INTRAMOLECULAR MIZOROKI-HECK REACTION IN THE SYNTHESIS OF HETEROCYCLES: STRATEGIES FOR THE GENERATION OF TERTIARY AND QUATERNARY STEREOCENTERS

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Abstract. *The intramolecular Mizoroki-Heck (M-H) reaction is a powerful carbon-carbon bond-forming process for the construction of small and medium-size carbocycles and heterocycles. Different strategies have been developed to avoid the syn β-hydride elimination on the carbon directly involved in bond formation, so that the elimination takes place in another β′ position, allowing the generation of tertiary and quaternary stereocenters. In this review, the most significant strategies used for the generation of stereocenters in its application to the synthesis of heterocyclic systems will be discussed, including cascade processes.*

Contents

1. Introduction

The intramolecular Mizoroki-Heck (M-H) reaction of aryl and vinyl halides/triflates with alkenes is a powerful carbon-carbon bond-forming process for the construction of small and medium-size carbocycles and heterocycles.[1] The control of the β-hydride elimination step allows the generation of tertiary and quaternary stereocenters. The reactions are generally highly diastereoselective and the use of chiral ligands for palladium, such as chiral bidentate phosphines (*e.g.* (*R*)-BINAP), has allowed the development of an enantioselective variant, which has become an important tool in natural product and pharmaceutical syntheses.[2] Different strategies have been developed to avoid the *syn* β-hydride elimination on the carbon directly involved in bond formation, so that the elimination takes place in another β′ position. First approaches implied blocking the β-hydride elimination on an acyclic alkene, or alternatively, the use of cyclic alkenes, where conformational rigidity and, hence, restricted rotation around the C-C bonds steers β-hydride elimination away from the newly formed C-C bond. Other strategies involved the introduction of a heteroatom in an allylic position of the olefin, either to promote the elimination of a good leaving group or a tautomerization reaction as a thermodynamic driving force in favor of β′-hydride elimination. Finally, cascade reactions, where β-hydride elimination is avoided by involving the alkylpalladium intermediate in another coupling reaction or in an anion capture event, have also been successfully applied for this purpose.

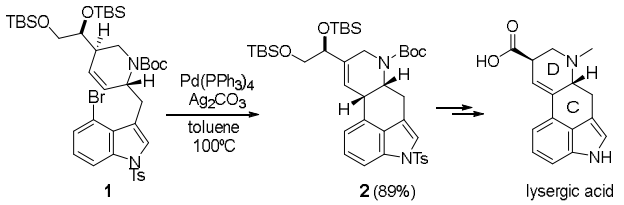
The recent advances in all variants of the Mizoroki-Heck reaction have led to a great number of reports. In addition, excellent and comprehensive reviews have appeared[1,2] that focus on different aspects

such as enantioselective variants[3] or cascade reactions.[4] The present review will not attempt to provide exhaustive coverage of the literature, but it is intended to focus on the most significant strategies used for the generation of stereocenters in its application to the synthesis of heterocyclic systems, including our investigations on the subject.

2. Intramolecular Mizoroki-Heck reaction for the generation of stereocenters

2.1. Approaches based on blocking the β-hydride elimination: cyclic alkenes as coupling partners

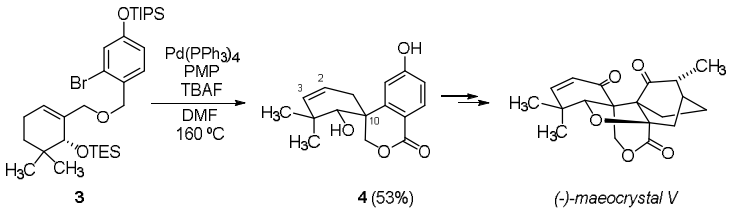
The use of cyclic alkenes as coupling partners is one of the first strategies used for the generation of stereocentres. In this case, *syn* β-hydride elimination is avoided, as rotation of the C-C bond of the intermediate alkyl palladium species formed after carbopalladation is not possible. Since the first examples of intramolecular Mizoroki-Heck reaction using cyclic alkenes reported by Shibasaki[5] and Overman,[6] this protocol has become an excellent tool for the construction of cyclic frameworks generating tertiary and quaternary stereocenters in the asymmetric synthesis of natural products and pharmaceuticals. In this context, Tietze synthesis of steroids[7] and (-)-cephalotoxine alkaloid[8] for the generation of tertiary stereocenters, or the assembly of spirocyclic oxindoles and the synthesis of mesembrine alkaloids reported by Overman[9] and Evans,[10] respectively, for the formation of quaternary stereocenters are relevant examples of the diastereoselective variants of these reactions. More recently, Fukuyama has accomplished a total synthesis of lysergic acid, whose key steps include stereoselective construction of the stereogenic centers at the allylic positions by using Evans aldol reaction, and a ring-closing metathesis to obtain **1**, whose intramolecular Heck reaction forms D ring on **2** (Scheme 1).[11]



1 **2** (89%) lysergic acid

Scheme 1. Diastereoselective Heck reaction in the synthesis of lysergic acid.

On the other hand, Thomson[12] reported the enantioselective total synthesis of a cytotoxic polycyclic diterpene, (−)-maoecrystal V, where the construction of the critical C-10 spirocyclic quaternary stereocenter was achieved through a completely diastereoselective Heck reaction on **3**. Formation of the 2,3-alkene as the major product **4** could be rationalized by olefin isomerization to the more thermodynamically stable isomer by reinsertion of the intermediate Pd−hydride complex formed after initial spirocyclization (Scheme 2).

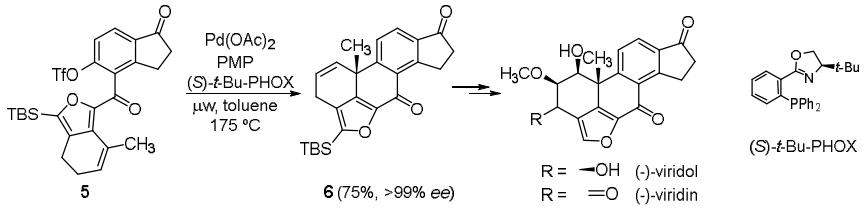


3 **4** (53%) *(-)-maeocrystal V*

Scheme 2. Diastereoselective Heck reaction for the synthesis of (-)-maeocrystal V.

The enantioselective variant has been employed in the asymmetric synthesis of natural products using chiral ligands for palladium. The development of new chiral ligands has allowed great advances in the area, although some limitations remain because the understanding of how different parameters of a M-H reaction affect the stereochemical outcome is difficult to rationalize. Nevertheless, enantioselective intramolecular Mizoroki-Heck reaction using cyclic alkenes is nowadays used as a routine procedure in organic synthesis.[3] In this context, a convergent approach for the synthesis of furanosteroids (−)-viridin and (−)-viridiol has

been reported which employs an enantioselective intramolecular Heck reaction on aryl triflate **5** to set the absolute stereochemical configuration of the quaternary stereocenter in **6**. The use of (*S*)-*t*-Bu-PHOX ligand and PMP was crucial to achieve high enantioselectivity (Scheme 3).[13]

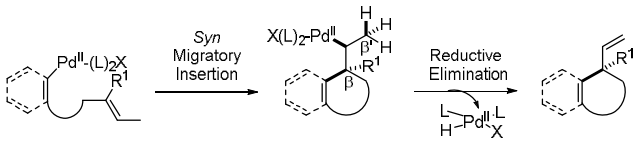


5 **6** (75%, >99% *ee*)

Scheme 3. Enantioselective intramolecular Heck reaction for the synthesis of (-)-viridin and (-)-viridiol.

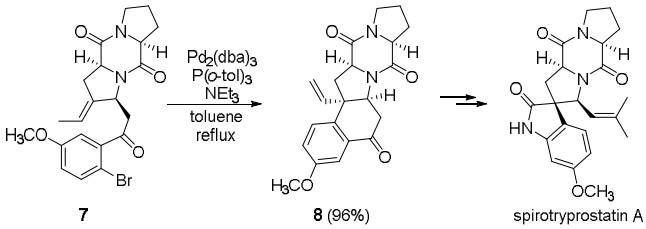
2.2. Approaches based on blocking the β-hydride elimination: use of tri- and tetrasubstituted acyclic alkenes as coupling partners

The use of tri- and tetrasubstituted acyclic olefins as coupling partners in intramolecular M-H reactions can lead to the generation of quaternary stereocenters (Scheme 4). The introduction of substituents in the carbon atom of the acyclic olefin that suffers directly the coupling drives the hydride elimination to a contiguous β′-position, though in some cases steric hindrance could decrease their reactivity leading to low conversions or yields.



Scheme 4. Blocking the β-hydride elimination in acyclic alkenes.

In this context, the pioneering work of Overman[14] showed that the intramolecular Heck reaction of *o*-iodoacrylamides gave oxindoles, generating a quaternary stereocenter in an enantioselective fashion using (*R*)-BINAP as chiral ligand. Depending on the use of Ag_3PO_4 or PMP as halide scavenger, either of the enantiomers of the oxindole could be obtained. The procedure was applied to the synthesis of (+)-asperazine.[15] Later, Curran[16] demonstrated that, when acrylamides with axial chirality are used, the chirality can be efficiently transferred obtaining the oxindoles with a quaternary center with high enantiomeric purity. This strategy has allowed the development of new methodologies for the synthesis of complex natural products as spirotryprostatin A (Scheme 5). Thus, Fukuyama[17] achieved the asymmetric synthesis of this alkaloid by using a diastereoselective intramolecular Heck reaction on aryl bromide **7** to introduce the quaternary spiro center on **8**, whose stereochemistry was controlled by the diketopiperazine scaffold.

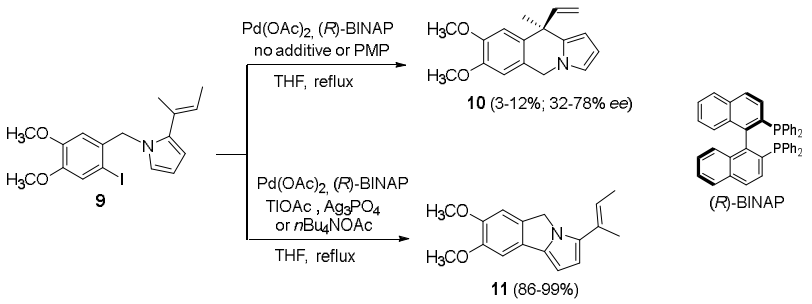


7 **8** (96%) spirotryprostatin A

Scheme 5. Diastereoselective Heck reaction for the synthesis of spirotrypostatin A.

Our group has also studied the generation of a quaternary stereocenter on C-10 of pyrrolo[1,2-*b*]isoquinolines such as **10**, starting from 2-alkenyl substituted pyrroles as **9**, in which the

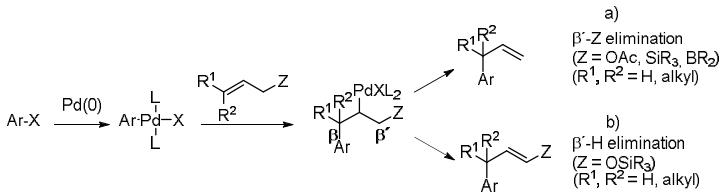
β-elimination is blocked by a substituent.[18] The cyclizations proceeded with moderate to good yields and enantioselectivity when using chiral phosphines as ligands. (*R*)-BINAP provided the best enantioselectivity (up to 78% *ee*) with $Pd(OAc)_2$, but the yield was low (Scheme 6). The enantioselectivity of the reaction is attributed to the migratory insertion into the alkene. Therefore, the reaction conditions that favor a cationic mechanism in which no dissociation of the ligands occurs (often bidentate phosphines) are usually critical to obtain good enantioselectivity. However, in our case, the use of additives as silver or thallium salts to promote a cationic mechanism, favored the direct arylation reaction on the pyrrole ring, leading to the formation of pyrroloisoindoles **11**. The direct arylation reaction is also the preferred reaction pathway when the formation of larger rings is attempted. In these cases, the competition between Mizoroki-Heck and direct arylation[19] could not be controlled by changing the catalytic system or experimental conditions.



Scheme 6. Intramolecular Heck reaction for the synthesis of pyrroloisoquinolines.

2.3. Approaches based on the use of a leaving group: allylsilanes, ethers, esters, and boronates as coupling partners.

The introduction of a heteroatom in an allylic position of the alkene (Z, Scheme 7) can promote the elimination of a good leaving group, instead of hydride elimination (Scheme 7a). On the contrary, a tautomerization reaction could be the thermodynamic driving force in favor of a β′-hydride elimination (Scheme 7b). Thus, allyl esters, allyl silyl ethers, allylsilanes, and allylboronates can be used for the formation of tertiary and quaternary stereocenters.

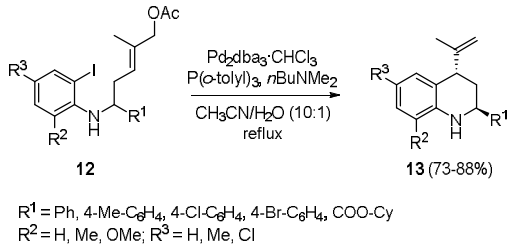


Scheme 7. Strategies for the generation of tertiary and quaternary stereocenters with allylic substrates.

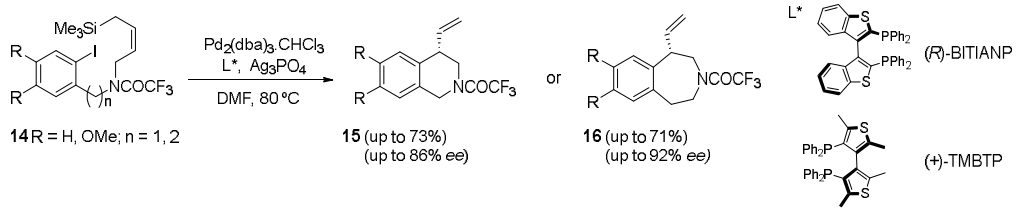
Although the intermolecular M-H coupling of aryl halides or triflates with allyl esters (acetates, carbonates) has been widely used,[20] the intramolecular variant has been less explored. Lautens reported a representative example in the intramolecular M-H reaction of aryl iodides **12** for the synthesis of *trans*-2,4-disubstituted 1,2,3,4-tetrahydroquinolines **13** (Scheme 8).[21] In this approach, the generation of the tertiary stereocenter at C-4 of the isoquinoline framework *via* elimination of β′-acetoxy group took place with complete diastereoslectivity to afford the *trans* diastereomers (Scheme 8). The reaction was extended to the construction of five- to seven-membered carbo- and heterocycles with the same catalytic system using carbonates as leaving groups and microwave-assisted conditions.

In his seminal work, Tietze[22] had demonstrated that a highly regio- and enantioselective intramolecular Heck reaction could be carried out on aryl halides with a tethered allylsilane moiety, whose elimination led to the construction of the tetralin framework of norsesquiterpenes with a tertiary stereocenter. This

methodology was later applied to the enantioselective synthesis of tetrahydroisoquinolines **15** and benzazepines **16** from iodides **14** using (+)-TMBTP and (*R*)-BITIANP as chiral ligands (Scheme 9).[23]

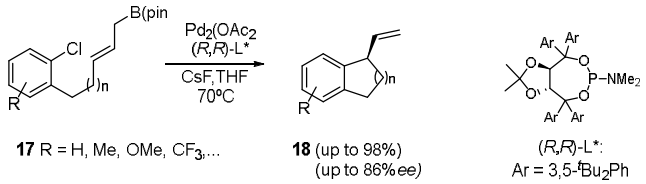


Scheme 8. Allyl acetates as coupling partners in the generation of a tertiary stereocenter for the diastereoselective synthesis of 2,4-disubstituted tetrahydroquinolines



Scheme 9. Allylsilanes as coupling partners in the generation of a tertiary stereocenter for the enantioselective synthesis of tetrahydroisoquinolines and benzazepines.

More recently, aryl chlorides **17**, with tethered allylboronate units, underwent intramolecular M-H reaction in an enantioselective fashion using phosphoramidites derived from TADDOL as chiral ligands, though the procedure has only been applied to the construction of five-, six-, and seven-membered carbocycles **18** (Scheme 10).[24]

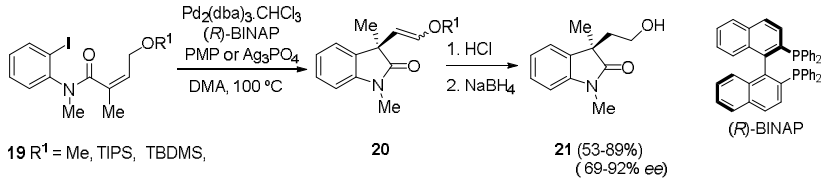


Scheme 10. Allylboronates as coupling partners in the generation of a tertiary stereocenter in the enantioselective synthesis of carbocycles.

On the other hand, the work of Shibasaki on the synthesis of (-)-eptazocine[25] set the basis for the asymmetric generation of benzylic quaternary stereocenters using allyl silyl/alkyl ethers as coupling partners in the M-H cyclization of aryltriflates, being the formation of an enol ether the driving force of the reaction. Later on, Overman[26] reported the intramolecular M-H reaction of substituted *N*-(*o*-iodophenyl)acrylamides **19** using (*R*)-BINAP as chiral ligand (Scheme 11). The cyclization provided substituted oxindoles **20** with high regio- and enantioselectivity, using $Pd_2(dba)_3 \cdot CHCl_3$ either in the presence of Ag_3PO_4 (cationic pathway) or a base as PMP (neutral pathway). In this case, silyloxy or alkoxy groups are retained in the coupling step, and β'-hydride elimination is favored obtaining enol ethers **20** that could afterwards be cleaved by acidic hydrolysis and reduced to alcohols **21**.

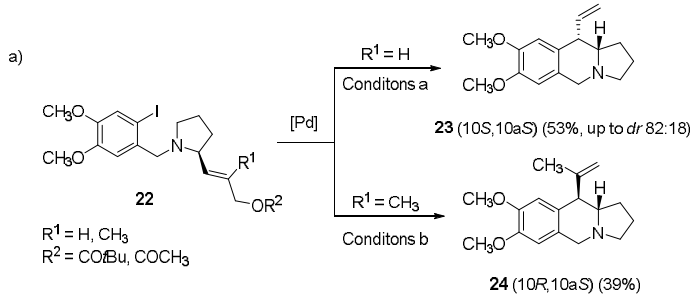
We have developed similar approaches for the generation of tertiary and quaternary stereocenters by Mizoroki-Heck reaction of *N*-(*o*-iodobenzyl)pyrrolidine derivatives **22** and **25** with a protected allyl alcohol moiety.[18] A change in the protecting group of the alcohol allows the selective β′-leaving group elimination

(when pivalate or acetate is used, Scheme 12a, **22**) or β′-hydride elimination (when TBDMS is used, Scheme 12b, **25**) leading to the corresponding functionalized pyrrolo[1,2-*b*]isoquinolines.

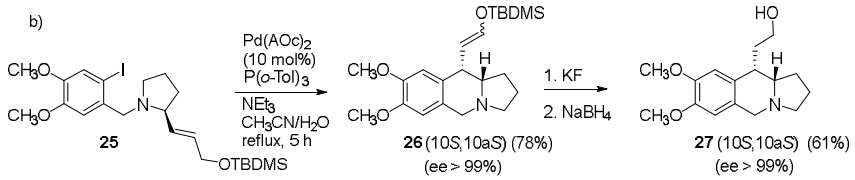


19 R^1 = Me, TIPS, TBDMS, **20** **21** (53-89%) (69-92% *ee*)

Scheme 11. Allyl siliylethers as coupling partners in intramolecular Mizoroki-Heck reaction for the enantioselective synthesis of indolinones.



Conditions a. $Pd_2(dba)_3.CHCl_3$, NEt_3, P(*o*-tolyl)$_3$, $CH_3CN : H_2O$ (10:1), reflux.
Conditions b. $Pd_2(dba)_3.CHCl_3$, NEt_3, P(*o*-tolyl)$_3$, DMF, 130 °C.



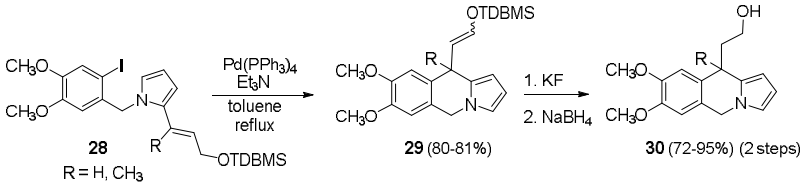
Scheme 12. Protected allyl alcohols as coupling partners in intramolecular Mizoroki-Heck reaction for the asymmetric synthesis of tetrahydropyrrolo[1,2-*b*]isoquinolines.

Thus, the intramolecular M-H reaction of enantiomerically pure *N*-(*o*-iodobenzyl)pyrrolidine derivatives **22** took place with β′-alkoxy group elimination to afford 10-vinyl substituted pyrroloisoquinoline **23** in moderate yields and diastereoselectivities (Scheme 12a, conditions a). Different catalytic systems and experimental conditions have been tried to control the stereoselectivity of these reactions, but only moderate diastereoselectivity (82:18) was obtained. When a substituted alkene is used (R^1=CH_3), the diastereoselectivity is reversed to obtain **24**, but only in low yield (Scheme 12a, conditions b). On the contrary, when allyl silyl ether **25** was used as coupling partner, β-hydride elimination took place leading to pyrroloisoquinoline **26**, which could be derivatized to the corresponding enantiomerically pure alcohol **27** (Scheme 12b). This strategy could also be applied to the corresponding pyrrole derivatives **28** generating both tertiary and quaternary stereocenters in pyrroloisoquinolines **29**, with excellent yields, that were transformed into alcohols **30** (Scheme 13). However, the enantioselective variant using $Pd(OAc)_2$ or $Pd_2(dba)_3$ and (*R*)-BINAP, or other chiral ligands, under different experimental conditions, only led to low enantiomeric excesses (up to 18% *ee*).

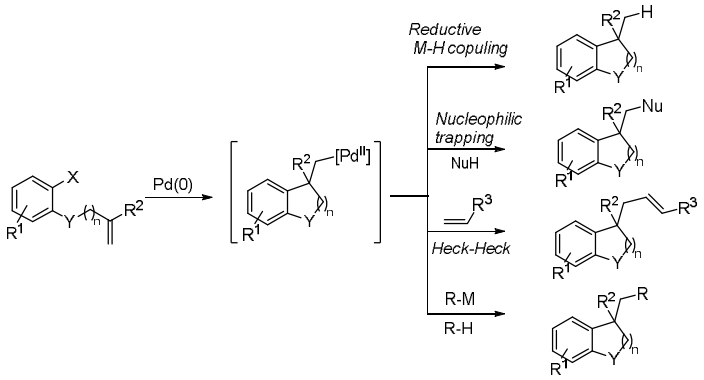
3. Cascade reactions initiated by intramolecular carbopalladation

Palladium-catalyzed cascade cyclizations are powerful tools for the synthesis of heterocycles with stereocenters.[27] The Mizoroki-Heck reaction is an ideal starting point for a cascade reaction, as the

intermediate C(sp^3)-Pd(II) species obtained after intramolecular carbopalladation could be further functionalized. In many occasions a 1,1-disubstituted alkene is used as coupling partner to prevent β-hydride elimination, generating a quaternary center, but tertiary centers can be formed as well. This intermediate σ-alkylpalladium (II) species can be involved afterwards in different processes, as summarized in Scheme 14. Reductive Heck cyclizations can be developed in the presence of hydride donors, or alternatively, the intermediate can be trapped with different nucleophiles. Besides, functionalization can also be introduced through further coupling reactions, such as M-H, Suzuki, Sonogashira, or direct arylation reactions, among others. Selected examples of the application of these strategies, starting with an intramolecular carbopalladation, will be discussed in the following sections.



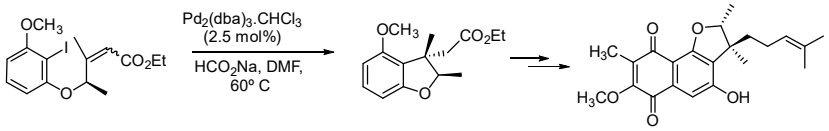
Scheme 13. Allyl silylethers as coupling partners in intramolecular Mizoroki-Heck reaction for the synthesis of dihydropyrrolo[1,2-*b*]isoquinolines.



Scheme 14. Cascade reactions initiated by intramolecular carbopalladation.

3.1. Reductive Mizoroki-Heck coupling

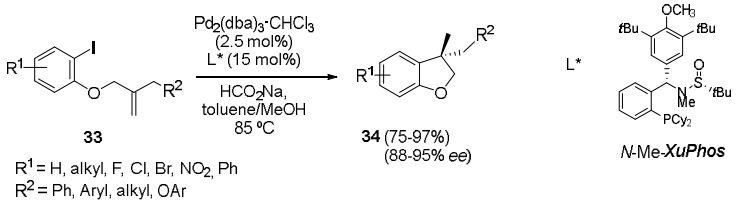
The reductive M-H coupling has been well-studied and applied in synthesis,[28] since the seminal work on hydroarylation of alkenes reported by Cacchi.[29] Tertiary amines and sodium formate have been the most commonly used hydride sources. Thus, a quaternary stereocenter was generated with complete diastereoselectivity by cyclization of enantiomerically pure aryl ethers **31** (*E*/*Z* 1:1) to afford **32**. This cyclization was the key to stablish the 2,3-*cis*-dimethyldihydrobenzofuran moiety, present in natural products such as (+)-3-*epi*-Furaquinocin C (Scheme 15).[30] A related strategy had been previously applied by the same group for the diastereoselective generation of a quaternary stereocenter in the enantioselective synthesis of (–)-Galanthamine.[31]



(*R*)-**31** (*E*/Z: 1:1) (*2R, 3S*)-**32** (92%) (+)-3-*epi*-furaquinocin C

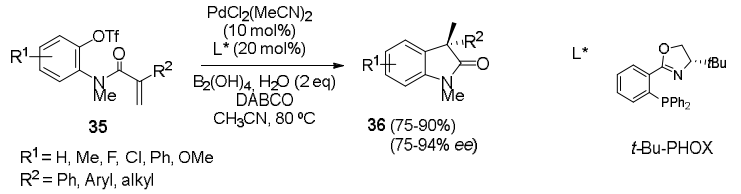
Scheme 15. Diastereoselective reductive M-H reaction for the synthesis of dihydrofuran framework

A highly enantioselective variant of this reaction has been developed only recently. Thus, the cyclization of allyl aryl ethers **33** was studied in the presence of chiral ligands for palladium (Scheme 16).[32] Modest conversions and enantioselectivities (28-78% *ee*) were obtained using commercially available ligands, such as BINAP and XylBINAP, or with PHOX ligands. However, the design of a new chiral sufinamide phosphine ligand (*N*-Me-***XuPhos***) was crucial to obtain consistently good yields and excellent enantioselectivities (>90% *ee*) for the formation of the quaternary center in dihydrofuran **34**, with a wide variety of substitution patterns.



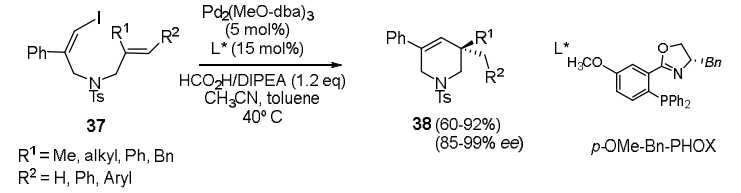
Scheme 16. Enantioselective reductive M-H reaction for the synthesis of dihydrofuran framework

An enantioselective synthesis of 3,3-disubstituted oxindoles has also been reported using diboron-water as hydride source (Scheme 17).[33] In this case, when triflates of general structure **35** were used as substrates, *t*-Bu-PHOX ligand gave the best enantioselectivity (75-94% *ee*) for the formation of the quaternary center on **36**. Again, ligands as BINAP or SEGPHOS gave lower conversions and enantioselectivity. Besides, the structure of the base was also important, as the use of DIPEA, or DBU gave low conversions. Interestingly, the reaction took place using sodium formate as hydride source, although with a lower enantioselectivity (70% *ee*). Although the reduction step is not involved in the stereodeterminant step, the presence of a nucleophile (HCO_2Na) might modify the coordination sphere of the metal and, as a result, the enantioselectivity of the carbopalladation. This gives an idea of the difficulty in developing these enantioselective reactions, in which multiple variants have to be controlled.



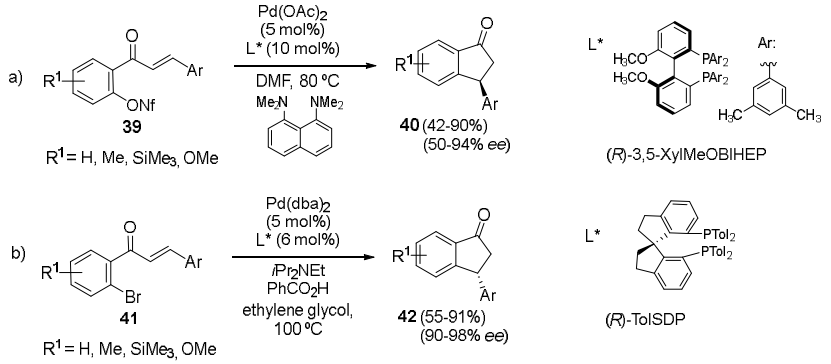
Scheme 17. Enantioselective reductive M-H reaction for the synthesis of oxindole framework

Most of the examples described involve 5-*exo* cyclizations, but the formation of a quaternary stereocenter through a 6-*exo* cyclization has also been accomplished (Scheme 18).[34] Vinyl halides **37** were cyclized to afford tetrahydropyridines **38** with good to excellent enantioselectivities using a PHOX ligand. As in the previous example, the hydride source also had an impact on enantioselectivity, as the use of HCO_2H/DIPEA gave higher enantioselectivity than the use of HCO_2H/Et_3N.



Scheme 18. Enantioselective reductive M-H reaction for the synthesis of tetrahydropyridine framework.

Tertiary centers can also be generated through reductive M-H reactions, but in this case it is necessary to avoid the undesirable β-hydride elimination. Two significant examples are shown on Scheme 19, although they have been applied to the synthesis of carbocycles. Buchwald described the intramolecular insertion of aryl nonaflates of structure **39** onto an enone moiety to obtain dihydroindenones **40**. Thus, β-hydride elimination is precluded by the initially formed *cis*-configured palladium enolate intermediate, allowing hydride transfer. In this case, the proton sponge (Scheme 19a) is used as hydride donor in the presence of (*R*)-3,5-XylMeOBIHEP as chiral ligand.[35] More recently, a related strategy has been described using aryl bromides **41**, with a combination of benzoic acid and DIPEA in ethylene glycol to form an alkylamonium salt *in situ*, which acts as hydrogen bond donor to help halide dissociation, driving the reaction through a cationic mechanism. The best enantioselectivities for the formation of **42** were obtained with (*R*)-TolSDP, while BIHEP or SEGPHOS ligands gave much lower enantioselectivities (Scheme 19b).[36]



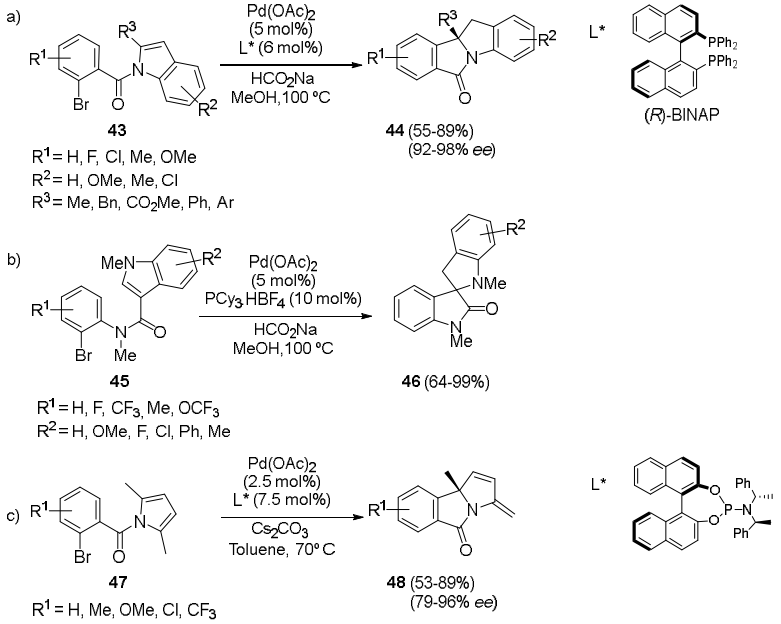
Scheme 19. Enantioselective reductive M-H reaction for the generation of tertiary stereocenters

A different strategy for the generation of a stereocenter is through a dearomatization reaction. In this context, in a seminal contribution to this area, Buchwald developed an intramolecular enantioselective dearomatization reaction of anilines, obtaining 3,3-disubstituted-3a*H*-indoles with excellent enantioselectivity in the presence of base,[37] though the reaction does not proceed through a Heck-type carbopalladation mechanism. However, an asymmetric arylative dearomatization of indoles **43** *via* reductive M-H reaction has been developed for the generation of C-2 quaternary stereocenters in **44** with good yields and excellent enantioselectivities. The reaction could be carried out using a combination of formic acid with different bases (Et_3N, TMDA, DIPEA), but the best results were obtained with sodium formate as hydride donor. Ligand screening indicated that bidentate phosphines were efficient (SEGPHOS, SYNPHOS), but the best results were obtained with (*R*)-BINAP (Scheme 20a).[38] Modifying the structure of the substrates to 3-substituted indoles **45**, the same group has extended the reaction to the synthesis of spiropyrrolidine oxindoles **46**, although in the racemic version (Scheme 20b).[39] The asymmetric dearomatization of pyrroles **47** has also been developed through a M-H reaction, although in this case there is no reduction of the alkyl palladium intermediate. Thus, pyrrolines **48** bearing a quaternary stereocenter could be obtained in the presence of Feringa's phosphoramidite. Notably, PHOX ligands or SEGPHOS gave high yields but very poor enantioselectivities (Scheme 20c).[40]

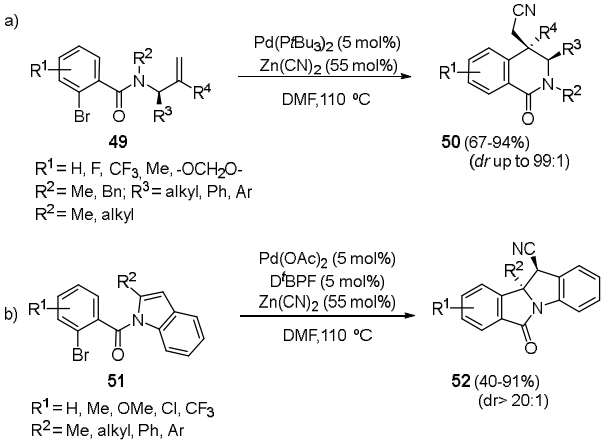
3.2. Carbopalladation followed by nucleophilic trapping

Different types of nucleophilic trapping reactions have been described. A versatile approach is the trapping with cyanide which was first developed by Grigg using KCN as the cyanide source.[41] Improved conditions were later reported using $K_4[Fe(CN_6)]$.[42] A diastereoselective variant has been more recently developed by Lautens on enantiomerically pure *N*-allylcarboxamides **49**, that uses substoichiometric ammounts of $Zn(CN)_2$ as cyanide source. Its highly covalent nature leads to decreased amounts of free cyanide, preventing catalyst deactivation. Dihydroisoquinolinones **50** are obtained in excellent yields and high diastereoselectivities (Scheme 21a).[43] Following this work, the same group described a more complex

bisfunctionalization reaction, initiated by dearomatization of indoles **51**, leading to the formation of complex indolines **52** bearing contiguous tertiary and quaternary carbons, with excellent yields and diastereoselectivities (Scheme 21b).[44] More recently, this type of intramolecular arylcyanation reactions have been described to proceed efficiently using nickel catalysis, instead of palladium.[45]



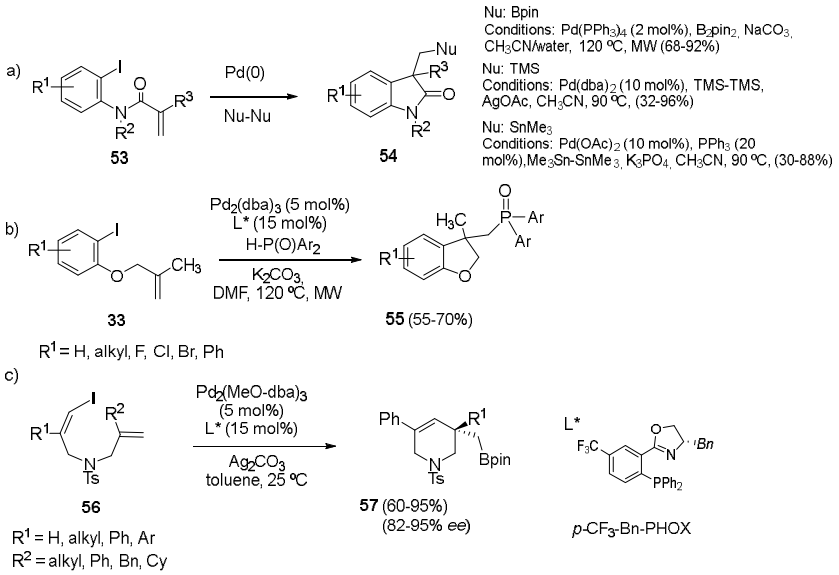
Scheme 20. Dearomative M-H reaction for the generation of quaternary stereocenters.



Scheme 21. Carbopalladation followed by cyanide trapping.

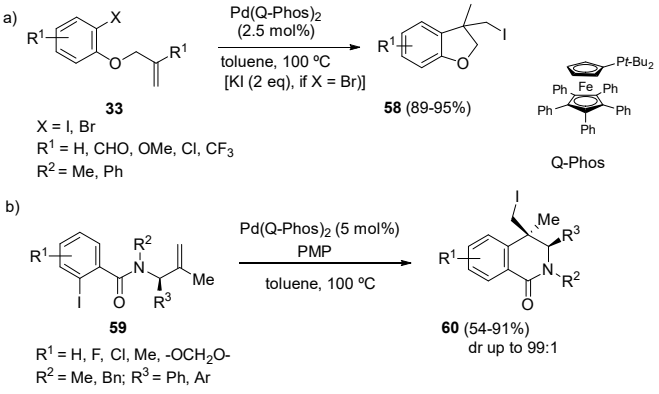
Different functionalization can be introduced varying the type of nucleophile used. Thus, borylation, silylation and stannilation reactions have been developed for the synthesis of functionalized oxoindolines **54** from acrylamides **53**, by trapping the alkyl palladium intermediate with *bis*(pinacolato)diborane,[46] hexamethyldisilane or hexamethyldistannane,[47] respectively (Scheme 22a). Alternatively, phosphorylation reactions have also been accomplished using arylphosphine oxides under MW irradiation for the synthesis of

dihydrofurans **55** from allyl ethers **33** (Scheme 22b).[48] An enantioselective variant for vinylborylation reaction on tosylamines **56** has been also developed for the synthesis of tetrahydropyridines **57** in the presence of a PHOX ligand with high enantioselectivity and moderate to good yields (Scheme 22c), although in this case the authors proposed a mechanism in which the transmetalation would be prior to the carbopalladation.[49]



Scheme 22. Carbopalladation followed by C-B, C-Si, C-Sn or C-P bond formation.

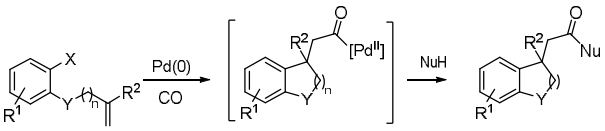
Carboiodination reactions have also been developed but, in this case, instead of an external anion capture event, the C-I bond is formed through reductive elimination of the alkylpalladium iodide initially formed when extremely bulky phosphines (such as Q-Phos) are used (Scheme 23a). This way, 3-iodomethylbenzofurans **58** could be obtained from allyl ethers **33** in excellent yields, forming two new bonds and incorporating all substrate atoms (**33**, X=I) in the product.[50] The reaction could be extended to the formation of chromanes and isochromanes,[51] and also to the use of aryl bromides (**33**, X=Br), simply adding an excess of potassium iodide.



Scheme 23. Carboiodination reactions.

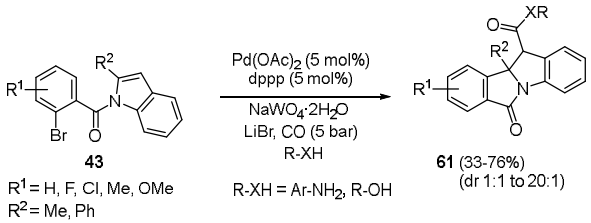
The use of bulky phosphines is crucial for the reactivity. Computational studies showed that, after migratory insertion, a tricoordinate alkylpalladium species is formed, which undergoes reductive elimination to form the alkyl iodide. The use of less bulky phosphines leads to tetracoordinated species that do not undergo reductive elimination.[52] The procedure has been extended to the synthesis of enantioenriched dihydroisoquinolines **60** by diastereoselective carboiodination of *N*-allylcarboxamides **59**.[53] The addition of PMP significantly increases the diastereoselectivity in the presence of Q-Phos (Scheme 23b). More recently, these carboiodination reactions have also been developed under nickel catalysis.[54]

An interesting alternative, that increases the versatility of these reactions, is to carry out an insertion of CO after carbopalladation, generating an acylpalladium intermediate that can afterwards be trapped with different nucleophiles either in an inter- or intramolecular fashion (Scheme 24). The first applications of this methodology were reported by Grigg,[55] but the enantioselective variants have been described only recently.



Scheme 24. Carbopalladation followed by CO insertion reactions and nucleophilic trapping.

In this context, the first example of a dearomative carbonylation reaction of indoles of general structure **43** has been recently reported using CO (5 bar), and anilines or alcohols as nucleophiles. The reaction conditions had to be optimized to avoid side reactions, such as direct carbonylation of the precursor. Under the optimized conditions, in the presence of dppp, moderate to good yields of indolines **61** were obtained, although with generally modest diastereoselectivities and yields (Scheme 25).[56]

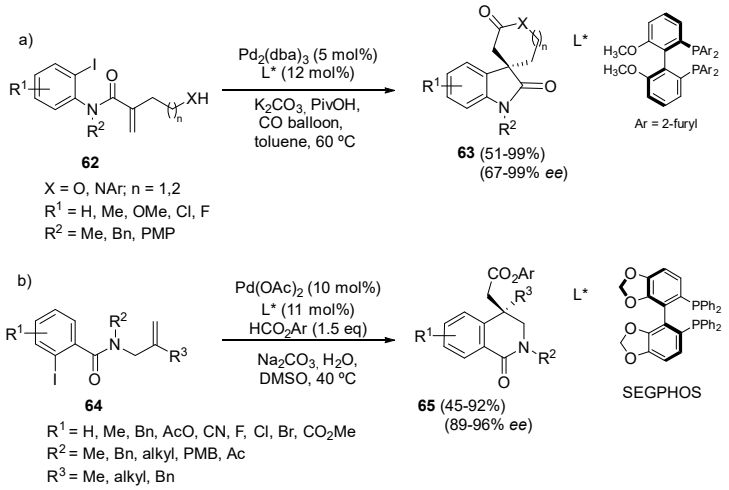


Scheme 25. Dearomative carbonylative dearomatization for the synthesis of indolines.

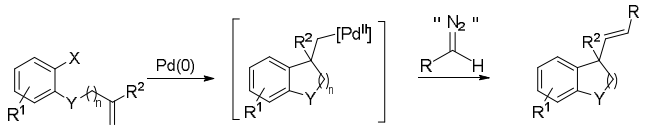
On the contrary, when an oxygen or nitrogen-based nucleophile is tethered to the alkene, a second cyclization reaction takes place. The ring size can be modulated changing the tether between the alkene and the nucleophilic atom on functionalized acrylamides **62**. Thus, spirofused lactones and lactams **63** have been obtained in excellent yields and enantioselectivity when the reaction is carried out in the presence of chiral biphosphine ligands (Scheme 26a).[57] Formate esters have also been used as a source of CO. Thus, under the reaction conditions, aryl formates generate CO and phenols, that after CO insertion, act as the nucleophiles. Thus, 3,4-dihydroisoquinolinones **65** have been obtained from amides **64** in generally high yields and enantioselectivity using SEGPHOS as chiral ligand (Scheme 26b).[58]

In a different termination approach, reaction of the alkylpalladium intermediate with a carbene precursor would give an alkene, *via* carbene insertion and β-hydride elimination (Scheme 27). In this context, tosylhydrazones are efficient carbene precursors that are frequently used in metal catalyzed cross coupling reactions.[59] Thus, oxoindolines **66** that incorporate a new alkene functionality have been obtained by reaction of acrylamide **53** with a variety of *N*-tosylhydrazones with good yields (Scheme 28a).[60] The reaction can also be extended to the use of enolizable ketone-derived tosylhydrazones with allyl ethers **33** (Scheme 28b). The regioselectivity of the final β-hydride elimination can be controlled using bulky ligands, such as XPhos. This way, the less substituted alkene is formed with complete regio- and stereoselectivity, obtaining a wide variety of functionalized dihydrobenzofurans **67**.[61] The procedure cannot be applied to the formation of tertiary stereocenters because β-hydride elimination after carbopalladation is faster than

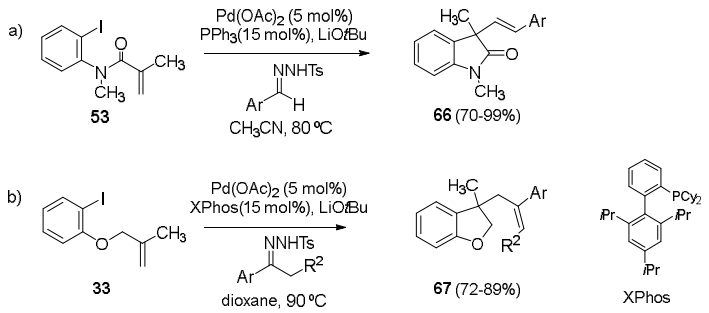
carbene insertion. Thus, a substituent is required in the alkene to avoid this elimination. Besides, when bromides are used as precursors, direct carbene coupling product is observed.



Scheme 26. Enantioselective Heck carbonylative reactions.



Scheme 27. Carbopalladation followed by carbene insertion/elimination.



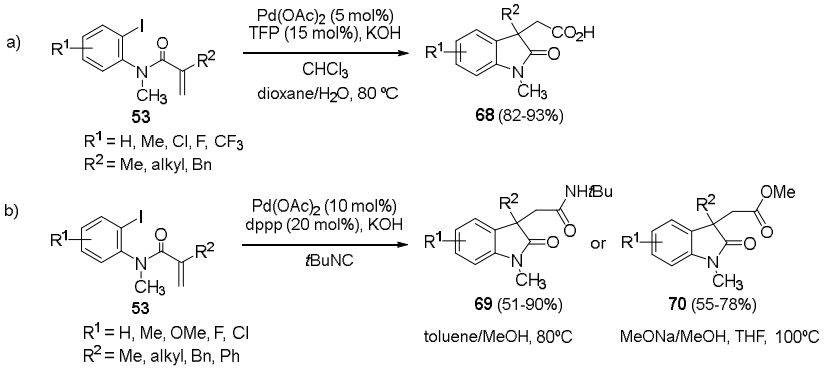
Scheme 28. Carbopalladation/carbene insertion for the synthesis of oxindolines and benzofurans.

Alternatively, chloroform has been used as a dichlorocarbene precursor. Thus, coordination of the alkylpalladium intermediate formed after carbopalladation of acrylamides **53** with dichlorocarbene, followed by hydrolysis under aqueous basic conditions, produces carboxylic acids **68**. Thus, $CHCl_3$ would be an alternative to carbonylation reactions (Scheme 29a).[62] In a related fashion, the alkylpalladium formed after carbopalladation can also undergo migratory insertion of isocyanide. Depending on the reaction conditions, amides **69** or esters **70** could be selectively obtained (Scheme 29b).[63]

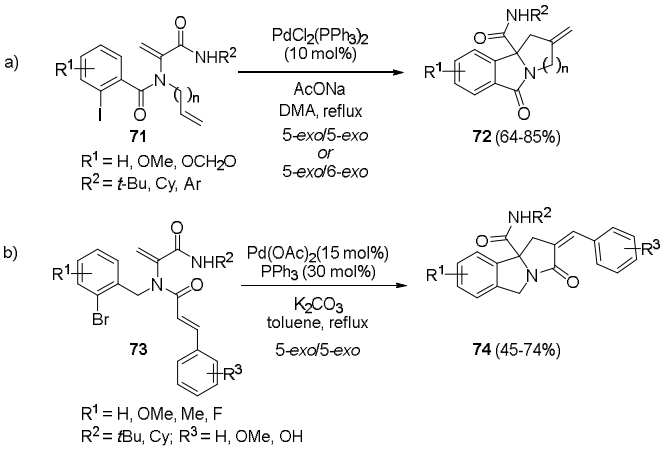
3.3. Heck-Heck cascade reactions: polyene cyclizations

In Heck-Heck cascade reactions, the σ-alkylpalladium(II) intermediate is inter- or intramolecularly trapped by a second alkene, so two or more rings can be generated, significantly increasing molecular

complexity in a single step.[64] The first example of an enantioselective palladium-catalyzed polyene cyclization was reported by Overman in the synthesis of spirocyclic trienones.[65] A nice application of this strategy is the total synthesis of the marine natural product (+)-Xestoquinone described by Keay.[66] Fused indolizidine **72** and pyrrolizidine **74** frameworks have been efficiently assembled in one step *via* a Heck-Heck reaction of structurally related amides **71** or **73**. Significantly, in both cases, the first 5-*exo* carbopalladation reaction with the enamide moiety to generate the quaternary center is favored over a possible 6-*exo* process with the other alkene (Scheme 30).[67]



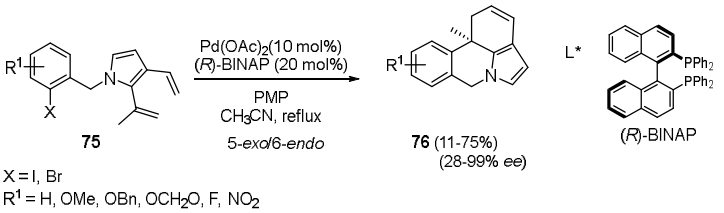
Scheme 29. Carbopalladation followed by carbene or isocyanide insertion for the synthesis of carboxylic acids, esters or amides.



Scheme 30. 5-*exo*/5-*exo* and 5-*exo*/6-*exo* Heck-Heck reactions for the synthesis of fused pyrrolizidines and indolizidines.

In this context, we have developed an asymmetric Heck-Heck 6-*exo*/6-*endo* reaction for the enantioselective synthesis of Lycorine-type alkaloids **76** starting from *N*-benzyl 2,3-dialkenylpyrroles **75** using different chiral ligands (Scheme 31).[68] Although bidentate and monodentate phosphines (such as DIOP, SEGPHOS, Xyl-BINAP, CHIRAPHOS or TADDOL-based phosphoramidites) were able to promote the cyclization in generally good yields, (*R*)-BINAP gave the best enantioselectivity, up to 99% *ee*, using $Pd(OAc)_2$ as catalyst and PMP as base in acetonitrile. The reaction is compatible with a wide variety of substitution patterns on the aromatic ring, and also with heteroaromatic rings. The reaction is completely selective, and no other cyclization pathways are observed. Thus, the first 6-*exo* carbopalladation generates the quaternary stereocenter, which is followed by a second 6-*endo* carbopalladation and elimination.

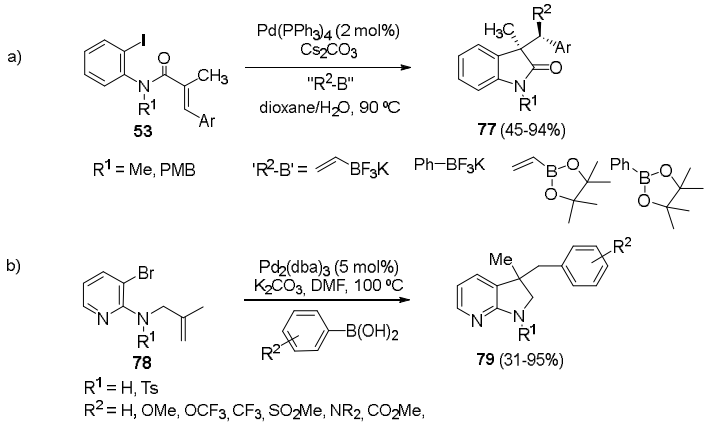
Previous DFT studies on related 6-*exo*/6-*endo* cascades have shown that the main factor controlling the exo/endo selectivity at thermodynamic and kinetic levels is the relative stability of the cyclic system resulting from migratory insertion.[69]



Scheme 31. Enantioselective Heck-Heck cascade reaction in the synthesis of Lycorane-type alkaloids.

3.4. Carbopalladation followed by other couplings

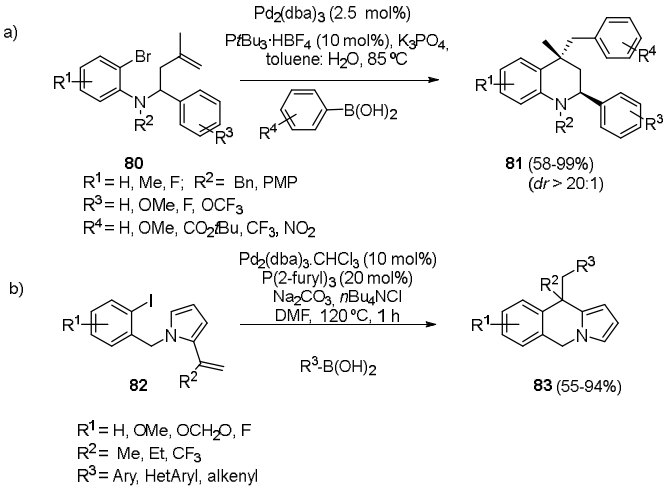
As shown in Scheme 14, the σ-alkylpalladium(II) intermediate obtained after the starting carbopalladation can participate in a second intermolecular cross coupling reaction. Different termination events have been developed, that imply Suzuki or Sonogashira couplings, and direct C-H arylation reactions. For these tandem reactions to proceed efficiently is important to find the adequate catalyst and experimental conditions to suppress the direct coupling with the aryl halide precursor, and allow the carbopalladation to proceed first. Consequently, the starting carbopalladation is generally a 5-*exo* process, so this method has been applied mainly for the construction of functionalized five-membered heterocycles. In this context, the first examples of a Heck cyclization in tandem with a Suzuki reaction were reported by Grigg.[70] More recently, this type of domino carbopalladation/cross-coupling reaction has been used for the diastereospecific construction of 3,3-disubstituted oxindoles **77** starting from substituted *N*-(*o*-iodophenyl)acrylamides **53** with different substitution patterns and different organoborane species (Scheme 32a).[71] The stereospecific initial *syn* palladation step allowed the generation of the two vicinal stereocenters with complete diastereoselectivity. The substituent on nitrogen (R^1) is essential for the rate of carbopalladation to compete with the direct Suzuki coupling, as unsubstituted amides (R^1=H) led to direct cross coupling products. Besides, a series of azaindolines **79** with a quaternary stereocenters at C-3 were obtained by applying this type of palladium-catalyzed domino reaction on pyridin-2-amines **78** using arylboronic acids (Scheme 32b).[72] The reaction works with unprotected amines (R^1=H) using $Pd(OAc)_2$ with phosphines, such as JohnPhos or P(*o*-Tol)$_3$. However, $Pd_2(dba)_3$ promoted the reaction in the absence of phosphines.



Scheme 32. 5-*exo* carbopalladation/Suzuki cascade for the synthesis of oxindoles and azaindolines.

The procedure is compatible with a wide range of functional groups and can be extended to the preparation of all four azaindoline isomers. The enantioselective version was attempted using chiral phosphines, but racemic compounds were obtained. More recently, the preparation of 3,3-disubstituted oxindoles by similar Ni-catalyzed Heck/Suzuki cascade reaction has been reported.[73]

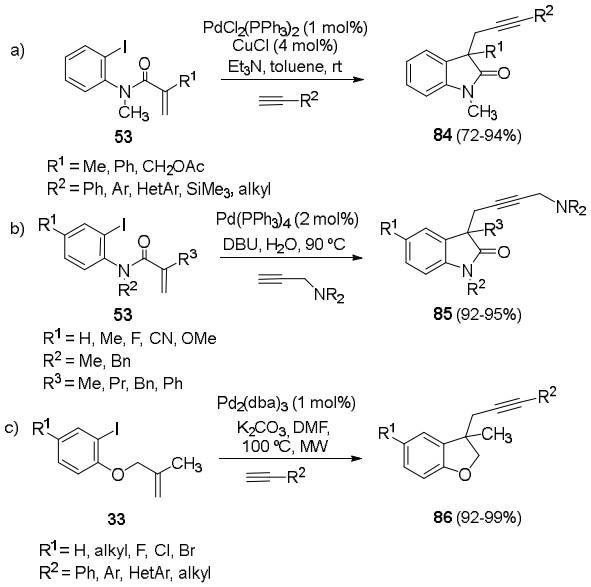
There are few examples of formation of six-membered heterocycles by carbopalladation/Suzuki coupling. An illustrative example is the reaction of functionalized *o*-bromoanilines **80** with boronic acids for the diastereoselective synthesis of 2,4,4-trisubstituted tetrahydroquinolines **81** (Scheme 33a).[74] The reaction works in the presence of other phosphines, such as X-Phos, PCy_3 or PPh_3 but leads to the tetrahydroquinolines **81** with lower levels of diastereoselectivity. As discussed earlier, the use of secondary amines as substrates (**80**, R^2=H) led only to direct cross coupling products. Our group has recently shown that *N*-benzylalkenylpyrroles **82** undergo 6-*exo* carbopalladation/Suzuki coupling with arylboronic acids to generate C-10 disubstituted pyrrolo[1,2-*b*]isoquinolines **83** (Scheme 33b).[75] A phosphine free precatalytic system could be used in order to favor the 6-*exo* carbopalladation reaction *vs*. the direct Suzuki coupling, although also a 7-*endo* process can be competitive in some cases. Nevertheless, the 7-*endo* process can be suppressed in the presence of phosphine ligands, such as tri(furan-2-yl)phosphine, leading to a significant increase in the yields of the pyrroloisoquinolines **83**. The presence of nBu$_4$NCl is crucial to allow the 6-*exo* carbopalladation to occur at a competitive rate, avoiding the direct Suzuki coupling. Electron rich and electron deficient arylboronic acids can be used, although coupling with alkenyl or heteroaryl (thiophenyl) boronic acids provides lower yields. The use of chiral non racemic phosphines has also been attempted, although only low enantioselectivities (up to 44% *ee*) were obtained.



Scheme 33. 6-*exo* carbopalladation/Suzuki cascade for the synthesis of tetrahydroquinolines and pyrroloisoquinolines.

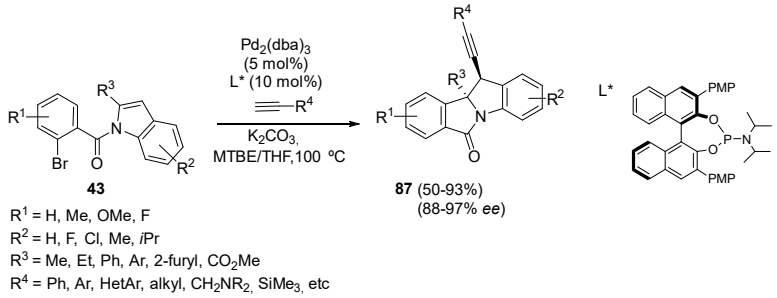
Another termination event is the coupling with alkynes in a Sonogashira reaction (Scheme 34). Thus, this type of reaction has been developed on acrylamides **53** or allyl ethers **33** to access to 3,3-disubstituted oxindoles **84**, **85** and dihydrobenzofurans **86**, respectively. In the first case (Scheme 34a),[76] screening of reaction conditions showed that $PdCl_2(PPh_3)_2$ was the best catalyst using CuCl as co-catalyst. These conditions could be applied to a wide range of terminal alkynes obtaining excellent yields of oxindoles **84**. However, when the corresponding esters or thioesters (O or S instead of N-Me in **53**) were submitted to the optimized reaction conditions, only the direct Sonogashira coupling products were obtained. These reactions have been also developed using water as solvent in the absence of copper co-catalyst using propargyl amines as coupling partners (Scheme 34b).[77] In addition, cyclization of allyl ethers **33** could be accomplished under microwave assisted conditions using low catalyst loadings in the absence of copper (Scheme 34c).[78] Thus,

dihydrobenzofurans **86** were obtained in almost quantitative yields in very short reaction times (15 min MW *vs* 24 h thermal conditions).



Scheme 34. Carbopalladation/Sonogashira cascade for the synthesis of oxindoles and dihydrobenzofurans.

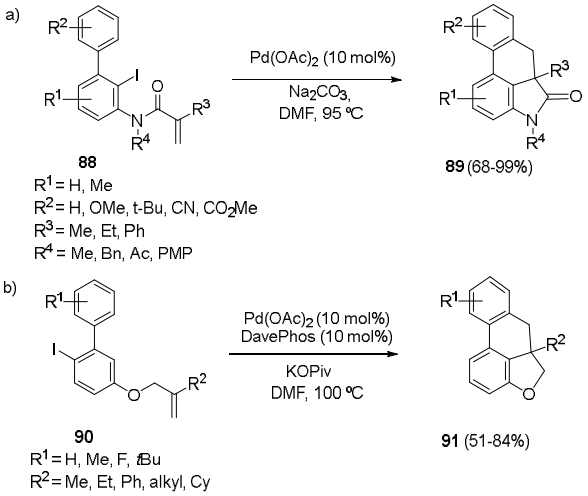
An enantioselective variant of this cascade process has also been described that involved a dearomatization reaction of an indole **43** (Scheme 35).[79] Interestingly, the addition of CuI completely suppressed the reactivity, so the reactions were carried out using $Pd_2(dba)_3$ in the presence of base. The BINOL based phosphoramidite ligand gave the best enantioselectivity. A wide variety of alkynes could be coupled efficiently to obtain indolines **87**, bearing quaternary and tertiary vicinal stereocenters, with excellent enantiomeric purities.



Scheme 35. Enantioselective dearomative Heck/Sonogashira cascade.

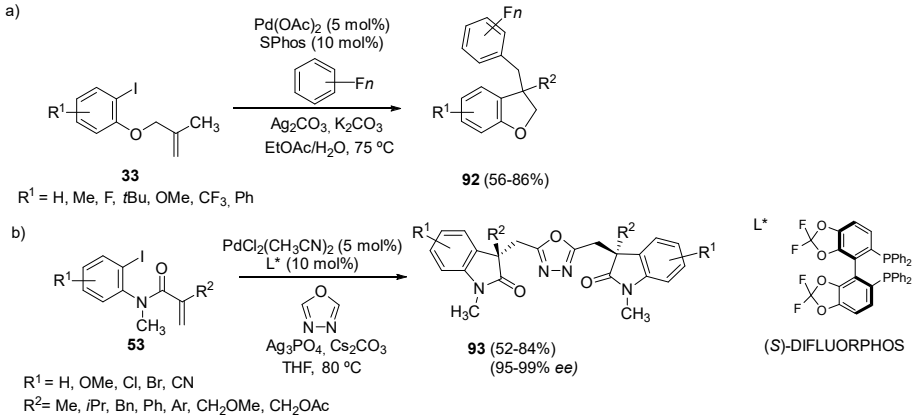
Cascade processes involving a C-H direct arylation event have also been described in both intra- and intermolecular fashion. In the intramolecular variant, the alkylpalladium intermediate formed after carbopalladation would be able to carry out a C-H activation in a conveniently tethered aromatic or heteroaromatic ring, generating a palladacycle that forms the C-C bond *via* reductive elimination. The first examples of this type of reactions for the synthesis of heterocycles were reported by Grigg over twenty years ago,[80] but synthetic applications to more elaborated systems, as well as mechanistic studies, are currently

being developed.[81] Recent examples are depicted in Scheme 36. For instance, when biarylic acrylamides **88** are treated with $Pd(OAc)_2$ and base in DMF, fused indolinones **89** are obtained in good yields (Scheme 36a),[82] forming two C-C bonds and a quaternary stereocenter. Around the same concept, more complex sequences have also been developed. Thus, it has been recently shown that the iodide atom does not need to be *ortho* to the tethered alkene to start the carbopalladation. As depicted in Scheme 36b, a sequence involving oxidative addition on iodides **90** followed by two consecutive [1,4]-palladium migrations using the *ortho* aromatic ring as conveyor, allows the intramolecular carbopalladation of the alkene followed by a C-H activation to obtain fused dihydrofurans **91**.[83]



Scheme 36. Intramolecular carbopalladation followed by intramolecular C-H arylation for the synthesis of tetracyclic frameworks.

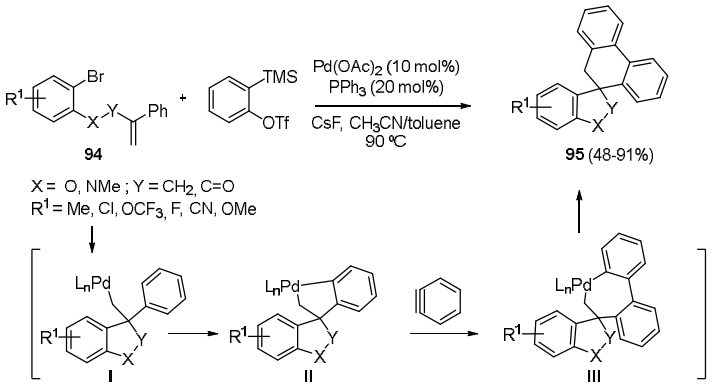
As depicted in Scheme 37, electron deficient polyflouroarenes can be used for the intramolecular C-H arylation of the alkylpalladium intermediates obtained from **33** to obtain polyfluorinated dihydrobenzofurans **92** (Scheme 37a).[84]



Scheme 37. Intramolecular carbopalladation followed by intermolecular C-H arylation.

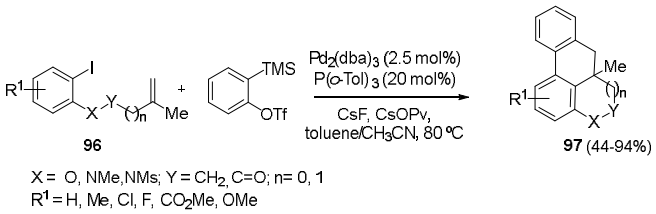
Heteroarenes have also been used as coupling partners for the formation of functionalized oxindolines.[85] Moreover, enantioselective variants have been developed starting from acrylamides **53** and oxazoles using PHOX ligands obtaining oxindoles that were further elaborated to pyrroloindolines.[86] This reactivity has been also used for the double carbopalladation/C-H arylation of acrylamides **53** to obtain **93** with consistently very high enantiomeric purities, in the presence of a chiral bidentate phosphine (Scheme 37b).[87]

More complex cascade reactions have been also developed taking advantage of the versatility of the alkyl palladium(II) intermediate (**I**, Scheme 38).[88] Thus, the palladacycle **II** formed after C-H activation can be trapped with an aryne generated *in situ* to obtain **III**. In this case, both the substrate and the reaction conditions have to be designed to match the formation rates of the alkylpalladium and the aryne, avoiding [1,4]-palladium shift on **I**, which would lead to the formation of byproducts. Thus, under the optimized conditions, ethers or amines or amides of general structure **94** gave [4,5]-spirocycles **95** with complete regioselectivity in generally high yields. Interestingly, using substrates in which the initial carbopalladation occurs *via* a 6-*exo*-trig cyclization, mixtures of regioisomers are obtained due to competing C-H activation reactions. In a further extension of this methodology, palladacycles of structure **II** have also been trapped with carbenoid precursors, such as α-diazocarbonyl compounds, to obtain spirocycles.[89]



Scheme 38. Intramolecular carbopalladation followed by C-H arylation and aryne insertion

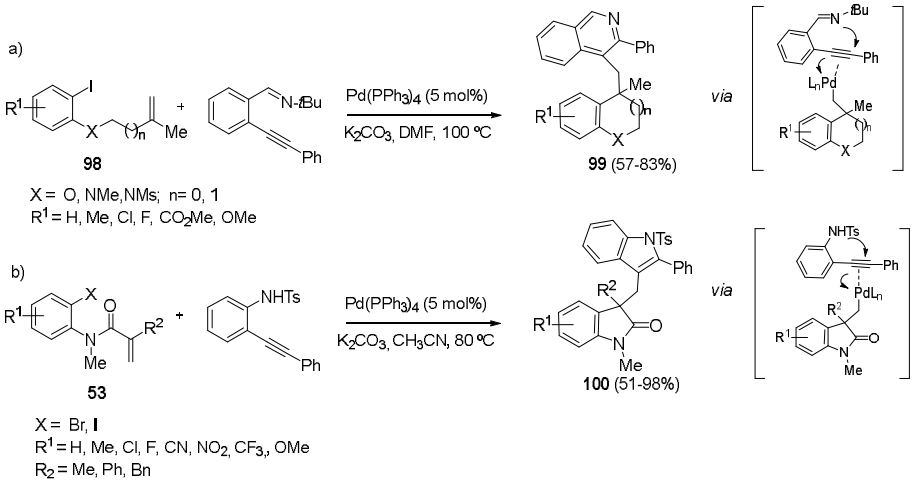
In a related strategy, the use of substrates **96**, in which the β-elimination is blocked by an alkyl substituent, instead of an aromatic ring, leads to the formation of heterocycle fused 9,10-dihydrophenenthrenes **97** (Scheme 39).[90] The use of CsOPiv as base was crucial as other organic or inorganic bases gave only low yields. In general, electron withdrawing substituents in the aryl iodide resulted in higher yields, which is consistent with a base induced palladation in the C-H functionalization step. In this case, the formation of a six membered ring through a 6-*exo* initial carbopalladation is possible, obtaining fused quinoline systems in good yields (**97**, X=NMe, NMs; Y=CH_2, n=1).



Scheme 39. Intramolecular carbopalladation followed by aryne insertion and C-H arylation

The alkylpalladium(II) species obtained after intramolecular carbopalladation can be involved in a wide variety of reactions. In a different approach, these intermediates have been used to promote cyclization

of alkynes containing a proximate nucleophilic group (Scheme 40). Thus, functionalized isoquinolines **99**[91] have been obtained from allyl and homallyl amines or ethers **98**, and indoles **100** were obtained from acrylamides **53** in good yields forming two cycles, two C-C and a C-N bond in a single step using .[92]



Scheme 40. Intramolecular carbopalladation followed by alkyne insertion and nucleophilic attack.

7. Conclusions

The intramolecular Mizoroki-Heck reaction constitutes a powerful tool for the construction of small and medium-sized carbocycles and heterocycles. The control of the β-hydride elimination step allows the generation of tertiary and quaternary stereocenters. On the other hand, the rich reactivity of the alkylpalladium(II) species obtained after intramolecular carbopalladation of well-designed substrates makes them highly valuable intermediates to participate in further functionalization reactions, forming various cycles and C-C or C-X bonds in one step, and generating a quaternary stereocenter. The use of chiral ligands for palladium has allowed the development of enantioselective variants that are widely used in synthesis. However, the advance in enantioselective variants for the carbopalladation-initiated cascades is not straightforward, as the presence of other reagents, such as external nucleophiles, may alter the coordination of palladium and have an impact in the enantioselectivity. Thus, besides the great number of applications described, the discovery and application of cascade processes with high regio- and stereoselectivity is a highly active area.

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References

1. For selected reviews on the intramolecular Mizoroki-Heck reaction, see: (a) Geoghegan, K.; Evans, P. In *Science of Synthesis. Cross Coupling and Heck-Type Reactions 3. Metal-Catalyzed Heck-Type Reactions and C-H Couplings via C-H Activation*; Larhed, M., Ed., Georg Thieme Verlag: Stuttgart, 2013, 391-439. (b) Stwart, S. G. In *Science of Synthesis. Cross Coupling and Heck-Type Reactions 3. Metal-Catalyzed Heck-Type Reactions and C-H Couplings via C-H Activation*; Larhed, M., Ed., Georg Thieme Verlag: Stuttgart, 2013, 441-519.

2. (a) Broggini, G.; Borsini, E.; Piarulli; U. In *Science of Synthesis. Cross Coupling and Heck-Type Reactions 3. Metal-Catalyzed Heck-Type Reactions and C-H Couplings via C-H Activation*, Larhed, M., Ed., Georg Thieme Verlag: Stuttgart, 2013, 521-583.
3. For selected reviews, see: (a) Sibashaki, M.; Boden, C. D. J; Kojima, A. *Tetrahedron*, **1997**, *53*, 7371-7395. (b) Dounay, A. N.; Overman, L. *Chem. Rev*. **2003**, *103*, 2945-2963. (c) Tietze, L. F.; Ila. H.; Bell, H. P. *Chem. Rev*. **2004**, *104*, 3453-3516. (d) Mc Cartney, D.; Guiry, P. J. *Chem. Soc. Rev*. **2011**, *40*, 5122-5150.
4. (a) Ohno, H. *Asian J. Org. Chem*. **2013**, *2*, 18-28. (b) Biemolt, J.; Ruijter, E. *Adv. Synth. Catal.* **2018**, *360*, 3821-3871. (c) Blouin, S.; Blond, G.; Donnard, M.; Gulea, M.; Suffert, J. *Synthesis*, **2017**, *49*, 1767-1784. (d) Ohno, H.; Inuki, S. *Synthesis*, **2018**, *50*, 700-710. (e) Ping, Y.; Li, Y.; Zhu, J.; Kong, W. *Angew. Chem. Int. Ed*. **2019**, *58*, 1562-1573.
5. Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738-4739.
6. Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959-6964.
7. (a) Tietze, L. F.; Petersen, S. *Eur. J. Org. Chem.* **2000**, 1827-1830; (b) Tietze, L. F.; Petersen, S. *Eur. J. Org. Chem.* **2001**, 1619-16.24; (c) Tietze, L. F.; Krahnert, W. R. *Chem. Eur. J.* **2002**, *8*, 2116-2125.
8. Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264-10269.
9. Overman, L. E.; Watson, D. A. *J. Org. Chem.* **2006**, *71*, 2587-2599.
10. Geoghegan, K.; Evans, P. *J. Org. Chem.* **2013**, *78*, 3410-3415.
11. Umezaki, S.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2013**, *15*, 4230-4233.
12. Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2014**, *136*, 17750-17756.
13. Del Bel, M.; Abela, A. R.; Ng, J. D.; Guerrero, C. A. *J. Am. Chem. Soc.* **2017**, *139*, 6819-6822.
14. Ashimori, A.; Bachand, B.; Calter, M. A.; Overman, L.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477-6487; erratum: Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **2000**, *122*, 192-192.
15. Govek, S. P.; Overman, L. E. *Tetrahedron* **2007**, *63*, 8499–8513.
16. Lapierre, A. J. B.; Geib, S. J.; Curran, D. P. *J. Am Chem. Soc.* **2007**, *129*, 494-495.
17. Kitahara, K.; Shimokawa, J.; Fukuyama, T. *Chem. Sci*. **2014**, *5*, 904-907.
18. Rebolledo-Azcargorta, A.; Coya, E.; Barbolla, I.; Lete, E.; Sotomayor, N. *Eur. J. Org. Chem.* **2016**, 2054-2063.
19. (a) Lage, S.; Martínez-Estibalez, U.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal.* **2009**, *351*, 2460-2468. (b) Coya, E.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal.* **2014**, *356*, 1853-1865.
20. For a review see: Pan, D.; Jao, N. *Synlett*, **2010**, *2010*, 1577-1588.
21. Lautens, M.; Tayama, E.; Herse, C. *J. Am. Chem. Soc*. **2005**, *127*, 72-73.
22. (a) Tietze, L. F.; Schimpf, R. *Angew. Chem. Int. Ed.* **1994**, *33*, 1089-1091; (b) Tietze, L. F.; Raschke, T. *Synlett* **1995**, 597-598; (c) Tietze, L. F; Raschke, T. *Liebigs Ann.* **1996**, 1981-1987.
23. Tietze, L. F.; Thede, K.; Schimpf, R.; Sannicolò, F. *Chem. Commun*. **2000**, 583-584.
24. Schuster, C. H.; Coombs, J. R.; Kasun, Z. A.; Morken, J. P. *Org. Lett.* **2014**, *16*, 4420-4423.
25. Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc*. **1993**, *125*, 8477-8478; correction: Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 11207-11207.
26. (a) Overman, L. E.; Poon D. J. *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 518-521. (b) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488-6499. (c) Dounay, B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261-6271.
27. For general reviews, see: (a) Xu, P.-F.; Wang, W., Eds., *Catalytic Cascade Reactions*, John Wiley & Sons, Inc.: Hoboken, 2014. (b) Tietze, L. F., Ed., *Domino Reactions: Concepts for Efficient Organic Synthesis*, Wiley-VCH: Weinheim, 2014. For recent reviews on Palladium-Catalyzed Cascade reactions, see reference 4.
28. For recent reviews: (a) Oxtoby, L. J.; Gurak, J. A.; Wisniewski, S. R.; Eastgate, M. D.; Engle, K. M. *Trends in Chemistry* **2019**, *1*, 572-586. (b) Gosh, T. *ChemistrySelect* **2019**, *4*, 4747-4755.
29. Cacchi, S.; Arcadi, A. *J. Org. Chem*. **1983**, *48*, 4236-4240.

30. Pu, L.-Y.; Chen, J.-Q.; Li, M.-L.; Li, Y.; Xie, J.-H.; Zhou, Q.-L. *Adv. Synth. Catal*. **2016**, *358*, 1229-1240.
31. Chen, J.-Q.; Xie, J.-H.; Bao, D.-H.; Liu, S.; Zhou, Q.-L. *Org. Lett*. **2012**, *14*, 2714-2717.
32. Zhang, Z.-M.; Xu, B.; Qian, Y.; Wu, L.; Wu, Y.; Zhou, L.; Liu, Y.; Zhang, J. *Angew. Chem. Int. Ed*. **2018**, *57*, 10373-10377.
33. Kong, W.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed*. **2017**, *56*, 3987-3991.
34. Hou, L.; Yuan, Y.; Tong, X. *Org. Biomol. Chem*. **2017**, *15*, 4803-4806.
35. Minatti, A.; Zheng, X.; Buchwald, S. L. *J. Org. Chem*. **2007**, *72*, 9253-9258.
36. Yue, G.; Lei, K.; Hirao, H.; Zhou, J. *Angew. Chem. Int. Ed*. **2015**, *54*, 6531-6535.
37. García-Fortanet, J.; Kessler, F.; Buchwald, S. L. *J. Am. Chem. Soc*. **2009**, *131*, 6676-6677.
38. Shen, C.; Liu, R.-R.; Fan, R.-J.; Li, Y.L.; Xu, T.-F.; Gao, J.-R.; Jia, Y.-X. *J. Am Chem. Soc*. **2015**, *137*, 4936-4939.
39. Liu, R.-R.; Xu, Y.; Liang, R.-X.; Xiang, B.; Xie, H.-J.; Gao, J.-R.; Jia, Y.-X. *Org. Biomol. Chem*. **2017**, *15*, 2711-2715.
40. Yang, P.; You, S.-L. *Org. Lett*. **2018**, *20*, 7684-7688.
41. Grigg, R.; Santhakumar, V.; Sridharan, V. *Tetrahedron Lett*. **1993**, *34*, 3163-3164.
42. (a) Jaegli, S.; Vors, J. P.; Neuville, L.; Zhu, J. *Synlett* **2009**, *2009*, 2997-2999. (b) Jaegli, S.; Vors, J. P.; Neuville, L.; Zhu, J. *Tetrahedron* **2010**, *66*, 8911-8921.
43. Yoon, H.; Petrone, D. A.; Lautens, M. *Org. Lett*. **2014**, *16*, 6420-6423.
44. Petrone, D. A.; Yen, A.; Zeidan, N.; Lautens, M. *Org. Lett*. **2015**, *17*, 4838-4841.
45. Yen, A.; Lautens, M. *Org. Lett*. **2018**, *20*, 4323-4327.
46. Vachhani, D. D.; Butani, H. H.; Sharma, N.; Bhoya, U. C., Shan, A. K.; Van der Eycken, E. V. *Chem. Commun.* **2015**, *51*, 14862-14865.
47. Xiao, G.; Chen, L.; Zhou, B.; Deng, G.; Gong, J.; Liang, Y. *Adv. Synth. Catal*. **2018**, *360*, 3477-3481.
48. Ramesh, K.; Satyanarayana, G. *Eur. J. Org. Chem*. **2019**, 3856-3866.
49. Juang, Z.; Hou, L.; Ni, C.; Chen, J.; Wang, D.; Tong, X. *Chem Commun*. **2017**, *53*, 4270-4273.
50. Newman, S. G.; Lautens, M. *J. Am. Chem. Soc*., **2011**, *133*, 1778-1780.
51. Petrone, D. A.; Malik, H. A.; Clemenceau, A.; Lautens, M. *Org. Lett*. **2012**, *18*, 4806-4809.
52. Lan, Y.; Yoon, H.; Weinstabl, H.; Lautens, M. *Angew.Chem. Int. Ed.* **2014**, 53, 7908-7912.
53. Petrone, D. A.; Malik, H. A.; Clemenceau, A.; Lautens, M. *Org. Lett*. **2012**, *18*, 4806-4809.
54. (a)Yoo, H.; Marchese, A. D.; Lautens, M. *J. Am. Chem. Soc*., **2018**, *140*, 10950-10954. (b) Marchese, A. D.; Lind, F.; Mahon, A. E.; Yoon, H.; Lautens, M. *Angew. Chem. Int. Ed.,* **2019**, 58, 5095-5099.
55. Representative examples: (a) Grigg, R.; Sridharan, V. *Tetrahedron Lett*. **1993**, *34*, 7471-7474. (b) Anwar, U.; Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron*, **2001**, *57*, 1361.1367.
56. Wang, H.; Wu, X.-F. *Org. Lett*. **2019**, *21*, 5264-5268.
57. Hu, H.; Teng, F.; Liu, J.; Hu, W.; Luo, S.; Zhu, Q. *Angew. Chem. Int. Ed.* **2019**, *58*, 9225-9230.
58. Cheng, C.; Wan, B.; Zhou, B.; Gu, Y.; Zhang, Y. *Chem. Sci*, **2019**, *10*, 9853-9858.
59. Barluenga, J.; Valdés, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 7486-7500.
60. Liu, X.; Ma, X; Huang, Y.; Gu, Z. *Org. Lett.* **2013**, *15*, 4814-4817.
61. Gao, Y.; Xiong, W.; Chen, H.; Wu, W.; Peng, J.; Gao, Y.; Jiang, H. *J. Org. Chem*. **2015**, *80*, 7456-7467.
62. Liu, X.; Li, B.; Gu, Z. *J. Org. Chem*. **2015**, *80*, 7547-7554.
63. Kong, W.; Wang, Q. Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 9714-9718.
64. For selected reviews on palladium-catalyzed polyene cyclizations, see: (a) Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure Appl. Chem.* **1992**, *64*, 1813-1819. (b) Tietze, L. F.; Levy, L. M. In *The Mizoroki-Heck Reaction*, Oestreich, M. Ed., Wiley: Chichester, 2009, 281-344.
65. Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846-5848.
66. Maddaford, S. P.; Andersen, N. G.; Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10766-10773.
67. (a) García-González, M. C.; Hernández-Vázquez. E.; Gordillo-Cruz, R. E.; Miranda, L. D. *Chem. Commun*. **2015**, *51*, 11669-11672. (b) Miranda, L. D.; Hernández-Vázquez. E. *J. Org. Chem*. **2015**, *80*, 10611-10623.

68. (a) Coya, E.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal.* **2015**, *357*, 3206-3214. (b) Blázquez-Barbadillo, C.; Aranzamendi, E.; Coya, E.; Lete, E.; Sotomayor, N.; González-Díaz, H. *RSC Advances*, **2016**, *6*, 38602-38610.
69. Balcells, D.; Maseras, F.; Keay, B. A.; Ziegler, T. *Organometallics* **2004**, *23*, 2748-2796.
70. (a) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65-87. (b) Grigg, R.; Sansano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thornton-Pett, M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803-11826.
71. Seashore-Ludlow, B.; Somfai, P. *Org. Lett.* **2012**, *14*, 3858-3861.
72. Schempp, T. T.; Daniels, B. E.; Staben, S. T.; Stivala, C. E. *Org. Lett*. **2017**, *14*, 3616-3619.
73. Li, Y.; Wang, K.; Ping, Y.; Wang, Y.; Kong, W. *Org. Lett.* **2018**, *20*, 921-924.
74. Wilson, J. E. *Tetrahedron Lett.* **2012**, *53*, 2308-2311.
75. Barbolla, I.; Sotomayor, N.; Lete, E. *J. Org. Chem*. **2019**, *84*, 10183-10196.
76. Zhou, M. B.; Huang, X. C.; Lui, Y. Y.; Song, R. J.; Li, J. H. *Chem. Eur. J.* **2014**, *20*, 1843-1846.
77. Wang, D. C.; Wang, H. X.; Hao, E. J.; Jiang, X. H.; Xie, M. S.; Qu, G. R.; Guo, H. M. *Adv. Synth. Catal.* **2016**, *358*, 494-499.
78. Karu, R.; Gedu, S. *Green Chem*. **2018**, *20*, 369-374.
79. Liu, R.-R.; Wang, Y.-G.; Li, Y.-L.; Huang, B.-B.; Liang, R.-X.; Jia, Y.-X. *Angew. Chem. Int. Ed*. **2017**, *56*, 7475-7478.
80. For the first examples of Heck cyclization/intramolecular direct C-H arylation for the synthesis of spiroheterocycles, see: (a) Grigg, R.; Fretwell, P.; Meerholtz, C.; Sridharan, V. *Tetrahedron* **1994**, *50*, 359-370. (b) Brown, D.; Grigg, R.; Sridharan, V.; Tambyrajah, V. *Tetrahedron Lett.* **1995**, *36*, 8137-8140.
81. Ye, J.; Shi, Z.; Sperger, T.; Yasukawa, Y.; Kingston, C.; Schoenebeck, F.; Lautens, M. *Nat. Chem*. **2017**, *9*, 361-368.
82. Saha, N.; Wang, H.; Zhang, S.; Du, Y.; Zhu, D.; Hu, Y.; Huang, P.; Wen, S. *Org. Lett*. **2018**, *20*, 712-715.
83. Li, P.; Li, Q.; Weng, H.; Diao, J.; Yao, H.; Lin, A. *Org. Lett*. **2019**, *21*, 6765-6769.
84. Wu, X.-X; Chen, W.-L; Shen, Y.; Chen, S.; Xu, P.-F; Liang, Y.-M. *Org. Lett*. **2016**, *18*, 1784-1787.
85. Sharma, U. K.; Sharma, N.; Kumar, Y.; Singh, B. K.; Van der Eycken, E. V. *Chem. Eur. J*. **2016**, *22*, 481-485.
86. Kong, W.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc*. **2015**, *137*, 16028-16031.
87. Tong, S.; Limouni, A.; Wang, Q.; Wang, M.-X.; Zhu, J. *Angew. Chem. Int. Ed*. **2017**, *56*, 14192-14196.
88. (a) Pérez-Gómez, M.; García-López, J. A. *Angew. Chem. Int. Ed*. **2016**, *55*, 14389-14393. (b) Yoon, H.; Lossouarn, A.; Landau, F.; Lautens, M. *Org. Lett*. **2016**, *18*, 6324-6327. (c) Pérez-Gómez, M.; Navarro, L.; Saura-Llamas, I.; Bautista, D.; Lautens, M.; García-López, J. A. *Organometallics*, **2017**, *36*, 4465-4476.
89. Pérez-Gómez, M.; Hernández-Ponte, S.; Bautista, D.; García-López, J. A. *Chem. Commun*. **2017**, *53*, 2842-2845.
90. Yao, T.; He, D. *Org. Lett*. **2017**, *19*, 842-845.
91. Yao, T.; Liu, T.; Zhang, C. *Chem. Commun*. **2017**, *53*, 2386-2389.
92. Yan, K.; Liu, L.; Chen, J.; Guo, J.; Yao, H.; Lin, A. *Org. Lett*, **2018**, *20*, 3477-3481.