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The Palladium/Norbornene-Catalyzed Annulation Chemistry: Rapid Access to Diverse Ring Structures

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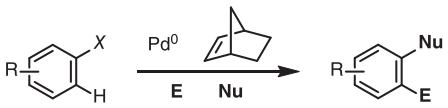
1.1 Introduction

Palladium–norbornene (NBE) cooperative catalysis, commonly known as the Catellani reaction, constitutes a general and straightforward method to sequentially difunctionalize a haloarene at the *ortho* and *ipso* positions, with two different reagents [1–6]. These reagents are typically opposite in reactivity, as the first to react does so as an electrophile (**E**), which will functionalize the *ortho* site, while the second serves as a terminating reagent, which is often a nucleophile in character (**Nu**), which will add at the *ipso* position (Scheme 1.1). This sequence is made possible due to a unique combination of characteristics, including NBE's exceptional reactivity due to the strain, the resulting rigid framework that creates a transient directing group, and lack of accessible β-hydrogens, that prevent side reactions.



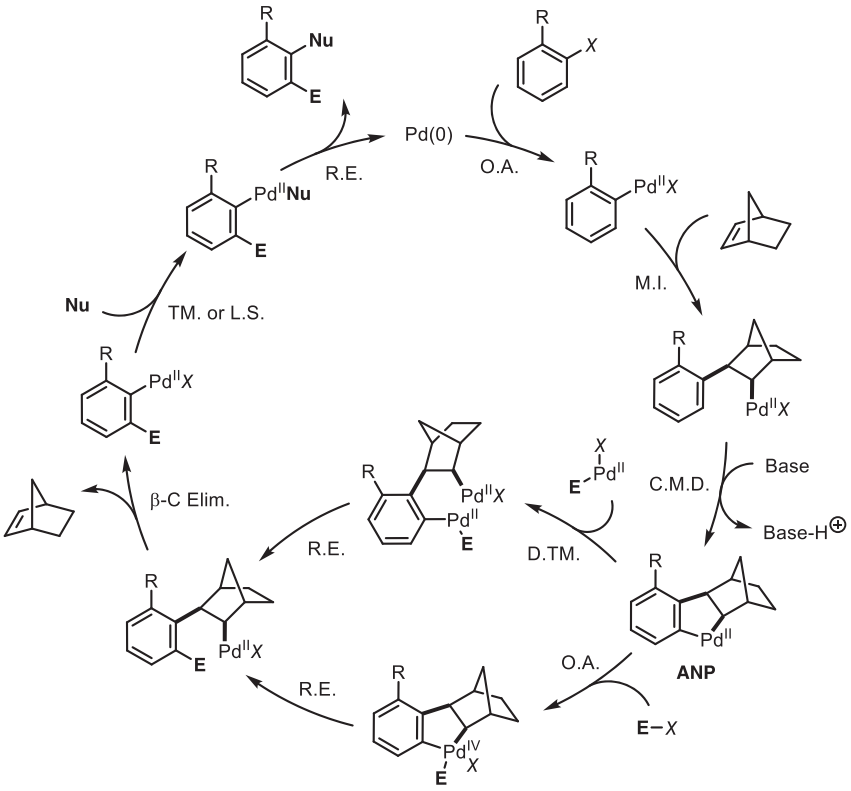
X: I, Br, OTf

Scheme 1.1 The general Catellani reaction.

The mechanism has been investigated in detail. Following oxidative addition into the C—X bond, the initial arylpalladium(II) species preferentially reacts with NBE via carbopalladation in order to release its ring strain rather than with the terminating reagent (Scheme 1.2). Every Catellani reaction subsequently generates a key intermediate, known as the arylnorbornyl palladacycle (**ANP**), which is typically formed after concerted metalation deprotonation (CMD) occurs at the *ortho* position in the presence of a base. The electrophile is then installed via one of two possible pathways: (i) oxidative addition to form a Pd(IV) intermediate followed by reductive elimination or (ii) dinuclear transmetalation [7–9]. Due to the steric congestion,

Palladium and Norbornene Cooperative Catalysis: Fundamentals and Applications, First Edition. Edited by Guangbin Dong.

NBE is then extruded *via* β–C elimination, giving rise to a new *ortho*-functionalized arylpalladium(II) species that can now react with the terminating reagent.



Scheme 1.2 The general mechanism of the Catellani reaction.

In most cases, the aryl group bears one *ortho*-substituent to avoid di-*ortho*-functionalization with the electrophile or NBE-integrated side-products and ultimately, a lower yield of desired product [9]. This requirement is known as the *ortho* constraint. To tackle this issue, various modified NBE scaffolds have been developed to successfully employ *ortho*-unsubstituted aryl halides as substrates that give good to excellent yields [10–12].

Chapter 1 presents various cyclization methodologies harnessing Pd-NBE cooperative catalysis. The first section describes the most common way of forming rings, i.e. intramolecular cyclization, where two or all three out of the aryl halide, electrophile or terminating reagent are tethered to one another. The second section reports annulations involving sequential intermolecular *ortho*-functionalization

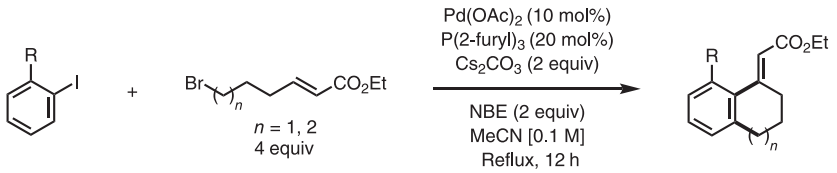
and ring closure steps with external reagents. Three-membered rings constitute the focus of section three, where their innate strain turns them into valuable electrophiles and terminating reagents upon ring opening, thereby forming five-membered rings. Reactions where NBE and its analog norbornadiene find themselves incorporated in the final annulated product instead of solely being used as transient directing groups are included in section four. The final section is comprised of reactions where the annulation step occurs after the catalytic cycle.

1.2 Intramolecular Cyclizations

1.2.1 Electrophile Tethered to Terminating Reagent

1.2.1.1 *Ortho* Alkylation

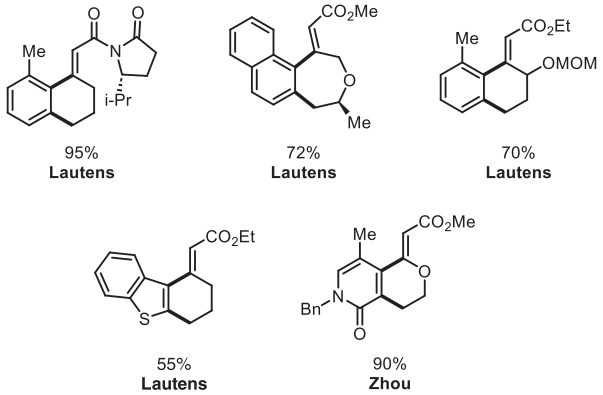
Ipso Heck Termination The original 1997 report by Catellani described a reaction between an unsubstituted or *para* substituted aryl iodide, an alkyl halide, and a Heck acceptor [1]. The catalyst, known as the PNP complex, was a phenyl norbornyl palladium halide dimer prepared from phenyl mercuric chloride, NBE, and palladium chloride. In 1999, $Pd(OAc)_2$ in DMF was shown to be a suitable combination for reacting *ortho*-substituted aryl iodides [13]. In 2000, Lautens developed an annulative process and reported what have become the most widely used conditions, namely $Pd(OAc)_2$, phosphines, acetonitrile, and cesium carbonate (Scheme 1.3). In this example, the electrophile, i.e. the alkyl bromide, is tethered to the Heck acceptor providing access to fused ring systems [14].



Scheme 1.3 First annulative Catellani methodology.

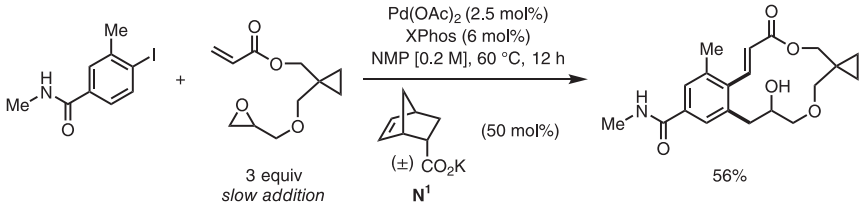
This set of conditions paved the way for subsequent ring-forming processes, generating a variety of benzofused carbo- and heterocycles via *ortho*-alkylation and *ipso*-Heck termination under identical or modified conditions (Scheme 1.4) [15–19]. Some of these examples illustrate that heterocycles are tolerated, which was not possible until Lautens' report in 2006 [18].

Alkyl bromides were generally preferred over the analogous iodides likely due to potential side reactions, namely oxidative addition of Pd(0) into the $C(sp^3)$–I bond followed by β–H elimination and reductive elimination to give the corresponding olefin and HI [13]. However, the iodides were ideal electrophiles in a β-fluoroalkylation process [20]. Alkyl tosylates were also found to be compatible electrophiles in the Catellani reaction [21].



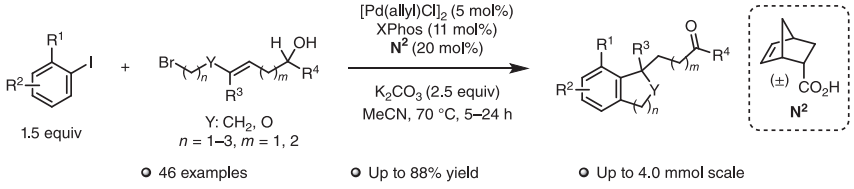
Scheme 1.4 Examples of *ortho*-alkylation/*ipso*-Heck-termination annulative methodologies.

The Zhou group identified epoxides as alkylating reagents in a macrocyclization event using the potassium salt of 5-NBE-2-carboxylic acid **N[1]** (Scheme 1.5) [22].



Scheme 1.5 Macrocycle formation using an epoxide as an alkylating reagent.

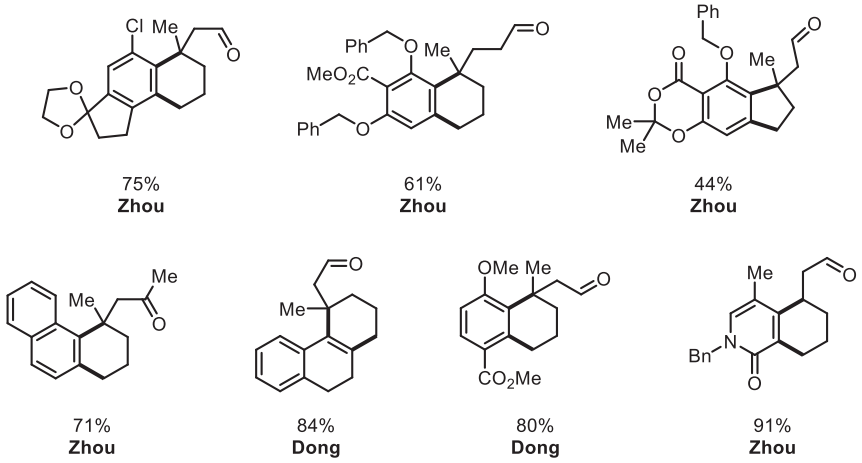
(Homo)allylic alcohols were suitable as the Heck acceptor, furnishing the corresponding carbonyl compounds via a redox-relay Heck cyclization (Scheme 1.6) [23].



Scheme 1.6 First methodology using (homo)allylic alcohols as the Heck acceptor.

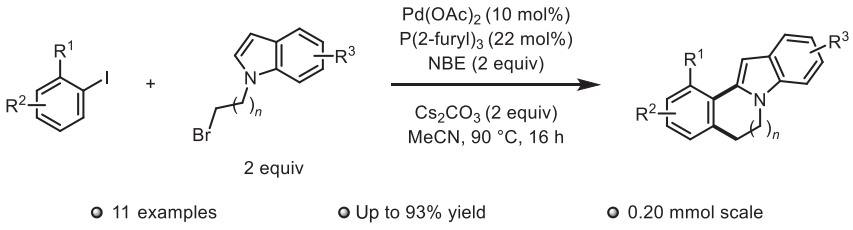
Zhou was able to generate ring sizes ranging from five to seven [19, 24, 25]. Dong was also able to provide aldehyde-tethered rings using modified procedures (Scheme 1.7) [26, 27].

Ipso C–H Arylation The first examples of annulative C–H arylation were reported by Lautens in 2005. The use of an unfunctionalized arene offers an attractive alternative to cross-coupling reactions where both arenes typically need a compatible



Scheme 1.7 Examples of *ortho*-alkylation/*ipso*-redox-relay Heck annulative methodologies.

functional group. Lautens showcased the power of C–H arylation by generating annulated indoles (Scheme 1.8) [28].



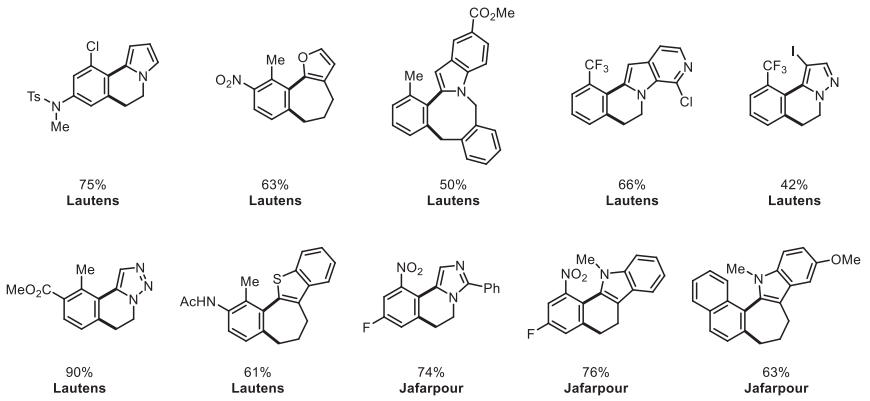
Scheme 1.8 Synthesis of annulated indoles via *ipso* C–H arylation.

This concept was generalized to include the synthesis of related hetero- and carbocycles (Scheme 1.9) [29–36].

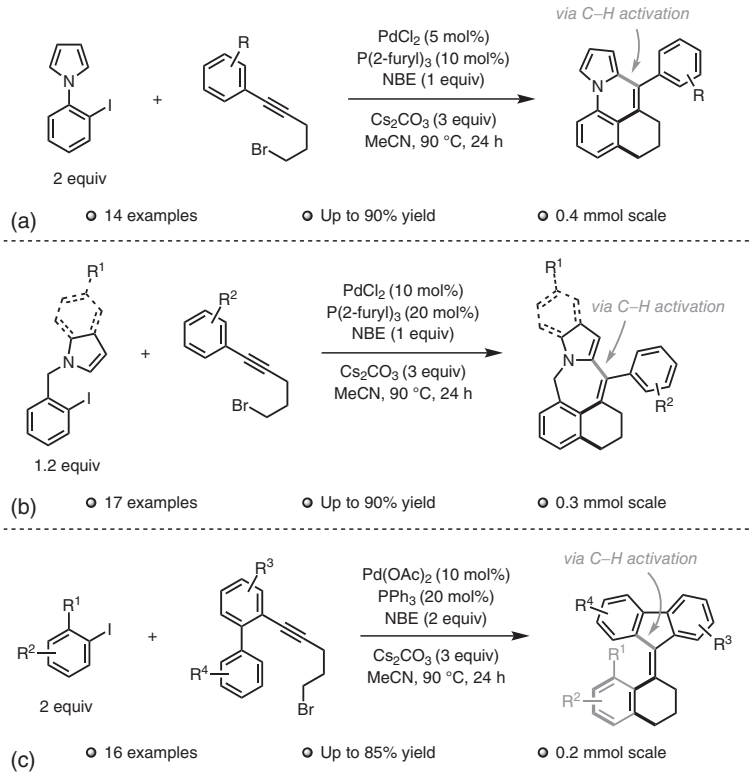
***Ipso* Alkyne Insertion** Following *ortho*-alkylation and NBE extrusion, the resulting arylpalladium(II) species may undergo a migratory insertion relay step, followed by subsequent annulation reactions that increase molecular complexity.

Lautens reported reactions of alkyne-substituted alkyl halides that lead to *ipso*-alkyne insertion and C–H functionalization, leading to tetracyclic-fused pyrrole and indole derivatives. Carbopalladation of the alkyne precedes the C–H activation (Scheme 1.10a,b) [37, 38]. A related approach was reported a few years later to furnish tetrasubstituted helical alkenes (Scheme 1.10c) [39].

The vinyl-Pd(II) species can undergo an *exo*-migratory insertion across NBE or norbornadiene followed by C–H activation to incorporate the bicycle in the final product. This method provided a different kind of tetrasubstituted helical alkenes as a single diastereomer (Scheme 1.11a) [40]. Interestingly, using chiral bromoalkyl aryl alkynes resulted in moderate diastereoselectivities (Scheme 1.11b) [41]. It was proposed the R^4 substituent induces helical chirality upon *ipso*-alkyne insertion and the resulting major vinylpalladium(II) species is favored over the minor due

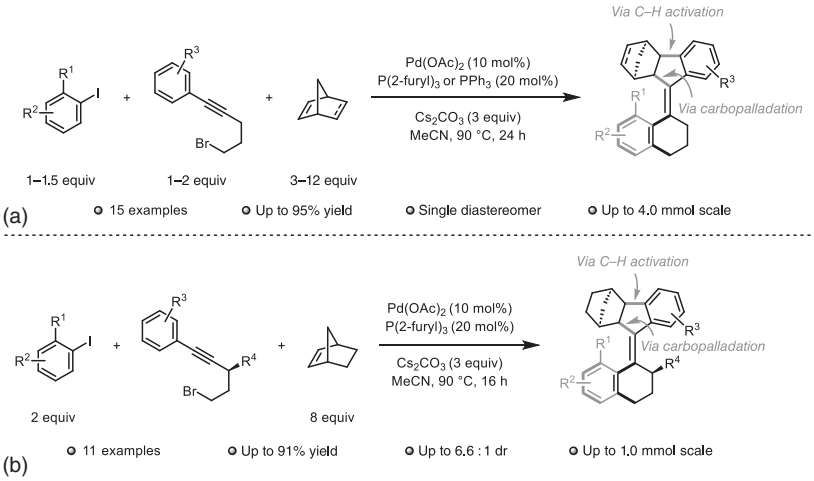


Scheme 1.9 Examples of *ortho*-alkylation/*ipso*-C–H arylation annulative methodologies.



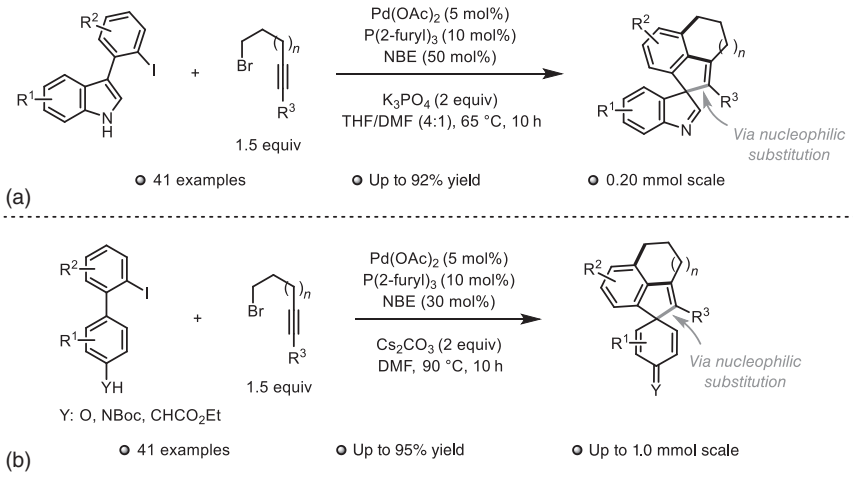
Scheme 1.10 *Ipso*-alkyne insertion followed by C–H activation to form (a) tetracyclic-fused pyrrole derivatives (b) tetracyclic-fused indole derivatives (c) tetrasubstituted helical alkenes.

to 1,3-allylic strain between the pseudoequatorial R^4 substituent and R^3-aryl ring [42, 43]. In both cases, NBE undergoes *exo*-insertion into the C–Pd(II) bond with its methylene group facing away from R^1. Subsequently, C–H activation onto the alkyne-tethered arene occurs, followed by reductive elimination.



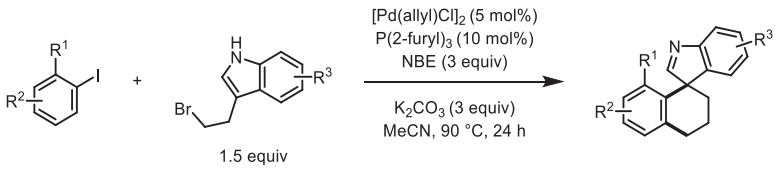
Scheme 1.11 Syntheses of tetrasubstituted helical alkenes (a) initial report (b) subsequent work using enantiomerically pure bromoalkyl aryl alkynes.

Nucleophilic attack on the vinyl-Pd(II) species can also occur. The Luan group reported two methodologies involving the dearomatization of indole and a phenol system, respectively, thereby forming a spiro palladacycle upon nucleophilic substitution (Scheme 1.12) [44, 45]. In a related report, Zhang, Liang, Li, and Quan synthesized indoles via a concerted C–N bond forming and N–S bond cleaving process following *ipso*-alkyne insertion [46].



Scheme 1.12 *Ipso*-alkyne insertion followed by dearomatization of (a) indoles (b) phenols.

Ipso Dearomatization Using a similar bromoalkyl-tethered indoles with a free N–H group, a dearomatization step can occur in the presence of a base. The *ortho*-functionalized arylpalladium(II) intermediate undergoes a ligand substitution with the deprotonated indole at its 3-position to subsequently provide spiroindolenines (Scheme 1.13) [47].



Scheme 1.13 Synthesis of spiroindolenines.

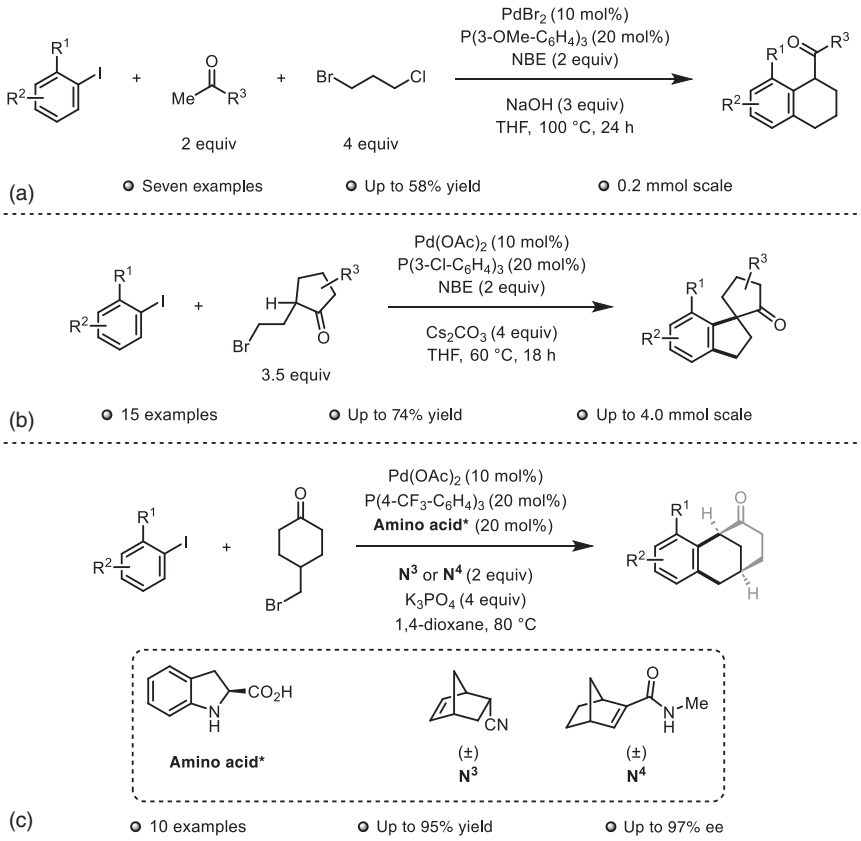
Ipso Enolate Termination A related carbon-based nucleophile can be generated as a metal-enolate. Zhou developed a three-component synthesis of 1,8-disubstituted tetralines from 2-substituted aryl iodides, aryl methyl ketones and 1-bromo-3-chloropropane (Scheme 1.14a). It was proposed the aryl methyl ketones reacted with 1-bromo-3-chloropropane under the basic conditions via an S_N2 reaction to form a bromoalkyl-tethered ketone prior to entering the catalytic cycle [48]. Liang synthesized spirodihydroindenones using a bromoalkyl-tethered cyclopentanone bearing an acidic α-proton (Scheme 1.14b) [49]. Zhou reported an enantioselective annulative process using a bromomethyl-tethered cyclohexanone that formed an enamine *in situ* with a chiral amino acid catalyst (Scheme 1.14c) [50].

Ipso C–Alkyl Termination Alkyl nucleophiles using organometallic reagents are generally considered to be less successful in transition-metal-catalyzed reactions compared to aryl or vinyl nucleophiles due to the increased number of possible side-reactions that may occur, for instance β–H elimination and the more difficult transmetallation processes. As such, using an alkyl carbagermatrane as a fine-tuned organogermanium reagent, Xiao was able to construct carbocycles with ring sizes ranging from six to eight (Scheme 1.15) [51].

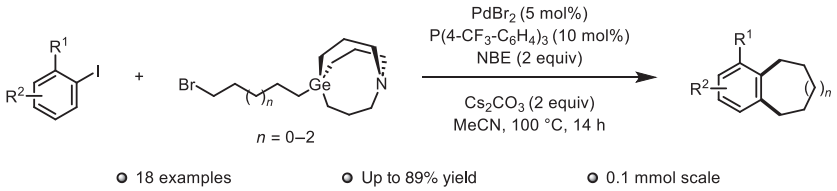
Ipso C–N Termination A nucleophilic heteroatom can also be employed as a compatible *ipso* terminating reagent. Using brominated alkylamines, Lautens was able to furnish indolines and tetrahydroquinolines depending on the alkyl chain's length (Scheme 1.16) [52, 53]. It was established that a *para*-nitrophenyl group as R^4 was the optimal nitrogen-protecting group for the synthesis of indolines. Phenyl and ethoxycarbonyl were the only other groups that were found to be compatible.

1.2.1.2 *Ortho* Arylation

Ipso C–N Termination *Ortho*-arylation is usually conducted with a less reactive haloarene than the one meant to undergo sequential *ortho*- and *ipso*-functionalizations. Typically, the former is an aryl bromide and the latter, an aryl iodide. The



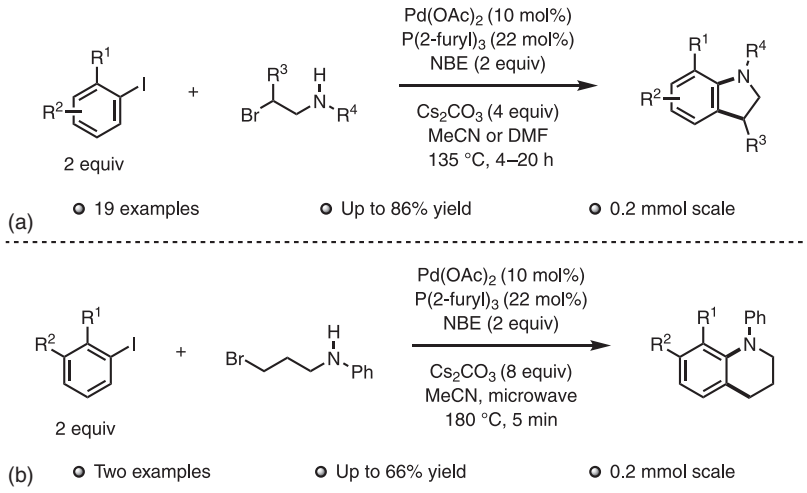
Scheme 1.14 Harnessing *in situ* generated enolates to synthesize (a) tetralines (b) spirodihydroindenones (c) bridged ketones.



Scheme 1.15 Synthesis of carbocycles using alkyl carbagermatranes.

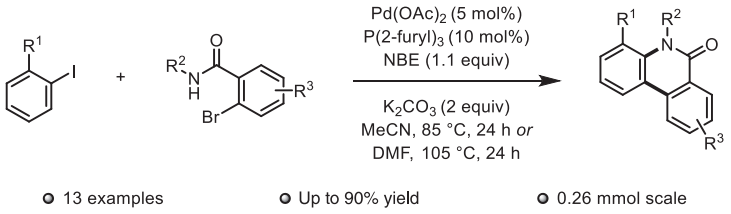
careful choice of different haloarenes ensures Pd(0) oxidatively adds into the more reactive C–I bond preferentially and that the **ANP** then reacts with the less reactive aryl bromide. Lautens showed aryl triflates can be used instead of aryl iodides [54], while aryl chlorides can also constitute the *ortho*-arylating reagent [54–56]. Two bromoarenes can also be used as coupling partners, although significant electronic differences make one more reactive than the other [57].

Catellani applied this reasoning in her synthesis of 6-phenanthridinones by reacting iodoarenes with 2-bromobenzamides (Scheme 1.17) [58]. Once *ortho*-arylation



Scheme 1.16 Synthesis of (a) indolines and (b) tetrahydroquinolines via *ortho*-alkylation and *ipso*-Buchwald–Hartwig coupling.

and NBE extrusion occurred, an *ipso*-C–N coupling took place to furnish the desired azacycles.



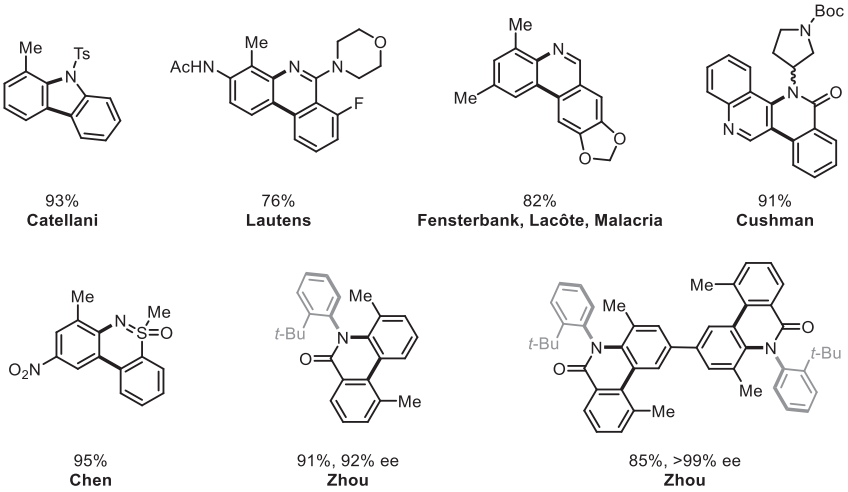
Scheme 1.17 Synthesis of 6-phenanthridinones.

Various N-heterocycles of different ring sizes were synthesized based on this method (Scheme 1.18) [54, 55, 57, 59–66].

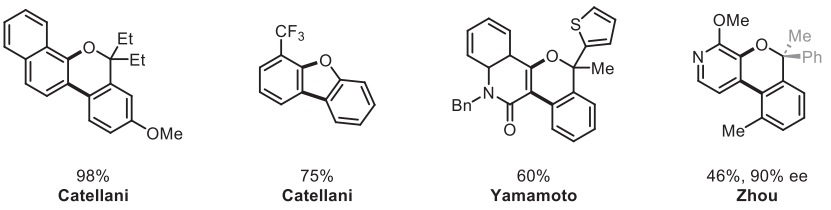
Ipso C–O Termination Similarly, C—O bond formation can occur using the appropriate terminating reagents (Scheme 1.19 [67–70].

Various C=X Bonds as Ipso Heck Terminating Reagents Carbonyls can serve as *ipso*-terminating reagents, although their reactivity differs significantly depending on the functional group to which they belong and on the reaction conditions. Lautens was able to synthesize 9*H*-fluoren-9-ols from ketones as well as 9*H*-fluoren-9-ones from esters and aldehydes via direct addition to the carbonyl (Scheme 1.20) [56].

Using a chiral NBE derivative, Zhou was able to generate fluorenols enantioselectively (Scheme 1.21) [71].



Scheme 1.18 Subsequent examples of *ortho*-arylation/*ipso*-C–N termination annulative methodologies.



Scheme 1.19 Examples of *ortho*-arylation/*ipso*-C–O termination annulative methodologies.

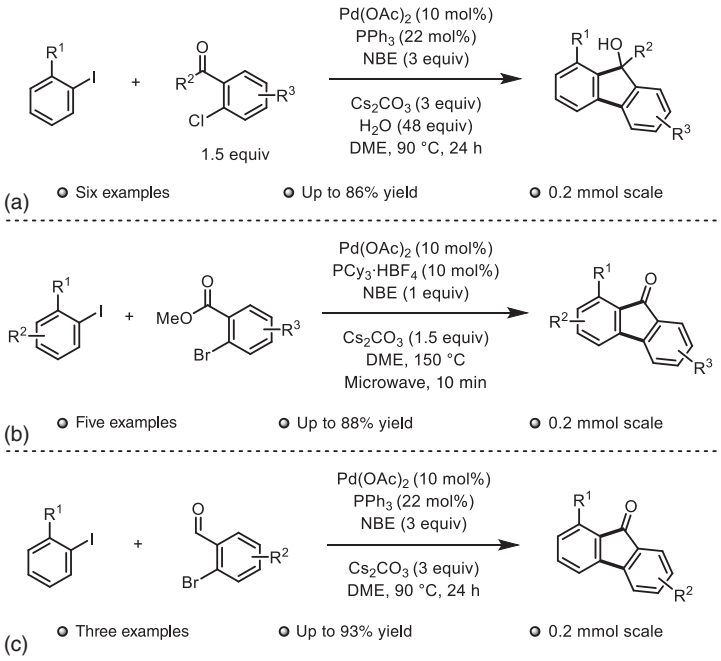
2-Bromoarylaldehyde hydrazones were used in a denitrogenative synthesis of fluorenes (Scheme 1.22) [72]. It was determined the reaction pathway does not proceed via carbene insertion.

Ipso Enolate Termination The Lautens group included three examples of enolates as terminating reagents in their work on carbonyls as *ipso* terminating reagents (Scheme 1.23) [56]. Tweaking the conditions by removing water and changing the solvent from DME to acetonitrile modulated the system's reactivity and favored enolate formation rather than the direct addition of the arylpalladium(II) intermediate to the ketone.

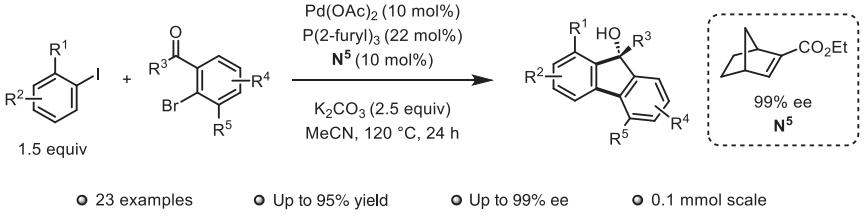
1.2.1.3 *Ortho* Acylation

Ipso Heck Termination Using a mixed anhydride, Dong discovered how to *ortho*-acylate aryl iodides [73]. Subsequently, an extension of this method was developed to generate macrocycles via an *ipso*-Heck termination step (Scheme 1.24) [74].

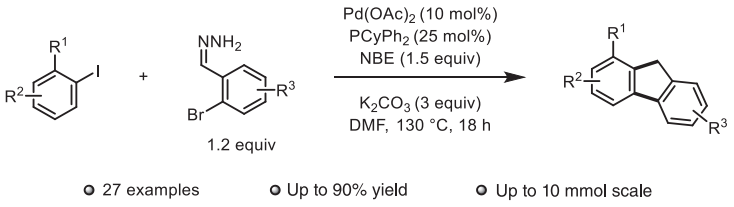
Smaller ring systems were also accessible using an analogous reagent (Scheme 1.25) [11]. A mixed anhydride could also be generated *in situ* from



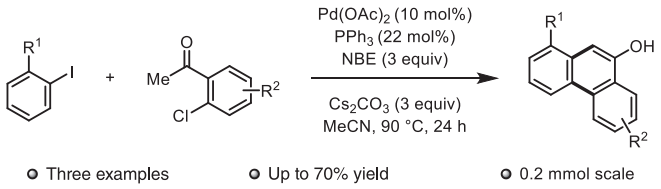
Scheme 1.20 *Ortho*-arylation/*ipso*-C=X termination methodologies for the synthesis of (a) 9*H*-fluoren-9-ols from ketones (b) 9*H*-fluoren-9-ones from esters (c) 9*H*-fluoren-9-ones from aldehydes.



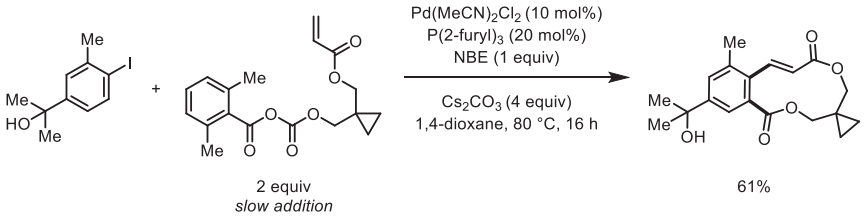
Scheme 1.21 Enantioselective synthesis of fluorenols.



Scheme 1.22 Synthesis of fluorenes via denitrogenation.

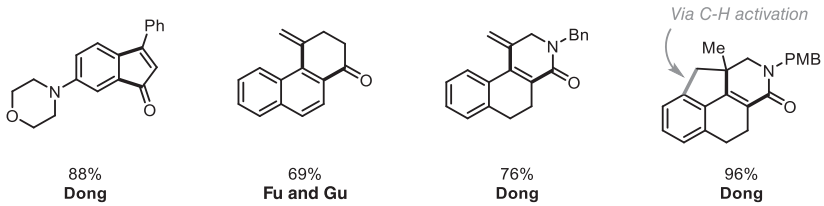


Scheme 1.23 Synthesis of phenanthren-9-ols.



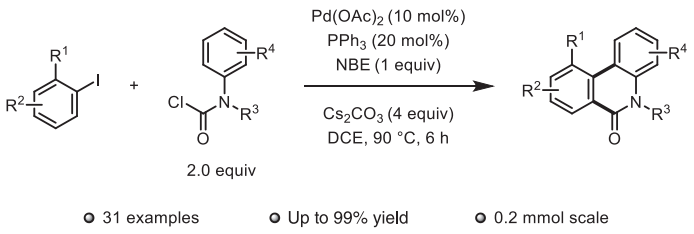
Scheme 1.24 Macrocycle formation via *ortho*-acylation and *ipso*-Heck termination.

the corresponding carboxylic acid and the Yamaguchi reagent [75]. Carbamoyl chlorides were developed as alternative *ortho*-acylating reagents, giving access to related carbocycles [76, 77].

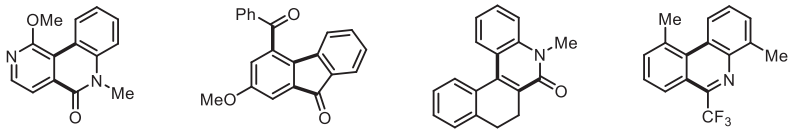


Scheme 1.25 Subsequent examples of *ortho*-acylation/*ipso*-Heck termination annulative methodologies.

Ipso C–H Arylation Jiao was the first to use carbamoyl chlorides as *ortho*-acylating reagents in Pd/NBE chemistry. These reagents were tethered to aryl rings, thereby leading to an intramolecular *ipso* C–H arylation termination, which furnished the corresponding phenanthridinones (Schemes 1.26, 1.27) [77].



Scheme 1.26 First use of carbamoyl chlorides in Pd/NBE chemistry.

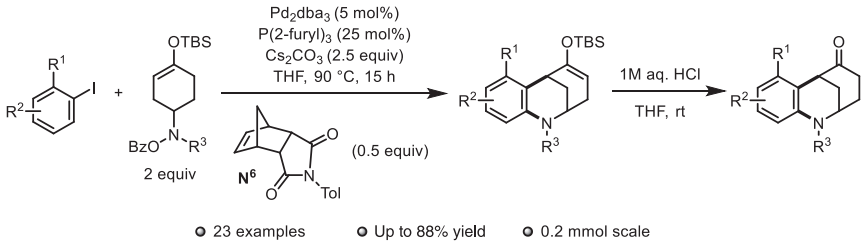


Scheme 1.27 Subsequent examples of *ortho*-acylation/*ipso*-C–H arylation annulative methodologies.

Dong obtained a fluorenone as a side-product in one of the scope examples of their reaction using benzoic anhydride and an isopropyl carbonate anhydride derived from benzoic acid (Scheme 1.27) [73]. Lumb and Luan obtained a similar side-product during the optimization of their reaction using benzoic anhydride as well [78]. Dong reported a single example starting from an alkenyl triflate [76]. Chen and Zhu demonstrated fluorinated imidoyl chlorides could also be used as *ortho*-acylating reagents [79].

1.2.1.4 *Ortho* Amination and *Ipso* Heck Termination

A significant advance in Catellani methodology was the *ortho*-amination using Pd/ NBE cooperative catalysis, as reported by Dong in 2013, using *O*-benzoylhydroxylamines. This finding was the first time a heteroatom was introduced at the *ortho* position [80]. Since then, multiple reports have made use of this methodology to generate aminated arenes as well as N-heterocycles. For example, Zhou developed an amination reagent tethered to a silyl enol ether to make N-containing bridged scaffolds (Scheme 1.28) [81].

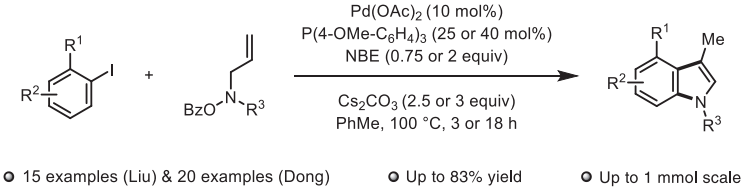


Scheme 1.28 Synthesis of N-containing bridged scaffolds via *ortho*-amination/*ipso*-Heck annulation.

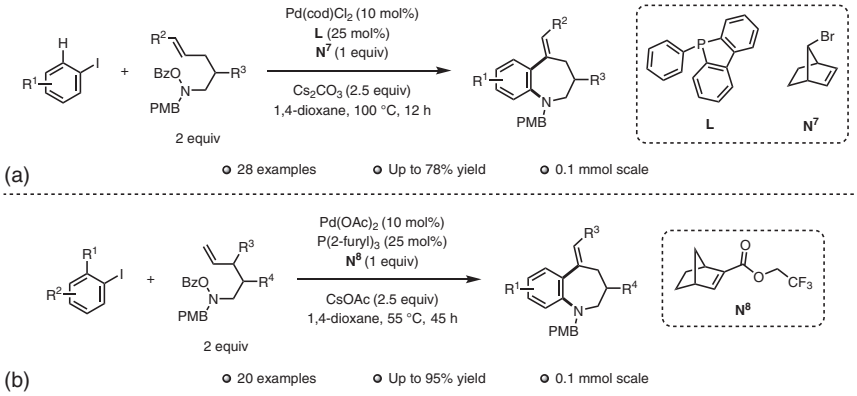
The Liu and Dong groups concurrently published on a related topic in which C3,C4-disubstituted indoles were synthesized using near-identical conditions (Scheme 1.29) [82, 83].

Shortly after, Dong discovered that a C7-brominated NBE (**N^7**) was key in generating tetrahydrobenzo[*b*]azepines using *ortho*-unfunctionalized aryl iodides as substrates (Scheme 1.30a) [12].

This methodology bypasses the long-standing "*ortho* constraint." All but two products were accompanied by a minor regioisomer arising from reinsertion



Scheme 1.29 Synthesis of C3,C4-disubstituted indoles via *ortho*-amination/*ipso*-Heck termination.



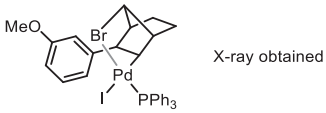
Scheme 1.30 Synthesis of tetrahydrobenzo[b]azepines using (a) C7- and (b) C2-substituted NBEs.

of the Pd–H species wherein the alkene ends up inside the seven-membered ring in conjugation with the aryl ring. It was postulated that the absence of an *ortho*-substituent leads to a Pd–H reinsertion step, thereby furnishing a tertiary C(sp^3)–Pd(II) intermediate that undergoes β–H elimination inside the ring. When using *ortho*-functionalized aryl iodides, no isomerized products were obtained, most likely due to the *ortho*-substituents' bulkiness (Scheme 1.30b). Optimization of this reaction demonstrated C2-substituted NBE **N^8** constituted the most appropriate bicyclic alkene to direct the transformation.

A crystal structure of the complex shown in Scheme 1.31 was obtained, wherein the bromine atom acts as an L ligand coordinating to d^8 Pd, thereby reducing side reactions by stabilizing reaction intermediates. The bromo substituent is proposed to stabilize the β–C elimination transition state to promote NBE extrusion rather than a second *ortho*-C–H activation step, which would lead to *ortho*-difunctionalization. Additionally, the bromine's electronegativity hinders direct C–C reductive elimination from the **ANP** due to charge repulsion with the metalated aryl ring. Lastly, although the Br substituent is more sterically hindered than a hydrogen, it is not bulky enough to prevent the **ANP** from reacting with the electrophile.

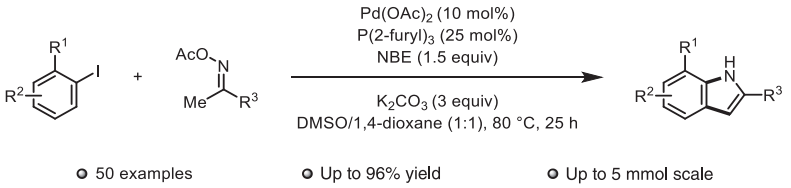
1.2.1.5 *Ortho* Alkenylation and *Ipso* Amination via Reversal of Regioselectivity

Interestingly, using oxime acetates derived from methyl ketones led to formal *ortho*-alkenylation and *ipso*-amination (Scheme 1.32) [84]. Following the **ANP**'s



Scheme 1.31 Br on a modified NBE's C7 acting as an L ligand coordinating to d^8 Pd.

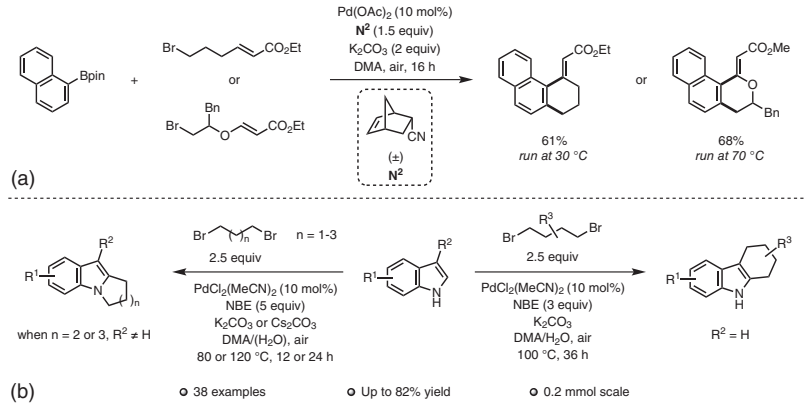
oxidative addition into the oxime acetate's N–O bond, the resulting Pd–N-bound isomer tautomerizes to its corresponding Pd–C-bound isomer. This process subsequently leads to a C–C reductive elimination at the *ortho*-position and a C–N reductive elimination at the *ipso*-position.



Scheme 1.32 Indole formation via reversal of traditional regioselectivity of the electrophilic and terminating groups.

1.2.1.6 Pd(II)-Initiated Annulations

Aryl (pseudo)halides and palladium(0) complexes are not the only entry points for Catellani reactions. Alternatively, boronic esters and free (N–H) indoles can react with Pd(II) complexes to initiate the desired transformation, as first demonstrated by Bach for intermolecular reactions (Scheme 1.33) [85–88]. In the case of boronic esters, reductive elimination generates Pd(0) after the formation of the ring via a Heck reaction step. Therefore oxygen must be present in the reaction mixture to oxidize Pd(0) to Pd(II) to complete the catalytic cycle. As for free (N–H) indoles, protodepalladation occurs after formation of the ring to regenerate the active Pd(II) catalyst, thereby avoiding the zero oxidation state.



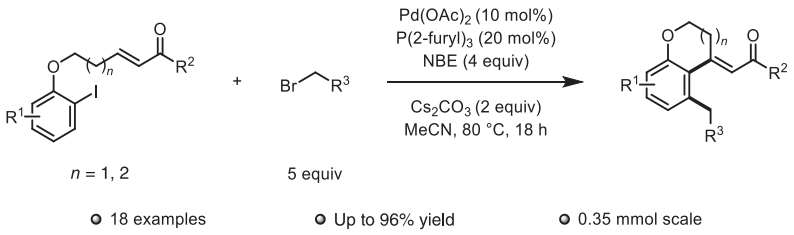
Scheme 1.33 Pd(II)-initiated annulative methodologies using (a) boronic acids and (b) free (N–H) indoles as entry points.

1.2.2 Aryl Halide Tethered to Terminating Reagent

1.2.2.1 *Ortho* Alkylation, *Ortho* Arylation and *Ortho* Amination

A second type of intramolecular cyclization involves functionalizing the haloarene *ortho*-C–H bond followed by *ipso*-annulation with an already existing functional group tethered to the haloarene. The biggest challenge to overcome is the direct *ipso*-annulation, which would occur if the *ortho*-functionalization via an intermolecular formation of the **ANP** were too slow relative to the intramolecular cyclization step.

Lautens was the first to successfully report this annulative strategy, which provided *ortho*-alkylated benzoxacycles (Scheme 1.34) [89]. Only one other example involving *ortho*-alkylation followed by an intramolecular Heck reaction has been reported [90].



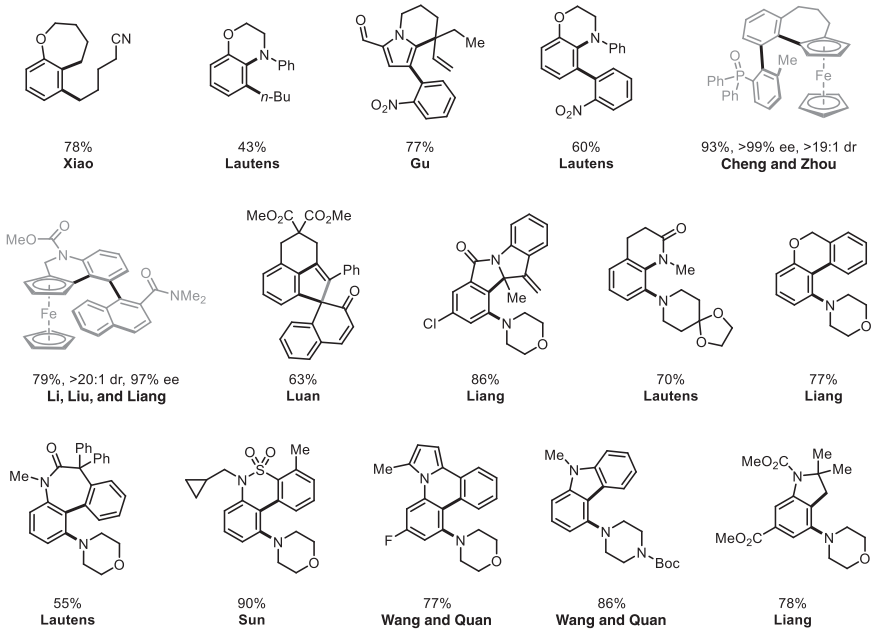
Scheme 1.34 First methodology of *ortho*-functionalization with an external reagent followed by intramolecular *ipso*-termination.

Subsequent methodologies based on this type of cyclization have generated various carbo- and heterocycles (Scheme 1.35). Other methodologies employing *ortho*-alkylations have been paired with *ipso* C–alkyl [91] and C–N terminations [92]. O*rtho*-arylations have been combined with *ipso*-functionalizations such as Heck [93, 94]), C–N [92], C–H arylations [95, 96], and alkyne insertion [97]. As for *ortho*-aminations, these have been matched with *ipso*-Heck [90]), C–N [98], C–H arylation [99–103], and C–H alkylation terminations [102, 104].

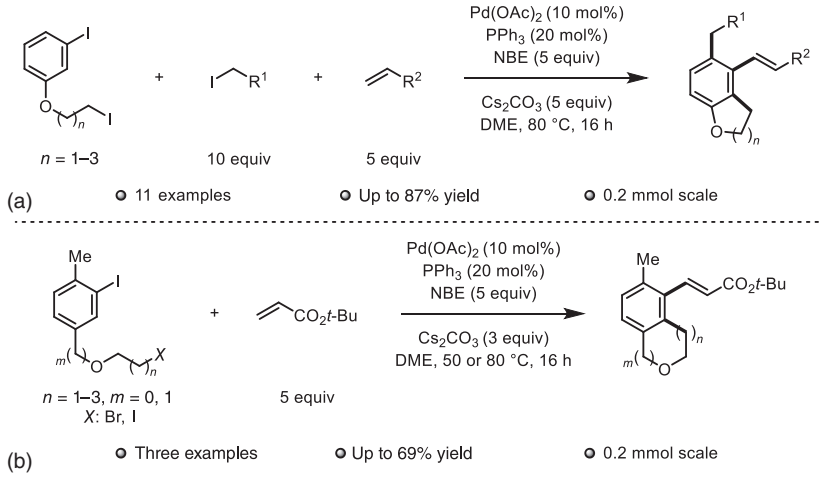
1.2.3 Aryl Halide Tethered to Electrophile

1.2.3.1 *Ortho* Alkylation

The third type of intramolecular cyclization involves functionalizing the haloarene substrate's *ortho*-C–H bond with an already existing functional group tethered to the haloarene followed by intermolecular *ipso*-annulation. In a seminal report, Lautens used *meta*-substituted iodoarenes to functionalize both *ortho*-positions with two different electrophiles, one being the tethered alkyl halide and the other, an external alkyl halide (Scheme 1.36a) [105]. A Heck termination constituted the *ipso*-functionalizing step. Aryl iodides with substituents at the 2- and 5-positions relative to the C–I bond were also compatible. However no external alkyl halide was added due to there being only one available *ortho*-C–H bond (Scheme 1.36b).



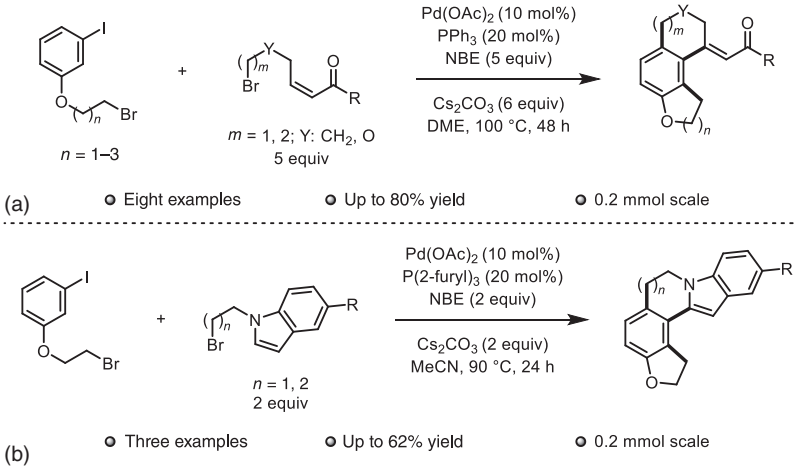
Scheme 1.35 Subsequent examples of *ortho*-functionalization with an external reagent followed by intramolecular *ipso*-termination.



Scheme 1.36 First methodology of ortho-functionalization with a tethered electrophile followed by intermolecular *ipso*-termination. (a) Unsymmetrical di-*ortho*-alkylation (b) Mono *ortho*-alkylation.

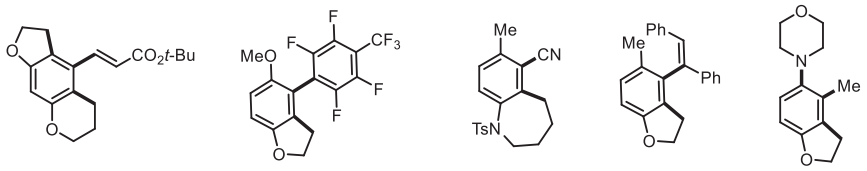
This method was subsequently combined with the original intramolecular cyclization strategy using a difunctional ambident species (bromoenoate or bromoalkyl indole) (Scheme 1.37) [106].

Since then, various groups have devised variations on the method, using Heck couplings [53, 107–111] as well as different terminations, including C(sp^2)–H



Scheme 1.37 Combining an iodoarene tethered to an electrophile with an electrophile tethered to a terminating group. (a) bromoenoate (b) bromoalkylindole.

activation [112]), cyanation [111, 113, 114], carbene insertion [115], Suzuki [111], and Sonogashira coupling [111], Miyaura borylation [111], and hydride reduction (Scheme 1.38) [111].



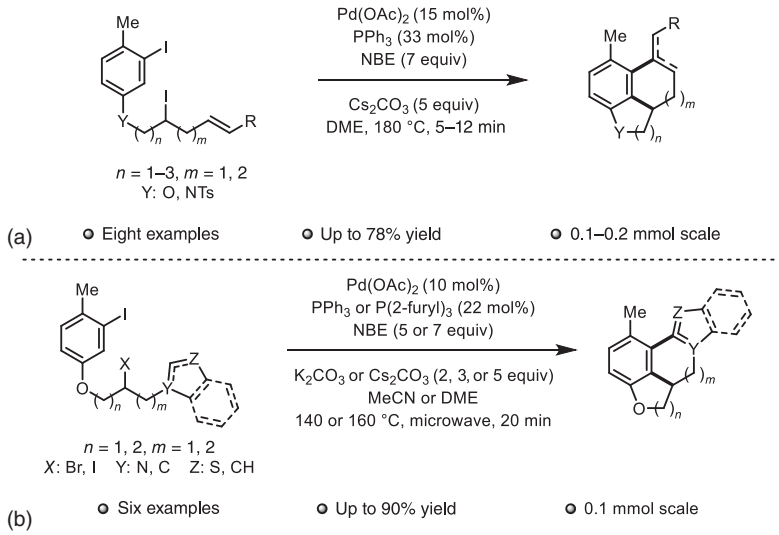
Scheme 1.38 Subsequent examples of intramolecular *ortho*-functionalization followed by intermolecular *ipso*-termination.

1.2.4 Aryl Halide Tethered to Electrophile and Terminating Reagent

1.2.4.1 *Ortho* Alkylation

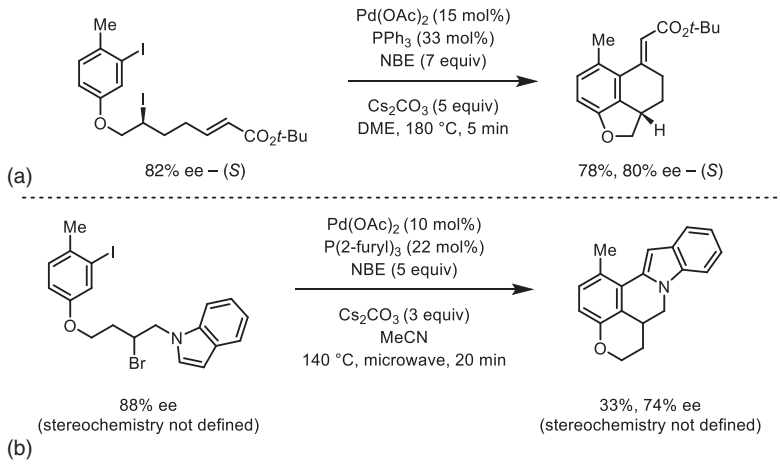
The final type of intramolecular cyclization consists of making the electrophilic and terminating groups part of the same molecule as the substrate haloarene. Only two reports of such a strategy have been disclosed, both by Lautens (Scheme 1.39) [53, 108].

The use of enantioenriched substrates led to the corresponding enantioenriched products with an overall inversion of configuration at the stereocenter with either minimal or significant decrease in ee depending on the substrate class and reaction conditions. In Scheme 1.40a, a mere 2% decrease in ee was observed when converting the alkyl iodide substrate to the corresponding tricyclic product. On the other hand, in Scheme 1.40b, subjecting the alkyl bromide substrate to the reaction conditions resulted in a cyclized product with a net −14% ee difference. Mechanistic



Scheme 1.39 Intramolecular *ortho*-alkylation followed by intramolecular (a) *ipso*-Heck termination (b) *ipso* C—H arylation.

studies showed CsI formed under the reaction conditions can racemize the substrate's chiral center in MeCN (Scheme 1.40b), but not in DME (Scheme 1.40a) due to the salt's increased solubility in the former solvent. It was proposed that inversion of configuration takes place at the oxidative addition step from Pd(II) to Pd(IV) via an S_N2 mechanism, as reductive elimination from Pd(IV) to Pd(II) occurs via retention of configuration [116–118].



Scheme 1.40 Study on the erosion of enantiomeric excess using enantioenriched substrates in (a) DME and (b) MeCN as solvents.

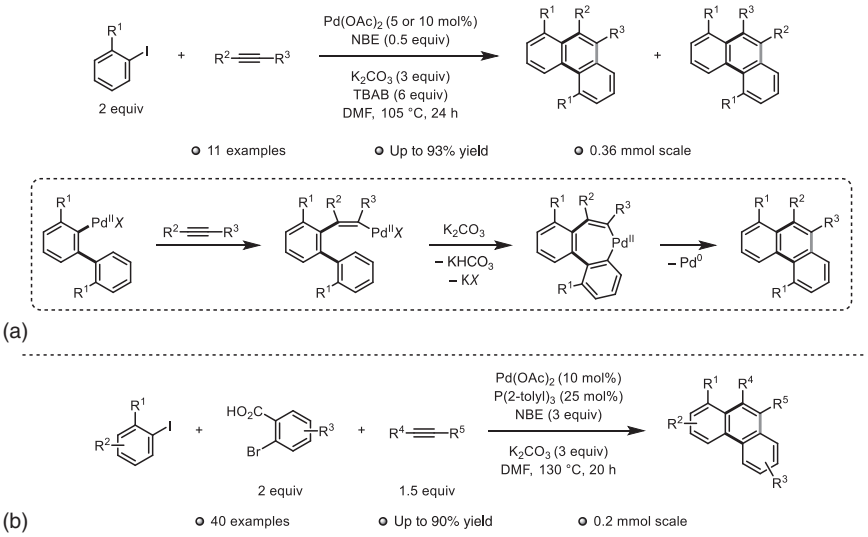
1.3 Intermolecular Cyclizations Following Intermolecular *Ortho* Functionalization

Contrary to Section 1, which focused on annulations wherein at least two out of the aryl halide, electrophile and terminating reagent components are tethered to one another, Section 2 describes ring-closing methods in which all three constitute separate molecules that react sequentially.

1.3.1 *Ortho* Arylation

1.3.1.1 *Ipso* Alkyne Insertion and *Ipso* Formal Benzyne Insertion

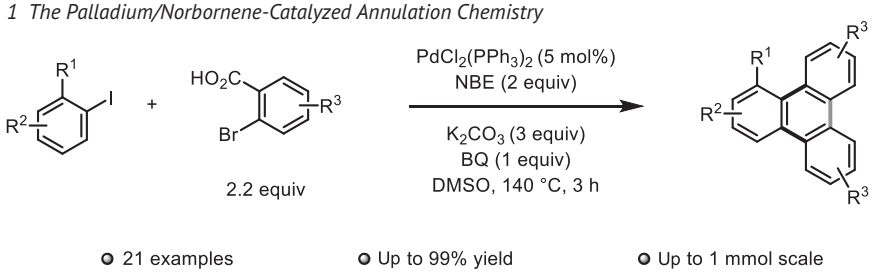
Catellani synthesized phenanthrenes using two equivalents of an *ortho*-substituted aryl iodide, one of them acting as the electrophile, and an alkyne partner to close the ring via sequential carbopalladation and reductive elimination (Scheme 1.41) [119]. Kwong also developed a regioselective synthesis of phenanthrenes, this time from two different aryl halides that allowed greater molecular complexity in the final product. CO_2 was extruded as a result of decarboxylation of the *ortho*-bromoarylcarboxylic acid in the catalytic cycle [120].



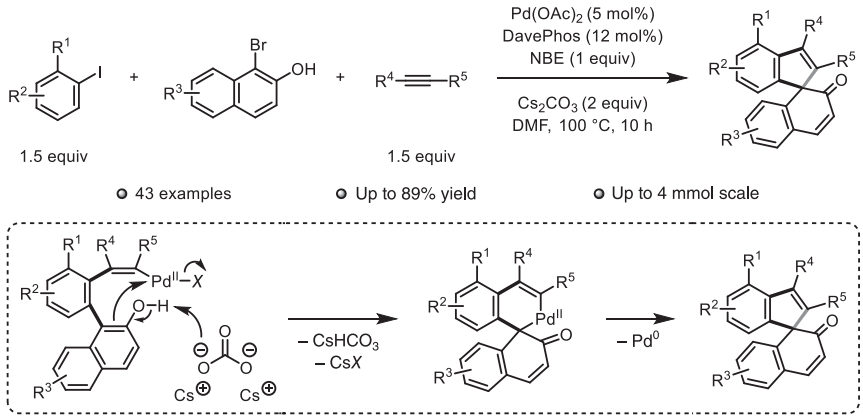
Scheme 1.41 Synthesis of phenanthrenes from an alkyne and (a) two identical aryl iodides (b) two different aryl halides.

Triphenylenes were synthesized by Liang and Yang according to a similar method to Catellani's wherein two equivalents of an *ortho*-bromoarylcarboxylic acid were needed (Scheme 1.42) [121].

Luan synthesized spirocycles via a three-component reaction using bromonaphthols as electrophiles, which ultimately underwent a dearomatization process in order to close the catalytic cycle (Scheme 1.43) [97].



Scheme 1.42 Synthesis of triphenylenes from an aryl iodide and two *ortho*-bromoarylcarboxylic acids.



Scheme 1.43 Synthesis of spirocarbocycles from aryl iodides, bromonaphthols, and alkynes.

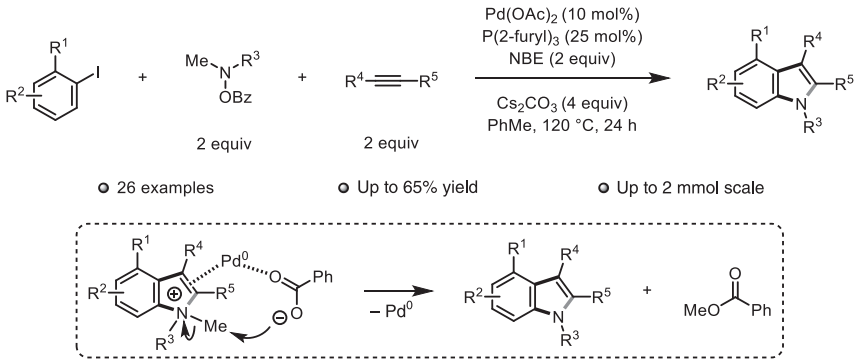
1.3.2 *Ortho* Amination

1.3.2.1 *Ipso* Alkyne Insertion

Zhang et al. synthesized indoles via an interesting process (Scheme 1.44). The final steps of the reaction first involve the formation of an intermediary indole quaternary ammonium salt, which is postulated to weaken the N–Me bond. A final S_N2 displacement with a benzoate anion gives rise to the desired indole and methyl benzoate as the by-product [122].

1.4 Cyclizations with Three-Membered Heterocycles as Both the Electrophile and Terminating Reagent

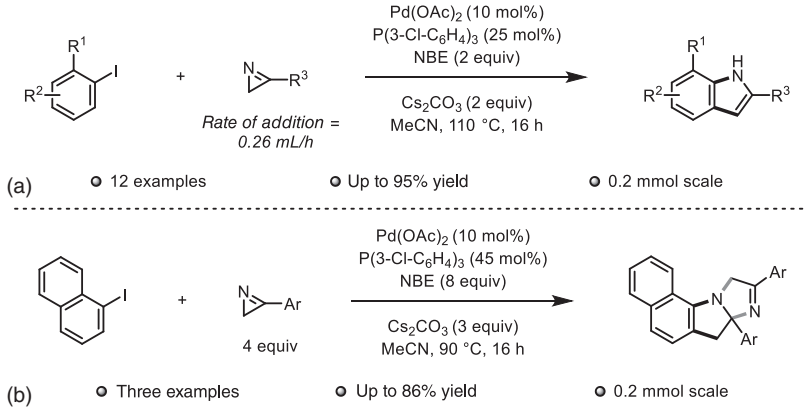
Three-membered heterocycles can serve as both the electrophile and the terminating agent. Their innate strain renders them reactive to the oxidative addition step with the **ANP**, thereby breaking one of the C–heteroatom bonds. A chemoselective C–C reductive elimination occurs to functionalize the haloarene's *ortho*-position. Following NBE extrusion, C–N or C–O reductive elimination takes place to furnish a new heterocyclic five-membered ring.



Scheme 1.44 Synthesis of indoles from aryl iodides, *O*-benzoylhydroxylamines, and alkynes.

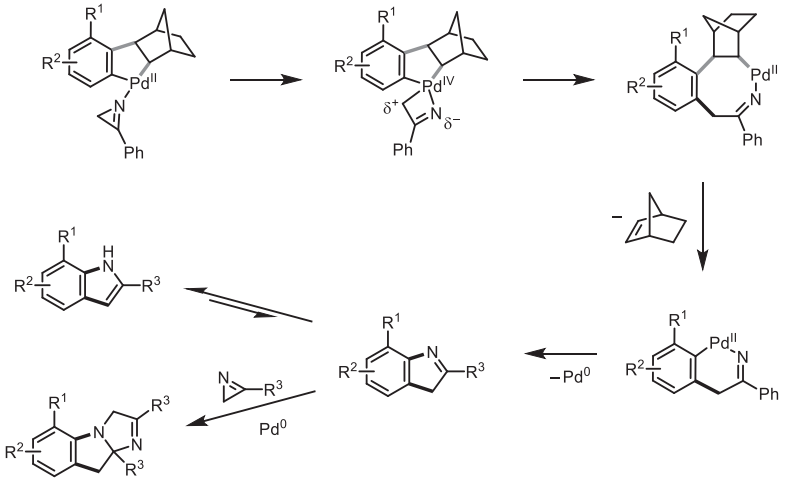
1.4.1 2*H*-Azirines

Lautens reported the synthesis of indoles using 2*H*-azirines, which were added via slow addition to the reaction mixture and resulted in a 1:1 ratio relative to the aryl iodide (Scheme 1.45a) [123]. Excess 2*H*-azirine resulted in the formation of dihydroimidazoles (Scheme 1.45b).



Scheme 1.45 Synthesis of (a) indoles and (b) dihydroimidazoles from aryl iodides and 2*H*-azirines.

Coordination of the nitrogen lone pair to the **ANP**'s Pd(II) center weakens the 2*H*-azirine's bonds, which allows oxidative addition of the Pd(II) into the ligand's C–N single bond to occur to furnish the corresponding Pd(IV) complex (Scheme 1.46) [124–129]. Reductive elimination via a chemoselective C–C bond formation leads to an eight-membered palladacycle, which is followed by NBE extrusion to give rise to a more stable six-membered palladacycle. A 3*H*-indole is then formed by a final reductive elimination, thereby regenerating the active Pd(0) catalyst. Tautomerization to the more thermodynamically stable 1*H*-indole takes place when no excess 2*H*-azirine is present. However, exposure to another

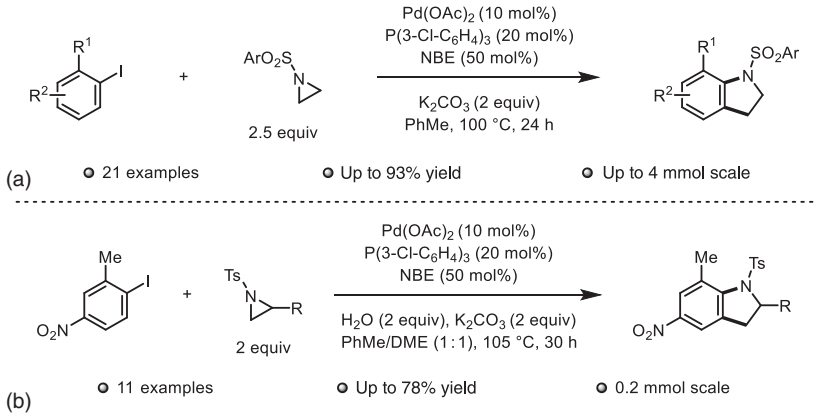


Scheme 1.46 Proposed mechanism for the formation of indoles and dihydroimidazoles from the **ANP** and 2*H*-azirine(s).

equivalent of 2*H*-azirine leads to a dihydroimidazole via a postulated Pd(0)-catalyzed formal [3 + 2]-cycloaddition.

1.4.2 Aziridines

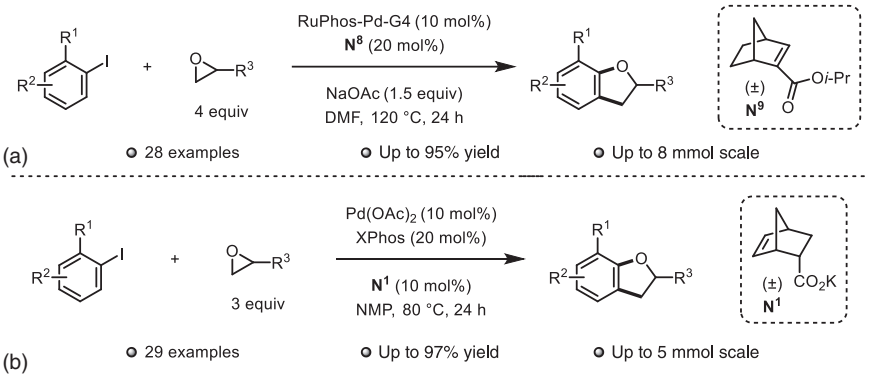
Similarly, Bi and Liang generated indolines from aryl iodides and aziridines (Scheme 1.47) [130]. These make analogous products to those previously reported by Lautens using bromoethylamines (Scheme 1.17) [52]. The latter initially thought the formation of aziridines from bromoethylamines by intramolecular nucleophilic displacement had to be avoided for the reaction to work. However, Bi and Liang's report suggests that the formation of the aziridine might have been the productive reaction pathway.



Scheme 1.47 Synthesis of indolines from aryl iodides and (a) 2-unsubstituted aziridines (b) 2-substituted aziridines.

1.4.3 Epoxides

Dong synthesized 2,3-dihydrobenzofurans from aryl iodides and epoxides (Scheme 1.48a) [131]. The same family of products was later generated by Cheng and Zhou under considerably different conditions (Scheme 1.48b) [132].



Scheme 1.48 Synthesis of 2,3-dihydrobenzofurans from aryl iodides and epoxides (a) conditions developed by Dong (b) conditions developed by Cheng and Zhou.

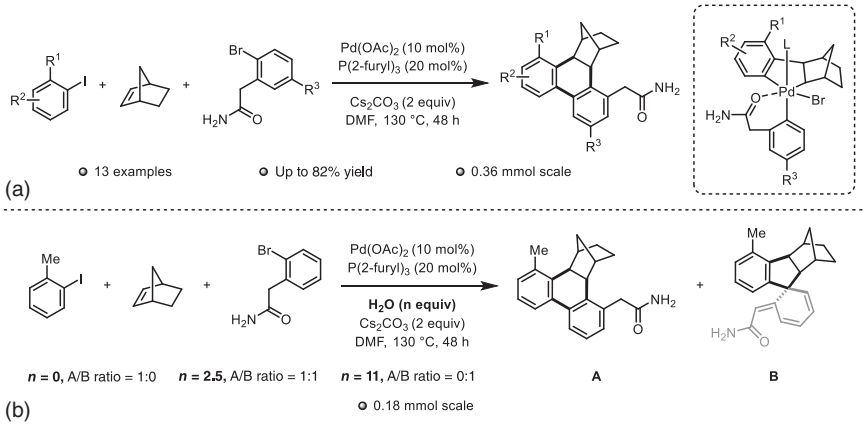
Both methodologies include an example of an enantiopure epoxide that leads to a stereoretentive annulation without any loss of ee in the product. Subsequently, Dong reported an enantioselective version of the reaction using racemic epoxides with an enantiopure chiral NBE derivative that furnished the corresponding 2,3-dihydrobenzofurans in moderate ee [133].

1.5 Norbornene/Norbornadiene-Integrated Cyclizations

1.5.1 Norbornene

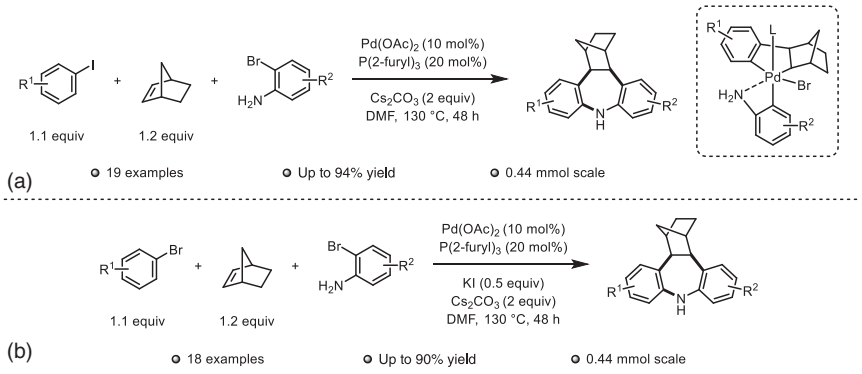
Although NBE is usually used as a transient directing group, it can sometimes be integrated in the final product to form different types of ring systems. Some reports have even disclosed results showing that exceptions to the general rules in Catellani chemistry exist.

For example, NBE-incorporated adducts derived from $C(sp^2)$–$C(sp^3)$ reductive elimination from the Pd(IV) intermediate were generated instead of products derived from the usual $C(sp^2)$–$C(sp^2)$ reductive elimination (Scheme 1.49a) [134]. This outcome could be explained due to chelation of the amide moiety of the 2-bromophenylacetamide that generates steric strain in the transition state that would lead to $C(sp^2)$–$C(sp^2)$ reductive elimination, thereby hindering this pathway. However, it was observed that adding water leads to $C(sp^2)$–$C(sp^2)$ reductive elimination due to displacement of the $P(2\text{-furyl})_3$ ligand, thereby decreasing the steric strain in the corresponding transition state and favoring this pathway. Water also hampered NBE extrusion and rather led to a dearomatized product via sequential 5-*exo*-migratory insertion and β–H elimination (Scheme 1.49b).



Scheme 1.49 Synthesis of NBE-containing adducts due to a coordinating amide-moiety (a) general reaction conditions (b) study of the effect of added water on the selectivity of the reaction.

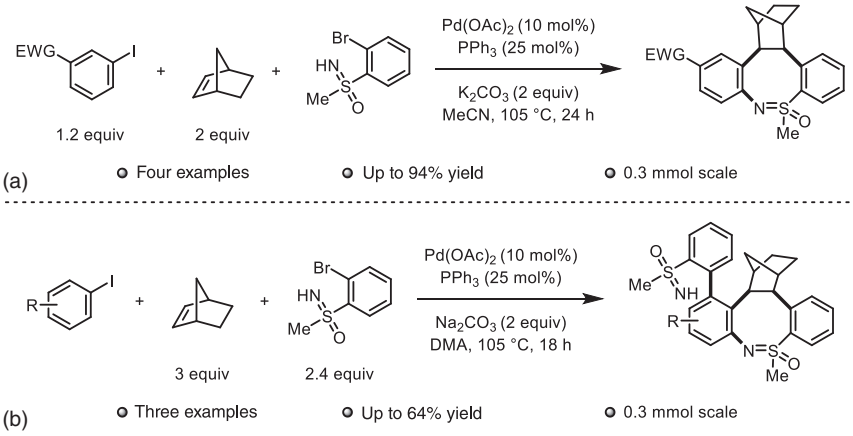
Similarly, dihydrodibenzoazepine derivatives were synthesized from aryl iodides, *ortho*-bromoanilines, and NBE (Scheme 1.50a) [135]. These compounds resulted from C(sp^2)–C(sp^3) reductive elimination from the Pd(IV) intermediate due to the chelation of the *ortho*-bromoaniline's amino group to palladium. A subsequent report used aryl bromides instead of aryl iodides with potassium iodide as an additive (Scheme 1.50b) [136].



Scheme 1.50 Synthesis of NBE-containing azacycles following C(sp^2)–C(sp^3) reductive elimination using (a) aryl iodides (b) aryl bromides.

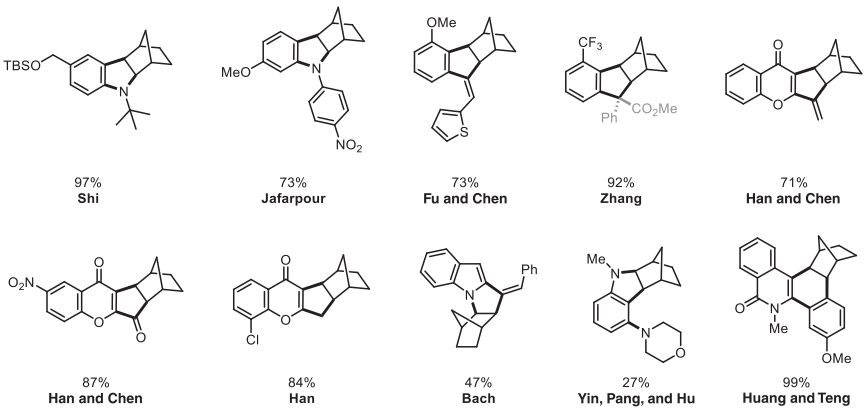
Interestingly, while combining *ortho*-substituted aryl iodides with 2-bromo-*N*H-sulfoximines leads to the usual C(sp^2)–C(sp^2) reductive elimination, aryl iodides containing electron-withdrawing groups at the *meta*-position led to NBE-containing adducts resulting from C(sp^2)–C(sp^3) reductive elimination (Scheme 1.51a) [62]. Increasing the equivalents of 2-bromo-*N*H-sulfoximine led to adducts bearing two sulfoximine moieties (Scheme 1.51b).

Other examples involve various termination steps that outcompete NBE extrusion [137–147]. For example, these steps may involve nucleophilic substitution on the



Scheme 1.51 Synthesis of NBE- and sulfoximine-containing adducts using (a) one equivalent of 2-bromo-NH-sulfoximine (b) two equivalents of 2-bromo-NH-sulfoximine.

norbornylpalladium(II) intermediate or a migratory insertion into the C–Pd bond of that intermediate (Scheme 1.52).



Scheme 1.52 Subsequent examples of NBE-containing adducts.

As mentioned earlier (Section *Ipso* Alkyne Insertion), Lautens was able to incorporate NBE in the final product following *ortho* and *ipso* functionalization to provide tetrasubstituted helical alkenes (Scheme 1.11) [40, 41].

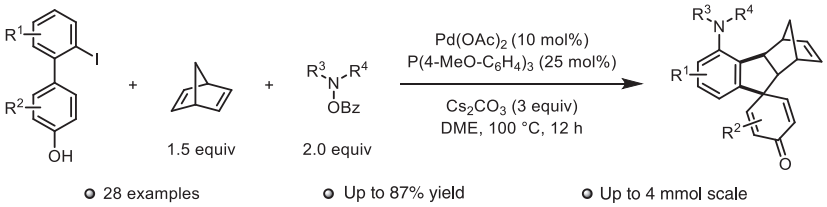
1.5.2 Norbornadiene

Although rarely used, norbornadiene can replace NBE and be a compatible partner in Catellani-type reactions. Both of their alkenyl hydrogens deviate in the *endo* direction relative to the C1–C2 plane, with an angle of 7° for NBE and about 2–4° for norbornadiene (Scheme 1.53) [148]. In both cases, the fact the alkene moiety is pyramidalized instead of flat is a result of the system attempting to

minimize torsional strain and therefore the distortion energy. This leads to a distortion-accelerated reaction upon submitting the bicyclic alkene to a compatible reagent.

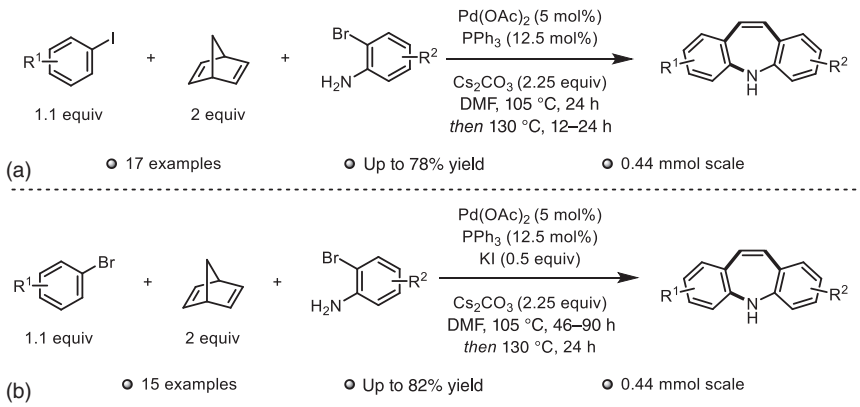
Scheme 1.53 Structural comparison between NBE and norbornadiene.

In 2017, Luan reported the synthesis of aminated spirocarbocycles having integrated a norbornadiene fragment (Scheme 1.54) [149]. Following *ortho*-amination, palladium-induced phenol dearomatization outcompetes norbornadiene extrusion via ligand substitution on the metal.



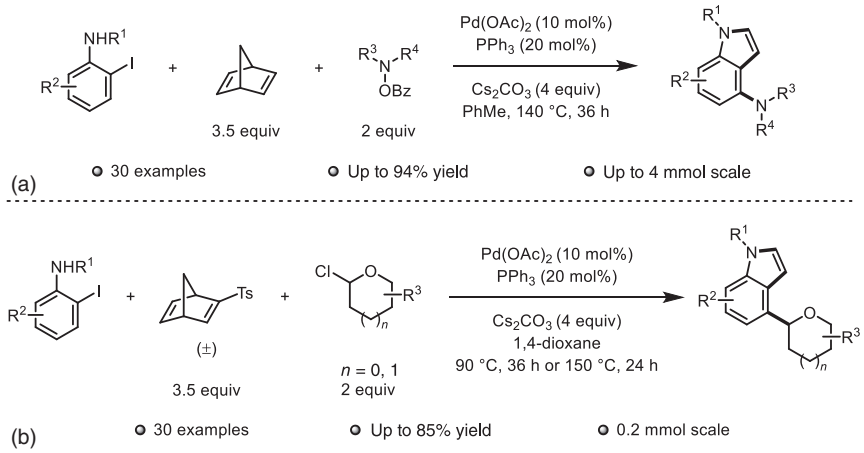
Scheme 1.54 Synthesis of norbornadiene-fused spirocarbocycles via phenol dearomatization.

Incorporation of a retro-Diels–Alder step formally installs a molecule of acetylene into the product, ejecting a molecule of cyclopentadiene. Derat and Catellani demonstrated this concept in their synthesis of dibenzoazepines by replacing NBE with norbornadiene (Scheme 1.55a) [135]. Della Ca' used an aryl bromide instead of an aryl iodide and obtained analogous results (Scheme 1.55b) [136].

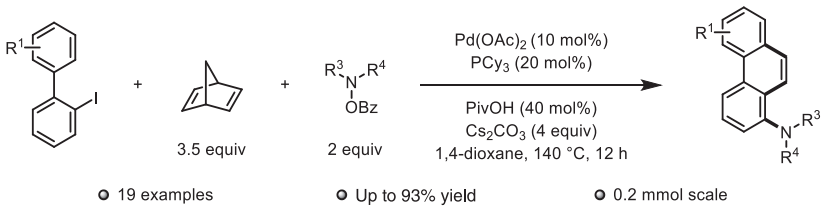


Scheme 1.55 Synthesis of dibenzoazepines following $C(sp^2)-C(sp^3)$ reductive elimination using (a) aryl iodides (b) aryl bromides.

Lautens had shown that *ortho*-bromoanilines and *ortho*-chlorobenzamides react with norbornadiene in the presence of palladium, and undergo a retro Diels–Alder step to provide access to indoles and isoquinolinones [150]. The Liang group adapted this strategy and added in a Catellani step to construct C4-functionalized indoles via *ortho*-amination or *ortho*-glycosylation, with the C2 and C3 atoms being provided by norbornadiene or its tosylated derivative (Scheme 1.56) [151, 152]. Using 2-iodobiphenyls as substrates, Liang was able to generate 1-aminated phenanthrenes (Scheme 1.57) [153]. A concurrent synthesis of such products was also developed by Yang and Liang using similar conditions [154].



Scheme 1.56 Synthesis of C4-functionalized indoles via (a) *ortho*-amination (b) *ortho*-glycosylation.



Scheme 1.57 Synthesis of aminated phenanthrenes.

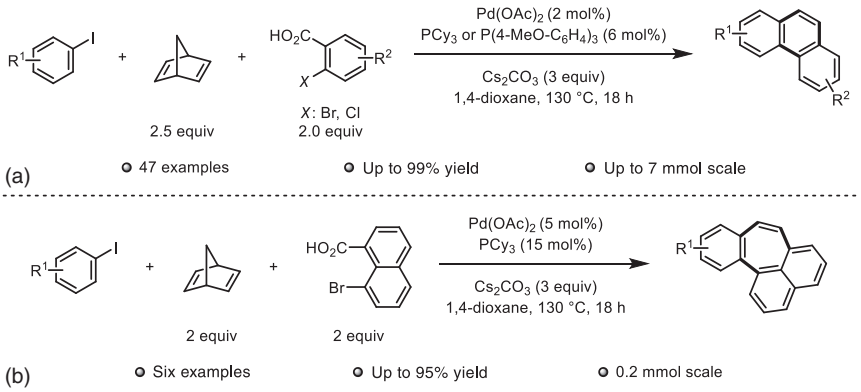
Finally, Lin and Kwong employed 2-haloarylcarboxylic acids and 8-bromo-1-naphthoic acid to provide the phenanthrene and benzo[4,5]cyclohepta[1,2,3-*de*] naphthalene derivatives, respectively (Scheme 1.58) [155].

1.6 One-Pot Postcatalytic Intramolecular Cyclizations

1.6.1 Postcatalytic Intramolecular Michael Additions

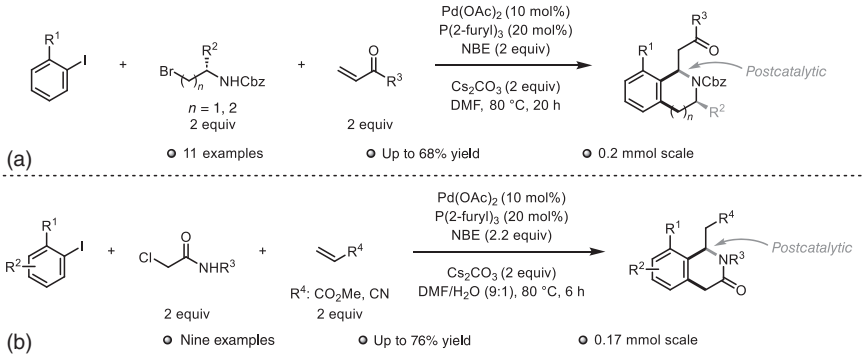
1.6.1.1 *Ortho* Alkylation

In some cases, the product of the catalytic reaction does not yet contain a ring, but subsequent cyclization can occur after the catalytic cycle. For example, using



Scheme 1.58 Synthesis of (a) phenanthrene derivatives and (b) heptagon-embedded aromatic compounds via *ortho*-arylation.

N-Cbz-bromoalkylamines and α-chloroamides as the electrophile and activated alkenes as the *ipso*-Heck acceptor, Ferraccioli synthesized six- and seven-membered N-heterocycles via a postcatalytic aza-Michael addition (Scheme 1.59) [156–158].

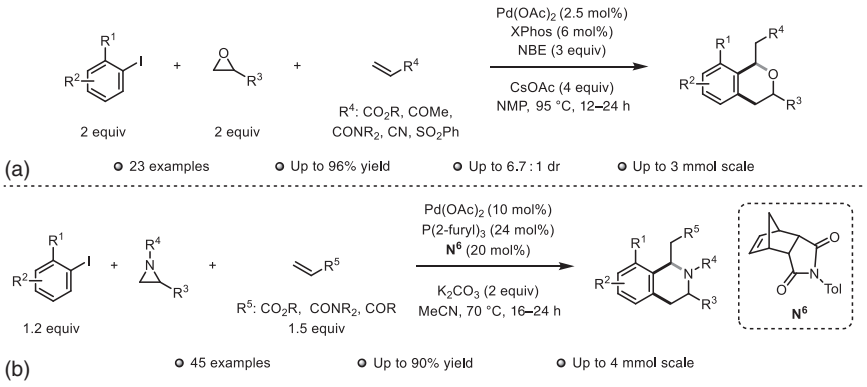


Scheme 1.59 Synthesis of N-heterocycles via a postcatalytic aza-Michael addition using activated alkenes and (a) N-Cbz-bromoalkylamines (b) α-chloroamides.

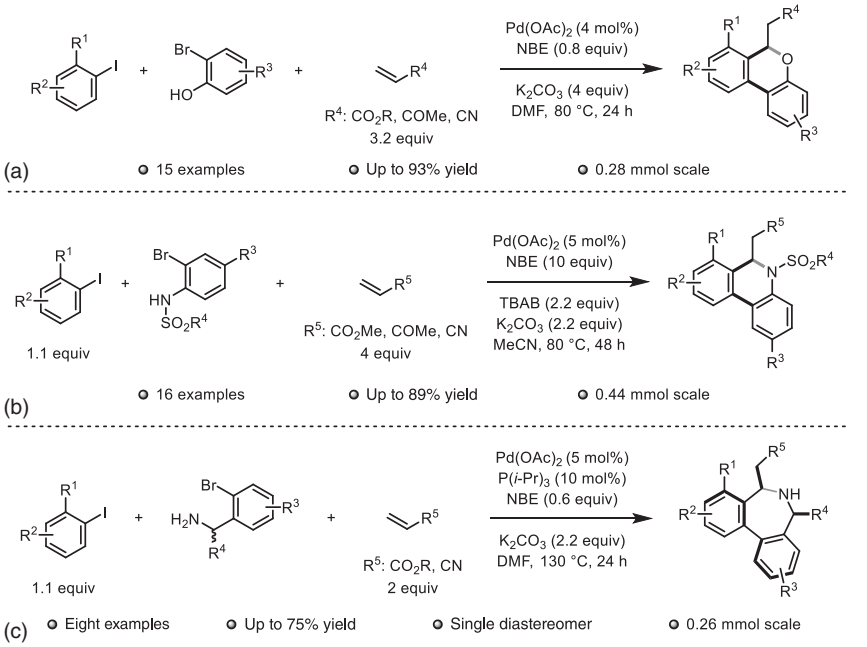
Epoxides and aziridines have also been used as electrophiles by Cheng and Zhou that, respectively, formed alcohols and amines as products after the catalytic cycle, respectively. Similarly to Ferraccioli's work, oxa- and aza-Michael additions then took place to form the corresponding oxa- and azacycles (Scheme 1.60) [22, 159, 160].

1.6.1.2 *Ortho* Arylation

Bromoarenes have also been used in this type of process to synthesize 6*H*-dibenzopyrans, dihydrophenanthridines, and dibenzoazepines (Scheme 1.61) [161–164]. 6*H*-Dibenzopyrans were subsequently generated enantioselectively using a cinchona alkaloid cocatalyst [165].



Scheme 1.60 Synthesis of O- and N-heterocycles via postcatalytic oxa- and aza-Michael additions using (a) epoxides and (b) aziridines.

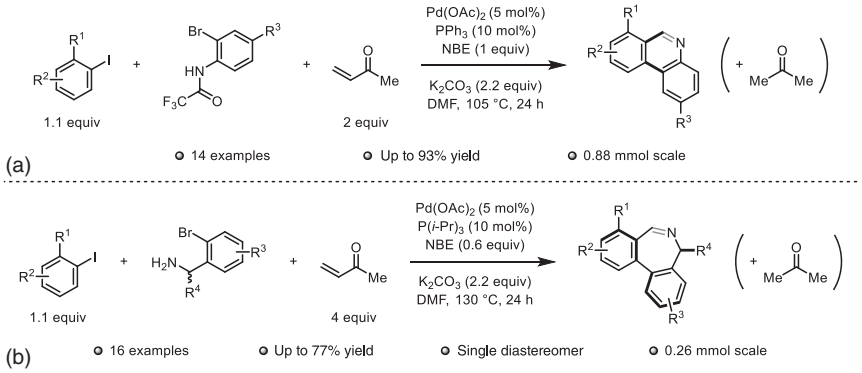


Scheme 1.61 Synthesis of dibenzocycles using (a) *ortho*-bromophenols, (b) *ortho*-bromoanilines and (c) *ortho*-bromobenzylamines.

Interestingly, using methyl vinyl ketone as the *ipso*-terminating reagent leads to a retro-Mannich reaction to furnish the corresponding phenanthridines and imines (Scheme 1.62) [164, 166].

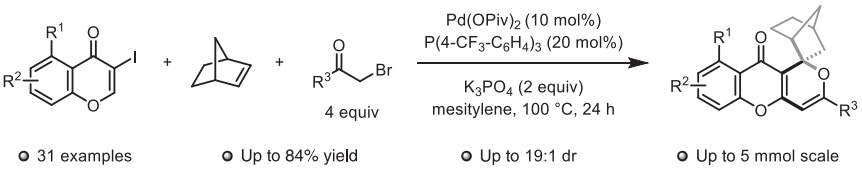
1.6.2 Postcatalytic Intramolecular Addition to Norbornyl Moiety

Finally, an interesting NBE-containing scaffold could be obtained using 3-iodochromones, α-bromoacetophenones and NBE (Scheme 1.63) [167]. Instead of



Scheme 1.62 Postcatalytic retro-Mannich reactions using MVK as the *ipso*-terminating reagent to form (a) phenanthridines and (b) imines.

the usual β-C elimination step resulting in the extrusion of NBE, a base-mediated β-H elimination step took place, which kept the norbornyl fragment in the product. Keto-enol tautomerization followed by intramolecular cyclization was proposed to deliver the spirocycle in a formal $(2+3+1)$ annulation. A subsequent report using tetracyclododecene instead of NBE led to a formal $(2+2+1)$ annulation [168].



Scheme 1.63 Postcatalytic intramolecular Michael addition onto an NBE moiety.

1.7 Summary

Since the first report by Catellani in 1997, the use of NBE to temporarily direct C–H functionalization has become of increasing interest in the synthesis of functionalized aromatic compounds. Lautens first introduced phosphine ligands to the catalytic system, which are now broadly used in this type of reaction. Lautens also reported the first annulative approach using the Catellani reaction. In the intervening two decades, many research groups have contributed to the reaction and to annulation strategies specifically. Ring formation can occur in many ways, including by tethering the electrophile or nucleophile, intermolecularly following *ortho* functionalization with an external electrophile, by using a three-membered ring as the coupling partner, by integrating NBE or norbornadiene in the final scaffold, and following of the catalytic cycle. The future of this field looks brighter with each passing year as more groups provide creative approaches that incorporate annulative Catellani reactions.

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