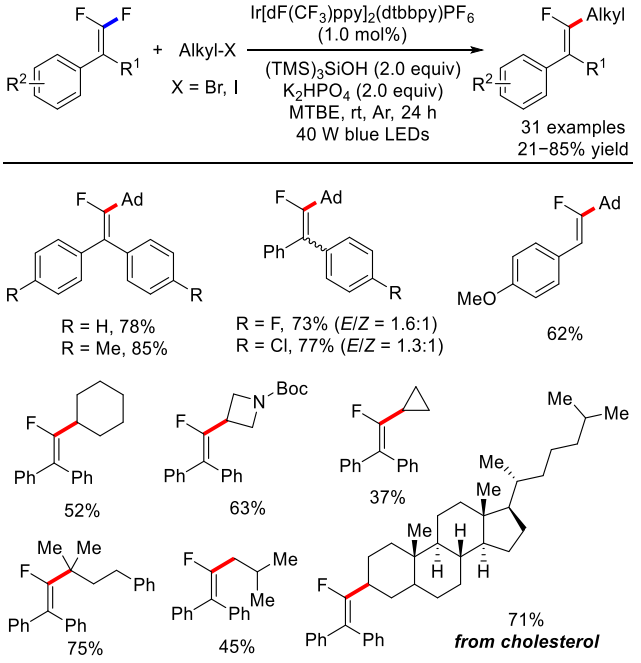
Scheme 531. Visible-Light-Promoted Defluorinative Alkylation of *gem*-Difluoroalkenes with DHPs



heteroaryl halides. Of note, the ability to scale up the reaction and be used for cholesterol demonstrated its applicability for late-stage monofluoroalkenylation reactions.

A more recent report by Crudden *et al.* demonstrated that redox-active alkylsulfones could also be employed as feasible coupling partners in the photocatalytic desulfonylative

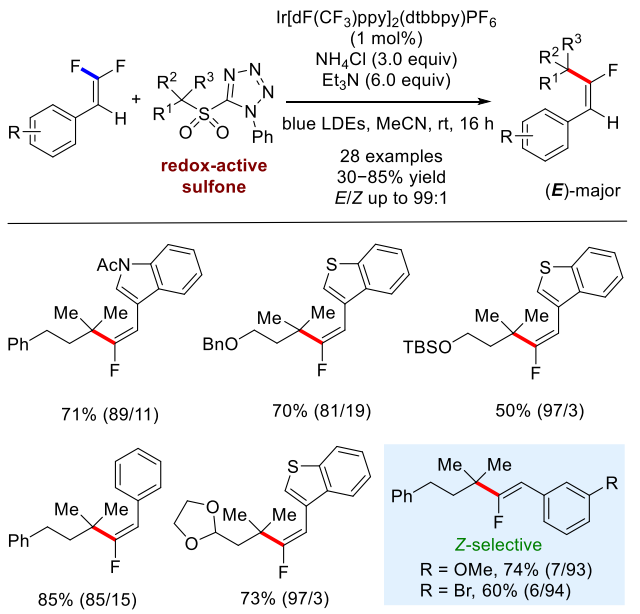
Scheme 532. Silyl Radical-Mediated Dehalogenative Coupling of *gem*-Difluoroalkenes with Alkyl Halides



alkylation of *gem*-difluoroalkenes, allowing an efficient access to diverse (*E*)-fluoroalkenes bearing quaternary centers in decent yields (30–85%). Both the Ir catalyst and NEt_3 were essential to generate the products. Of note, this protocol was applicable to a broad range of *gem*-difluoroalkenes with different substitution patterns. Cyclic tertiary sulfones were also compatible in this case, albeit with a decreased efficiency. However, desulfonylative coupling reactions with electron-neutral or electron-rich *gem*-difluorostyrenes preferentially afforded the *Z*-isomers (Scheme 533).[835]

Apart from the above-mentioned C–C bond formation reactions, visible-light-mediated defluorinative cross-coupling

Scheme 533. Visible-Light-Promoted Defluorinative Coupling of Alkylsulfones with *gem*-Difluoroalkenes



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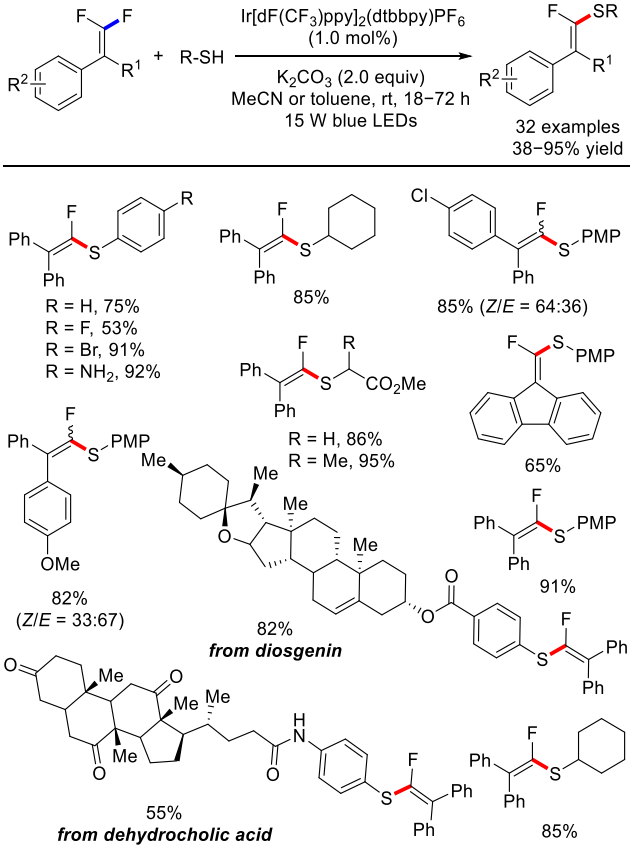
reactions of *gem*-difluoroalkenes to forge various C−X bonds were also extensively investigated in recent years. Specifically, the group of Yang and Xia in 2019 explored a visible-light-induced monofluoroalkenylation *via* the defluorination of *gem*-difluoroalkenes, followed by the cross-coupling with a series of aryl, benzyl, and alkyl thiols (Scheme 534).[836] This protocol

Scheme 534. Visible-Light-Mediated Defluorinative Cross-Coupling of *gem*-Difluoroalkenes with Thiols

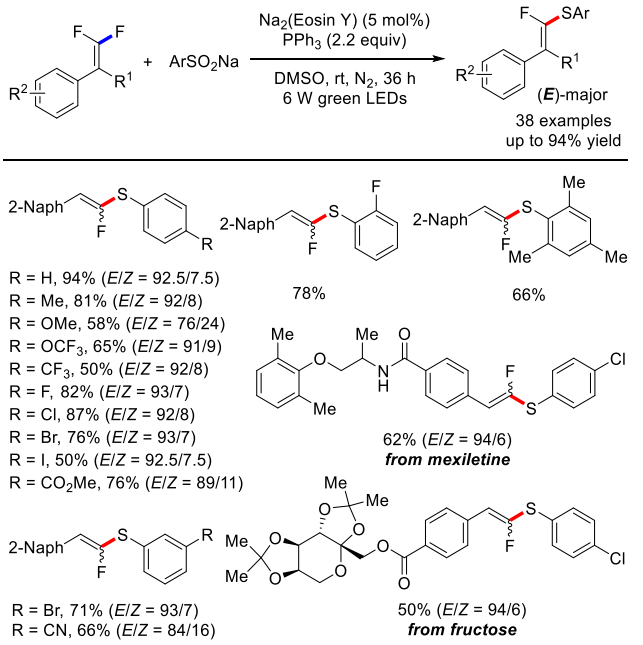


presents as a practical way to construct multisubstituted fluorinated vinylsulfides under benign conditions with good tolerance of functional groups. As a particular highlight, the potential of this strategy was showcased by late-stage modification of dehydrocholic acid and diosgenin derivatives.

An efficient regioselective synthesis of diverse α-fluoro-β-arylalkenyl sulfides with *gem*-difluoroalkenes and sodium sulfinates as starting materials was realized by Shi and co-workers under green LED irradiation conditions (Scheme 535).[837] In this work, the authors employed Na_2(eosin Y) as a photosensitizer in conjunction with PPh_3 as a reductant to undergo a phosphine-associated deoxygenative functionalization of S−O bonds. Control experiments were carried out to ascertain the thiol radicals and anions as key intermediates in the proposed mechanism. Remarkably, regioselective isomerization of the C=C bond (from *Z* to *E*) was observed using green light without the presence of a photoinitiator.

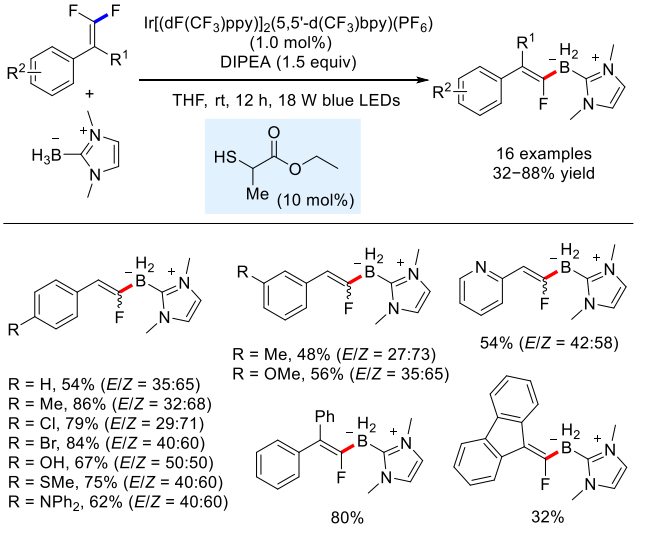
Fluorinated organoboron compounds are synthetically usefully building blocks in organic chemistry. In 2020, Wu's group successfully developed a photocatalyzed defluoroborylation *via* a straightforward B−H activation of an *N*-heterocyclic carbine (NHC) borane with *gem*-difluoroalkenes, affording a series of monofluoroalkenylboranes in 32−88%

Scheme 535. Highly *E*-Selective Synthesis of α-Fluoro-β-arylalkenyl Sulfides *via* Visible-Light-Induced Deoxygenation/Isomerization



yield with moderate *Z*-selectivity (Scheme 536).[838] This strategy is highly atom-economic and regioselective, simple

Scheme 536. Photocatalyzed Defluoroborylation B−H Activation of an *N*-Heterocyclic Carbine (NHC) Borane



to operate, and remarkably allows for the defluoroborylation of a wide substrate scope of multifluorinated compounds such as polyfluoroarenes, *gem*-difluoroalkenes, and trifluoromethylalkenes.

7.5. Annulation Reactions

With respect to the synthesis of heterocycles, *gem*-difluoroalkenes can also be used as starting materials together with transition-metal catalysts. In such instances, one or more F atoms usually undergo substitution to form new C−C or C−heteroatom bonds. Specifically, Ichikawa and collaborators in 2005 expanded their base-promoted nucleophilic 5-*endo*-*trig*

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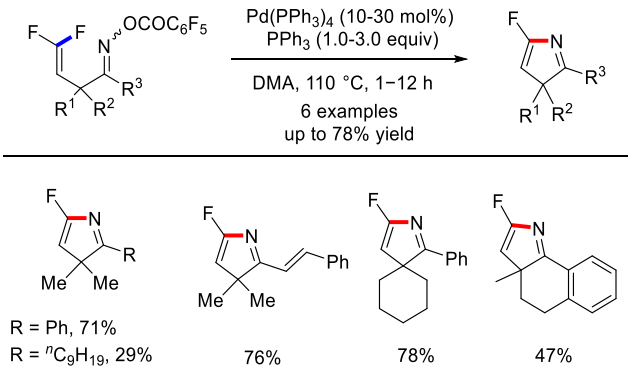
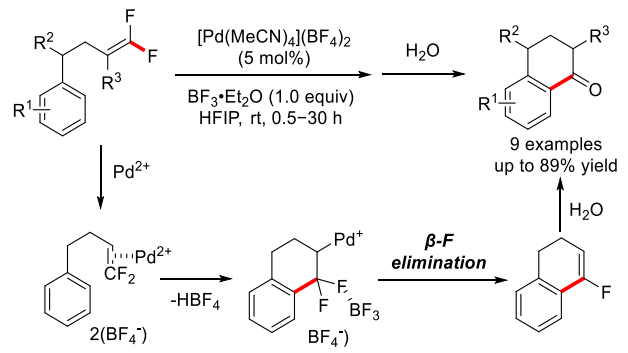
cyclization strategy of 1,1-difluoro-1-alkenes with an *N,O* or a *C*-nucleophile to assemble diverse fluorinated heterocycles[839−842] and reported an intramolecular Pd-catalyzed Heck-type 5-*endo-trig* cyclization reaction of 3,3-difluoroallylketone *O*-pentafluorobenzoyloximes *via* aminopalladium species, affording an efficient access to 5-fluoro-3*H*-pyrroles. This protocol can also be applied to the construction of fused tricyclic system, albeit in a moderate yield (Scheme 537).[843]

Scheme 537. Synthesis of 5-Fluoro-3*H*-pyrroles *via* Intramolecular Heck-Type 5-*endo-trig* Cyclization



Later, the same group further discovered a cationic palladium-promoted Friedel−Crafts-type cyclization of 1,1-difluoro-1-alkenes with cationic $[Pd(MeCN)_4](BF_4)_2$ as a catalyst (Scheme 538).[844] Through the formation of metal−

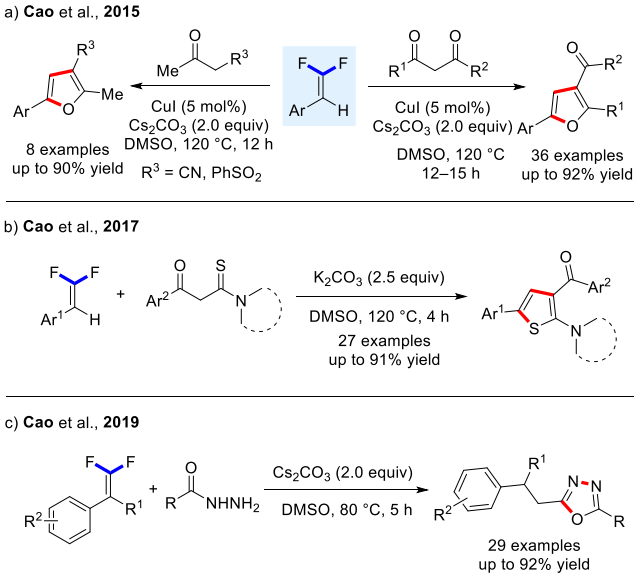
Scheme 538. Palladium(II)-Catalyzed Friedel−Crafts Cyclization of 4,4-(Difluorohomoallyl) arenes



alkene complexes, the electrophilic activation of electron-deficient alkene by the cationic palladium(II) catalyst enables the intermediary α,α-difluoroalkyl palladium species to be readily generated *via* a Friedel−Crafts-type cyclization. In the presence of BF_3•Et_2O, subsequent β-fluorine elimination was greatly accelerated to form 4-fluoro-1,2-dihydrophenanthrenes, which finally underwent hydrolysis to afford the corresponding cyclic ketones.

Cao's group expanded their C−F bond functionalization strategy and illustrated the divergent synthesis of a broad range of heterocycles. For example, they reported in 2015 an unprecedent Cu(I)-catalyzed domino reaction for the construction of multisubstituted furans through the cyclization of *gem*-difluoroalkenes with a series of activated methylene carbonyls such as 1,3-dicarbonyl compounds, acetoacetonitrile, and phenylsulfonylacetone (Scheme 539a).[845] Subsequently, the further established a practical strategy for the rapid

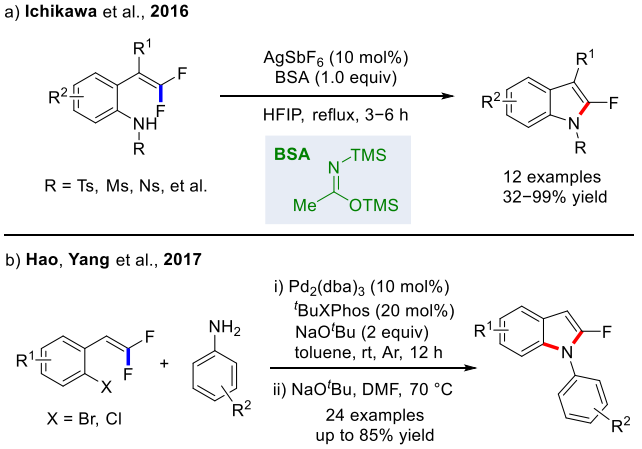
Scheme 539. Divergent Synthesis of Structurally Diverse Heterocycles from *gem*-Difluoroalkenes



synthesis of highly functionalized aminothiophenes through the cyclization reaction of *gem*-difluoroalkenes with a diverse array of β-keto tertiary thioamides (Scheme 539b).[846] The reaction took place smoothly in the presence of K_2CO_3 without the need for transition-metal catalysts, giving synthetically valuable *N,N*-disubstituted 2-aminothiophenes in 51−91% yield. The same group also discovered that the reaction of *gem*-difluoroalkenes with acyl hydrazides in DMSO under heating afforded a variety of 1,3,4-oxadiazoles in modest to excellent yields (Scheme 539c).[847]

An intramolecular electrophilic 5-*endo-trig* cyclization of β,β-difluoro-*o*-sulfonamidostyrenes to the direct synthesis of 2-fluoroindoles *via* β-F elimination was reported by Ichikawa's group using $AgSbF_6$ as the catalyst and *N,O*-bis(trimethylsilyl)-acetamide (BSA) as a fluoride captor (Scheme 540a).[848] In a subsequent report, Hao and Yang demonstrated that primary arylamines can couple efficiently with 1-halo-2-(2,2-difluorovinyl)benzene to produce a range of fluorine-containing indole derivatives (Scheme 540b).[849] First, Buchwald−Hartwig cross-coupling occurred in the presence

Scheme 540. Synthesis of 2-Fluoroindoles from *gem*-Difluoroalkenes *via* Alkenyl C−F Bond Activation



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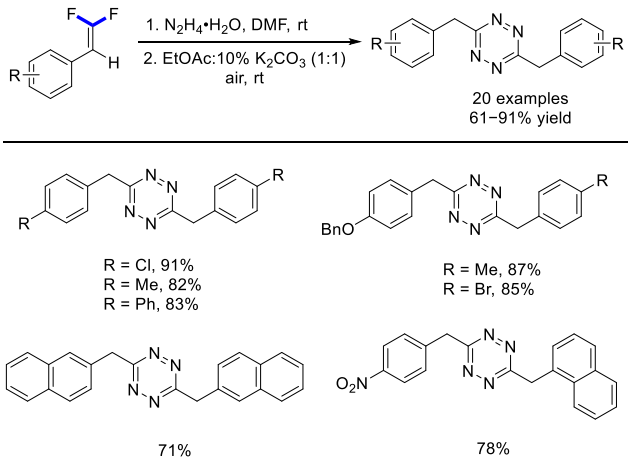
of Pd catalyst to generate 2-amino-(2,2-difluorovinyl)benzene. Then, base-promoted 5-*endo*-trig intramolecular nucleophilic attack by *N* on *gem*-difluoroalkene occurs, followed by *β*-fluoride elimination to afford a wide variety of 2-fluoroindoles.

The 1,2,4,5-tetrazine heterocyclic ring is one of the most versatile aromatic heterocycles, and its rapid synthesis is of particular interest arcoss both organic and inorganic community.[850] In 2017, Hu's group reported a practical strategy for the straightforward construction of synthetically appealing aromatic tetrazines from the corresponding *gem*-difluoroalkenes, a large variety of both symmetrical and asymmetrical 3,6-disubstituted 1,2,4,5-tetrazines can be readily prepared in 61−91% yield under ambient conditions (Scheme 541).[851]

Scheme 541. Synthesis of 1,2,4,5-Tetrazines from *gem*-Difluoroalkenes

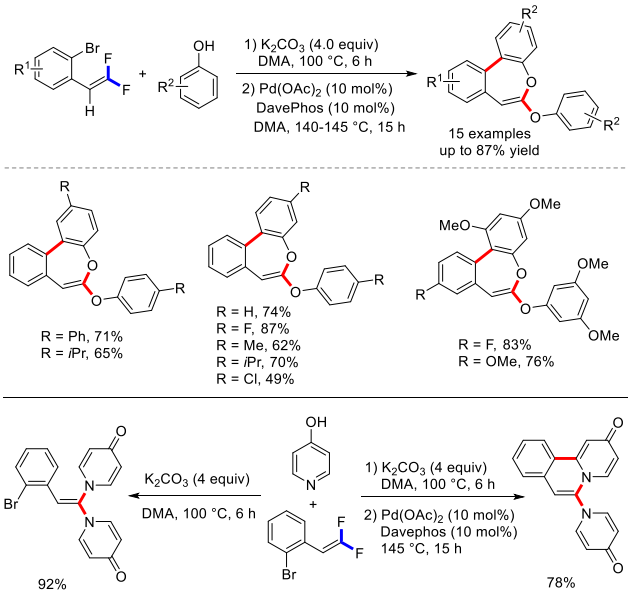


Langer's group in 2018 disclosed a base-promoted synthesis of dibenzo[*b*,*d*]oxepines *via* a vinylic C−F activation of 1-bromo-2-(2,2-difluorovinyl)benzenes with structurally diverse phenols, followed by a Pd(II)-catalyzed intramolecular C−H arylation, thereby giving rise to a crucial class of pharmaceutically relevant oxepine derivatives in modest to excellent yields (Scheme 542).[852] Apart from reactions with phenols, 4-hydroxypyridine was also a competent nucleophile to participate in such transformations. Reacting 4-hydroxypyridine with 1-bromo-2-(2,2-difluorovinyl)benzene in the presence of K_2CO_3 and $Pd(OAc)_2$ catalyst resulted in the formation of a cyclic product with *N*-vinylic-4-pyridone as a likely key intermediate.

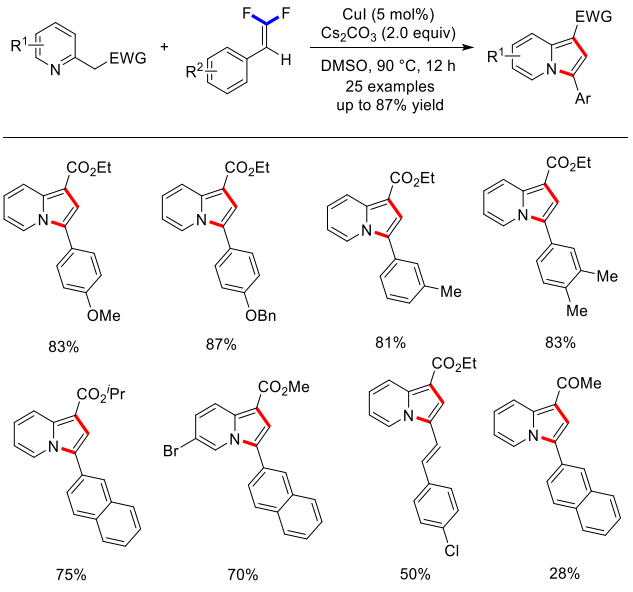
In 2020, Lu's group was able to prepare substituted indolizines *via* a Cu(I)-catalyzed cyclization reaction between 2-(pyridin-2-yl)acetates and *gem*-difluoroalkenes (Scheme 543).[853] This strategy exploited the cleavage and further functionalization of vinylic C−F bonds, thereafter allowing an effective approach to synthesize a series of indolizine derivatives in up to 87% yield along with excellent functional group tolerance.

By taking advantage of 2,2-difluorovinyl tosylate as the fluorinated synthon, the group of Wu and Wang in 2004 elaborated the direct synthesis of 2-fluoroindolizines from *in situ* generated *N*-ylides of pyridiniums (Scheme 544a).[854] Inspired by this precedential work, Ren's group recently illustrated a base-promoted oxidative annulation reaction of *gem*-difluoroalkenes and pyridinium ylides with ambient air as

Scheme 542. Base-Promoted One-Pot Synthesis of Dibenzo[*b*,*d*]oxepines



Scheme 543. Cu(I)-Catalyzed Cyclization of 2-(Pyridin-2-yl)acetates and *gem*-Difluoroalkenes



the sole oxidant under benign conditions (Scheme 544b).[855] The protocol underwent a formal [3 + 2] annulation process of the generated pyridinium ylide with *gem*-difluoroalkenes followed by facile *β*-F elimination to afford a series of multisubstituted 2-fluoroindolizines in good yields. Almost simultaneously, Peng's group also presented an analogous cycloaddition procedure by means of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) as the base (Scheme 544c).[856]

More recently, the group of Li and Wang disclosed an effieient one-pot procedure for the rapid preparation of fluorinated polyfused heterocycles such as benzofuro[3,2-*b*]pyridines, 5*H*-indeno-[1,2-*b*]pyridines, and 5,6-dihydrobenzo[*h*]quinolines *via* the TfOH-promoted domino cyclization of azadienes with readily available difluoroenoxysilanes (Scheme 545).[857] This formal [4 + 2] cyclization strategy undergoes 1,4-difluoroalkylation, desulfonylation,

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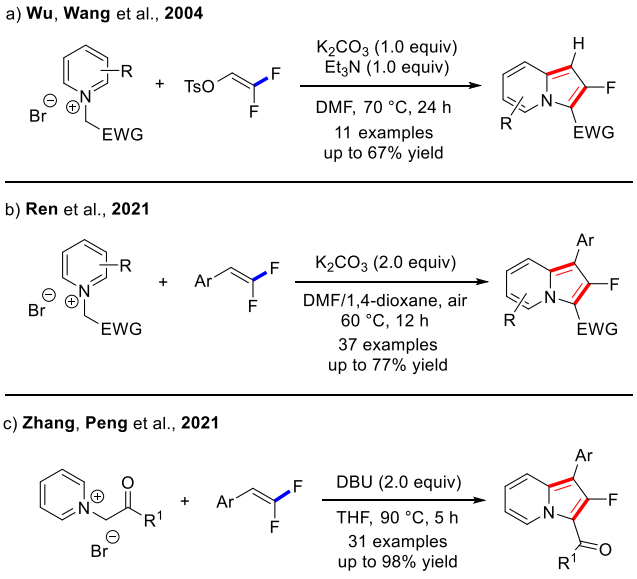
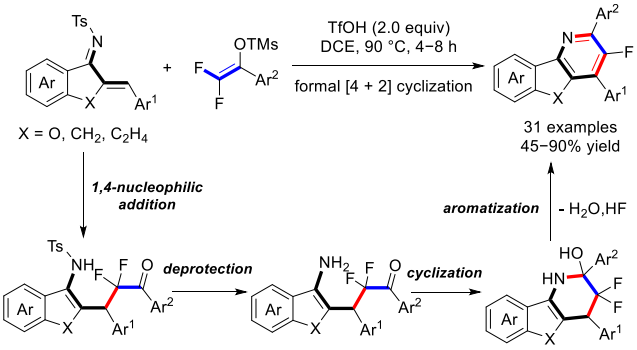
Scheme 544. Synthesis of 2-Fluoroindolizines through Oxidative [3 + 2] Annulation of Pyridinium Salts and *gem*-Difluoroalkenes



Scheme 545. Cu(I)-Catalyzed Cyclization of 2-(Pyridin-2-yl)acetates and *gem*-Difluoroalkenes

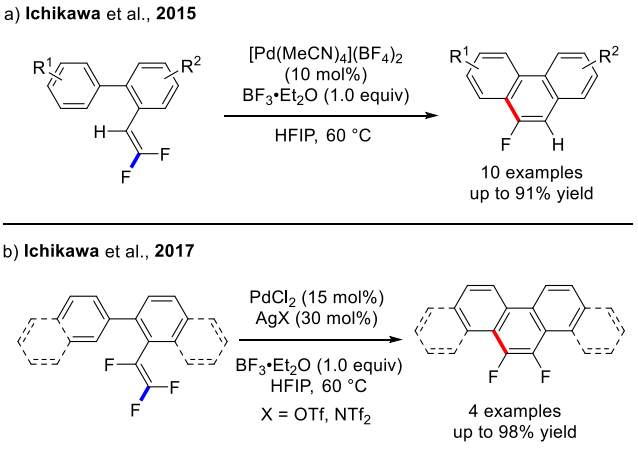


intramolecular cyclization, and dehydrated and dehydrofluorinated aromatization sequences.

Phenacenes are an important and versatile subclass of polycyclic aromatic hydrocarbons (PAHs) which can serve as organic semiconducting materials.[858] In the presence of a cationic Pd(II) catalyst, *gem*-difluoroalkenes such 1,1-difluoro-1-alkenes[859,860] or 1,1,2-trifluoro-1-alkenes[861] can undergo electrophilic Friedel−Crafts-type cyclizations to synthesize a broad array of highly appealing pinpoint-fluorinated phenanthrenes (Scheme 546a) or phenacenes (Scheme 546b). Mechanistically, the Pd catalyst first coordinated to the trifluoroalkene to form a π-complex. Electrophilic Friedel−Crafts-type carbopalladation and rearomatization occurred to produce a cyclic Pd(II)-alkyl intermediate, which then experienced β-F elimination assisted by BF_3•Et_2O to afford the fluorinated phenacenes and regenerate the active cationic Pd(II) catalyst.

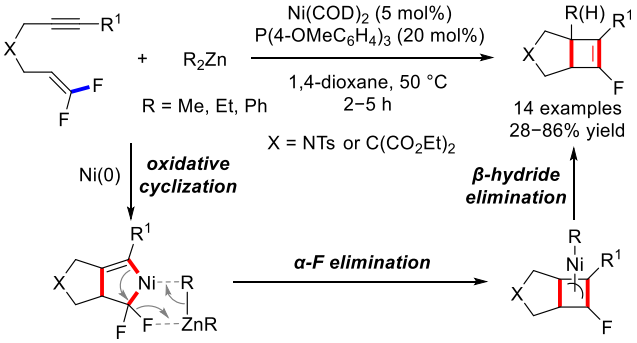
In contrast to the above-mentioned β-F elimination process, Chatani and colleagues in 2010 reported the elegant work of nickel-catalyzed cyclization of 1,1-difluoro-1,6-enynes with organozinc reagents involving α-F elimination.[862,863] Mechanistically, the process is initiated by an oxidative cyclization of both alkene and alkyne moieties with the Ni^0 complex,

Scheme 546. Synthesis of Fluorinated Polycyclic Aromatic Hydrocarbons *via* Palladium-Catalyzed Electrophilic Friedel−Crafts-Type Cyclization



resulting in the formation of intermediary α,α-difluoronickelacyclopentenes. The authors claimed that the organozinc reagent serves as a bifunctional activator, a Lewis base with respect to Ni^{II} and a Lewis acid with respect to the C−F bond, which greatly facilitated subsequent α-F elimination to generate the bicyclo[3.2.0]heptene derivatives (Scheme 547).[864]

Scheme 547. Nickel-Catalyzed Cyclization of 1,1-Difluoro-1,6-enynes with Organozinc Reagents



Inspired by this work, Ichikawa's group in 2015 realized an unprecedented nickel-catalyzed [2 + 2 + 2] cyclization of 1,1-difluoroethylene with alkynes to directly assemble a series of tetrasubstituted fluoroarenes by sequential α-F elimination of α,α-difluorinated nickelacycloheptadiene species, generated by the oxidative cyclization of 1,1-difluoroethylene and alkynes with nickel(0) and subsequent β-H elimination of the intermediary cyclohexadienylnickel(II) fluoride (Scheme 548a).[865] Afterward, the group of Ogoshi and Ohashi elaborately explored the nickel(0)-mediated defluorinative coupling of tetrafluoroethylene (TFE) with styrenes. In the presence of $Ni(cod)_2$ and PCy_3, exposure of styrene to TFE resulted in the formation a well-defined nickelacycle possessing a unique η^3-π-benzyl structure in 89% isolated yield (Scheme 548b).[866] Treating this nickelacycle with BF_3•Et_2O at room temperature smoothly generated 1,2-difluoro-3-phenyl cyclobutene in 60% yield through sequential both α- and β-F eliminations.

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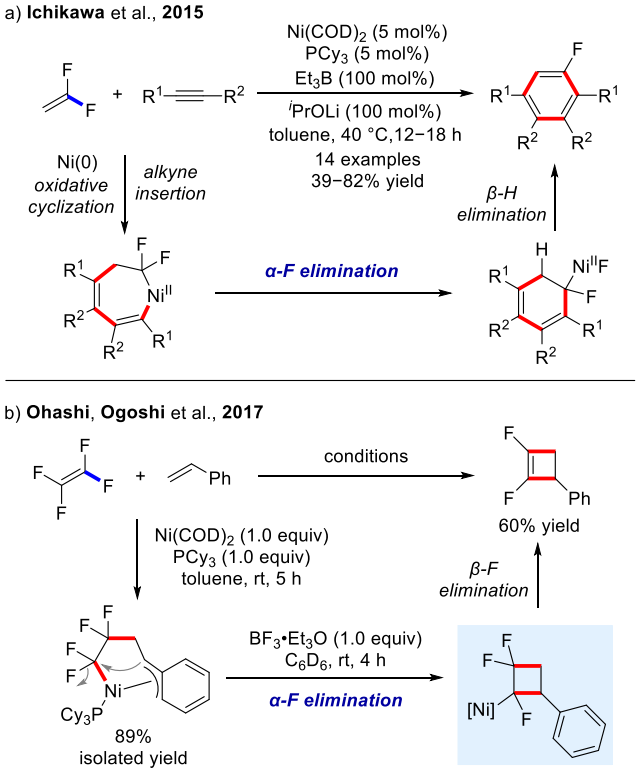
Scheme 548. Defluorinative Cyclization Reaction of Fluoroolefins through α-Fluorine Elimination



8. CONCLUSIONS AND OUTLOOK

In this comprehensive review, we summarized the latest developments in alkenyl sp^2 C−H and C−F bond functionalization reactions. The development of practical and broadly applicable methods for alkenyl sp^2 C−H bond functionalization has attracted tremendous attention because they can provide efficient access to synthetically important functionalized alkenes and diene derivatives from easily accessible simple alkenes. Significant advances in developing new catalytic systems that can effectively carry out alkenyl C−H bonds of alkenes and their derivatives have been made in the past decades. Nevertheless, there are still many challenges remain. Outstanding problems that remained to be solved include the development of alkenyl sp^2 C−H and C−F bond functionalization that can work under greener and milder reaction conditions. Unfortunately, many of the reported methods still require the use of expensive transition metals such as palladium and rhodium catalysts. In addition, the catalytic loading of these catalysts remained high, and there were very few reports that used less than 1 mol % of the catalysts. The use of cheaper main group catalysts such as Fe is still rare and not to mention the development of metal-free systems. Metal-free photoredox methods is an attractive approach, and a few reports have emerged in recent years. In many cases, these reactions were carried out in organic solvents under high temperature. Moreover, the development of new and innovative alkenyl sp^2 C−H and C−F bond functionalization that can work under metal-free, biocompatible reaction condition will be an fascinating area to explore in the coming years.

For these reactions to be fully adopted for the synthesis of pharmaceuticals and complex molecules, it is extremely important that the scope and limitations of these methods be well studied. As shown in this review, many types of alkenes and coupling partners have been shown to work effectively. There are only sporadic examples using simple alkenes, alkyl halides/alcohols, or alkanes as coupling partners. Additional work to widen the scope of alkenes and the coupling partners will further help to expand the synthetic utility of these methods for the synthesis of complex molecules.

Another problem in this area of research is the lack of stereochemical studies (regio, *E*/*Z*, enantioselective, *etc.*) in this exciting area. Although the use of various methods such as the use of steric effect, directing groups and 1,*n*-metal shift strategies have been successfully reported, the use of catalyst to control the regio- and *E*/*Z* selectivities is still lacking. More research in the asymmetric areas such as kinetic resolution, enantioselective control, *etc.*, will certainly make this method an extremely attractive strategy for the stereoselective synthesis of alkenes.

Another area that needs to be expanded is the development of new intramolecular versions and annulation methods for the construction of cyclic alkenes. Although sporadic reports on the intramolecular coupling for the synthesis of macrocycles have been reported by Loh and other researchers, extensive work to expand to different macrocycles will greatly expand the scope of this method. Reports on the annulation to construct smaller rings such as 5, 6, *etc.*, are still rare.

In summary, this comprehensive review covers most of the published work in the fertile area of alkenyl sp^2 C−H and C−F bond functionalizations. Due to their high efficiency, atom-economy nature as well as easy accessibility of the starting materials, these methods have emerged rapidly as useful strategies for the construction of pharmaceuticals, functional materials, and bioactive natural products. Meanwhile, they may serve as alternative or complementary strategies to classical cross-coupling reactions, Wittig or olefin metathesis for stereoslective synthesis of highly functionalized alkenes. We anticipate that this review will contribute to inspire broad research interest and stimulate new breakthroughs in the development of innovative and broadly applicable strategies to expand the research of alkenyl sp^2 C−H and C−F bond functionalization reactions.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Jeffrey Goh was born in Singapore in 1992. He earned a Diploma in Chemical Process Technology (Industrial Chemistry) from Singapore Polytechnic in 2012 and subsequently went on to Nanyang Technological University to complete his B.Sc. (Highest Distinction) in Chemistry and Biological Chemistry in 2018. He is currently working on his Ph.D. under the supervision of Prof. Teck-Peng Loh, focusing on the development of water-based C−X bond forming reactions. His research interests include green chemistry, C−H activation, and asymmetric catalysis.

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Teck-Peng Loh is a distinguished university professor of Chemistry at Nanyang Technological University, Singapore. Under the tutelage of Professor E. J. Corey, he obtained his Ph.D. (1994) from Harvard University. He has been awarded outstanding researcher awards from both National University of Singapore and Nanyang Technological University. In 2017, he received the Yoshida Prize (Japan) and the prestigious President's Science Award (individual) Singapore. He has been elected Fellow, Academia of Sciences, Singapore (2018), and Fellow of Academia of Sciences, Malaysia, since 2010. His research work mainly focuses on the development of new synthetic methodology, green chemistry, and synthesis of natural and unnatural products.

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