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Review

Palladium in action: domino coupling and allylic substitution reactions for the efficient construction of complex organic molecules☆

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Abstract

The palladium-catalyzed arylation and alkenylation of alkenes, generally called the Heck reaction, has been applied to a number of new concepts. Starting from simple, oligohalogenated alkenes and arenes, the synthesis of a variety of highly functionalized carbon skeletons has been established. The domino-type combination of an intramolecular Heck with an inter- or intramolecular Diels–Alder reaction has been shown to provide facile access to interesting bicyclic and tetracyclic frameworks. While intramolecular Heck reactions on trisubstituted, cyclopropylidene-terminated alkenes proceeded with retention of the cyclopropyl moiety, tetrasubstituted alkenes with methylenecyclopropane end groups reacted with ring opening to yield cross-conjugated trienes. The study of the palladium-catalyzed oligocyclizations of 2-bromoalka-1,(ω-1)-diene-*n*-ynes has revealed interesting and useful systematics as to achievable ring size combinations and skeletal types. Highly functionalized methylenecyclopropanes are conveniently accessible via palladium-catalyzed allylic substitution reactions of 1-ethenylcyclopropyl sulfonates and chlorides as well as cyclopropylideneethyl esters which proceed with complete regioselectivity in most cases.

Keywords: Heck reaction; Cross-coupling reactions; Domino reaction; Multi-component reaction; Biologically active compounds

1. Introduction

Transition metal-catalyzed C,C-bond forming reactions have gained steadily increasing importance over the last decade. The development and fine tuning of reaction parameters for known and newly discovered metal-catalyzed transformations have had an important impact on remarkable successes in the synthesis of natural and non-natural biologically active compounds, as well as theoretically interesting molecules of high complexity [1]. In addition, process development for valuable intermediates in the pharmaceutical and agrochemical industry as well as research towards new materials have benefited a great deal. One of the most general and widely used palladium-catalyzed cross-coupling reactions is the arylation and alkenylation of alkenes, generally known as the Heck reaction [2]. This account focuses on new applications of Heck reactions and mechanistically related cross-coupling reactions from the author's own laboratory, and only briefly points out the important contributions of other groups within the full spectrum of palladium-catalyzed reactions including Suzuki [3a], Stille [3b], Sonogashira–Stephens–Castro [4], Wacker type [5], Trost cycloisomerization [6], pallada-ene [7] and related reactions. Finally, the palladium-catalyzed allylic substitu-

☆ Dedicated to Professor Richard F. Heck and Professor Jiro Tsuji, two pioneers in palladium-catalyzed C,C-bond forming reaction.

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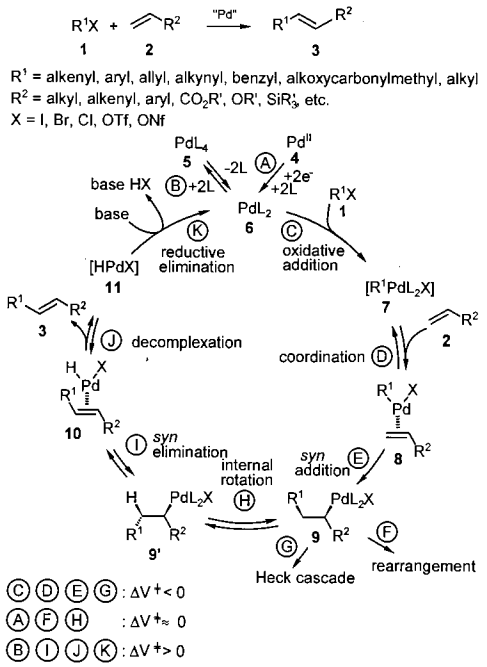


Scheme 1. Palladium-catalyzed coupling of aryl and alkenyl halides: mechanism and opportunities.

tion of alkenylcyclopropyl and cyclopropylideneethyl esters leading to highly functionalized methylenecyclopropane derivatives, also developed by the author's group, is described.

The scope of metal-catalyzed reactions can often be broadened significantly by letting the same reaction type under the same conditions repeat itself several times, by combining it with a different type of metal-catalyzed or even simply thermal reaction occurring under the same conditions [8]. Such strategies can be subdivided into: (a) multiple cross-coupling processes—iterative reactions of the same type with the same reagent; (b) domino reactions (also called 'cascade reactions' [9])—sequential reactions with several steps of the same mechanistic type but with a changing substrate, and (c) domino reactions (also called cascade reactions [9])—sequential reactions with several steps of two or more different mechanistic types. Such multiple step sequential processes offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural operation, frequently with enhanced regio-, diastereo-, and even enantioselectivity for the overall transformation [10].

2. Heck-type reactions: past–present–future

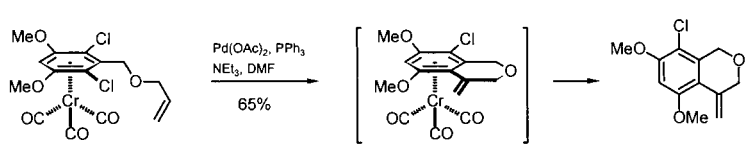
2.1. The mechanism

The palladium-catalyzed arylation and alkenylation of alkenes, discovered independently by Mizoroki et al. in Japan [11] and Heck et al. in the US [12] around 1970—now generally called the Heck reaction—has become one of the most frequently applied metal-catalyzed C–C bond forming processes in the last 10–15 years and has therefore attracted a great deal of interest [2,13,14]. The rapid development of new and vastly improved reaction protocols, the discovery of diastereoselective and—since 1989—even ligand-induced enantioselective couplings [15] has made it possible to apply the Heck reaction in elegant syntheses of various biologically active compounds. Recent work has also led to a deeper insight into the key steps of the widely accepted mechanism of this reaction [16].

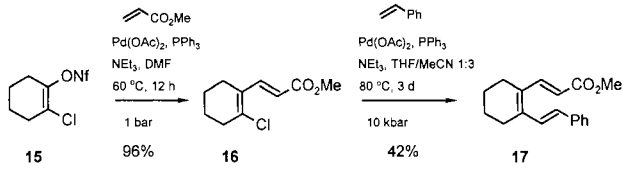
2.2. Rate enhanced under high pressure

It is generally assumed that the rate determining step in the catalytic cycle of the Heck reaction usually is the oxidative addition (C [17–20] in Scheme 1). This is consistent with the low reaction rate of aryl and alkenyl chlorides which less readily undergo oxidative addition than bromides and iodides. Chlorides can be induced to react at elevated temperatures with the use of more nucleophilic trialkylphosphane ligands [21], or, as shown more recently, palladium catalysts which are sufficiently stable at higher reaction temperatures [22,23]. Of course, activation of the aromatic chloride by electron withdrawing groups can enhance the reactivity [22,24], one of the most recent example being that highly substituted tricarbonyl chromium complexes of type **12** readily undergo an intramolecular Heck reaction to give methylene isochromanes like **14**. In this case, even methoxy groups, well known to notoriously retard Heck reactions, may be present in the chloroarene [25] (Scheme 2).

It has also been discovered that the application of high pressure (2–10 kbar) enhances the rate of the Heck reaction in general, and thus high pressure can be



Scheme 2. An example of a tricarbonylchromium complex of a chloroarene undergoing a facile intramolecular Heck reaction.



Scheme 3. Rate enhancement of the Heck reaction under high pressure.

applied to couple alkenyl and aryl chlorides at ordinary temperatures with better yields [26] (Scheme 3).

2.3. Rate enhancement of the Heck reaction under high pressure

By simple analogy with other types of reactions it can be predicted that steps (C), (D), (E) and (K) in the catalytic cycle (Scheme 1) should be accelerated, whereas steps (B), (I), and (J) should be retarded by high pressure [27,28].

A more detailed kinetic study monitoring the Heck reactions under high pressure by on-line FT-IR spectroscopy has revealed that alkenyl iodides have a lower activation entropy, activation volume and rate coefficient than aryl iodides. Interestingly, the reaction rates of aryl bromides depend more strongly on the pressure than those of aryl iodides, and hence can more efficiently be forced to react by increased pressure rather than by elevated temperature [29] (Fig. 1).

2.4. Multiple cross couplings: synthesis of theoretically interesting molecules

The application of palladium-catalyzed cross-coupling reactions on oligohaloalkenes and -arenes can most elegantly and simply lead to highly substituted carbo- and heterocyclic systems [1,2,13]. By far the shortest and most efficient route to symmetrically substituted dibenzoannelated [2.2]paracyclophanedienes of type **21** is the one applying a 4-fold Heck reaction to 1,2,9,10-tetrabromo[2.2]paracyclophanediene (**18**) with styrene and various substituted styrenes **19**, and subsequent 6π-electrocyclization followed by aromatization [30]. It is important to note that good yields in these multiple Heck-coupling reactions were only achieved under the modified conditions of Jeffery [31] employing a base like potassium carbonate and a phase-transfer catalyst (a quaternary ammonium salt) rather than the classical Heck conditions (tertiary amine base in the presence of a phosphane) [32] (Scheme 4).

Under analogous conditions, the readily available 4,5,12,13- and 4,7,12,15-tetrabromo[2.2]paracyclophanes were coupled with styrenes to yield the hydrocarbons **22** and **23** (7–70% isolated), with phenylacetylene under palladium-copper co-catalysis (Yamamoto protocol) [33] to give the tetraalkynylated [2.2]paracyclophane derivative **24** (70%), and with phenylmagnesium bromide to yield 4,7,12,15-tetraphenyl[2.2]paracyclophane (**25**), albeit in low yield (6%) [34]. The tetraalkynyl-substituted compound **24** follows in the footsteps of the hexakisalkynylbenzene derivatives **26** of Moroz et al. [35], Vollhardt et al. [32], Praefcke et al. [37] and Heck et al. [32]. Various 1,2-, 1,3-, 1,4-di-, 1,2,3-, 1,3,5-tri- and 1,2,4,5-tetrasubstituted benzene derivatives such as **27**, **28** and **29** were also prepared by this protocol [38,39] (Fig. 2).

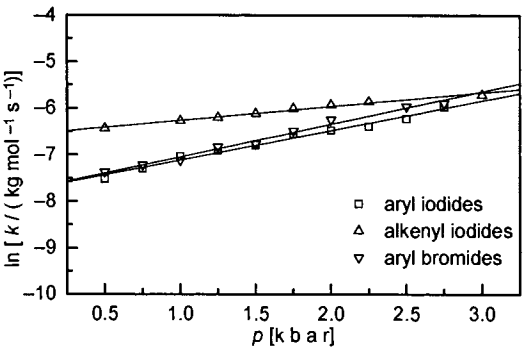
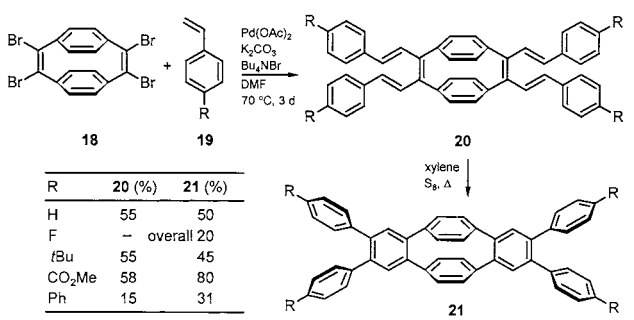


Fig. 1. Pressure dependence of the overall rate coefficients for the Heck reactions of different organyl halides [29].

Surprisingly, the 2-fold alkenylations of *cis*-1,2-dibromoethene, 1,2-dibromocyclopentene (**30**) and 1,2-dibromocyclohexene (**31**) proceed with better yields under the classical Heck conditions [40a]. The resulting (*E,Z,E*)-hexatrienes **32**, **33** reasonably cleanly undergo 6π-electrocyclizations upon heating to 130–150°C in an inert solvent such as di-*n*-butyl ether or xylene in the absence of oxygen to give the ring-annelated *cis*-5,6-disubstituted cyclohexadienes **34** and **35**. In the presence of oxygen these products are easily dehydrogenated to the corresponding ring-annelated benzene derivatives (Scheme 5).

The central tetrasubstituted and thereby most nucleophilic double bonds in the trienes **32**, **33** can be selectively epoxidized with various reagents. The resulting dialkenylepoxides **38**, **39** are set up for a Cope



R	20 (%)	21 (%)
H	55	50
F	–	overall 20
*t*Bu	55	45
CO_2Me	58	80
Ph	15	31

Scheme 4. 1,2:9,10-Dibenzo[2.2]paracyclophanedienes by 4-fold Heck reactions followed by 6π-electrocyclizations.

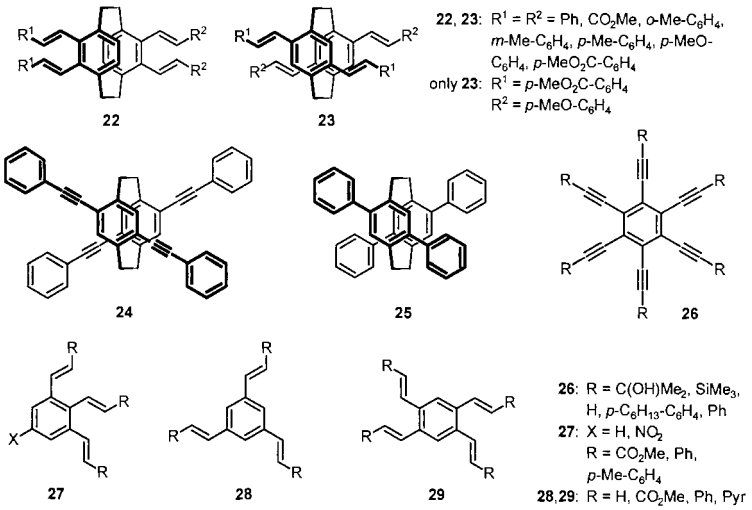


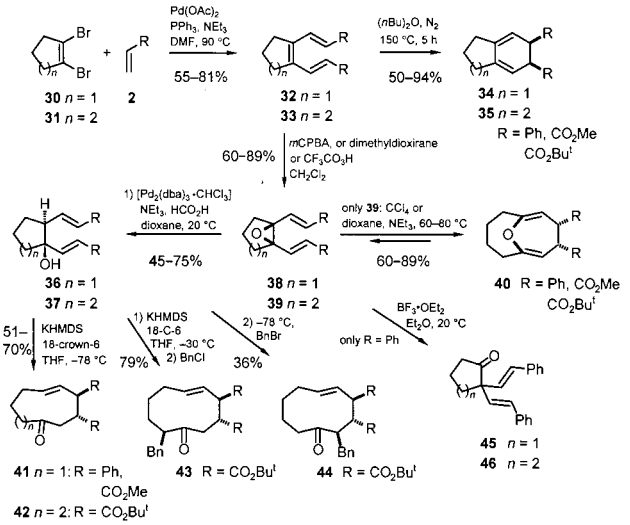
Fig. 2. Highly alkenylated and alkynylated benzene derivatives by palladium-catalyzed multifold cross-coupling reactions.

rearrangement. But only the six-membered ring derivatives **39** equilibrate at elevated temperatures (60–80°C) via Cope rearrangement with the oxygen-bridged cyclodeca-1,5-dienes **40** which are strained bridgehead dienes. The five-membered ring derivatives **38** do not rearrange to the corresponding more highly strained oxygen-bridged cyclononadienes, but undergo an irreversible acid-catalyzed 1,2-alkenyl shift to the cyclopentanone derivatives **45** when heated for extended times. The same rearrangement of **38**, **39** (R = Ph) can be brought about with a drop of acid (e.g. $BF_3 \cdot OEt_2$) at room temperature to yield **45**, **46**. In pure $BF_3 \cdot OEt_2$ even the diester **38** ($R = CO_2Me$) undergoes this 1,2-alkenyl shift while the diester **39** ($R = CO_2Me$) undergoes ring contraction by 1,2-alkyl shift to yield a cyclopentanone derivative [40b].

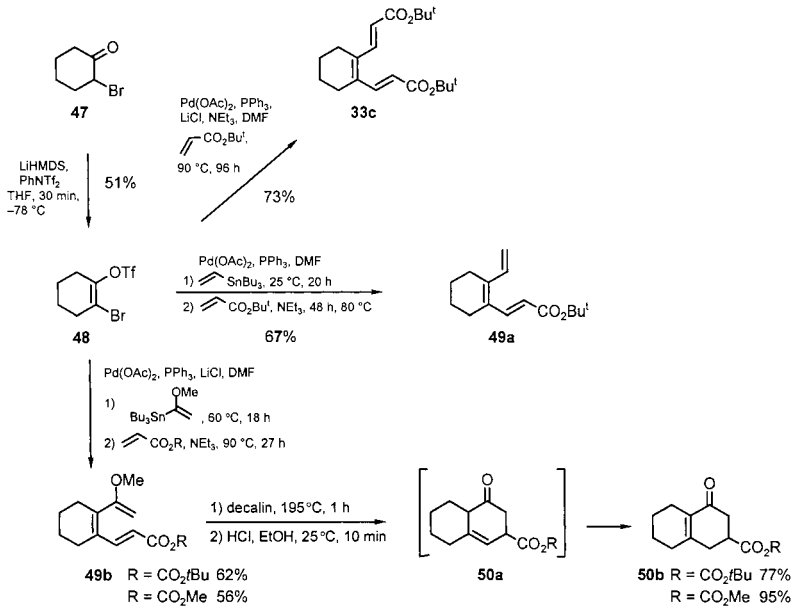
On the other hand, both types of epoxides can selectively be ring-opened by palladium-catalyzed reduction according to the protocol developed by Tsuji and Shimizu et al. [41] for vinyloxiranes. The resulting alcohols **36**, **37**, upon deprotonation at −78°C, undergo an oxyanion-accelerated [42] Cope rearrangement to give the *trans*-3,4-disubstituted *trans*-cyclonon-5-en-1-ones **41** and *trans*-cyclodec-5-en-1-ones **42**, respectively. The intermediate enolates in this rearrangement can be trapped with other electrophiles such as benzyl halides. Surprisingly, with the less reactive benzyl chlorides at −30°C, only the 8-benzyl derivative **43** (structure and configuration proved by X-ray crystal structure analysis) was obtained in high yield (79%). The more reactive benzyl bromide, however, traps the initially formed enolate at lower temperature (−78°C) to give the 10-benzyl derivative **44** (structure also proved by X-ray structure analysis), albeit in lower yield (36%), and accompanied by the 8-benzyl derivative (31% yield) [45].

Essentially, an enantioselective variant for the preparation of such highly substituted cyclononenones and cyclodecenones **41**–**44** can be developed, as the enantioselective desymmetrization of the dialkenylepoxides **38**, **39** by palladium-catalyzed reduction can be effectuated in the presence of chiral ligands. So far, a β-(naphthylphenyl)phosphinocarboxylate ligand derived from *tert*-butyl myrtenate [43] with $[Pd_2(dba)_3 \cdot CHCl_3]$ gave a ligand-induced enantiomeric excess (e.e.) of 15%, with (*R*)-PROPHOS [44] as a ligand the e.e. was raised to 36%. An optimization of this procedure is underway [45].

The scope of the 2-fold coupling to give 1,3,5-hexatrienes could be extended by applying the 1-bromo-2-(trifluoromethanesulfonyloxy)cyclohexene (**48**) which was easily prepared from 2-bromocyclohexanone (**47**). Favorably, the yield in the 2-fold Heck coupling of **48**



Scheme 5. A {2 + 2 + 2} assembly to yield six-membered rings, and a four-carbon ring-enlargement methodology.

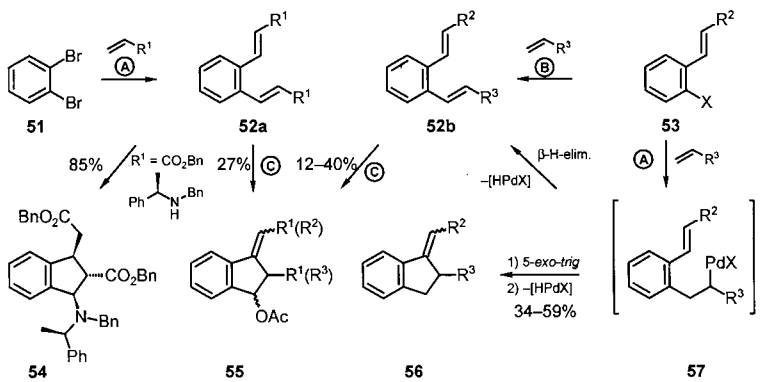


Scheme 6. A route to unsymmetrically 1,6-disubstituted 1,3,5-hexatrienes like **50a,b** from 2-bromocyclohexanone (**47**).

with *t*-butyl acrylate was considerably higher than that obtained from 1,2-dibromocyclohexene (**31**). In addition, a sequence of a Stille coupling with a vinylstannane and a Heck reaction with an alkene can be applied to **48** in a one-pot operation to give unsymmetrically 1,6-disubstituted 1,3,5-hexatrienes such as **49a**,**b** [45]. The thermal 6π-electrocyclization of **49b** can be brought about by heating at 195°C in decalin to yield, after acidic work-up, the double-bond-shifted octahydronaphthalenone **50b**. This protocol thus provides a six-membered ring annelation complementary to the established Robinson annelation as it leads to a different distribution of the functionalities (Scheme 6).

With appropriate nucleophiles, the 1,6-bis(alkoxycarbonyl)-substituted hexatrienes **33** undergo a completely diastereoselective domino-Michael reaction, e.g. with ammonia equivalents, to yield protected five-membered ring β-amino acids which are *cis*-pentacin analogs. The analogous domino-Michael reactions to give the corresponding indane derivatives **54** have been carried out with the 2-fold coupling products **52** of *o*-dibromobenzene (**51**) with acrylates [46].

Five-membered ring closure has also been observed under palladium catalysis when *o*-halostyrene derivatives **53** were coupled with alkenes [47]. Apparently an intramolecular carbopalladation with 5-*exo*-trig ring closure can favorably compete with β-hydride elimination in the intermediate β-(*o*-ethenylphenyl)ethylpalladium halide **57**. This reaction mode for **53** is observed especially under Jeffery conditions when R^3 in **57** is H, Me or OR. Under the same conditions, however, *o*-dibromobenzene (**51**) gives very high yields of *o*-dialkenylbenzene derivatives **52** [38,46]. The *o*-dialkenyl-benzenes **52** can also be cyclized to indane



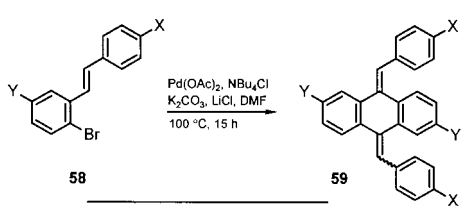
R¹ = H, Ph, CO_2Me, CO_2Bn; R² = H, R³ = Ph; R² = H, R³ = CO_2Bu^t; R² = Me, R³ = Me; X = Br, I

Scheme 7. Vicinal dialkenylbenzene derivatives and their follow-up reactions. **A**: $Pd(OAc)_2$, K_2CO_3 (or $KHCO_3$), LiCl, Bu_4NBr, DMF (or NMP), 60–100°C.—**B**: $Pd(OAc)_2$, PPh_3 [or P(*o*-Tol)$_3$], NEt_3, MeCN (or NMP), 60–100°C.—**C**: $Pd(OAc)_2$, benzoquinone, MnO_2, HOAc, 40–50°C.

derivatives **55** under palladium(II) catalysis (Wacker-type conditions), albeit the yields in this latter process are moderate at best [47] (Scheme 7).

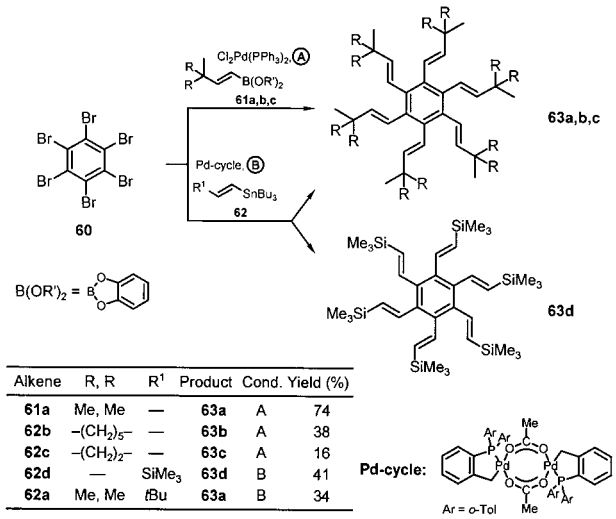
Yet another cyclization was observed for *o*-bromostilbenes **58** which actually competes with the second coupling step of *o*-dibromobenzene when only one equivalent of styrene is used. *o*-Bromostilbene (**58a**) and substituted analogs **58b**–**g**, prepared from *o*-bromobenzaldehydes by Wittig–Horner–Emmons olefinations, undergo efficient cyclodimerization to (*E*/*Z*)-9,10-dibenzylidene-9,10-dihydroanthracenes **59a**–**g**. The (*Z*)-diastereomers of the parent compound **59a**—characterized by an X-ray crystal structure analysis—and its dimethyl derivative **59b** preferentially crystallize from the crude mixtures, while the (*E*)-diastereomers could never be obtained in pure crystalline form. When heated to over 120°C in solution, the (*Z*)-form isomerizes into the (*E*)-form and back [48] (Scheme 8).

A 6-fold Heck coupling of hexabromobenzene (**60**) with styrene and substituted styrenes under conditions of the Jeffery protocol readily occurred [49]. The products obtained in high yields all showed a dominant molecular ion peak for the correct mass in the mass spectrum, however, according to the ^{1}H- and ^{13}C-NMR spectra as well as a HPLC analysis, they were mixtures of a large number of isomers, apparently formed by additional intramolecular cyclization of intermediates of type **57**, and these isomers could not be separated [50,51]. Since such σ-alkyl intermediates are not formed in Suzuki- and Stille-type couplings, the 6-fold coupling reaction of **60** with the alkenylboronate **61a** prepared by hydroboration of *tert*-butylacetylene with catecholborane worked marvelously to give the C_6-symmetric hydrocarbon **63a** in analytically pure crystalline form in up to a 74% yield [52]. It turned out that the *t*-butyl groups in **61** are essential for the success, as alkenylboronates with other *t*-alkyl groups like **61b**,**c** and even 2-adamantylethenylboronates underwent the 6-fold coupling reasonably well, while unbranched *n*-alkenylboronates did not give any of the corresponding 6-fold coupling products. An interesting self-organizing effect associated with the bulky alkyl groups and van der Waals attractive interactions may play an important role in these couplings. The compound **63a** as well as the analogous hexakis(trimethylsilylethenyl)benzene **63d** could also be obtained by 6-fold Stille coupling of **60** with the corresponding alkenylstannanes **62a** and **63d**. Both **63a** and **63d** are cup-shaped molecules with six arms rotated about 50° out of the plane of the central ring, all to one side [52] (Scheme 9).



	X	Y	%	*E*/*Z*
a	H	H	80	1:2.9
b	Me	H	75	1:2
c	OMe	H	70	1:2
d	CO_2Me	H	72	1:1
e	NO_2	H	56	1.8:1
f	H	CO_2Et	78	~1:1
g	OMe	CO_2Et	64	~1:1

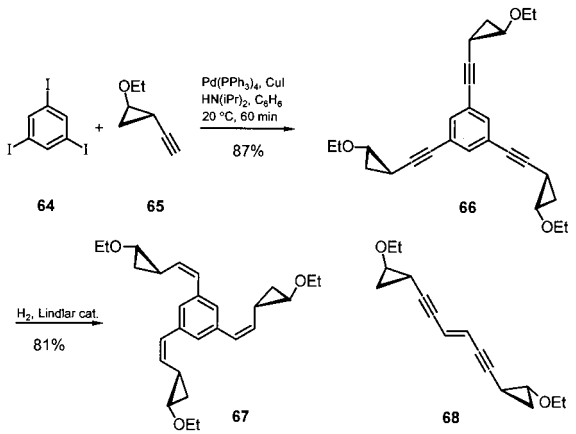
Scheme 8. Cyclodimerization of *o*-bromostilbenes to 9,10-dibenzylidene-9,10-dihydroanthracenes.



Alkene	R, R	R^1	Product	Cond.	Yield (%)
61a	Me, Me	—	**63a**	A	74
62b	$-(CH_2)_5-$	—	**63b**	A	38
62c	$-(CH_2)_2-$	—	**63c**	A	16
62d	—	$SiMe_3$	**63d**	B	41
62a	Me, Me	*t*Bu	**63a**	B	34

Scheme 9. 6-fold Suzuki and Stille couplings of hexabromobenzene. **A**: $[PdCl_2(PPh_3)_2]$, NaOH, toluene/THF (1:1), 100°C, 24 h.—**B**: Pd-cycle from $Pd(OAc)_2$ and P(*o*-Tol)$_3$, toluene, 100–120°C, 1–4 days [52].

Multifold coupling reactions of oligohaloarenes with alkynes under palladium–copper co-catalysis (Sonogashira–Hagihara protocol) apparently are not a problem as impressively demonstrated for hexabromobenzene with various alkynes [36] and even butadiynes [53]. The 3-fold coupling of the enantiomerically pure ethoxyethynylcyclopropane **65** with 1,3,5-triiodobenzene (**64**) therefore went smoothly and led to the C_3-symmetric product **66** (87% yield). Partial hydrogenation of the triple bonds furnished the final product, an interesting model compound for chiral discotic liquid crystals [54]. The analogous 2-fold intermolecular cross coupling of ethynylcyclopropane **65** with 1,4-diiodobenzene proceeded with a 71% yield, while that with *cis*- and *trans*-dibromoethene gave modest yields (24 and 19%, respectively). Interestingly, however, the cross coupling of the chlorozinc derivative prepared from **65** by lithiation at the acetylene terminus, and metal–metal exchange, with the mixture of *cis*- and *trans*-1,2-dibromoethene gave a high yield (76%) of only the *trans*-configurated enediyne **68** with two terminal 2-ethoxycyclopropyl substituents [54]. Terminally substituted vinylcyclopropanes are also accessible by



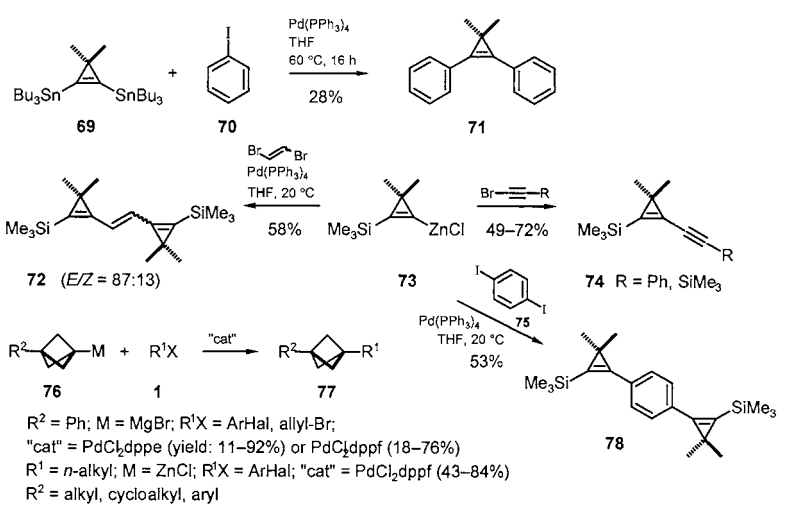
Scheme 10. Multifold Sonogashira–Hagihara coupling reactions.

hydroalumination of ethynylcyclopropanes followed by palladium-catalyzed cross coupling with e.g. iodoarenes [55] (Scheme 10).

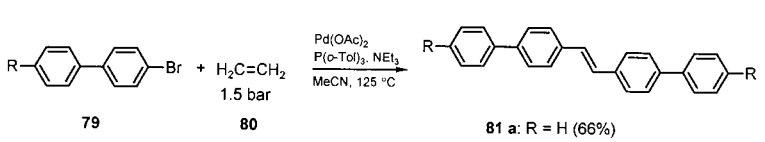
Even highly strained cyclopropenes which are known to undergo various transition-metal catalyzed co-oligomerization reactions [56], can be cross coupled with aryl, alkenyl and alkynyl halides under Pd or Pd–Cu catalysis via zinc and tin derivatives. The 1,2-bis(trimethylstannyl)-3,3-dimethylcyclopropene (**69**) undergoes a 2-fold Stille coupling with iodobenzene (**70**) to give diphenylcyclopropene **71**, while the chlorozinc derivative **73** could be coupled with haloalkenes such as 1,2-dibromoethene to yield 1-alkenylcyclopropenes such as **72**, as well as with haloalkynes to yield 1-alkynylcyclopropenes like **74** [57]. Bridgehead bromomagnesium **76-MgBr** and chlorozincbicyclo[1.1.1]pentane derivatives **76-ZnCl** can be cross coupled with aryl and alkyl halides under palladium(0) catalysis to give various 1,3-disubstituted bicyclo[1.1.1]pentyl derivatives of type **77**, some of which have quite interesting liquid crystalline properties and are not easily accessible by any other routes [58] (Scheme 11).

As was pointed out by Heck et al. in one of their early publications [59], the palladium-catalyzed alkenylation of aryl halides can very well be performed with ethene itself. The 2-fold Heck coupling of ethene (**80**) with 4-bromobiphenyl derivatives **79** can favorably be employed to prepare 4,4′-diarylstilbenes **81a** and **81b** which are used as laser dyes [60] (Scheme 12).

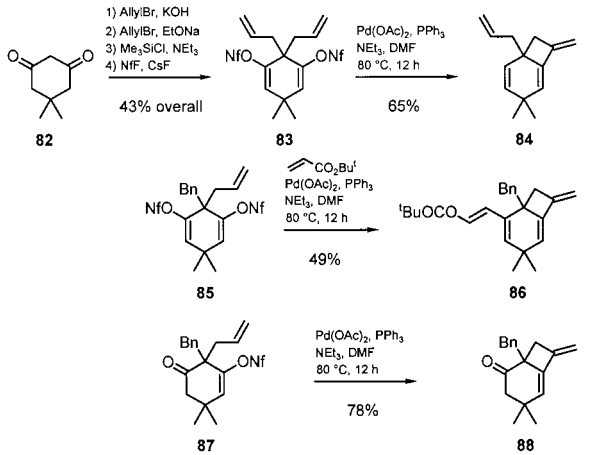
The enantioselective formation of quaternary stereogenic centers has always been one of the ultimate targets in stereoselective organic synthesis [61]. This issue has been addressed in the elegant work of Shibasaki et al. [15a,62] which has led to a desymmetrization in a Heck reaction of a diene moiety by way of a chiral ligand on the catalyst. More recently, we have developed the intramolecular Heck coupling of the bisnonaflate **85** with two enantiotopic leaving groups [63]. This reaction as well as that of the bisnonaflate **83**, prepared in four steps from dimedone (**82**), which gives rise to rather strained 8-methylenebicyclo[4.2.0]octa-1(2),4-dienes **84**, **86**, present themselves for ligand-controlled stereo selection yet the enan-



Scheme 11. Metallated cyclopropenes and bicyclo[1.1.1]pentanes as coupling partners.



Scheme 12. Efficient 2-fold Heck couplings with ethene.

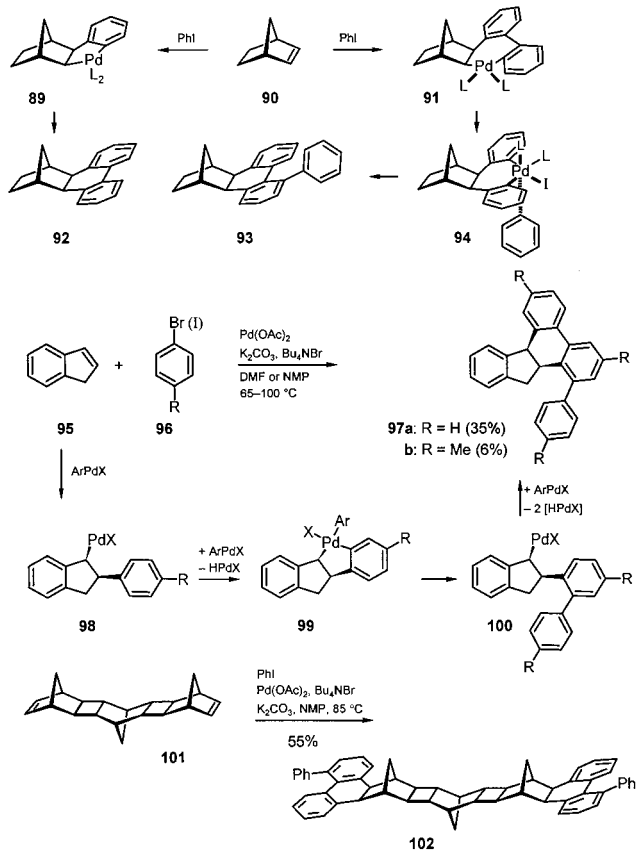


Scheme 13. Facile preparation of 8-methylenebicyclo[4.2.0]oct-1(2),4-diene derivatives by intramolecular Heck reactions.

tiomeric excesses achieved with chiral catalysts, have been rather low ($\leq 30\%$) so far. A competing Cope rearrangement, as observed in the Heck reactions of open-chain 1,5-hexadienes [64,65], was not observed in these cases; apparently, the transition structure of such a Cope rearrangement would be highly strained. The second nonafluorosulfonyloxy group in **83** was reductively removed under the reaction conditions. In the presence of an acrylate, the second nonaflate leaving group in **85** took part in the sequential reaction consisting of an intramolecular and an intermolecular Heck coupling to give the bicyclic product **86**. Similarly, alkynes could be applied to terminate this sequence (Scheme 13).

2.5. Palladacycle intermediates: obstacles and new opportunities

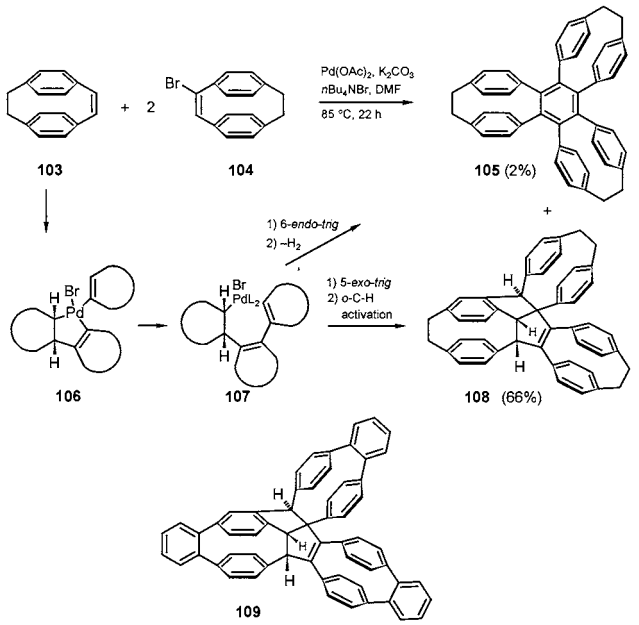
Quite unusual domino-type multiple coupling reactions can be performed with certain cyclic alkene substrates, when the first *syn*-carbopalladation leads to an alkylpalladium intermediate which cannot undergo a *syn*-β-hydride elimination. The σ-alkylpalladium intermediate then continues to react with another alkene, another alkenyl halide or aryl halide. The outcome of such reactions which have been thoroughly investigated by Chiusoli et al. [66] particularly for the strained alkene norbornene, can be 2:1, 1:2 or even 1:3 coupling products of the alkene with an alkenyl halide or an aryl halide, respectively. Palladacycles such as **89** which are formed by hydrogen halide elimination from the *syn*-carbopalladation product, and alkyldiarylpalladium(IV) halide intermediates of type **94** play a key role in these reactions. Under traditional Heck conditions, the 1:2 cross-coupling-cyclization product **92** is obtained [66], whereas under Jeffery conditions the 1:3 coupling product **93** is exclusively formed [67,68] (Scheme 14).



Scheme 14. A domino-Heck coupling of norbornene, indene, and norbornadiene trimer involving an *ortho*-C–H activation.

Indene (**95**) undergoes *syn*-carbopalladation with arylpalladium halides regioselectively to give **98** which reacts further via the palladacycles **99** and intermediate **100** to yield 1:3 coupling product **97** analogous to the products of type **93** from norbornene, but differs in its regiochemistry [67]. 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 **101** which is obtained by $Ni(COD)_2$-catalyzed trimerization of norbornadiene, can be transformed to **102** by a 1:6 coupling with iodobenzene performed in a single operation with a 55% yield [69].

In essence, these domino-coupling reactions form cyclohexadiene fragments from three two-carbon fragments. The 1:2 coupling of norbornene and iodobenzene discovered by Chiusoli et al. [66] can also be adopted to couple norbornene with β-bromostyrene [68,70,71]. In an attempt to apply this palladium-catalyzed $(2+2+2)$ assembly for an alternative and more productive access to Hopf's trifoliaphane **105** [72], a 1:2 mixture of [2.2]paracyclophan-1-ene (**103**) and 1-bromo[2.2]paracyclophan-1-ene (**104**) was treated with palladium acetate under Jeffery conditions. Surprisingly, the expected dihydro derivative of **105** was not found at all, and **105** was obtained as a minor by-



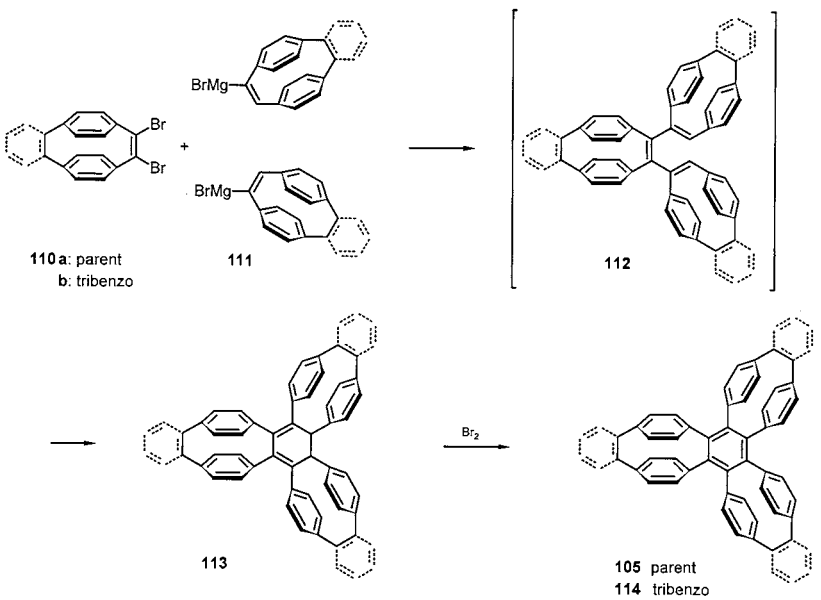
Scheme 15. Unusual hydrocarbons formed by 1:2 couplings of strained alkenes with strained alkenyl bromides.

product (2%) only. The main product was the hydrocarbon **108** consisting of three [2.2]paracyclophane units linked by a common bicyclo[3.3.0]octene unit [73] (Scheme 15).

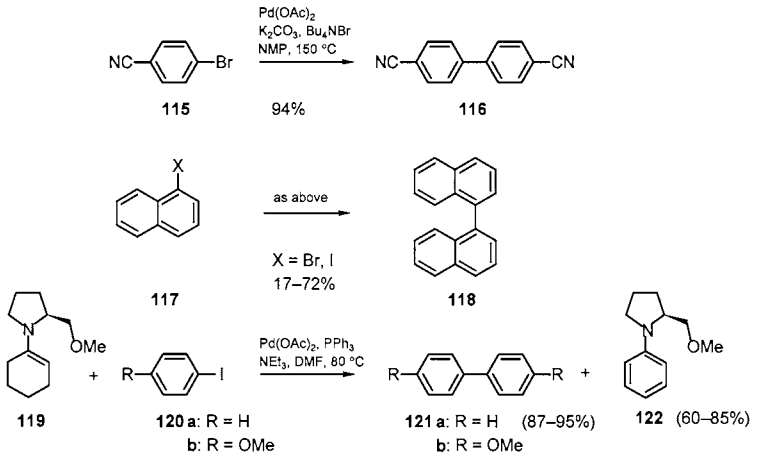
Apparently, the key intermediate **107** formed via the palladacycle **106**, an alkyldialkenylpalladium(IV) species, preferentially undergoes a 5-*exo*-*trig* carbopalladation with subsequent formation of another palladacycle by *ortho*-attack on the neighboring aromatic ring, rather than 6-*endo*-*trig* carbopalladation to give the precursor to **105**. The tribenzoanalog of **108**, the interesting $C_{60}H_{38}$ hydrocarbon **109**, was obtained in a 52% yield from 9,10-benzo[2.2]paracyclophan-1-ene and 9,10-benzo-1-bromo[2.2]paracyclophan-1-ene (1:2 ratio) under the same conditions [73]. Similar types of C–H activation have been observed by Dyker et al. in the Heck-type reactions of *o*-iodo-*tert*-butyl- and *o*-iodomethoxyarenes to give defined polycondensed oligomers [74].

However, trifoliaphane **105** could be obtained in remarkably good yields (47% overall) by a palladium-catalyzed 2-fold coupling of 1,2-dibromo[2.2]paracyclophane-1-ene (**110a**) with [2.2]paracyclophane-1-magnesium bromide (**111a**) leading to the 1,3,5-hexatriene intermediate **112** which underwent 6π-electrocyclization under the coupling conditions (Scheme 16). The dihydrotrifoliaphane **113** upon treatment with bromine cleanly underwent aromatization (Scheme 16). The same sequence carried out with 9,10-benzo-1,2-dibromo[2.2]paracyclophane **110b** and the Grignard reagent **111b** gave the new tribenzotrifoliaphane **114** in a 40% overall yield [73].

It is interesting to note in this context that aryl–aryl homocouplings were observed as side reactions under the conditions for the preparation of **93**, **97**, **102** etc [75]. This may be explained by an additional oxidative addition of an aryl halide to the aryl palladium halide, which reacts more slowly in the presence of highly substituted or/and electron rich alkenes. In fact, this side reaction has been further elaborated to an efficient biaryl synthesis [69,76] from aryl halides in the absence of alkenes and does not require the unpleasant triphenylarsine additive as in a previously published procedure [77]. The advantage of the palladium-catalyzed coupling in comparison to the well established



Scheme 16. Facile synthesis of trifoliaphane **105** and tribenzotrifoliaphane **114** [73].



Scheme 17. Palladium-catalyzed homocoupling of haloarenes to give biaryls.

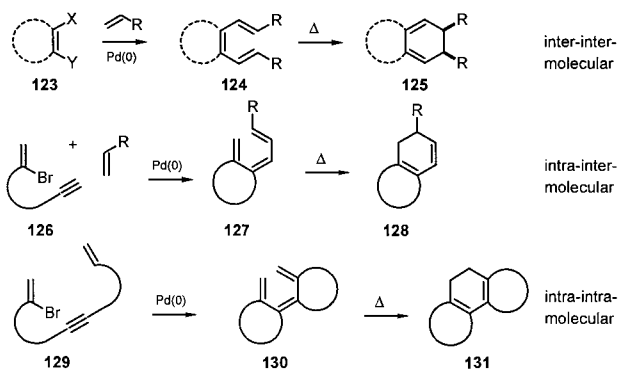
Ullmann reaction in its various forms is that with only catalytic amounts of palladium acetate used, the work-up and purification of the products is easier [69,76]. In an attempt to perform a Heck coupling of the chiral enamine **119** with iodobenzene (**120a**) only biphenyl (**121a**) and the *N*-phenylpyrrolidine **122** were obtained. The latter apparently arises by oxidation of the enamine **119** as evidenced by the fact that no cross-over product was obtained with *p*-methoxyiodobenzene (**120b**). This oxidation of enamines can be viewed as an efficient access to *N*,*N*-disubstituted aromatic amines [78] (Scheme 17).

2.6. Reaction cascades starting with one or more Heck reactions: facile formation of bicycles, tricycles, tetracycles and more

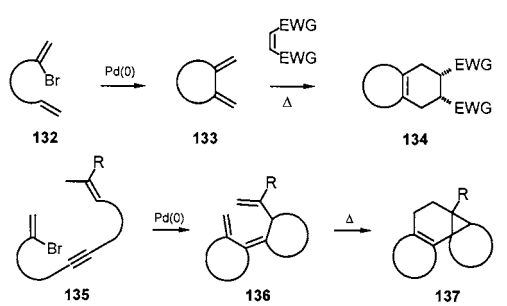
Non-aromatic polycyclic systems play an important role as skeletons of many biologically active compounds. Because of their high efficiency, domino-type and other sequential reactions have attracted a great deal of interest in recent years [8,79]. An in depth investigation into the scope and limitations of reaction cascades consisting of several inter- or intramolecular Heck-type couplings followed by a purely thermal reaction such as a 6π-electrocyclization (Scheme 18) or a cycloaddition (Scheme 19) has unveiled a number of highly efficient processes for the construction of complex oligocyclic skeletons [80–83].

The combination of two intermolecular Heck reactions on a 1,2-dihalocycloalkene **30**, **31** with a subsequent thermal 6π-electrocyclization of the resulting 1,3,5-hexatrienes **32**, **33** leads to ring-annelated *cis*-5,6-disubstituted cyclohexadienes **34**, **35** (see Scheme 5). In these cases, the 6π-electrocyclization requires significantly higher temperatures (50–70°C higher) than the Heck reaction. The sequence of an intra- and an intermolecular Heck reaction followed by a 6π-electrocyclization gives the ring-annelated aromatic compounds, from 2-bromoalkeneynes, such as **138**, and alkynes [84] and yet can also yield ring-annelated cyclohexa-1,3-dienes of the type **140** in particular when performed with enol ethers as an alkene component (Scheme 20) [84].

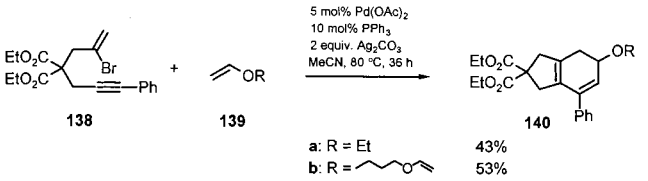
The fully intramolecular version of this three-step sequential reaction for 2-bromododeca-1,11-diene-6-ynes like **141**, **143**, 2-bromotrideca-1,12-diene-7-ynes like **145** and -6-ynes like **147**, in which an alkenyl bromide starter, an alkynyl relay and an alkenyl terminator are all tethered in a single acyclic precursor



Scheme 18. Possible domino reactions consisting of Heck couplings and consecutive 6π-electrocyclizations.



Scheme 19. Conceivable domino reactions consisting of one or more Heck couplings and subsequent inter- or intramolecular cycloadditions.



Scheme 20. Sequences of intra- and intermolecular Heck reactions followed by 6π-electrocyclization.

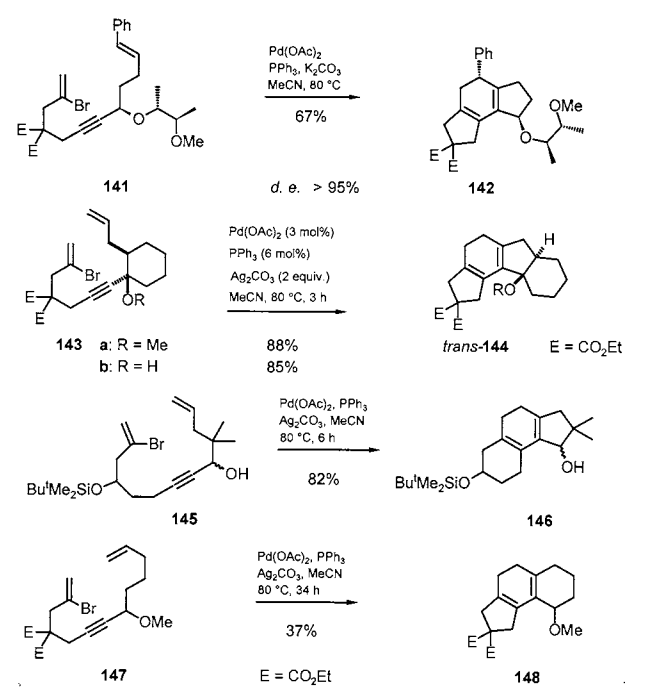
molecule, proceeds smoothly to form three new cycles in a tricyclic array with a central cyclohexa-1,3-diene moiety (Scheme 21) [85]. In all of these cases the 6π-electrocyclization occurs under the conditions of the Heck reaction (60–100°C), and the yields are good to excellent (up to 95%), as long as only five-membered rings are formed in the Heck-type cyclization steps. The overall yields are not as good when one of the Heck-type cyclizations leads to a six-membered ring, especially if this is the second cyclization step as in the transformation **147**→**148** [86].

An analogous sequence of events occurs in the palladium-catalyzed tricyclization of enediynes developed by Trost et al. [87] in which the initiating step is an addition of a hydridopalladium species to a triple bond rather than an oxidative addition of an alkenyl bromide to a Pd(0) complex.

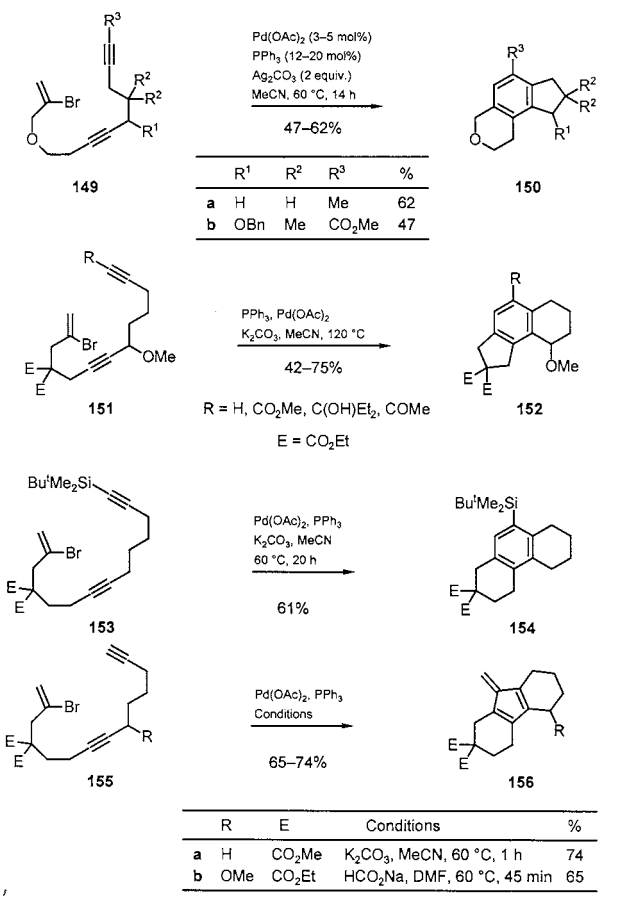
A complementary cascade tricyclization of 2-bromoalk-1-enediynes such as **149**, **151**, **153** leads to angularly bisannelated benzene derivatives (Scheme 22) [87,88]. This tricyclization results in reasonable yields of even octahydrophenanthrene skeletons such as **154**, but only when the precursor bromoenediyne is terminally substituted with a trialkylsilyl group. Terminally unsubstituted bromoenediynes like **155a**,**b** apparently undergo a 5-*exo*-*trig* instead of a 6-*endo*-*trig* cyclization in the third step, with further cyclization and rearrangement to eventually yield the bisannelated fulvenes **156a**,**b** in quite good yields [84] (Scheme 22).

Nitrogen and oxygen containing tricyclic dienes analgous to the skeleton of **142** can be prepared from appropriately substituted acyclic 2-bromodieneyne precursors without problems. Thus, the diaza- **158** and dioxatricycle **160** were obtained from **157a** and **159** in 55 and >80% yields, respectively (Scheme 23) [89]. The crude yield of **158** is actually much better, and higher yields can be obtained in larger scale runs in which losses upon purification are minimized. Surprisingly, the dibromodieneyne **157b** could also be cyclized into the same tricyclic product **158**. This reaction involves a reduction analogous to the one in the palladium-catalyzed homocoupling of arylhalides (see above).

The cascade tricyclization presented above can be used to construct oligocyclic skeletons of various natural products such as the steroids. Two strategies can be envisaged to approach the tetracyclic system of steroids



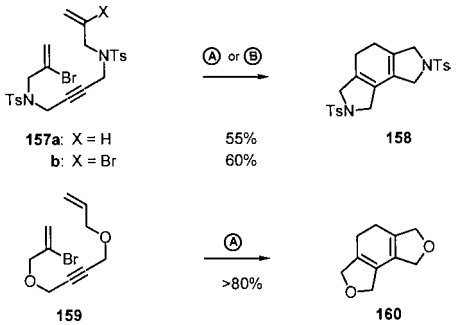
Scheme 21. Sequences of two intramolecular Heck-type reactions immediately followed by 6π-electrocyclization.



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

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

Scheme 22. Angularly bisannelated benzene derivatives and fulvenes obtained by palladium-catalyzed tricyclization cascades.

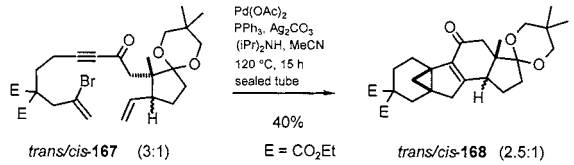


Scheme 23. Bisheterotricyclic skeletons by a Heck–Heck-6π-electrocyclization sequence. **A**: Palladacycle from $Pd(OAc)_2 + (o\text{-}Tol)_3P$ (see Scheme 9), MeCN, K_2CO_3, 80°C, 48 h.—**B**: $Pd(OAc)_2$, PPh_3, DMF, K_2CO_3, 100°C, 4 days.

(**I** and **II** in Scheme 24). Starting with the five-membered D-ring as a monocyclic precursor with two appropriately functionalized tethers as in **161**, the Pd-catalyzed tricyclization would be expected to lead to **163**, a steroid with a cyclohexadiene B-ring, while a six-membered ring, serving as the later A-ring, with the two appropriate tethers as in **164**, would yield the corresponding tetracycle **166** with a diene unit in the C-ring (**II** in Scheme 24).

The feasibility of the second strategy has been demonstrated by Trost et al. [87] applying the related enediyne cycloisomerization methodology and by Negishi et al. [90].

The first strategy (see Scheme 24) appeared to be particularly attractive to approach a steroid with all the essential functionalities, since a precursor like **161** should be accessible even in enantiomerically pure form from the Hajos–Wiechert ketone [91] developed in the context of other steroid total syntheses. Several monocyclic bromodieneynes of type **161**, including the diastereomeric mixture *trans*/*cis*-**167**, were thus assembled. Cyclization of the latter under palladium catalysis, surprisingly gave the pentacyclic compounds *trans*/*cis*-**168**, as revealed by an X-ray crystal structure analysis of *cis*-**168**, rather than the expected tetracyclic system of type **163** [92] (Scheme 25).

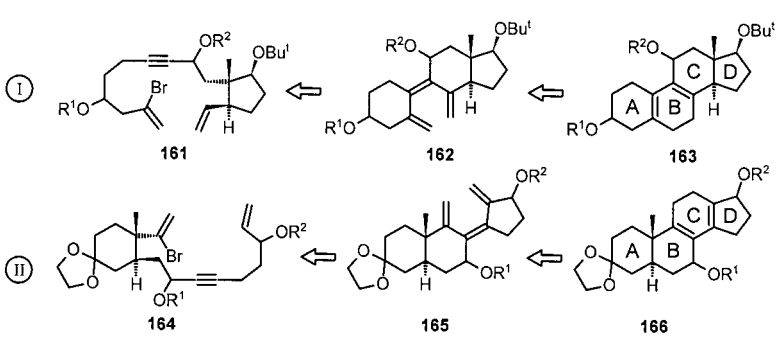


Scheme 25. Multiple intramolecular palladium-catalyzed cross coupling in the construction of the steroid skeleton and the [4.3.1]propellane obstacle.

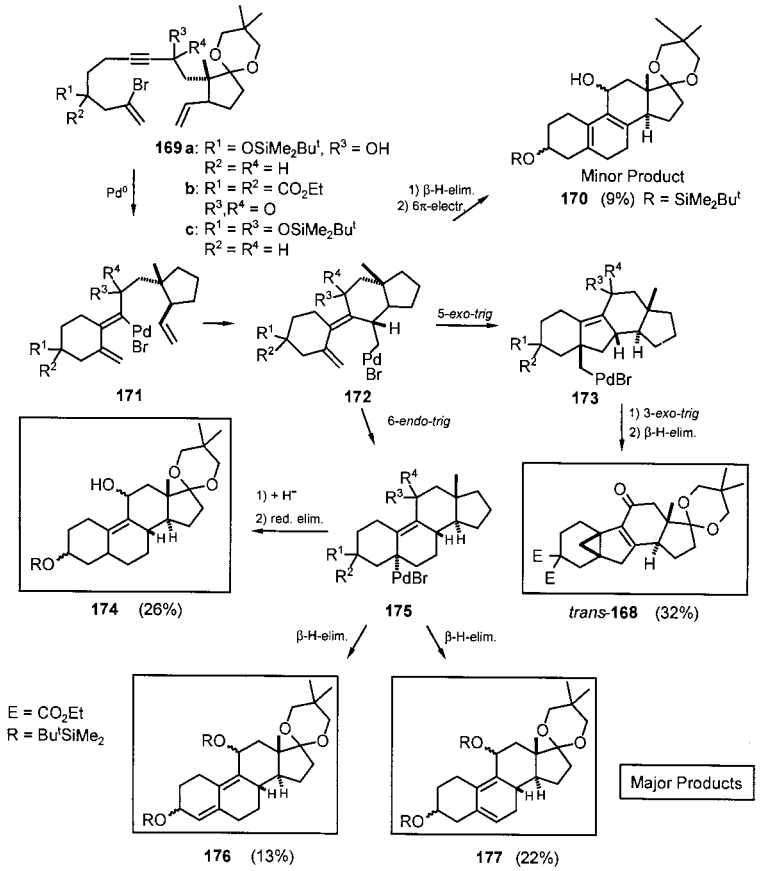
Bromodieneynes **169a** and **169c** with a different type of substitution and combination of substituents, under optimized conditions eventually gave the steroid-type tetracyclic compounds **170**, **174**, **176**, and **177**, albeit in poor yields. It is obvious that the β-hydride elimination in the intermediate **172** formed by the second 6-*exo*-*trig* cyclization, must be relatively slow so that the normal tricyclization product **170** was observed as a minor product only from **169a** (Scheme 26). Two intramolecular carbopalladations successfully compete with the β-hydride elimination in **172**, a 5-*exo*-*trig* to give **173b** from **172b** and subsequent 3-*exo*-*trig* cyclization eventually leading to *trans*-**168**, and a 6-*endo*-*trig* process apparently favored in **172c** to give **175c** which can lead to **174**, **176** and **177** [92] (Scheme 26).

A vast series of cyclization studies, carried out on simple bromodieneyne model compounds with different tether lengths between the bromoene starter unit, the alkyne triple bond relay and the alkene terminator, revealed that the Heck–Heck-6π-electrocyclization cascade is not a feasible process to assemble the decahydrophenanthrene skeleton **181** (Scheme 27). The tricyclization works particularly well for angular 5.6.5 tricycles **179** and reasonably well for 6.6.5 systems **183**. When the second intramolecular Heck-type coupling leads to a six-membered or larger ring, the process works less efficiently as in the case of the 5.6.6 system **187** or not at all as in the case of **189** (Scheme 27).

According to these systematic model studies, the strategy **II** above (see Scheme 24) should not only be much more feasible than strategy **I**, but also a workable strategy to yield a fully functionalized steroid analog with a cyclohexadiene unit in the C-ring. It should be



Scheme 24. Two new strategies for the construction of the steroid skeleton.



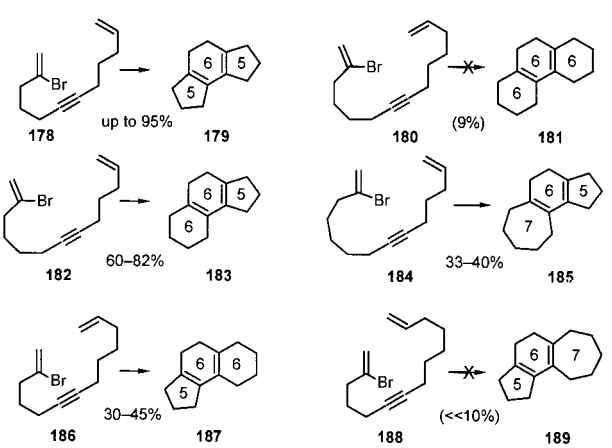
Scheme 26. Mechanistic details concerning formation of the steroid skeleton and a pentacyclic analog from bistethered cyclopentanone derivatives **169**. (For clarity, substituents have been omitted from presumed intermediates).

noted in this context that it is essential to add a silver salt to the mixture or use silver carbonate as a base to prevent the intermediate hexatriene of the type **130** from isomerization.

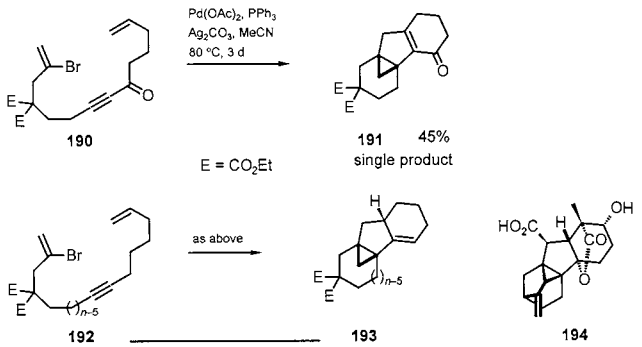
Even though the tricyclization does not work well for angular arrangements of three six-membered rings, the cascade all-intramolecular Heck-type coupling reaction of corresponding 2-bromotetradeca-1,13-diene-7-ynes **190** and **192a** leads to the interesting and potentially useful tetracyclic systems **191** and **193a**, respectively, with a bridging cyclopropane ring joining the A- and B-rings (Scheme 28). At least one natural product, the plant growth regulator 3α-hydroxy-9,15-cyclogibberelin A (**194**) [93] contains the same basic skeleton as **193a**.

The same tetracyclization is also very efficient for the next higher homologue of **192a**, the bromopentadecadieneyne **192b**, in which the first cyclization yields the seven-membered ring in the final product **193b**, and even the eight-membered ring containing tetracycle **193c** could be isolated in a 30% yield from the corresponding precursor **192c** [84]. The bridging cyclopropane ring as in **191**, **193** is an equivalent of an angular methyl substituent. A tetracycle of the type **193** was obtained as a by-product (5–10% yield) even from the oxabromodieneyne precursor **195a** which was set up to give the 6.6.5 tricyclic combination **200**. The tetracycles **197b,c** were obtained in a 62 and 71% yield, respectively, from the corresponding acyclic precursor **195b,c** with substituents $R^1 \neq H$ preventing β-hydride elimination at the intermediate stage **196** (Scheme 29).

Apparently, there are no rules without exceptions. In the above mentioned cascade Heck-type tetracycliza-



Scheme 27. Rules for achievable ring sizes in palladium-catalyzed tricyclizations of 2-bromoalka-1,($n+m$)-diene-($n+1$)-ynes. (Substituents of actual model compounds left off for clarity).



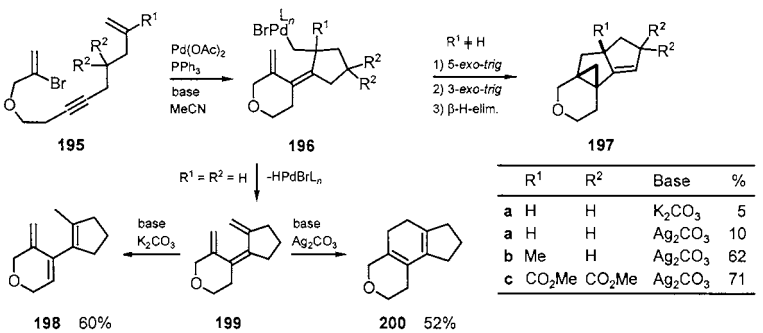
	n	%	
a	6	74	single prod.
b	7	76	single prod.
c	8	30	

Scheme 28. Efficient tetracyclizations of 2-bromotetradeca-1,13-diene-7-ynes and homologues to give [n.3.1]propellanes.

tions, substituents in the acyclic precursors can play a major role and cause the sequential reaction to proceed in an unprecedented direction. The bromodieneyne **201** with a terminal phenyl group apparently sequentially cyclizes to the usual neopentylpalladium intermediate **202** which, due to the proximity of the phenyl group, undergoes an intramolecular electrophilic substitution [94] to give the pentacycle **203** rather than a system corresponding to **193a** by 3-*exo*-*trig* cyclization and β-hydride elimination (Scheme 30). On the other hand, the acyclic precursors **204a**,**b** which differ from **190** and **192** only by their 9-methoxy or 9-silyloxy substituent, eventually yield the novel tetracyclic systems **206a**,**b**, as established by an X-ray crystal structure analysis for compound **206a**. This sequence must also proceed via the tricyclic intermediates **205**, however, it is unclear whether **206** is simply formed by an unprecedented γ-hydride elimination or along a more complicated route.

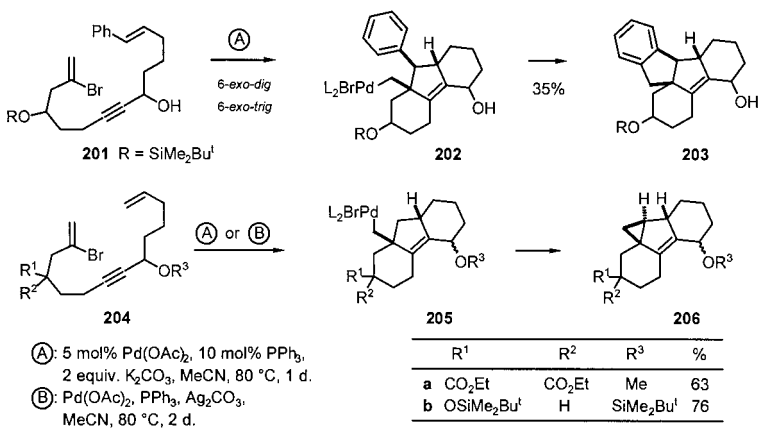
2.7. Domino Heck–Diels–Alder reactions

A variety of fascinating cascade reactions consisting of one or more intra- or intermolecular cross-coupling reactions and some other reaction types have been developed by several groups [2,8,79]. Among the reactions which achieve the most striking increase in molecular complexity from starting material to product are the molecular zipper reactions by Negishi et al. [95], Trost et al. [96], Overman et al. [97], the tri- and tetracyclizations of 2-bromodieneynes by de Meijere et al. [80–86] and the carbonylation intramolecular cross-coupling cascades by Negishi et al. [98] in which up to seven new carbon–carbon bonds are formed in a single operation. Another potentially powerful sequence arises



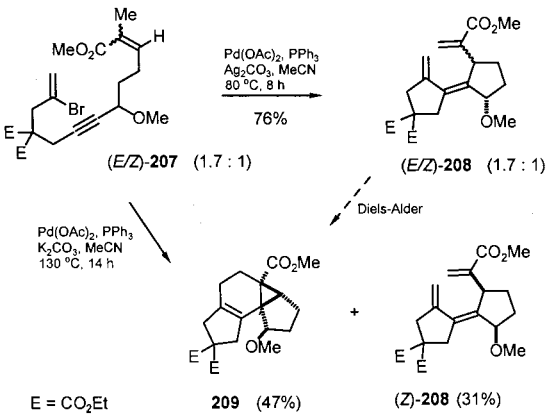
	R1	R2	Base	%
a	H	H	K_2CO_3	5
a	H	H	Ag_2CO_3	10
b	Me	H	Ag_2CO_3	62
c	CO_2Me	CO_2Me	Ag_2CO_3	71

Scheme 29. Tetracyclization of 4-oxa-2-bromotrideca-1,12-diene-7-ynes.

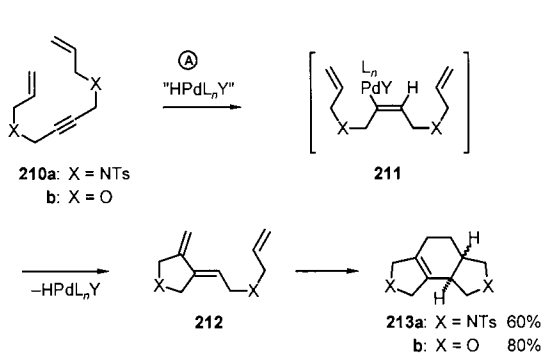


	R1	R2	R3	%
a	CO_2Et	CO_2Et	Me	63
b	$OSiMe_2Bu^t$	H	$SiMe_2Bu^t$	76

Scheme 30. Two other types of tetracyclization of 2-bromotetradeca-1,13-diene-7-ynes caused by a terminal phenyl or a 9-alkoxy substituent.



Scheme 31. The intramolecular domino Heck–Diels–Alder reaction.



Scheme 32. A domino of eneyne cycloisomerization and intramolecular [4 + 2] cycloaddition. **A**: $Pd_2(dba)_3 \cdot CHCl_3$, AcOH (one equivalent), PPh_3, C_6H_6, 80°C, 100 min.

by combining one or two intramolecular Heck-type couplings with an intra- or intermolecular Diels–Alder addition [99]. An all-intramolecular version of such a sequence has been shown to proceed reasonably smoothly for terminally alkoxycarbonyl-substituted 2-bromotrideca-1,11-diene-6-ynes (*E*/*Z*)-**207** 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 (*E*/*Z*)-**208** (Scheme 31), apparently only the (*E*)-isomer (*E*)-**207** undergoes the intramolecular Diels–Alder reaction, as (*Z*)-**208** was observed as unchanged in the mixture with **209**.

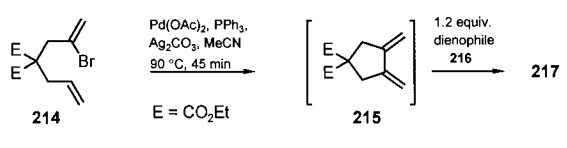
Obviously systems which can undergo intramolecular Diels–Alder reactions can also be set up by a Trost-type eneyne cycloisomerization. Thus, the dieneynes **210a**,**b** upon treatment with $[Pd_2(dba)_3 \cdot CHCl_3]$ in the presence of acetic acid and triphenylphosphane at 80°C gave the bisheterotricycles **213a**,**b** in good to very good yields (Scheme 32) [89]. It is particularly noteworthy that the intermediate triene **212** formed via **211** undergoes the intramolecular Diels–Alder reaction under the conditions of the eneyne cycloisomerization **210** → **212**, i.e. at 80°C.

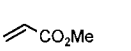
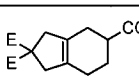
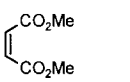
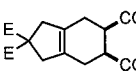
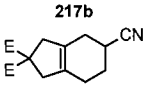
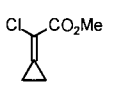
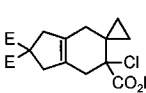
The intermolecular version of this domino Heck–Diels–Alder process has previously frequently been exercised in two steps, especially by Trost et al. [100] and Grigg et al. [101] who have developed the palladium-catalyzed eneyne cycloisomerization [6], the bromoeneyne cyclization-anion capture sequence [102], and the intramolecular Heck coupling of a 2-bromoalka-1,ω-diene to form vicinal dialkylidenecycloalkanes [103].

Since an intramolecular coupling always wins over an intermolecular coupling by at least a factor of 10^5, such a sequential reaction consisting of an intramolecular Heck coupling or eneyne cycloisomerization and an intermolecular Diels–Alder addition, can be favorably performed in a single one-pot operation in the presence of the dienophile, except with dienophiles such as tetracyanoethene (TCNE) and benzoquinones which are strong oxidants [65,104]. The yields without isolating the intermediate dimethylenecyclopentane derivatives **215** are consistently higher than those obtained in two steps (Scheme 33).

This single-operation domino process was further developed to conveniently prepare heteroanalogous bicyclo[4.3.0]non-1(6)-ene derivatives **219** from appropriate acyclic bromodiene precursors **218** [105].

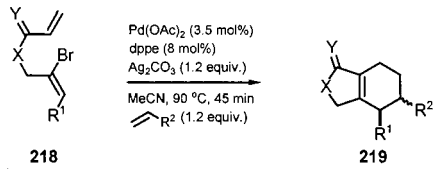
These examples (Scheme 34) demonstrate that the Thorpe–Ingold effect exerted by the *gem*-diester groups in the model 2-bromohepta-1,6-dienes **214** is not essential for the cyclization to occur. In fact, carbocyclic bicyclo[4.3.0]nonene derivatives without the malonate moiety like **219g** (Scheme 34) are also formed without problems. The intramolecular Heck coupling has certain advantages over the eneyne cycloisomerization methodology by Trost et al. [6], i.e. it also works



Dienophile	Product	Yield (%)
 **216a**	 **217a**	93[a] 60[b]
 **216b**	 **217b**	93[a] 67[b]
 **216c**	 **217c**	83[a] 70[b]
 **216d**	 **217d**	83[a] 61[b]

[a] One-pot procedure. - [b] Overall yield in two-step procedure.

Scheme 33. Examples of the intra–intermolecular domino Heck–Diels–Alder reaction which yield bicyclo[4.3.0]non-1(6)-ene skeletons.



218 219

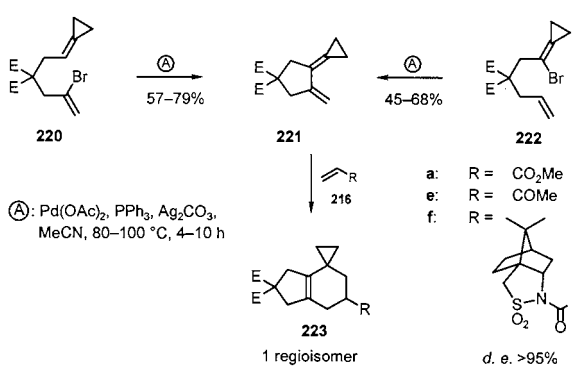
	X	Y	R^1	R^2	%
a	O	H_2	Me	CO_2Me	55[a]
b	OCH–N	H_2	H	CO_2Me	62
c	Bn–N	H_2	H	CO_2Me	46
d	Ac–N	H_2	H	CO_2Bu^t	63
e	p-NO_2-$C_6H_4SO_2$–N	H_2	H	CO_2Bu^t	72
f	Bn–N	O	Me	CO_2Me	51[b]
g	CHOH	H_2	H	CO_2Me	87[c]
h	$CH_2CHOSiMe_2Bu^t$	Me_2	H	CO_2Me	67[d]

[a] Mixture of regioisomers and diastereomers, *cis*-2,3-(*quasi-ortho*) predominating (67%). – [b] Mixture of regioisomers and diastereomers, *cis*-2,3-predominating (71%). – [c] PPh_3 used instead of dppe. – [d] Mixture of regioisomers and diastereomers.

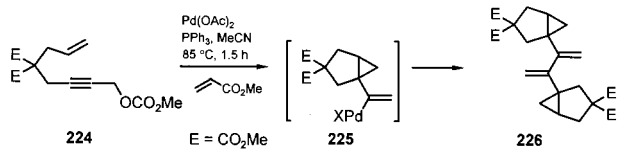
Scheme 34. Examples of the domino Heck–Diels–Alder reaction forming heterobicyclo[4.3.0]non-1(6)-enes **219a–f** and carbocyclic analogs **219g,h**.

reasonably well for the formation of six-membered rings as shown by the examples **219h** from **218h** (Scheme 34). The other advantage is its applicability to 2-bromo-1,6-dienes of the type **220** and **222** with a methylenecyclopropane terminator and a methylenecyclopropane starter moiety, respectively. Both compounds cyclize smoothly in the presence of dienophiles **216** to give the Diels–Alder adducts **223**, derived from the rather sensitive intermediate diene **221**, as single regioisomers without destruction of the three-membered ring as was observed in the attempted cyclization of an eneyne corresponding to **220** [106].

The domino reaction carried out in the presence of the chiral non-racemic acrylamide **216f** gave the cycloadduct **223f** as a single diastereo- and enantiomer (Scheme 35) [107]. These domino cyclizations resulting in spiro(cyclopropane-1,2′-bicyclo[4.3.0]non-1′(6′)-ene) derivatives in high yields are quite remarkable as methylenecyclopropane derivatives have previously been observed to undergo ring-opening under Heck reaction conditions [108,109].



Scheme 35. The domino Heck–Diels–Alder reaction leading to spiro(cyclopropane-1,2′-bicyclo[4.3.0]nonenes).



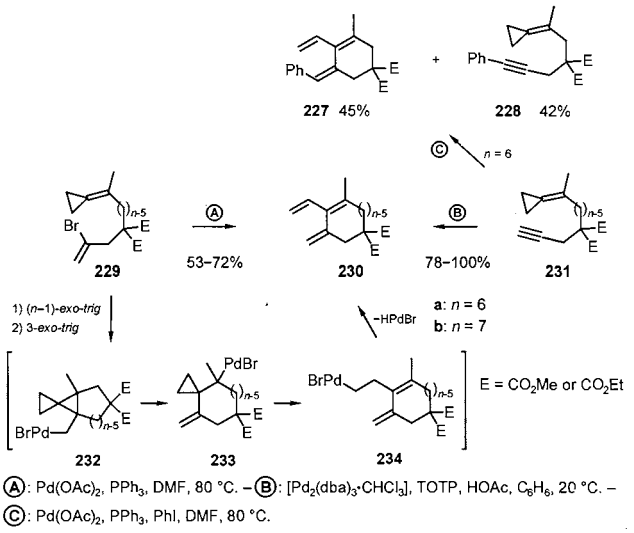
224 E = CO_2Me 225 226

Scheme 36. Unprecedented formation of a 1-ethenylbicyclo[3.1.0]hexane dimer.

In an attempt to prepare the Diels–Alder adduct of the eneallene corresponding to **221** by a domino reaction, the propargyl carbonate **224** [110] was treated with $Pd(OAc)_2$ and PPh_3 in the presence of methyl acrylate. But rather than the expected domino reaction product, only the interesting 1-ethenylbicyclo[3.1.0]hexane dimer **226** was isolated, seemingly as a single diastereomer [111]. This product must have been formed via an ethenylpalladium intermediate of type **225** most probably arising by a 3-*exo*-*trig* cyclization of an intermediate which could have led to the expected eneallene by β-hydride elimination. Surprisingly, the coupling product arising from **225** and methyl acrylate was not observed [112] (Scheme 36).

2.8. Dendralenes by intra- and intermolecular Heck-reaction-rearrangement cascades

Bromodienes with methylenecyclopropane moieties such as **220** and **222** cleanly undergo the intramolecular Heck reaction to give allylidenecyclopropanes of the type **221** (see above). A different situation arises when the methylenecyclopropane moiety has a tetrasubstituted double bond as in compounds **229a**,**b** which are readily accessible by Pd-catalyzed substitution on 1-propenylcyclopropyl tosylate or chloride [113]. The intramolecular Heck reactions of **229a**,**b** do not proceed by simple (*n*–1)-*exo*-*trig* cyclization to give a cyclopropylpalladium intermediate, but probably a sequence of (*n*–1)-*exo*-*trig* and 3-*exo*-*trig* cyclizations, followed by a cyclopropylcarbinyl to homoallyl rearrangement of an intermediate spiropentylmethylpalladium halide **232**, which overall corresponds to an *n*-*endo*-*trig* process [114], to yield the cyclopropylcarbinylpalladium species **233** which rapidly ring-opens to the homoallylpalladium intermediate **234**. Subsequent β-hydride elimination eventually leads to the cross-conjugated trienes **230** [64], so-called [3]dendralenes. Under the conditions of the cycloisomerization developed by Trost et al. [6] the 1,6- **231a** and 1,7-enyne **231b** gave the [3]dendralenes **230a** ($n = 6$) and **230b** ($n = 7$) in a 78 and 100% yield, respectively. In the presence of iodobenzene under Heck conditions the eneyne **231a** gave the (*Z*)-phenylsubstituted [3]dendralene **227** (45%) together with the phenylsubstituted eneyne **228** (42%) (Scheme 37).

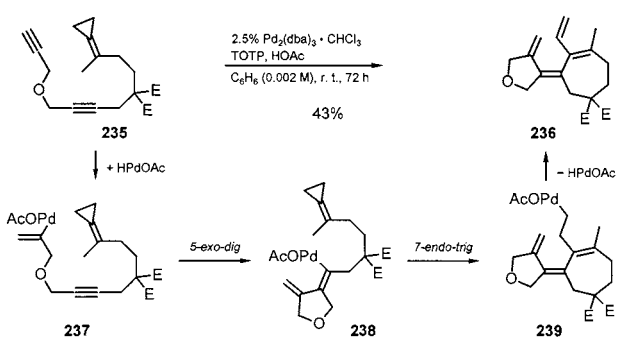


Scheme 37. A Heck-reaction rearrangement cascade forming cross-conjugated trienes, so-called [3]dendralenes.

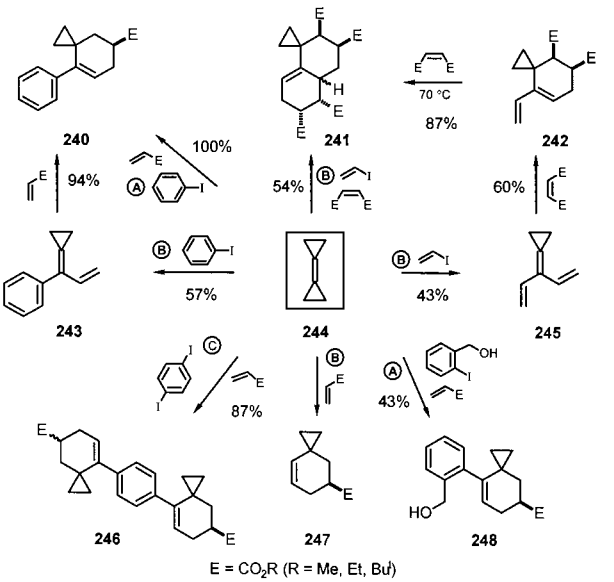
The same cascade reaction was successful in transforming the enediyne **235** to the cross-conjugated tetraene **236** via the intermediates **237**–**239** [107] (Scheme 38).

In spite of their tetrasubstituted double bonds these methylenecyclopropane derivatives are outstandingly reactive towards intramolecular Heck coupling which must be attributed to the relief of strain upon any addition to such a double bond, and to the high lying HOMO of any methylenecyclopropane derivative which makes them particularly good ligands for transition metals [115].

The extremely strained and highly nucleophilic [116] bicyclopropylidene (**244**) which is readily available from methyl cyclopropanecarboxylate in three efficient steps [117], surpasses even styrene and methyl acrylate in its reactivity towards alkenyl- and arylpalladium intermediates formed under Heck reaction conditions from the corresponding halides or perfluoroalkanesulfonates [64,118]. Thus, **244** reacts with iodobenzene or iodoethene in the presence of methyl acrylate or dimethyl maleate in an inter-intermolecular domino Heck–Diels–Alder reaction to give the spiro[2.5]octane



Scheme 38. Facile formation of dendralenes: the tetraene case

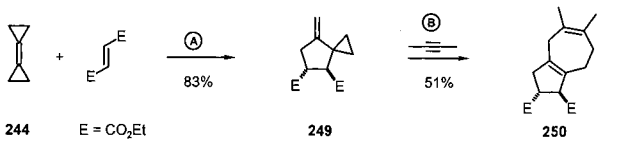


Scheme 39. Inter-intermolecular domino Heck–Diels–Alder reactions with bicyclopropylidene. **A**: $Pd(OAc)_2$ (5 mol%), PPh_3 (15 mol%), NEt_3, DMF, 80°C, 20 h–5 days.—**B**: $Pd(OAc)_2$, PPh_3, NEt_3, DMF, 80°C, 4 h.—**C**: As in **A**, but under 10 kbar.

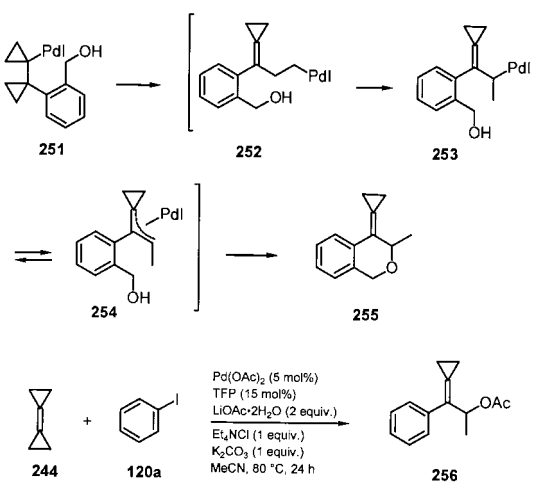
and (spirocyclopropane)bicyclo[4.4.0]decene derivatives **240** and **241** in a 100 and 54% yield, respectively, when performed in highly concentrated solutions [118]. Surprisingly, the direct Heck coupling product of iodobenzene, methyl acrylate, and methyl cinnamate was formed as a trace by-product only (Scheme 39).

The overall yields from these inter-intermolecular domino Heck–Diels–Alder reactions can also be improved, as demonstrated for the reaction of 1,4-diiodobenzene when performed under 10 kbar pressure, as high pressure accelerates both the Heck (see above) and the Diels–Alder reaction; thus, this formal five-component reaction of 1,4-diiodobenzene with two molecules each of bicyclopropylidene (**244**) and methyl acrylate gave the product **246** in an 87% yield [118]. The corresponding domino reaction of **244** with *o*-iodobenzyl alcohol and methyl acrylate furnished the axially and centrally chiral adduct **248** as a mixture of two diastereomers in a ratio of 2.5:1.

In the absence of an aryl or alkenyl halide, bicyclopropylidene (**244**) undergoes a palladium-catalyzed rearrangement to allylidenecyclopropane which reacts with added acrylate to the Diels–Alder adduct **247** [118]. A different mode of ring opening in bicyclopropylidene (**244**) occurs upon the palladium-catalyzed codimerization with α,β-unsaturated esters and strained alkenes leading to ring-fused vinylcyclopropanes in a formal [3 + 2] cycloaddition [119]. This type of reaction of **244** with e.g. diethyl fumarate yields the methylenespiro[2.4]heptane derivative **249** which is set up for a subsequent rhodium(I)-catalyzed formal [5 + 2] cycloaddition of an alkyne such as 2-butyne to give **250** with a seven-membered ring annelated to a five-mem-



Scheme 40. Palladium(0)-catalyzed [3 + 2] cocyclization of bicyclopropylidene with diethyl fumarate and rhodium(I)-catalyzed intermolecular [5 + 2] cycloaddition of the resulting vinylcyclopropane.



Scheme 41. A reaction channel from Heck to π-allyl chemistry.

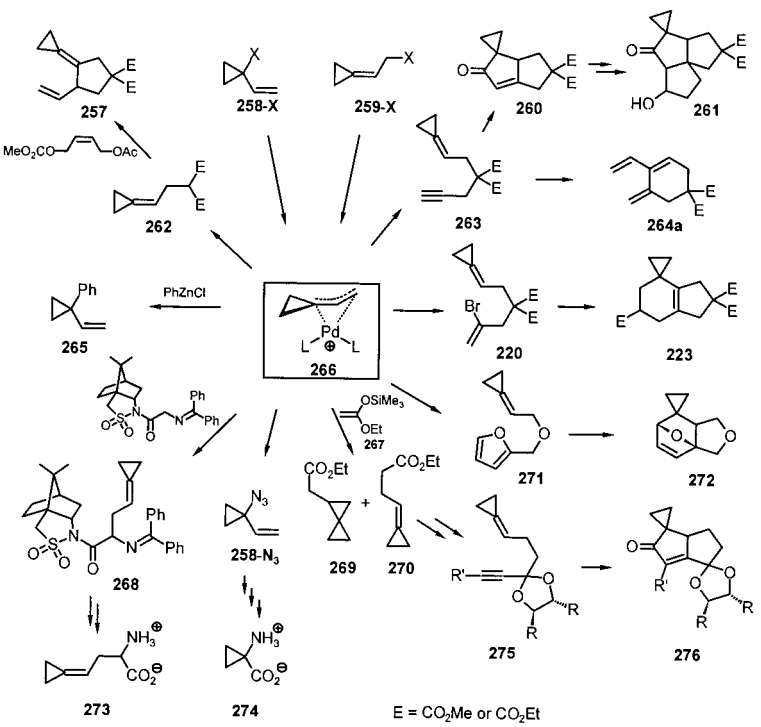
bered ring. The latter sequence of metal-catalyzed cocyclizations of bicyclopropylidene (**244**) obviously bears great potential for the assembly of terpene skeletons (Scheme 40).

2.9. π-Allyl chemistry with strained building blocks

The reaction of bicyclopropylidene (**244**) with *o*-iodobenzyl alcohol in the presence of methyl acrylate not only gave the cross-coupling Diels–Alder adduct **248** (Scheme 39), but also **255** as a by-product (Scheme 41).

The latter apparently arose by an intramolecular allylic substitution in the cyclopropylidenepropyl palladium complex which must have formed by 1,2-hydrogen–metal disposition in the homoallylpalladium iodide intermediate **252** [120]. When the coupling of **244** with iodobenzene was performed in the presence of trisfurylphosphane, a ligand which is well known to slow down the β-hydride elimination [121], and additional lithium acetate, the domino Heck-coupling allylic substitution product, the acetate **256** could be isolated in a 50% yield [118]. This development opens up new avenues for multistep domino processes.

The regioselectivity observed in this allylic substitution leading to **255** had previously been established in a thorough investigation of allylic substitution reactions on vinylcyclopropyl and cyclopropylideneethyl esters. Although the nucleophilic substitution on a cyclo-



Scheme 42. The multitude of cyclopropane derivatives accessible by Pd-catalyzed nucleophilic allylic substitution on ethenylcyclopropyl and cyclopropylidenylethyl esters as a key step.

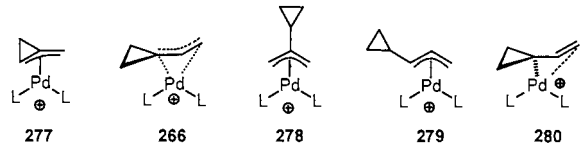
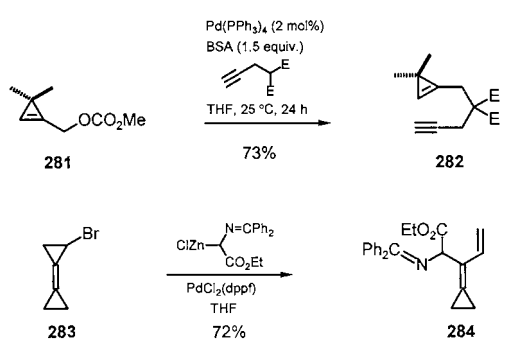


Fig. 3. Possible π-allyl and π-propargyl complexes with cyclopropyl moieties.

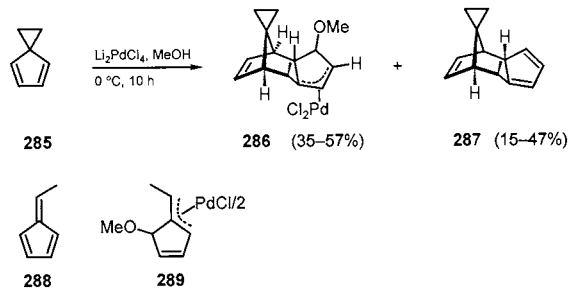
propane ring is strongly retarded under both S_N2 and S_N1 conditions [122], ethenylcyclopropyl halides, sulfonates and other esters **258-X** with good enough leaving groups when treated with palladium(0) catalysts, cleanly react just like the isomeric cyclopropylideneethyl esters of type **259-X**, with a large variety of nucleophiles completely regioselectively. Malonate enolates, other stabilized enolates, carboxylates, alkoxides, and sulfonylamides only yield cyclopropylideneethyl derivatives, whereas hydride donors like butylzinc chloride and non-stabilized carbanionic reagents such as phenylzinc chloride solely give ethenylcyclopropyl derivatives in excellent yields [123–133]. Ketene silyl acetals **267** are an exception in that they attack the π-allylpalladium intermediate **266** at the central carbon atom to give spiropentylacetates **269** along with the 4-cyclopropylidenebutyrate **270** [134], and azide forms the 1-ethenylcyclopropyl azide (**258-N_3**) as the sole product, but this most probably arises by the [3,3]-sigmatropic shift of the primarily formed cyclopropylideneethyl azide. Many of the cyclopropane derivatives thus accessible can favorably serve as key intermediates on route to natural products or their analogs and other interesting molecules (Scheme 42) [135,136].

The reactive intermediate in these palladium-catalyzed nucleophilic substitutions on cyclopropane derivatives, the palladium complex **266**, is one of the five possible π-allyl or π-propargyl complexes containing a cyclopropyl moiety (Fig. 3). The chemistry of them all except for **278** has been investigated, at least to some extent.

The cyclopropenylmethyl ester **281**, a precursor to an intermediate of type **277**, smoothly undergoes substitution with e.g. the enolate of propargylmalonate to give the highly strained disubstituted malonate **282** by regioselective attack of the nucleophile at the less substituted site of the intermediate allyl complex of type **277**, while tertiary cyclopropenylmethyl esters yield 2-substituted 1-methylenecyclopropanes [107]. However, 2-bromobicyclopropylidene (**283**), upon palladium-catalyzed coupling with the chlorozinc enolate of ethyl *N*-diphenylmethyleneaminoacetate, undergoes ring-opening to give the butadiene derivatives **284** (Scheme 43) [137].



Scheme 43. Palladium-catalyzed substitution on methylenecyclopropane and cyclopropenylmethyl derivatives.



Scheme 44. Palladium-mediated dimerization of spiroheptadiene.

In the context of further developing the palladium-catalyzed 1,4-oxidation of dienes [138], spiro[2.5]heptadiene (**285**) was treated with Li_2PdCl_4 in methanol, as it was anticipated to react via a π-allyl complex intermediate of type **279** [139]. Interestingly, the formal dimer **287** was isolated along with the unusual tricyclic π-allyl complex **286**. These may arise via methylfulvene (**288**) and the π-allyl complex **289** as primarily formed intermediates, which cycloadd to **285** in [6 + 4] mode [140] (Scheme 44).

3. Conclusions and future perspectives

Although various types of palladium-catalyzed cross-coupling reactions have originally been discovered several decades ago, their application towards real problems in organic synthesis has appeared only in the last decade. Along with drastically improved protocols for practical performance of such reactions came elaborate studies into their scope and limitations.

The current collection of multifold and domino-type transformations which lead to an impressive increase in molecular complexity in a single operation offers convincing evidence that the next decades and well into the next century will see a continuing growth and advancement of this chemistry. Obvious further improvements will be achieved by applying novel low cost multifunctional building blocks, developing more environmentally friendly reaction conditions such as ambient temperature for the coupling with the application of more active and reusable catalysts. This will undoubtedly lead to an ever increasing use in industrial pro-

cesses especially for the production of high-end chemical products such as pharmaceuticals, as well as modern agrochemicals, and eventually highly advanced new materials for the electronics industry.

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