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Transition-metal-catalyzed alkene-relayed intermolecular C–H activation

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Alkene-relayed C–H activation constitutes a novel strategy for selective C–H functionalization. In this context, intermolecular reactions that incorporate alkenes into the final products are of significant interest. During these transformations, alkenes not only act as a relay for C–H activation but also serve as carbon synthons, becoming integral components of the product architecture. This dual role enhances their utility in transition-metal-catalyzed C–H activation, broadening the scope of synthetic applications. This review systematically summarizes such alkene-relayed C–H functionalization reactions. The discussed reactions are categorized based on alkene type, metal catalyst, and transformation class, with detailed mechanistic insights provided for representative examples. Additionally, the review highlights current challenges and future prospects for research in this evolving field.

1. Introduction

Direct C–H functionalization is of significant importance in organic synthesis and catalysis.[1] This innovative strategy eliminates the need for prefunctionalized starting materials, reduces the generation of chemical waste, and decreases the number of synthetic steps. Consequently, it lowers both the complexity and cost of reactions while enhancing synthetic efficiency. Furthermore, C–H activation offers new disconnection pathways in retrosynthetic analysis, enabling novel approaches to molecular design. Over the past few decades, remarkable advancements in C–H functionalization have led to its widespread application in diverse fields, including organic synthesis, medicinal chemistry and materials science.[2]

While the ubiquity of C–H bonds in organic molecules presents immense opportunities for C–H activation, it also poses significant challenges in selectively functionalizing a specific C–H bond—a critical requirement for developing synthetically useful reactions. To address this challenge, the most common approach relies on directing groups (DGs).[3] These groups guide metal catalysts into proximity with a targeted C–H bond within a molecule, facilitating selective cleavage of the bond. However, this strategy is inherently limited to activating C–H bonds located near the directing group. For example, in most DG-assisted C–H functionalization reactions of arenes, activation occurs predominantly at the *ortho* position relative to the directing group. Although methods for *meta*-C–H functionalization have been developed, such examples remain relatively scarce.[4] Consequently, developing

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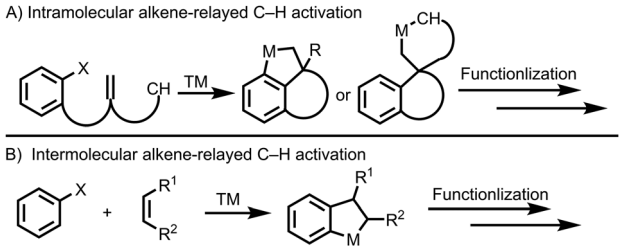

Fig. 1 Transition-metal-catalyzed alkene-relayed C–H activation.

novel strategies to expand the scope of C–H activation remains a high priority in the field.

Alkene-relayed C–H activation constitutes an innovative reaction paradigm for selective C–H functionalization. In this approach, the alkene relay guides metal catalysts to target specific C–H bonds, serving as both a valuable complement and a significant expansion to the conventional directing group-dependent strategies that dominate C–H functionalization.[5] Furthermore, alkene-relayed C–H activation is often integrated with multicomponent coupling, cyclization, or cascade reactions. This synergy enables the efficient formation of multiple chemical bonds in a single step, streamlining synthetic routes and enhancing overall efficiency.[6]

A major class of alkene-relayed C–H activation reactions is the palladium-catalyzed intramolecular alkene-relayed C–H activation process (Fig. 1(A)). These reactions typically utilize alkene-tethered aryl (pseudo)halides as substrates. The alkene moieties direct the palladium catalyst to activate C–H bonds remote from the (pseudo)halide groups. This strategy enables cleavage of C–H bonds that are otherwise challenging to activate using conventional directing group approaches. Since intramolecular alkene-relayed C–H activation reactions have been comprehensively reviewed,[7] they will not be discussed here.

Intramolecular alkene-relayed C–H activation reactions suffer from a significant limitation: they require substrates with relatively complex structures, which limits the availability of applicable starting materials and restricts the diversity of accessible products. Additionally, synthesizing these intricate substrates often necessitates multistep reactions, further limiting their practicality. Intermolecular reactions between arenes and alkenes offer a solution to this limitation, as they enable the use of simple, readily available substrates, thereby vastly expanding the accessible substrate scope (Fig. 1(B)). However, developing such intermolecular systems is inherently challenging. These reactions often involve alkyl metallic intermediates, which are prone to β-hydride elimination—a side reaction that undermines efficiency. Furthermore, intermolecular alkene-relayed C–H functionalization often involves multicomponent processes, adding another layer of complexity. Despite these hurdles, many successful examples of intermolecular alkene-relayed C–H functionalization have been reported.

This review provides a chronological overview of these intriguing reactions, organized by alkene type, metal catalyst, and transformation type. By highlighting major advances and mechanistic insights, we aim to offer a comprehensive resource for researchers in the field and inspire further innovation in alkene-mediated C–H functionalization strategies.

2. Norbornene-relayed C–H activation

Norbornene (NBE) and its derivatives play a significant role and holds a unique position in the field of C–H activation. The rigid framework and highly strained structure of NBE endow it with distinctive reactivity, making it widely employed in palladium-catalyzed C–H activation reactions.[8]

As early as 1985, Catellani and co-workers discovered that, in the presence of $Pd(PPh_3)_4$ and potassium *tert*-butoxide, bromobenzene could undergo a reaction with NBE to afford compound **3** in 65% yield, along with a minor amount of benzocyclobutene derivative **4** as a byproduct (Scheme 1(a)).[9] Based on these observations, they hypothesized

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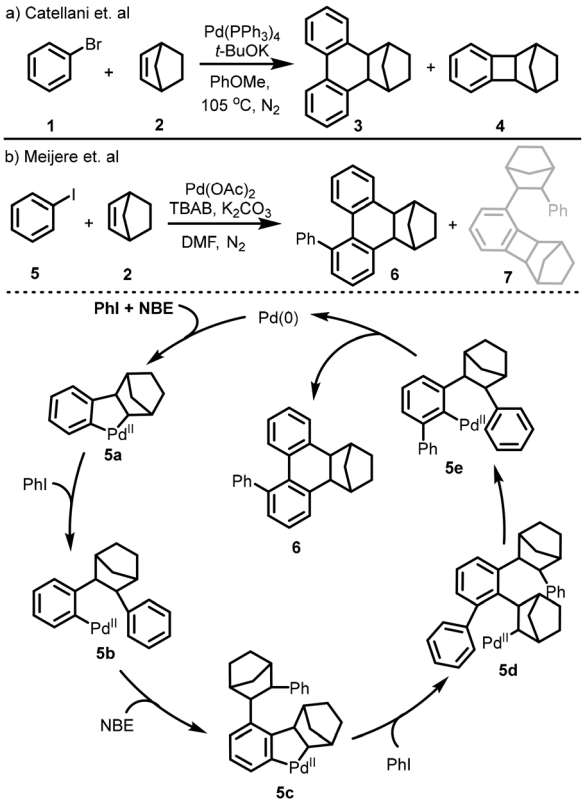
Yanghui Zhang received his BS and MS in chemistry at Tongji University in Shanghai, China. After 3 years' research experience at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, he moved to the University of Georgia in Athens, USA to start his PhD studies under the direction of Professor Geert-Jan Boons in 2002, and obtained his PhD degree in 2007. He was a postdoctoral fellow in the research group of Professor Jin-Quan Yu at The Scripps Research Institute in La Jolla, USA for approximately 3 years. Currently, he is a professor in the Department of Chemistry of Tongji University.



Scheme 1 Earlier works on NBE-relayed C–H activation.

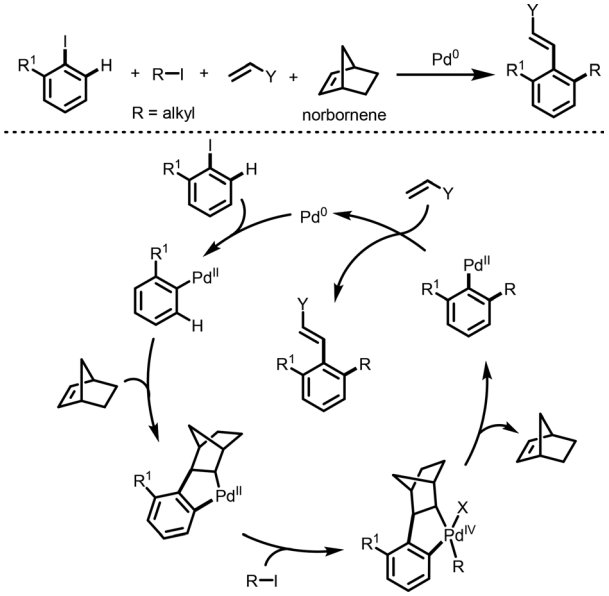


Fig. 2 The classical Catellani reaction.

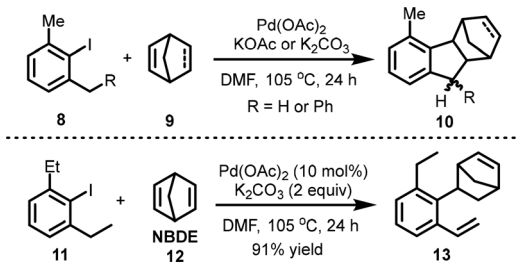
the involvement of a Pd(IV) intermediate. This hypothesis was later substantiated by the successful isolation and structural characterization of a Pd(IV) complex bearing a norbornane moiety, providing strong experimental support for their mechanistic proposal.[10] In subsequent studies conducted in 1989 and 1991, Meijere and co-workers further examined the palladium-catalyzed reaction between iodobenzene and NBE, leading to the formation of a novel compound **6** (Scheme 1(b)).[11,12] Building upon this work, Catellani later replaced $Pd(OAc)_2$ with $Pd(dba)_2$ and observed the formation of **6** again, alongside a small amount of compound **7**.[13] Mechanistically, Catellani and Motti proposed that arylnorbornylpalladacycles (ANPs) such as **5a** and **5c** serve as key intermediates in the catalytic cycle. These palladacycles undergo oxidative addition with iodobenzene, followed by reductive elimination to generate intermediates **5b** or **5d**, respectively. Intermediate **5d** can subsequently react with a second equivalent of NBE to afford **5e**, which then undergoes intramolecular C–H activation and cyclization to deliver the final product **6**.[14]

In 1997, Catellani and co-workers reported a seminal Pd(0)/NBE co-catalyzed reaction involving the *ortho*-C–H alkylation and *ipso*-olefination of aryl iodides (Fig. 2).[15] In this transformation, aryl iodides undergo difunctionalization at both the *ortho* and *ipso* positions *via* a NBE-relayed C–H activation pathway. This transformation has since been formally termed the Catellani reaction. The Catellani reaction represents a novel strategy for C–H functionalization. Over the past decades, a wide variety of Catellani-type reactions have been developed. Many reviews on this reaction have been reported.[16] Therefore, the Catellani reaction is not covered in this review, and only NBE-relayed reactions with NBE incorporated into the final products are discussed.

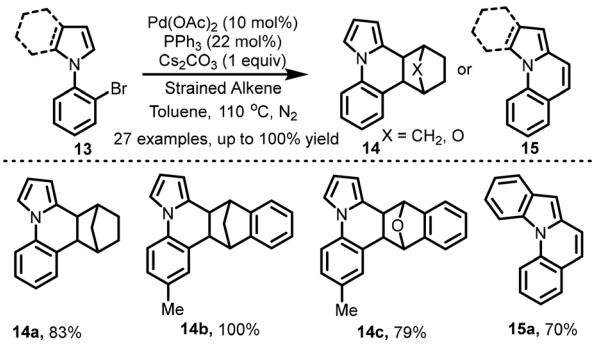
2.1 Pd(0)-catalyzed C–H activation of haloarenes relayed by NBE and its derivatives

In 2000, Catellani and Motti discovered that in the norbornadiene (NBDE)-relayed C–H activation reaction of 2,6-dimethyl iodobenzene, the arylnorbornylpalladacycle intermediate underwent direct reductive elimination, affording the cyclopentene derivative **10** as the major product.[17] Subsequently, in 2008, they extended this strategy by replacing one of the methyl groups with a benzyl group, and observed a similar transformation. Interestingly, when the substituent was changed to an ethyl group, the reaction proceeded *via* a dehydrogenation pathway to afford olefine product **13** (Scheme 2).[18]

In 2007, Lautens and co-workers reported an unexpected outcome in the palladium-catalyzed reaction of *ortho*-(pyrrol-1-yl)aryl bromides with NBE, wherein six-membered ring products **14** and **15** were obtained instead of the anticipated benzo[*c*]cyclobutene derivative (Scheme 3).[19] These heterocyclic



Scheme 2 NBDE-relayed benzyl C(sp^3)–H activation.



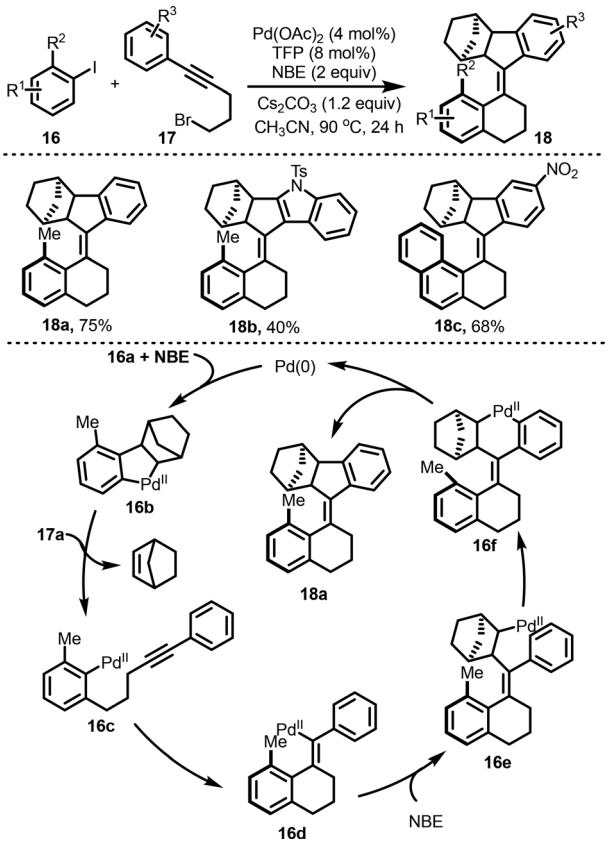
Scheme 3 NBE and its derivatives-relayed C–H annulation for the synthesis of six-membered heterocyclic scaffolds.

products, incorporating the NBE moiety, represent a novel class of structures with potential to improve the lipophilicity of drug molecules. Notably, the scope of the reaction was subsequently expanded to other strained alkenes, including oxabicycloalkenes and NBDE, thereby broadening the utility of this transformation in the context of organic synthesis and pharmaceutical development.

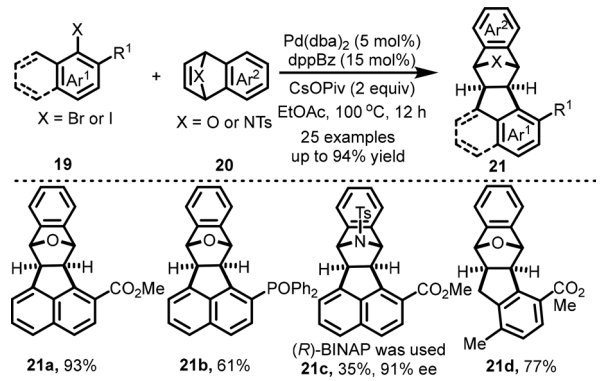
In 2009, Lautens and co-workers reported a Pd-catalyzed multicomponent domino reaction for the synthesis of tetrasubstituted helical alkenes **18** *via* two sequential C–H activations (Scheme 4).[20] This strategy formed four C–C bonds in one step, with NBE serving both as a transient mediator and a structural component of the product. The reaction proceeded under mild conditions with good to excellent yields and broad functional group tolerance. It was further extended to indole systems, and the resulting helicenes show promise in photoresponsive materials. In 2012, the group also achieved stereoselective synthesis using chiral alkynyl bromides derived from lactones.[21]

In 2022, Li and co-workers developed a Pd-catalyzed annulation reaction between aryl halides and highly strained alkenes *via* C(sp^2)–H or C(sp^3)–H activation (Scheme 5).[22] The transformation proceeds through migratory insertion of arylpalladium(II) species into the strained alkenes, followed by intramolecular C–H activation, enabling the efficient construction of epoxybenzo[*k*]-fluoranthenes, epoxy-5*H*-benzo[*b*]fluorenes, and their aza analogues **21**. A broad substrate scope was demonstrated, encompassing various aryl halides and strained bicyclic alkenes such as 7-oxa- and 7-azabenzonorbornadienes. Notably, an enantioselective variant was also explored using a chiral ligand, affording up to 97% ee, albeit with a moderate yield (35%).

In the above transformations, arylnorbornylpalladacycles generated *via* NBE-relayed C–H activation undergo direct reductive elimination to deliver NBE-containing products. Alternatively, these palladacycles can be intercepted by external difunctionalization reagents to afford structurally diverse frameworks. In 2007, Cheng and colleagues reported a three-component cross-coupling reaction using benzyne precursors as arylation reagents, yielding 9,10-dihydrophenanthrene derivatives **25** (Scheme 6).[23] The cyclized product, oxabenzonorbornadiene, could be further transformed into polycyclic aromatic hydrocarbons under Lewis acid catalysis.

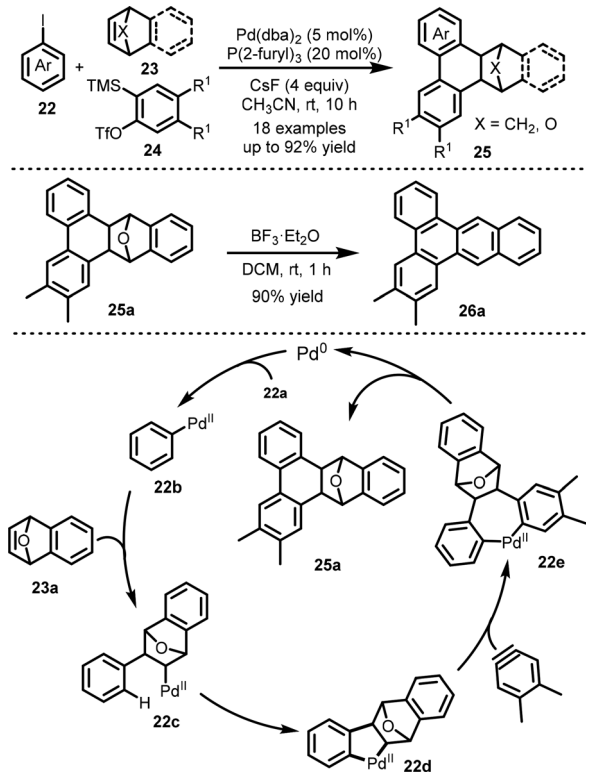


Scheme 4 NBE-relayed C–H alkylation for multicomponent domino synthesis of tetrasubstituted helical.

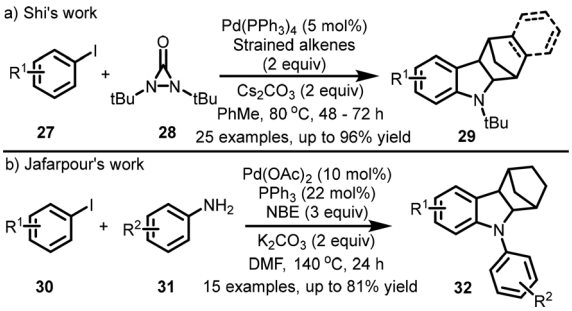


Scheme 5 NBE derivatives-relayed naphthyl C(sp^2)–H and benzylic C(sp^3)–H annulation.

NBE-relayed C–H activation enables not only the formation of C–C bonds but also facilitates the efficient construction of C–N bonds. In 2014, Shi and co-workers developed a Pd(0)-catalyzed cascade sequence involving a Heck reaction, C–H activation, and amination using di-*tert*-butyldiaziridinone as the aminating reagent (Scheme 7(a)).[24] This one-pot transformation simultaneously forged three key bonds—C(sp^3)–C(sp^2), C(sp^3)–N, and C(sp^2)–N—to access polycyclic indoline derivatives **29**. Remarkably, the reaction achieved direct *ortho*-C–H



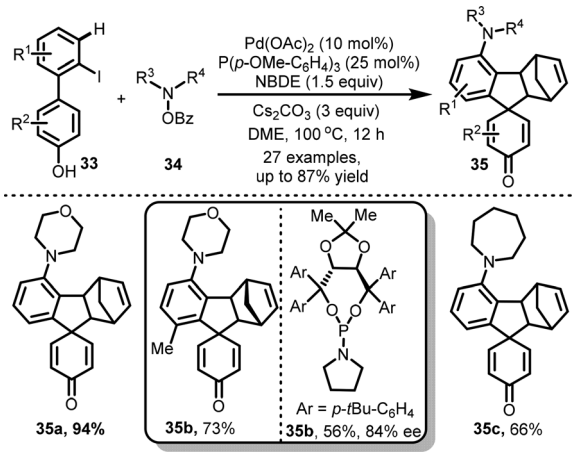
Scheme 6 NBE and its derivatives-relayed C–H arylation through three-component cross-coupling.



Scheme 7 NBE and its derivatives-relayed C–H amination.

amination of aryl iodides under oxidant- and ligand-free conditions, offering high atom economy and synthetic efficiency. In 2015, Jafarpour extended the amination scope to include simple anilines as nitrogen sources (Scheme 7(b)).[25]

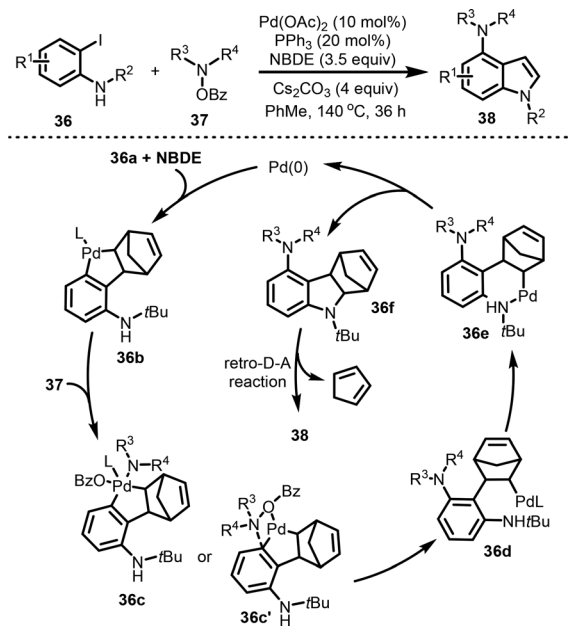
Hydroxylamine derivatives have also been employed as effective aminating reagents in NBE-relayed C–H functionalization reactions. In 2016, Luan and co-workers reported a Pd-catalyzed three-component domino reaction enabling the rapid synthesis of highly functionalized spiro[4.5]indene derivatives **35** (Scheme 8).[26] This transformation involved aryl phenols, *N*-benzoyloxyamines, and NBDE to construct one C–N bond and two C–C bonds in a single synthetic operation. Notably, asymmetric induction was achieved using chiral ligands, delivering the corresponding products with high enantioselectivity. The



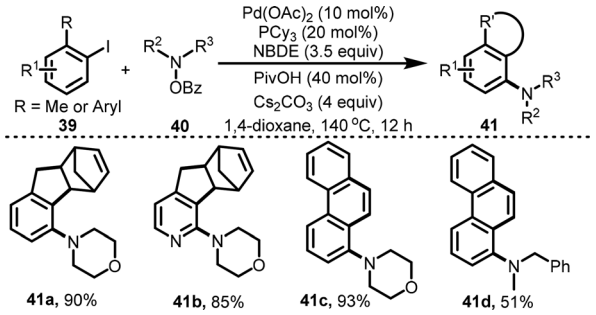
Scheme 8 NBDE-relayed C–H amination/phenol dearomatization.

methodology demonstrated broad substrate scope with respect to aryl groups, amines, and functional groups, providing a versatile platform for the synthesis of structurally diverse spirocyclic compounds.

Hydroxylamine derivatives were further applied to the transformation of *o*-iodoanilines by Liang and co-workers in 2019, offering an efficient approach for the synthesis of C4-aminated indoles (Scheme 9).[27] In this reaction, the NBE-incorporated intermediate **36f** underwent a retro-Diels–Alder process to generate the indole products **38**. DFT calculations revealed that when the protecting group is *tert*-butyl, the energy barrier for Buchwald-type coupling exceeds that of C–H activation, rendering the latter pathway more favorable. This strategy demonstrated broad substrate compatibility with various *o*-iodoanilines, *N*-benzoyloxyamines, and NBDE derivatives. By bypassing conventional multistep routes, the method enabled



Scheme 9 NBDE-relayed C–H amination of iodoanilines.



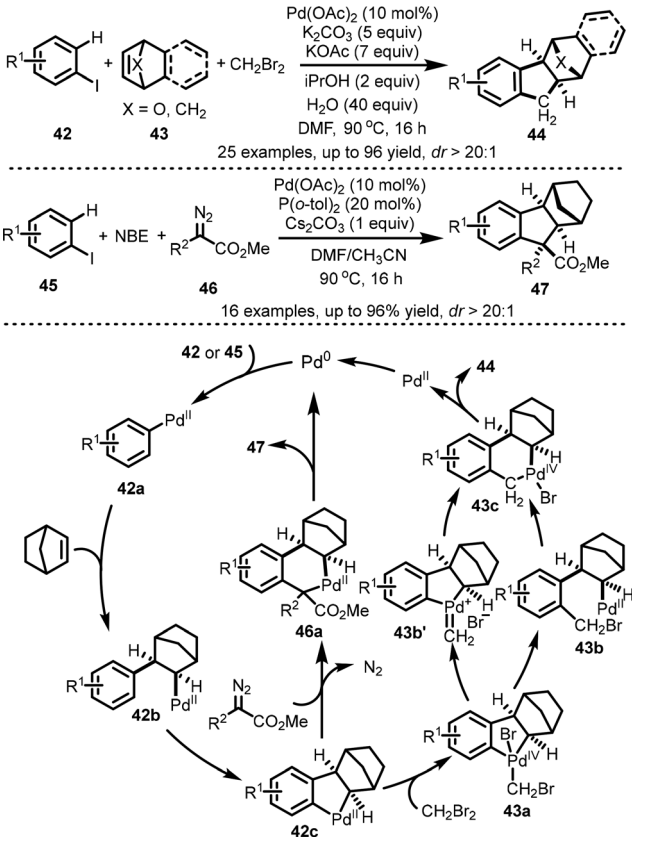
Scheme 10 NBDE-relayed cascade C–H amination and [2+3]/[2+4] cyclization *via* C–H activation.

streamlined access to C4-aminated indole scaffolds under mild conditions with high efficiency.

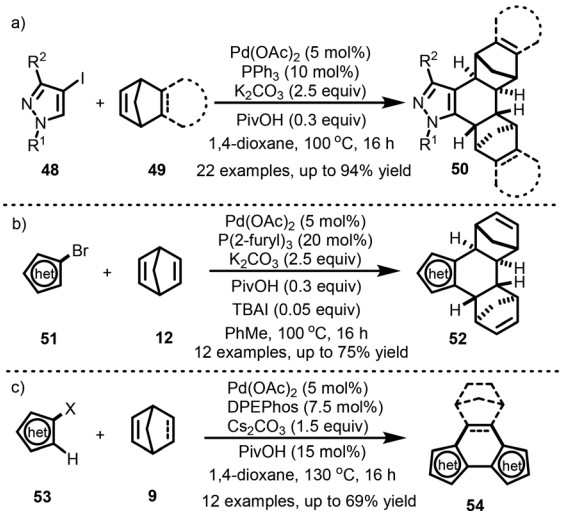
In 2021, the Liang and Yang group reported an intriguing NBDE-relayed dual C–H functionalization reaction (Scheme 10).[28] Employing hydroxylamine derivatives as aminating agents, *o*-methyl- and *o*-phenyl-substituted aryl iodides initially underwent NBDE-mediated C–H amination. Notably, the resulting norbornylpalladium(II) species subsequently activated the C–H bonds of the *o*-methyl and *o*-phenyl substituents to form palladacyclic intermediates. These intermediates then underwent cyclization to afford the final products **41**. Similar results were independently reported by Yang and colleagues around the same time.[29]

Beyond interception by amination reagents, ANP intermediates have also been demonstrated to react with CH_2Br_2 and α-diazoesters, enabling the efficient synthesis of norbornane-fused indanes. In 2020, Zhang and co-workers developed a palladium-catalyzed three-component cascade reaction involving aryl iodides, NBE, and either CH_2Br_2 or α-diazoesters (Scheme 11).[30] In this transformation, CH_2Br_2 or α-diazoesters served as functionalizing agents for the ANP intermediates, yielding norbornane-fused indanes **44** and **47** in good to excellent yields with broad substrate compatibility. Notably, reactions employing α-diazoesters proceeded with excellent stereoselectivity, affording products bearing fully substituted quaternary carbon centers. Mechanistically, the palladacycles (**42c**) are formed as the key intermediates in the same manner as previously described. The insertion of α-diazoesters gives six-membered palladacycle intermediates (**46a**), which undergo reductive elimination to afford the final products **47**. In the reaction with CH_2Br_2, the oxidative addition of CH_2Br_2 to **42c** generates intermediates **43a**. **43a** are converted into palladacycle **43c** *via* either intermediates **43b** or carbene complexes **43b′**. Reductive elimination from **43c** produces the final products **44** and releases Pd(II), which is reduced to Pd^0 by reductants such as isopropanol or DMF.

Intriguingly, ANP intermediates can also undergo reactions with NBE derivatives. In 2020, the Joo research group reported a palladium-catalyzed 1 : 2 coupling reaction between five-membered heteroaryl halides and NBE derivatives, enabling the efficient construction of rigid, non-planar polycyclic heterocycles **50** and **52** (Schemes 12(a) and (b)).[31] This methodology

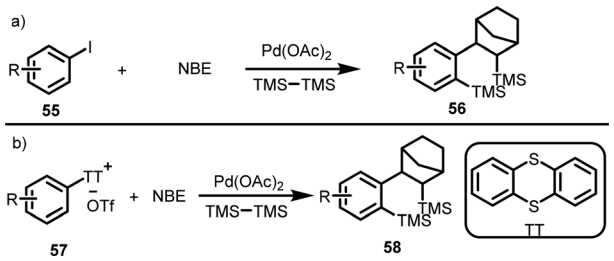


Scheme 11 NBE and its derivatives-relayed C–H alkylation for synthesis of norbornane-fused indanes.



Scheme 12 NBE and its derivatives-relayed C–H annulation of heteroaryl halides.

exhibited broad substrate scope, accommodating various five-membered heteroaryl halides such as pyrazole, thiophene, furan, and indole derivatives. The reaction proceeded with excellent regio- and *trans*-selectivity, effectively suppressing undesired isomer formation. The resulting structurally diverse

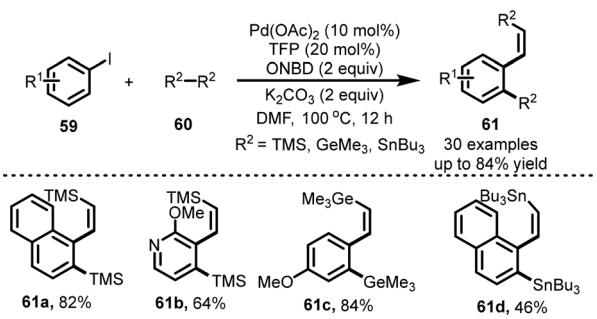


Scheme 13 NBE-relayed C–H silylation.

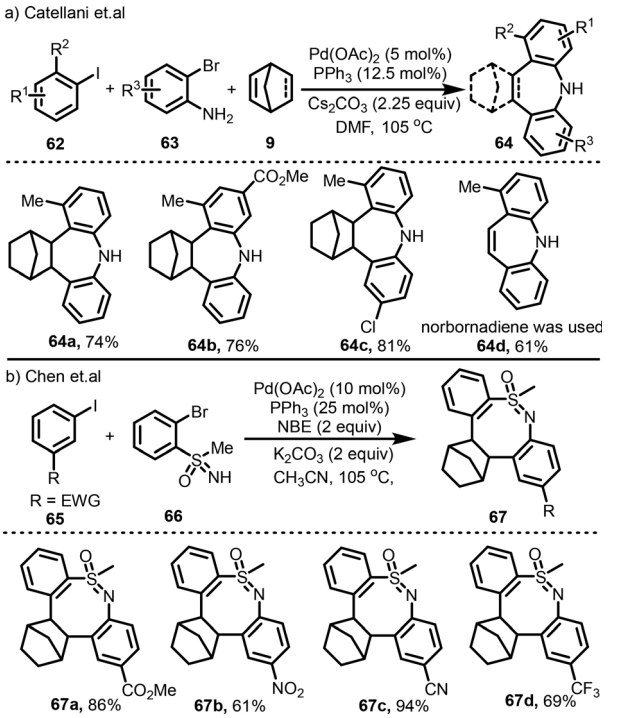
nitrogen-containing heterocycles have been demonstrated as valuable precursors for fluorescent materials, pharmaceutical intermediates, and monomers in optoelectronic applications, underscoring their significant practical potential. Moreover, through ligand and base optimization, the authors developed a complementary 2 : 1 coupling reaction between five-membered heteroaryl halides and NBE derivatives, affording a series of π-extended haloheteroarenes **54** (Scheme 12(c)).[32]

Organosilicon compounds have garnered significant attention due to their broad applications in materials science and organic synthesis, driving ongoing efforts to develop novel synthetic methodologies.[33] In 2018, the Zhang group reported the disilylation of *C*,*C*-palladacycles with disilanes, demonstrating efficient transformation of various *C*,*C*-palladacycles—generated *via* C–H activation—into disilylated products.[34] In the same year, Liang and Yang independently disclosed Pd-catalyzed disilylation reactions facilitated by C–H activation.[35] This strategy was further extended to NBE-relayed C–H silylation protocols (Scheme 13(a)).[36,37] More recently, Yan and co-workers reported an analogous NBE-relayed C–H silylation of arylsulfonium salts (Scheme 13(b)).[38]

Utilizing oxanorbornadiene (ONBD) as a relay, the Cheng group developed a novel Pd-catalyzed C–H silylation method for synthesizing vinylsilanes (Scheme 14).[39] Initially, disilylated intermediates were formed as observed in the reactions outlined in Scheme 13(a). These intermediates subsequently underwent a retro Diels–Alder reaction, furnishing (*Z*)-β-substituted vinylsilanes as the final products. Notably, this protocol was also successfully extended to digermanylation and distannylation reactions. Building on this work, the group



Scheme 14 ONBD-relayed C–H silylation, germanylation, and stannylation.

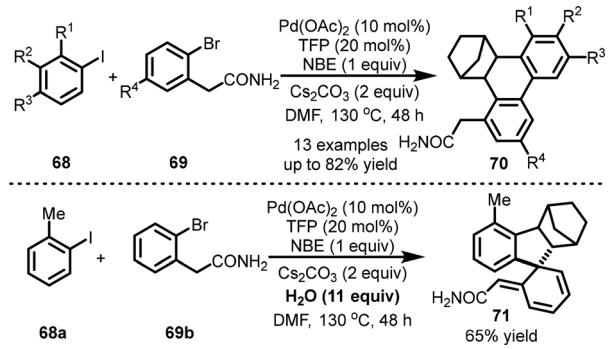


Scheme 15 NBE-relayed C–H arylation using *ortho*-bromoanilines as arylating agents.

further expanded the methodology to encompass C–H silylation mediated by other norbornene derivatives.[40]

In 2011, Catellani and co-workers reported a Pd-catalyzed three-component cross-coupling of iodobenzenes, *ortho*-bromoanilines, and NBE (Scheme 15(a)).[41] In this transformation, iodobenzenes first underwent selective reaction with NBE to form ANP intermediates, which then engaged in oxidative addition with *ortho*-bromoanilines to generate Pd(IV) species. The subsequent dual reductive elimination then delivered the final products **64**. The amino group of *ortho*-bromoanilines played a key role by coordinating to the ANP intermediate, thereby facilitating the oxidative addition of *ortho*-bormoanilines to the ANP to form Pd(IV) species. Notably, the reductive elimination of the Pd(IV) intermediates exhibited excellent regioselectivity. The reductive elimination formed C(aryl)–C(norbornyl) bonds, rather than C(aryl)–C(aryl) bonds, selectively. Therefore, the products resulted from the formation of C(aryl)–N and C(aryl)–C(norbornyl) bonds were obtained as the single regioisomers. When NBDE was employed, the resulting products underwent retro-Diels–Alder reactions to give dibenzoazepine derivatives. In 2018, Chen and co-workers extended this strategy by replacing *ortho*-bromoanilines with *ortho*-bromobenzenesulfonimides, enabling the synthesis of eight-membered heterocyclic sulfonimide scaffolds while retaining the NBE framework, when electron-deficient aryl iodides were used (Scheme 15(b)).[42]

This strategy using an *ortho*-substituent as the coordinating group opened a new avenue for developing cross-coupling reactions of *C*,*C* pallacycles with aryl halides.[43] Building on

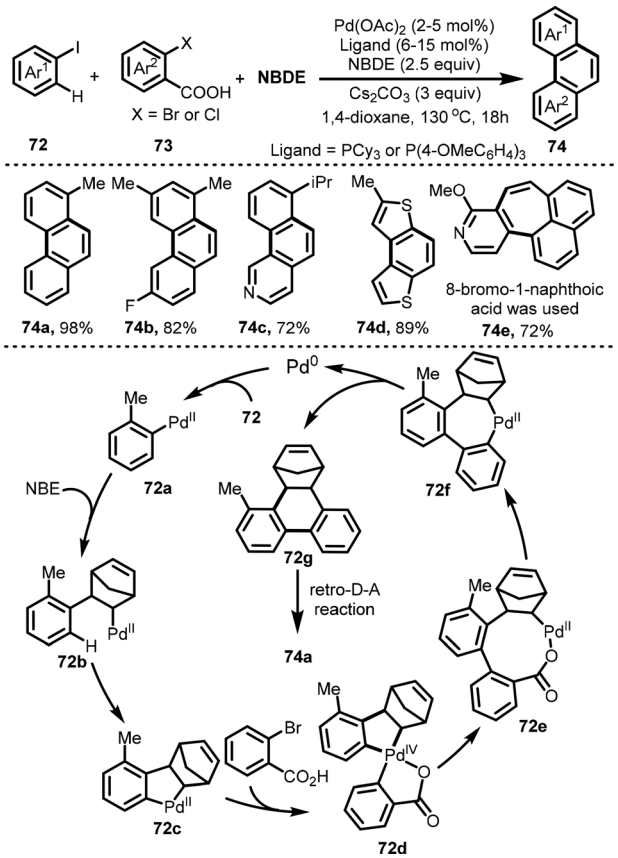


Scheme 16 NBE-relayed C–H arylation using *ortho* bromophenylacetamide as the arylating agents.

this concept, various NBE-relayed C–H arylation reactions of aryl iodides have been developed using different coordinating groups. In 2011, Malacria and Lacôte reported a three-component reaction involving iodobenzenes, NBE, and aryl bromides bearing *ortho*-amide groups (Scheme 16).[44] The reaction proceeded *via* selective reductive elimination from Pd(IV) intermediates to form C(aryl)–C(norbornyl) bonds. Subsequent *ortho*-C–H activation of the aryl bromides led to C(aryl)–C(aryl) coupling, affording final products **70**. Interestingly, in the presence of excess water, dearomatized product **71** was obtained instead. DFT calculations suggested that the *ortho*-amide group facilitated selective C(aryl)–C(norbornyl) bond formation *via* chelation. However, water disrupted this chelation, altering the reaction pathway to favor C(aryl)–C(aryl) coupling, thus accounting for the observed product shift.

Carboxyl groups can also serve as effective directing groups in NBE-relayed C–H arylation reactions. In 2017, Kwong and co-workers developed a three-component cross-coupling protocol involving aryl halides, 2-haloaryl carboxylic acids, and NBDE, enabling the efficient construction of polycyclic and heptagon-embedded aromatic compounds **74** (Scheme 17).[45] In this transformation, the Pd(IV) intermediate **72d** underwent reductive elimination to form a C(aryl)–C(aryl) bond. The resulting norbornyl Pd(II) species **72e** then underwent decarboxylation followed by a second reductive elimination, affording intermediate **72g**. A subsequent retro-Diels–Alder reaction of **72g** delivered the final product **74**. This strategy provides a concise and regioselective approach to asymmetric polycyclic aromatic frameworks, effectively circumventing the isomeric complexity often observed in conventional methods. DFT calculations suggested that the Pd(II) to Pd(IV) oxidative addition step is the rate-determining step. Beyond carboxylic acids, other *ortho*-halogenated aromatic substrates—such as aryl acyl chlorides,[46] esters,[47] boronic acids,[48] and bromothiophenes[49]—have also been successfully employed in similar transformations, yielding structurally related polycyclic products.

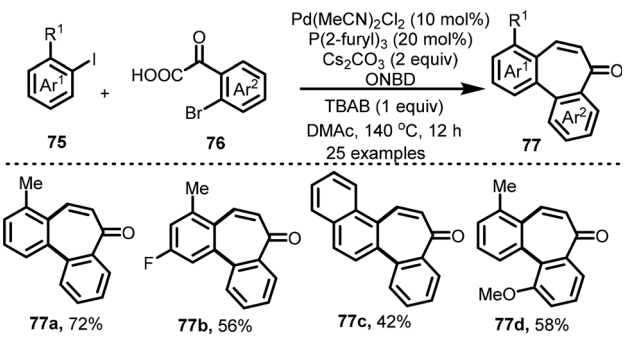
ortho-Bromoaryl oxocarboxylic acids have also been employed as arylating agents in NBE-relayed C–H arylation reactions. In 2024, Yang and Liang reported a Pd-catalyzed three-component reaction involving these substrates, aryl halides, and ONBD, enabling the efficient synthesis of



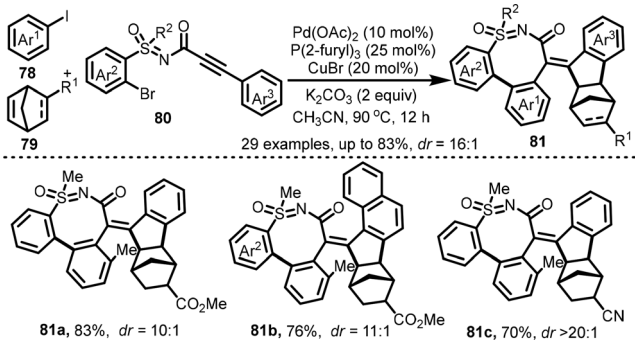
Scheme 17 NBDE-relayed C–H arylation using *ortho* halogenated benzoic acid as arylating agents.

dibenzo[*a*,*c*]cycloheptenone derivatives **77** (Scheme 18).[50] The reaction sequence proceeded through decarboxylation and retro-Diels–Alder steps, facilitating the construction of the seven-membered ring system in a streamlined manner.

In 2024, Li and Chen reported a Pd-catalyzed three-component reaction involving aryl iodides, NBE derivatives, and *ortho*-bromoarylsulfoximine propiolamide **80** (Scheme 19).[51] This transformation proceeded *via* dual NBE-relayed C–H arylation, efficiently constructing polyheterocyclic eight-membered sulfoximines bearing an indene-fused moiety as the final products **81**.



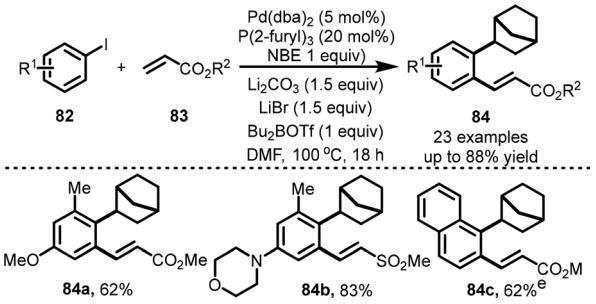
Scheme 18 ONBD-relayed C–H arylation using *ortho*-bromo aryl oxocarboxylic acids as the arylating agents.



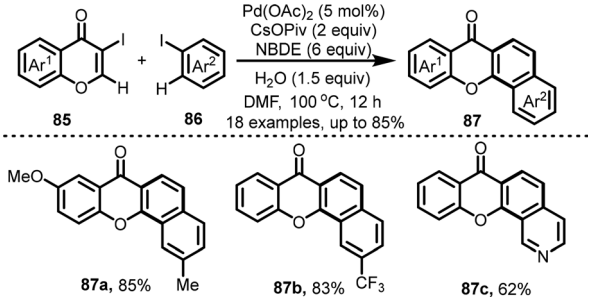
Scheme 19 NBE and its derivatives-relayed dual C–H arylation.

NBE-relayed C–H activation reactions typically form *C*,*C*-palladacycles as the intermediates. The palladacycles usually react with electrophiles. As a consequence, the reactions form products with C–H bonds functionalized by electrophiles. In 2020, the Dong group reported an unusual *ortho*-Heck reaction within a Pd/NBE catalytic system, markedly distinct from the conventional *ipso*-Heck pathways commonly observed in Catellani-type processes (Scheme 20).[52] Mechanistic studies, including systematic deuterium-labelling experiments, revealed that the transformation proceeds through a 1,4-palladium migration followed by an intramolecular hydrogen transfer, rather than *via* the traditional ANP intermediate.

In addition to facilitating arene C–H activation, NBE-relayed strategies have also been successfully applied to the functionalization of vinylic C–H bonds. In 2013, the Hu group developed a palladium-catalyzed cascade reaction for the efficient synthesis of annulated xanthones from 3-iodochromones, aryl iodides, and NBDE (Scheme 21).[53] Distinct from the classical Catellani reaction, which typically proceeds *via* a $C(sp^2)$–$C(sp^2)$ coupling, this transformation involved a $C(sp^2)$–$C(sp^3)$ reductive elimination pathway, delivering compound **87** as the final product. The methodology demonstrated broad substrate scope and excellent functional group compatibility. Subsequently, the Han and Wu groups expanded the scope of this strategy by employing diverse coupling partners such as benzyl bromide, trimethyl orthoformate, and α-bromoacetophenone, thereby establishing a suite of NBE-relayed vinylic C–H functionalization protocols.[54–62]



Scheme 20 NBE-relayed C–H alkenylation.



Scheme 21 NBDE-relayed vinylic C–H arylation.

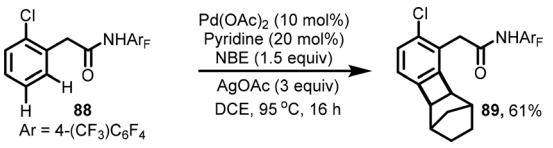
2.2 Pd(II)-catalyzed dual C–H activation relayed by NBE derivatives

All aforementioned NBE-relayed C–H functionalization reactions are based on Pd(0) catalysis and utilize organohalides as substrates. In contrast, a significant advancement was reported by the Yu group in 2015, who developed a Pd(II)/NBE co-catalyzed *ortho*- and *meta*-C–H functionalization of phenylacetic amide derivatives.[63] In this transformation, initial *ortho*-C–H activation was directed by the amide functionality under Pd(II) catalysis, followed by a second NBE-relayed C–H activation at the *meta*-position. This strategy marked a major breakthrough in site-selective C–H functionalization by accessing otherwise challenging *meta*-C–H bonds. The reaction afforded benzocyclobutene products **89** (Scheme 22). Subsequently, a series of related *meta*-C–H functionalization reactions employing similar Pd(II)/NBE strategies have been reported.[64]

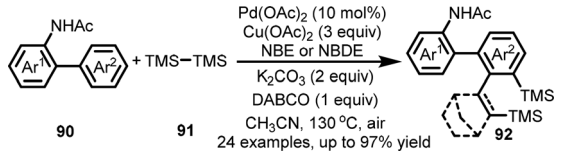
In 2019, the Yang and Liang research group reported a palladium(II)-catalyzed, NBE-relayed interannular C–H silylation reaction (Scheme 23).[65] By fine-tuning the structure of NBE derivatives, the regioselectivity of the silylation process could be precisely modulated, allowing for either *ortho*-C–H alkylation or *meta*-C–H silylation. This methodology exhibited a broad substrate scope, enabling efficient C–H silylation of a wide range of aryl halides and substituted biaryls.

In 2024, Li and co-workers developed a Pd(II)-catalyzed *meta*-selective C–H silylation reaction of primary benzamides (Scheme 24).[66] In this transformation, NBE acted as a relay group to activate *meta*-C–H bonds, yielding disilylated compounds **94** as the final products. Notably, the amide directing group can be efficiently removed either through C–C bond cleavage or converted into a nitrile through a dehydration process, further enhancing the synthetic utility and versatility of the method.

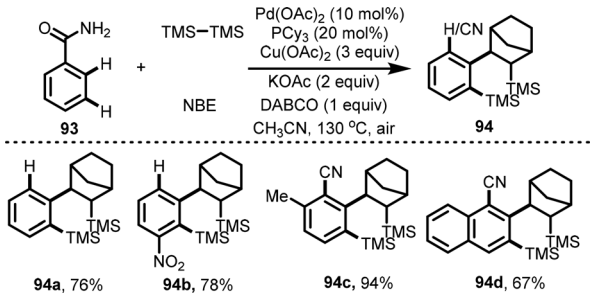
In the same year, the authors further developed a NBE-relayed Pd(II)-catalyzed C–H activation strategy for the regioselective silylation of free NH-indoles (Scheme 25).[67] For indoles without 2-substituents, silylation occurred selectively at the C2



Scheme 22 NBE-relayed *meta*-C–H functionalization.



Scheme 23 NBE and its derivatives-relayed interannular C–H silylation.



Scheme 24 NBE-relayed *meta* C–H silylation.

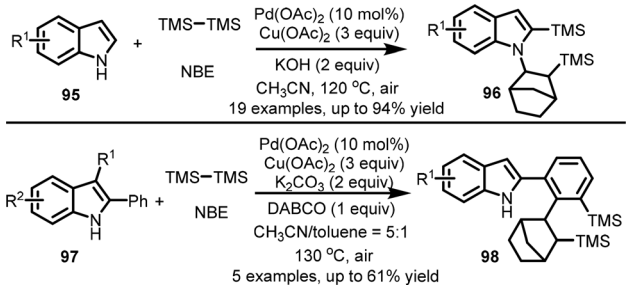
position, affording products **96**. In contrast, for 2-phenylindole substrates, the silylation selectively targeted the phenyl ring, yielding products **98**.

Pd(II)-initiated NBE-relayed C–H activation can also be achieved using arylboronic acids as substrates. In 2023, Li and co-workers reported a Pd(II)-catalyzed *ortho*-C–H silylation of arylboronic acids mediated by NBE and its derivatives, affording organosilicon compounds **101** (Scheme 26).[68] By using NBE, the silylated products could further undergo retro-Diels-Alder reaction, yielding vinylsilanes such as **101d** as the final products.

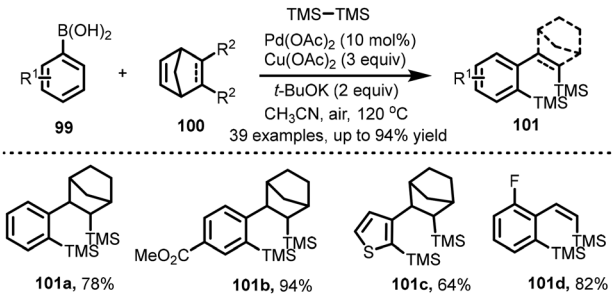
Pd(II)-catalyzed NBE-relayed C–H arylation reactions have also been advanced. In 2023, Jafarpour and co-workers reported a three-component reaction involving arylboronic acids, *ortho*-bromobenzoic acids, and norbornene derivatives (Scheme 27).[69] Under NaOAc/DMF conditions, dihydrophenanthrene derivatives **104** were obtained. In contrast, in the K_2CO_3/DMSO system, the high polarity of the solvent facilitated decarboxylation, leading to the formation of triphenylenes **107**.

2.3 Rh(III)-catalyzed dual C–H activation relayed by azabicyclic olefins

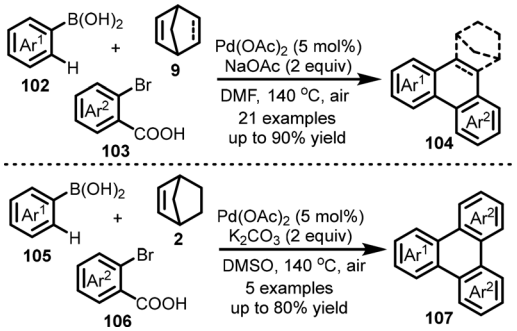
Beyond palladium catalysis, NBE-relayed C–H activation has also been achieved under rhodium catalysis. In 2019, the Li



Scheme 25 NBE-relayed C–H silylation of free NH-indoles.



Scheme 26 NBE and its derivatives-relayed C–H silylation of arylboronic acids.

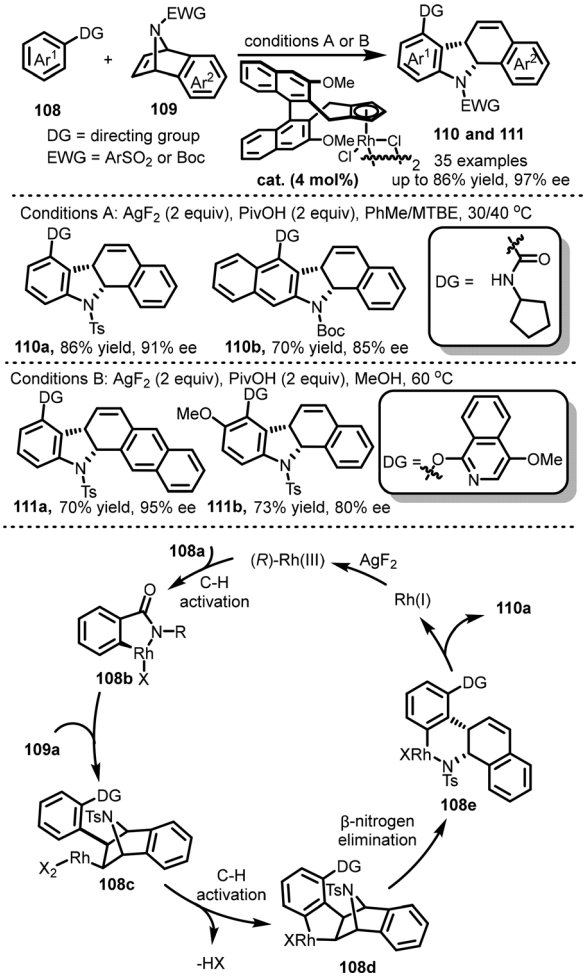


Scheme 27 NBE derivatives-relayed C–H arylation of arylboronic acids.

group reported a Rh(III)-catalyzed C–H activation strategy employing azabicyclic olefins as coupling partners for the enantioselective synthesis of *cis*-fused dihydrocarbazole derivatives **110** and **111** (Scheme 28).[70] This approach simultaneously activates both *ortho*- and *meta*-C–H bonds of arene substrates using azabicyclic olefins as relays, affording products with excellent stereoselectivity and high enantioselectivity. Utilizing a chiral cyclopentadienyl ligand alongside AgF_2 as the oxidant, the reaction achieved enantiomeric excesses up to 95%. The method exhibited broad substrate scope and good tolerance toward various substituted benzamides and azabicyclic olefins, demonstrating its versatility. Kinetic isotope effect (KIE) studies indicated that the initial *ortho*-C–H activation is the rate-determining step. Moreover, the authors successfully isolated and characterized a chiral rhodacycle intermediate, providing valuable mechanistic insight into the transformation.

2.4 Ni(0)-catalyzed C–H activation relayed by NBE derivatives

Nickel-catalyzed NBE-relayed C–H activation has also been achieved very recently. In 2023, the Dong group reported the first nickel-catalyzed Catellani-type annulation of aryl triflates and aryl halides with norbornenes, enabling the efficient synthesis of a series of fused benzocyclobutene derivatives **114** (Scheme 29).[71] Mechanistic studies revealed that the reaction proceeds *via* an ''outer-sphere concerted metalation/deprotonation'' pathway to form key nickelacycle intermediates. The base and the triflate group played crucial roles in the process.

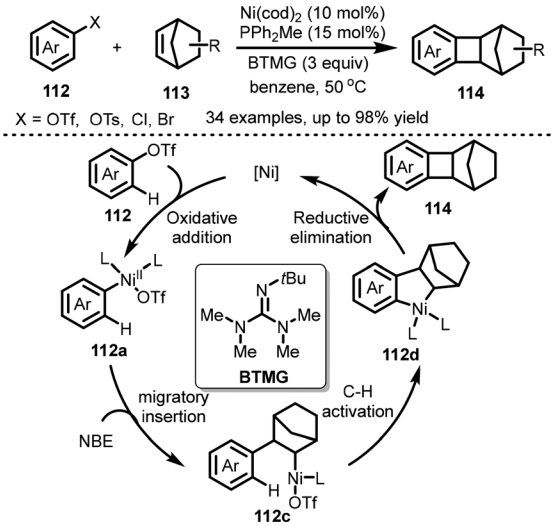


Scheme 28 Rhodium-catalyzed [3+2] annulation *via* NBE derivatives-relayed C–H activation.

3. Maleimide-relayed C–H activation

Maleimides are essential building blocks in organic synthesis and have been applied to the synthesis of various organic compounds. In particular, maleimides have also been extensively used as coupling partners in transition-metal-catalyzed transformations. Different from common alkenes, maleimides often undergo protonation instead of β–H elimination in Pd-catalyzed reactions. This unique reactivity provides opportunities to exploit maleimides as a relay for Pd-catalyzed C–H activation. Furthermore, maleimide and many of its derivatives are commercially available and low-cost.

NBE and its derivatives had been almost the only alkene relays for intermolecular transition metal-catalyzed C–H activation, until maleimides-relayed reactions were developed recently. Maleimide has found significant applications in organic synthesis, drug development, and polymer chemistry.[72] For instance, maleimide exhibits rapid and highly selective reactivity towards thiol groups, making it an ideal candidate for the development of bioconjugation reagents.[73] Such reactions proceed under mild conditions, enabling their widespread applications in biolabeling and drug delivery systems.



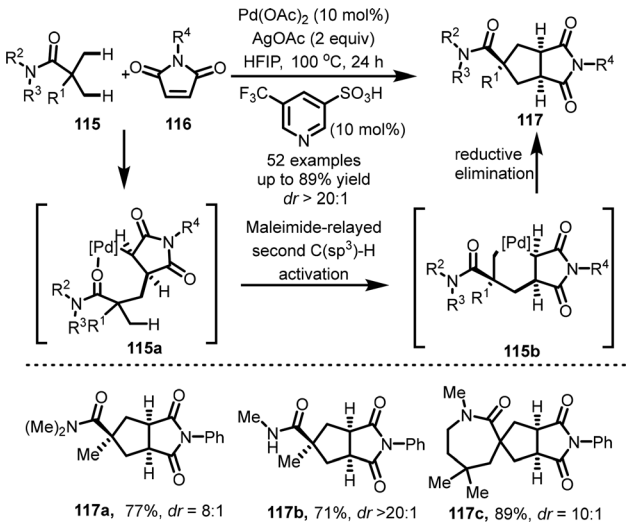
Scheme 29 Nickel-catalyzed [2+2] annulation *via* NBE and its derivatives-relayed C–H activation.

Furthermore, maleimide serves as a prototypical dienophile, Michael acceptor, playing a crucial role in the construction of fused, heterocyclic, macrocyclic, and bridged ring systems.[74] Maleimide can also undergo radical polymerization to generate high-performance polymers, which are extensively utilized in polymeric materials (*e.g.*, heat-resistant polyimides) and optoelectronic materials (*e.g.*, conductive polymers).[75] Additionally, transition-metal-catalyzed transformations of maleimide and its derivatives have also been extensively studied.

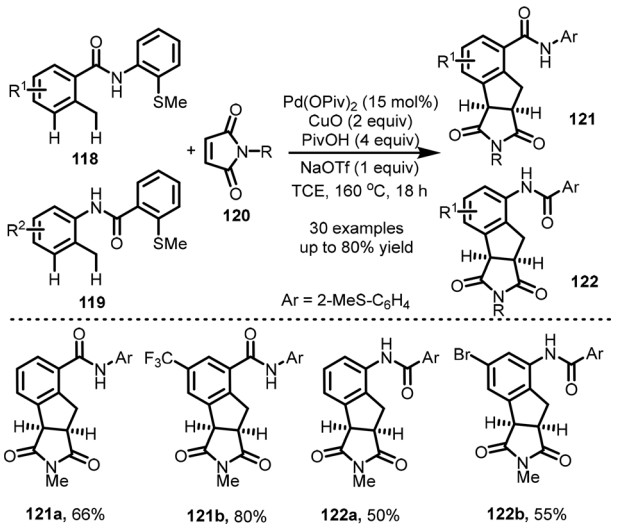
3.1 Pd(II)-catalyzed dual C–H activation relayed by maleimide

In 2020, Yu and co-workers reported a Pd(II)-catalyzed [3+2] cycloaddition of aliphatic amides with maleimides, enabled by two sequential C(sp^3)–H activations that constructed the three-carbon unit required for the formal cycloaddition (Scheme 30).[76] The reaction commenced with β-C(sp^3)–H activation of the aliphatic amide, followed by migratory insertion of the maleimide to generate a succinimidyl–palladium intermediate **115a**. A second C(sp^3)–H activation, relayed by the maleimide moiety, formed a six-membered *C*,*C*-palladacycle **115b**, which underwent reductive elimination to furnish bicyclic products **117**. The weakly coordinating amide group acted as a directing group, facilitating both C–H activations and promoting catalyst turnover. Additionally, pyridine-3-sulfonic acid was identified as a key additive in enhancing the efficiency of the C(sp^3)–H activation. This protocol displayed broad substrate scope, accommodating a range of aliphatic amides with high efficiency.

In the same year, the Chatani group reported an analogous Pd-catalyzed [3+2] annulation reaction through maleimide-relayed C–H activation (Scheme 31).[77] The reaction was initiated by bidentate directing group-assisted benzylic C(sp^3)–H activation, followed by maleimide-relayed aryl C(sp^2)–H activation. Density functional theory (DFT) studies conducted by Mori[78] and Datta[79] highlighted the critical role of



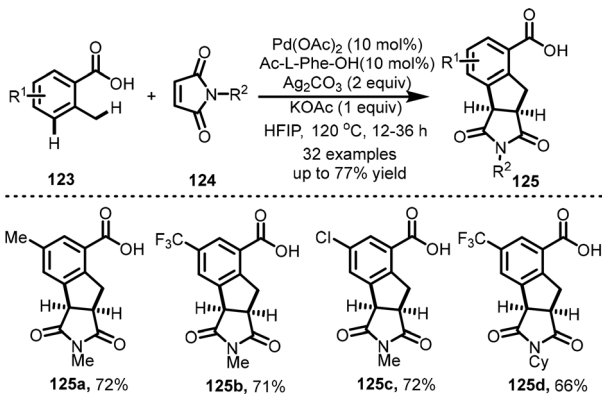
Scheme 30 Pd(II)-catalyzed [3+2] annulation *via* maleimide-relayed C(sp^3)–H activation.



Scheme 31 Pd(II)-catalyzed [3+2] annulation *via* maleimide-relayed C(sp^2)–H activation.

the bidentate directing groups, which not only enhanced the thermodynamic stability of the system but also improved the kinetic feasibility of the [3+2] annulation, thereby facilitating the formation of cyclic products **121** and **122**. Deuterium-labelling experiments further elucidated the reaction mechanism, indicating that benzylic and *meta*-C–H activations were irreversible, while C–H activations at the 5- and 6-positions were reversible.

Inspired by these two seminal works, a variety of such Pd(II)-catalyzed [3+2] annulation reactions have since been developed using different directing groups. In 2022, the Jeganmohan group reported a Pd-catalyzed [3+2] annulation of 2-methylbenzoic acids with maleimides, in which the carboxyl group served as the directing group to promote benzylic C–H activation (Scheme 32).[80] This reaction efficiently afforded

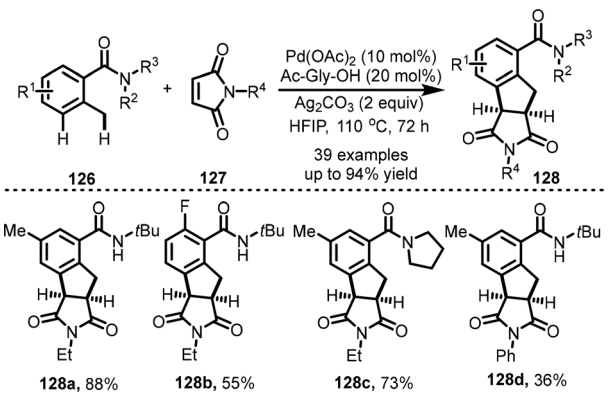


Scheme 32 Pd(II)-catalyzed [3+2] annulation of aromatic acids with maleimides.

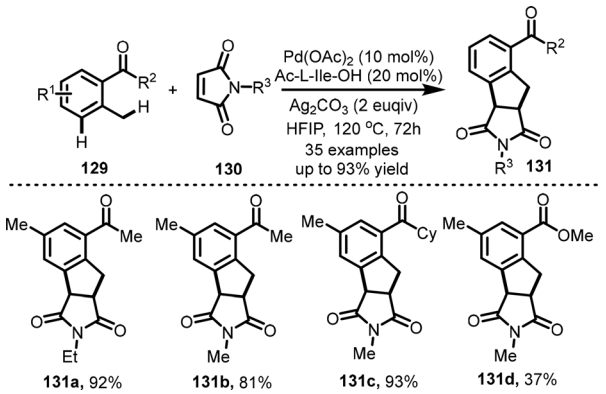
tricyclic heterocycles **125** as the products. Notably, the use of a mono-protected amino acid (MPAA) ligand was essential for achieving high efficiency. In its absence, the desired products were obtained in yields below 15%. Additionally, prolonging the reaction time enabled decarboxylation of the annulation products, thereby broadening the synthetic utility of this transformation.

Subsequently, the Jeganmohan group reported analogous maleimide-relayed [3+2] annulation reactions of aromatic amides, aryl ketones, and aryl esters by using amido, carbonyl, and ester groups as the directing groups for the benzylic C–H activation respectively (Schemes 33 and 34).[81,82] In all these reactions, mono-protected amino acids were crucial to achieve high yields. The mechanisms of the reactions depicted in Schemes 31–34 are fundamentally analogous to that in Scheme 30, with the key distinction being that the reaction in Scheme 30 involves maleimide-relayed C(sp^2)–H activation.

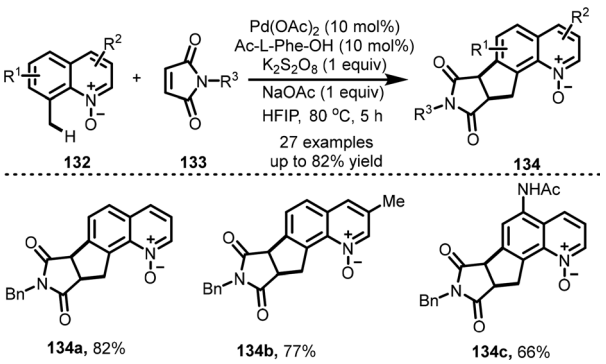
The N-oxide group is also an effective directing group in maleimide-relayed annulation reaction. In 2024, the Punniyamurthy group described Pd(II)-catalyzed [3+2] annulation reaction of 8-methylquinoline N-oxides with maleimides, leading to the formation of the tetracyclic framework **134** (Scheme 35).[83] This reaction exhibited a broad substrate scope and good



Scheme 33 Pd(II)-catalyzed [3+2] annulation of aromatic amides with maleimides.



Scheme 34 Pd(II)-catalyzed [3+2] annulation of aryl ketones and esters with maleimides.



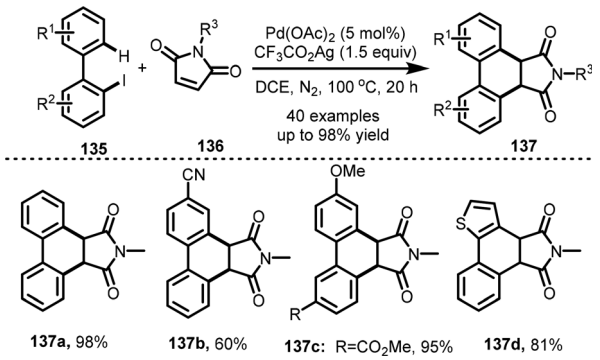
Scheme 35 Pd(II)-catalyzed [3+2] annulation of 8-methylquinoline N-oxides with maleimides.

functional group tolerance. Moreover, the reaction was scalable to the gram scale while maintaining a high product yield.

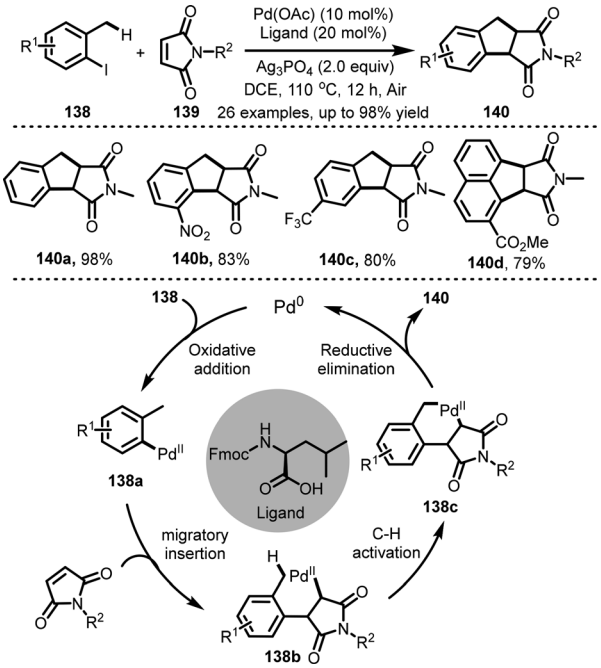
3.2 Pd(0)-catalyzed C–H activation of haloarenes relayed by maleimides

In addition to Pd(II) catalysis, maleimide-relayed C–H activation can also be accomplished under Pd(0) catalysis using haloarenes as starting materials. In 2022, Zhang and co-workers reported a Pd(0)-catalyzed annulation of 2-iodobiphenyls with maleimides, which served as a relay to promote 1′-C–H activation (Scheme 36).[84] This transformation afforded succinimide-fused 9,10-dihydrophenanthrenes **137** with high efficiency and broad substrate scope, offering a streamlined approach to access these polycyclic frameworks. More recently, Xiang and co-workers disclosed a related maleimide-relayed annulation strategy.[85]

Pd(0)-catalyzed maleimide-relayed C(sp^3)–H activation of aryl halides has also been achieved. In 2024, Zhang and co-workers reported a palladium-catalyzed annulation of *ortho*-iodotoluenes with maleimides *via* maleimide-relayed benzylic C(sp^3)–H activation (Scheme 37).[86] Mechanistically, the reaction proceeds through the formation of arylpalladium species **138a**, which undergo migratory insertion with maleimides to



Scheme 36 Pd-catalyzed annulation of 2-iodobiphenyls with maleimides through maleimides-relayed C(sp^2)–H activation.



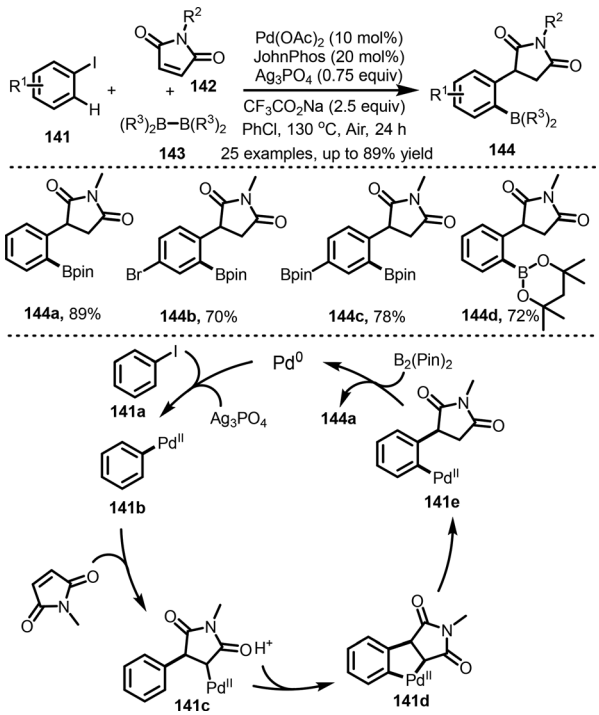
Scheme 37 Pd-catalyzed annulation of 2-iodotoluenes and 1-bromonaphthalenes with maleimides *via* maleimides-relayed C(sp^3)–H activation.

afford intermediate **138b**. Subsequent C(sp^3)–H activation by the resulting alkyl–Pd(II) species leads to the formation of palladacycle **138c**, which undergoes reductive elimination to deliver the final polycyclic products **140**. This transformation offers an efficient approach to complex polycyclic scaffolds from simple aryl iodide substrates. Notably, the use of mono-protected amino acids (MPAAs) as ligands was found to be critical for the reaction, which is rarely observed in C–H activation reactions of organohalides.

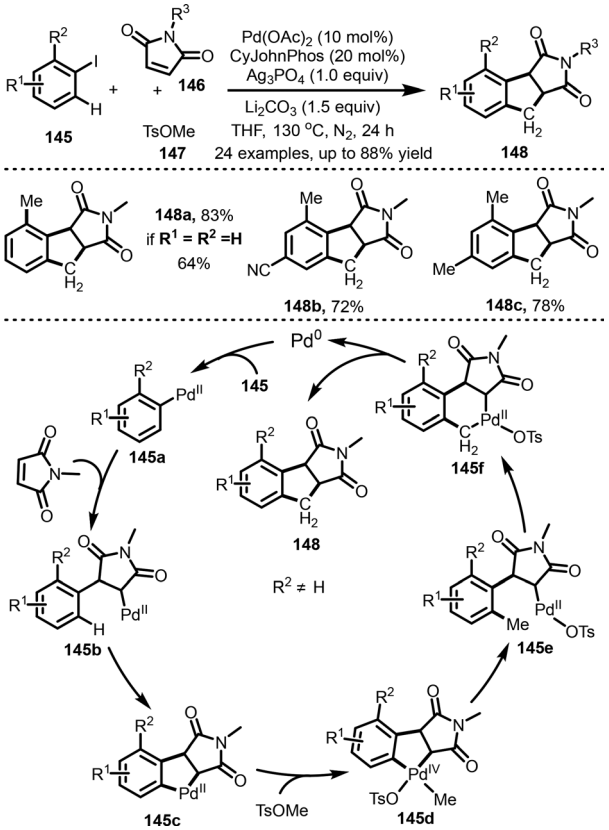
All the aforementioned maleimide-relayed C–H functionalization reactions proceed *via* cascade C–H activation followed by intramolecular cyclization. An intriguing alternative involves intercepting the arylpalladium(II) intermediate with an external reagent. However, developing such a transformation presents a

significant challenge, as it requires efficient orchestration of a three-component process. In 2024, Zhang and co-workers reported a maleimide-relayed *ortho*-C–H borylation of aryl iodides (Scheme 38).[87] In this transformation, both the *ortho*-C–H bonds and the *ipso*-positions of aryl iodides were selectively functionalized through borylation and alkylation, respectively. The resulting boronate group offers synthetic versatility, as it can be readily converted into a range of functional groups. This strategy not only provides a novel approach for *ipso*, *ortho*-difunctionalization of aryl halides *via* C–H activation, but also enables modular access to functionalized 3-aryl succinimides. The proposed mechanism involves the formation of a five-membered *C*,*C*-palladacycle intermediate **141d** *via* maleimide-relayed C–H activation. The protonation of **141d** yields aryl–Pd(II) species **141e**. Subsequent transmetalation or metathesis with $B_2(pin)_2$ furnishes the desired product **144a**.

Maleimide-relayed C–H methylation has also been realized by the same group. In 2024, Zhang and co-workers developed a palladium-catalyzed three-component reaction involving aryl iodides, maleimides, and methyl tosylate (TsOMe) as the methylating agent (Scheme 39).[88] In this transformation, the *ortho*-C–H bonds of aryl iodides underwent methylation *via* a maleimide-relayed C–H activation pathway. Notably, following methylation, the C–H bonds of the newly introduced methyl groups were further activated, leading to the formation of fused bicyclic succinimide-containing tricyclic products (**148**). In the case of iodobenzenes lacking *ortho*-substituents, both *ortho*-C–H positions were methylated, involving triple C–H activation and the formation of three new C–C bonds. Mechanistically, the reaction proceeds through formation of palladacycles **145c** *via* maleimide-relayed C–H activation. These intermediates undergo oxidative addition with TsOMe to form Pd(IV) species **145d**, followed by reductive elimination to furnish methylated intermediates **145e**. Subsequent benzylic C(sp^3)–H activation and intramolecular reductive elimination afford the cyclized products **148**. For unsubstituted iodobenzenes, a second methylation occurs *via* a similar sequence.



Scheme 38 Maleimides-relayed *ortho*-C–H borylation of aryl iodides.

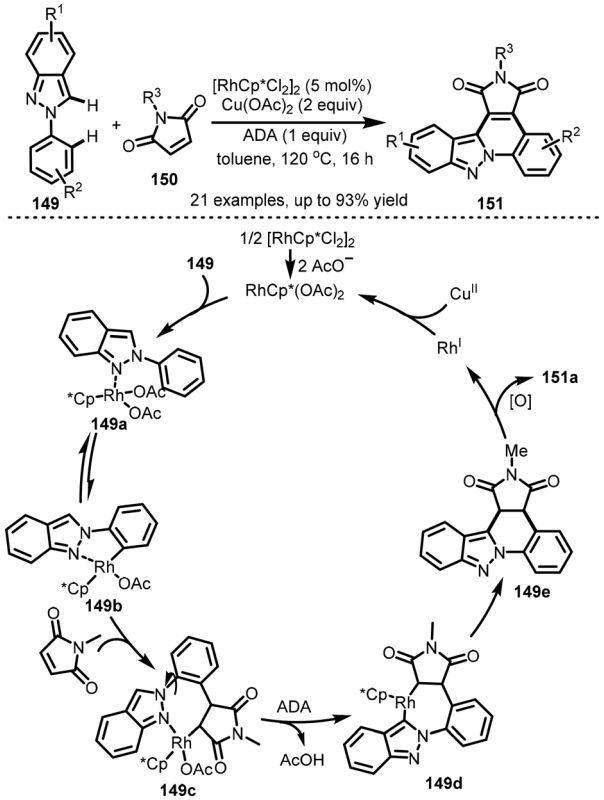


Scheme 39 Maleimides-relayed *ortho*-C–H methylation of aryl iodides.

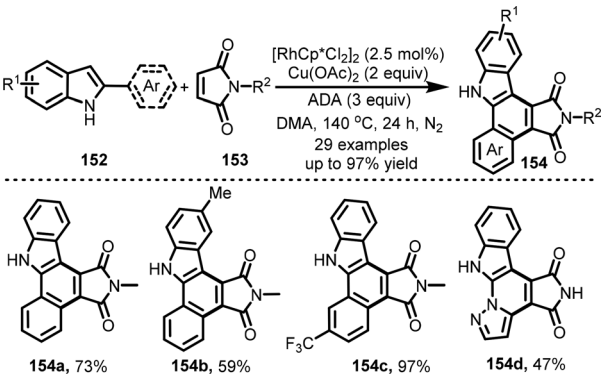
3.3 Rh(III)-catalyzed C–H activation relayed maleimides

In addition to palladium catalysis, rhodium catalysis has also proven effective in enabling maleimide-relayed C–H activation. In 2019, Zhang and Fan's group reported a Rh(III)-catalyzed dehydrogenative annulation reaction between 2-arylindazoles and maleimides, providing access to fused polyheterocyclic compounds (Scheme 40).[89] This cascade transformation begins with Rh(III)-mediated C–H activation to form a five-membered rhodacycle intermediate **149b**, followed by maleimide insertion to generate intermediate **149c**. Subsequent activation of the pyrazole C–H bond under acidic conditions forms a *C*,*C*-rhodacycle **149d**, which undergoes reductive elimination to furnish the fused-ring product indazolo[2,3-*a*]pyrrolo[3,4-*c*]quinolinones **151a**. The reaction displays broad substrate scope, efficiently accommodating 2-arylindazoles with diverse substituents.

In 2021, Kumar and co-workers developed a Rh(III)-catalyzed annulation reaction of 2-arylindoles and 3-arylindoles with maleimides *via* maleimide-relayed C–H activation (Scheme 41).[90] This



Scheme 40 Rhodium-catalyzed cycloaddition of 2-arylindazoles with maleimides through maleimides-relayed C–H activation.

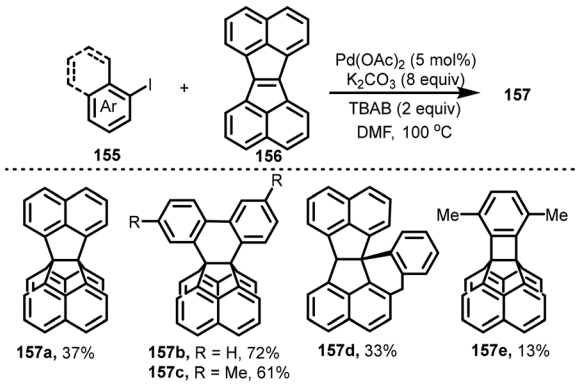


Scheme 41 Rhodium-catalyzed cycloaddition of 2-arylindoles with maleimides through maleimide-relayed C–H activation.

transformation afforded benzo[*a*]pyrrolo[3,4-*c*]carbazole-1,3(2*H*,8*H*)-diones **154** as the final products. The reaction proceeds through dual C–H activation and the formation of two C–C bonds, providing a concise and efficient approach to the synthesis of benzo[*a*]carbazole frameworks.

4. Other alkenes-relayed C–H activation

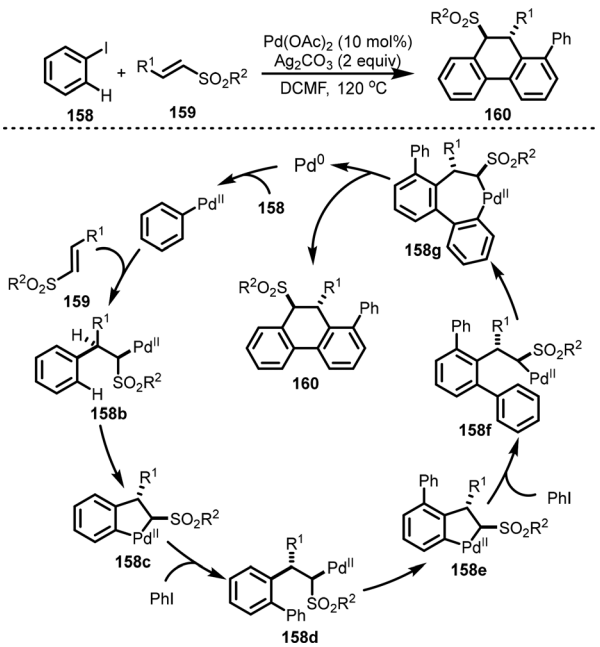
Other alkene-relayed C–H activation reactions are still rare and underdeveloped. As early as 1993, Dyker reported a palladium-



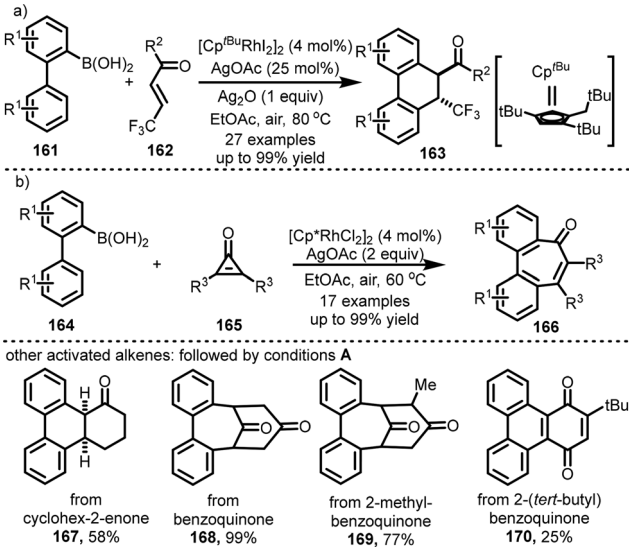
Scheme 42 Acenaphthylene derivatives-relayed C–H activation.

catalyzed cyclization of aryl iodides with acenaphtho[1,2-*a*]acenaphthylene (Scheme 42).[91] In this transformation, acenaphtho[1,2-*a*]acenaphthylene functioned as a relay to facilitate C–H activation, enabling the one-step synthesis of polycyclic propellane structures **157**. Propellanes possess unique topological architectures that confer distinctive chemical and physical properties, with benzannulated propellanes such as [4.4.4]propellane attracting considerable interest due to their inherent ring strain. Building on this pioneering work, Zhang and co-workers in 2020 extended this strategy by developing acenaphthylene-relayed C–H activation of 2-iodobiphenyls, thus achieving efficient synthesis of polycyclic propellanes.[84]

In 2001, Mauleón and co-workers reported a seminal palladium-catalyzed C–H arylation reaction relayed by α,β-unsaturated vinyl sulfones (Scheme 43).[92–94] In this transformation, the intermediate **158b** underwent intramolecular C–H activation rather than the conventional β-hydride elimination, primarily due to coordination of the sulfone group to Pd(II),



Scheme 43 α,β-Unsaturated vinyl sulfones-relayed C–H activation.



Scheme 44 Rhodium-catalyzed, activated alkenes-relayed C–H action of 2-biphenylboronic acids.

which effectively suppressed β-hydride elimination. The resulting *C*,*C*-palladacycle **158c** then reacted with iodobenzenes to form intermediate **158d**, which subsequently underwent a second analogous C–H arylation to afford diarylated intermediate **158f**. **158f** underwent the third C–H activation to yield the polycyclic product 1-phenyl-9-phenylsulfonyl-9,10-dihydrophenanthrene **160**. This four-component tandem reaction enables precise formation of multiple C–C bonds, facilitating the efficient construction of complex dihydrophenanthrene frameworks.

In 2021, Li, Chang, and colleagues reported a Rh(III)-catalyzed cyclization reaction of 2-biphenylboronic acids with CF_3-substituted enones *via* enones-relayed C–H activation (Scheme 44).[95] A sterically demanding cyclopentadienyl ligand (Cp*t*Bu) was found to be critical, as it effectively promoted the reductive elimination step while suppressing the formation of undesired 1,4-addition byproducts. This annulation furnished CF_3-substituted dihydrophenanthrene derivatives **163**. Similarly, cyclopropenone- and benzoquinone-relayed C–H alkylation/cyclization reactions have been developed, delivering seven-membered ring products **166** and bridged cyclic compounds **167–170**, respectively.

5. Conclusions

Alkene-relayed C–H activation represents a novel strategy for selective C–H functionalization, serving as both a valuable complement to and a significant expansion of conventional directing group-dependent approaches. A major class of these reactions is the palladium-catalyzed intramolecular alkene-relayed C–H activation process. However, such reactions typically require substrates with complex structures, which limits the availability of applicable starting materials and restricts the diversity of accessible products. Intermolecular reactions address this limitation by enabling the use of simple, readily available substrates, thereby vastly expanding the range of accessible compounds. The Catellani reaction exemplifies a prominent category of intermolecular alkene-relayed C–H functionalization. In this process, norbornenes act as transient catalysts and are not incorporated into the final products. In contrast, other intermolecular alkene-relayed C–H activation reactions allow the alkenes to become part of the final product. These transformations often proceed through cascade multi-component processes, enabling the efficient formation of multiple chemical bonds in a single step. This streamlined approach provides novel strategies for constructing complex molecular architectures while enhancing synthetic efficiency. Traditionally, NBE and its derivatives have been the predominant alkenes employed. Recently, however, maleimides have gained significant attention as effective relays for C–H activation. Palladium remains the dominant catalyst for these reactions, though rare examples of rhodium-catalyzed systems have also been documented.

Despite significant advances in intermolecular alkene-relayed C–H functionalization, several critical challenges remain to be addressed in future research. A major limitation lies in the restricted scope of applicable alkenes. Current systems are largely confined to norbornenes and maleimides, while the development of reactions employing other alkenes—particularly simple straight alkenes—as relays remains a significant challenge. Moreover, in intermolecular alkene-relayed C–H functionalization, intermediates generated *via* C–H activation can be intercepted by external reagents. However, the range of compatible reagents must be further expanded to diversify accessible products, particularly for maleimide- and other alkene-relayed systems. Lastly, alkene-relayed C–H activation inherently generates two chiral centers, presenting compelling opportunities for asymmetric catalysis. Nevertheless, enantioselective variants of these transformations remain largely underexplored. Addressing these challenges will not only advance the field of alkene-relayed C–H activation but also unlock unprecedented opportunities for developing new asymmetric reactions.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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