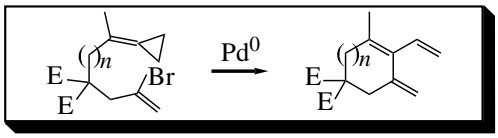

IV.3 Palladium-Catalyzed Tandem and Cascade Carbopalladation of Alkynes and 1,1-Disubstituted Alkenes

IV.3.1 Palladium-Catalyzed Cascade Carbopalladation: Termination with Alkenes, Arenes, and Related π-Bond Systems

STEFAN BRÄSE and ARMIN DE MEIJERE

A. INTRODUCTION

Domino or cascade reactions provide valuable approaches, especially to various carbo- and heterocyclic 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, the termination of these processes by alkenes, arenes, and related π-bond systems such as alkynes and allenes will be described. A cascade Heck reaction is considered to consist of an oxidative addition of a heteroatom–carbon bond to palladium (starter), carbopalladation of a nonaromatic carbon–carbon double or triple bond without immediate dehydropalladation (relay), one, two, or more further carbopalladation(s) of a carbon–carbon double or triple bond, and eventually ensuing dehydropalladation. Crucial for a cascade reaction of this kind to occur is the blockage or retardation of a dehydropalladation at one of the intermediate stages by using 1,1-disubstituted alkenes and appropriately substituted cycloalkenes, bicycloalkenes, or alkynes as relays since they give kinetically stable alkyl- or alkenylpalladium intermediates, respectively.

B. INTER–INTRAMOLECULAR CASCADE CARBOPALLADATIONS

B.i. Termination by Alkenes

Five-membered ring closure has been observed when *o*-halostyrene derivatives were coupled with alkenes under palladium catalysis.[1] Apparently an intramolecular carbopalladation

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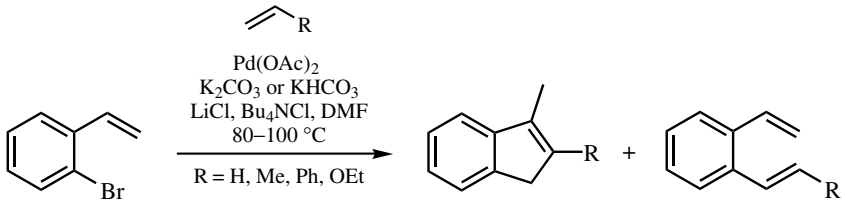
with 5-*exo-trig* ring closure can favorably compete with β-hydride elimination in the intermediate β-(*o*-ethenylphenyl)ethylpalladium halide. This reaction mode for the halostyrene is observed especially under Jeffery conditions when the alkene is ethene, propene, or an alkenyl ether (R = H, Me or OR) (**Scheme 1**).[1] Under the same conditions, however, *o*-dibromobenzene gives very high yields of *o*-dialkenylbenzene derivatives (see **Sect. IV.2.1**).[2],[3]

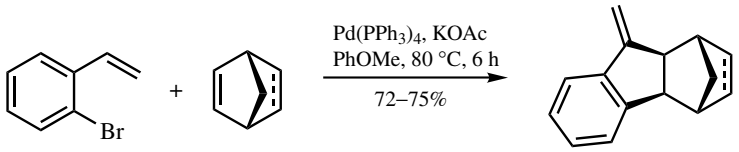


R	Base, Temperature	Yield (%) Indene	Yield (%) Dialkenylarene
H	$KHCO_3$, 100 °C	59	12
Me	$KHCO_3$, 100 °C	13	38
Ph	$KHCO_3$, 100 °C	2(53)[a]	12
OEt	K_2CO_3, 80 °C	49(9)[b]	0

[a] Mixture of double bond isomers.
[b] Mixture of regioisomers.

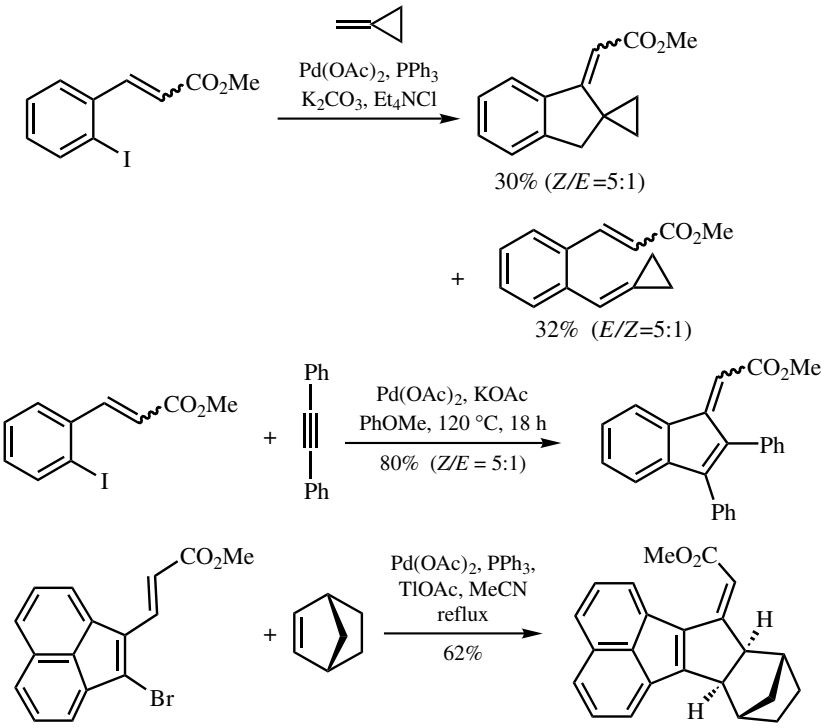
Scheme 1

When the carbopalladated relay is less prone to undergo β-hydride elimination (as, e.g., a corbopalladated methylenecyclopropane moiety) or the β-hydride elimination is even completely blocked [as, e.g., an alkyne, norbornene (**Scheme 2**)[4], or acenaphthylene (**Scheme 3**)] and the respective cyclopentannelation products can be isolated in moderate to good yields (**Scheme 3**).[5]



Scheme 2

Yet another type of cyclization was observed for *o*-bromostilbenes, which actually competes with the second coupling step of *o*-dibromobenzene with styrene when only 1 equiv of styrene is used. *o*-Bromostilbene and substituted analogs, prepared from *o*-bromobenzaldehydes by Wittig–Horner–Emmons olefinations, undergo efficient



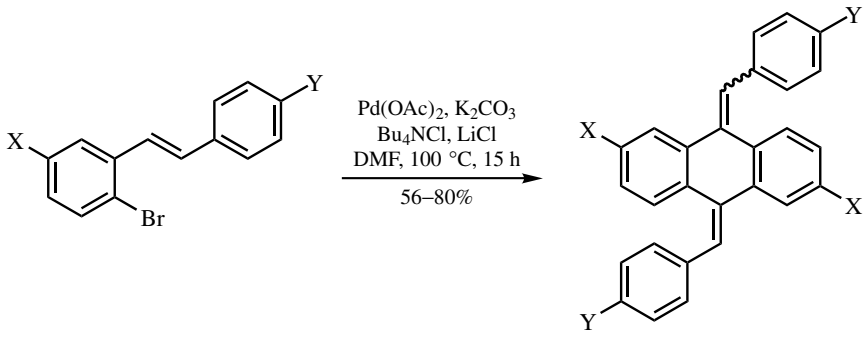
Scheme 3

dehydrobrominative cyclodimerization to (*E/Z*)-9,10-dibenzylidene-9,10-dihydroanthracenes (**Table 1**). The (*Z*)-diastereomers of the parent compound—characterized by an X-ray crystal structure analysis—and its dimethyl derivative preferentially crystallize from the crude mixtures, while the (*E*)-diastereomers could never be obtained pure in crystalline form. When heated to over 120 °C in solution, the (*Z*)-form isomerizes to the (*E*)-form and back (**Scheme 4**).[6]

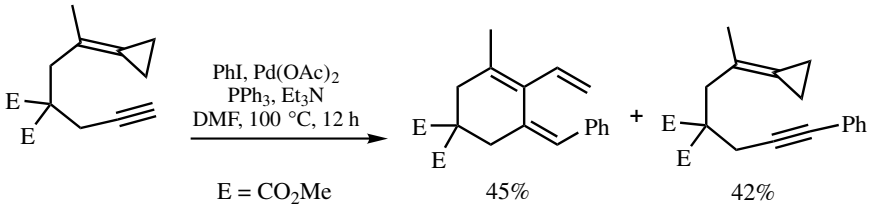
Carbopalladation by an arylpalladium iodide across the triple bond of a 1,6-enyne with a methylenecyclopropane terminus under Heck conditions led to a phenyl-substituted cross-conjugated triene (a so-called dendralene) along with terminally phenylated enyne (**Scheme 5**).[7]

TABLE 1. Inter–Intramolecular Cascade Heck Reaction to Form 9,10-Dibenzylidenedihydroanthracenes (for Details See Scheme 4)

Y	X	Yield (%)	*E/Z*
H	H	80	2.9:1
Me	H	75	1:2
OMe	H	70	1:2
CO_2Me	H	72	1:1
NO_2	H	56	1.8:1
H	CO_2Et	78	≈1:1
OMe	CO_2Et	64	≈1:1

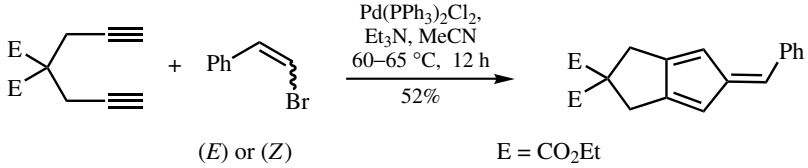


Scheme 4



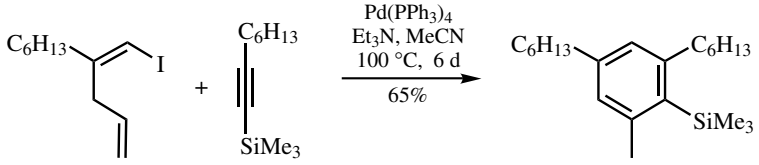
Scheme 5

An inter–intra–intermolecular cascade coupling of a 1,6-diyne with (*E*)- or (*Z*)-β-bromostyrene led to five-membered ring-annelated fulvenes (**Scheme 6**).[8],[9] As in many other cases with a formal [2 + 2 + 2] assembly using a terminal alkyne as terminator, the six-membered ring was not observed.



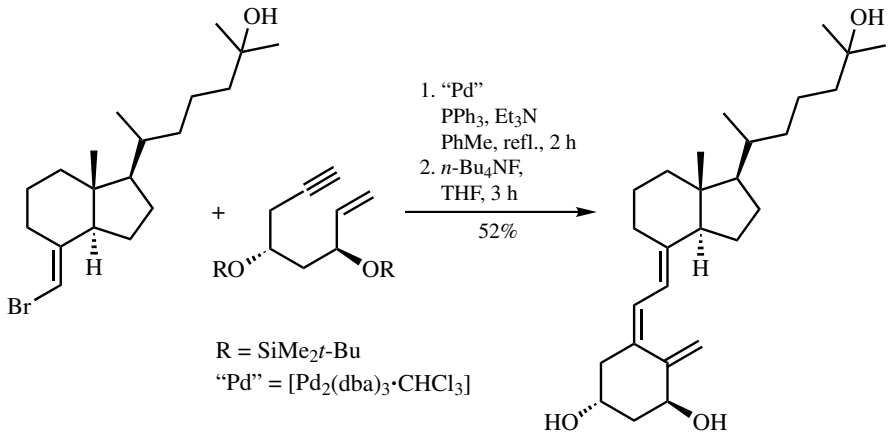
Scheme 6

However, highly substituted arenes are attainable from iododienes and alkynes with a high degree of regioselectivity (**Scheme 7**).[10] Apparently, the primarily formed trienes rearrange to the aromatic system.



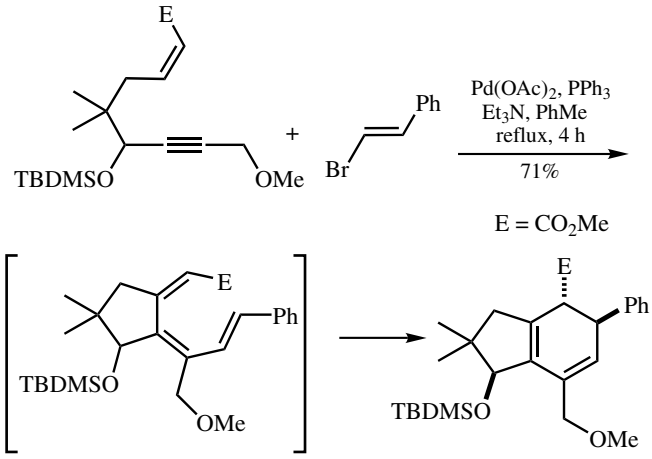
Scheme 7

An inter–intramolecular cascade starting with a bromoalkene and a 1,7-enyne was developed as an elegant access to calcitriol (**Scheme 8**).[11],[12]



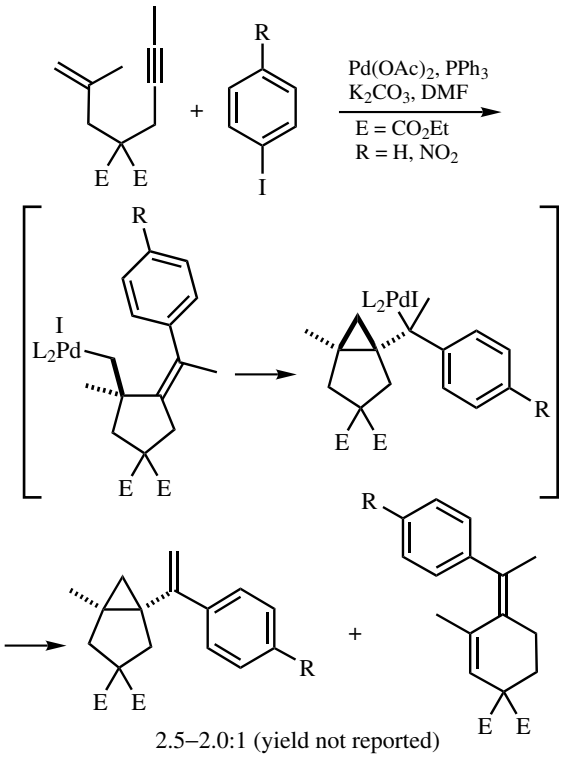
Scheme 8

A similar assembly starting with β-bromostyrene and a 1,6-enyne gave rise to a five-membered ring-annelated cyclohexadiene formed by a subsequent 6π-electrocyclization of the intermediate (*E,Z,Z*)-configurated 1,3,5-hexatriene. The disrotatory electrocyclization placed the two substituents on opposite sides of the six-membered ring (**Scheme 9**).[13]



Scheme 9

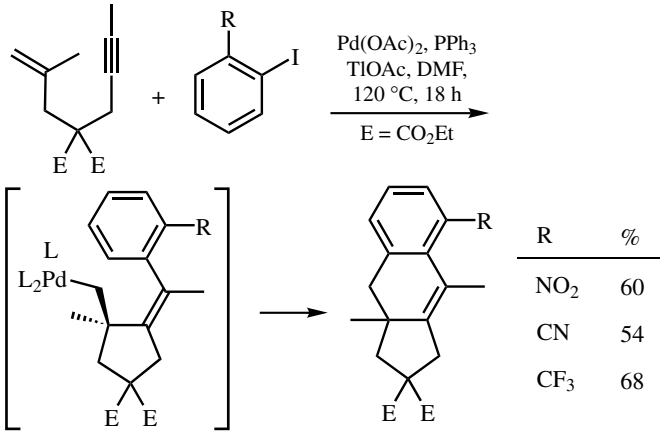
2-Substituted 1,6-enynes react with iodobenzene and *p*-nitroiodobenzene according to a different pattern. After the inter- and subsequent intramolecular carbopalladation, the palladium residue ends up in a neopentyl position with a γ,δ double bond. An ensuing 3-*exo-trig* carbopalladation then leads to a cyclopropylcarbinylpalladium halide that can undergo rearrangement with subsequent β-hydride elimination to yield a benzylidenecyclohexene or direct β-hydride elimination to give a bicyclo[3.1.0]hexane derivative (**Scheme 10**).[14]



Scheme 10

B.ii. Termination by Arenes

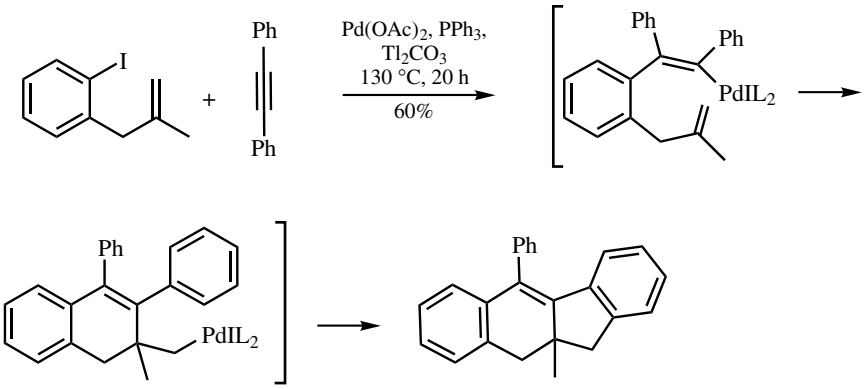
Remarkably, iodoarenes with electron-withdrawing substituents in the *ortho*-position and 1-iodonaphthalene react with the same enyne under slightly different conditions with *ortho*-C—H activation and cyclization to yield tri- or tetracyclic systems incorporating the aromatic ring (**Scheme 11**).[14],[15]



R	%
NO_2	60
CN	54
CF_3	68

Scheme 11

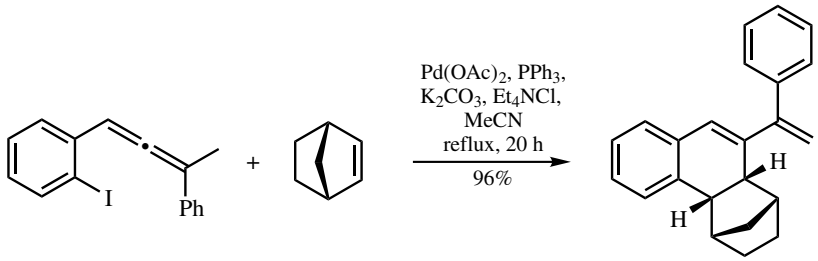
The carbopalladation of a triple bond is faster than that of a double bond, even when the alkene is tethered to the initially formed arylpalladium halides. This is exemplified by the formation of a tetracyclic system from *o*-isobutenyliodobenzene and diphenylethyne. This process is also terminated by *ortho* attack of the intermediate neopentyl-type alkylpalladium halide on one of the arene rings (**Scheme 12**).[16]



Scheme 12

B.iii. Termination by Allenes

Since strained alkenes and cycloalkenes are particularly good ligands for palladium, even an *ortho*-allenyl-substituted arylpalladium iodide will first carbopalladate a norbornene intermolecularly before the allenyl unit intercepts the relay norbornylpalladium species intramolecularly (**Scheme 13**).[17]



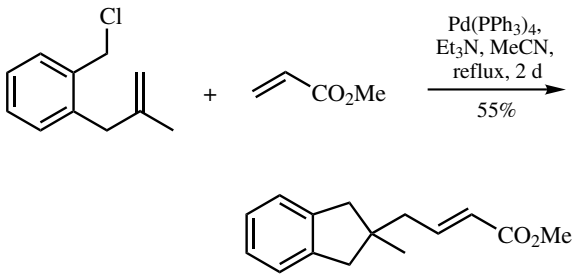
Scheme 13

C. INTRA–INTERMOLECULAR CASCADE CARBOPALLADATIONS

Intramolecular carbopalladations usually are fast processes, which are terminated by dehydropalladation unless the carbopalladation leads to an alkenyl- or neopentylpalladium intermediate, in which cases cascade carbopalladation sequences can be set off with other externally or internally available π-systems.

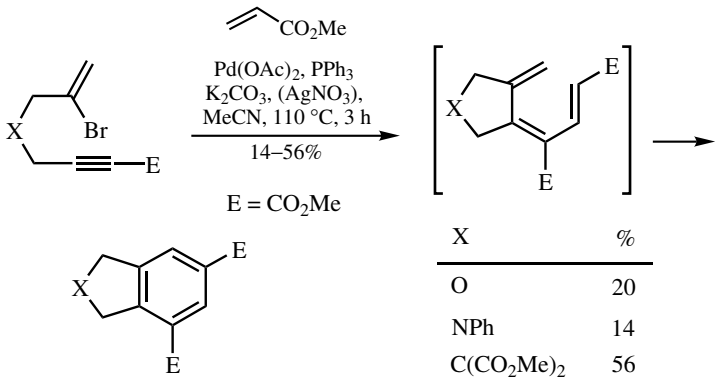
C.i. Termination by Alkenes

Alkenes are the most common terminators for intra–intermolecular cascade processes. This is exemplified by the intramolecular benzylpalladation leading to a neopentyl relay with ensuing termination by methyl acrylate yielding a 2,2-disubstituted indane (**Scheme 14**).[18]



Scheme 14

The intramolecular carbopalladation starting from a 2-halo-1,6-enyne leads to a terminal alkenylpalladium halide relay that can be trapped by an external alkene or alkyne. With the former, the cascade process leads to a 1,3,5-hexatriene that undergoes rapid 6π-electrocyclization to a five-ring-annelated cyclohexadiene and this, in turn, is easily dehydrogenated to the corresponding aromatic compound (**Scheme 15**).[19] With an external alkyne trapping the intermediate, a 1,3,5-hexatrienylpalladium intermediate will be formed and can either cyclize by intramolecular carbopalladation or 6π-electrocyclization before termination by dehydropalladation will occur.[8]

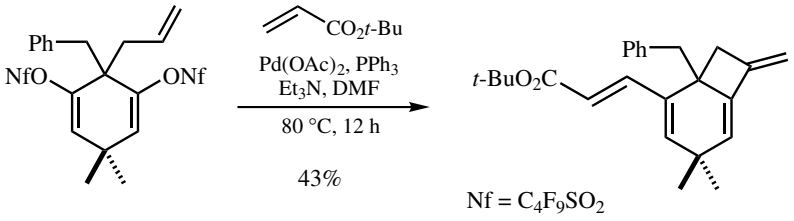


X	%
O	20
NPh	14
$C(CO_2Me)_2$	56

Scheme 15

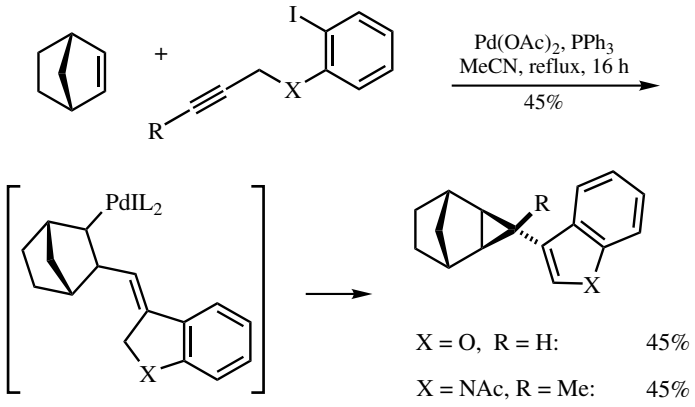
Starting from dimedone, 3-allyl-substituted cyclohexa-1,4-diene-2,4-diyl bisnonafluorobutanesulfonates have been prepared in four efficient steps. These 1,5-hexadienes under palladium catalysis first undergo intramolecular carbopalladation followed by dehydropalladation to yield a 8-methylenebicyclo[4.2.0]octa-1,4-dien derivative, which subsequently couples intermolecularly with added *tert*-butyl acrylate. In the presence of

(*R,R*)-BINAP as a chiral ligand, the product was obtained with a moderate enantiomeric excess (up to 53% ee) (**Scheme 16**).[20]



Scheme 16

Norbornene can serve as an excellent external relay, for example, for the alkenylpalladium species first formed by intramolecular carbopalladation of an *ortho*-alkynyl-substituted arylpalladium halide. The 2-alkenylnorbonylpalladium halide formed by intermolecular carbopalladation then undergoes another intramolecular carbopalladation, this one in a 3-*exo-trig* mode, and subsequent β-hydride elimination terminates the cascade process to yield a cyclopropanated norbornene derivative (**Scheme 17**).[21],[22]



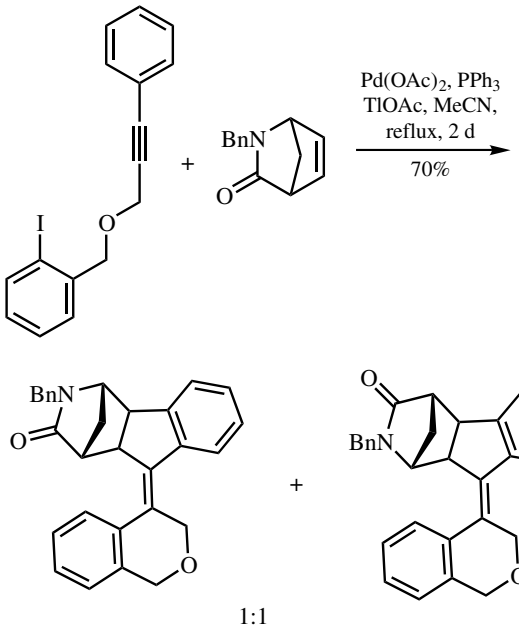
Scheme 17

C.ii. Termination by Arenes

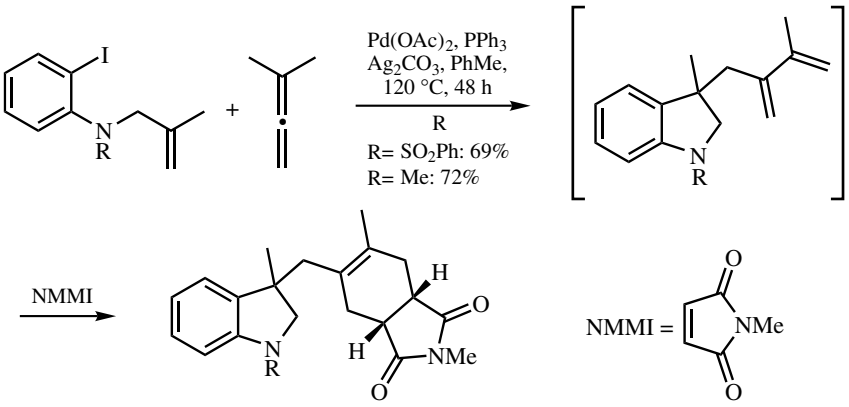
When the *ortho*-alkynyl tether on the iodoarene bears a terminal aryl group the cascade process after the intra–intermolecular carbopalladation sequence may be terminated by an *ortho* attack of the norbornylpalladium intermediate on the previously terminal aryl group (cf. **Scheme 10**) to yield an oligocyclic system (**Scheme 18**).[22]

C.iii. Termination by Allenes

The intra–intermolecular cascade can also be terminated with an external allene, like 1,1-dimethylallene, leading to a 2,3-disubstituted 1,3-diene that can subsequently be trapped by an added dienophile in a Diels–Alder reaction (**Scheme 19**).[23]



Scheme 18

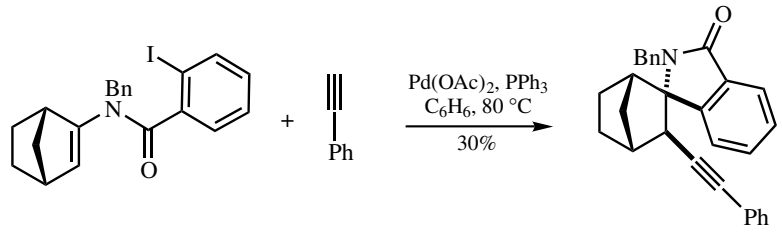


Scheme 19

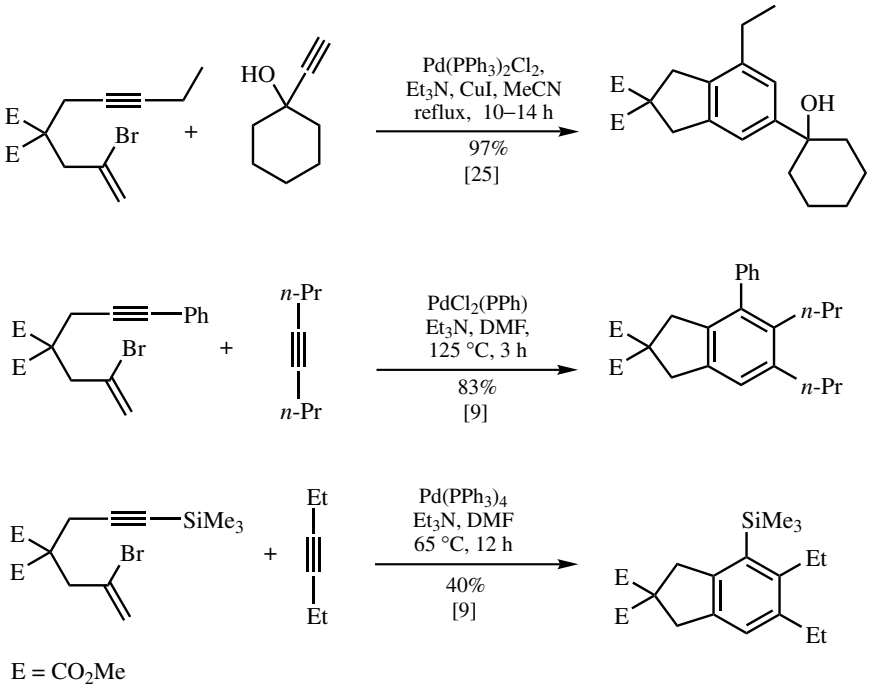
C.iv. Termination by Alkynes

A norbornylpalladium intermediate, for example, generated in an intramolecular carbopalladation, may react with an external terminal alkyne in terms of a simple C_{sp^3}–C_{sp} cross-coupling reaction (**Scheme 20**).[24]

On the other hand, an alkenylpalladium intermediate formed by intramolecular carbopalladation from a 2-bromo-1-en-6-yne carbopalladates an external mono- or disubstituted alkyne, and the cascade process is terminated by cyclization of the 1,3,5-hexatrienylpalladium intermediate through intramolecular carbopalladation or 6π-electrocyclization and ensuing dehydropalladation (**Scheme 21**).[8],[9],[25]



Scheme 20



Scheme 21

D. ALL-INTRAMOLECULAR CASCADE CARBOPALLADATIONS

Systems that contain a haloalkene starter, at least one relay, and an alkene or arene terminator in one and the same molecule can undergo a Pd-catalyzed cascade reaction involving two or more intramolecular carbopalladations and termination by dehydropalladation. The increase in molecular complexity is particularly impressive in such cases, in which up to seven new carbon–carbon bonds and also new cycles have been formed in a single procedural step. Various combinations of reactive units and geometries have been applied, and although most of the mechanics are now well understood, a certain flair of unpredictability still remains, especially as one proceeds to unprecedented combinations of ring sizes to be stitched or zipped together. A variety of fascinating cascade reactions consisting of at least one and often more than one intra- or intermolecular cross-coupling reaction as well as possibly one or more other reaction types have been developed by several groups. Among the ones that achieve the

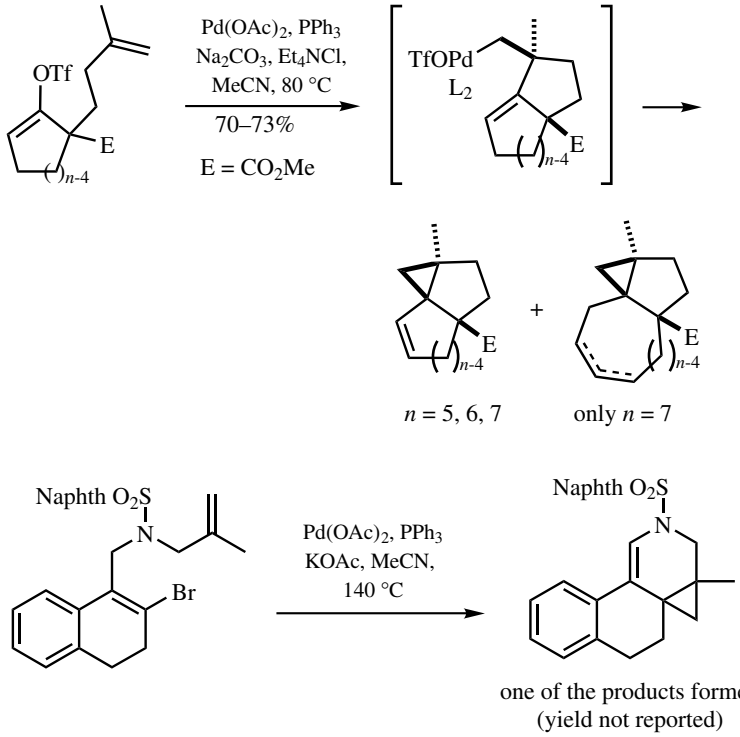
most striking increase in molecular complexity from starting material to product are the molecular zipper reactions by Negishi,[26] Trost and Shi,[27],[28] and Overman et al.,[29] the tri- and tetracyclizations of 2-bromodienynes by de Meijere and co-workers,[30] and the carbonylative intramolecular cross-coupling cascades by Negishi and co-workers[31] in which up to seven new carbon–carbon bonds are formed in a single operation.

D.i. Termination by Alkenes

Cascade carbopalladation sequences after attack on an alkene are most commonly terminated by dehydropalladation, if a β-hydride is present in a *syn*-orientation (see above).

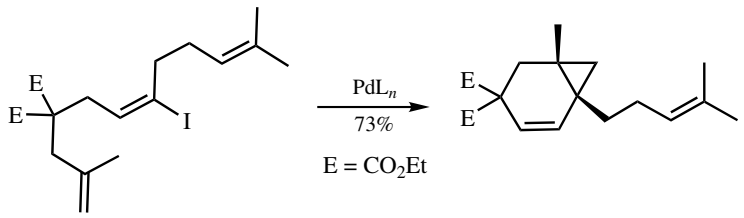
For cascades with intramolecular carbopalladations, smaller ring sizes are preferred by entropic terms, 1,1-disubstituted alkenes suitably located in the chain might serve as the relay without the formation of the larger ring size caused by insertion of the terminator.

D.i.a. ***Formation of Cyclopropane Derivatives by Two Successive Intramolecular Carbopalladations.*** Intramolecular carbopalladation starting from 1,($n-1$)-dienes with a suitable leaving group at the 2-position and a substituent at the ($n-1$)-position of the alkene terminator leads to a neopentylpalladium intermediate, which can only continue the cascade by a 3-*exo-trig*-carbopalladation to eventually form bicyclo[($n-2$).1.0]alkenes. This sequence works equally well for ring sizes five, six, and seven in the first formed ring (**Scheme 22**)[32] and even heterocyclic systems can be constructed by this mode (**Scheme 22**).[33]



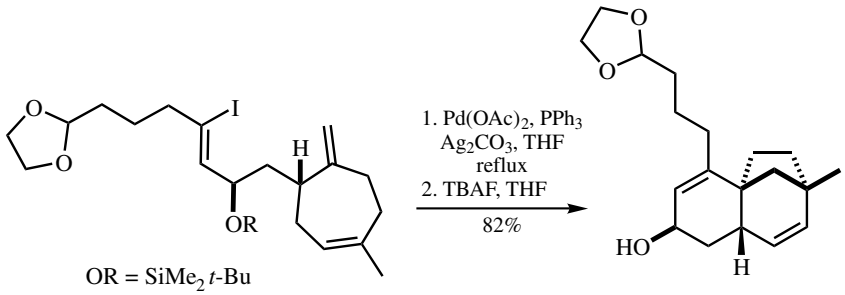
Scheme 22

The 3-*exo-trig* cyclization often wins over a 5-*exo-trig* process, even though both are possible in the second step as exemplified by the cyclization of a triene with two suitable terminators (**Scheme 23**).[34]



Scheme 23

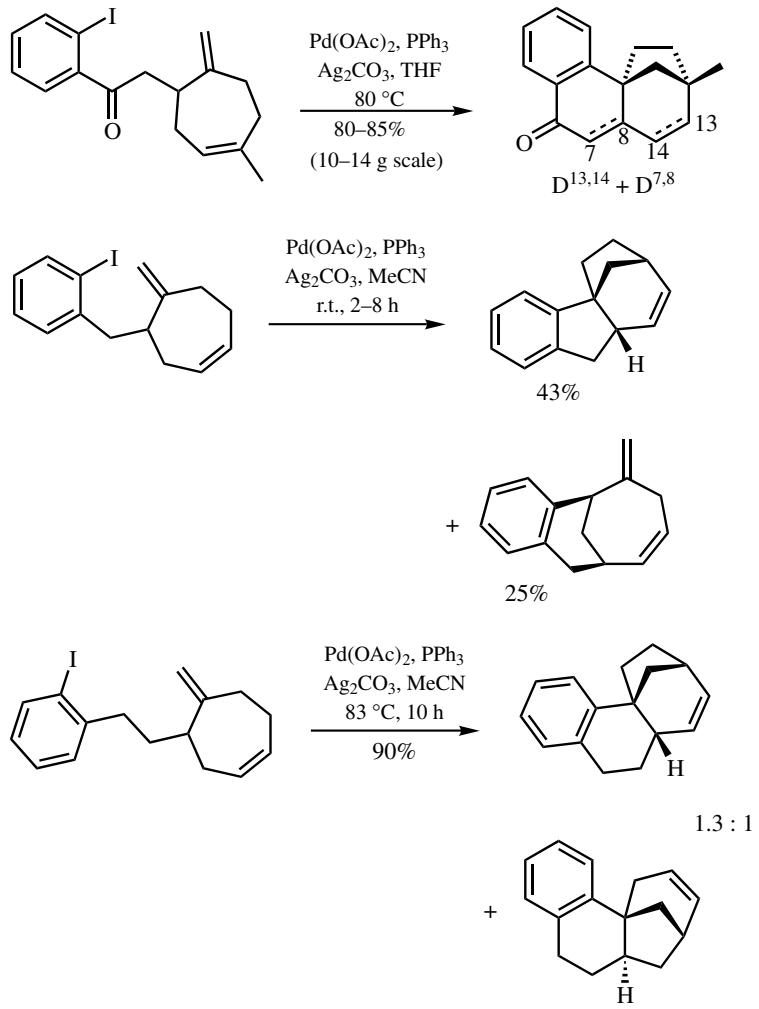
D.i.b. ***Insertion of Another Alkenyl Unit.*** In certain cases, however, the 3-*exo-trig* process may be retarded and an additional alkene moiety participates in the cascade carbopalladation. A pioneering example of this kind has been demonstrated by Overman and co-workers in their total synthesis of scopadulcic acid A, starting from an iodoalkenyl-substituted methylenecycloheptene derivative (**Scheme 24**). The first intramolecular carbopalladation occurs across the disubstituted double bond of the exomethylene group, and the trisubstituted endocyclic double bond acts as the terminator to give a tricyclic system, which was further elaborated to the natural product (**Scheme 24**).[35] It is remarkable that all three quaternary carbon centers can be created by intramolecular Heck reactions.



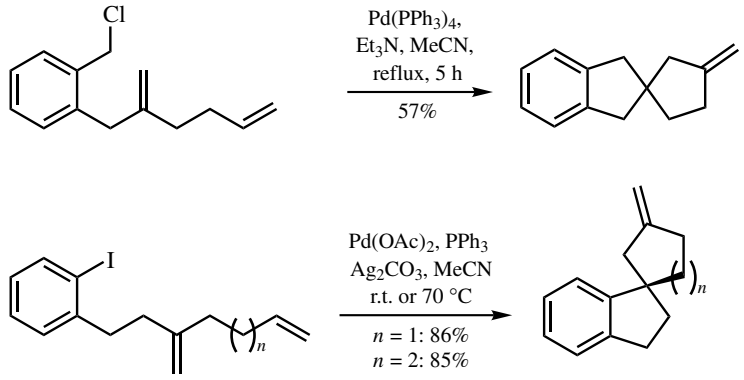
Scheme 24

The same tricyclic skeleton with an annelated benzene ring was prepared as a precursor to scopadulcic acid B (**Scheme 25**),[36] starting from an *ortho*-iodobenzoyl-substituted methylenecycloheptene derivative, and the *o*-iodobenzyl derivative with a shorter tether, led to the benzene-annelated lower homologue of the tricycle (**Scheme 25**).[37]

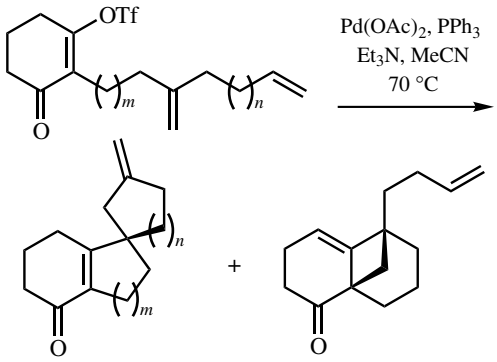
Three simpler *ortho*-substituted iodobenzene derivatives with two alkene moieties in the side chains have been cascade cyclized to give methylenespiroalkane-annelated indanes (**Scheme 26**)[18],[37] and bicyclic systems (**Scheme 27**).[38] This outcome clearly demonstrates that the intramolecular carbopalladations are determined by entropic factors, which always favor the formation of the smaller possible ring sizes.



Scheme 25



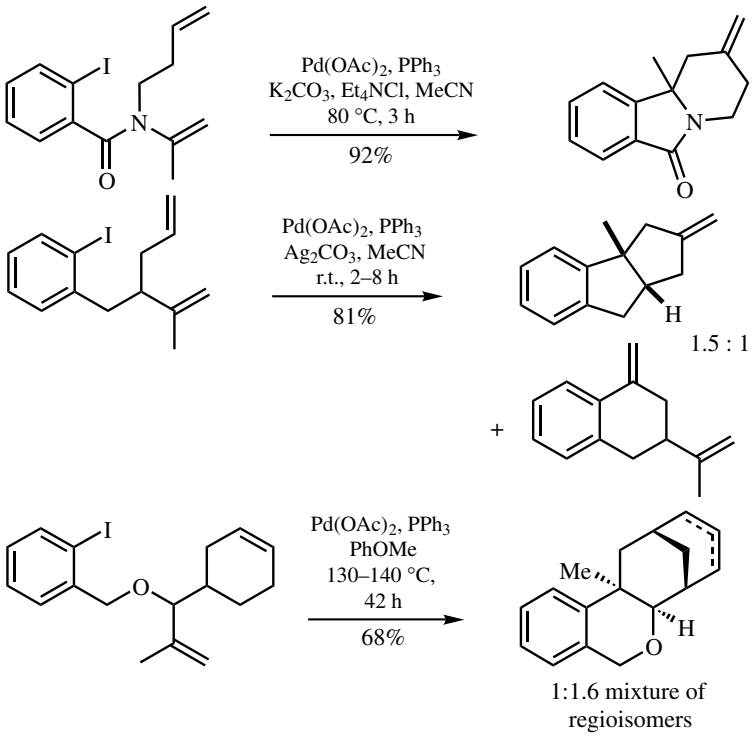
Scheme 26



m	*n*	%	%
1	1	72	0
1	2	70	0
2	1	53	5
2	1	50	0

Scheme 27

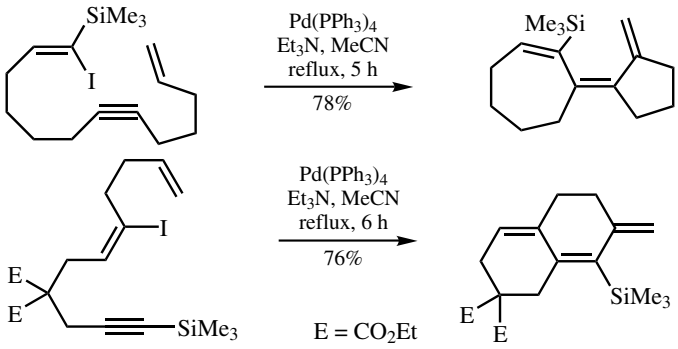
With the neopentyl relay in one of the side chains, the competition between five- and seven-membered ring formation is clearly in favor of the five-membered ring to be formed while the discrimination between five- and six-membered ring formation is not so clear-cut (**Scheme 28**).[37],[39] Tetracyclic systems are formed when the terminating double bond itself is in a ring (**Scheme 28**).[40]



Scheme 28

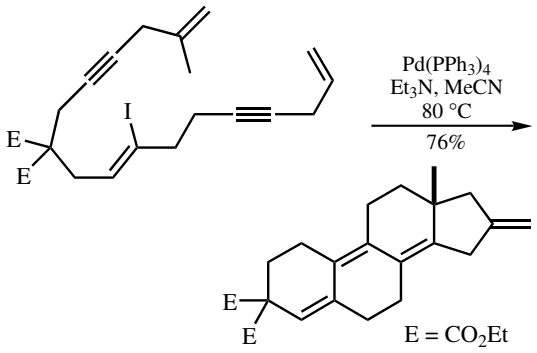
D.i.c. ***Alkyne Relay.*** The alkyne relay has frequently been used for zipper mode processes involving intramolecular carbopalladation reactions. Since the carbon–carbon triple bond possesses a higher reactivity than the C,C double bond, alkynyl groups are easily introduced into organic molecules with simple starting materials, and reactions across alkynyl groups occur with a high degree of stereoselectivity (because of their high predisposition for *exo*-dicyclizations), alkynyl groups are ideal relays.

The Pd-catalyzed intramolecular cascade cross-coupling of 1-halo-1,($\omega-1$)-dienynes [for 2-halo-1,($\omega-1$)-dienynes see **Scheme 32**] with a terminal double bond leads to 2-methylenecycloalkylidenecycloalkenes (**Scheme 29**),[10] whereas halodienynes with the initiating iodoalkenyl unit incorporated in the chain between the alkynyl relay and the alkenyl terminator yield methylenebicycloalkadienes (**Scheme 29**).[10]



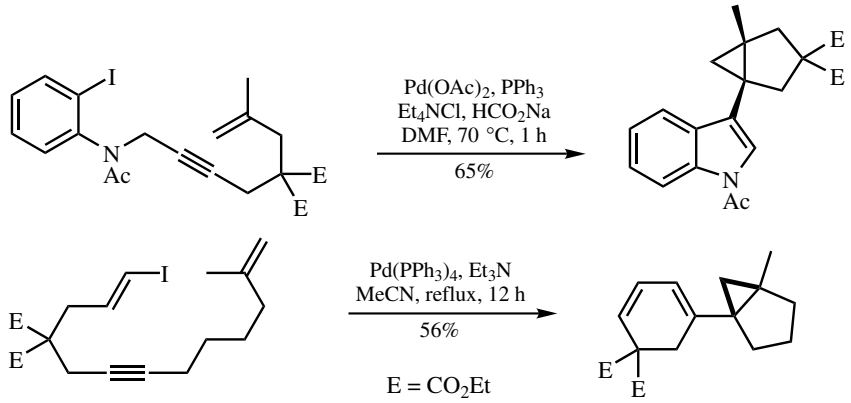
Scheme 29

Even the tetracyclic steroid skeleton was successfully assembled in a zipper mode from an open-chain trienediyne with two alkynyl groups and a 2,2-disubstituted terminal double bond functioning as relays, as demonstrated by Negishi and co-workers (**Scheme 30**).[41]



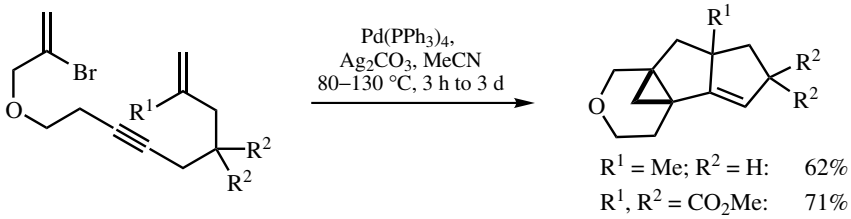
Scheme 30

Termination by 2,2-disubstituted alkenyl groups can lead to bicyclo[*n*.1.0]alkane derivatives if the starting unit is an *ortho*-substituted iodoaryl or a 1-haloalkenyl moiety (**Scheme 31**).[10],[21],[42]



Scheme 31

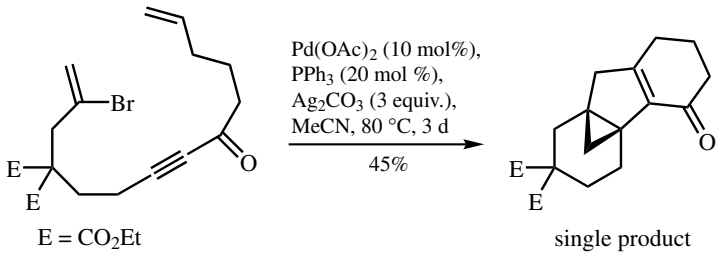
However, a halodienyne with a 2-haloalkenyl moiety as a starter and a 2,2-disubstituted terminal double bond yields a tetracyclic system with the three-membered ring bridging the bond common to the A- and B-rings (**Scheme 32**).[43]



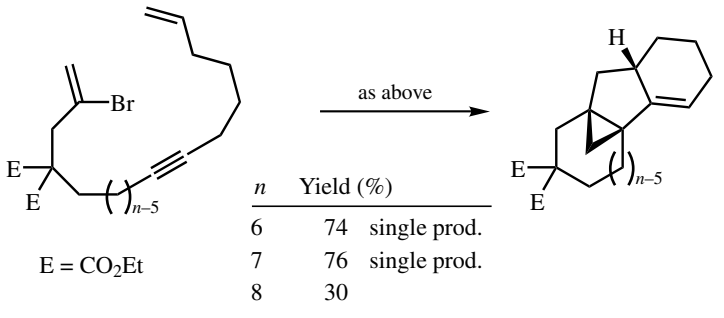
Scheme 32

The same tetracyclization mode is observed for any 2-halodienyne in which the two tethers between the 2-haloethenyl starter and the alkynyl relay as well as between the latter and the terminal double bond are four or more atoms long, even when the alkenyl terminator is not substituted in the 2-position (**Scheme 33**, Eqs. 1 and 2).[30] Thus, a cyclopentanone derivative fitted with a 3-ethenyl and a 2-(8′-bromo-2′-oxonon- 8′-en-3′-ynyl) tether did not cyclize to the tetracyclic steroid skeleton, but to the pentacycle with a five-membered B-ring and a bridging cyclopropane moiety, as was proved by an X-ray crystal structure analysis of the *cis*-diastereomer (**Scheme 33**, Eq. 3).[30]

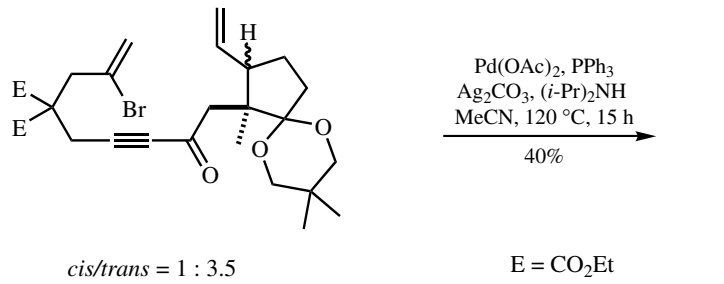
2-Halo-1,(ω−1)-dienynes, in which at least one of the tethers between the multiple bonds is only three atoms long, generally undergo a two-stage intramolecular cascade carbopalladation terminated by dehydropalladation to yield a bicyclic 1,3,5-hexatriene, which, under the same conditions, cyclizes to a tricyclic system with a central cyclohexadiene. The yields are best when both rings formed by intramolecular cross-coupling are five-membered, and they are consistently better when the first formed ring is five-membered. With a substituent at the olefinic terminus, the final 6π-electrocyclization apparently proceeds with a high degree of rotaselectivity, as the terminal substituent ends up *trans* with respect to the former propargylic substituent that stands finally in the other ring. Starting with a bromodienyne tethered to a ring, a tetracyclic system is produced by this cascade (**Scheme 34**).[44]–[47]



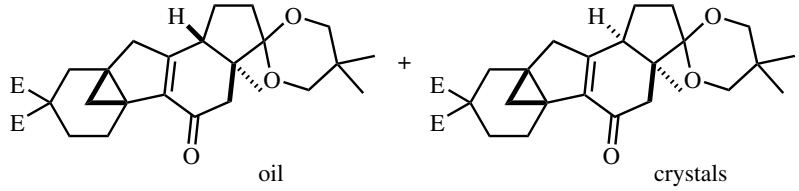
(1)



(2)

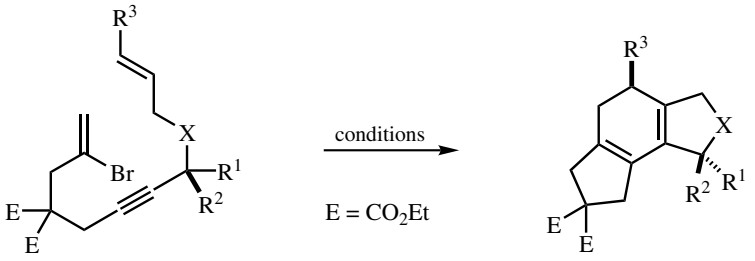


(3)



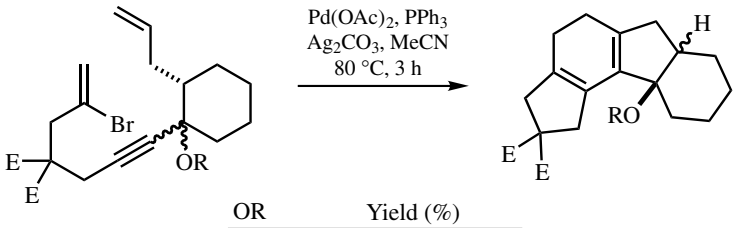
Scheme 33

Nitrogen- and oxygen-containing tricyclic dienes can be prepared from heteroatom-containing and appropriately (on nitrogen) substituted acyclic 2-bromodienynes without problems. Thus, a number of diaza- and dioxatricycles were obtained in moderate to good yields from the corresponding precursors, respectively (**Scheme 35**).[48] Surprisingly, a diazadibromodienyne underwent tricyclization to the same product as the diazamonobromodienyne. This transformation involves a reduction analogous to the one in the Pd-catalyzed homocoupling of aryl halides (see above).



X	R^1	R^2	R^3	Conditions[a]	Yield (%)
CMe_2	H	OMe	H	A	60
$C(CH_2)_5$		OMe	H	A	87
CMe_2	H	OMe	H	A	60
CMe_2	H	OAllyl	H	B	58[b]
O	H	OMe	H	C	84
O	H	OEt	H	D	81
O	H	O*i*-Pr	H	E	95
O	H	OPh	H	F	51
O	H	OPMB	H	G	25
CH_2	H	OMe	Ph	H	83

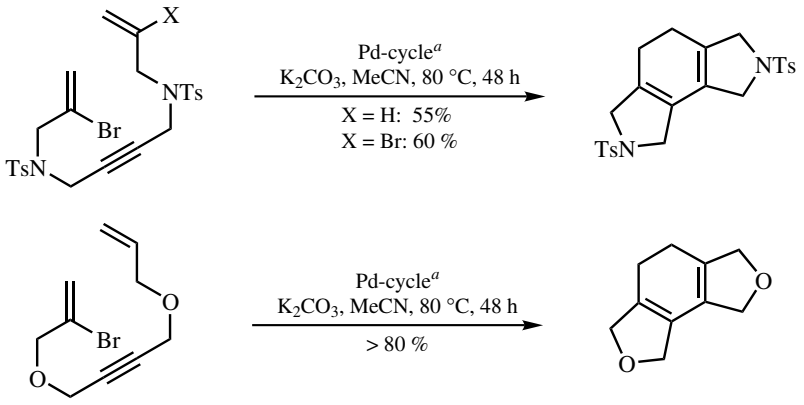
[a] A: $Pd(OAc)_2$, PPh_3, Ag_2CO_3, MeCN, 80 °C, 36 h. – B: As in A, but 60 °C, 6 h. – C: As in A, but 9 h. – D: As in A, but 6 h. – E: As in A, but 60 °C, 4 h. – F: As in A, but 12 h. – G: As in A, but 110 °C, 7 h. – H: $Pd(OAc)_2$, PPh_3, K_2CO_3, MeCN, 110 °C, 3 d.
[b] A dihydroindenotetrahydrofuran (23%) was also isolated.



OR	Yield (%)	
OMe	*cis* (*trans*)	48 (88)
OH	*cis* (*trans*)	80 (85)

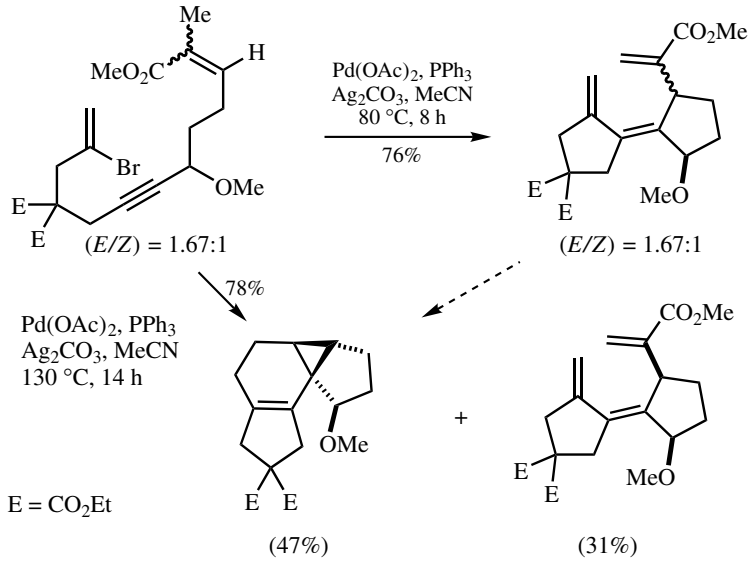
Scheme 34

Another potentially powerful sequence arises by combining one or two intramolecular Heck-type couplings with an intra- or intermolecular Diels–Alder addition (for early examples of inter–intermolecular one-pot domino Heck–Diels–Alder reactions see Refs. [49] and [50]). An all-intramolecular version of such a sequence has been shown to proceed reasonably smoothly for terminally alkoxycarbonyl-substituted 2-bromotrideca-1,11-dien-6-ynes under palladium catalysis at 130 °C. At 80 °C, the sequential reaction stops after the two consecutive Heck-type cyclizations and subsequent β-hydride elimination to give a 1,3,6-triene; apparently only the (*E*)-isomer undergoes the intramolecular Diels–Alder reaction, as the (*Z*)-1,3,6-triene is observed accompanying the tetracyclic system obtained at 130 °C (**Scheme 36**).



[a]Pd-cycle = palladacycle (**1a** in **Section IV.1**) prepared from $Pd(OAc)_2$ and P(*o*-Tol)$_3$

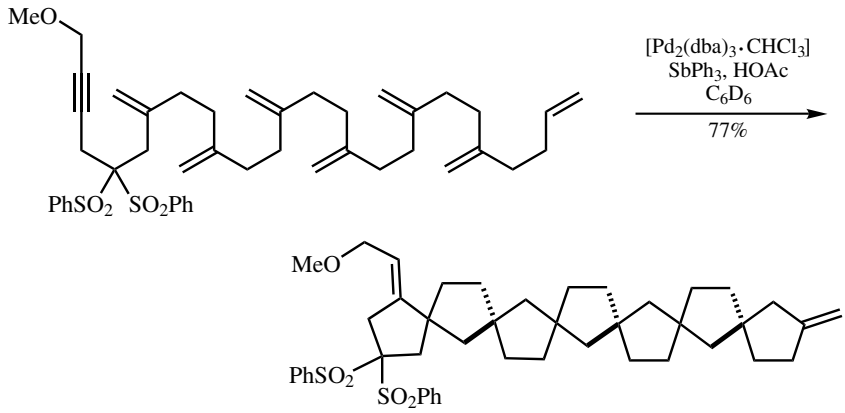
Scheme 35



Scheme 36

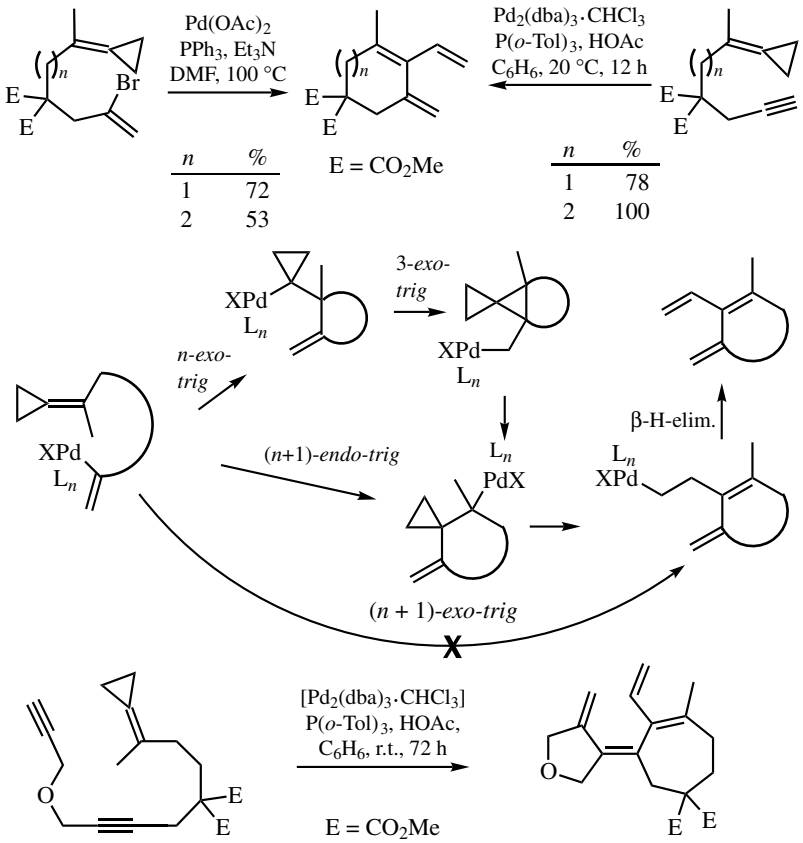
The cycloisomerization reaction of dien- and oligoenynes has been developed by Trost and Shi and shows its remarkable potential by the palladium zipper, which has been used to create seven carbocyclic rings in one step (**Scheme 37**).[28]

Cycloisomerization reactions of dienynes having methylenecyclopropane moieties with tetrasubstituted double bonds, which are readily accessible by Pd-catalyzed substitution on 1-propenylcyclopropyl tosylate or chloride,[51] give rise to the formation of cyclopropane-ring-opened products. This reaction most probably does not proceed by simple ($n-1$)-*exo-trig* cyclization to give a cyclopropylpalladium intermediate, but a sequence of ($n-1$)-*exo-trig* and 3-*exo-trig* cyclizations, followed by a cyclopropylcarbinyl to homoallyl rearrangement of an intermediate spiropentylmethylpalladium compound,



Scheme 37

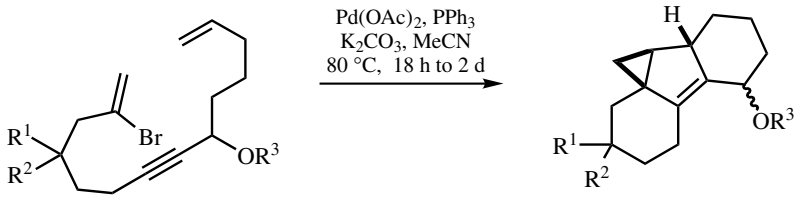
which overall corresponds to an *n-endo-trig* process,[34] to yield a cyclopropylcarbinyl-palladium species that rapidly ring-opens to another homoallylpalladium intermediate. Subsequent β-hydride elimination eventually leads to the cross-conjugated triene, (**Scheme 38**).[7]



Scheme 38

As had previously been proved, most or all putative 6- and 7-*endo-trig* carbopalladations proceed by a sequence of ($n-1$)-*exo-trig* and 3-*exo-trig* cyclizations and subsequent ring-enlarging cyclopropylcarbinyl to homoallyl rearrangement.[34] Thus, the seemingly reversed regioselectivity observed in the cascade cyclizations of 2-bromo-1,6-hepta- and 2-bromo-1,7-octadienes with 1;1′-disubstituted methylenecyclopropane end groups (**Scheme 38**) most probably also starts with a normal ($n-1$)-*exo-trig* followed by a 3-*exo-trig* cyclization, although this leads to a highly strained spiropentylmethylpalladium intermediate, which subsequently undergoes two consecutive cyclopropylcarbinyl to homoallyl rearrangements, before β-hydride elimination ensues to give the final product. The intermediacy of the second cyclopropylmethylpalladium intermediate was proved by isolation of a by-product that could only have been formed by β-hydride elimination in that intermediate. This, at the same time, excluded a direct ($n-1$)-*exo-trig* carbopalladation across the cyclopropyl single bond. Analogous precursors with a 1′-monosubstituted methylenecyclopropane end group react in the usual way to give vicinal exodimethylenecycloalkanes, which cycloadd dienophiles like methyl acrylate to yield tricyclic compounds (**Sect. IV.2**, **Scheme 8**). Under appropriate conditions, 1,6- and 1,7-enynes react analogously to furnish the corresponding cross-conjugated trienes, so-called dendralenes, in certain cases with better yields (**Scheme 38**). The 12-ene-1,6-diyne with a 1,1′-disubstituted methylenecyclopropane end group undergoes a cascade cyclization in the same sense to yield a cross-conjugated tetraene.

In the above-mentioned Heck-type cascade tetracyclizations, substituents in the acyclic precursors can play a major role and cause the sequential reaction to proceed in an unprecedented direction. A particularly striking example is presented in **Scheme 39**. The acyclic precursors differ from those that undergoe the other type of cascade tetracyclization (see above **Scheme 33**) only by the propargylic methoxy (silyloxy) group, yet yield — under the typical conditions — an unprecedented tetracyclic system, the structure of which has been proved by X-ray analysis.[30] This cascade reaction may involve an unusual γ-hydride elimination as the last step, or an unprecedented dehydrobromination on an alkylpalladium bromide intermediate to yield a palladiumcarbene species that subsequently undergoes an intramolecular cheletropic addition across the distal double bond to yield the cyclopropane ring.



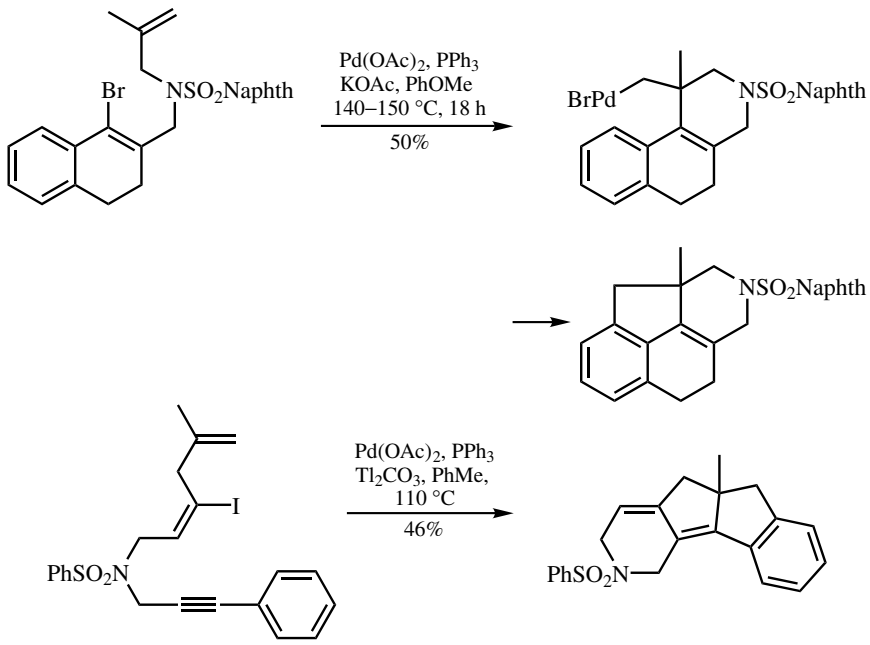
R^1	R^2	R^3	%
CO_2Et	CO_2Et	Me	63
$OSiMe_2t$-Bu	H	$OSiMe_2t$-Bu	76

Scheme 39

D.ii. Termination by Arenes

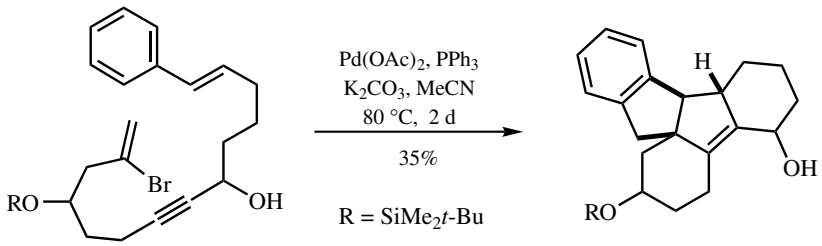
Termination of cascade carbopalladation sequences by arylation plays a major role in systems that form a reasonably long-lived palladium intermediate and contain a proximal suitably functionalized arene moiety. In many cases, neopentylpalladium species have

been found to add to an adjacent arene moiety (**Scheme 40**)[33].[14],[52] This type of reaction has previously been regarded as involving *ortho*-C—H activation, but the term "Friedel–Crafts-type" alkylation might be more appropriate in view of the probable mechanism of this process (**Scheme 40**).[52]



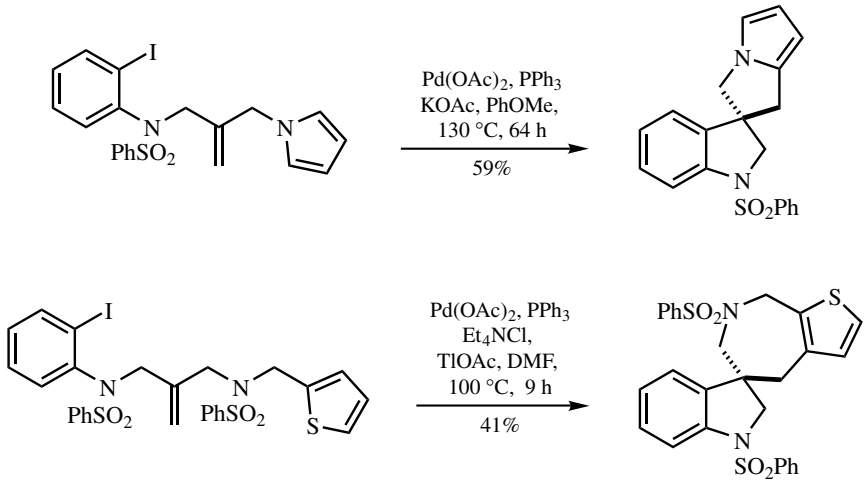
Scheme 40

A 2-bromotetradeca-1,13-dien-7-yne with a terminal phenyl group apparently also prefers to cascade-cyclize via a neopentylpalladium intermediate with attack on the proximal phenyl group to yield a pentacyclic system (**Scheme 41**)[44] rather than following the carbopalladation sequence to yield a tetracycle with a bridging cyclopropane ring as observed for other 2-bromo-1,13-diene-7-ynes (see above, **Scheme 33**).



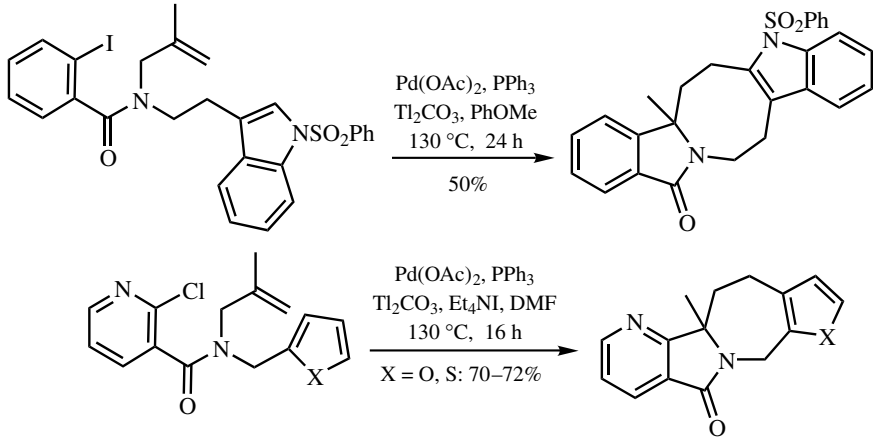
Scheme 41

When the neopentyl relay is incorporated in the tether between the haloarene or haloalkane starter and an arene terminator, spirocyclic oligocycles can be formed (**Scheme 42**).[53]



Scheme 42

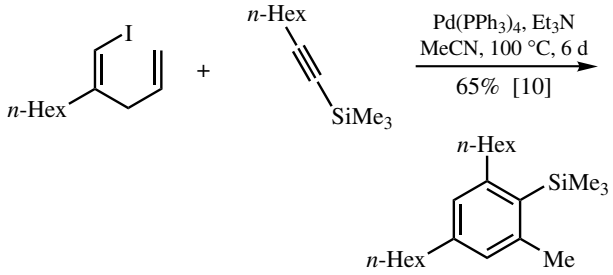
Annelated oligocyclic systems of various ring sizes are formed when the methallyl group is dangling on the tether between the starter and the terminator of the cascade cyclization precursor (**Scheme 43**).[52]



Scheme 43

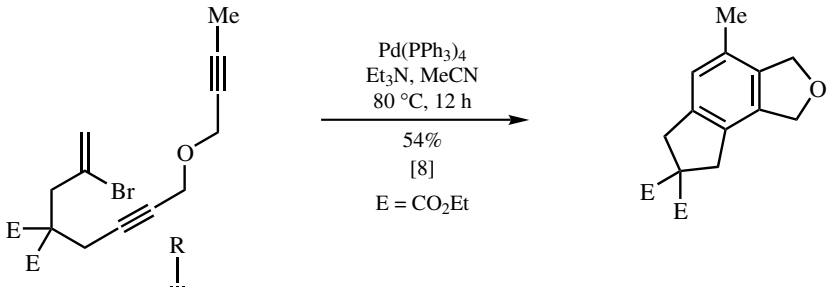
D.iii. Termination by Related π-Bonding Systems

D.iii.a. ***Termination by Alkynes.*** Some of the metal-catalyzed [2 + 2 + 2] cocyclizations of three alkynes, which have recently been developed into viable methods for the preparation of oligo-substituted benzene derivatives,[54] involve a cascade carbopalladation sequence. The fully intermolecular version, however, does not generally provide a good control of chemo- and regioselectivity (see above, **Sect. B**). High regiocontrol can be accomplished by combining an intra- with an intermolecular carbopalladation step as has been demonstrated for a variety of examples (**Schemes 29**, **44**).[9],[10],[25]

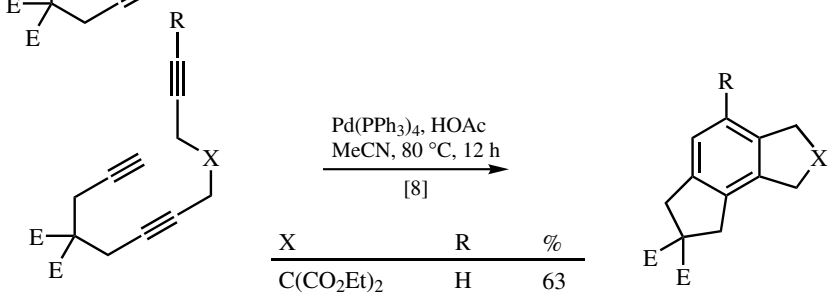


Scheme 44

The fully intramolecular Pd-catalyzed cascade cyclization of 2-bromo-1-ene-*n,m*-diynes is a reliable access to tricyclic systems in which the central benzene moiety is formed by a formal [2 + 2 + 2] assembly as long as both rings initially formed by intramolecular carbopalladation are five-membered or at most six-membered (**Scheme 45**).[8],[55] The yields range from 42 to 75%, and one or both rings annelated on the central benzene may contain heteroatoms.



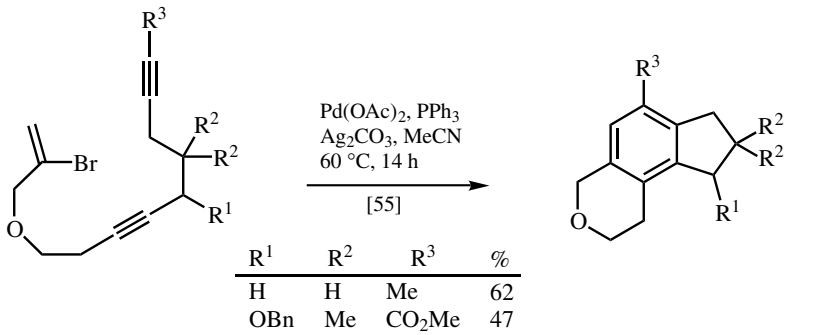
(1)



(2)

X	R	%
$C(CO_2Et)_2$	H	63
O	Me	67[a]

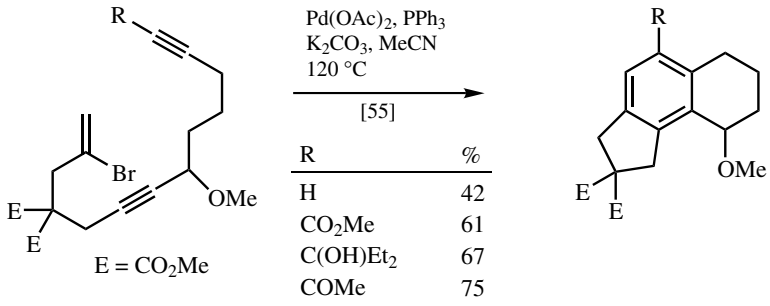
[a] According to NMR



(3)

R^1	R^2	R^3	%
H	H	Me	62
OBn	Me	CO_2Me	47

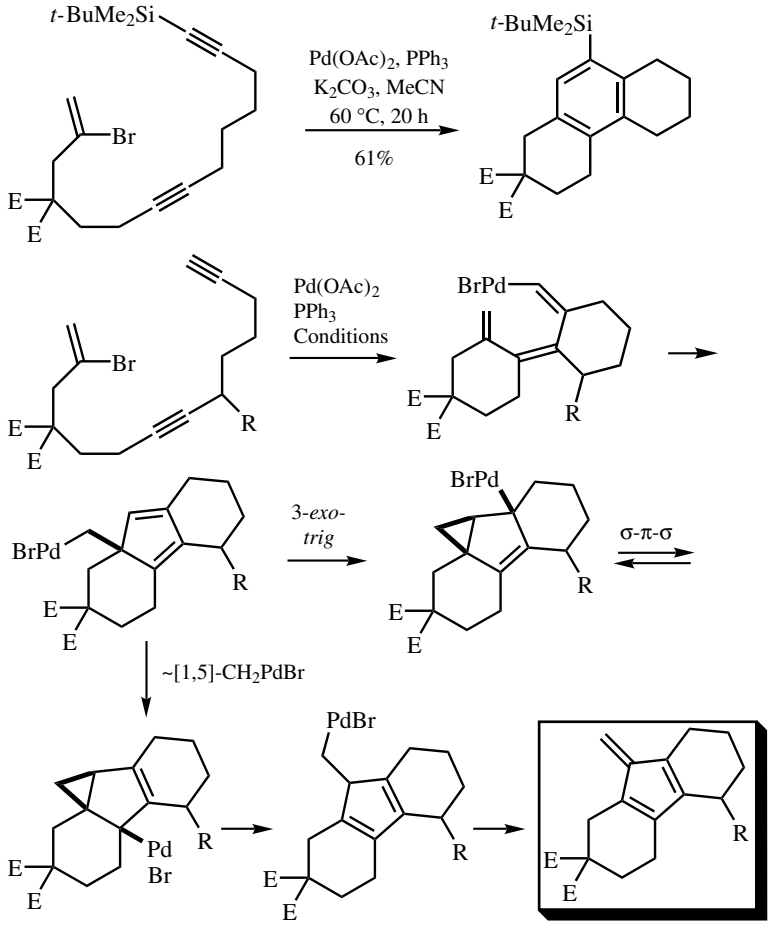
Scheme 45 (*Continued*)



(4)

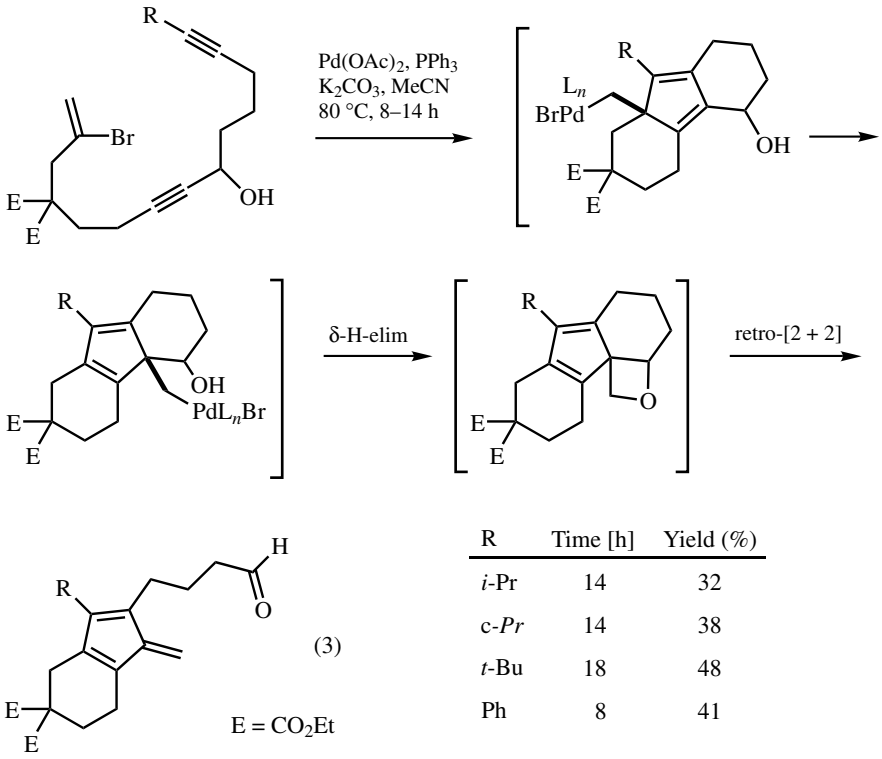
Scheme 45

The octahydrophenanthrene skeleton is also formed from 2-bromotetradeca-1-ene-7,13-diynes with a trialkylsilyl-substituted terminal triple bond (**Scheme 46**, Eq. 1). With an unsubstituted terminal acetylene, the same bromoenediynes yield bisannelated fulvenes by a completely different cascade carbopalladation mode involving a 5-*exo-trig* cyclization and a [1,5]-sigmatropic shift of the CH_2PdBr group or a 3-*exo-trig* cyclization



Scheme 46

R	E	Conditions	Yield (%)
H	CO_2Me	K_2CO_3, MeCN, 60 °C, 1 h	74
OMe	CO_2Et	HCO_2Na, DMF, 60 °C, 45 min	65



R	Time [h]	Yield (%)
i-Pr	14	32
c-*Pr*	14	38
t-Bu	18	48
Ph	8	41

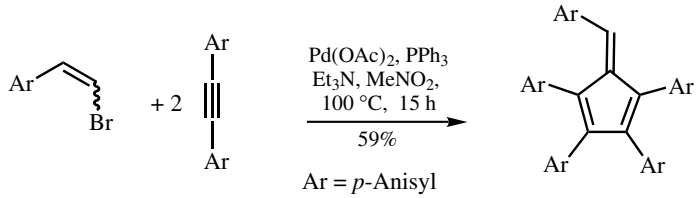
Scheme 46 (*Continued*)

followed by a $\sigma-\pi-\sigma$-allylpalladium rearrangement (**Scheme 46**, Eq. 2). With a free propargylic hydroxy group on the bromoenediyne, the cascade reaction takes yet another course terminating with a fragmentation to yield a bicyclic fulvene with an aldehyde side chain (**Scheme 46**, Eq. 3).[56]

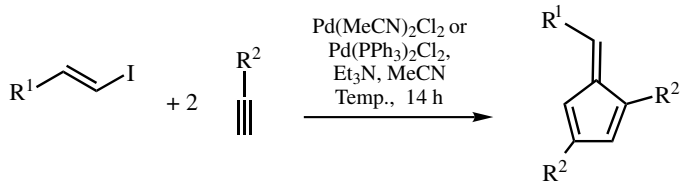
E. THREE- AND MULTIPLE-COMPONENT CASCADE CARBOPALLADATIONS

E.i. Termination by Alkenes

The inter–intermolecular carbopalladation cascade, starting with the palladium intermediate from β-halostyrene derivatives and two molecules of an alkyne, does not yield a benzene, but highly substituted fulvene derivatives, albeit in moderate yields only (**Scheme 47**, Eqs. 1 and 2).[57] Fulvene derivatives are also formed from 1-haloalkenes and 1,6-diynes (**Scheme 47**, Eq. 3).[58]

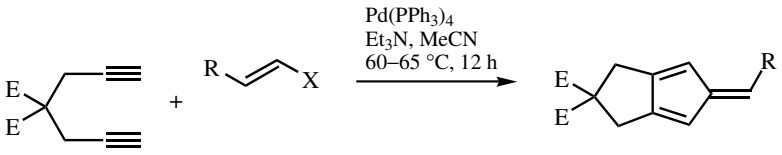


(1)



(2)

R^1	R^2	Temperature (°C)	Yield (%)
Ph	$SiMe_3$	25	44
C_6H_4-4-OMe	$SiMe_3$	25	46
C_6H_4-4-OMe	*n*-Bu	100	33
2-Naphth	$SiMe_3$	25	43
3-Thienyl	$SiMe_3$	25	44



(3)

R	X	Yield (%)
Ph	Br	52
n-Bu	I	40

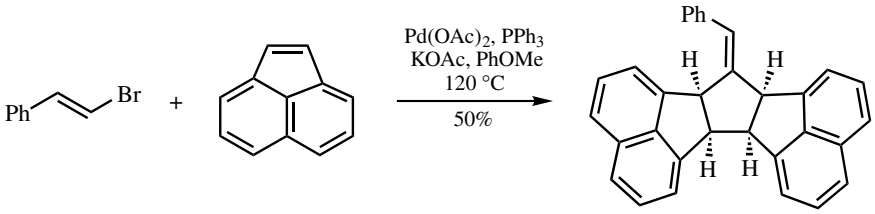
$E = CO_2Et$

Scheme 47

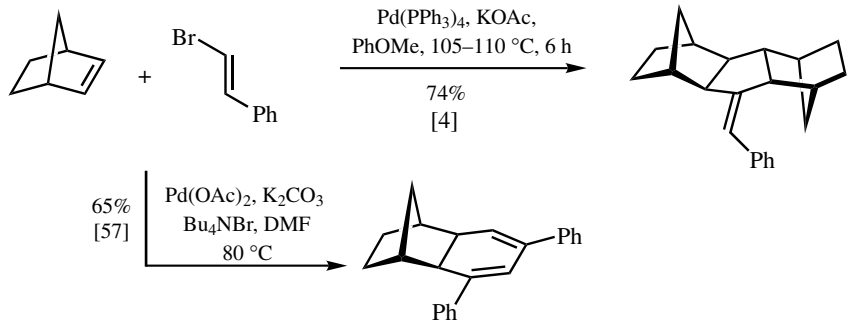
An analogous reaction mode is followed in the 1:2 cross-coupling of 2-bromostyrene with acenaphthylene, which yields a bisannelated tetrahydrofulvene (**Scheme 48**).[5]

Norbornene can favorably serve as a relay for cascade carbopalladations as the β-hydride elimination is virtually impossible. The reaction always starts with an alkenyl- or arylpalladium starter, generated either by oxidative addition of an alkenyl or aryl halide to a palladium(0) species or by hydro- or carbopalladation of an alkyne, adding to the double bond. With β-bromostyrene, norbornene can yield the same type of bisannelated tetrahydrofulvene derivative[4] as with acenaphthylene, but under different reaction conditions can also react with a 2:1 stoichiometry to give a cyclohexadiene-annelated norbornane derivative (**Scheme 49**).[59]

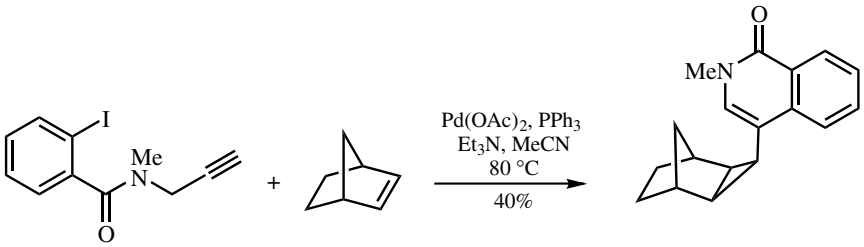
Under yet different conditions, the carbopalladation product from an alkenylpalladium intermediate undergoes a 3-*exo-trig* cyclization and subsequent β-hydride elimination leading to a 2,3-methanobicyclo[2.2.1]heptane derivative (**Scheme 50**).[21]



Scheme 48



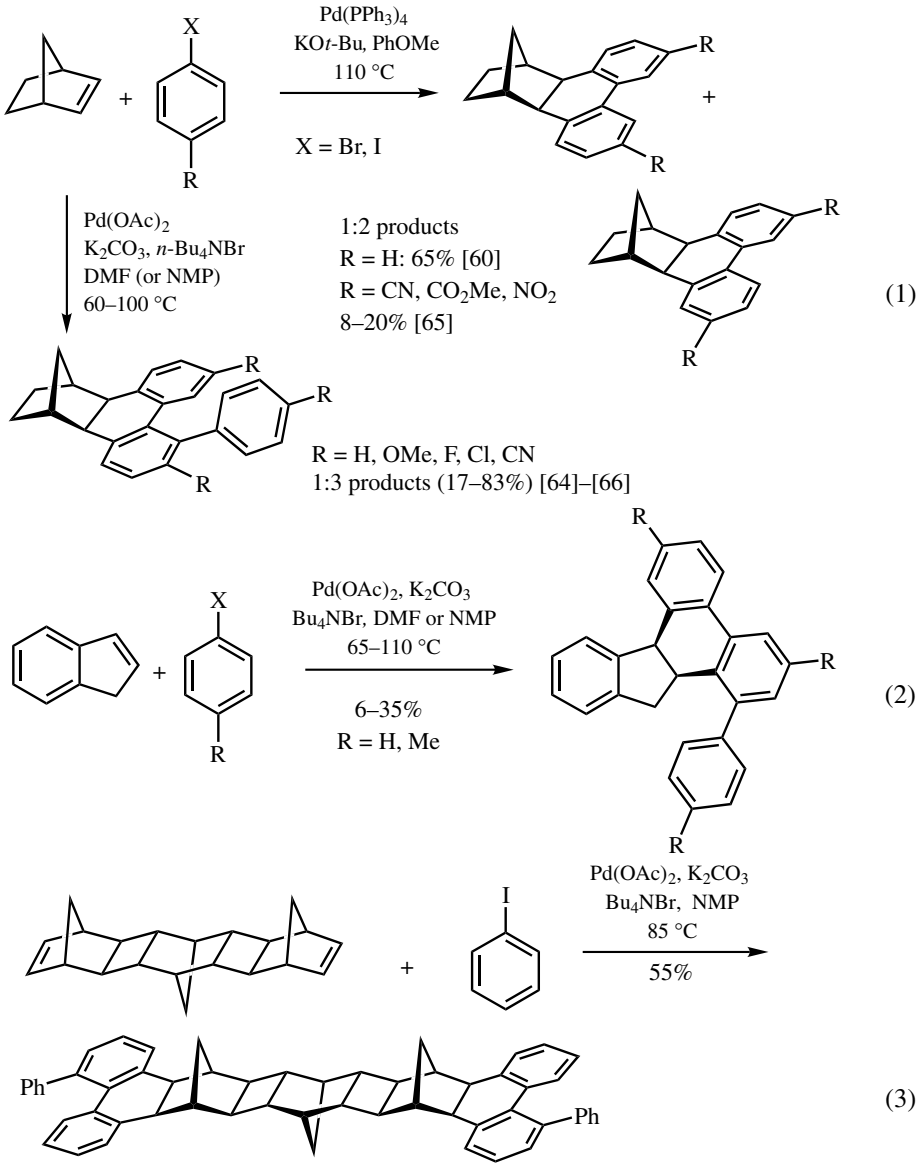
Scheme 49



Scheme 50

E.ii. Termination by Arenes

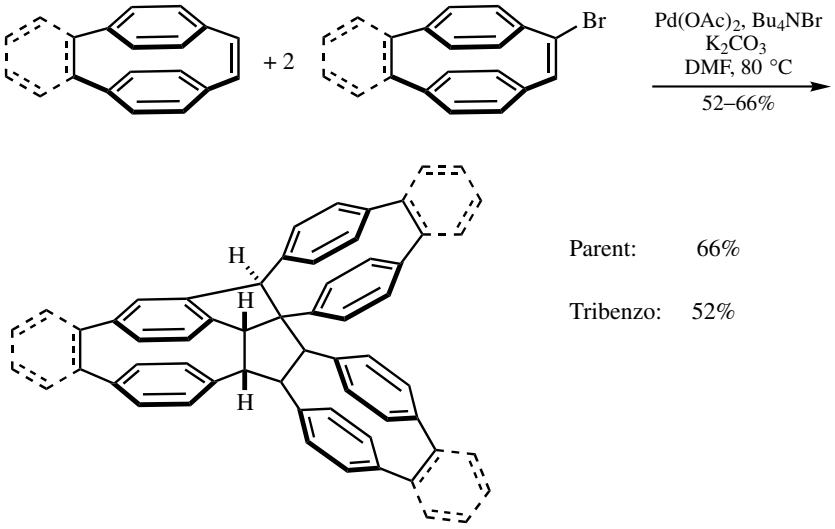
Quite unusual domino-type multiple coupling reactions occur with certain cyclic alkene substrates, which, upon *syn*-carbopalladation with an alkenyl- or arylpalladium species, yield an alkylpalladium intermediate that cannot undergo a *syn*-β-hydride elimination. The σ-alkylpalladium intermediate then continues to react either with another alkene, another alkenyl halide, or another aryl halide molecule. The outcome of such reactions, which have been thoroughly investigated especially for the strained alkene norbornene,[60],[61] can be 1:1,[62] 2:1,[63] 1:2, or even 1:3 coupling products of the alkene with an alkenyl halide or an aryl halide, respectively. Palladacycles, which are formed by hydrogen halide elimination from the *syn*-carbopalladation products, and alkyldiarylpalladium(IV) halide intermediates play a key role in these reactions. Under traditional Heck conditions, the 1:2 cross-coupling–cyclization product is obtained (**Scheme 51**, Eq. 1),[60] whereas under Jeffery conditions the 1:3 coupling product is formed almost exclusively, except for aryl halides with acceptor substituents such as CN, CO_2Me and NO_2.[64]–[66]



Scheme 51

Indene undergoes *syn*-carbopalladation with arylpalladium halides regioselectively to give a *syn*-carbopalladation product, which reacts further via a palladacycle to yield 1:3 coupling products corresponding to the products from norbornene, but differs in its regiochemistry (**Scheme 51**).[64] This methodology can be used to annelate 5- or 8-substituted 9,10-dihydrophenanthrene units to strained cyclic alkenes of the indene and norbornene type. Thus, the extended norbornene-type hydrocarbon, which is obtained by $Ni(COD)_2$-catalyzed trimerization of norbornadiene, can be transformed to an extended hydrocarbon by a 1:6 coupling with iodobenzene performed in a single operation with 55% yield (**Scheme 51**, Eq. 3).[67]

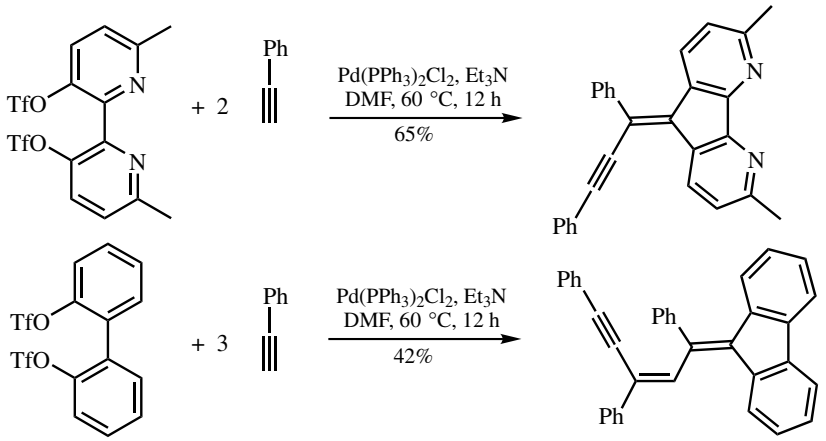
In essence, these domino-coupling reactions form cyclohexadiene fragments from three two-carbon fragments. The 1:2 coupling of norbornene and iodobenzene discovered by Catellani and Chiusoli[60] can also be adopted to couple norbornene with β-bromostyrene.[59],[65] In an attempt to apply this Pd-catalyzed [2 + 2 + 2] assembly for an alternative and more productive access to Hopf's trifoliaphane,[68] a 1:2 mixture of [2.2]paracyclophan-1-ene and 1-bromo[2.2]paracyclophan-1-ene was treated with palladium acetate under Jeffery conditions. The main product was the hydrocarbon consisting of three [2.2]paracyclophane units linked by a common bicyclo[3.3.0]octene unit (**Scheme 52**).[69],[70] Apparently, the key intermediate formed via a palladacycle preferentially undergoes a 5-*exo-trig* carbopalladation with subsequent formation of another palladacycle by *ortho* attack on the neighboring aromatic ring, rather than 6-*endo-trig* carbopalladation, to give the precursor to the isolated product.[69] Similar types of C—H activation have been observed by Dyker in the Heck-type reactions of *o*-iodo-*tert*-butyl- and *o*-iodomethoxyarenes to give defined polycondensed oligomers.[71],[72] However, trifoliaphane could be obtained in remarkably good yields (47% overall) by Pd-catalyzed twofold coupling of 1,2-dibromo[2.2]paracyclophane-1-ene with [2.2]paracyclophane-1-magnesium bromide, leading to a 1,3,5-hexatriene with one central and two terminal [2.2]paracyclophane units,[69] which underwent 6π-electrocyclization under the coupling conditions. The dihydrotrifoliaphane upon treatment with bromine cleanly underwent aromatization.[69]



Scheme 52

E.iii. Termination by Alkynes

Starting from 5,5′-dimethyl-2,2′-bipyridye-3,3′-diyl bistriflate, coupling with two molecules of an alkyne yields a diazafluorene derivative, which arises from an intramolecular 5-*exo-dig*-carbopalladation of the first formed 1:1 cross-coupling product and subsequent cross-coupling with another molecule of the alkyne (**Scheme 53**).[73] The 1,1′-biphenyl-2,2′-diyl bistriflate even reacts with three molecules of an alkyne in a cascade reaction including three carbopalladation steps (**Scheme 53**); the corresponding 1:2 coupling product had been reported earlier in good yield (78%).[74]

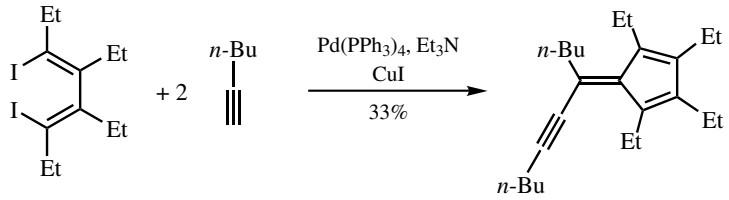


Scheme 53

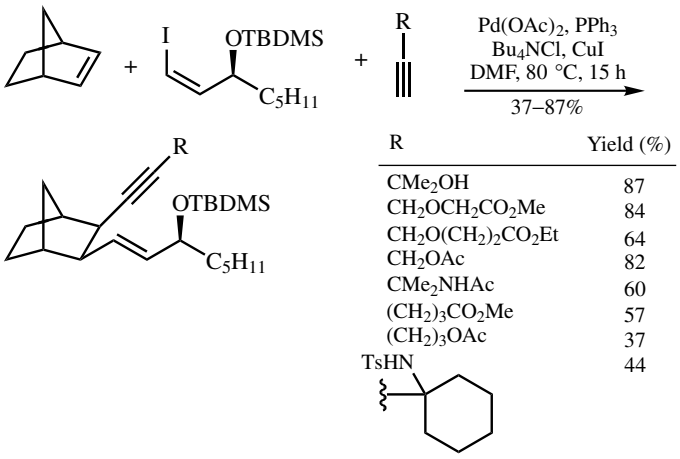
The same strategy has been applied to prepare fulvenes in moderate yields starting from appropriately substituted 1,4-diiodo-1,3-dienes (**Scheme 54**).[75]

A rather efficient three-component reaction starts with an iodoalkene, uses norbornene as relay, and finishes with a cross-coupling to an alkyne (**Scheme 55**).[76]

However, the analogous three-component reaction with a bromoalkyne instead of a haloalkene proceeds in a more complicated manner to form a product from two molecules



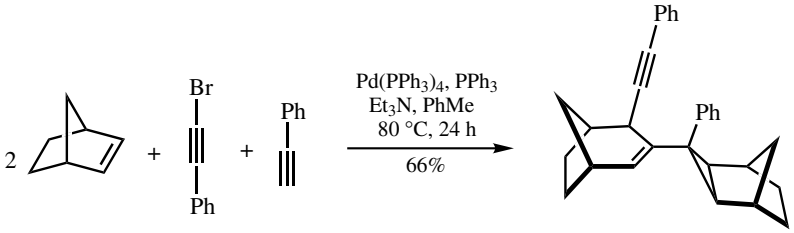
Scheme 54



R	Yield (%)
CMe_2OH	87
$CH_2OCH_2CO_2Me$	84
$CH_2O(CH_2)_2CO_2Et$	64
CH_2OAc	82
CMe_2NHAc	60
$(CH_2)_3CO_2Me$	57
$(CH_2)_3OAc$	37
TsHN	44

Scheme 55

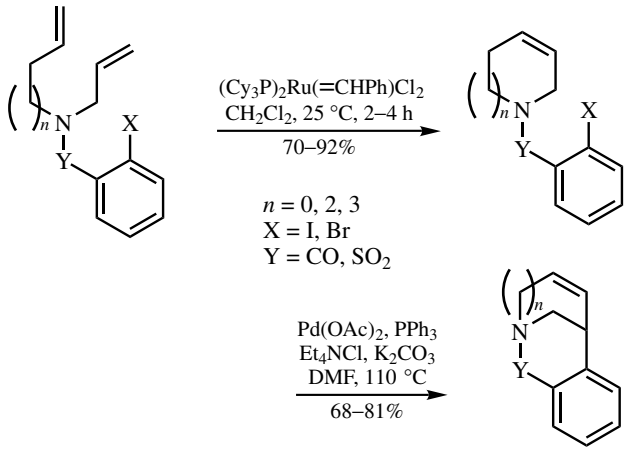
of norbornene, one bromoalkyne, and one molecule resulting from expansion of an intermediate (alkynylecyclopropa)bicyclo[2.2.1]heptylpalladium compound to a bicyclo[3.2.1]octenylpalladium derivative (**Scheme 56**).[77]



Scheme 56

F. MISCELLANEOUS DOMINO REACTION TYPES

Various types of domino reactions have been reported in the recent past. The sequential or cascade combination of an olefin metathesis with an intramolecular Heck reaction provides access to various bicyclic spirocyclic ring systems in good yields. Recently, a one-pot metathesis–Heck cascade was employed in the construction of various ring systems (**Scheme 57**).[78]



Scheme 57

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