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REVIEW

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Cite this: *Org. Chem. Front.*, 2020, **7**, 1527

Transition metal-catalyzed coupling of heterocyclic alkenes *via* C–H functionalization: recent trends and applications

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Received 9th March 2020,
Accepted 28th April 2020

DOI: 10.1039/d0qo00279h

rsc.li/frontiers-organic

Heterocyclic alkenes represent an important class of reactive feedstock and valuable synthons for the synthesis of biologically important heterocyclic scaffolds. Although functionalized heterocyclic alkenes and their derivatives can be accessed *via* metal-catalyzed cross-coupling reactions, yet the prefunctionalisation of starting materials makes the process a bit cumbersome. On the other hand, transition-metal-catalyzed C–H functionalization is one of the most persuasive and front-line research areas in modern synthetic organic chemistry for atom/step-economy, viability and high efficacy. This critical review highlights the recent advances in coupling of heterocyclic alkenes by transition-metal-catalyzed reactions with special emphasis on arylation, alkenylation, alkylation, hydroarylation, ring-opening addition and annulation/cyclization *via* the C–H functionalization strategy reported since 2015.

1. Introduction

Heterocyclic alkenes are one of the most privileged structural scaffolds in synthetic, medicinal and materials sciences (Scheme 1).[1,2] Consequently, the functionalization of heterocyclic alkenes is one of the exciting research areas and has

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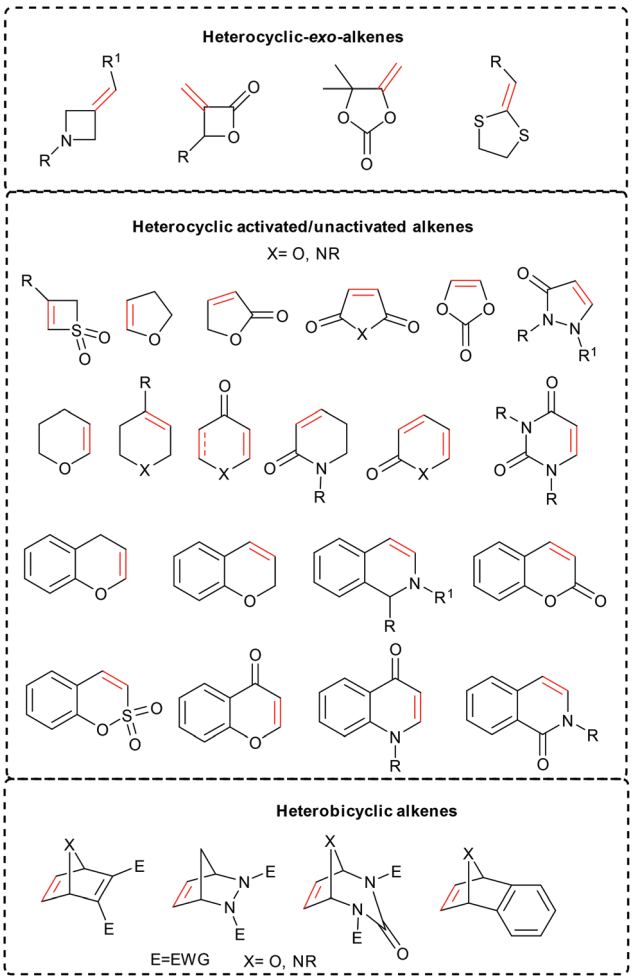
Sonbidya Banerjee

Sonbidya Banerjee was born in West Bengal, India. She received her B.Sc. at West Bengal State University. After obtaining her M.Sc. from Calcutta University, she joined the group of Professor T. Punniyamurthy as a PhD student at the Indian Institute of Technology Guwahati where she studies transition-metal-catalyzed C–H functionalization by chelation assistance.

gained considerable attention. Heterocyclic alkenes such as pyrones, pyridones, coumarins and isoquinolones are important key intermediates, which possess two or more feasible reactive C–H sites, thereby making the selective C–H functionalization very challenging. Similarly, the functionalization of unsymmetrical heterocyclic alkenes is also a formidable task owing to the two possible competitive reactive sites. Maleimides are also useful activated alkenes, which have been largely studied in diverse reactions such as conjugate addition, cycloaddition, cross-coupling and Diels–Alder reactions[3] to give the succinimide architecture that are broadly wielded in natural and bioactive compounds.[4] Heterobicyclic alkenes are another class of valuable strained ring systems that have an innate reactivity and possess a unique template to obtain natural products[5] and complex heterocycles with two or multiple chiral centres, and a variety of reactions including ring-opening, cycloaddition and isomerization have been explored.[6]

Though metal-catalyzed cross-coupling reactions[7] have been one of the most promising synthetic approaches for accessing the functionalized heterocyclic alkenes, their application is inevitably associated with shortcomings such as the requirement of a pre-functionalized substrate precursor.[8] Transition-metal-catalyzed C–H functionalization has thus emerged as a corner-stone research topic in catalysis and has heralded a new synthetic era, with methodologies that afford a crisp route to obtain complex molecules in an atom- and step-economical fashion with broad substrate scope.[9] Among these, the C–H activation reaction involves the cleavage of C–H bonds to form a reactive M–C intermediate that interacts with the coupling partner to afford the functionalized product.



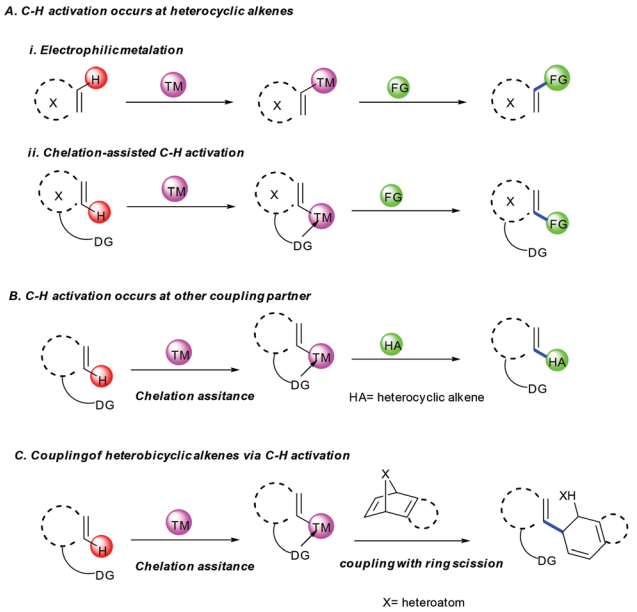
Scheme 1 Some selected examples of heterocyclic alkenes.

Tharmalingam Punniyamurthy

Tharmalingam Punniyamurthy received his Ph.D. from the Indian Institute of Technology Kanpur (Professor J. Iqbal, 1995). After postdoctoral research at North Dakota State University (Prof. M. P. Sibi, 1995–1996), Kyushu University (Professor T. Katsuki, 1997–1999) and Montpellier University II (Professor A. Vioux and Professor J. J. E. Moreau, 2000–2001), he joined the Indian Institute of Technology Guwahati and became HAG Professor in 2015. He is a visiting Professor at Oxford University (2007), Kyushu University (2013) and the Scripps Research Institute San Diego (2014). He is an elected fellow of The Indian Academy of Sciences (2015), The National Academy of Sciences (2018) and The Royal Society of Chemistry (2014). His research interests include the study of sustainable synthetic methodologies for organic transformations.

Importantly, the nature of M–C insertion depends on the substrate, solvent, additive, transition-metal and ligand. Mainly four types of mechanisms, σ-bond metathesis in early transition-metal complexes, oxidative addition in electron-rich late transition-metal complexes, electrophilic activation in electron-deficient late transition-metal complexes and Lewis-base assisted metalation, are involved.[10]

Recently, the Miura group reviewed the functionalization of pyridones,[11] while McGlacken[12a] and Hong[12b] groups covered pyrone/pyridone and coumarin/chromene functionalization, respectively.[12] Later, the coupling of maleimides was reviewed by Jeganmohan and co-workers.[13] Much progress has been made in the coupling of heterocyclic alkenes *via* C–H activation. This review will deliberate transition-metal-catalyzed coupling of the heterocyclic alkenes including *exo*-heterocyclic alkenes *via* an organometallic C–H functionalization strategy and depict their development since 2015 to present, except the reactions involving radical intermediates. The focus will be on highlighting the feasibility in terms of catalytic competence, selectivity and mechanistic manifolds. The literature has been classified based on reaction types and further arranged by substrate complexity.



Scheme 2 General coupling patterns of heterocyclic alkenes.

1.1. General coupling patterns of heterocyclic alkenes

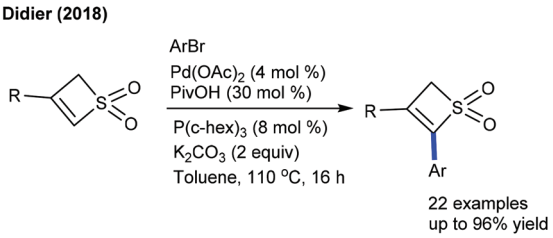
Coupling of heterocyclic alkenes can be achieved specifically by C–H activation *via* two types of approaches (Scheme 2).

- C–H activation at heterocyclic alkenes (pyrones, pyridones, coumarins, chromenes and quinolones)
- C–H activation at another coupling partner (arenes or heteroarenes).

In the first case, C–H activation takes place *via* electrophilic metalation *e.g.* concerted metalation deprotonation (CMD) followed by coupling with the other partner or chelation assisted C–H activation and subsequent coupling with the other reacting partner (Scheme 2A(i) and (ii)). In the second case, the C–H activation occurs at another partner (arene/heteroarene) by chelation assistance that interacts with the heterocyclic alkene, leading to coupling *via* migratory insertion and reductive elimination or protonation of the M–C bond (Scheme 2B). While heterobicyclic alkenes have inherent reactivity owing to the ring strain, which can couple in various ways. In general, C–H activation takes place first at arenes, which interact with the heterobicyclic alkene and subsequently migratory insertion and ring scission induced by β-heteroatom elimination afford the final product (Scheme 2C). A comprehensive view of the mechanistic aspects of every type of the reaction is discussed in the appropriate places of the article.

2. Arylation

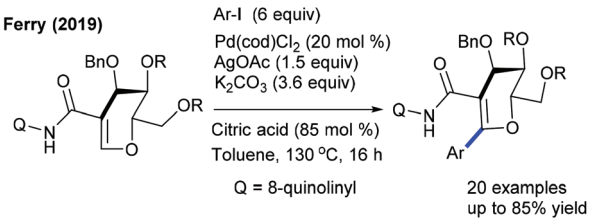
Arylation *via* C–H activation leads to an important C–C bond formation. Aryl halides/-boronic acids/-carboxylic acids have been generally utilized as the aryl source. The coupling of thietes with aryl bromides has been achieved by Pd-catalysis (Scheme 3).[14] A series of substrates are compatible with functional group tolerance. The C–H activation most likely arises through a base-assisted internal substitution (BIES) rather than the CMD process. Some of the arylated thietes inhibit the tubulin polymerization.



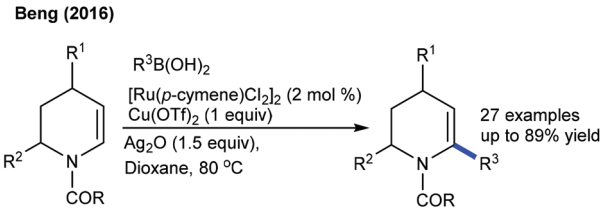
Scheme 3 Arylation of thietes.

Recently, the Ferry group showed the arylation of anomeric C–H bonds of glycals with aryl iodides (Scheme 4).[15] Irrespective of the electronic properties, aryl iodides are tolerated. Besides, D-galactal and D-lactal prove to be good coupling partners. Control studies exclude the possibility of usual carbopalladation and β-elimination. In 2016, Ru-catalyzed regioselective C–H arylation of cyclic enamides has been achieved (Scheme 5).[16] The reaction takes place selectively at the sp^2 α-C–H bond rather than the sp^3 α-C–H bond that allows the access of a range of heteroaryl dehydropyrrolidines. Piperidine and azepenes furnish the desired products, while alkenyl/styrenyl boronic acids participate albeit giving less yield.

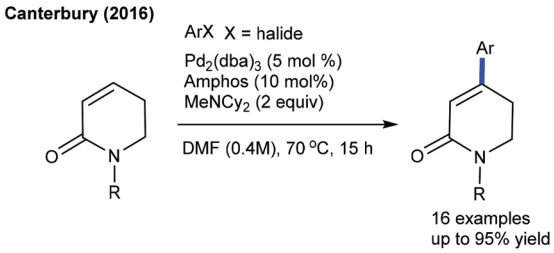
The Canterbury group presented a Pd-catalyzed β-selective arylation of α,β-unsaturated valerolactams (Scheme 6).[17] Among the tested phosphine-based ligands, amphos provides the best results. The procedure is more sensitive towards the substitution on the aryl ring and *N*-substitution of the lactams. The C6-arylation of pyridones can be achieved with aryl trifluoroborates employing Rh-catalysis (Scheme 7).[18] Aryl trifluoroborates with varied electronic properties afford a small



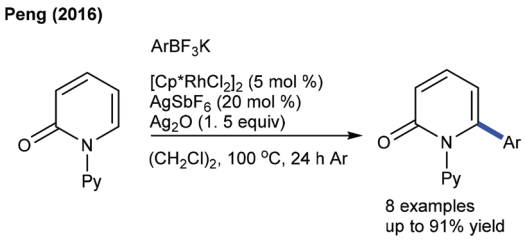
Scheme 4 Arylation of glycals.



Scheme 5 Arylation of cyclic enamides with boronic acids.



Scheme 6 β-Arylation of α,β-unsaturated valerolactams.

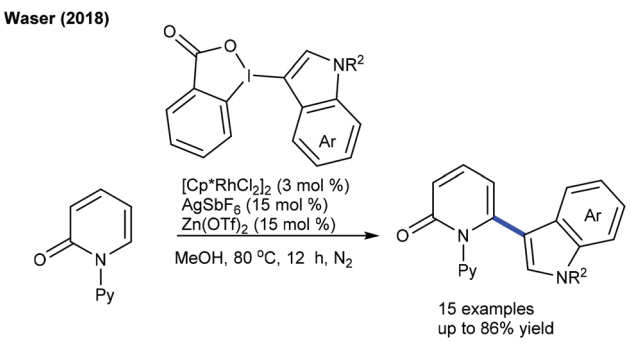


Scheme 7 Arylation of pyridones using aryl trifluoroborates.

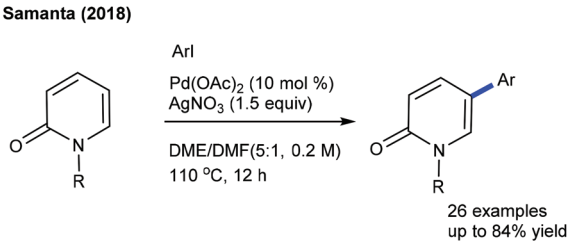
library of desired products, while a steric effect notably affects the reaction.

The synthesis of heteroarylated phenols can be achieved *via* the C6-arylation of pyridones using quinine diazides.[19] This oxidant-free procedure is studied with diverse pyridine substrates. Recently, Waser and co-workers carried out C6-indolation of pyridone (Scheme 8).[20] The combination of the additive $AgSbF_6$ and Lewis acid $Zn(OTf)_2$ plays a crucial role. Functional group tolerance and construction of valuable indole-tethered heterocycles are the important features; however the scope of the indole is rather limited. Pd-Catalyzed C5-arylated pyridones are obtained by the reaction of pyridones with aryl iodides (Scheme 9).[21] Addition of $AgNO_3$ confers the electrophilic nature of the Pd-catalyst; however, it aids in resuming the activity of the active catalyst. A wide range of electronically diverse substrates are compatible although the products are formed in moderate yields.

The arylation has been found to be successful utilizing an arene as an aryl source, which is attractive due to its atom



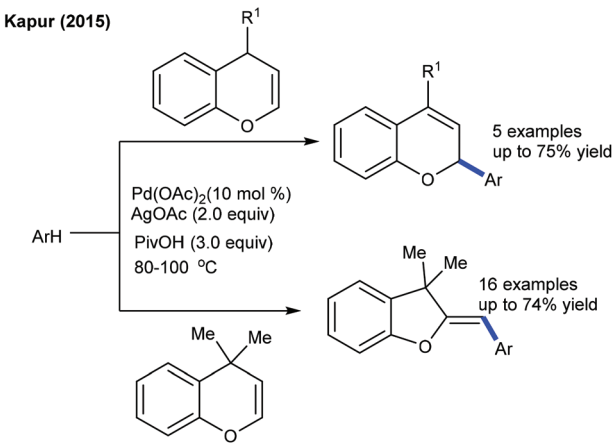
Scheme 8 C6-Indolation of pyridones.



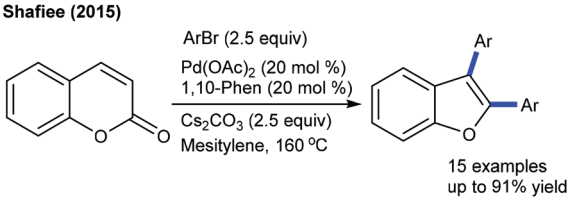
Scheme 9 C5-Arylation of pyridones.

economy (Scheme 10).[22] The reaction of C4-monosubstituted chromenes provides C2-arylation products. In contrast, C4-disubstituted chromenes give benzopyrans. Furthermore, electron-deficient arenes yield C3-arylated products. A similar kind of ring contraction is observed with the coupling of coumarins using aryl bromides as the aryl source (Scheme 11).[23] This reaction is compatible with a broad range of substrates.

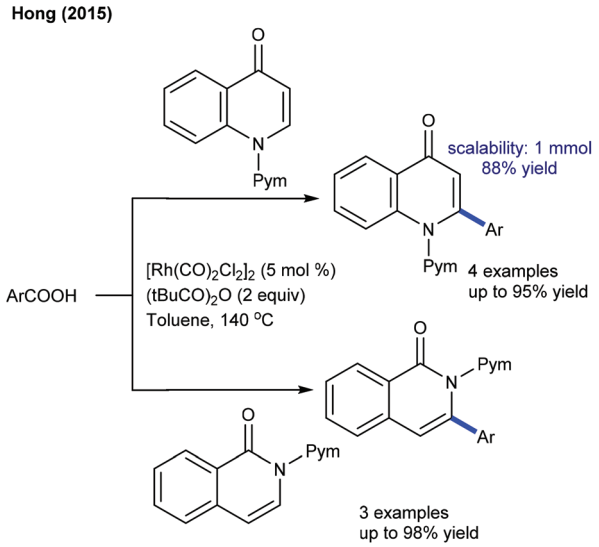
The decarboxylative coupling of aryl carboxylic acids is effective at the C2 position of quinolone and isoquinolone at elevated temperature (Scheme 12).[24] The Hong group successfully developed the catalyst controlled C4-arylation of isoquinolones using diaryliodonium salts as an aryl source.[25] Ar_2IBF_4 is the best coupling partner, although *ortho*-substituted iodonium salts are less reactive. They further showed an inherent reactivity and site-selectivity in the C–H functionalization of enaminones and chromones (Scheme 13).[26] According to Kapur's report (Scheme 10), they have utilized an excess of an arene as the aryl source. The following conclusions are observed:



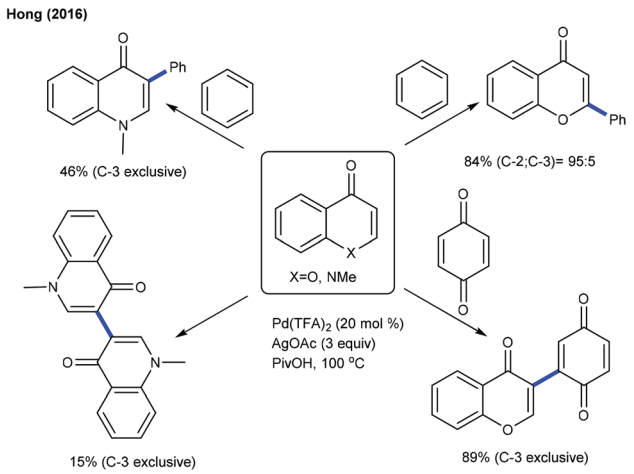
Scheme 10 Synthesis of benzopyran *via* C–C bond migration.



Scheme 11 Domino C–H and C–C activation of coumarins.



Scheme 12 C2-Arylation of quinolones/isoquinolones.



Scheme 13 Functionalization of enaminones and chromones.

• The site-selectivity differs on switching the mechanism between CMD and carbopalladation.

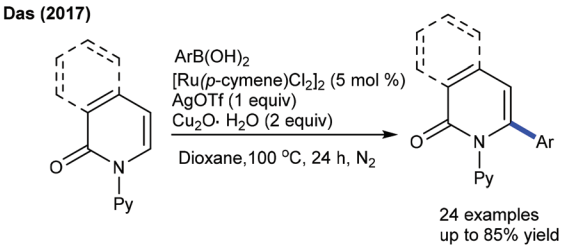
• The C–H activation of an enaminone and a chromone occurs *via* CMD more readily at the π-electron rich position and affords obvious selectivity at C-3.

• Arylation of the enaminone generally provides a C-3 arylated product due to the high activation barrier at C-2.

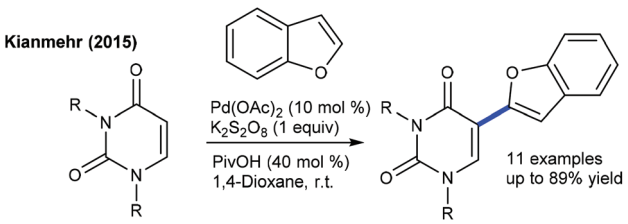
• Arylation of the chromone occurs favourably at C-2 *via* carbopalladation since a metal interacts more strongly at C-2 compared to C-3.

Later, the arylation of 2-pyridones and 1-isoquinolones is accomplished using Ru-catalysis (Scheme 14).[27] The trio Ru/Cu/Ag catalytic system provides an effective synthetic tool to access the arylated products.

Efforts are made towards the functionalization of uracil. The dehydrogenative coupling with benzofurans is successful using PivOH at room temperature (Scheme 15).[28] The scope of

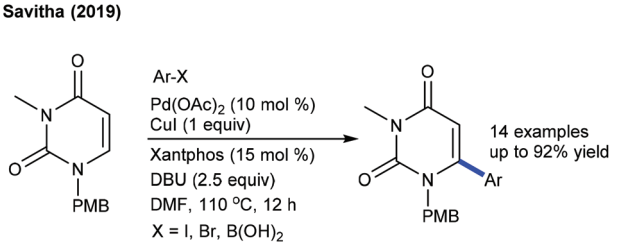


Scheme 14 Arylation of 2-pyridones/1-isoquinolones with aryl boronic acids.

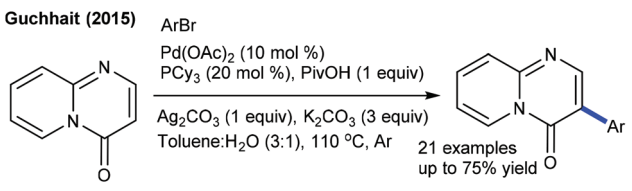


Scheme 15 Dehydrogenative coupling of uracil with benzofurans.

the procedure is somewhat limited, and the mechanism involves an electrophilic palladation, while the C6-arylation employing aryl halides and boronic acids is effective at 110 °C (Scheme 16).[29] The combination of $Pd(OAc)_2$, CuI, xantphos and DBU is essential. Aryl iodides/-bromides provide the best results, while $ArB(OH)_2$/$ArBF_3K$ give inferior results. Xantphos accelerates the oxidative addition and reductive elimination steps. A similar strategy is used for the C3-arylation of pyrido[1,2-*a*]pyrimidin-4-ones using aryl bromide (Scheme 17).[30] Ag-Salt plays a dual role as an oxidant and a halo-sequestering agent. A ligand is necessary for this coupling, and PCy_3 shows promising results. A broad range of aryl bromides are coupled.



Scheme 16 C6-Arylation of uracil with aryl halides/-boronic acids.

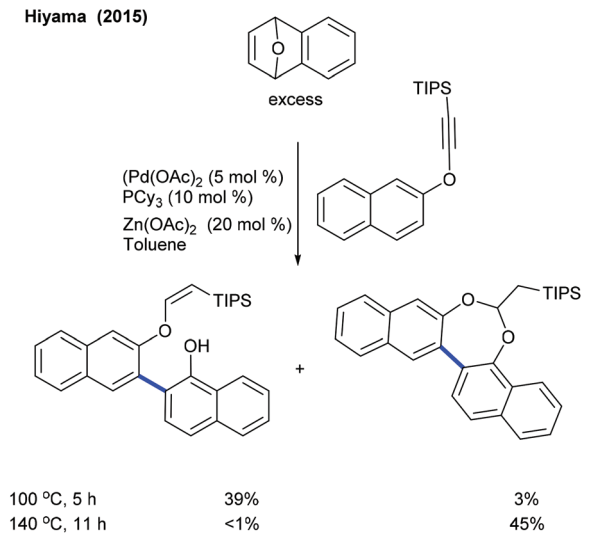


Scheme 17 C3-Arylation of pyrido[1,2-*a*]pyrimidin-4-ones.

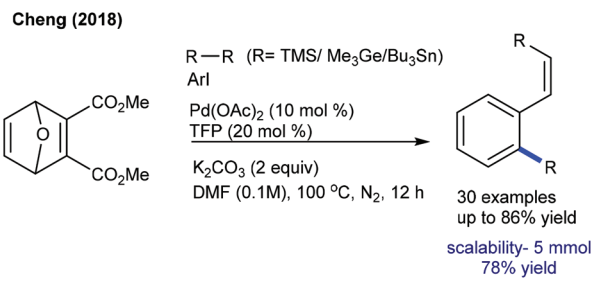
Aryl iodides exhibit similar reactivities, whereas aryl chloride remains intact. Other coupling partners such as aryl triflate and -tosylate exhibit less reactivity.

The functionalization of oxabicyclic alkenes is attractive. The Hiyama group showed an example of an alkynyloxy group as a hydrogen accepting director for the arylation of an oxabicyclic alkene (Scheme 18).[31] This reaction at 100 °C provides a mixture of naphthylated and cyclized products in lower yields. However, at elevated temperature (140 °C), the cyclized product is formed in moderate yield. Cheng and co-workers examined the Catellani-type reaction of aryl iodides, oxanorbornadiene and hexamethyldisilane (Scheme 19).[32] A heterocyclic alkene plays a twin role as an *ortho* C–H activator and an ethylene surrogate. In particular, estrone, amino acids and heterocyclic iodides prove to be competent substrates. Organogermananes/-stannanes also work well; however, the latter needs a K_3PO_4 additive instead of K_2CO_3 though it provides less yield. They extended the study to norbornenes under slightly modified conditions.[33] Solvents play a leading role, and the generality is evaluated with diverse aryl iodides and norbornenes.

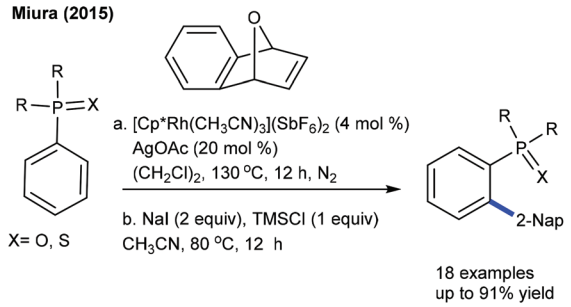
Oxabicyclic alkenes are found to be valuable 2-naphthylation sources and have been considerably investigated. This



Scheme 18 Functionalization with oxabenzonorbornadienes.



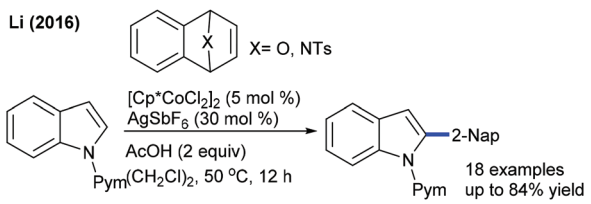
Scheme 19 Synthesis of (*Z*)-β-substituted vinylsilanes by Catellani-type reaction.



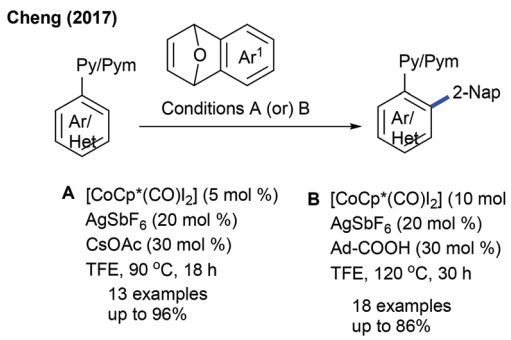
Scheme 20 Coupling of heterobicyclic alkenes with aryl phosphines.

reaction generally comprises a C–H activation, ring-opening, addition and hydration sequence. The Miura group disclosed the Rh-catalyzed coupling of oxabicyclic alkenes with aryl phosphines (Scheme 20).[34] Phosphine oxide shows an excellent directing ability compared to phosphine sulfide, which may be due to the latter's thiophilic nature. This procedure provides good yields of products, and some derivatives give a mixture of aromatized and hydroarylated products.

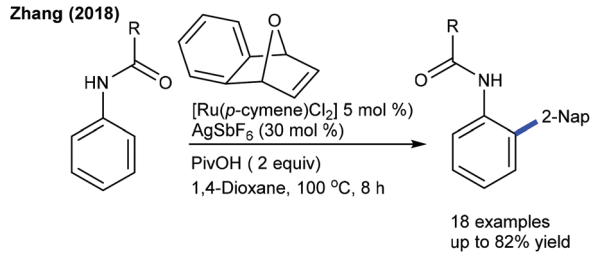
Li and co-workers described a Co-catalyzed C2-naphthylation of indoles (Scheme 21).[35] A blend of AcOH and $AgSbF_6$ effectively promotes the reaction ($AgSbF_6$ acts as a Lewis acid). With slightly tuned conditions, sterically congested C-3 and C-7 substituted indoles can be functionalized. The mechanism involves the reversible C–H cleavage *via* the CMD pathway. This strategy is extended to the coupling of arenes with oxabenzonorbornadienes (Scheme 22),[36] where *N*-pyrimidinylbenzimidazoles deliver oxa-bicycle core retained products. Under modified conditions, a series of electronically diverse 2-arylpyridines serve as efficient coupling partners,



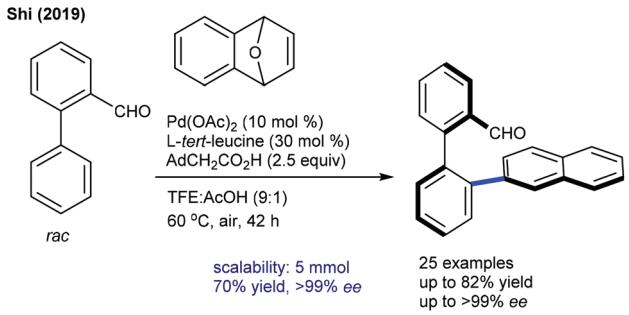
Scheme 21 C2-Naphthylation of indoles.



Scheme 22 Addition of arenes with oxabenzonorbornadienes.



Scheme 23 Naphthylation of anilides with oxabenzonorbornadienes.



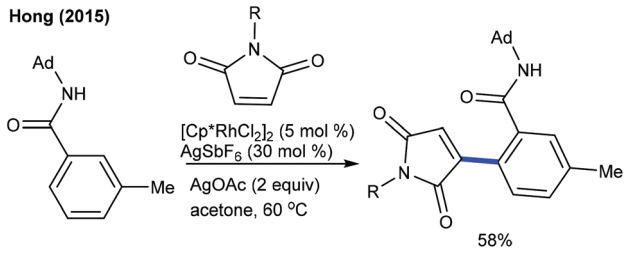
Scheme 24 Naphthylation of *rac*-biaryl aldehydes.

giving naphthylated products. This method is complementary to the Li procedure (Scheme 21); however, it requires higher reaction temperature. Recently, Ru-catalyzed C–H naphthylation of anilides with oxabenzonorbornadienes has been achieved (Scheme 23).[37] Electron-rich anilides display a higher reactivity and the C–H activation occurs *via* a redox-neutral pathway.

More recently, Shi and co-workers reported an elegant route to obtain an axial chiral aldehyde *via* a Pd-catalyzed, atroposelective C–H naphthylation of *rac*-biaryl aldehydes with oxabenzonorbornadienes (Scheme 24).[38] L-*tert*-Leucine serves as a chiral transient directing group and stereocontrolling unit. A series of substituted biaryl and oxabenzonorbornadienes react efficiently with excellent ee (up to >99%). Yet the aryl part having F or 1,3-dioxole groups in oxabenzonorbornadienes are less reactive though without sacrificing the ee. Particularly, an undehydrated product is observed with electron-deficient oxabenzonorbornadiene. The outcome of the chiral aldehyde is further transformed into the active chiral catalyst, which is evaluated for the asymmetric reaction of (*E*)-chalcone with glycine-derived amides or peptides.

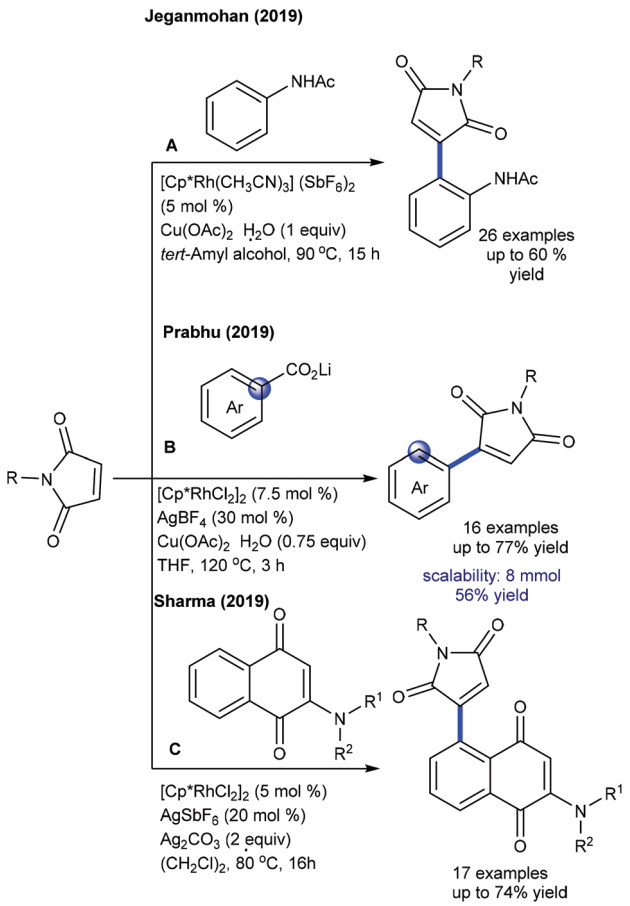
3. Alkenylation

Alkenylation of arenes with cyclic alkenes is one of the puzzling tasks, because of the formation of a rigid bicyclic intermediate, and unavailability of *syn* β-hydrogen for elimination. This kind of reaction is mostly expected to give a Michael type of product. Nevertheless, the Hong group showed a single example of alkenylation utilizing maleimide under mild reaction conditions (Scheme 25).[39]



Scheme 25 Coupling of benzamide with maleimides.

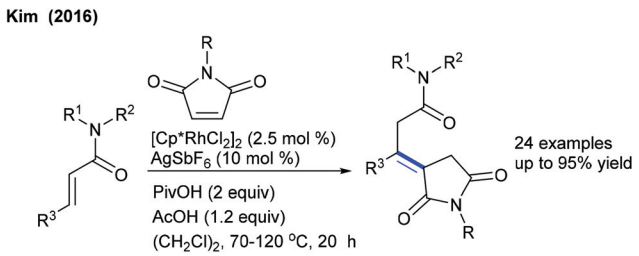
Later, the coupling of aryl ketones with maleimide has been successfully achieved.[40] Ag_2CO_3 plays a vital role. Electronically diverse maleimides are tolerated, and electron-rich aryl ketones display better reactivity. This strategy has been extended to indoles using $COCF_3$ chelation assistance.[41] An additive and an oxidant play an indispensable role. Ag_2CO_3 gives the Heck-type product, while a AgOAc and ACOH combination leads to hydroarylation. The procedure can be utilized for the alkenylation of aryl acetamides.[42] *para*-Substituted aryl acetamides exhibit good reactivity, while *ortho*-/*meta*-substituted substrates are less effective. Similarly, the alkenylation of acetanilides can be accomplished (Scheme 26A).[43] In addition,



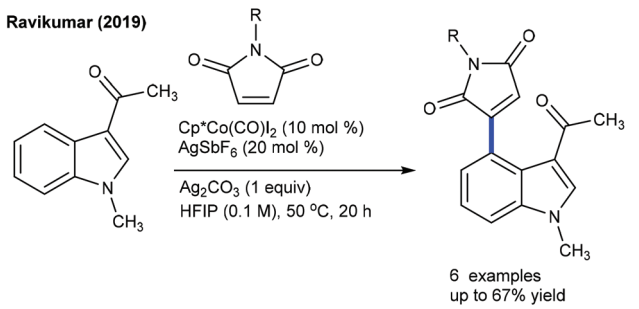
Scheme 26 Alkenylation using maleimides.

the carboxylate directed C–H activation/decarboxylative Heck-type coupling of benzoic acid is achieved (Scheme 26B).[44] The selectivity depends on the reaction medium. THF enables alkenylation, whereas TFE produces the annulation product. Similarly, the C5-alkenylation of 2-amino-1,4-naphthoquinones can be accomplished (Scheme 26C).[45] The product selectivity depends on the reaction conditions. For instance, alkenylation (45–74%) is observed under basic conditions, whereas acidic conditions give the alkylation product. Moreover, the coupling of acrylamides is effective *via* C–H alkylation and alkene migration (Scheme 27).[46] Integration of a cationic rhodium catalyst with PivOH significantly promotes the reaction. The coupling of a range of acyl amides is shown, although secondary and tertiary substrates give a mixture of *E*- and *Z*-products. Weakly coordinating ketone directed Co-catalyzed C4-alkenylation of indole with active alkenes including maleimides is successful (Scheme 28).[47] Modest yields of the desired products are obtained, and a significant influence of the electronic effect is noted. However, the scope of the reaction is rather limited.

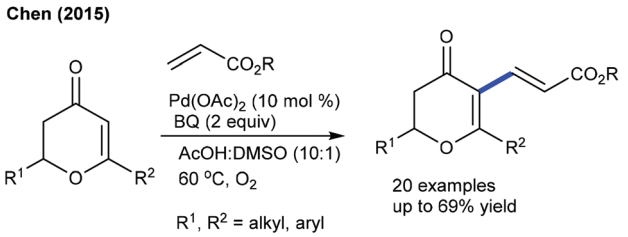
Alkenylation of other types of heterocyclic alkenes has been achieved by exploiting electron-deficient alkenes, styrenes and alkenoic acids where C–H activation takes place at the heterocyclic alkene part through an electrophilic metalation pathway. A Pd-catalyzed C–C coupling of dihydropyranones with acrylates is successful under mild conditions (Scheme 29).[48] An electron-deficient alkene is competent in delivering the product, whereas styrene is less effective. However, pyrones readily undergo C3 C–C coupling with styrenes (Scheme 30).[49] Electronically varied styrenes are tolerated. At slightly elevated temperature, pyridones also react. The Li group presented the



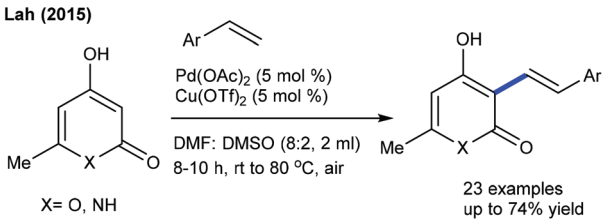
Scheme 27 Cross-coupling of acrylamides with maleimides.



Scheme 28 C4-Alkenylation of indoles with maleimides.



Scheme 29 C3-Alkenylation of dihydropyranones.

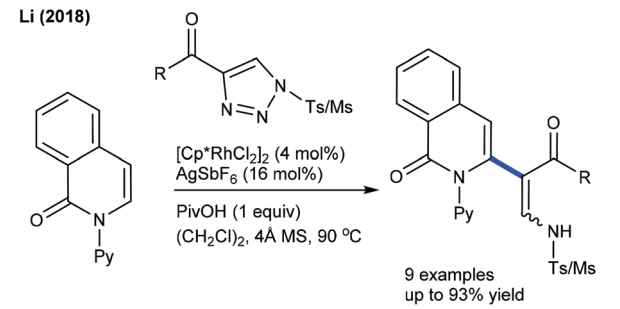


Scheme 30 C3-Alkenylation of pyrones/pyridones with styrenes.

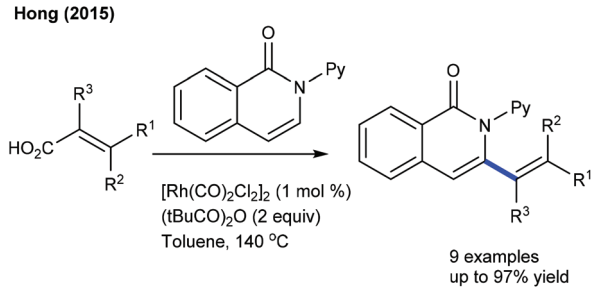
Rh-catalyzed redox-neutral coupling of 4-acyl-1-sulfonyl triazoles with isoquinolones in the presence of PivOH (Scheme 31).[50] However, this reaction suffers due to the *E*,*Z*-mixture of isomers and limited substrate scope.

Efforts are made towards achieving decarboxylative couplings. A Rh(I)-catalyzed reaction of quinolones and isoquinolones with aryl and alkyl alkenoic acids is accomplished (Scheme 32).[24] Low catalyst loading and broad substrate scope are important features, although a high temperature (140 °C) is mandatory. A similar catalytic system is applied for the coupling of 2-/4-pyridones and isoquinolones with cinnamic acids (Scheme 33).[51]

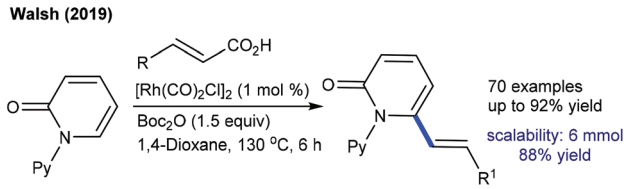
The coupling of acrylate with pyridones is studied for a solvent-controlled C6-alkenylation/alkylation at moderate temperature (Scheme 34).[52] Reaction in DMF gives an alkenylated product and under modified conditions styrene also couples. Recently, the coupling of methylenecyclopropanes has been studied for both isoquinolones and pyridones (Scheme 35).[53] A combination of $[Cp^*RhCl_2]_2$ and $AgSbF_6$ yields the best results. Reaction kinetics and deuterium scrambling experiments show an involvement of the reversible C–H cleavage that probably might be the rate determining step (KIE = 5.4).



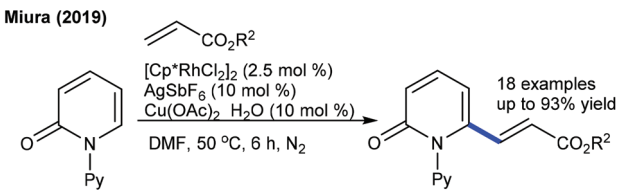
Scheme 31 Coupling of isoquinolones with 4-acyl-1-sulfonyl triazoles.



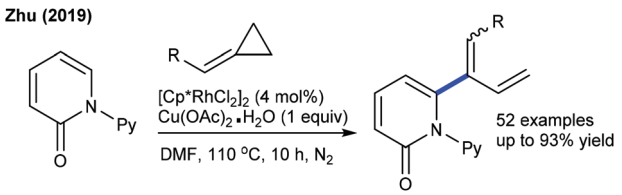
Scheme 32 Decarbonylative C–H alkenylation of quinolones/isoquinolones.



Scheme 33 Decarbonylative C–H alkenylation of pyridones.

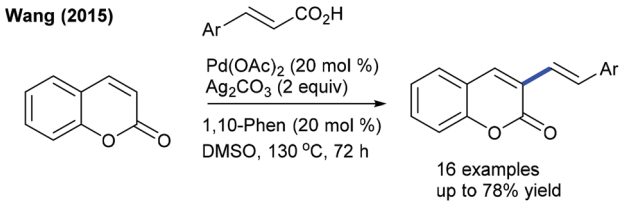


Scheme 34 C6-Alkenylation of pyridones.

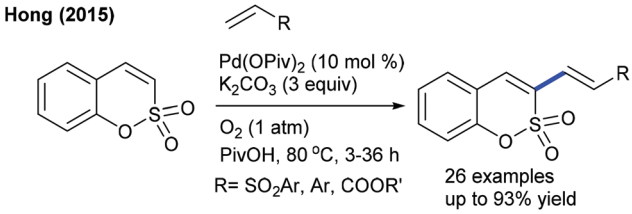


Scheme 35 Coupling of isoquinolones/pyridones with methylenecyclopropanes.

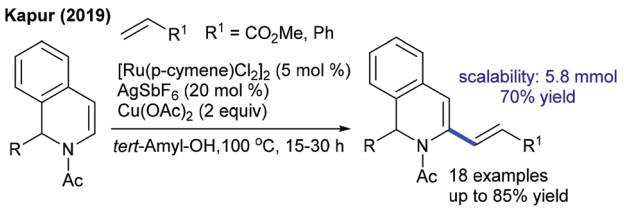
The decarboxylative coupling of cinnamic acids with coumarins can be achieved at elevated temperature by Pd-catalysis (Scheme 36).[54] The C3-alkenylation is effective with diverse functionalities. Electron-deficient cinnamic acid is less reactive compared to neutral and electron-rich substrates. Hong and co-workers developed the C–H alkenylation of sulfacoumarins with activated alkenes (Scheme 37).[55] The procedure is compatible with a wide range of styrenes and utilizes O_2 as the oxidant. Kapur and co-workers presented the assembly of C3-alkenated 1,2-dihydroisoquinolines (Scheme 38).[56] The acetyl group serves as a removable directing group and a wide range of alkenes including electronically biased alkenes react providing moderate yields, while electron-rich alkenes fail.



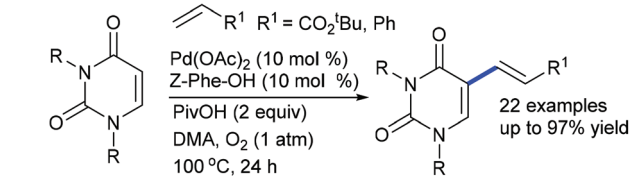
Scheme 36 C3-Alkenylation of coumarins *via* decarboxylative cross-coupling.



Scheme 37 C3-Alkenylation of sulfacoumarins.



Scheme 38 C3-Alkenylation of *N*-acetyl-1,2-dihydroisoquinolines.

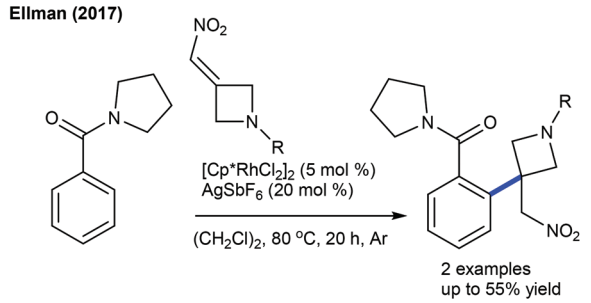


Scheme 39 C3-Alkenylation of uracils.

The Huang group reported an environmentally benign alkenylation of uracil (Scheme 39).[57] As mentioned above, this procedure also utilizes O_2 as the oxidant along with a ligand, and mono-*N*-protected amino acids (MPAAs) Z-Phe-OH are found to be superior. Electronic/steric effects significantly influence the reaction. For instance, sterically hindered styrenes exhibit less reactivity. Substituted alkenes are viable albeit they give a mixture of isomers, whereas C-6 substituted uracil and free (NH) uracil fail to give the products.

4. Alkylation

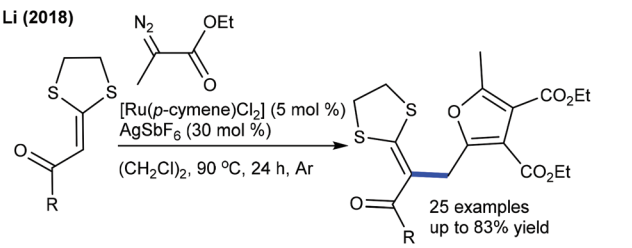
Alkylation is a crucial transformation; especially heterocyclic alkenes have potential to afford heterocycle containing alkyl-



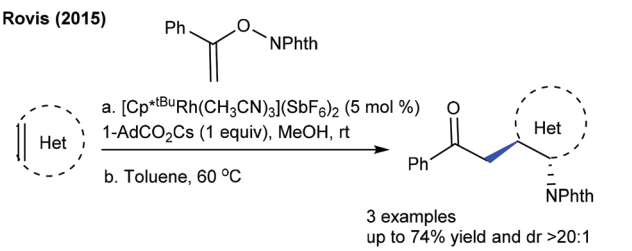
Scheme 40 Alkylation of cyclic benzamides with 3-(nitromethylene) azetidine.

ated products through a sustainable pathway. In 2017, Ellman showed the coupling of benzamides with 3-(nitromethylene) azetidine with moderate yields (Scheme 40).[58] Later, an interesting example of C–H furfurylation of α-acylketene dithioacetals with α-diazoketones has been reported (Scheme 41).[59] A variety of functional groups are compatible; however, an increase of the ring-size of dithioacetal hampers the reactivity.

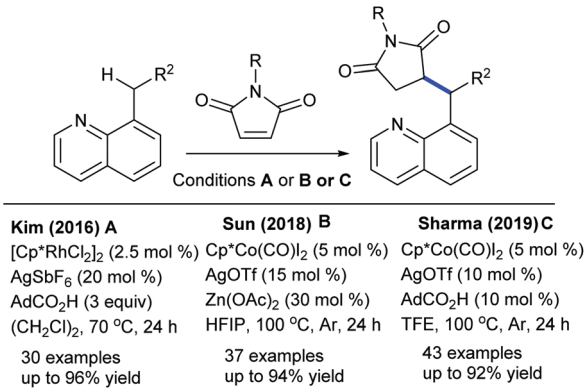
Maleimides are not only an efficient source of alkenylation reactions, but have also been proved to be a competent alkyl resource. Rovis and co-workers presented three examples of *syn*-carboamination of alkenes including heterocyclic alkenes using a transient directing group (Scheme 42).[60] The carboaminated products are obtained with electron-rich *t*-Bu-cyclopentadienyl cationic Rh-catalysis. The alkylation of the methyl group of 8-methylquinoline has been explored using maleimides (Scheme 43A).[61] This reaction utilizes $AdCO_2H$ as an additive and a broad range of substrates are found to be successful. Later, the Sun group reported the same coupling by Cp*Co(III)



Scheme 41 Furfurylation of α-acylketene dithioacetals with α-diazoketones.



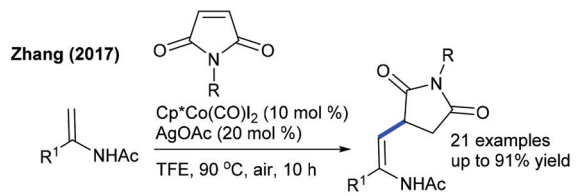
Scheme 42 *syn*-Carboamination of heterocyclic alkenes.



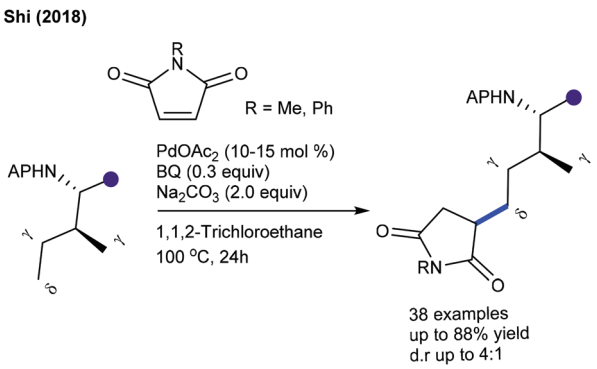
Scheme 43 C(sp^3)–H functionalization of 8-methylquinolins with maleimides.

catalysis (Scheme 43B).[62] Diverse substrates with a range of functional groups are compatible; however, 8-ethylquinoline and unprotected maleimides are unsuccessful substrates. To overcome this issue, a slightly modified Co-based catalytic system has been introduced (Scheme 43C).[63] Zhang and co-workers achieved coupling with enamides (Scheme 44).[64] A wide range of enamides react; however, the cyclic enamide is an unsuccessful substrate.

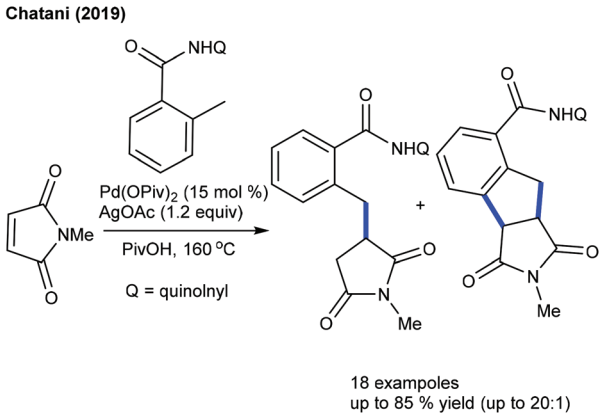
The δ-C(sp^3)–H alkylation of amino acids has been found to be successful by Pd-catalysis (Scheme 45).[65] This procedure displays functional group tolerance and a series of amino acids are alkylated, though L-norvalines produce less yield owing to competing *N*,*N*-coordination. Dipeptides, tripeptides and tetrapeptides are viable, giving a mixture of diastereomers (up to 4 : 1). Recently, the Chatani group reported C–H alkyl-



Scheme 44 Coupling of enamides with maleimides.



Scheme 45 Alkylation of amino acids/peptides.

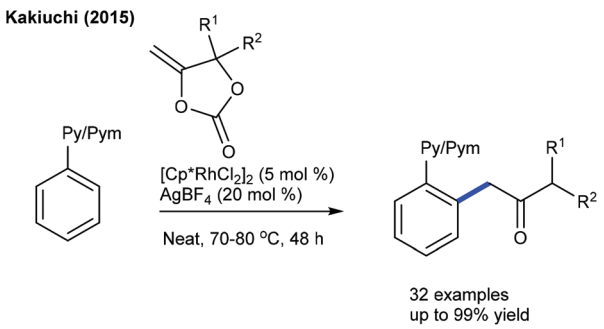


Scheme 46 Alkylation of *ortho*-methylbenzamide with maleimides.

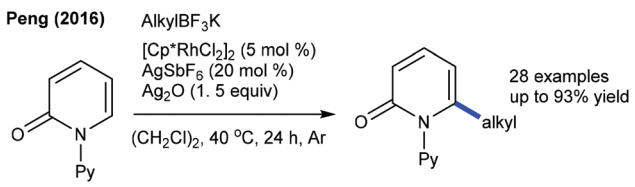
ation of the *ortho*-methyl group of aryl amides (Scheme 46).[66] Similar to Shi's procedure (Scheme 45), the preferential nature arises from the kinetically less favoured six-membered palladacycle in lieu of the kinetically favoured five-membered system, which is supported by DFT calculations. The mechanism involves the reversible C–H cleavage, migratory insertion of maleimide and protodemetalation.

The Rh-(III) catalytic system is explored for the installation of an α-acyl alkyl group *via* C–H activation of arenes employing cyclic alkenyl carbonate under neat conditions (Scheme 47).[67] Electron-deficient benzamides produce high yields, while the reaction of thiophene-2-carboxamide gives moderate yield. The products are converted to isocoumarin derivatives using AcOH.

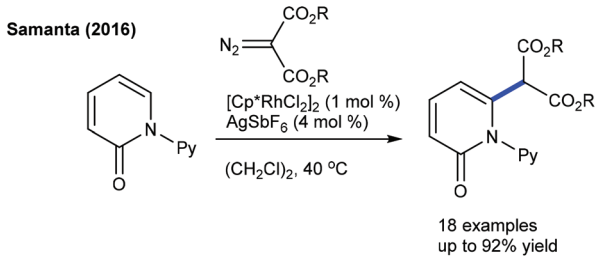
In 2016, the Peng group described the C6-alkylation of 2-pyridones with alkyl trifluoroborates (Scheme 48).[18] Ester,



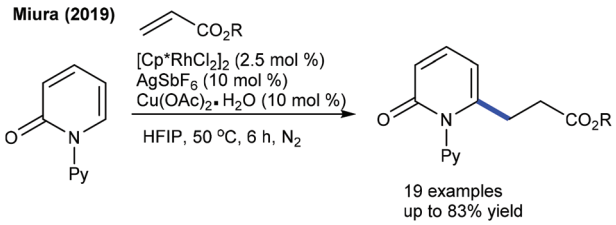
Scheme 47 Coupling of arenes with cyclic alkenyl carbonates.



Scheme 48 C6-Alkylation of pyridones.



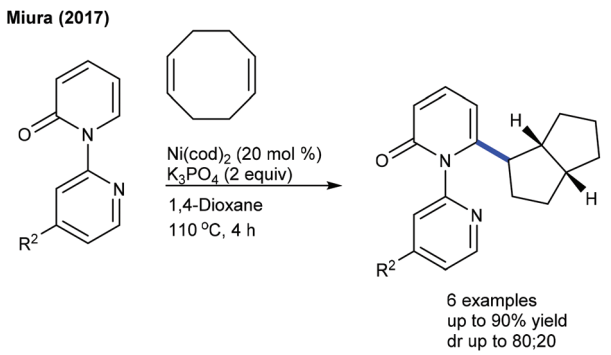
Scheme 49 C6-Alkylation of pyridones using diazo compounds.



Scheme 50 C6-Alkylation of pyridones with acrylates.

alkenyl and amide group attached alkyl trifluoroborates are compatible. This strategy is extended to the coupling of diazo compounds (Scheme 49).[68] A pyridine directing group produces superior results compared to pivaloyl, carbamoyl and methyl groups in *N*-protection. Low catalyst loading and mild reaction conditions are important features. Several electronically diverse pyridones, especially at the C3 position, give the best yield. The mechanism shows an involvement of the reversible electrophilic C–H activation. Furthermore, the coupling of acrylates is found to be successful (Scheme 50).[52] $Cu(OAc)_2{\cdot}H_2O$ gives an acetate ligand to Rh and enhances the life time of the catalyst by reoxidizing the generated Rh(I) species. Good yields are obtained in polar and protic HFIP solvents. The reaction is compatible with a range of substituted pyridones and acrylates and the C–H activation step is reversible.

A rare example of C6-selective ring-contracting C–H alkylation of 2-pyridones is achieved (Scheme 51).[69] This method is sensitive towards the steric and electronic features of pyridone.



Scheme 51 C6-Selective ring-contracting C–H alkylation of 2-pyridones.

Apart from cyclooctadiene, norbornadiene, norbornene and styrene react, whereas 1,3-diene affords a mixture of annulated and addition products.

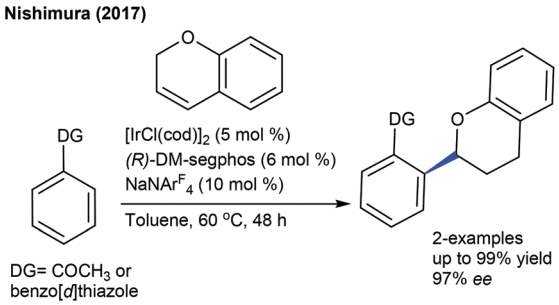
5. C–H addition to C=C bonds

5.1. Hydroarylation

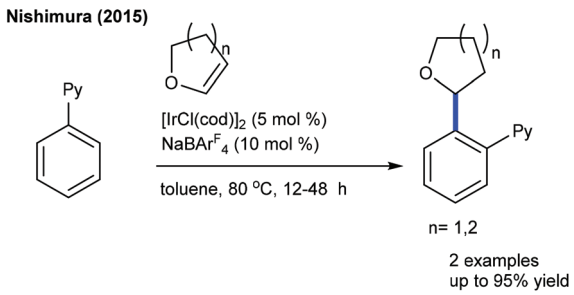
Hydroarylation of heterocyclic C=C bonds through C–H addition *via* chelation assistance has attracted much attention in recent years since it exemplifies a flexible atom-economical process. The Nishimura group reported a branch-selective hydroarylation of vinyl ethers, where the reaction of cyclic ethers occurs affording good yields (Scheme 52).[70] The coupling of α,β-unsaturated γ-lactones with dihydrofuran is successful (Scheme 53).[71] It is sensitive to the nature of the base and K_2HPO_4 or Na_2CO_3 affords the best results. *ortho*- and *meta*-substituted aryl amides give manoalkylation products and unsubstituted substrates produce dialkylation products, while α,β-unsaturated γ-lactones deliver diastereomeric mixtures.

Subsequently, an Ir-catalyzed enantioselective hydroarylation of alkenyl ethers is described through C–H activation and alkene isomerization (Scheme 54).[72,73] They extended the reaction scope with differently functionalized aromatic ketones and 2*H*-chromenes. Ketones having electron-donating groups at *ortho* or *para*-positions exhibit the best ee. Furthermore, they designed a diastereoselective synthesis of α- and β-glycosyl arenes using an iridium/chiral BINAP catalytic system.[74] Using (*R*)-BINAP provides a β-glycosyl arene, whereas the utilization of (*S*)-BINAP permits the generation of highly α-selective glycosyl arenes. A good to modest yield with excellent β-selectivity is obtained using (*R*)-BINAP with protected glycols, and (2-benzoimidazolinyl/2-benzoxazolyl) also acts as a good directing group. In contrast, acetophenone, acetophenone *O*-methyl oxime and *N*-(4-methoxyphenyl)-1-phenylethan-1-imine fail to react. Similarly, an *S*-BINAP based catalytic system gives the desired products with α-selectivity, while the selectivity drops when utilizing unprotected glycols. Pyrimidine, 2-benzoxazolyl and 2-benzothiazolyl are the workable directing groups, and the reaction of 1,3-di(2-pyridyl)-benzene/4,4′-di(pyridin-2-yl)-1,1′-biphenyl gives the dialkylated products in good yields.

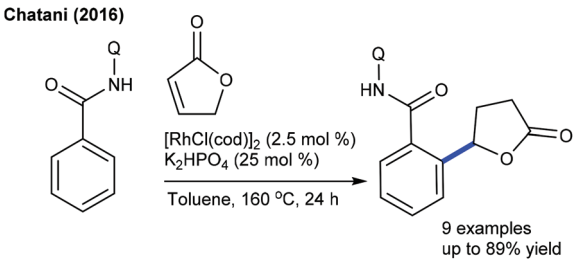
Several studies are focused on the coupling of maleimides with aryl systems. The Prabhu group reported coupling with arylacetophenone (Scheme 55A).[75] This protocol has some advantages such as the exclusive formation of the arylated product. This procedure is applicable to the coupling of *N*-benzoylindole,[76] which provides 3-(indol-2-yl)succinimides in a regioselective manner. This transformation proceeds providing good yields but the substrate scope is narrow. This strat-



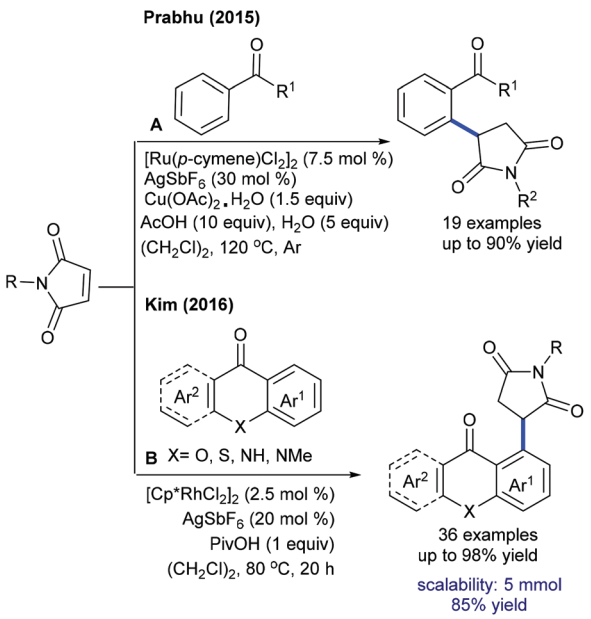
Scheme 54 Hydroarylation of cyclic ethers.



Scheme 52 Hydroarylation of cyclic ethers.



Scheme 53 Alkylation with α,β-unsaturated γ-lactones.

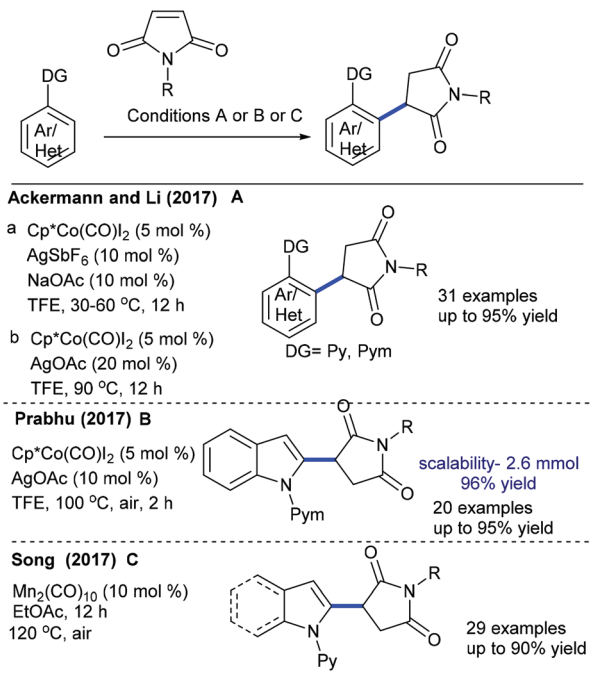


Scheme 55 Coupling of arylacetophenone/chromenes with maleimides.

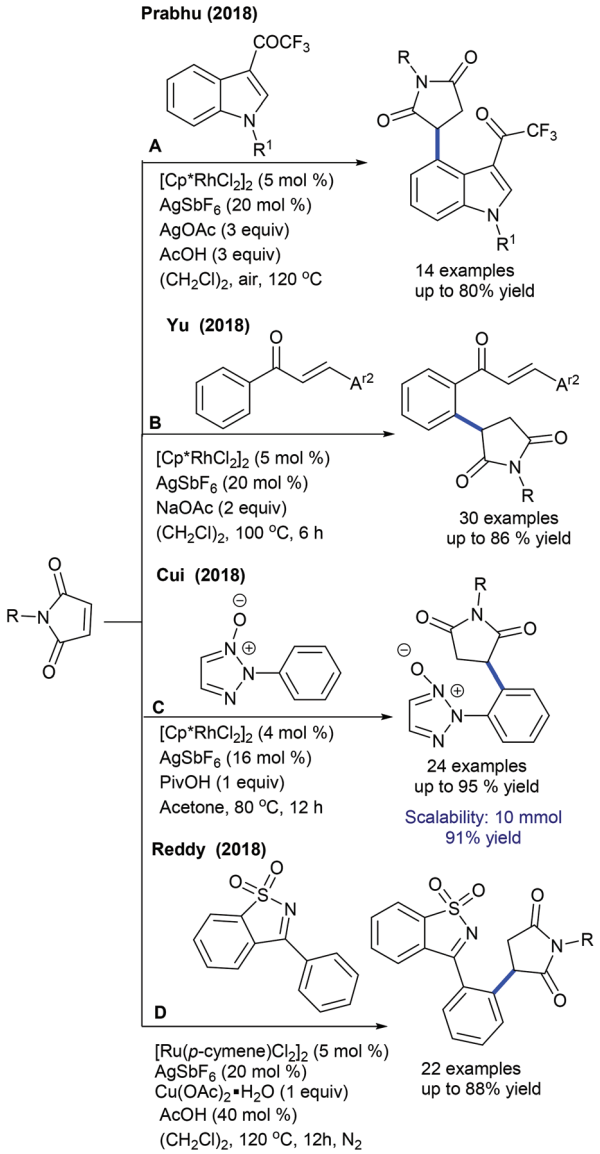
egy is further extended to the coupling with aryl amides to produce 3-aryl succinimides;[77] yet acetanilide gives less yield. Robust screening of the reaction conditions and directing ability of the various groups is covered. The C–C coupling with chromones has been successfully accomplished by Rh-catalysis (Scheme 55B).[78,79] This reaction is effective in the presence of PivOH. However, a sterically hindered substrate fails to give the desired product, while an electron-deficient substrate displays poor reactivity.

Ackermann and Prabhu groups demonstrated the Co-catalyzed coupling with arenes/indoles (Scheme 56A and B).[80,81] An array of the substituents in the indole and maleimide are tolerated. Modified reaction conditions accommodate diverse aryl compounds.[82] The hydroarylation of maleimides with indoles is successful in producing 2-indolylsuccinimides by Mn-catalysis (Scheme 56C).[83] Among a series of Mn-sources screened, $Mn_2(CO)_{10}$ displays the best results. Several electronically diverse 2-pyridylindoles and maleimides are tolerated, but C-3 substituted indole is less reactive due to a steric effect. However, 2-pyridyl pyrrole and oxabicyclic alkenes efficiently react.

Prabhu and co-workers reported carboxylic acids as traceless directing groups for the coupling of aryl nucleophiles.[84] This procedure is highly sensitive towards the electronic nature of the aryl ring. Electron-rich aryl carboxylic acids react, while electron-deficient or moderately electron-rich substrates show inferior results. Even NH-free maleimide is amenable, whereas furan and pyrrole carboxylic acids are unsuccessful substrates. They also showed C-4 alkylation of indoles with maleimide (Scheme 57A).[41] To attain finer results, 3 equiv. of



Scheme 56 Hydroarylation of heteroarenes with maleimides by Co-catalysis.



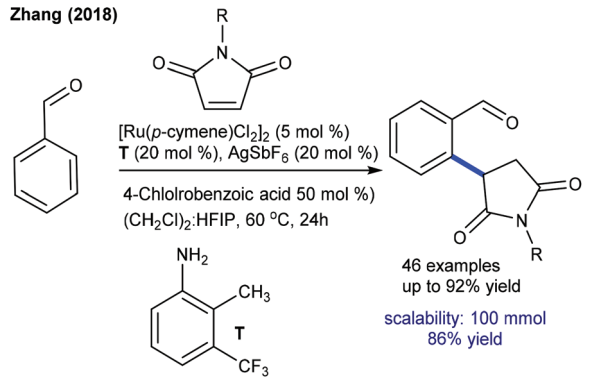
Scheme 57 Coupling of maleimides with different aryl coupling partners.

AgOAc are essential. H/D exchange studies show 66% D incorporation at C4 and C2 positions, which reveals that C–H activation might be a reversible process. Later, Rh(I)-catalyzed coupling of aryl amides with maleimides has been achieved.[85] The reaction is additive-free, and electronically diverse substrates are efficiently coupled. Furthermore, C7-coupling of indoline can be achieved.[86] Electron-rich indoline gives the best yields, while electron-deficient substrates are less reactive. Besides, a diastereomeric mixture of products is observed when the substrates with multiple stereocenters are reacted. Subsequently, enone carbonyl directed *ortho* C–H bond coupling of arenes is demonstrated (Scheme 57B).[87] A wide array of substituted chalcones react though a little influence of electronic effects is noted and the enone carbonyl group is essential to promote the C–H activation. The Cui group carried out *ortho*-alkylation of 2-aryl-1,2,3-triazole *N*-oxide (Scheme 57C).[88]

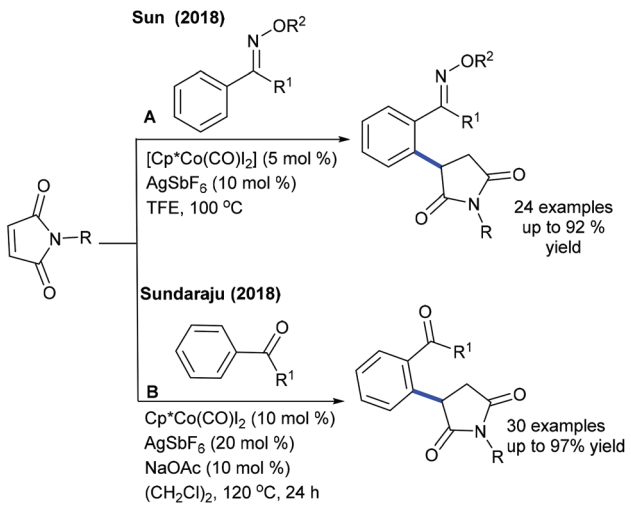
This method displays good efficiency using diverse substrates, while electron-deficient and sterically hindered substrates are less effective. In a related process, the Reddy group presented an *ortho*-C–H alkylation of *N*-sulfonylketimines (Scheme 57D).[89] A broad range of ketimines and maleimides are compatible. However, electron-deficient *N*-sulfonylketimine, and *n*-butyl and Boc substituted maleimides are unsuccessful substrates.

Transient directing group assisted *ortho*-alkylation of aryl aldehydes is achieved (Scheme 58).[90] The reaction proceeds selectively with high functional group tolerance. The reaction can be extended to aryl ketoximes by Co-catalysis (Scheme 59A).[91] A series of oximes and maleimides are amenable; however, sterically demanding oxime is unfruitful. The mechanism shows an involvement of reversible fast C–H metalation. In addition, the coupling with aryl ketones is successful (Scheme 59B).[92] High catalyst and additive loadings are required.

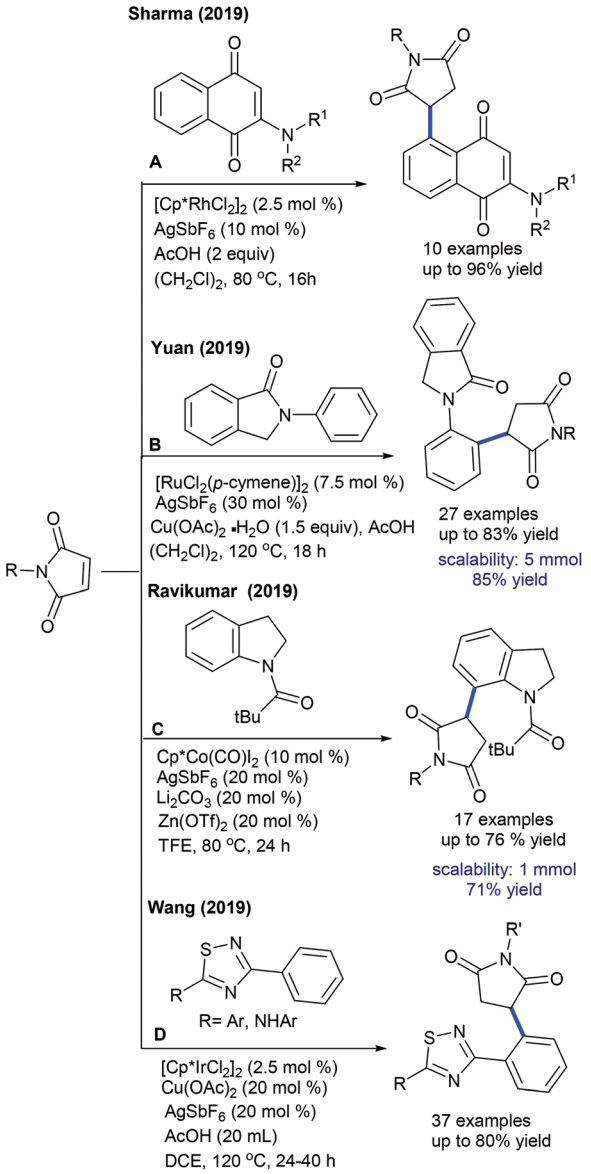
The C5-selective alkylation of 2-amino-1,4-naphthoquinones is found to be successful (Scheme 60A).[45] This synthetic procedure is fairly similar to the previously reported methods.



Scheme 58 *ortho*-Alkylation of aryl aldehydes with maleimides with a transient directing group.

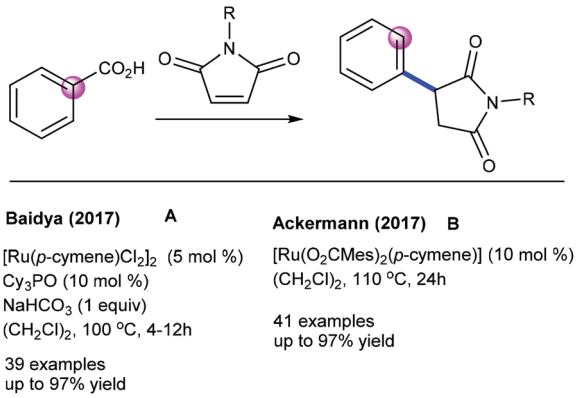


Scheme 59 Hydroarylation of arenes with maleimides.



Scheme 60 Coupling of maleimides with different aryl coupling partners.

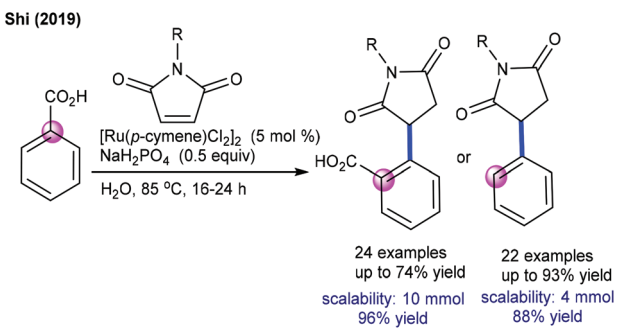
In addition, alkylation of cyclic amides is accomplished (Scheme 60B).[93] Electronic and steric effects significantly affect the reaction. Maleimides having different substitution patterns couple successfully, while unsubstituted N–H maleimide is less reactive. An analogue approach is applied for the synthesis of succinimides *via* C-7 hydroarylation of indoline with maleimide (Scheme 60C).[94] A pivaloyl directing group furnishes the best yield and addition of $Zn(OTf)_2$ is valuable. Recently, the hydroarylation of diphenyl-1,2,4-thiadiazole with maleimide has been achieved (Scheme 60D).[95] The use of an AcOH and $Cu(OAc)_2$ mixture is important. This method shows broad substrate scope, although electron-poor diphenyl-1,2,4-thiadiazole is less reactive. Mechanistic studies involve the generation of a five-membered iridacycle with the reversible C–H cleavage (KIE = 2.0).



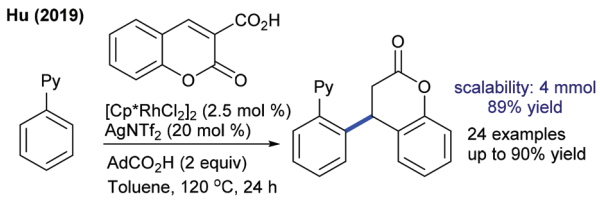
Scheme 61 Alkylation of benzoic acids with maleimides.

Later, Baidya and Ackermann groups reported a Cu- and Ag-free decarboxylative coupling. The combination of $[Ru(p\text{-cymene})Cl_2]_2$, Cy_3PO and $NaHCO_3$ is essential (Scheme 61A).[96,97] Notably, electron-rich benzoic acids react faster, and the C–H activation occurs at a less hindered site when *meta*-substituted benzoic acids are utilized. The Ackermann group demonstrated the catalysis of $[Ru(O_2CMes)_2(p\text{-cymene})]$ with a broad range of aryl and alkyl alkenoic acids and maleimides (Scheme 61B).[97] Kinetic isotopic experiments exhibit a negligible effect, indicating that C–H ruthenation is not a turn-over step. More recently, Shi and co-workers showed an environmentally benign protocol for the hydroarylation using benzoic acids in water (Scheme 62).[98] Depending on the electronic properties of the benzoic acids, two kinds of addition products are formed *viz.* a conjugate or a decarboxylative conjugate.

Coumarin carboxylic acids are excellent coupling partners. The decarboxylative conjugate addition of coumarins with aryl pyridines is found to be successful (Scheme 63).[99] The carboxylic acid group is essential, and a series of substrates react, while electron-deficient substrates show no reaction. In a subsequent study, they showed the stereoselective hydroacylation of bicyclic alkenes with 2-hydroxybenzaldehyde.[100] Instead of $[Ir(OH)(cod)]_2$, the use of $IrCl(cod)_2$ or $[Rh(OH)(cod)]_2$ shows no catalysis, while in the presence of KOH, the former gives comparable results, and the use of BINAP or $(^tBu)_3P$ completely inhibits the reaction. *Exo*-products are observed; however,



Scheme 62 Alkylation of benzoic acids with maleimides in water.

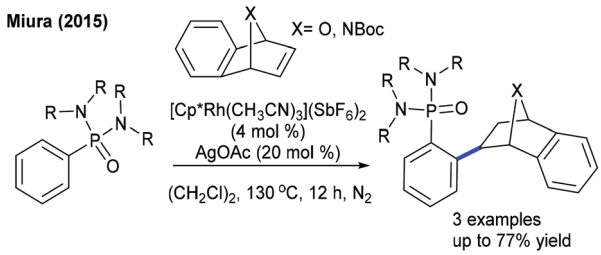


Scheme 63 Synthesis of 4-arylchroman-2-ones.

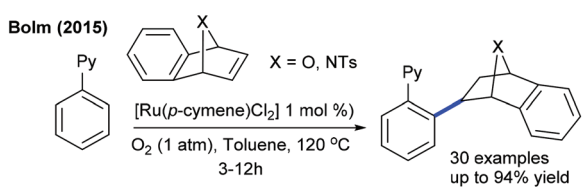
the scope of aldehydes is rather narrow. Later, they extended the hydroarylation of bicyclic alkenes to *N*-sulfonylbenzamides using a dippbz ligand.[101]

The Miura group showed the coupling of oxa/azaheterobicyclic alkenes with aryl phosphoramides (Scheme 64).[35] The electronic nature of the directing groups plays a critical role in achieving the selectivity. Bolm and co-workers disclosed a pioneering example for hydroarylation of heteroarenes with oxa/azabicyclic alkenes (Scheme 65).[102] Dioxygen plays a decisive role in producing the alkylated product. Low catalyst loading (1 mol%) is required and a wide range of heteroarenes and bicyclic alkenes are viable.

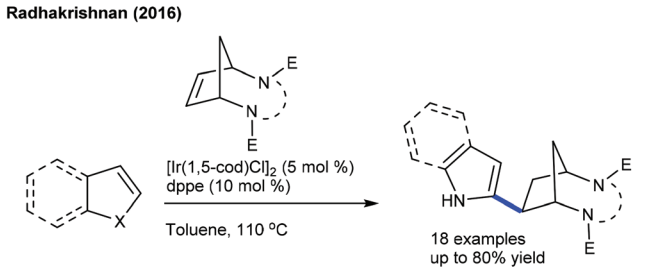
The hydroarylation of urea-derived bicyclic alkenes with heteroarenes is achieved (Scheme 66).[103] The C–H activation takes place at the C-2 position of the heteroarene. Later, Chatani and co-workers reported an *endo*-selective hydroarylation of norbornene (Scheme 67).[104] The reaction is quite efficient albeit high temperature is needed. The mechanism commences with the formation of Rh(I)X species ***a*** by the coordination of the substrate (Scheme 68). Electrophilic addition of the alkene provides complex ***b*** that undergoes a hydride shift to give the Rh–carbene complex ***c***. Oxidative addition of the *ortho*-C–H bond to the Rh center furnishes the complex ***d***, which can lead to the stereo-determining hydride



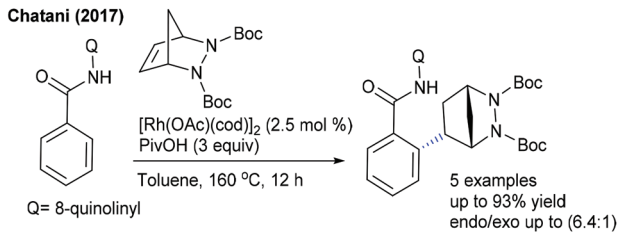
Scheme 64 Functionalization of arylphosphoramides.



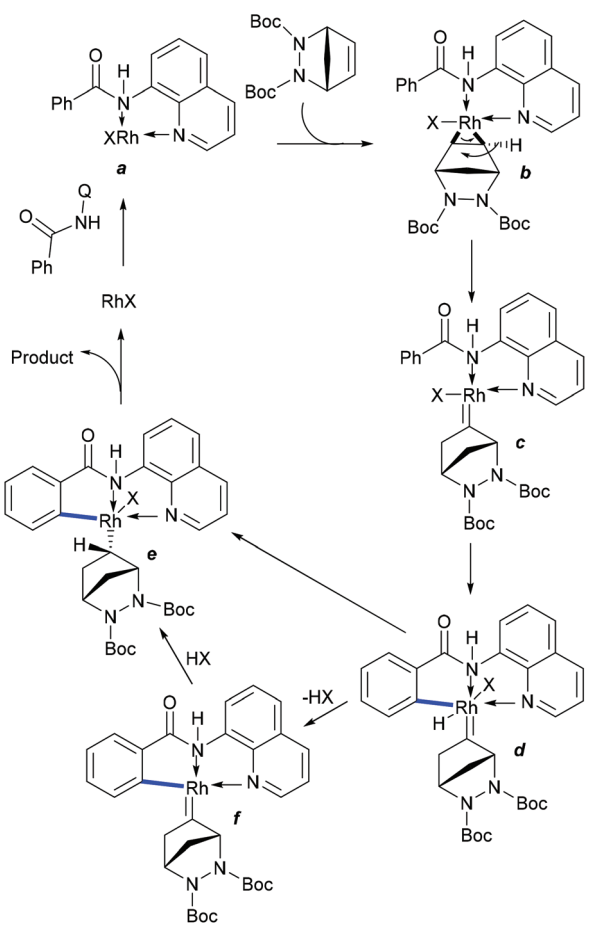
Scheme 65 Hydroarylation of heteroarenes with oxa/azabenzonorbornadienes.



Scheme 66 Hydroarylation of urea-derived bicyclic alkenes with heteroarenes.



Scheme 67 *endo*-Selective C–H hydroarylation of diazabicyclic alkenes.

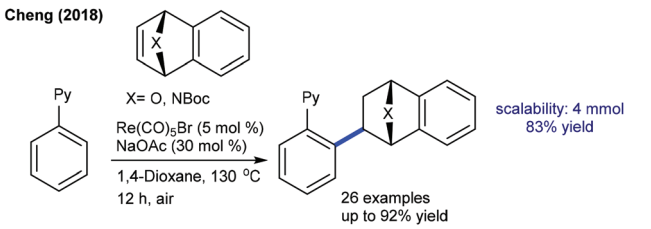


Scheme 68 Mechanism of *endo*-selective C–H hydroarylation of diazabicyclic alkenes.

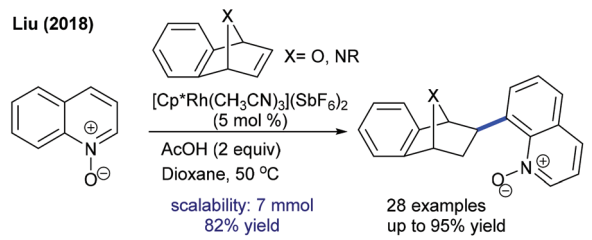
migration to give ***e***. Alternatively, *d* can convert to *e via* elimination and re-addition of HX, which cannot be excluded at this stage. Reductive elimination of ***e*** affords the product and regenerates the Rh(I) species.

Later, the hydroarylation of arenes with heterobicyclic alkenes by Re-catalysis was found to be successful (Scheme 69).[105] The reaction proceeds at high temperature (130 °C) in the presence of NaOAc. A wide range of arenes, heterobicyclic alkenes and heterocyclic azoles work effectively to generate the *exo*-products. Notably, 2-naphthyl pyridine gives a mixture of regioisomers.

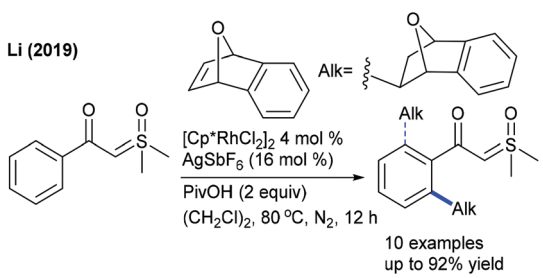
Recently, the hydroarylation of oxa-/azabenzonorbornadienes with quinoline-*N*-oxides has been accomplished (Scheme 70).[106] Electron-withdrawing group attached quinolone *N*-oxides are unsuccessful substrates. Furthermore, the chemo-divergent coupling of sulfoxonium ylides with oxa/azabicyclic alkenes is achieved (Scheme 71).[107] The reaction gives a dialkylated bicycle retained product using PivOH. The electronic properties of aryl sulfoxonium ylides are compatible to give the dialkylated product, while *ortho*-/*meta*-substituted thienyl and naphthyl substrates give the monoalkylated pro-



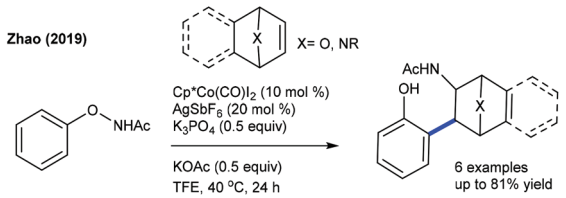
Scheme 69 Reaction of arenes with oxabenzonorbornadienes.



Scheme 70 Hydroarylation of oxa-/azabenzonorbornadienes with quinoline-*N*-oxides.



Scheme 71 Dialkylation of sulfoxonium ylides with oxabicyclic alkenes.

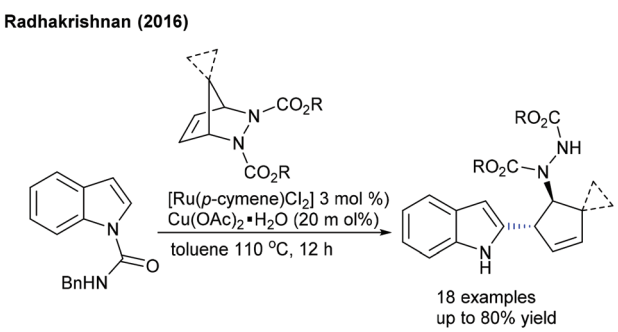


Scheme 72 Carbamination of heterobicyclic alkenes.

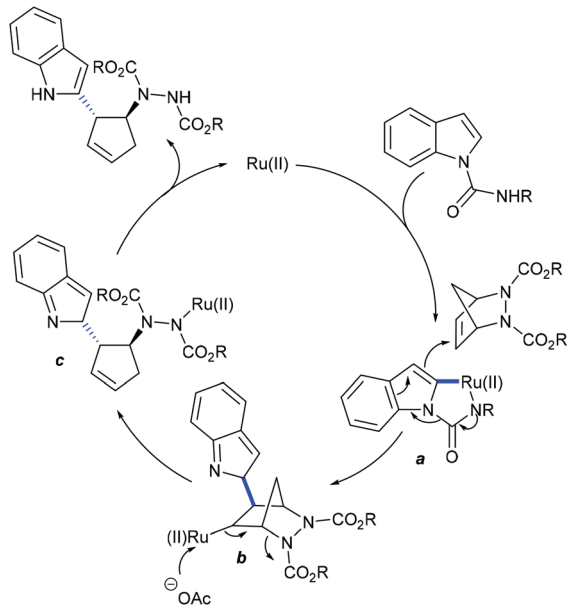
ducts. Furthermore, six examples of *ortho*-C–H functionalization of phenols are achieved *via* the carbamination of heterobicyclic alkenes (Scheme 72).[108] The ONHAc group acts as an oxidizing director, which permits the access to a diverse range of carbaminated products. Good yields are achieved using *N*-phenoxyamides with various bicyclic alkenes; however, the scope of the reaction is quite limited.

5.2. Ring-opening and addition

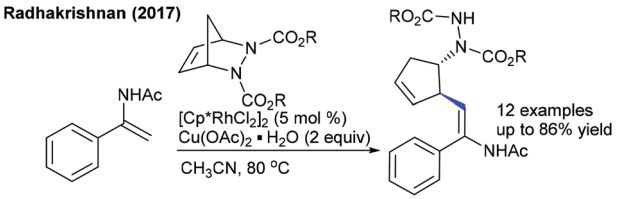
These reactions focus on the use of heterobicyclic alkenes as the coupling partner due to the inherent reactivity of the strained systems. The reaction is initiated by C–H activation of arenes to form the M–C bond and the subsequent interaction of the strained rings leads to the ring-opening and addition products. In 2016, the Radhakrishnan group showed a Ru-catalyzed C-2 functionalization of indole with heterobicyclic alkenes (Scheme 73).[103] Carboxamide serves as a directing group, which is cleaved at the end of the reaction. A substrate with a Ru catalyst can produce the ruthenacycle ***a*** *via* the C–H activation (Scheme 74). Cleavage of the C–N bond of the protecting group promotes the nucleophilic attack on the strained alkene to generate ***b***. The C–N bond cleavage of the bicyclic alkene by the *endo* face *via* addition of acetate to the ruthenium species can generate ***c***, which can undergo demetalation to afford the product and regenerate the Ru catalyst. Later, they have extended the strategy to the coupling of enamides using Rh-catalysis (Scheme 75).[109] They further achieved the synthesis of cyclopentene functionalized aryl ketones with the transient directing group, where an imine acts as an autocleavable directing group.[110] Typically, electron-rich aryl ketones



Scheme 73 C2-Functionalization of indoles with heterobicyclic alkenes.



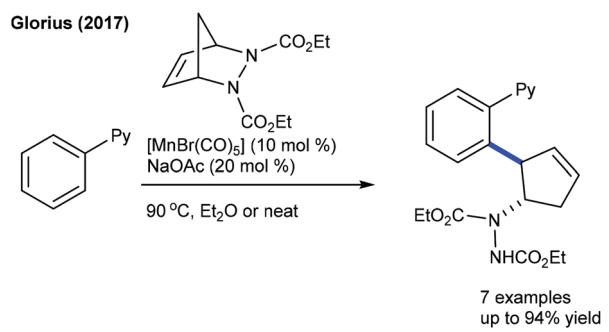
Scheme 74 Mechanism of C2-functionalization indoles with heterobicyclic alkenes.



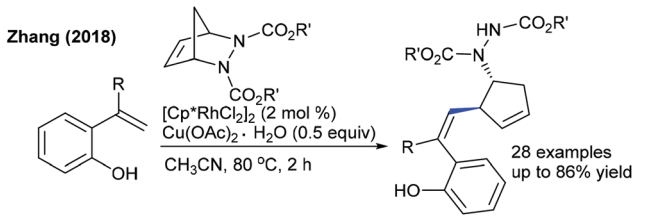
Scheme 75 Desymmetrization of diazabicyclic alkenes with enamides.

produce the best results, while highly electron-deficient NO_2 attached aryl ketones give inferior results.

The Glorius group disclosed a seminal example where $[MnBr(CO)_5]$ shows an excellent activity for the introduction of a cyclopentene unit in arenes with diazabicycles (Scheme 76).[111] Good yields are observed under solvent-free conditions albeit the substrate scope is limited. This reaction involves a C–H activation and six-membered ring scission sequence.



Scheme 76 Ring-opening and addition of arenes with diazabicyclic alkenes.

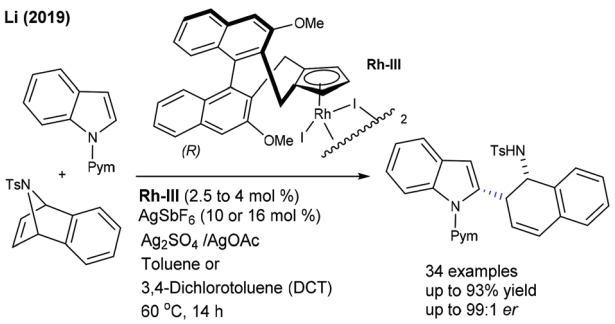


Scheme 77 Vinylic C–H activation-desymmetrization of diazabicyclic alkenes.

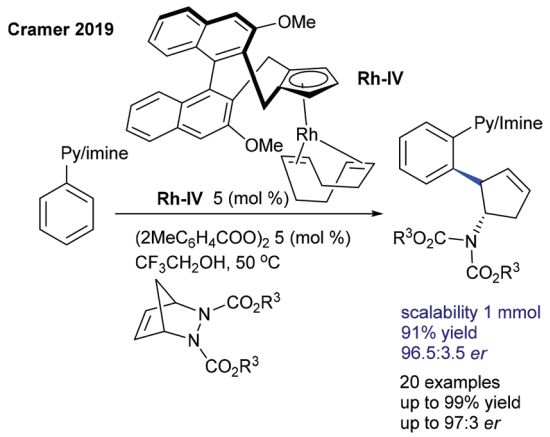
Later, the Zhang group showed a similar type of vinylic C–H activation-desymmetrization of diazabicyclic alkenes with *o*-vinyl phenols (Scheme 77).[112] The advantages of this protocol are low catalyst loading, moderate temperature, and short reaction time. This strategy is extended to the coupling of anilide with 7-azabicyclic alkene.[37] A range of substrates are compatible, while *ortho*-substituted anilides are less reactive. Kinetic isotope studies (KIE = 2.3 (competitive) and 2.7 (parallel)) suggest that the reaction involves the CMD pathway and the C–H cleavage might be the rate-determining step.

Li and co-workers developed the coupling of indole with 7-azabenzonorbornadiene using a Cramer-type $Cp^{x}Rh(III)$ complex (Scheme 78).[113] In search of additives, $AgOAc/Ag_2SO_4$ proves to be a good choice, which activates the alkene and facilitates the C–H activation. A variety of indoles and azabenzonorbornadienes tolerate the reaction. 7-Substituted indoles provide moderate ee, whereas 7-F indole affords high ee. The enantioselective model encompasses rapid rhodacycle formation (KIE = 1.3), alkene insertion and stereospecific β-nitrogen elimination. Subsequently, they came up with a seminal example of enantioselective [3 + 2]-annulation of benzamides with azabicyclic alkenes.[114] *N*-Alkyl substituents plays an indispensable role in the reactivity and selectivity and mainly *N*-cyclopentyl substituted amides provide a favourable result. The product yield and selectivity are significantly increased when the reaction is performed using a mixture of anisole and MTBE as a solvent.

The Cramer group pioneered the enantioselective synthesis of cyclopentylamines employing a chiral $Cp^{x}Rh(III)$-catalyzed C–H activation and ring-opening sequence (Scheme 79).[115] On screening of the chiral Rh precatalysts having different alkene partners, and different benzoate sources, $Cp^{x}RhI(cod)$ and bis(*o*-toluoyl) peroxide give the best results. The nature of alkenes and



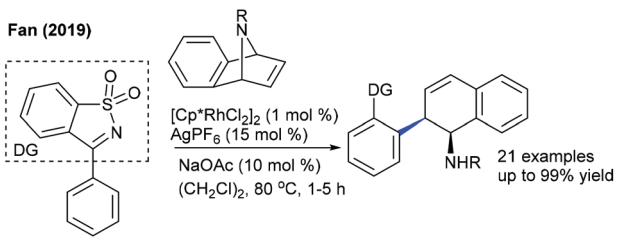
Scheme 78 Coupling of indole with 7-azabenzonorbornadienes.



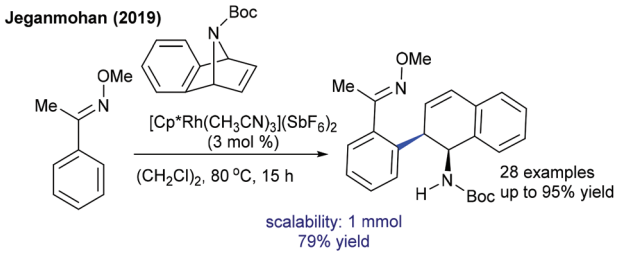
Scheme 79 Ring-opening reaction of arenes with diazabicyclic alkenes.

benzoate sources is largely influences in the reactivity and selectivity. The reaction tolerates a variety of oximes and diazabicycles, providing good ee. Subsequently, they evaluated a series of $Cp^{x}Rh(III)$ catalysts with differently substituted chiral backbones. MeO-biphep type catalysts show excellent reactivity.[116]

Fan and co-workers reported the ring-opening C–H addition of azabenzonorbornadienes with *N*-sulfonyl ketimines (Scheme 80).[117] Both the coupling partners react well, while a slightly lower yield is observed with the sterically congested substrates. Oxabenzonorbornadienes react albeit providing lower yield. They tried to achieve the asymmetric version employing chiral ligands such as (*R*)-BINAP, (*R*)-Difluorphos, (*R*,*S*)-PPF-$PtBu_2$ and (*R*)-SIPHOS-Ph-Mor. This strategy has been extended to the coupling of aryl ketoximes (Scheme 81).[118] The



Scheme 80 Coupling of 7-azabenzonorbornadiene with *N*-sulfonyl ketimines.



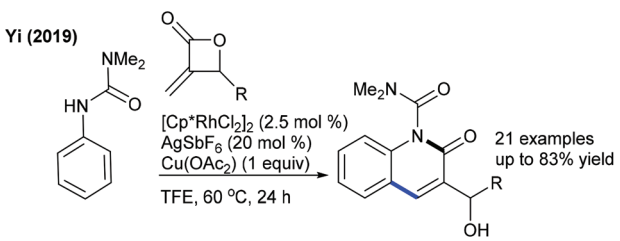
Scheme 81 Coupling of azabenzonorbornadienes with aromatic ketoximes.

reaction is related to Fan's work, however, without the use of an additive. 2-Arylated hydronaphthylamines are formed, which can lead to 13,14-dehydrobenzophenanthridine using HCl. Mechanistic studies include the isolated rhodacycle and H/D labelling experiments.

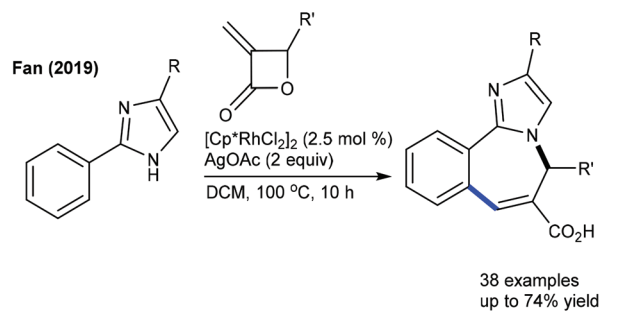
6. Annulation/cyclization

These reactions have been greatly explored. The tandem C–C and C–N coupling of methyleneoxetanones with *N*-phenoxyacetamides is pursued to produce chromene-3-carboxylic acids.[119] The reaction is extended to solvent-controlled cyclization with benzamides. Compared to allylation, 2.5 mol% catalyst is sufficient to carry out the benzoazepine synthesis. β-H elimination is the key step for the product selectivity. These reaction conditions with a slight modification are studied for the coupling of *N*-aryl urea to furnish quinolones (Scheme 82).[120] Product selectivity depends on the solvent choice. For instance, a cyclized product is observed in TFE. Furthermore, this strategy is successful for the [4 + 3]-annulation with 2-aryl-1*H*-imidazoles to give benzoazepines (Scheme 83).[121] In 2-aryl-1*H*-imidazole, the aryl part with *meta*-OMe gives a mixture of regioisomers, and especially the C–H activation occurs in a more hindered site when the reaction of the *meta*-fluoro derivative is studied. Waldmann groups developed the synthesis of JasCp ligands for enantioselective C–H activation of benzamides with alkenes including dihydrofuran (Scheme 84).[122]

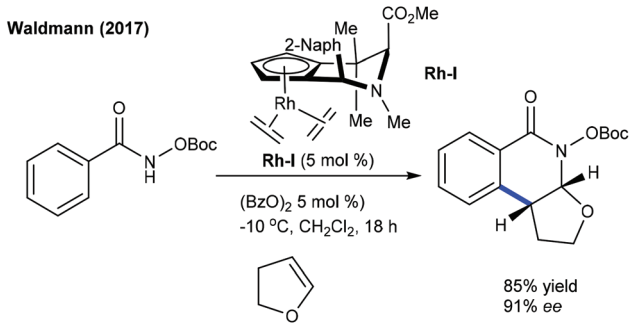
Miura and co-workers presented the oxidative coupling of benzamides with maleimides (Scheme 85A).[123] The use of



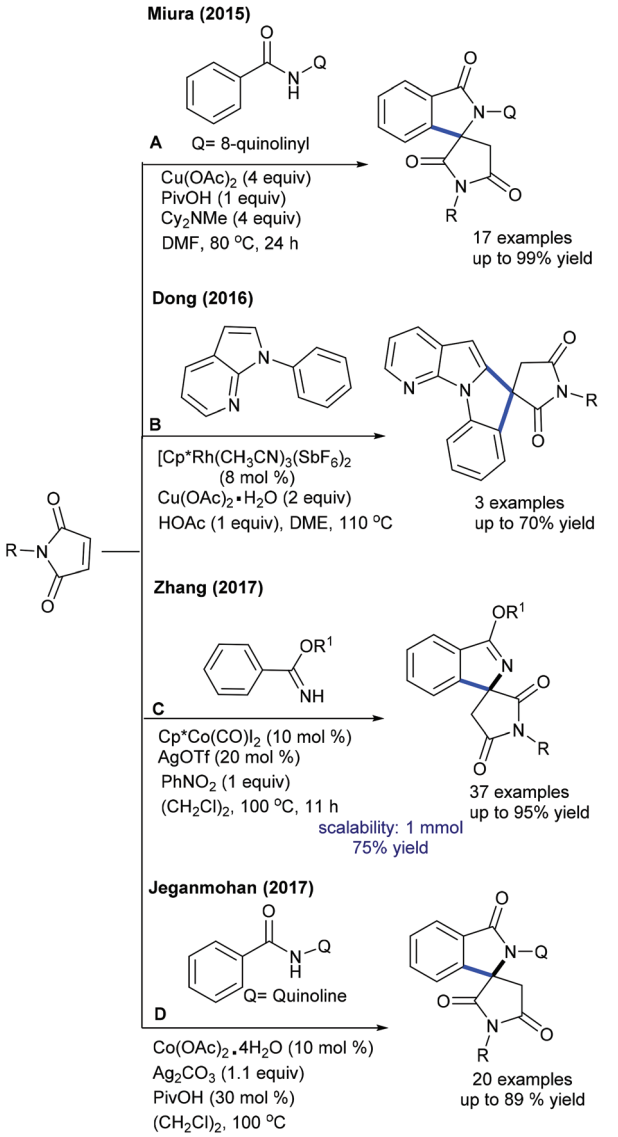
Scheme 82 Reaction of *N*-aryl ureas with methyleneoxetanones.



Scheme 83 Annulation of 2-aryl-1*H*-imidazoles with methyleneoxetanones.



Scheme 84 Coupling of benzamides with dihydrofuran.



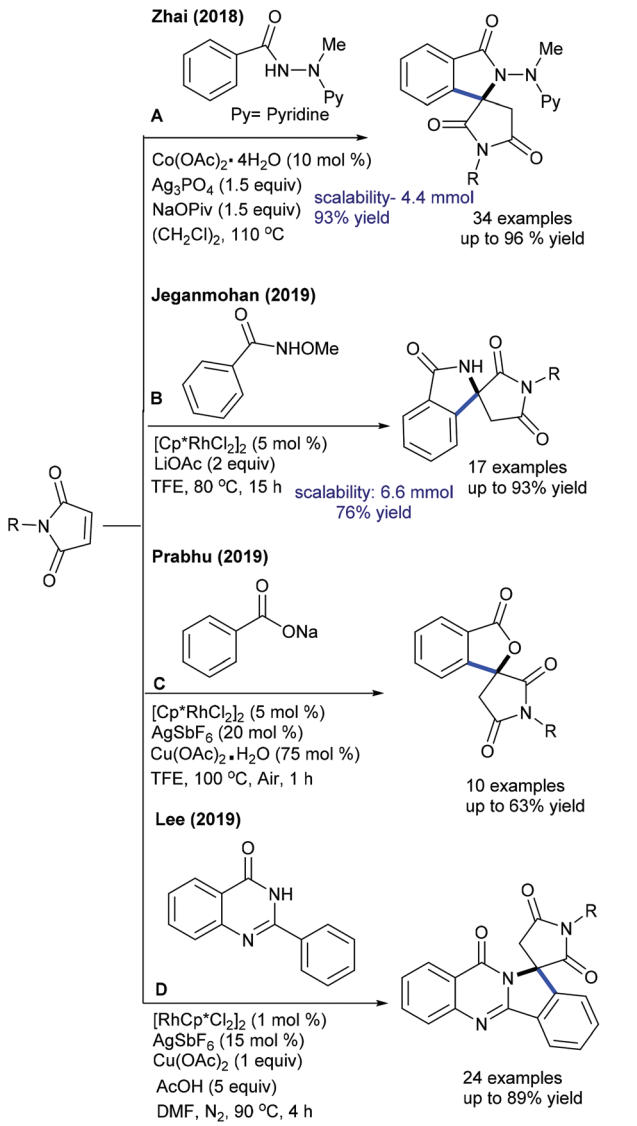
Scheme 85 Oxidative coupling of benzamides/arenes with maleimides.

Cy_2NMe improves the chemoselectivity and accelerates the reaction. Furthermore, the annulation with 7-azaindole is successful *via* a double C–H activation strategy to provide spiro

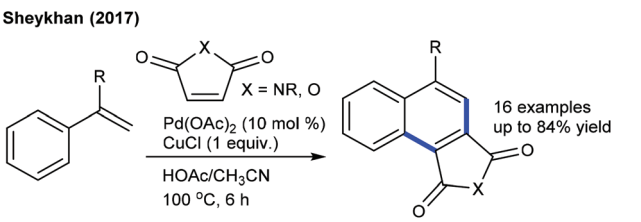
products in the presence of AcOH (Scheme 85B).[124] The oxidant-free coupling with benzimidates is successful in affording spirosuccinimides (Scheme 85C).[125] Excellent yields of the desired products are acquired with a series of substituted benzimidates and maleimides. Jeganmohan and co-workers focused on the synthesis of isoindolone spirosuccinimides (Scheme 85D).[126] The reaction involves a Co(I)/Co(III) catalytic cycle with irreversible fast C–H activation.

Later, the assembly of spirosuccinimides *via* directed C–H spirocyclization is achieved (Scheme 86A).[127] Functional group tolerance is an important feature, whereas the steric effects influence the reactivity. The directing group is cleavable *via* reductive cleavage by SmI_2. Recently, the use of oxidizing directing groups has attracted considerable attention because they obviate the utilization of stoichiometric external oxidants, and the C–H activation proceeds *via* the redox economy under mild reaction conditions.[128] The use of N–O oxidizing group directed C–H activation and 1,1 cyclization has been demonstrated for the coupling with *N*-methoxy benzamides (Scheme 86B).[129] Various functional groups tolerate the reaction, though a sterically encumbered substrate shows less reactivity. Interestingly, the reaction of 2-thienyl benzamide furnishes the alkenylated product instead of a cyclized one. A similar type of coupling is accomplished with sodium benzoate (Scheme 86C).[44] This solvent controlled cationic Rh-based reaction is applied for a small library of substrates. Furthermore, the coupling with pyrrolidinediones is studied to produce polyheterocycles (Scheme 86D).[130] This low catalyst loading method is applicable to diverse substrates to give the spiroproducts. The mechanism involves the reversible C–H cleavage (KIE = 2.33), migratory insertion of maleimide, E2-elimination and aza-Michael addition. Tandem reaction of maleimides with styrenes is accomplished using pseudo-Diels–Alder reaction (Scheme 87).[131] Substrates with various substitution patterns are compatible.

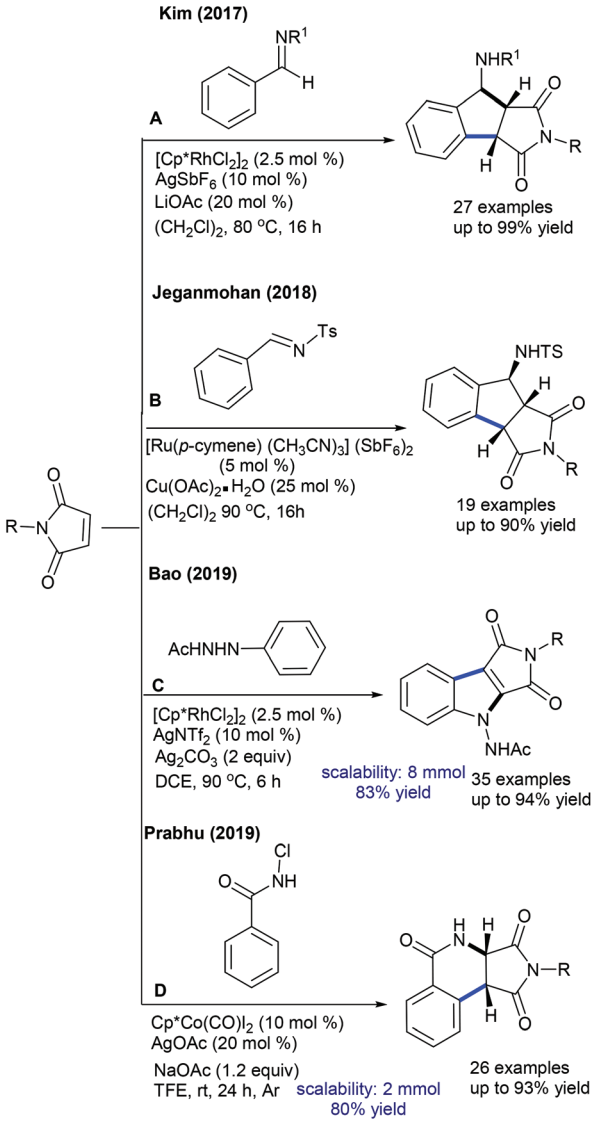
The coupling with *N*-sulfinyl ketoimine has been found to be effective.[132] An *in situ* formed cationic Rh-catalyst affords superior results compared to a cationic Rh-complex, and the *N-tert*-butylsulfinyl group plays a critical role. In addition, the coupling with azobenzenes produces oxindoles *via* a Rh-catalyzed C–H activation and Zn-mediated reductive cyclization.[133] These reaction conditions are extended to [3 + 2]-annulation with cyclic *N*-acyl ketimine to yield spiroisoindolinones,[134] while the coupling with *N*-sulfonyl aldimines readily takes place to afford 1-aminoindanes (Scheme 88A).[135] Pertinently, the *N*-sulfonyl part in aldimine is important, and on switching from the sulfonyl to aryl/alkyl/alkylsulfinyl group, the reaction fails. The Luo group has overcome the impediment of this procedure, as unactivated aromatic aldimines/ketimines are utilized for the synthesis of 1-aminoindanes.[136] This neutral Rh/Cu-based catalytic system is suited for a wide range of cyclic/acyclic ketimines/aldimines. Particularly, the electron-rich cyclic ketimines provide the best yields. In addition, the Jeganmohan group showed the Ru-catalyzed cycloaddition of *N*-sulfonyl aryl aldimines with maleimides (Scheme 88B).[137] The *N*-sulfonyl directing group and acetate ion sources are crucial for the success of this reaction. This strategy is extended to the construction of succinimide linked oxindoles.[138] An excess of $Cu(OAc)_2{\cdot}H_2O$ is required and several *N*-aryl acrylamides react with a range of maleimides, while a mixture of regioisomers is obtained with *meta*-halogen substituted aryl acrylamides. This strategy is extended to an oxidative



Scheme 86 Synthesis of polyheterocycles bearing pyrrolidinediones.



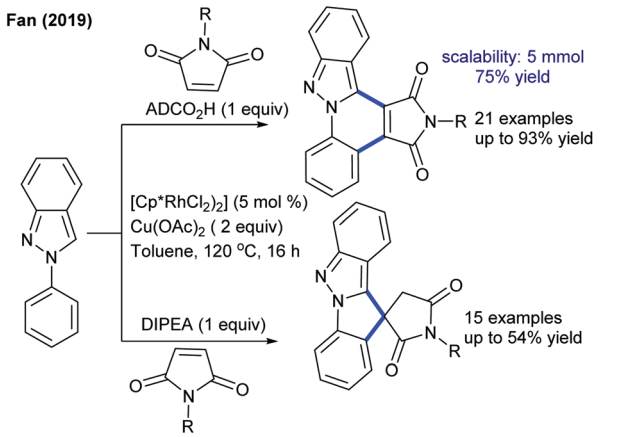
Scheme 87 Coupling of styrenes with maleimides.



Scheme 88 Synthesis of 1-aminoindanes/fused heterocycles.

[3 + 2]-annulation of 2-acetyl-1-arylhydrazines to give pyrrolo [3,4-*b*]indole-1,3-diones (Scheme 88C).[139] Hydrazine with an electron-withdrawing group displays less reactivity. Furthermore, the [4 + 2]-annulation of *N*-chlorobenzamides with maleimides is achieved (Scheme 88D).[140] The use of the N–Cl group plays a foremost role, whereas other oxidizing directing groups such as N–OMe and N–OH are unreactive. However, the sterically congested benzamide is less reactive. Variations of alkyl protected maleimides are applicable to afford the products in good yields.

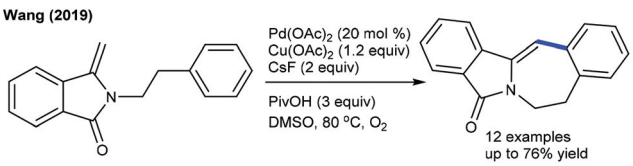
The coupling of maleimides has been further extended to the construction of fused and spiro polyheterocycles (Scheme 89).[141] $AdCO_2H$ serves as an additive to give fused heterocycles, while a spiro compound is formed using diisopropylethylamines. This switchable procedure is utilized to access fused or spiro polyheterocycles, though the basic conditions give a mixture of products. The mechanism involves



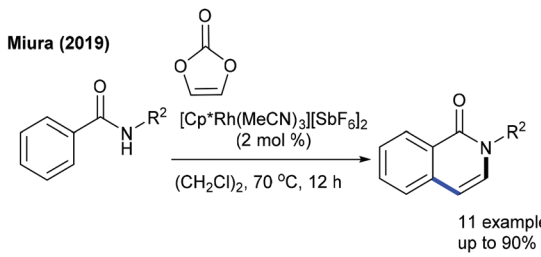
Scheme 89 Oxidative annulation of 2-aryl indazoles with maleimides.

Rh(III)/Rh(I) catalysis and kinetic isotope studies (KIE = 5.3) suggest that the C–H activation step might be the rate-limiting step. The Wang group described the arylation of enamides (Scheme 90).[142] Addition of a Brønsted acid promotes the reaction and O_2 serves as the oxidant. This protocol affords a small panel of fused N-heterocycles. A mixture of regioisomers is generated in 3-substituted substrates. Aporhoeadane alkaloids palmanine, lennoxamine and chilenamine can be synthesized in three or four steps.

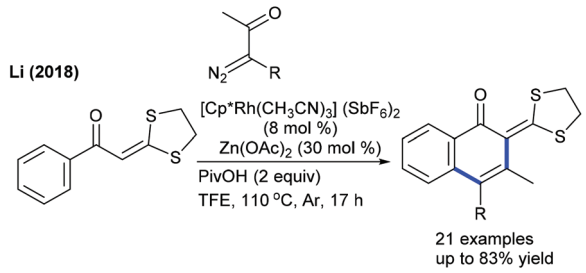
Recently, the Miura group has found the coupling of vinylene carbonate with benzamides (Scheme 91).[143] An external oxidant and a base are not required, as vinylene carbonate itself acts as an internal oxidant and acetylene surrogate. The tandem C–C coupling of α-benzoylketene dithioacetols with α-diazoketones is found to be successful in the presence of PivOH to give naphthalenones (Scheme 92).[59] This double C–H



Scheme 90 Direct intramolecular arylation of enamide by C–H activation.



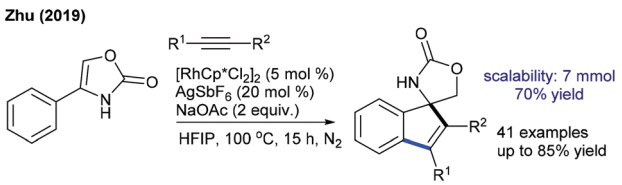
Scheme 91 Annulative coupling of vinylene carbonate with benzamide.



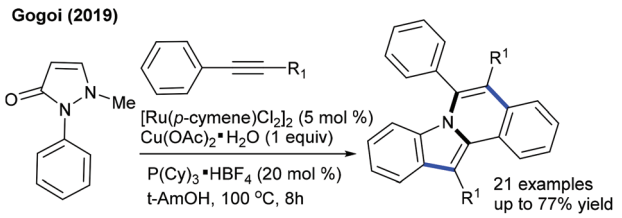
Scheme 92 Coupling of α-benzoylketene dithioacetols with α-diazoketones.

activation shows good functional group tolerance but the reaction of α-diazomalonate gives an uncyclized product.

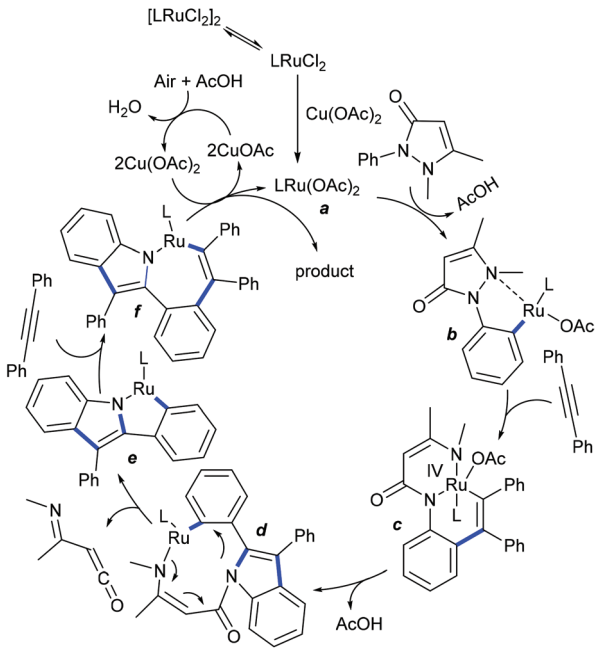
Few studies are focused on the coupling of alkynes to lead to polycyclic scaffolds. Redox-neutral coupling with 4-phenyl-1,3-oxazol-2(3*H*)-ones is realized to give spiro[indene-1,4′-oxazolidinones] (Scheme 93).[144] The reaction tolerates a broad range of substrates. An electron-rich alkyne couples efficiently, and even unsymmetrical and heterocyclic alkynes work albeit providing moderate yields. This strategy is extended to the oxidative annulation of antipyrine with alkynes *via* Ru catalysis (Scheme 94).[145] A broad range of substrates react, while unsymmetrical alkynes give a mixture of regioisomers. Ru(*p*-cymene)Cl_2 with $Cu(OAc)_2$ can generate the active Ru(II) catalyst ***a***, which can react with substrate *via* directed irreversible C–H to produce ***b*** (Scheme 95). Chelation of the alkyne and subsequent migratory insertion and cleavage of the N–N bond can produce the Ru(IV) complex ***c***. Reductive elimination of Ru-metal and additional C–H activation of the substituted phenyl ring of the indole derivative can deliver the nine-membered Ru-complex ***d***. Elimination of the ketene type fragment can give the ring contracted Ru-complex ***e***. Another molecule of alkyne insertion can give ***f*** that can lead to reductive elimination to furnish the product and Ru species, which is readily oxidized by $Cu(OAc)_2$ to fulfil the catalytic cycle.



Scheme 93 Coupling of 4-phenyl-1,3-oxazol-2(3*H*)-ones with alkynes.



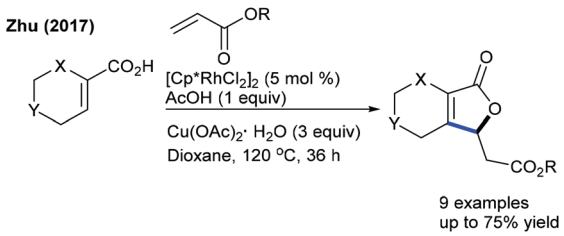
Scheme 94 Oxidative annulation of antipyrine with alkynes.



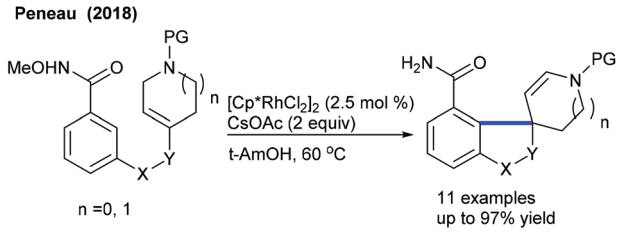
Scheme 95 Mechanism of Ru-catalyzed oxidative annulation.

Rh-Catalyzed coupling of acrylates with heterocyclic alkenyl carboxylic acids can be achieved to give furan-2(5*H*)-ones (Scheme 96).[146] High oxidant loading and longer reaction time are the notable issues. The reaction utilizes the carboxylic acid directed C–H activation, migratory insertion, β-hydride elimination and Michael addition processes. While many advances are made in the annulation of various coupling partners to diverse heterocycles,[147] limited studies are focused on the synthesis of spirocyclic compounds. The Peneau group showed the synthesis of spiropiperidines (Scheme 97).[148] The differently substituted aryl ring, linkers and ring-size of the N-heterocycles are tolerated to provide the target spirocycles, which can be converted to tetracyclic compounds by treatment with TFA. An electron-withdrawing protecting group on the nitrogen is necessary; however, a Cbz protected variant is an unsuccessful substrate.

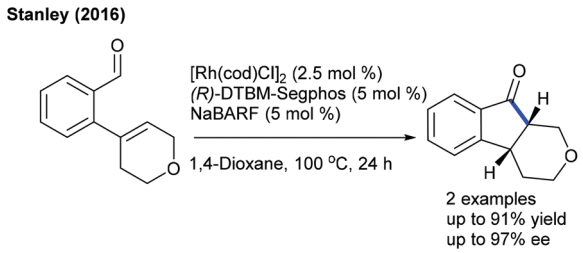
The Stanley group showed two examples of enantioselective Rh-catalyzed hydroacylation and α-epimerization (Scheme 98).[149] (*R*)-DTBM-Segphos is used as a chiral ligand and NaBARF (BARF = tetrakis(3,5-bis(trifluoromethyl)phenyl)-



Scheme 96 Reaction of heterocyclic alkene carboxylic acid with acrylates.



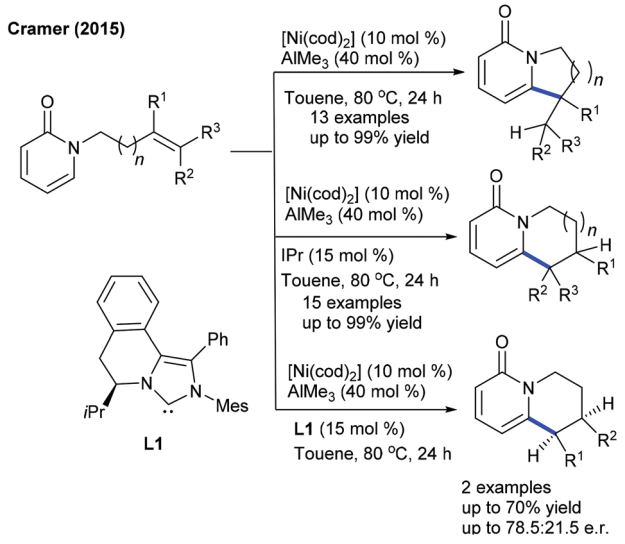
Scheme 97 Synthesis of spiropiperidine derivatives.



Scheme 98 Hydroacylation/α-epimerization of 2-(3,6-dihydro-2*H*-pyran-4-yl)aryl aldehydes.

borate) acts as an additive, which allows the intramolecular coupling of 2-(3,6-dihydro-2*H*-pyran-4-yl)benzaldehydes to provide the products with up to 97% ee. In contrast, other heterocyclic alkenes such as nitrogen and sulfur analogues are unsuccessful substrates.

Few studies are focused on the use of Ni-catalysis. The Cramer group reported regio-divergent annulation of pyridones (Scheme 99).[150] 1,6-Annulated pyridones are obtained and the ligand controls the mode of cyclization. For instance, cyclooctadiene fosters *exo*-cyclization, and the bulky N-heterocyclic carbene ligand induces *endo*-cyclization. Substrates bearing 1,2-disubstitution across the double bond

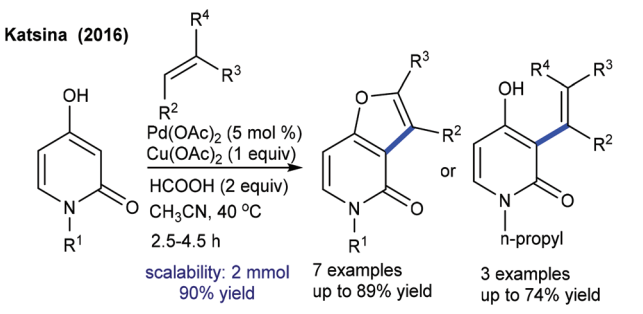


Scheme 99 Regio-divergent annulation of pyridones.

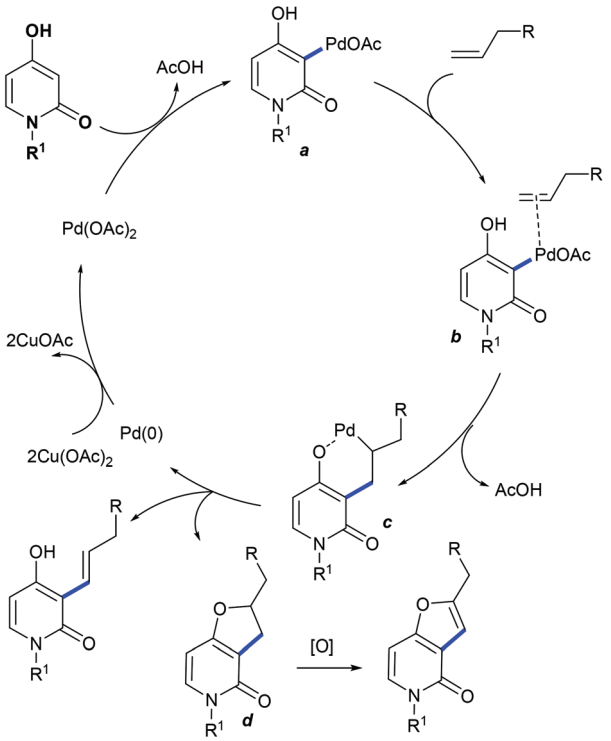
are coupled *via* both the modes. Furthermore, the enantioselective synthesis of 1,6-annulated 2-pyridones exploiting a chiral N-heterocyclic carbene **L1** is successful. The reaction proceeds through *endo*-cyclization to give the product in moderate ee. In continuation, the screening of various chiral N-heterocyclic carbene ligands is performed. A sterically congested NHC-ligand provides the best selectivity.[151] 2-Pyridones and 4-pyridones cyclize to enantiopure products, while *cis*- or *trans*-alkenes react well, albeit with lower selectivity.

The Katsina group showed the coupling of alkenes with 4-hydroxy-2-pyridones to give furo[3,2-*c*]-pyridones (Scheme 100).[152] Product selectivity depends on the nature of the solvent and additives. The reaction using HCOOH as an additive in CH_3CN provides the cyclized product along with a minor amount (>10%) of its regioisomer. A small panel of alkenes are studied, with 2-pentene and α-pinene affording uncyclized products. Electron-rich/unactivated alkenes are less reactive and the substrate scope is somewhat limited. A substrate with $Pd(OAc)_2$ can provide ***a*** *via* C–H activation (Scheme 101). Migratory insertion of pyridone–palladium species ***b*** to the alkene can give ***c***, which can lead to reductive elimination to yield ***d*** or the alkene and Pd(0) species that is oxidized by $Cu(OAc)_2$ to complete the catalytic cycle.

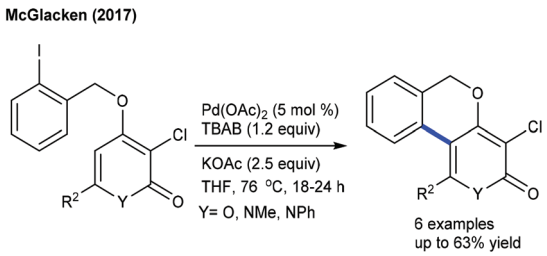
The regioselective arylation of 2-pyrones has been found to be successful.[153] PivOH significantly improves the reaction yield. A series of substrates are studied; however, 6-benzyl and 6-(4-iodophenyl) derivatives are unsuccessful substrates and a C-3 substituted 4-fluorophenyl derivative produces a mixture of regioisomers, while 2-coumarin, 2-pyridone and 2-quinolone are competent, and the procedure is also compatible with the arylation of 3-halo-2-pyrones.[154] PPh_3 is suitable for 3-bromo-2-pyrones, while 3-chloro-2-pyrone produces the best results using the bulkier $PCy_3{\cdot}HBF_4$. Ligand-free C5-arylation of pyrones and pyridones can be achieved (Scheme 102).[155] Blocking at the C3-position with a chlorine atom is essential; however, the protocol suffers from limited substrate scope. The cyclization of 4-phenoxy coumarin can be realised *via* double C–H activation.[156] This method obviates the use of activating groups (bromo and iodo groups), while it needs high temperature (140 °C). The synthesis of flemichapparin C is covered and the mechanism involves the reversible C–H activation (KIE = 1.08).



Scheme 100 Synthesis of functionalized furo[3,2-*c*]-pyridones.

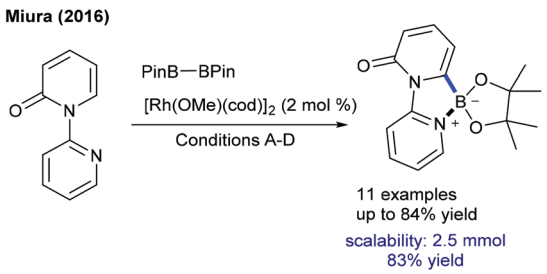


Scheme 101 Mechanism for the synthesis of functionalized furo[3,2-*c*]-pyridones.

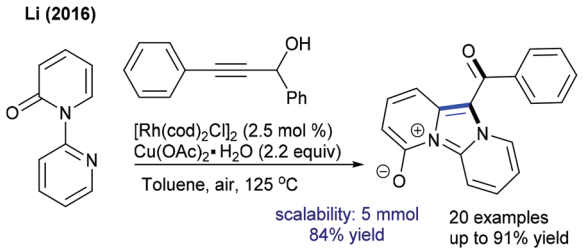


Scheme 102 Intramolecular C5-arylation of pyrones/pyridones.

The Miura group reported the C6-borylation of pyridones (Scheme 103).[157] This procedure is highly sensitive towards the electronic nature of the substrates. The products are useful compounds for further synthetic transformations albeit limited substrates scope is an issue of this process. Propargyl



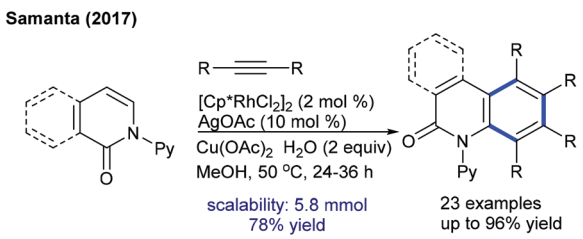
Scheme 103 C6-Borylation of pyridones.



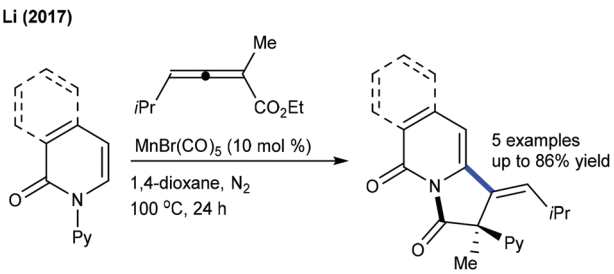
Scheme 104 Alkenylation and concomitant intramolecular annulation.

alcohols are coupled with 2*H*-[1,2′-bipyridin]-2-one (Scheme 104).[158] The reactivity of both the coupling partners is significantly disturbed by the steric and electronic nature of the functional groups. This strategy is extended to the coupling of anthranils with pyridones to produce quinolone-fused polycycles.[159] Internal alkynes can be coupled with pyridones/quinolones (Scheme 105).[160,161] The reaction involves the well-established Rh(III)/Rh(I) catalytic cycle and the final π-conjugated heterocycles display a good sensing ability in the detection of nitroaromatics. In addition, the diheteroarylation of allenes is successful *via* the integration of C–H activation and a Smiles rearrangement (Scheme 106).[162] These reaction conditions are extended to C–H prenylation of pyridine and isoquinolone with allenes employing NaOAc.[163] However, these reactions are limited to heterocyclic alkenes.

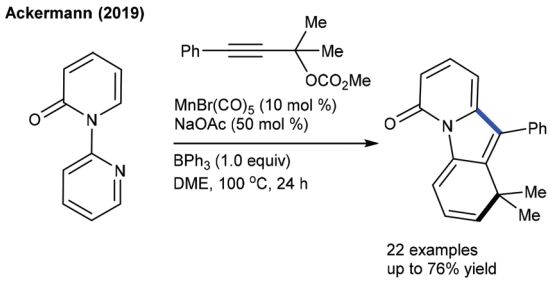
Recently, Ackermann and co-workers pioneered a pivotal example of the synthesis of structurally complex polycycles *via* a C–H activation, Diels–Alder reaction and alkyne annulation sequence (Scheme 107).[164] A variety of pyridones and substituted propargylic carbonates participate with good yields. The proposed mechanism involves a reversible fast C–H cleavage



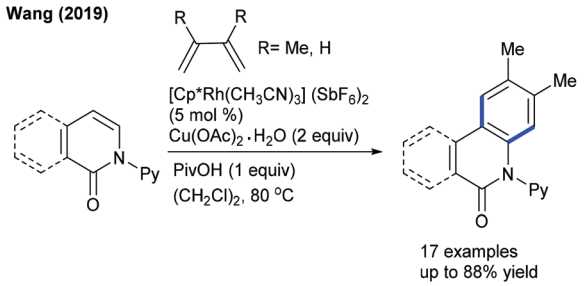
Scheme 105 Oxidative coupling of pyridones with alkynes.



Scheme 106 Diheteroarylation of allenes.



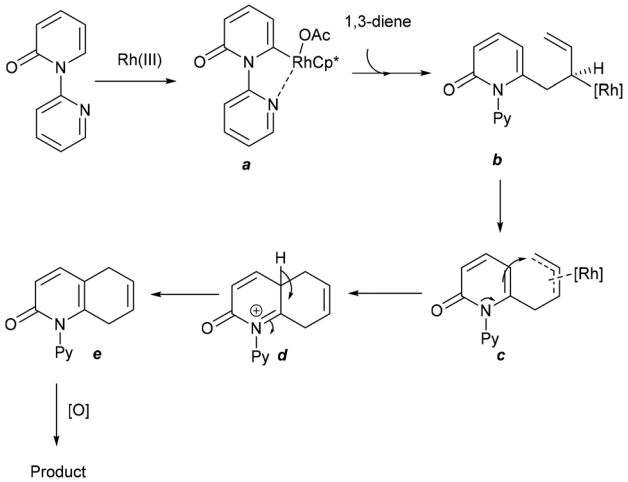
Scheme 107 Synthesis of structurally complex polycycles.



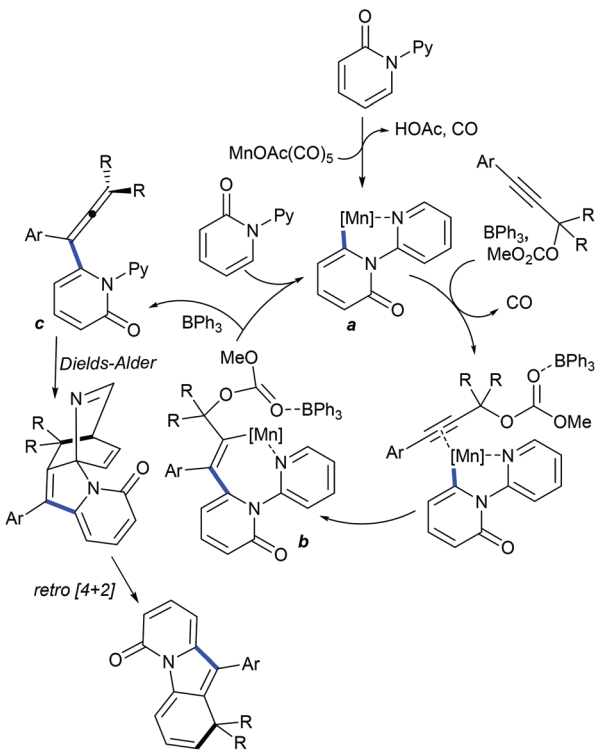
Scheme 109 [4 + 2]-Cycloaddition of pyridones/isoquinolones with 1,3 dienes.

(KIE = 1.2) *via* chelation assistance to afford a manganacycle ***a*** (Scheme 108). Alkyne insertion leads to the formation of ***b***. Subsequent β-oxygen elimination provides ***c*** and regenerates the active catalyst. A BPh_3-mediated Diels–Alder reaction with cyanide elimination *via* retro-Diels–Alder reaction affords the final product.

The Wang group reported a [4 + 2]-cycloaddition of heterocycles including pyridones and isoquinolones with 1,3 dienes (Scheme 109).[165] The mechanism involves Rh-catalyzed C–H activation to produce rhodacycle ***a*** (Scheme 110). Subsequent coordination and insertion of a 1,3-diene can form the σ-allyl metal species ***b***, which presumably exists in equilibrium with the π-allylmetal species ***c***, which may undergo intramolecular nucleophilic allylic substitution to deliver ***d*** that on deprotonation can give ***e***. The latter can convert to the product *via* an oxidation process. This strategy has been extended to the coupling of pyridones with 1,3-enynes to give quaternary ammonium salts.[166]

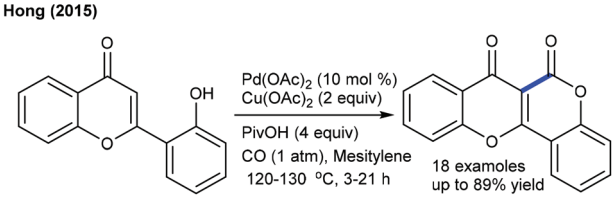


Scheme 110 Reaction pathway of [4 + 2]-cycloaddition of pyridones/isoquinolones with 1,3-dienes.

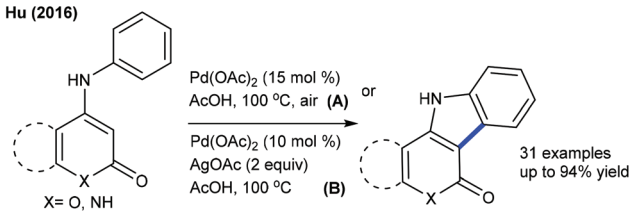


Scheme 108 Catalytic cycle of Mn-catalyzed synthesis of complex polycycles.

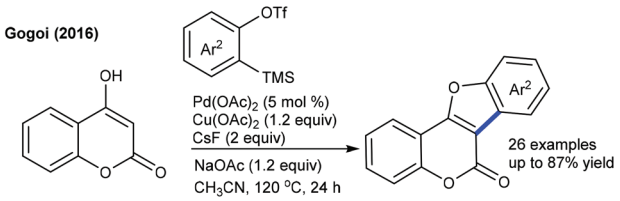
The carbonylation of 2-phenol chromone can be pursued to produce frutinone (Scheme 111).[167] Solvent plays the profound role, while $Cu(OAc)_2$ acts as the oxidant. A series of substrates are tolerated, with some derivatives inhibiting the activity of the CYP1A2 enzyme. Activation of the C–H bond occurs through electrophilic palladation. Hu and co-workers focused on intramolecular C–C coupling of coumarins to produce indole[3,2-*c*]coumarins (Scheme 112).[168,169] Method A utilizes air as the oxidant and excludes the use of an additional base though it needs higher catalyst loading (15 mol%), while



Scheme 111 Carbonylation of 2-phenolchromone.



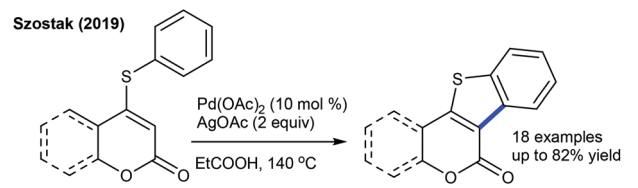
Scheme 112 Synthesis of indole[3,2-*c*]coumarins.



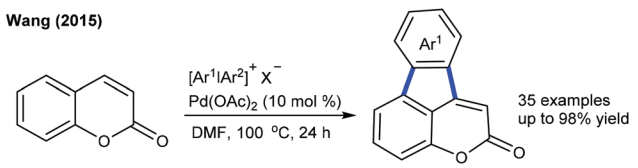
Scheme 115 Oxidative annulation of 4-hydroxycoumarins with an aryne.

method B uses AgOAc as the oxidant. The former is typically suitable for unsubstituted coumarin, while the later works well for the substituted coumarin. This method is extended to the synthesis of indolo[3,2-*c*]pyrones and indolo[3,2-*c*]quinolinones. Later, a couple of reports appeared on the synthesis of indole[3,2-*c*]coumarins that are closely related to the earlier methods.[170] A similar strategy is applied to benzothiophene synthesis (Scheme 113).[171] *ortho*-/*para*-Functionalized thiocoumarin/pyrone react well, while, the reaction of *meta*-functionalized substrates is not examined.

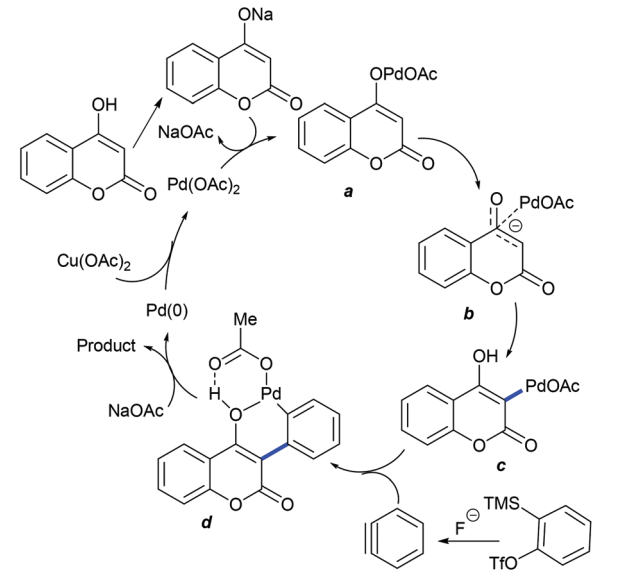
Apart from intramolecular C–C couplings, tandem inter and followed by intramolecular C–C couplings has also been explored.[172–174] Diaryliodinium salts couple with coumarin to yield 4,5-benzocoumarins (Scheme 114).[173] The reaction tolerates a broad range of functional groups, although disubstituted coumarins are less reactive. Furthermore, the coupling of 4-hydroxycoumarin with an aryne (generated *in situ*) is successful (Scheme 115).[174] Electron-deficient coumarins exhibit greater reactivity compared to electron-neutral/rich substrates. Mono-substituted arynes provide a mixture of regioisomers and the synthesis of flemichapparin C is covered. The proposed catalytic cycle begins with the Pd-salt ***a*** of 4-hydroxycoumarin (Scheme 116). Formation of the Pd(II) species ***b*** and the subsequent C-3 C–H activation occur to produce ***c***, which undergoes carbopalladation of the aryne to afford ***d***. Reductive elimination gives the product and Pd(0),



Scheme 113 Synthesis of benzothiophenes.



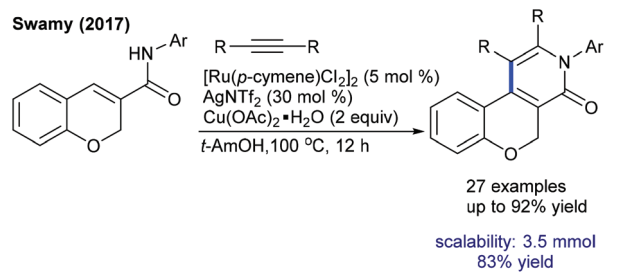
Scheme 114 Vicinal double C–H activation of diaryliodinium salts with coumarins.



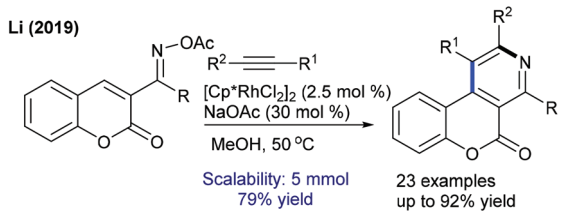
Scheme 116 Mechanism of coumestan synthesis from 4-hydroxycoumarins and benzyne.

which is reoxidized to Pd(II) by $Cu(OAc)_2$ to resume the catalytic cycle.

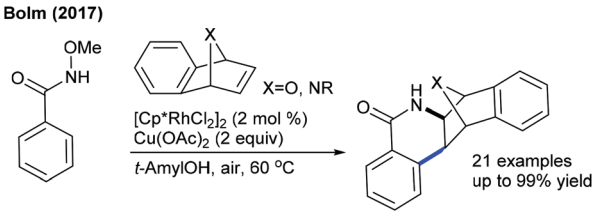
Swamy and co-workers reported carboxamide directed C–C and C–N couplings of 2*H*-chromenes with alkynes to produce benzopyrone-fused pyridones (Scheme 117).[175] The yields are good, although the substrate scope is rather constrained with respect to 2*H*-chromene. Double C–H activation is achieved with an excess alkyne; however, high catalyst loading (8 mol%) and elevated temperature are essential. Later, the coupling of alkynes with coumarinyl ketoxime esters can be accomplished under redox-neutral conditions (Scheme 118).[176] A set of func-



Scheme 117 Assembly of benzopyrone-fused pyridones.



Scheme 118 Annulation of coumarinyl ketoxime esters with alkynes.



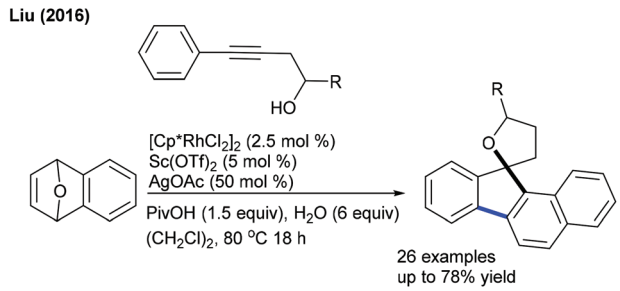
Scheme 121 Annulation of *N*-methoxybenzamides with heterobicyclic alkenes.

tionalized coumarinyl ketoxime esters are converted into the target compounds, while unsymmetrical alkynes give a mixture of regioisomers. The scope of alkynes is limited since the alkyl substituted alkynes and *Z*-ketoximes display no reaction.

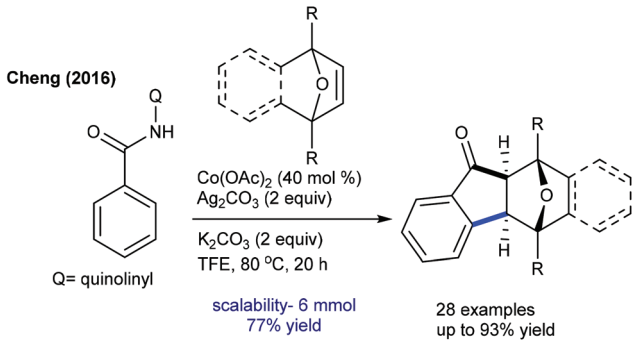
Heterobicyclic alkenes can be coupled by different pathways to produce the annulated compounds. In 2016, the coupling of alkynol with oxa/azabicyclic alkenes has been achieved (Scheme 119).[177] Using synergistic Rh(III) and Sc(II) catalysis, a broad range of substrates can be coupled. In the same year, the Co-catalyzed diastereoselective [3 + 2]-cycloaddition of bicyclic alkenes with aromatic amides was achieved (Scheme 120).[178] A wide range of substituted aromatic amides and oxabicyclic alkenes are efficiently coupled. However, azabicyclic alkenes show inferior results. The Bolm group accomplished a similar annulation of *N*-methoxybenzamides with heterobicyclic alkenes (Scheme 121).[179] Electron-rich oxabenzonorbornadienes give superior results. Similarly, the coupling of *N*-methoxyindazomides can be accomplished with heterobicyclic alkenes under Rh–Ag catalysis, which provides diverse indolo[3,2-*c*]heteroarenes.[180]

The Glorius group came up with a rare example of the synthesis of polycycles using the combination of C–H activation and Wagner–Meerwein-type reaction[181] of *N*-phenoxyacetamide with azabenzonorbornadiene (Scheme 122). NMR studies reveal that the reaction of a rhodacycle with an alkene at low temperature yields an alkene inserted Rh-complex and produces an unstable spirocyclopropane (detected by NMR), which on treatment with AcOH undergoes a rearrangement to give the product. The proposed catalytic cycle starts with the formation of rhodacycle ***a*** *via* irreversible fast C–H metallation (KIE = 1.0) (Scheme 123). Insertion of the alkene generates the seven-membered rhodacycle ***b***. Protonation using AcOH furnishes ***c***, which readily transforms to ***f*** *via* an intramolecular nucleophilic attack and acid promoted rearrangement of ***d*** to deliver the product. The protonation of ***e*** releases the active Rh(III) catalyst to complete the catalytic cycle. Later, they accomplished the dearomatization of *N*-(naphthalen-1-yloxy)acetamides with alkenes.[182] Oxabenzonorbornadienes are the amenable coupling partner. The naphthyl ring stabilizes the spirocyclopropane product. Furthermore, the synthesis of polycyclic hydrocarbon bearing cyclobutadienoid is achieved (Scheme 124).[183] Among a set of ligands screened, JohnPhos gives exclusively the single product. Generally, electron-rich aryl bromides produce the higher yield, in contrast electron-deficient aryl bromides shows less effective.

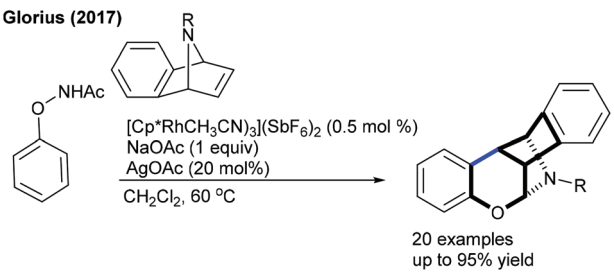
The Radhakrishnan group developed an annulation of enamides with diazabicyclic alkenes (Scheme 125).[109] Electron-poor substrates react efficiently. In addition, Tsuji–



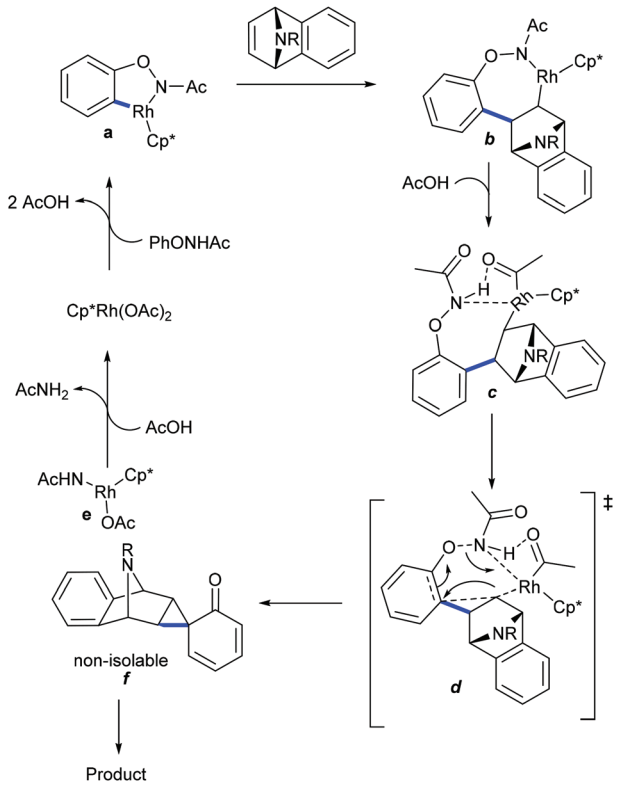
Scheme 119 Synthesis of spirocyclic dihydrobenzo[*a*]fluorenefurans.



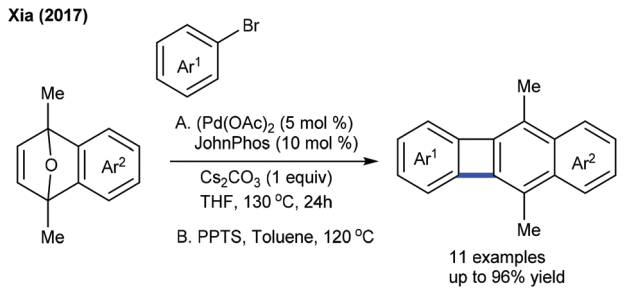
Scheme 120 [3 + 2]-Cycloaddition of aromatic amides with bicyclic alkenes.



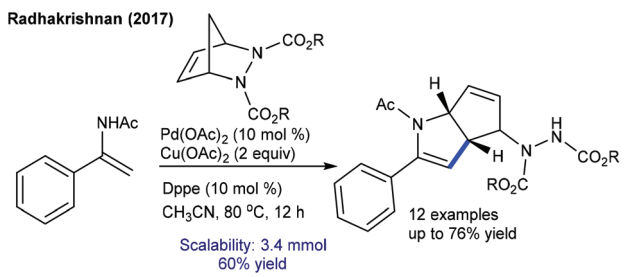
Scheme 122 Synthesis of bridged polycycles *via* combination of C–H activation and Wagner–Meerwein-type rearrangement.



Scheme 123 Mechanism of the combination of C–H activation and Wagner–Meerwein-type rearrangement.

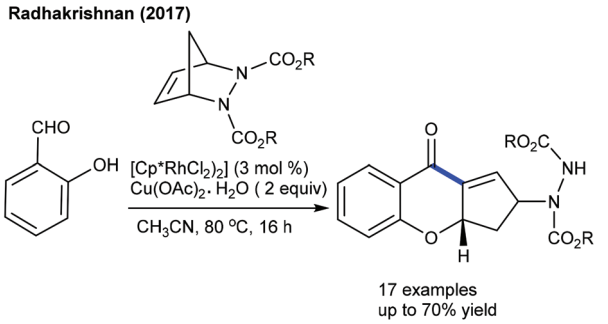


Scheme 124 Synthesis of polycyclic conjugated hydrocarbons.



Scheme 125 Oxidative annulation of enamides with diazabicyclic alkenes.

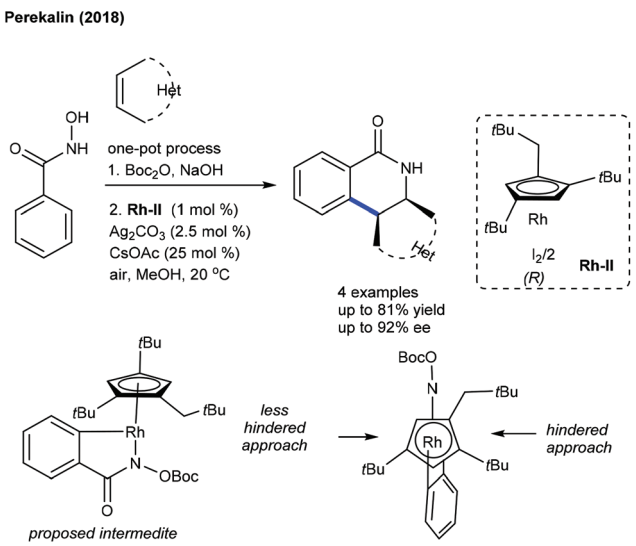
Trost and benzylic C–H activation of alkyl 2-iodo-3-methylbenzoate works well to produce cyclopentannulated indanes.[184] Furthermore, oxidative coupling of salicylaldehyde



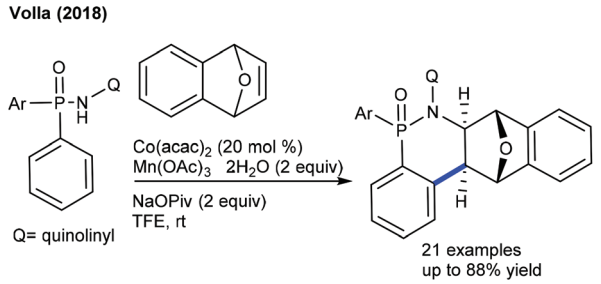
Scheme 126 Oxidative coupling of salicylaldehydes with diazabicyclic alkenes.

with bicyclic alkenes is achieved to give fused chromene (Scheme 126).[185] Relatively a similar reaction is applied for the construction of isoquinolone-fused heterocycles.[186] Diverse urea derived bicyclic alkenes and *o*-acetyl ketoximes are compatible. This reaction can be extended to benzamides using neutral Rh-catalysis to afford quinolones in good yields.

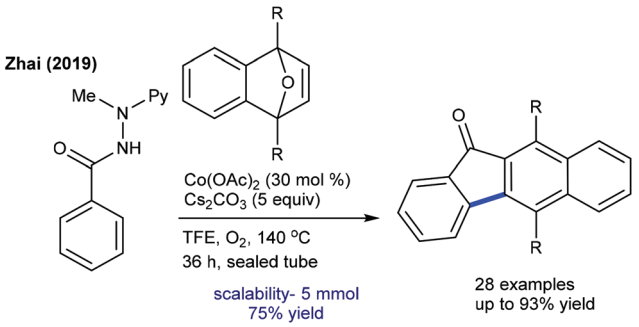
Perekalin and co-workers showed the assembly of enantiopure dihydroisoquinolines by chiral-planar Rh(III)-catalysis (Scheme 127).[187] The introduction of the Boc group is essential for the activation of phenylhydroxamic acid while Ag_2CO_3 acts as an iodide abstracting agent and CsOAc assists in the abstraction of the *ortho*-hydrogen atom of phenylhydroxamic acid. The origin of enantioselectivity is explained by a less-hindered side approach of the alkene. Furthermore, the synthesis of phosphorus heterocycles is successful using the [4 + 2]-cycloaddition of phosphinamide with oxabicyclic alkenes (Scheme 128).[188] A broad range of heterocyclic phosphinamides and azabicyclic alkenes are tolerated. This method is extended to the coupling of *N*-methoxybenzamides with heterobicyclic alkenes.[189] The N–OMe oxidizing group is essential, and compatible with a series of benzamides and alkenes.



Scheme 127 Synthesis of enantiopure dihydroisoquinolones.



Scheme 128 [4 + 2]-Cycloaddition of phosphinamides with heterobicyclic alkenes.

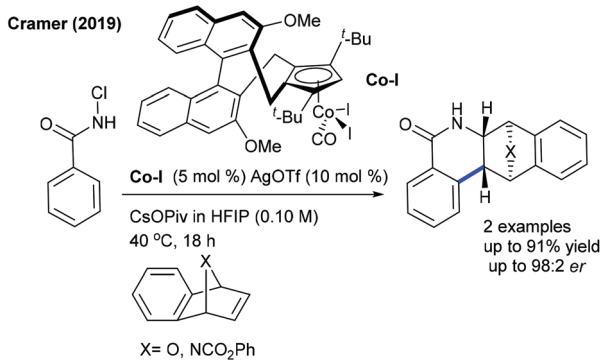


Scheme 131 Synthesis of benzo[*b*]fluorenones.

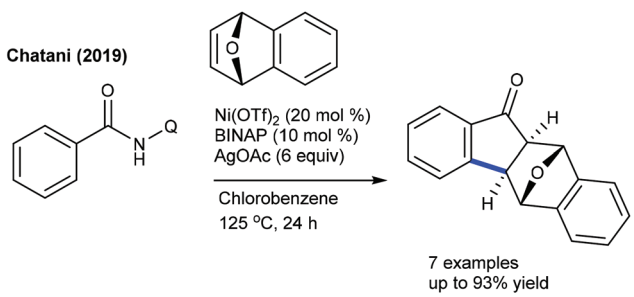
The synthesis and application of chiral $Cp^xCo(III)$-complexes for C–H activation of *N*-chlorobenzamides with alkenes including heterocyclic alkenes have been reported (Scheme 129).[190]

The Chatani group developed the synthesis of epoxybenzofluorenone through the coupling of benzamide with heterobicyclic alkenes (Scheme 130).[191] 8-Aminoquinoline chelation assistance is necessary, and the addition of excess AgOAc (6 equiv.) plays a valuable role in the removal of 8-aminoquinoline since it inhibits the catalytic activity of $Ni(OTf)_2$. Mechanistic experiments suggest an involvement of the irreversible C–H bond cleavage (KIE = 2.8 (one-pot) and 1.8 (parallel)) that might be the rate-limiting step. Furthermore, the synthesis of benzo[*b*]fluorenones is accomplished *via* a Co-catalyzed [3 + 2]-annulation, ring-opening and dehydration sequence (Scheme 131).[192] Diverse products are obtained utilizing O_2; however, the requirement of a higher amount of Cs_2CO_3 (5 equiv.) and elevated temperature (140 °C) limits their potential applications. The irreversible C–H cleavage is confirmed by H/D exchange studies, and the mechanism is related to Cheng's report (Scheme 120) *via* Cs_2CO_3-mediated ring-opening and dehydration. In addition, [4 + 2]-annulation of sulfoxonium ylides with oxa/azabicyclic alkenes is achieved.[106] Naphthalen-1(2*H*)-ones are formed in reasonable yields from diverse sulfoxonium ylides. The protocol is not limited to oxabicyclic alkenes alone, but azabicyclic alkenes having electronically varied groups are also coupled. The catalytic cycle involves oxygen directed irreversible C–H metalation (parallel KIE = 3.9).

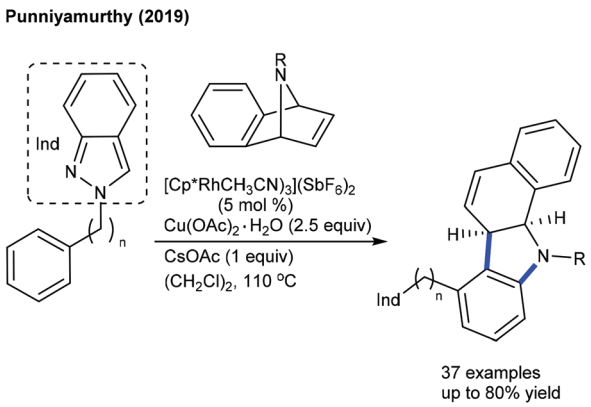
Our group showed the coupling of aryl-2*H*-indazoles with 7-azabenzonorbornadienes (Scheme 132).[193] This double C–H activation occurs at C-2′ and C-3′ instead of C-2′ and C-3 positions. A broad range of 7-azabenzonorbornadienes and aryl-2*H*-indazoles were evaluated, and steric and electronic effects were found to significantly affect the reaction. We extended this strategy to the dual C-7 and C-6 C–H functionalization of indolines with broad substrate scope and functional group tolerance.[194] The synthetic and mechanistic aspects are explored. Recently, a rare example of three-component [2 + 3 + 1]-annulation of 3-iodochromones, α-bromoacetophenones and nor-



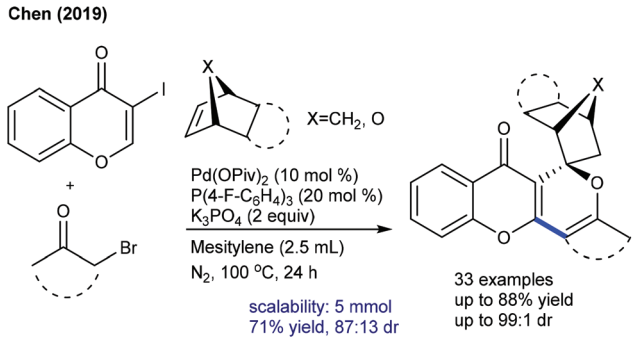
Scheme 129 Annulation of *N*-chlorobenzamides with heterocyclic alkenes.



Scheme 130 Reaction of benzamides with oxabenzonorbornadienes.



Scheme 132 Coupling of aryl-2*H*-indazoles with 7-azabenzo norbornadiene.



Scheme 133 Synthesis of chromone-fused polycycles.

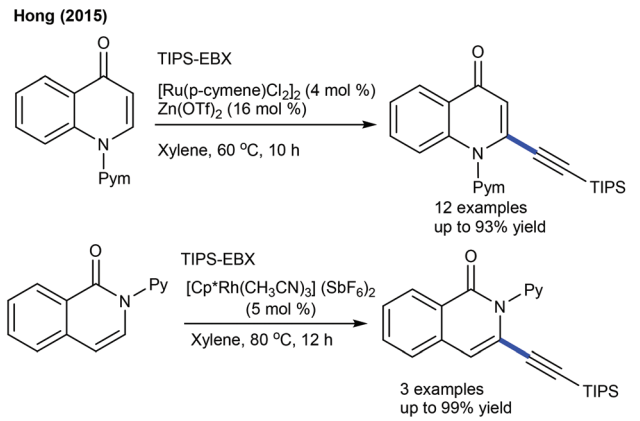
bornenes has been found to be successful (Scheme 133).[195] In search of ligands, electron-deficient ligands produced the best results and chromone-fused polycycles showed good diastereoselectivity.

7. Other reactions

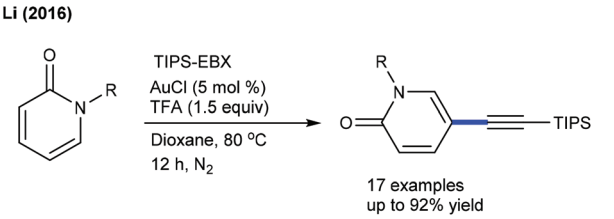
7.1. Alkynylation

Limited studies are focused on the alkynylation of heterocyclic alkenes. These reactions utilize a hypervalent iodine-alkyne reagent (TIPS-EBX) as an alkynyl source. The Hong group developed a Ru-catalyzed C-2 selective alkynylation of 4-quinolones to give a small library of alkynylated products (Scheme 134)[196] and three examples are focused on the C3-alkynylation of isoquinolones by Rh-catalysis (Scheme 134).[196] This strategy is extended to the C-6 alkynylation of pyridones.[197] Good yields are observed using a wide array of substrates. Alkynylating reagents such as TBDS-EBX and *t*Bu-EBX are effective, while TMS-EBX and Ph-EBX exhibit inferior results.

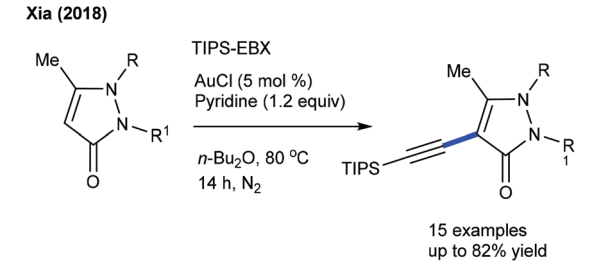
Au-catalysis was also explored for alkynylation. Li and co-workers described a C5-alkynylation of pyridones using TIPS-EPX as an alkynylating agent (Scheme 135).[197] A series of *N*-alkyl pyridones react affording good yields, while *N*-aryl pyridines are not effective substrates due to less nucleophilicity. Later, C4-alkynylation of pyrazolones was found to be successful using TIPS-EBX (Scheme 136).[198] The pyrazolones having different substituent patterns couple to afford good yields.



Scheme 134 C3-Alkynylation of isoquinolones employing TIPS-EBX.



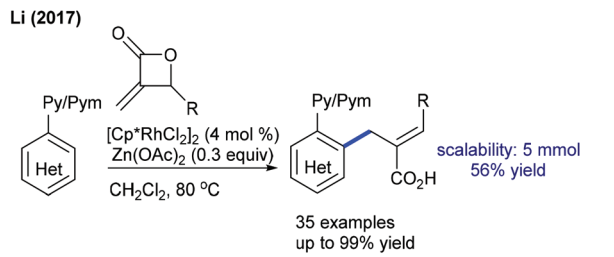
Scheme 135 C5-Alkynylation of pyridones using TIPS-EPX.



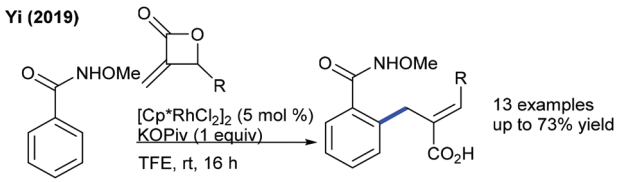
Scheme 136 C4-Alkynylation of pyrazolones.

7.2. Allylation

Allylation is explored using strained methyleneoxetanone as the coupling partner. Li and co-workers showed the redox-neutral allylation of arenes (Scheme 137).[199] This silver-free protocol is compatible with a wide range of substrates. The procedure is extended to 2-pyridone and isoquinolone. However, pyrimidyl-substituted benzimidazoles and carbazoles fail to give the desired products. Subsequently, Yi and co-workers described the allylation with benzamides (Scheme 138).[200] The reaction in trifluoroethanol (TFE) gives the allylated products, whereas in 1,2-dichloroethane (DCE), benzoazepines are formed. This switchable nature of the selectivity is studied using DFT, which advocates energetically favourable β-O elimination in TFE. This methodology is extended to the synthesis of *ortho*-allylated *N*-aryl ureas.[120]



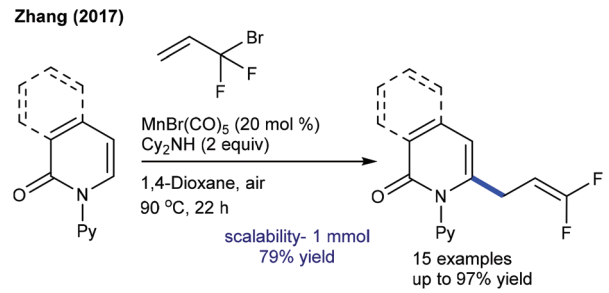
Scheme 137 Redox-neutral coupling of methyleneoxetanones with arenes.



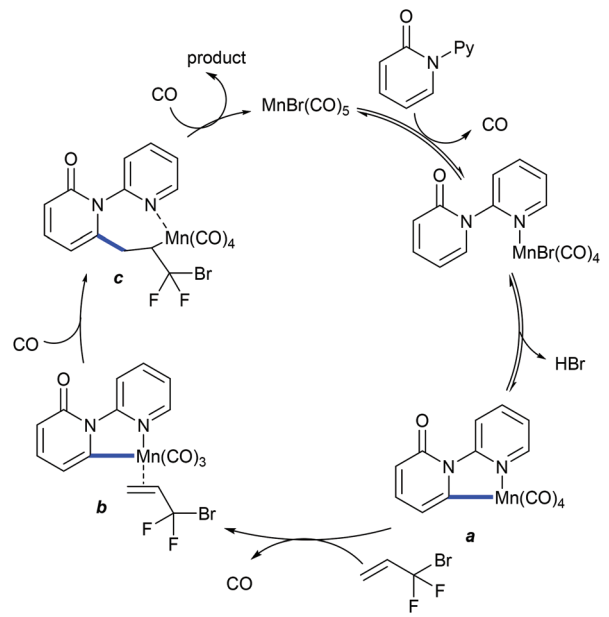
Scheme 138 Allylation of benzamides with methyleneoxetanones.

Changing the solvent from TFE (allylated product) to THF produces the annulated product.

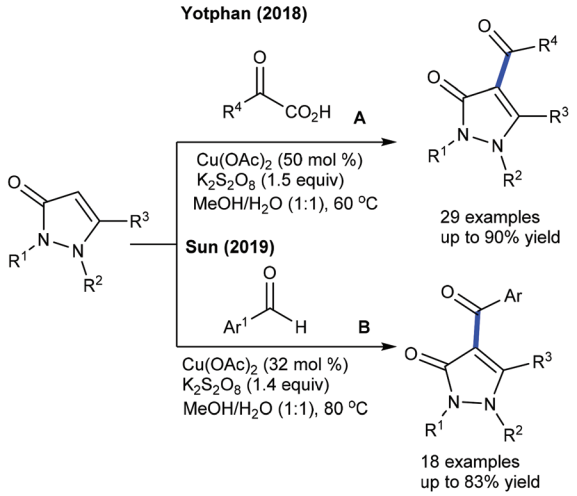
In 2017, the C2-selective 3,3-difluoroallylation of pyridones was devised using 3-bromo-3,3-difluoropropenes by Mn-catalysis (Scheme 139).[201] The "fluorine effect" strongly enhances the reaction efficiency. The proposed catalytic cycle involves the formation of manganacycle ***a*** through reversible C–H metalation (competitive KIE = 1.03 and parallel KIE = 1.06) (Scheme 140). Coordination with an alkene gives the π-alkenylmanganese complex ***b***. Migratory insertion provides



Scheme 139 3,3-Difluoroallylation of pyridones.



Scheme 140 Catalytic cycle of Mn-catalyzed C2-selective 3,3-difluoroallylation.



Scheme 141 Synthesis of acyl pyrazolones using aldehydes.

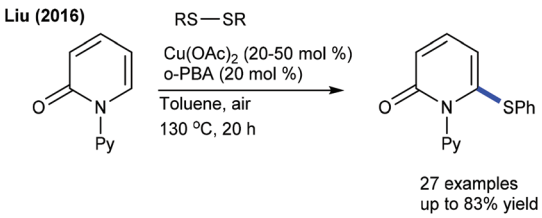
the seven-membered intermediate ***c***, which leads to β-bromo elimination to give the product and regenerate the active catalyst.

7.3. Acylation

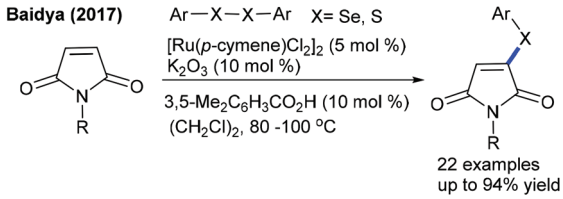
Few studies are available on acylation of heterocyclic alkenes. The acylation of pyrazolones is found to be successful using α-oxocarboxylic acids (Scheme 141A).[202] Electronic and steric factors of the substituted pyrazolones and α-oxocarboxylic acids influence the reaction. For instance, electron-rich substrates act as good coupling partners. The catalytic system is extended to the use of aldehydes as an acylating agent for the synthesis of acyl pyrazolones (Scheme 141B).[203] In comparison with Yotphan's process, 32 mol% of the metal salt is sufficient, which is applicable to access a variety of acylated pyrazolones. Nevertheless, alkyl and free NH pyrazolones are unsuccessful substrates.

7.4. Chalcogenation

Significant studies are focused on C–S and C–Se bond formation. The C6-selective C–S bond formation of pyridones with diaryl/dialkylsulfides is developed (Scheme 142).[204] Regardless of the electronic and steric properties, the substrates are readily coupled. Furthermore, a Ru-catalyzed coupling of maleimides with diaryl diselenides and diaryl disulfides is achieved (Scheme 143).[205] The reaction tolerates a



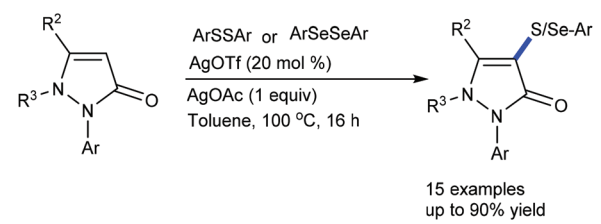
Scheme 142 C6-Thiolation of pyridones.



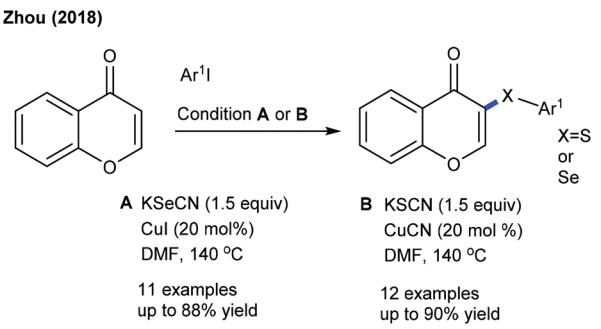
Scheme 143 Functionalization of maleimides using heteroaryl electrophiles.

series of maleimides with variable electronic features. However, the scope of diaryl diselenides is quite limited and elevated temperature is essential for diaryl disulfides that display poor reactivity. The procedure is extended to benzamides, which show moderate reactivity. Mechanistic studies corroborate the non-involvement of Kharasch type addition to the alkene. H/D-Exchange studies exclude β-hydride elimination, and probably involve the direct C–H functionalization.

The Ackermann group designed the thiolation/selenylation of pyrazolones (Scheme 144).[206] Triflate ions facilitate the base-assisted C–H metalation step. Good yields are obtained by coupling of pyrazolones with disulfides or diselenides; however, the scope of the reaction is somewhat limited. The Cu-catalyzed C–S/C–Se Bond formation of flavones with iodoarenes and KSCN/KSeCN is successful (Scheme 145).[207] The coupling proceeds at high temperature (140 °C). Aryl iodides are the better coupling partners. Recently, C–H thiolation and thiocyanation of uracil derivatives have been accomplished.[208]



Scheme 144 Thiolation/selenylation of pyrazolones.



Scheme 145 C-3 C–S/C–Se bond formation of flavones.

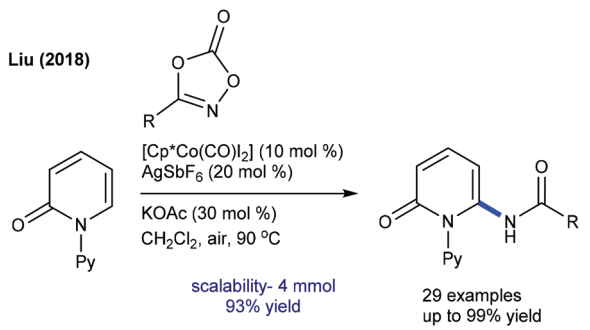
The combination of $Cu(OTf)_2$ and $K_2S_2O_8$ catalyzes the C–S/C–Se coupling. For thiocyanation, a catalyst along with a stoichiometric amount of I_2 is required, and apart from NH_4SCN and NaSCN, KSCN also shows a viable thiocyanating property. The electronic and steric aspects of disulfide and uracil strongly affect the outcome of the reaction.

7.5. Amidation

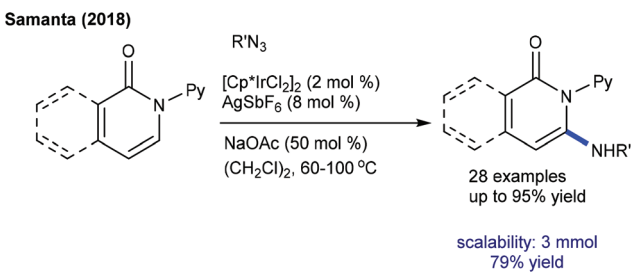
The Cp*Co(III)-catalyzed C6-amidation of pyridones using oxazolones is accomplished (Scheme 146).[209] A variety of pyridones and oxazolones are reacted. Isoquinolones and 4-pyridone prove to be viable substrates. Mechanistic studies suggest an involvement of electrophilic irreversible fast C–H cobaltation (KIE = 0.70 (one-pot) and 0.97 (parallel)). In addition, the amidation of isoquinolones and pyridones with azides is disclosed (Scheme 147).[210] Sulfonyl, benzoyl and diphenyl phosphoryl azides are compatible, though the reaction of phenyl azide or benzyl azide is incompetent. Additionally, a diverse array of isoquinolones and pyridines have been proved to be good substrates.

7.6. Miscellaneous reaction

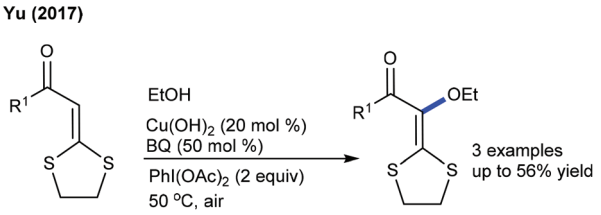
The ethoxylation of cyclic α-aroylketene dithioacetal using $Cu(OH)_2$ is shown in combination with $PhI(OAc)_2$ and benzoquinone as the oxidants (Scheme 148).[211] Two examples of C6-alkylation and C5-alkenylation of pyridones with acrylates have been reported (Scheme 149).[67] In addition, the C6-acetoxylation of pyridones can be achieved using PIDA.[212] However, the protocol has narrow substrate scope.



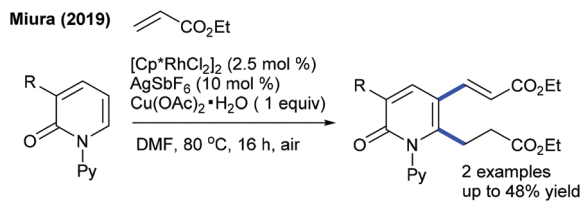
Scheme 146 C6-Amidation of pyridones.



Scheme 147 C3-Amidation of isoquinolones and pyridones with azides.



Scheme 148 Ethoxylation of cyclic α-aroylketene dithioacetal.



Scheme 149 Alkenylation of pyridones with acrylate.

8. Conclusion and outlook

Transition-metal-catalyzed coupling of heterocyclic alkenes *via* C–H activation has become one of the important synthetic strategies enabling the introduction of an incredibly diverse array of heterocyclic units to produce diverse heterocyclic motifs. Considerable efforts have been made in terms of reactions such as arylation, alkenylation, alkylation, hydroarylation, ring-opening, annulation and cyclization. Noble metals, such as Pd, Rh and Ru, have been mostly used for such transformations. Pd-catalysts are the best for the coupling of pyrones, chromenes, coumarins and related systems with the C–H activation occurring mostly through electrophilic C–H metalation, while Rh-catalysts are efficient at the coupling of other types of heterocyclic alkenes including pyridones/isoquinolones, and the C–H activation takes place *via* chelation assistance. Metal-catalysts such as Co(III), Cu(II), Mn(I) and Ni(II) have been successfully applied but except Co(III), all others have limited studies on them. These transformations most often require stoichiometric amounts of the oxidants. Thus, utilization of less toxic and environmentally benign air or O_2 is exceedingly anticipated and more attention should be paid. Furthermore, the C–H activation followed by multiple bond forming tandem reactions by Rh-catalysis shows the great tendency to assemble complex heterocyclic scaffolds. In addition, the coupling of heterocyclic alkenes *via* C–H activation of unactivated alkanes remains scarce until recently. Though promising findings have been reported, greater development of this field of research is still required. Furthermore, an enantioselective C–H activation route to coupling of heterocyclic alkenes is a challenging field and is in its primitive stage. Development of efficient catalysts and chiral ligands provides greater space for the synthetic community.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Dr. Tariq A. Shah of our group for his kind assistance in editing the manuscript.

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