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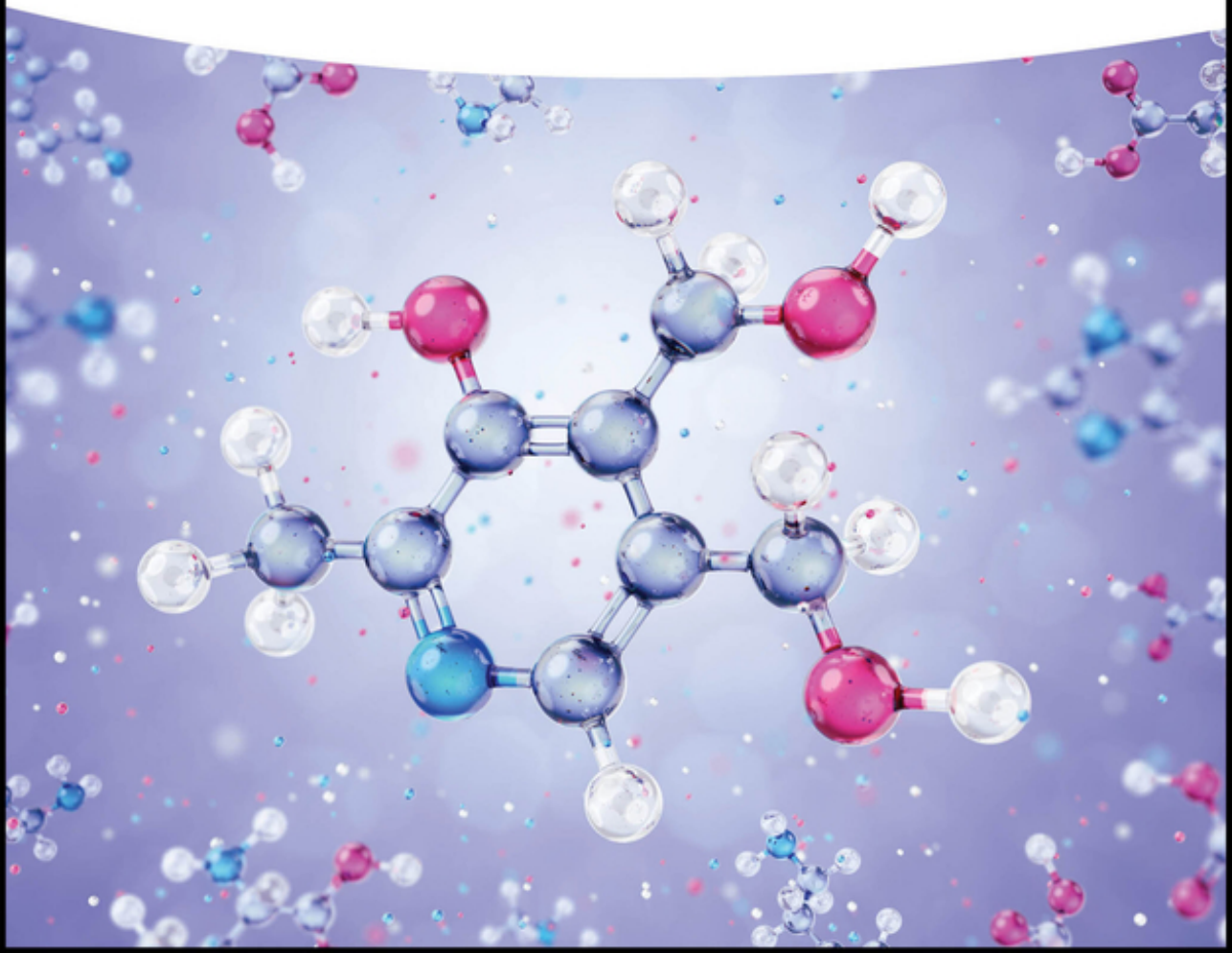
Palladium and Norbornene Cooperative Catalysis

Fundamentals and Applications



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Editor

Prof. Guangbin Dong
University of Chicago
5735 S. Ellis Ave.
Chicago 60637
IL, USA

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To my prior mentors: Professors Zhen Yang, Barry M. Trost, and Bob Grubbs

Contents

Preface

Poly-substituted arenes, heteroarenes, and alkenes are commonly found in bioactive compounds and organic materials. Devising efficient methods for constructing these structural motifs has been of long-standing interest in the synthetic community. While numerous arene-functionalization and alkene-synthesis approaches exist, those that can simultaneously introduce two or more different functional groups to arenes or alkenes in a regio- and site-selective manner are still rare. For example, the use of aryne chemistry for arene functionalization is generally constrained by substrate specificity and/or complexed by strongly basic conditions; the strategy of preparing tri- or tetra-substituted alkenes from internal alkynes often suffers from poor regioselectivity control and limits to linear substrates. So, *does an alternative strategy allowing general, rapid, site-selective functionalizations of arenes, heteroarenes, and alkenes exist?* I trust you can find answers in this book.

This book provides a comprehensive overview of the palladium/norbornene (Pd/NBE) cooperative catalysis, which represents a unique approach to enable site-selective vicinal difunctionalization of aryl and alkenyl substrates. Through forming the key aryl (alkenyl) norbornyl palladacycle (ANP) intermediate, the difunctionalization is typically realized through coupling a nucleophile at the *ipso* position and an electrophile at the *ortho* position, which represents the unique feature of the Pd/NBE catalysis. One can imagine that numerous coupling combinations and variations could stem from this distinctive reactivity mode, resulting in enormous opportunities for developing powerful synthetic methods. For example, using aryl halide substrates, termination with hydrogen at the *ipso* position can lead to functionalization of conventionally less reactive positions. In addition, as a multi-component reaction, the tethering of any reaction components in the Pd/NBE catalysis can deliver interesting, polycyclic scaffolds. Moreover, the merge of the Pd/NBE catalysis, electrophilic arene halogenation, and cross couplings can allow access to challenging benzenoid substitution patterns. Furthermore, the application of the *ortho* C—H amination to the enol system can result in carbonyl 1,2-transposition.

Since the landmark discovery of the *ortho* C—H alkylation by Professor Marta Catellani in 1997, the field of the Pd/NBE cooperative catalysis has evolved enormously. Especially in the past decade, a number of longstanding constraints and limitations have been overcome to enable more general and diverse transformations. New related reaction modes have also been uncovered, leading to exciting

applications. However, compared to the concurrently developed Buchwald–Hartwig couplings (i.e. amination, oxygenation, etc.), the Pd/NBE catalysis has received much less attention outside this field, particularly in the pharmaceutical industries. One possible reason could be due to the relatively complex reaction mechanism and catalyst system, making many people feel intimidated from trying this type of reactions. Thus, one main purpose of this book is to provide readers a systematic understanding of the Pd/NBE catalysis, including the mechanisms, scopes, and current limitations. It is our hope that this book will not only offer fundamental knowledge to students or entry-level researchers in the organic synthesis field, but also provide guidance to advance researchers about how to use this type of catalysis (e.g., how to choose the best reaction conditions or catalyst combination) to help their research.

This book contains eight chapters, each written by leading experts in the Pd/NBE catalysis field. It starts with the annulation chemistry by Abel-Snape and Lautens, given the importance of diverse ring structures in organic synthesis, which also sets the mechanistic foundation of the Pd/NBE catalysis. The following two chapters cover the scope of the *ipso* and *ortho* functionalization by the Liang group and my own group, respectively. Chapter 4 is centered on the asymmetric development, contributed by Professor Gu. Then, the book shifts to the discussion of the Pd(II)-initiated reactions by a team effort of Zhou and Yu, followed by a wonderful review of the Pd/NBE-catalyzed heteroarene functionalization from Professor Joo. Chapter 7 written by Professor Wu is centered on newly developed approaches to address various constraints in the Pd/NBE catalysis. The book closes with the summary of various applications in synthesis of complex molecules and organic materials by Professor Wang.

As the editor, I am very grateful to a large number of kind and outstanding people. First of all, I would like to thank all the chapter authors for their incredible passions and dedications. Note that they have made impressive contributions not only to the writing of the book but also to the field of the Pd/NBE catalysis. It is certainly my honor to work with all of them. In addition, Dr. Xin Liu is highly acknowledged for his kind help in proofreading all the chapters, and his insightful inputs are greatly appreciated. Moreover, Ms. Alia McDaniel is thanked for her dedicated administrative assistance during this process. Needless to mention, I am indebted to all my current and former students and postdocs who worked in the Pd/NBE catalysis projects for their exceptional creativity and persistence. Special gratitude to my former graduate student Dr. Zhe Dong—now a professor at SUSTech—who initiated and popularized the Pd/NBE catalysis project in my lab. Furthermore, I have to express my deepest appreciation to Professor Marta Catellani for her original and inspiring seminal works of the Pd/NBE chemistry, as well as her generous support!

Finally, I would like to thank my family, especially my wife and two daughters, for their unconditional love and support. This book would not have existed without them.

May 2024

Guangbin Dong
University of Chicago
Chicago, IL, USA

1

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

Mark Lautens and Xavier Abel-Snape

Davenport Research Laboratories, Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada

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.

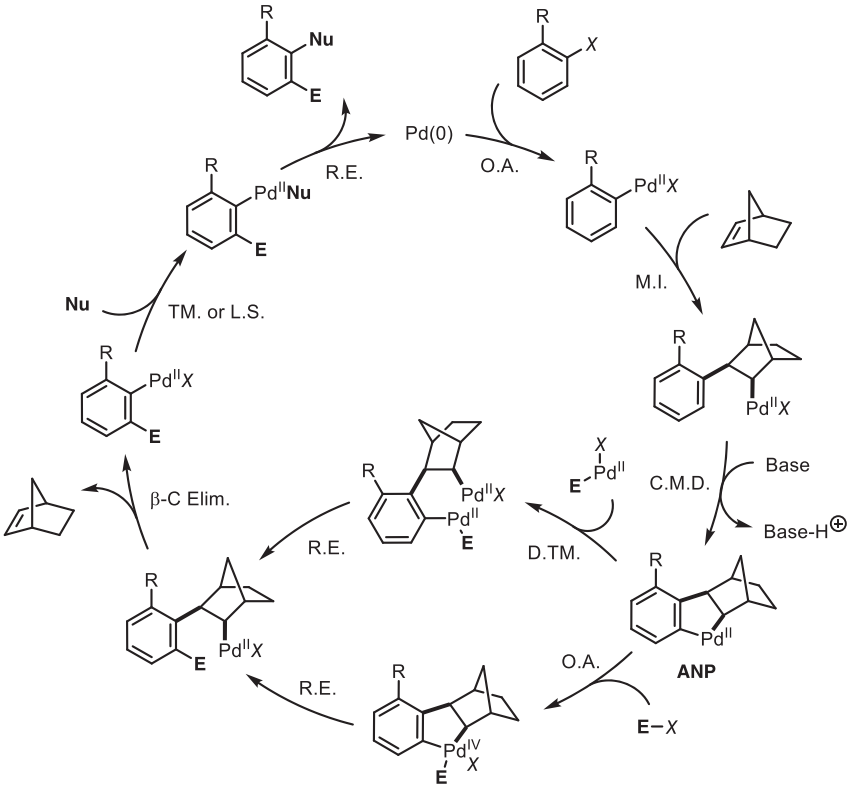
X: I, Br, OTf

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

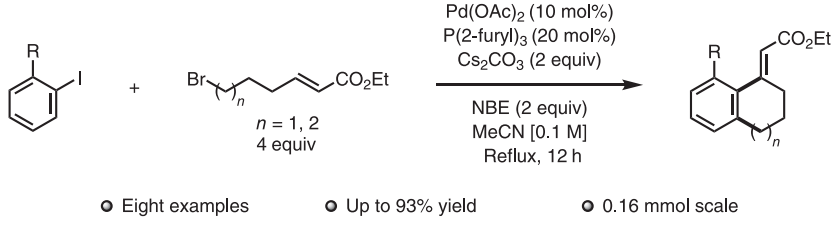
and ring closure steps with external reagents. Three-membered rings constitute the focus of section three, where their innate strain turns them into valuable electrophiles and terminating reagents upon ring opening, thereby forming five-membered rings. Reactions where NBE and its analog norbornadiene 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

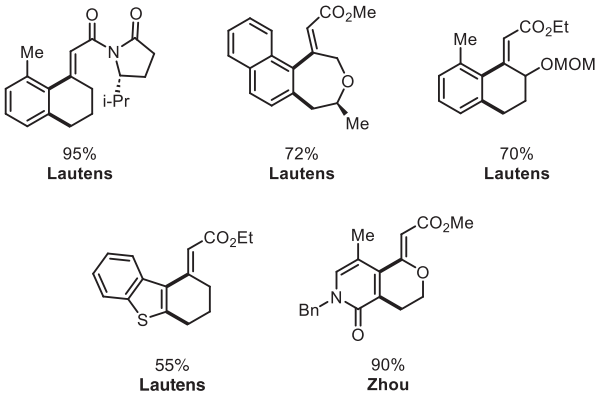
Ipso Heck Termination The original 1997 report by Catellani described a reaction between an unsubstituted or *para* substituted aryl iodide, an alkyl halide, and a Heck acceptor [1]. The catalyst, known as the PNP complex, was a phenyl norbornyl palladium halide dimer prepared from phenyl mercuric chloride, 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.

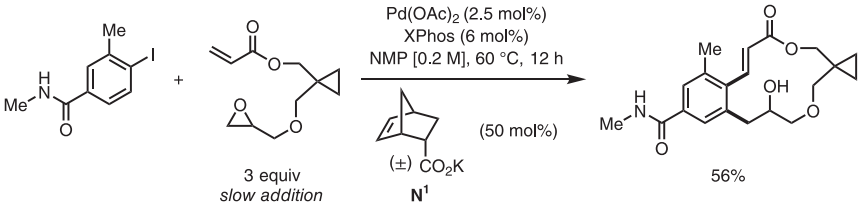
This set of conditions paved the way for subsequent ring-forming processes, generating a variety of benzofused carbo- and heterocycles via *ortho*-alkylation and *ipso*-Heck termination under identical or modified conditions (Scheme 1.4) [15–19]. Some of these examples illustrate that heterocycles are 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].



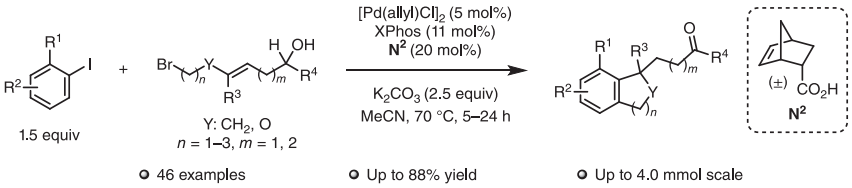
Scheme 1.4 Examples of *ortho*-alkylation/*ipso*-Heck-termination annulative methodologies.

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.

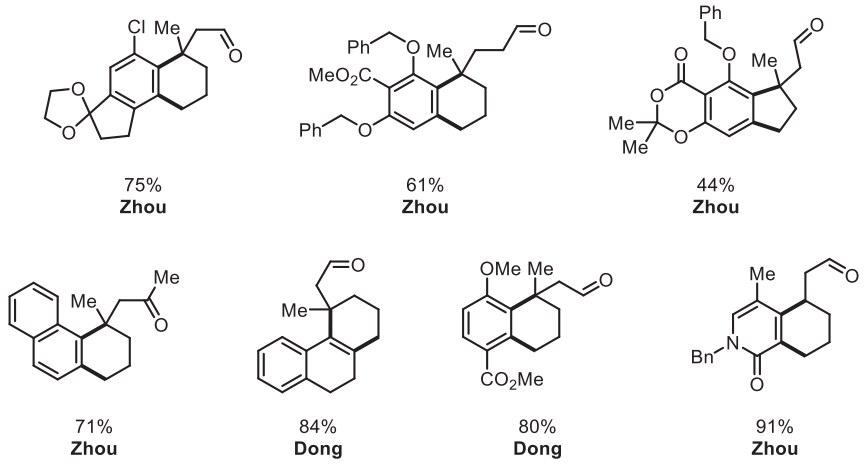
(Homo)allylic alcohols were suitable as the Heck acceptor, furnishing the corresponding carbonyl compounds via a redox-relay Heck cyclization (Scheme 1.6) [23].



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

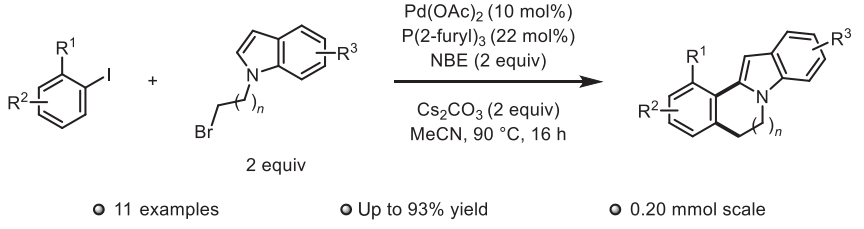
Zhou was able to generate ring sizes ranging from five to seven [19, 24, 25]. Dong was also able to provide aldehyde-tethered rings using modified procedures (Scheme 1.7) [26, 27].

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].



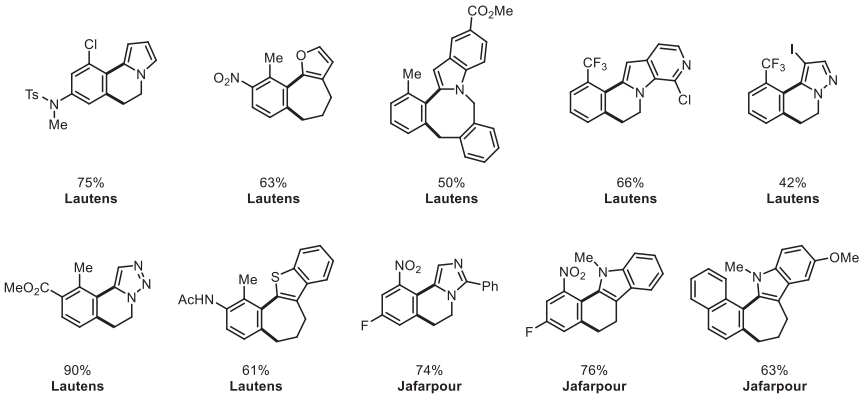
Scheme 1.8 Synthesis of annulated indoles via *ipso* C–H arylation.

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

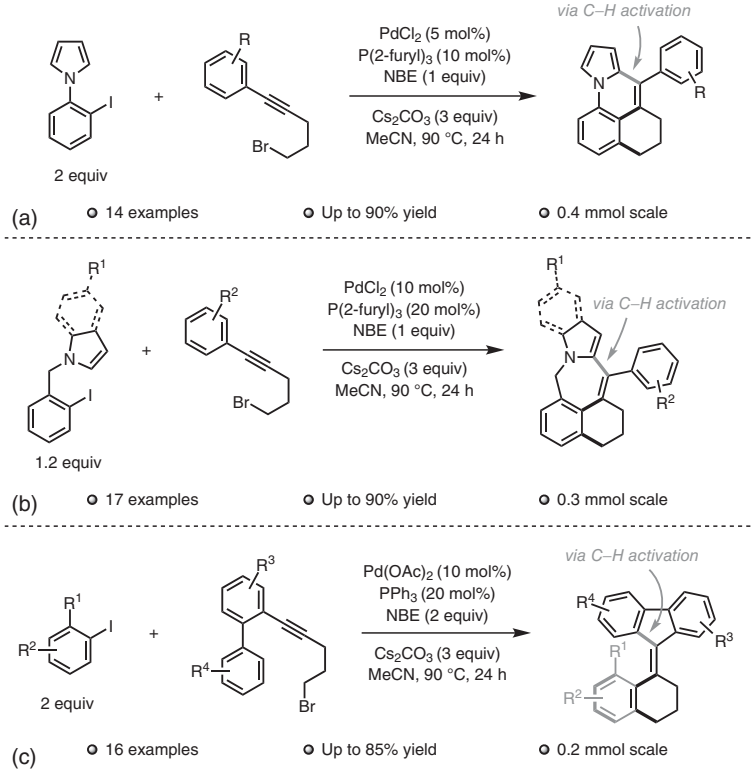
Ipso Alkyne Insertion Following *ortho*-alkylation and NBE extrusion, the resulting arylpalladium(II) species may undergo a migratory insertion relay step, followed by subsequent annulation reactions that increase molecular complexity.

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

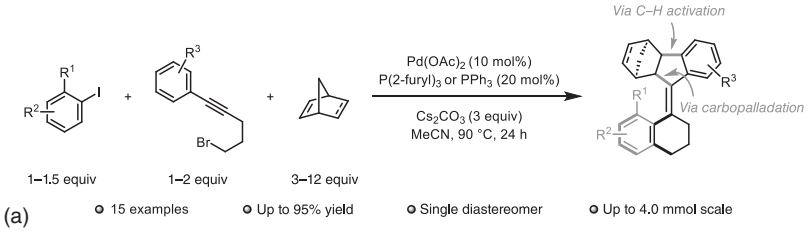


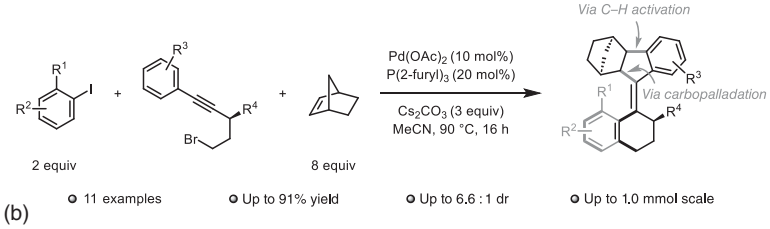
Scheme 1.9 Examples of *ortho*-alkylation/*ipso*-C–H arylation annulative methodologies.



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.

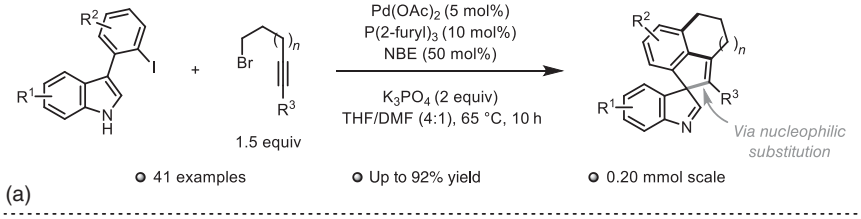
to 1,3-allylic strain between the pseudoequatorial R^4 substituent and R^3-aryl ring [42, 43]. In both cases, NBE undergoes *exo*-insertion into the C–Pd(II) bond with its methylene group facing away from R^1. Subsequently, C–H activation onto the alkyne-tethered arene occurs, followed by reductive elimination.

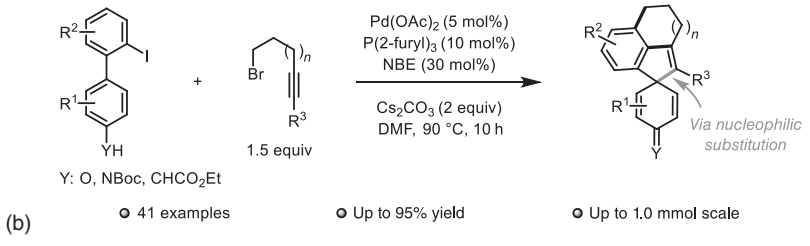




Scheme 1.11 Syntheses of tetrasubstituted helical alkenes (a) initial report (b) subsequent work using enantiomerically pure bromoalkyl aryl alkynes.

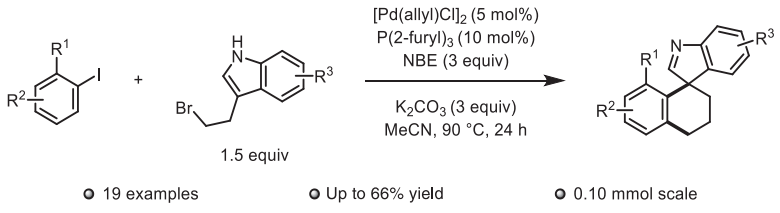
Nucleophilic attack on the vinyl-Pd(II) species can also occur. The Luan group reported two methodologies involving the dearomatization of indole and a phenol system, respectively, thereby forming a spiro palladacycle upon nucleophilic substitution (Scheme 1.12) [44, 45]. In a related report, Zhang, 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.

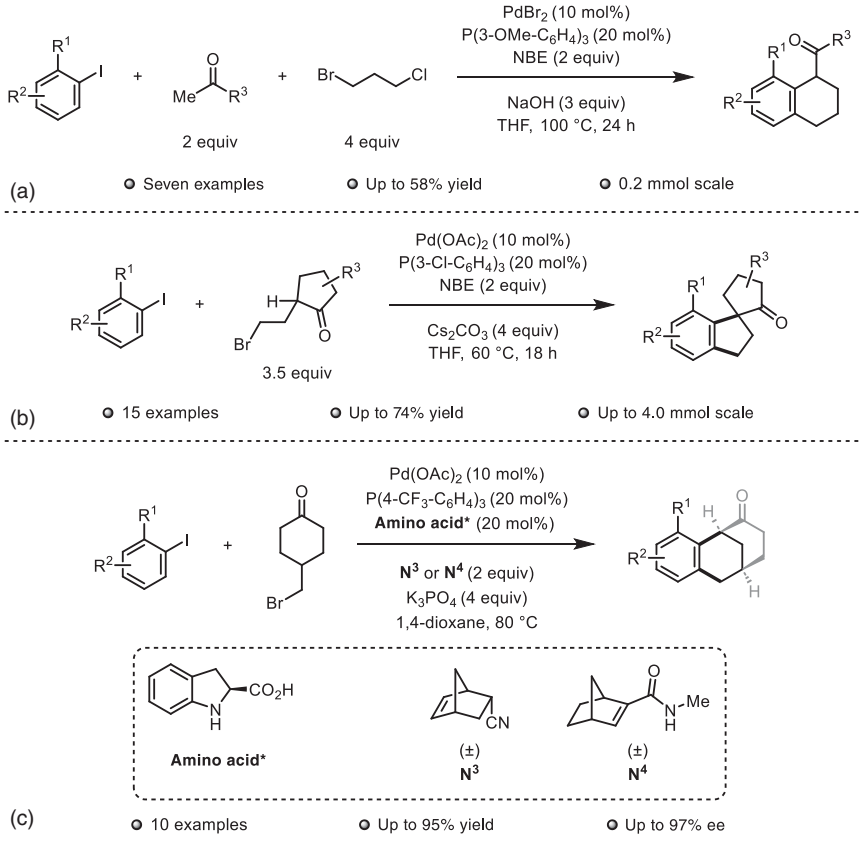
Ipso Enolate Termination A related carbon-based nucleophile can be generated as a metal-enolate. Zhou developed a three-component synthesis of 1,8-disubstituted tetralines from 2-substituted aryl iodides, aryl methyl ketones and 1-bromo-3-chloropropane (Scheme 1.14a). It was proposed the aryl methyl 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].

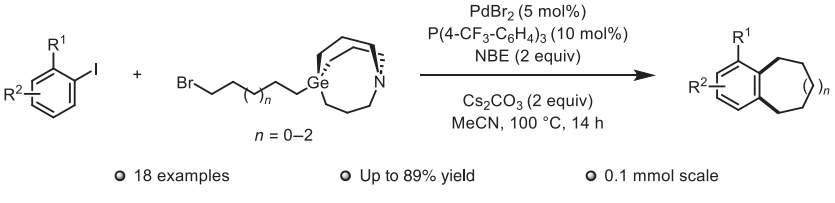
Ipso C–N Termination A nucleophilic heteroatom can also be employed as a compatible *ipso* terminating reagent. Using brominated alkylamines, Lautens was able to furnish indolines and tetrahydroquinolines depending on the alkyl chain's length (Scheme 1.16) [52, 53]. It was established that a *para*-nitrophenyl 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



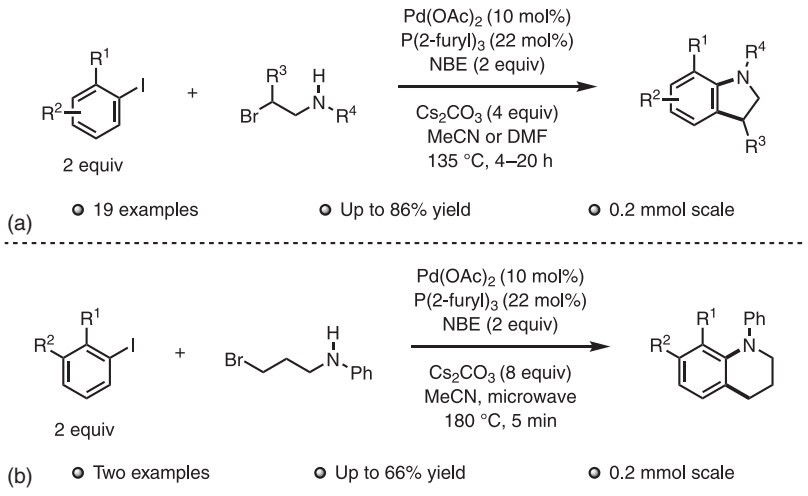
Scheme 1.14 Harnessing *in situ* generated enolates to synthesize (a) tetralines (b) spirodihydroindenones (c) bridged ketones.



Scheme 1.15 Synthesis of carbocycles using alkyl carbagermatranes.

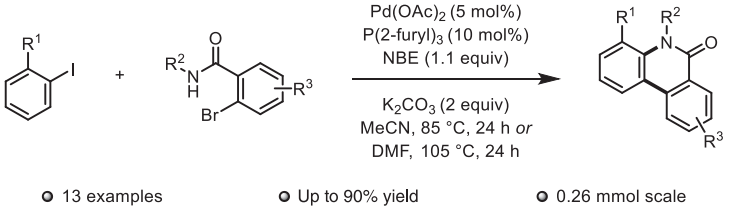
careful choice of different haloarenes ensures Pd(0) oxidatively adds into the more reactive C–I bond preferentially and that the **ANP** then reacts with the less reactive aryl bromide. Lautens showed aryl triflates can be used instead of aryl iodides [54], while aryl chlorides can also constitute the *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.



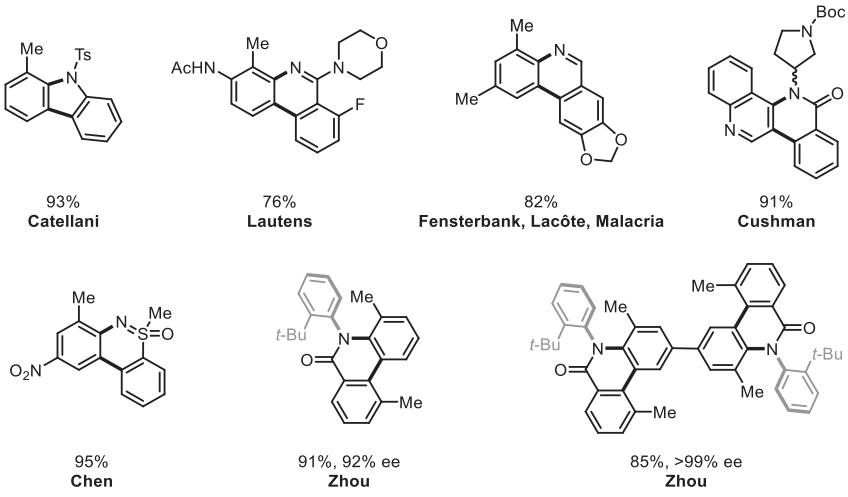
Scheme 1.17 Synthesis of 6-phenanthridinones.

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

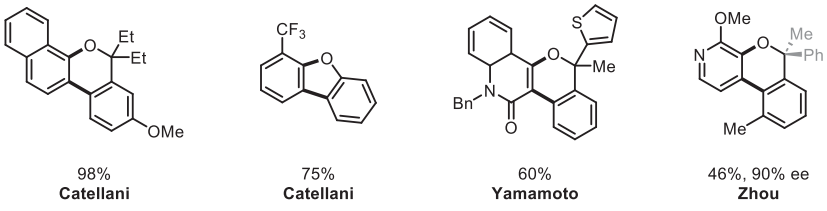
Ipso C–O Termination Similarly, C—O bond formation can occur using the appropriate terminating reagents (Scheme 1.19 [67–70].

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.

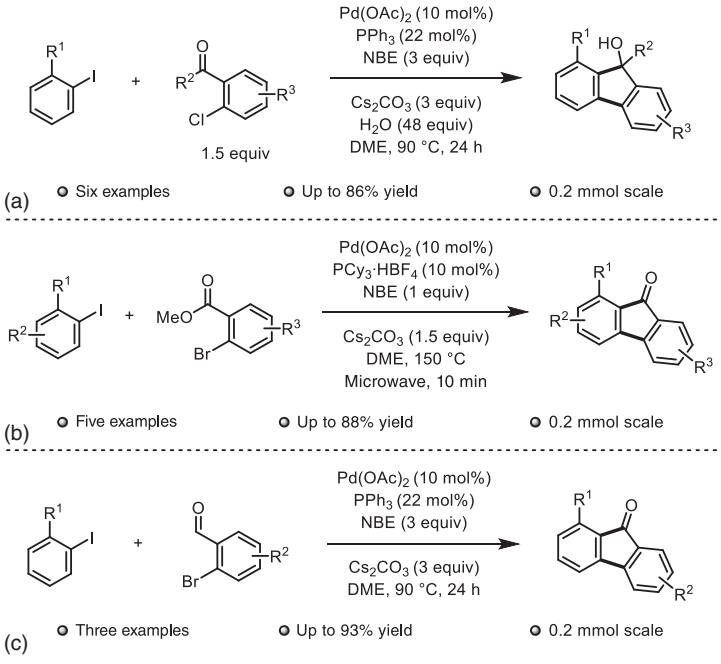
2-Bromoarylaldehyde hydrazones were used in a denitrogenative synthesis of fluorenes (Scheme 1.22) [72]. It was determined the reaction pathway does not proceed via carbene insertion.

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.

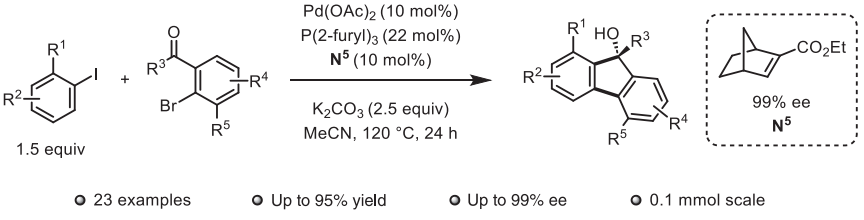
1.2.1.3 *Ortho* Acylation

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].

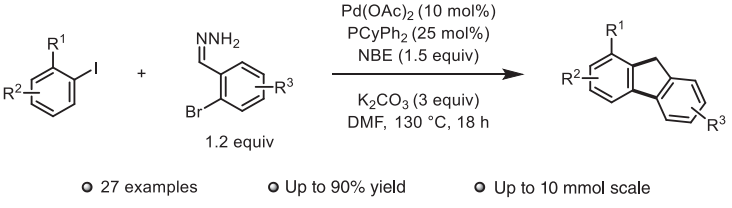
Smaller ring systems were also accessible using an analogous reagent (Scheme 1.25) [11]. A mixed anhydride could also be generated *in situ* from



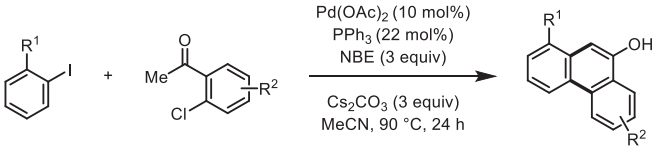
Scheme 1.20 *Ortho*-arylation/*ipso*-C=X termination methodologies for the synthesis of (a) 9*H*-fluoren-9-ols from ketones (b) 9*H*-fluoren-9-ones from esters (c) 9*H*-fluoren-9-ones from aldehydes.



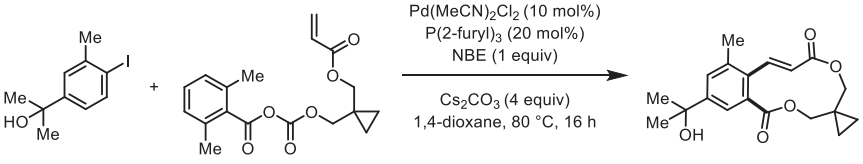
Scheme 1.21 Enantioselective synthesis of fluorenols.



Scheme 1.22 Synthesis of fluorenes via denitrogenation.

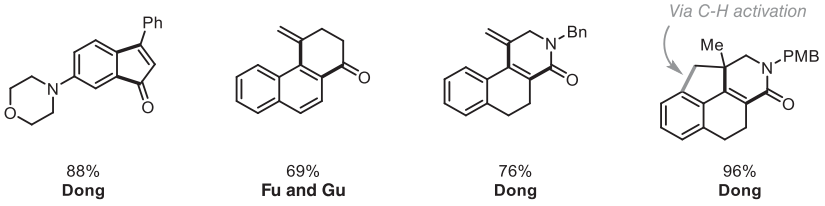


Scheme 1.23 Synthesis of phenanthren-9-ols.



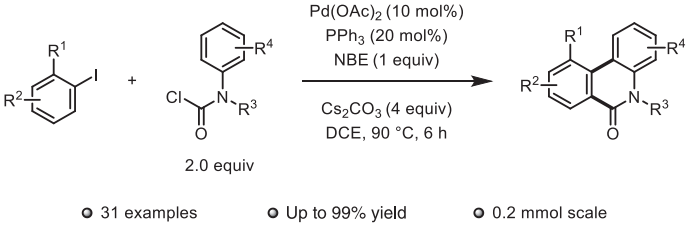
Scheme 1.24 Macrocycle formation via *ortho*-acylation and *ipso*-Heck termination.

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].

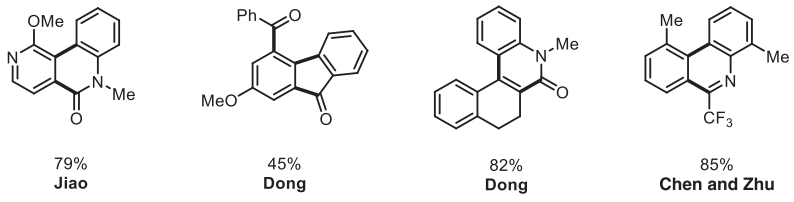


Scheme 1.25 Subsequent examples of *ortho*-acylation/*ipso*-Heck termination annulative methodologies.

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.

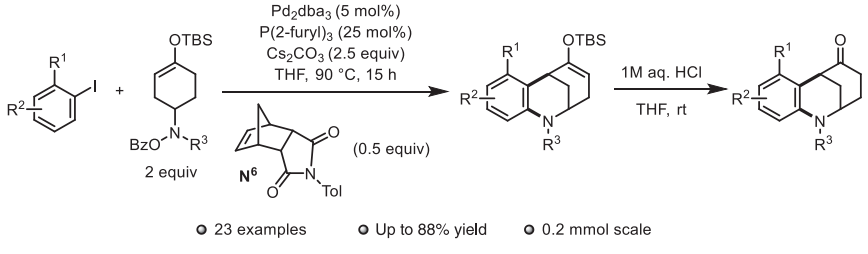


Scheme 1.27 Subsequent examples of *ortho*-acylation/*ipso*-C–H arylation annulative methodologies.

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