

IV.3.2 Palladium-Catalyzed Cascade Carbopalladation: Termination by Nucleophilic Reagents

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A. INTRODUCTION

Domino or cascade reactions are particularly valuable for the construction of various carbo- and heterooligocyclic systems with three, four, or even more annelated rings. The Heck reaction has successfully been employed in various inter–inter-, intra–inter-, inter–intra-, as well as all-intramolecular reaction cascades. In this section, such processes with a termination by attack of various nucleophiles will be described.

A cascade Heck reaction with termination by nucleophiles is considered to start with an oxidative addition of a heteroatom–carbon bond (starter) onto a palladium(0) species (startup reaction), followed by carbopalladation of a nonaromatic carbon–carbon double or triple bond without subsequent dehydropalladation (relay), a second and possibly further carbopalladation of a carbon–carbon double or triple bond (second etc. relay). The terminating step is a displacement of the palladium residue by an appropriate nucleophile. It is crucial for a successful cascade carbopalladation that no premature dehydropalladation takes place, and that can be prevented by using alkynes and 1,1-disubstituted alkenes (or certain cycloalkenes) as relay stations since they give kinetically stable alkenyl- or neopentylpalladium intermediates, respectively. In addition, reaction of haloalkenes with alkenes in certain cases may form π -allyl complexes, which are then trapped by various nucleophiles.

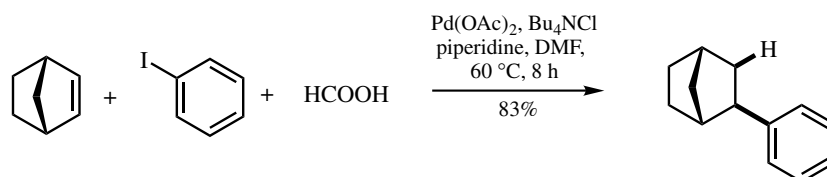
This section is organized in terms of decreasing molecularity types of termination reactions, and attainable ring sizes or ring combinations.

B. ALL-INTERMOLECULAR CASCADE CARBOPALLADATIONS

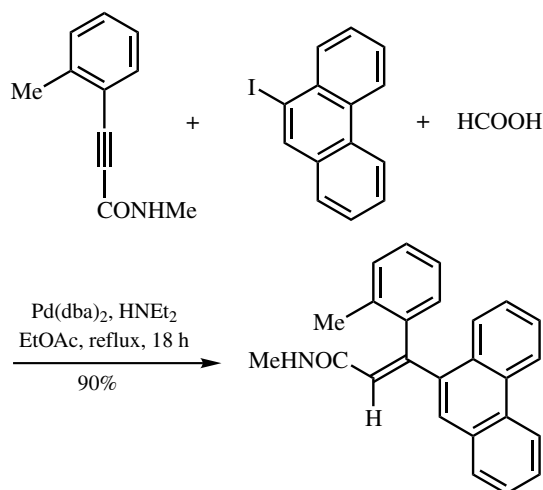
All-intermolecular cascade reactions involving nucleophilic attack at the end are at least three-component reactions. For a successful outcome the balance of reactivities of each component in the reaction mixture toward each other must be just right.

B.i. Termination by Hydride

The prototypic substrate for intermolecular cascade reactions is norbornene or one of its analogs. Starting from an aryl halide, addition of the formed palladium species to the strained double bond of norbornene yields a norbornylpalladium derivative, which cannot undergo β -hydride elimination but can accept hydride, for example, from piperidinium formate (**Scheme 1**)^[1] or potassium formate,^[2] the latter reaction occurring even at room temperature.

**Scheme 1**

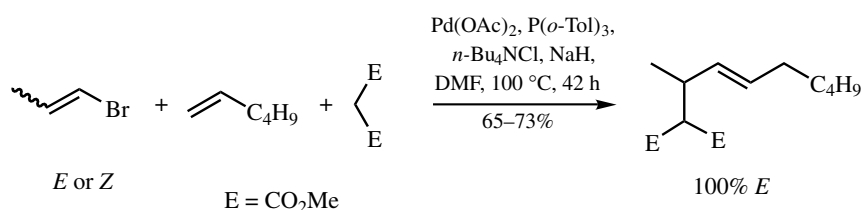
Other possible relays are mostly alkynes, which, after carbopalladation, undergo a surprisingly clean reductive demetallation with formic acid salts (**Scheme 2**).^[3] At this point it is crucial that the catalyst cocktail has the appropriate composition, as yields under different conditions can vary substantially.^{[4],[5]} The high degree of regioselectivity starting from propynoic acid amides has been attributed to coordination with the amide functionality.

**Scheme 2**

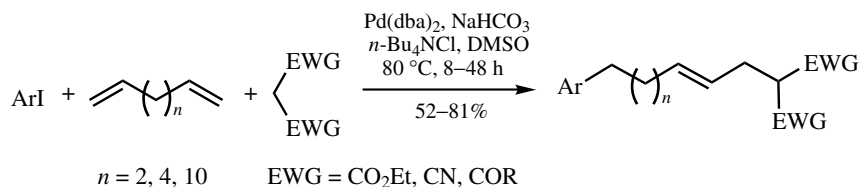
Similarly, α,β -unsaturated ketones and aldehydes react with aryl halides to give conjugate addition type products in the presence of formic acid and a base.^{[6]–[9]}

B.ii. Termination by Carbon Nucleophiles

B.ii.a. Coupling with Soft Carbon Nucleophiles. The coupling of haloalkenes with alkenes and dialkyl malonates in the presence of a suitable base is an efficient three-component reaction leading to substituted allylmalonates.^[10] Based on the constitution and configuration of the final products, it is assumed that the initially formed σ -homoallylpalladium intermediate rearranges—most probably by β -dehydropalladation and rehydridopalladation with reversed regiochemistry—to a π -allylpalladium complex, which is eventually attacked by the malonate enolate (**Scheme 3**). As far as the overall outcome is concerned, analogous intra-inter- as well as fully intramolecular cascade processes have been established (see below, **Schemes 22** and **35**).

**Scheme 3**

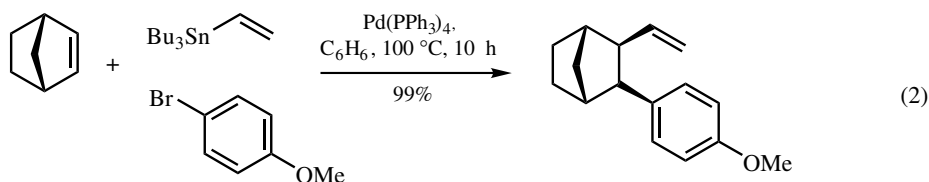
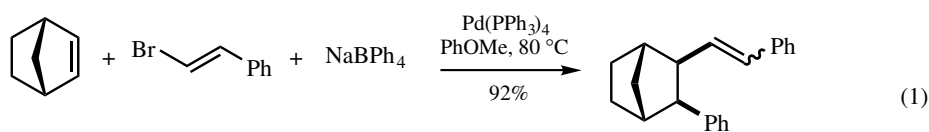
Aryl halides, nonconjugated dienes, and stabilized enolates can be coupled in high yields. Apparently, this process consists of an addition of an arylpalladium halide intermediate to the less hindered C,C double bond, palladium migration by a sequence of β -hydride elimination, and readdition steps with eventual formation of a π -allylpalladium complex and its coupling with a nucleophile (**Scheme 4**).^[11]

**Scheme 4**

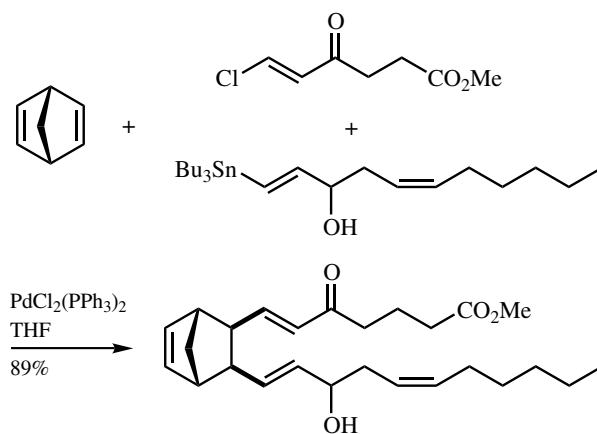
B.ii.b. Termination by Boronates (Heck–Suzuki Cascade), Stannanes (Heck–Stille Cascade), or Cyanide Ion. The Heck reaction of aryl or alkenyl halides with norbornene can be terminated by coupling with either a boronate (**Scheme 5**, Eq. 1)^[12] or an alkenylstannane (**Scheme 5**, Eq. 2)^[13] to stereoselectively formed vicinal biscoupling products with formation of two new C,C bonds.

Toward the synthesis of leukotriene model compounds, combinations of appropriately substituted alkenyl halides and alkenylstannanes have been used in this three-component reaction applied to norbornadiene (**Scheme 6**).^[14]

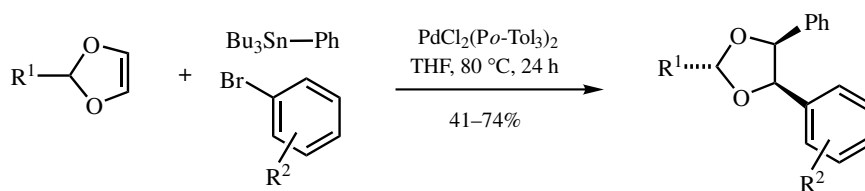
Besides norbornene and norbornadiene, 1,3-dioxolenes are possible partners in these ternary couplings. Hence, starting from unsubstituted or 2-substituted 1,3-dioxolene, tri-*n*-butylphenyltin, and various bromoarenes, *cis*-4,5-disubstituted 1,3-dioxolanes are obtained in good yields (**Scheme 7**).^[15]



Scheme 5



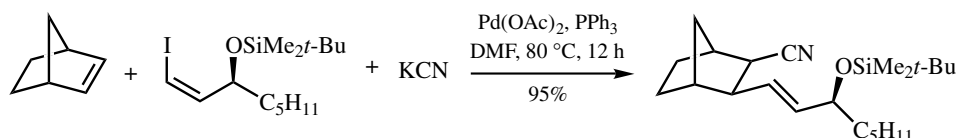
Scheme 6



R ¹	R ²	Yield (%)	R ¹	R ²	Yield (%)
H	H	74	H	<i>m</i> -COMe	62
H	<i>p</i> -NO ₂	57	H	<i>m</i> -Me	60
H	<i>p</i> -COMe	73	H	<i>m</i> -OH	55
H	<i>p</i> -CHO	70	H	<i>o</i> -NO ₂	41
H	<i>p</i> -Cl	67	H	<i>o</i> -Me	56
H	<i>p</i> -Me	65	H	<i>o</i> -OMe	64
H	<i>p</i> -OMe	57	Me	H	51
H	<i>p</i> -OH	59	<i>t</i> -Bu	H	61

Scheme 7

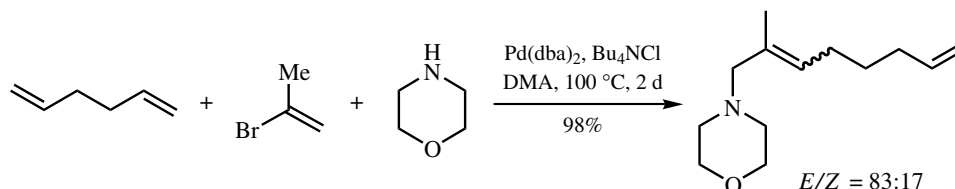
Alternatively, cyanide can act as a terminating nucleophile to form nitriles when starting from norbornene and an alkenyl halide (**Scheme 8**).^[16] Addition of the palladium intermediate of an enantiomerically pure haloalkene derivative to the double bond of norbornene produced only one of the two possible diastereomers, which was trapped by cyanide ion. Furthermore, the double bond in the product had (*E*)-configuration. Thus, the stereogenic center in the reactant fully controls the first newly formed stereogenic center in the product and, after the intermolecular carbopalladation step, an intramolecular 3-*exo-trig* carbopalladation followed by a cyclopropylcarbonyl- to homoallylpalladium rearrangement gives rise to the (*E*)-configured double bond of the product.



Scheme 8

B.iii. Termination by Amines

Early on, Heck and co-workers found that intra- and intermolecular coupling reactions of haloalkenes with alkenes in the presence of secondary amines gave allylamines.^{[17],[18]} Apparently, an intermediate π -allylpalladium complex is formed by rearrangement of the σ -homoallylpalladium intermediate (see above, **B.ii**) and in turn attacked by the nitrogen nucleophile. Excellent yields of tertiary allylamines are obtained in this three-component coupling (**Scheme 9**).^[19] As far as the outcome is concerned, analogous inter-intra- as well as fully intramolecular processes have been established (**Scheme 30**; see **Table 1**).^[20]



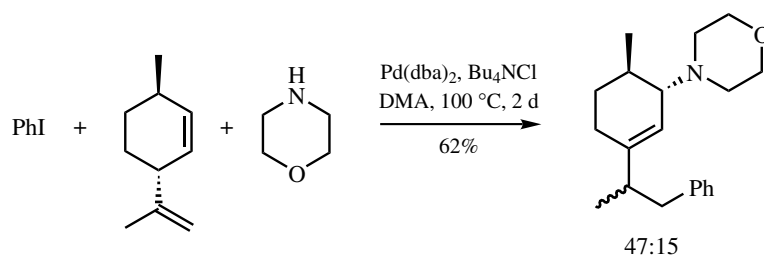
Scheme 9

At this point, it is interesting to note that nonconjugated dienes react first with one double bond and the π -allyl complex is formed by migration of the other double bond (**Scheme 10**).^[21] This three-component reaction can be carried out with a full range of linear and branched dienes. An appropriate composition of the palladium catalyst cocktail is crucial for good yields, since under certain conditions, which were used earlier for this transformation,^[22] substantial amounts of the diene or triene Heck coupling products were obtained.

Similar three-component reactions can also be carried out with bicyclopopylidene as an alkene partner. After carbopalladation across its double bond, rapid ring opening of the resulting 1-(cyclopropyl)palladium to a 3-cyclopropylidene-3-phenylpropylpalladium species occurs; subsequent rearrangement to a π -allylpalladium species and its trapping

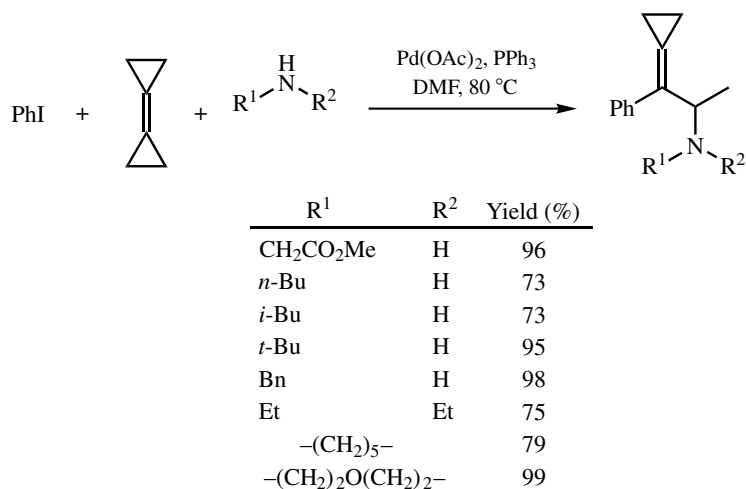
TABLE 1. Synthesis of Azabicyclo- and Azaspiroalkane Derivatives: Cascade Cyclization of 2-Halo-1, *n*-alkadienes with Tethered *N*-Tosylamino Groups^[79]

Starting Material ^a	Product	Temperature (°C)	Time (h)	Yield (%)
		65	48	78
		75	22	67
		75	n.r. ^b	ca. 50
		75	n.r.	ca. 50
		75	24	84
		60	48	58

^a Pd(OAc)₂, P(*o*-Tol)₃, Na₂CO₃, Bu₄NCl, DMF.^b n.r. = not reported.**Scheme 10**

with a primary or secondary amine then yields (73–99%) an allylamine with a methylene-cyclopropane end group (**Scheme 11**).^[23]

This transformation is related to the three-component reaction leading to 1-arylallylidenecyclopropane derivatives (see **Sect. IV.2.4**).^{[24],[25]}



Scheme 11

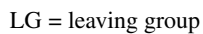
C. INTER-INTRAMOLECULAR CASCADE CARBOPALLADATIONS

An inter–intramolecular cascade carbopalladation involves a two-component coupling with subsequent trapping by a nucleophilic moiety already present in one of the two starting materials. Based on the findings of Heck and co-workers, Larock developed a methodology for the synthesis of a wide range of benzoannelated heterocycles starting from *o*-iodoamino and *o*-iodohydroxyarenes by reaction with various alkynes (to give indoles),^[26] certain alkenes such as norbornene,^[27] ethenylcyclopropanes and -cyclobutanes,^[28] allenes^{[29],[30]} (see also **Sect. V.2.1.10**), and 1,3-dienes^[31] as well as 1,4-dienes (**Schemes 12 and 13**).^[32] Allylic alcohols^[33] and enol triflates were also coupled with or without incorporation of carbon monoxide; however, these cascades do not include a termination by nucleophilic attack (for this chemistry see also **Sects. V.3.2 and V.3.3**).

This type of reaction can also be conducted with *o*-iodobenzylamines and -alcohols^{[30],[31],[34]} as well as with *o*-iodobenzoic acid derivatives to give lactones.^{[30],[34]} *o*-Halobenzaldehydes react also with alkynes to give indenones^[35]; however, this case might involve a C—H insertion of the preformed alkenylpalladium intermediate. Carbocyclic structures are attainable from *o*-iodophenylmalonates.^[30] In some cases, moderate to good enantiocontrol is achievable using chiral ligands of the bisoxazolinyl type.^[30]

C.i. Termination by Oxygen Nucleophiles

Since hydroxy groups do not interfere with palladium catalysts, the termination of carbopalladation cascades by oxygen nucleophiles has been employed in various cases. As

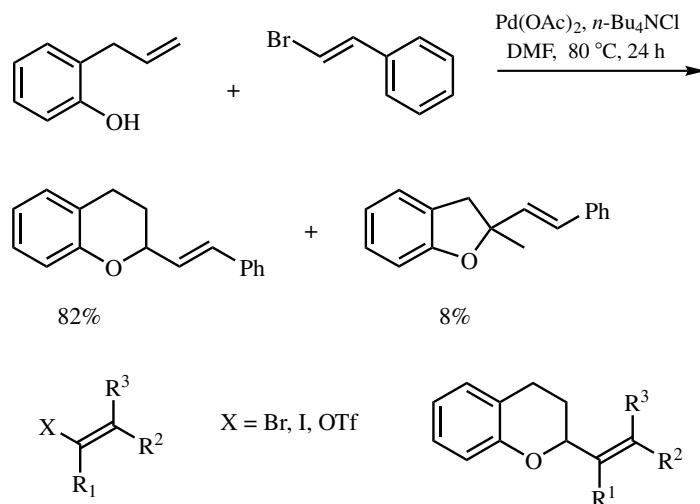


Scheme 12



Scheme 13

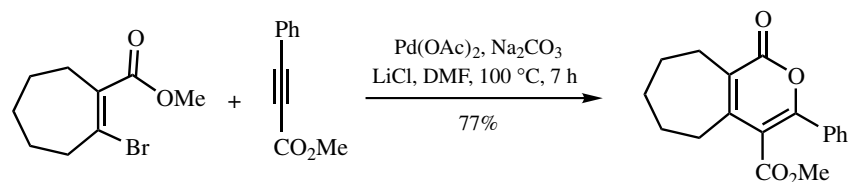
discussed above, the Pd-catalyzed couplings of alkenyl halides with alkenes can give rise to the formation of π -allylpalladium complexes, which can then be attacked by internal nucleophiles including hydroxy groups to yield various heterocyclic systems. For example, the coupling of *o*-allylphenol with β -bromostyrene as well as various other alkenyl and cycloalkenyl halides and triflates in each case predominantly yielded the correspondingly 6-substituted 1,2-benzodihydropyran derivatives (**Scheme 14**).^[36]



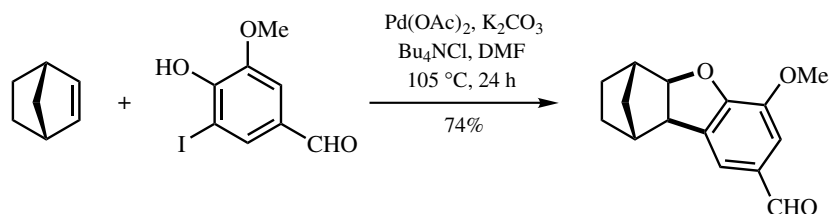
Scheme 14

α,β -Unsaturated or α -aryl esters with a β or an *ortho* leaving group (bromide, iodide, triflate) undergo coupling with internal alkynes to give substituted and ring-annulated 2-pyrone or isocoumarine derivatives, respectively, in good yields (**Scheme 15**).^{[37],[38]} As in other cases of alkyne couplings, the regioselectivity is very high with alkynes bearing a tertiary alkyl, an aryl, a trialkylsilyl, or other reasonably bulky groups to yield single products having the more bulky group in the position adjacent to the heteroatom. From the mechanistic point of view, the reaction is believed to occur via an attack of the carbonyl oxygen on the alkenylpalladium intermediate formed by addition of an aryl- or alkenylpalladium moiety to the alkyne.^[38]

The reactions of norbornene with *o*-iodo- and *o*-bromophenols proceed cleanly to give norbornane-annulated benzofurans (**Scheme 16**).^[27] The reactions of 1,4-dienes yield benzopyrans in good yields (**Schemes 12 and 13**).^[32]



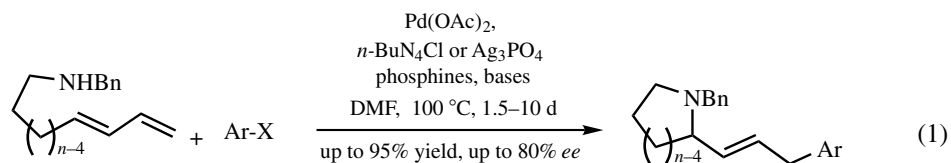
Scheme 15



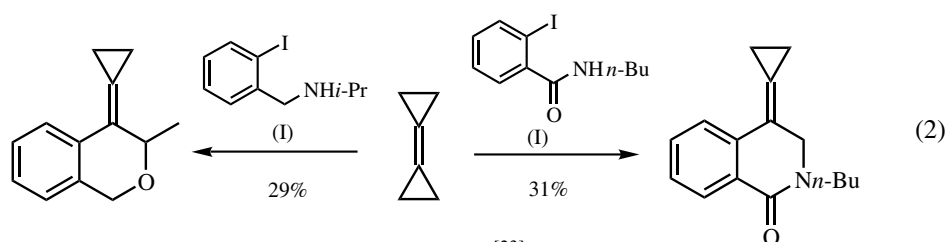
Scheme 16

C.ii. Termination by Nitrogen Nucleophiles

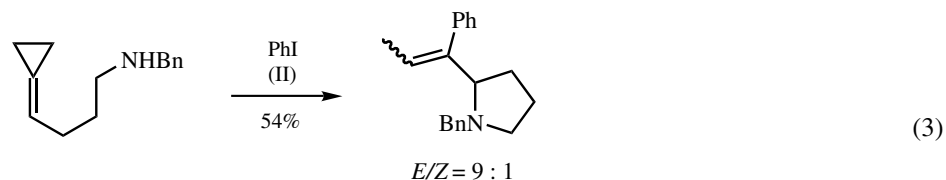
Because nitrogen-containing heterocycles are important building blocks for biologically active compounds including many natural products, efforts have been made to use an intermolecular C—C coupling with a subsequent internal heterocyclization. Thus, pyrrolidine derivatives are accessible by a cascade carbopalladation of a diene and intramolecular trapping of the intermediate π -allylpalladium complex by secondary amines. In this case, an efficient enantiocontrol has been achieved using chiral phosphine ligands (Scheme 17, Eq. 1).^[39] Similarly, the above mentioned three-component reaction with bicyclopropylidene (Scheme 11) has been performed with *o*-iodobenzyl alcohol to give a cyclopropylidene-substituted benzodihydropyran derivative (Scheme 17, Eq. 2). It is



$\text{Ar} = \text{Ph}, 2,6\text{-Me-C}_6\text{H}_3$; $\text{X} = \text{I}, \text{OTf}$
 $n = 5, 6$



(I): $\text{Pd}(\text{OAc})_2$, $(o\text{-Fur})_3\text{P}$, Et_3N , DMF, 80°C , 24 h.^[23]



$E/Z = 9 : 1$

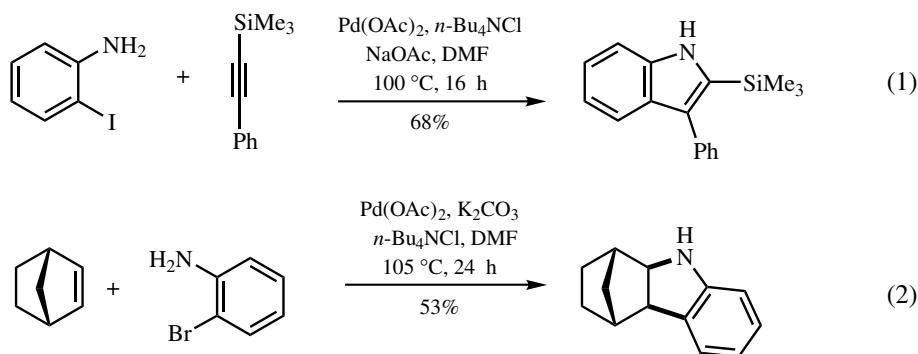
(II): $\text{Pd}(\text{dba})_2$, dppe , Et_3N , DMSO, 95°C , 42 h.^[41]

Scheme 17

interesting to note that even an *ortho*-positioned amide nitrogen is nucleophilic enough for an intramolecular attack.^{[23],[40]} An analogous reaction between a methylenecyclopropane derivative with a tethered benzylamino groups and phenyl iodide under palladium catalysis had previously been observed (**Scheme 17**, Eq. 3).^[41]

As mentioned before (see **Scheme 12**), indoles are attainable starting from *o*-iodoaniline and either an alkyne (**Scheme 18**, Eq. 1)^[42] or norbornene (**Scheme 18**, Eq. 2),^[27] respectively.

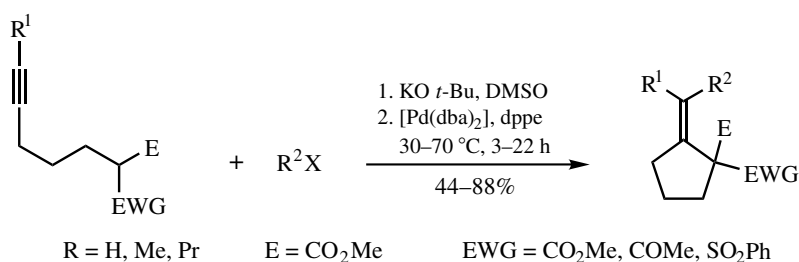
Quite a number of variations of this process have been reported in the past, for example, for the synthesis of medium-sized heterocycles.^[43]



Scheme 18

C.iii. Termination by Carbon Nucleophiles

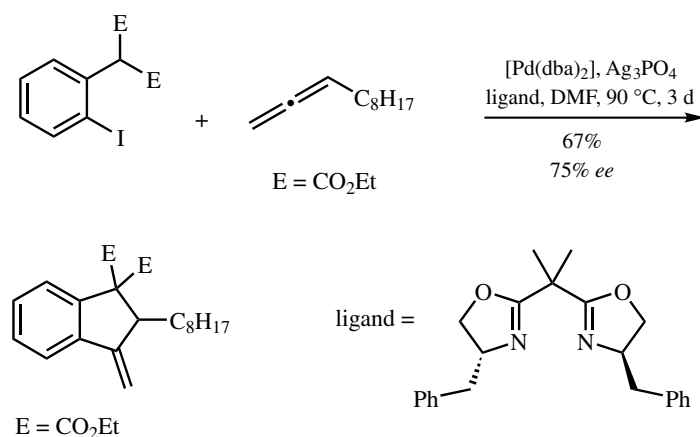
Intramolecular termination by carbon nucleophiles has been achieved with dialkyl malonate moieties. These cascade reactions, developed essentially by Balme, Gore, and colleagues, open an avenue especially to variously substituted methylenecyclopentane derivatives (**Scheme 19**,^[44] and **Sect. V.3.4**).



Scheme 19

This cyclization obviously does not proceed with an alkylation of a σ -alkenylpalladium complex but rather with a nucleophilic addition across the triple bond, which is activated by complexation with the arylpalladium halide intermediate. The (*E*)-configuration of the double bond clearly speaks in favor of this mechanism. More details of this reaction are described in **Sect. V.3.4**.

Besides these alkylations of soft nucleophiles with σ -alkenylpalladium intermediates, π -allylpalladium complexes, formed by carbopalladation of an allene with an arylpalladium halide intermediate, are able to cyclize by attacking a dialkyl malonate moiety (**Scheme 20**).^[30] Instead of allenes, which give methyleneindane derivatives, cyclic and acyclic 1,4-dienes have been employed to yield tetrahydronaphthalene derivatives in good yields.^[32]



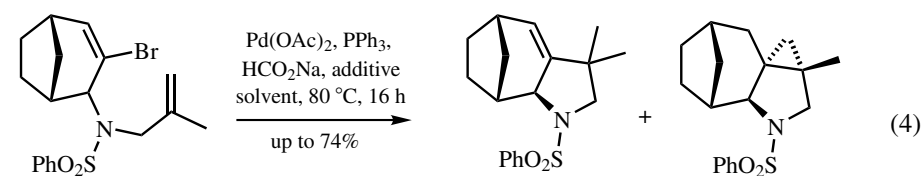
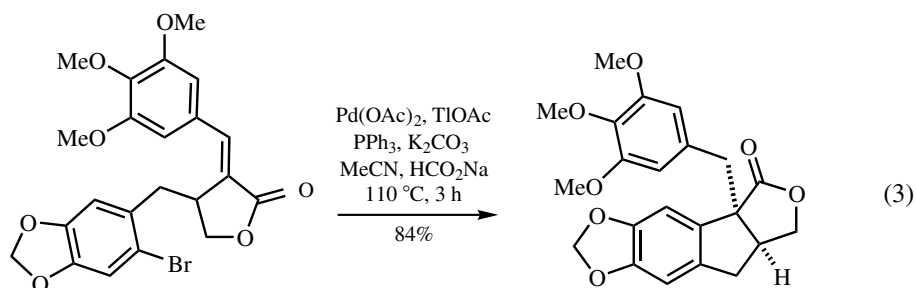
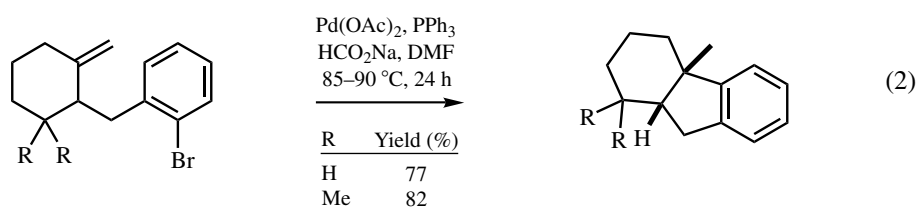
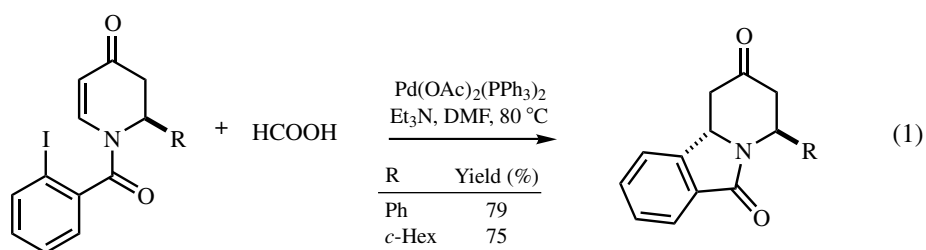
Scheme 20

D. INTRA-INTERMOLECULAR CASCADE CARBOPALLADATIONS

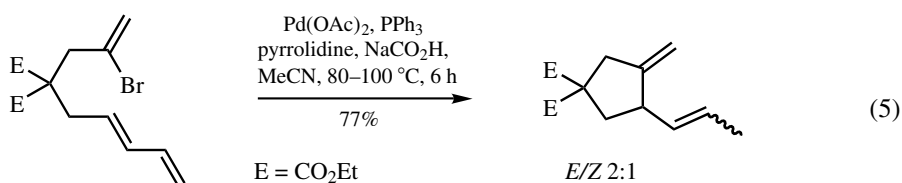
Intramolecular carbopalladations, which lead to five-, six-, and seven-membered rings very efficiently, have been combined with a subsequent intermolecular nucleophilic termination. In this case, rather unreactive nucleophiles such as acetates can be employed. This type of reaction has been termed an “anion capture” process by Grigg and co-workers implementing both ionic and non-ionic sources of the terminating agent.^{[45]–[47]}

D.i. Termination by Hydride

Intramolecular carbopalladations, as in the Heck reaction, with subsequent reduction by a hydride source have established themselves as an indispensable tool for the construction of various carbocyclic and heterocyclic skeletons. Such a reaction comes about when the *syn*-addition of an aryl- or alkenylpalladium species to a multiple bond leads to an intermediate that does not or cannot undergo a rapid *syn*- β -hydride elimination such as certain cycloalkyl- (**Scheme 21**, Eq. 1),^[48] neopentyl- (Eq. 2,^[49] Eq. 3,^[50] Eq. 4^[51]), or π -allylpalladium intermediates (Eq. 5).^[45] The most efficient reagents for the reduction are formic acid in the presence of secondary or tertiary amines and alkali metal formates such as sodium formate. In some cases tin hydrides have successfully been employed (**Scheme 33**, Eqs. 3–5).



Solvent	Additive	Yield (%)	Yield (%)
DMF	Et ₄ NCl	74	0
MeCN	AgClO ₄	67 ^a	33 ^a

^aRelative yields

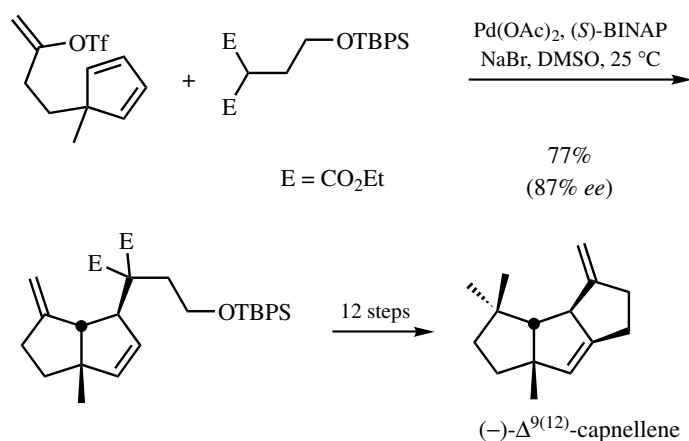
Scheme 21

D.ii. Termination by Carbon Nucleophiles

Intermolecular termination processes by carbon nucleophiles will be considered separately for reactions with soft nucleophiles (i.e., mostly stabilized enolates) and with organometallic compounds such as stannanes, boranes, and zincates.

D.ii.a. Termination by Soft Carbon Nucleophiles. Termination by stabilized enolates as carbon nucleophiles has mostly been achieved using dialkyl malonate enolates, which in general cause no problems in connection with palladium catalysts and have a high enough nucleophilicity.

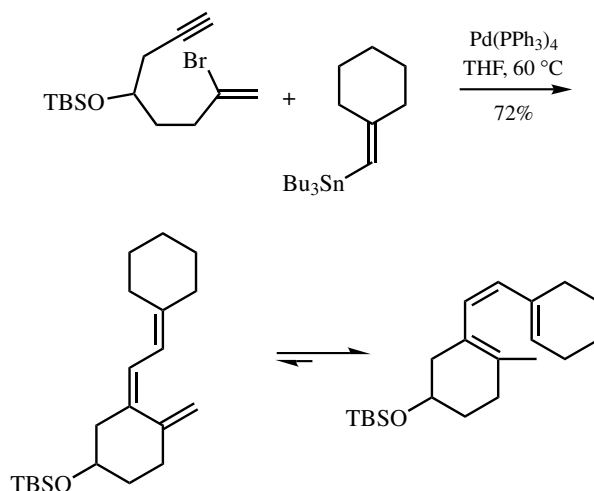
With this notion in mind, an elegant synthesis of the sesquiterpene (–)- $\Delta^{9(12)}$ -capnellene was developed starting from a cyclopentadienyl-substituted enol triflate. After insertion of the palladium into the carbon–oxygen bond of the starting material, the (*S*)-BINAP ligand on the palladium led to selective coordination to one of the two enantiotopic double bonds with subsequent cyclization to give the intermediate π -allyl complex. This was trapped stereoselectively by the external malonate enolate as a nucleophile due to interference of the bridgehead methyl group. Further elaboration gave the natural product in high optical purity (**Scheme 22**).^[52] The synthetic utility of this strategy has been demonstrated with various other examples.^[53]



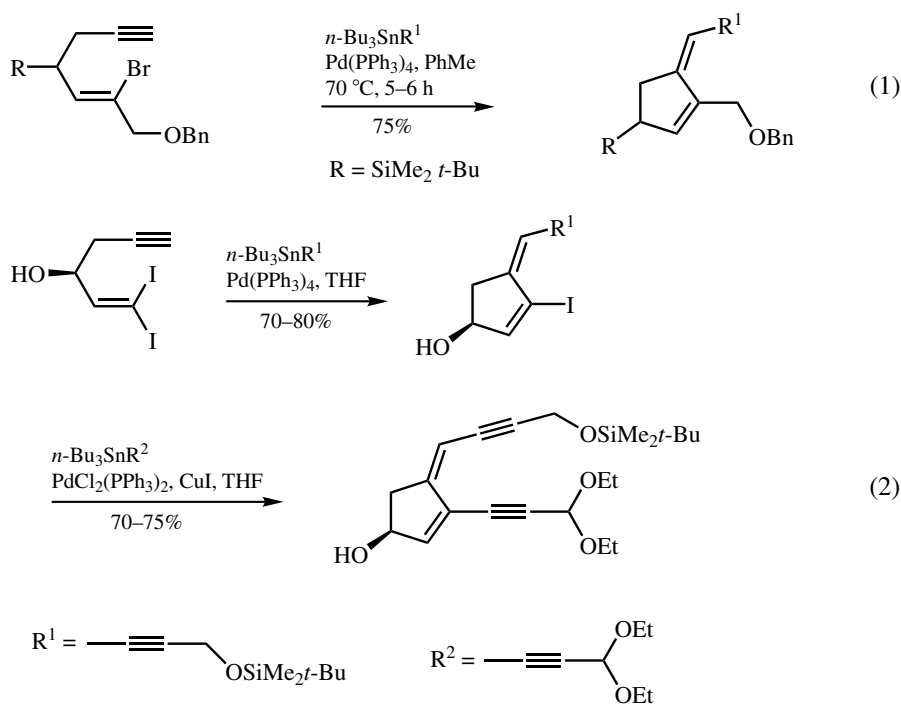
Scheme 22

D.ii.b. Termination by Stannanes (Heck–Stille Cascade). Stannanes have been used for a Heck–Stille cascade in various applications. The Pd-catalyzed cyclization of bromoenynes with subsequent trapping of the resulting σ -alkenylpalladium complex with an alkenyl- or alkynylstannane provides an elegant access to close precursors of calcitriol (**Scheme 23**).^[54]

The enediyne core structure of the neocarzinostatin chromophore has been assembled by combining an intramolecular carbopalladation starting from a bromoenediyne (**Scheme 24**, Eq. 1)^[55] or a 1,1-diiodoenediyne with a subsequent Stille coupling (**Scheme 24**, Eq. 2).^{[56],[57]} The latter synthesis of a dienediyne starting from the diiodoenediyne includes two Stille couplings, which can both be achieved in one step leading to an analogous dienediyne with identical substituents on both alkyne termini.



Scheme 23

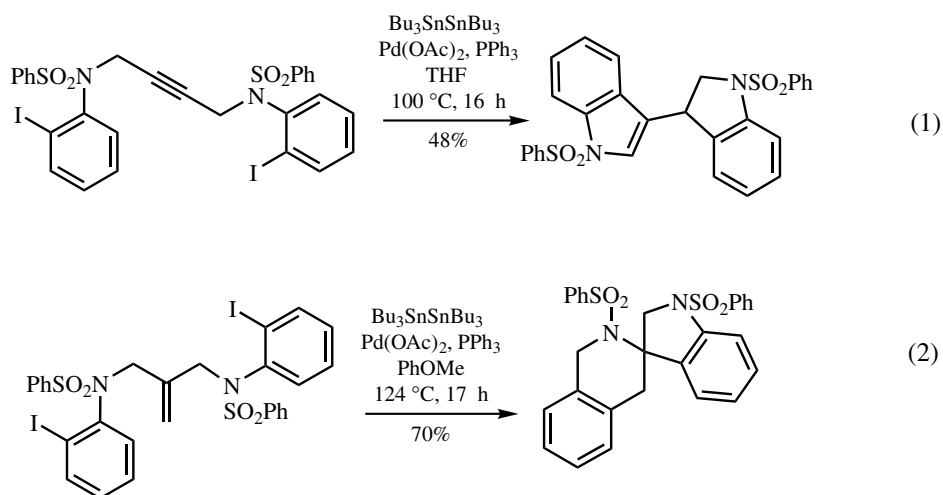


Scheme 24

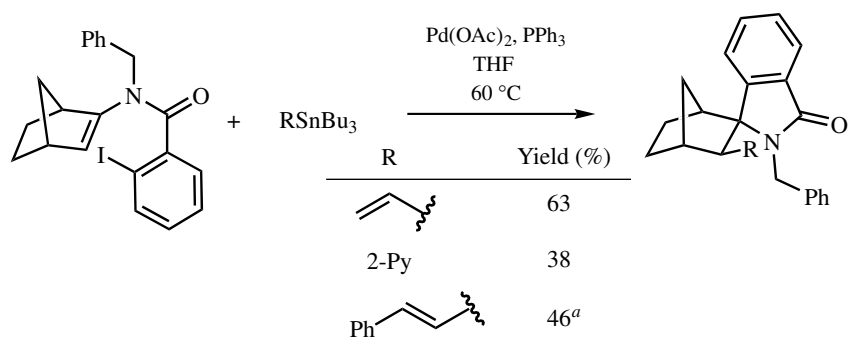
An analogous 5-*exo-dig* carbopalladation, performed on an iodoarene with an *ortho*-alkynylamino substituent in the presence of hexabutyldistannane, produces an alkenylstannane, which undergoes a second cyclization by intramolecular Stille cross-coupling with the second *o*-iodoaniline moiety in the molecule. The final product, though, arises by double bond migration (Scheme 25, Eq. 1).^[58] Alternatively, a 1,1-disubstituted alkene

moiety instead of a triple bond can play the role of the relay, in which case an unsymmetrical spiro compound is produced (**Scheme 25**, Eq. 2).

Similarly, the intramolecular arylation of a norbornene derivative produces a reasonably long-lived σ -norbornylpalladium species, which can subsequently be cross-coupled with an alkenylstannane to give interesting tricyclic systems (**Scheme 26**).^[59]



Scheme 25

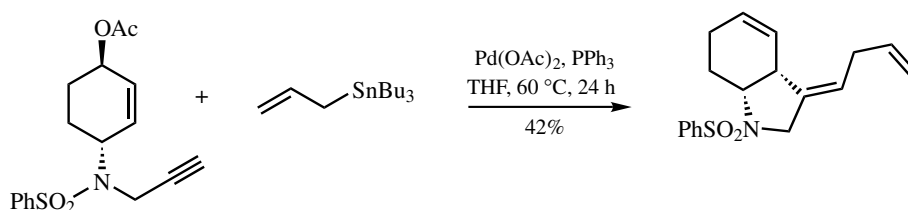


^a Mixture of diastereomers (1:1).

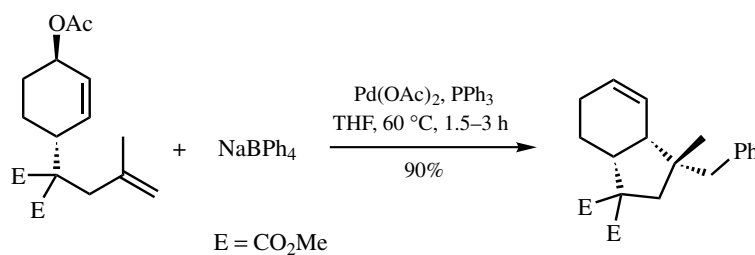
Scheme 26

The alkenylpalladium species resulting from electrophilic attack of a π -allylpalladium species, generated from an allyl acetate on a tethered alkynyl group, can also undergo an intramolecular Stille coupling with tributylallylstannane (**Scheme 27**).^[60]

D.ii.c. Termination by Boranes (Heck–Suzuki Cascade). Similarly, boranates and boronates are suitable reagents for the transfer of aryl or alkenyl groups to σ -alkyl-, σ -alkenyl-, and σ -arylpalladium complexes and hence are ideal for termination of cascade reactions. Tetraphenylboranate is the reagent of choice for the phenylation of organopalladium intermediates (**Scheme 28**).^[60]

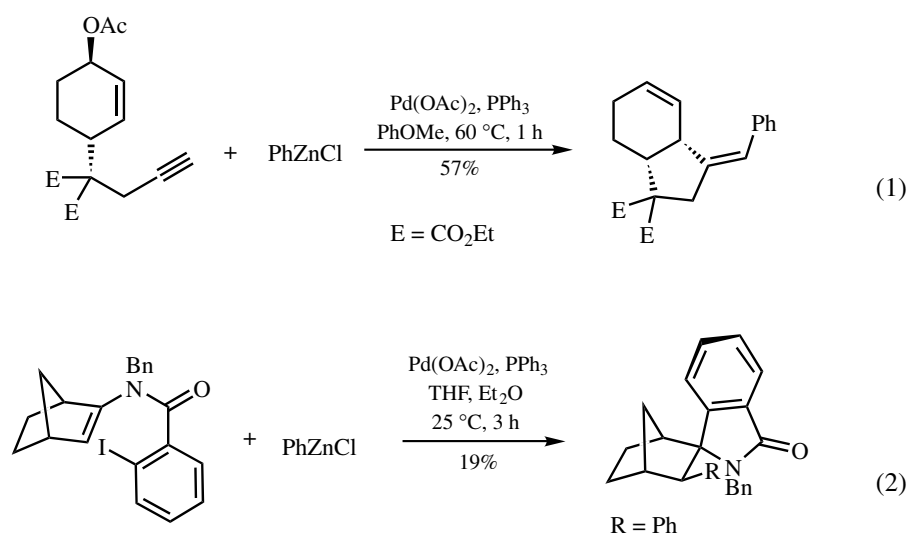


Scheme 27



Scheme 28

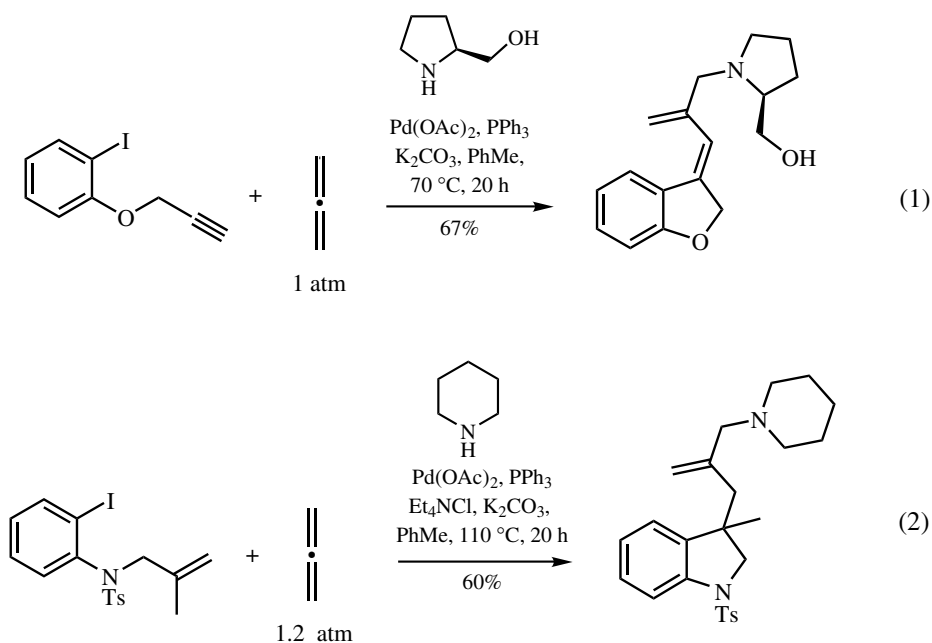
D.ii.d. Termination by Organozinc Compounds. Arylzinc halides, which are readily available directly from aryl iodides and zinc dust, or by transmetalation of arylmagnesium halides with zinc chloride, can play the same role as stannanes and boranes and be used to transfer aryl groups. The π -alkenyl- or σ -alkylpalladium intermediate can be generated by any of the above mentioned inter- or intramolecular processes (Scheme 29, Eq. 1,^[60] Eq. 2^[61]).^{[62],[63]}



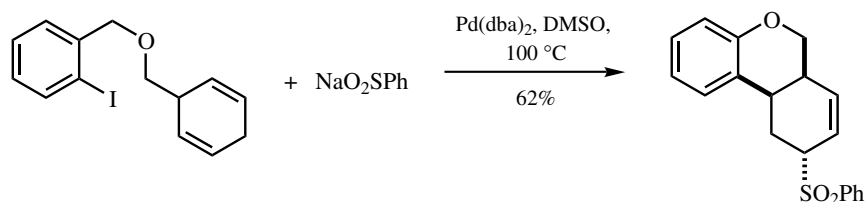
Scheme 29

D.iii. Termination by Nitrogen Nucleophiles

Termination by external nitrogen nucleophiles has been investigated for various systems (cf. Ref. [53]). Allenes, which are excellent relays for cascade reactions, give rise to the formation of π -allylpalladium complexes. The latter can be reacted in a straightforward manner with amines to yield highly functionalized allylamines (**Scheme 30**, Eqs. 1 and 2).^{[64],[65]}

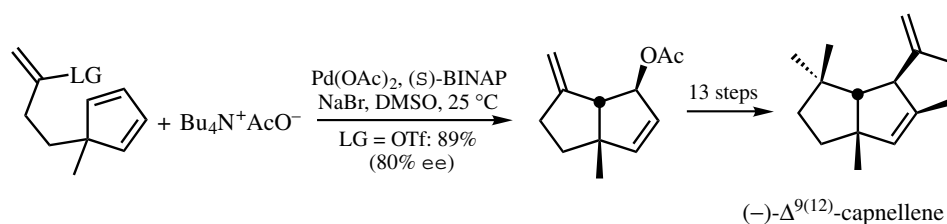
**Scheme 30****D.iv. Termination by Sulfur Nucleophiles**

Arylsulfinate anions have been employed as terminators of cascade carbopalladations.^[53] Starting from an iodoaryl-substituted 1,4-cyclohexadiene, treatment with a palladium catalyst led to an intermediate π -allyl complex, which was trapped with sodium benzenesulfinate to yield a tricyclic allylsulfone (**Scheme 31**).

**Scheme 31**

D.v. Termination by Oxygen Nucleophiles

Oxygen nucleophiles have not frequently been used as terminators in cascade carbometallation reactions.^[53] The intramolecular carbopalladation starting with an iodo- or trifluoromethylsulfonyloxyalkenyl-substituted derivative in the presence of tetrabutylammonium acetate led to a suitable precursor of the sesquiterpene (–)- $\Delta^{9(12)}$ -capnellene. In this case, desymmetrization of the prochiral precursor was achieved using (*S*)-BINAP as the ligand on the palladium catalyst (**Scheme 32**).^[52]

**Scheme 32****E. INTRA–INTRA–INTERMOLECULAR CASCADE CARBOPALLADATIONS**

Intra–intramolecular cascade reactions combined with termination by an external nucleophile provide access to various kinds of ring systems.

E.i. Termination by Hydride

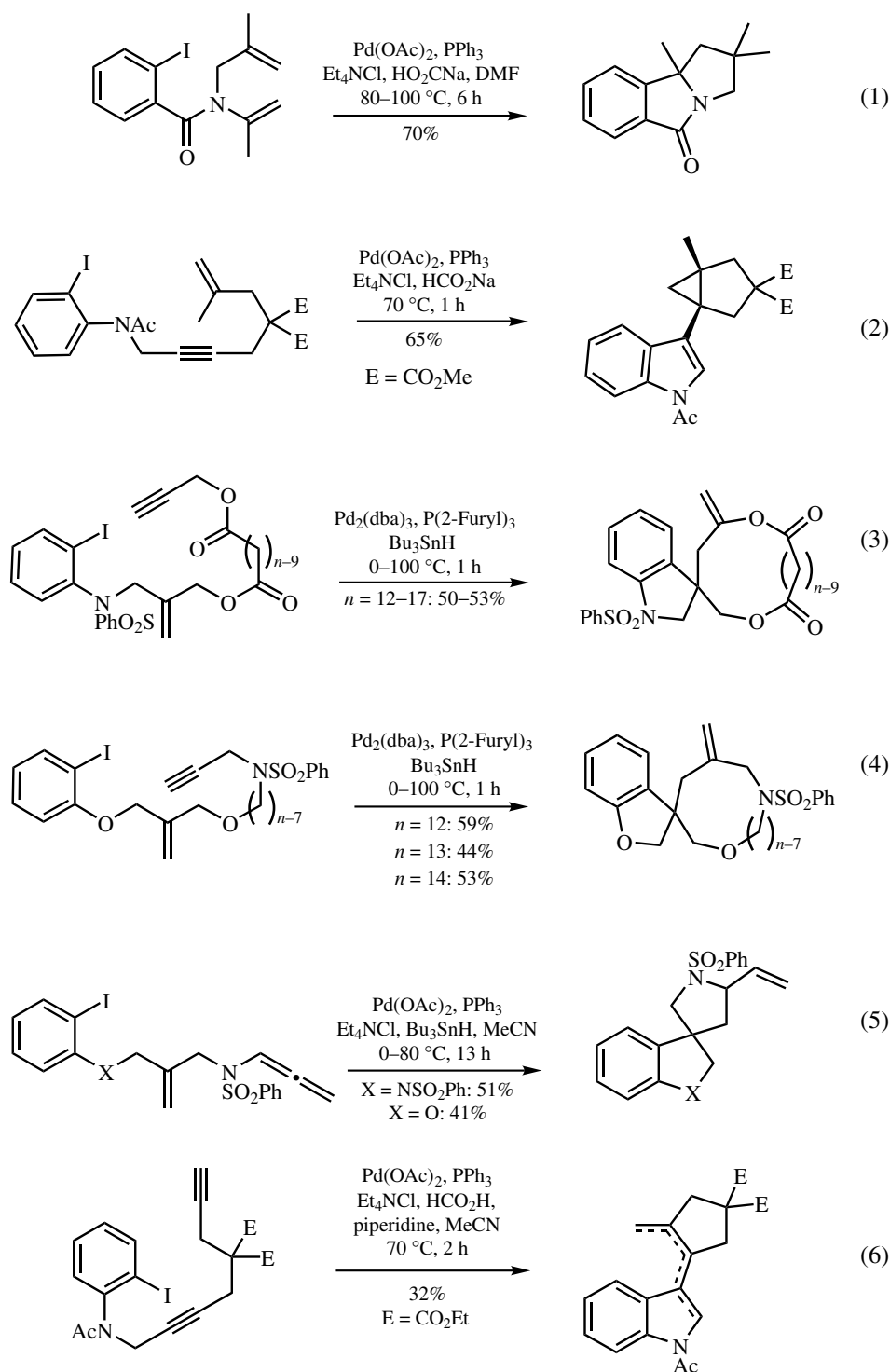
The Heck coupling with hydride trapping can be applied in all cases, in which neopentyl- (**Scheme 33**, Eqs. 1 and 2),^{[66]–[68]} σ -alkenyl- (**Scheme 33**, Eqs. 3, 4,^[69] and 6–8^[70]), or π -allylpalladium (**Scheme 33**, Eq. 5)^[71] are produced. Besides the presented examples, a vast number of other applications have been developed in the past.^{[4],[63],[72],[73]}

E.ii. Termination by Sulfur Nucleophiles

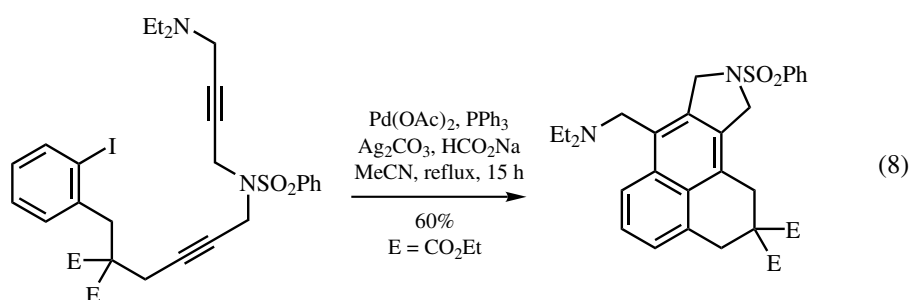
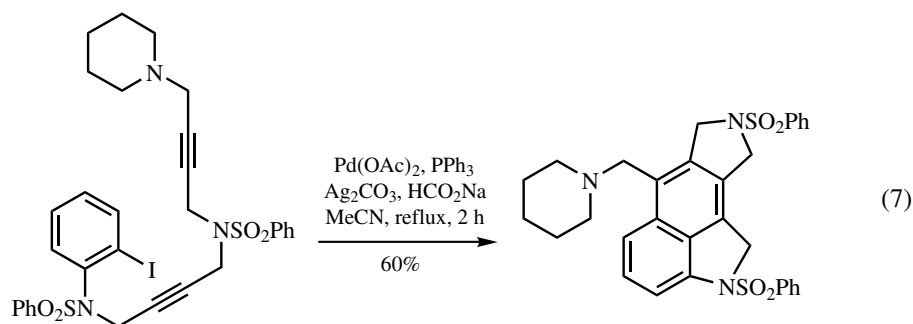
There are hardly any examples for the use of sulfur nucleophiles in terminating cascade carbopalladation sequences, in contrast to oxygen and especially nitrogen nucleophiles. One reason for this might be found in the problems associated with the high degree of coordination of the palladium with the less oxidized sulfur nucleophiles such as thiols. However, arylsulfonates are excellent nucleophiles for cascade termination reactions, as has been shown by Grigg et al. (**Scheme 34**).^[74]

F. ALL-INTRAMOLECULAR CASCADE REACTIONS

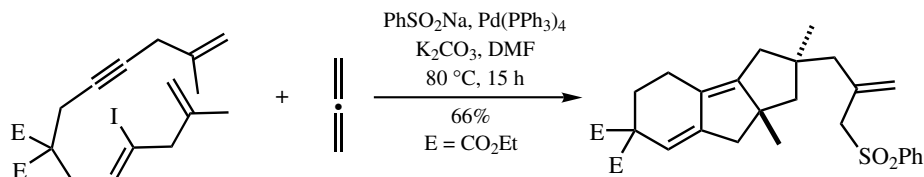
All-intramolecular cascade reactions provide an access to various ring systems with at least two newly formed rings. Stereoelectronic effects exerted by the metal and its ligands are remarkably high, and a vast number of accessible oligocyclic structures can be conceived. Interestingly, compared with a number of known examples for cascade



Scheme 33



Scheme 33 (Continued)



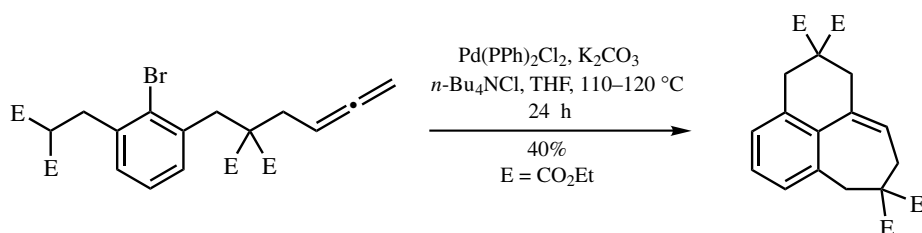
Scheme 34

reactions with termination by π -bond systems (Sect. IV.3.1), only a relatively small number of all-intramolecular cascade transformations with termination by nucleophilic attack have been carried out so far.

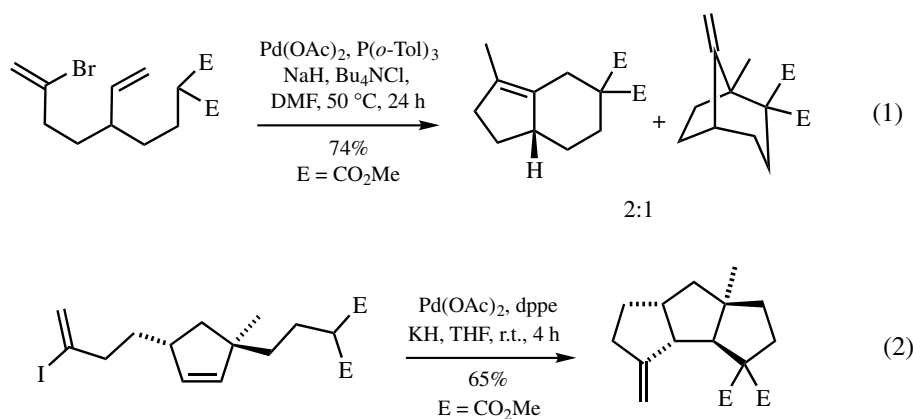
F.i. Termination by Carbon Nucleophiles

F.i.a. Soft Nucleophiles. As mentioned before, dialkyl malonate enolates are useful terminators for cascade carbopalladations, leading eventually to π -allylpalladium intermediates. This has been demonstrated by Ma and Negishi in their studies regarding allenes as relays for medium- to large-ring synthesis (Scheme 35).^[75]

However, even σ -alkylpalladium intermediates formed upon carbopalladation of simple alkenes, which are usually prone to rapid β -hydride elimination, may serve as relays as demonstrated in the synthesis of bicyclic (Scheme 36, Eq. 1)^[76] and tricyclic compounds (Scheme 36, Eq. 2),^{[77],[78]} the latter consisting of three annelated



Scheme 35

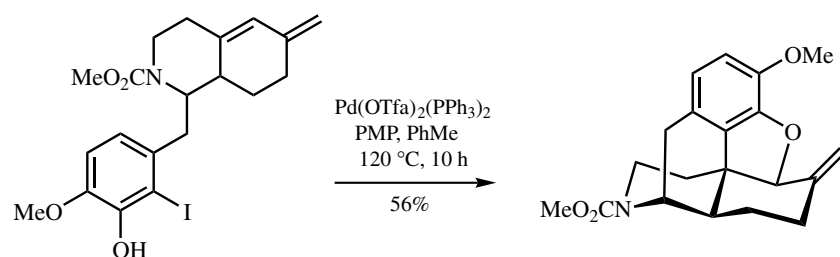


Scheme 36

five-membered rings (see also **Scheme 22**). The reason for the retarded β -hydride elimination might be found in a precoordination of the nucleophile, which has to be deprotonated by strong bases, to the σ -alkenylpalladium complex favoring the formation of a π -allyl complex.

F.iii. Termination by Nitrogen Nucleophiles

The same type of cascade cyclization was developed for 2-halo-1, *n*-dienes tethered to *N*-tosylated primary amines leading to various bi- and spirocyclic heterocycles (**Table 1**).^[79]



Scheme 37

F.iii. Termination by Oxygen Nucleophiles

Hong and Overman reported the intramolecular termination of cascade reactions by oxygen nucleophiles in their studies on a novel synthesis of morphine (**Scheme 37**).^[80] Starting from an iodophenol derivative tethered with an iodophenol silyl ether, intramolecular carbopalladation provided a bicyclic π -allylpalladium intermediate, which in turn was attacked by the oxygen functionality (**Scheme 37**).

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