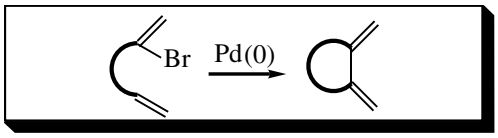

IV.2.2 Intramolecular Heck Reaction

IV.2.2.1 Synthesis of Carbocycles

STEFAN BRÄSE and ARMIN DE MEIJERE

A. INTRODUCTION

The possibility of constructing carbocycles by intramolecular Heck reaction makes it particularly versatile for organic synthesis.[1],[2] The starting materials, alkene-tethered haloalkenes and haloarenes, are in general readily available from simple precursors, and thus this strategy has been used for the preparation of various types of carbocyclic systems. In this section, the cyclization of haloalkadienes to give carbomonocyclic structures is described. While the carboannelation of heterocycles is included here, the domino and cascade reactions involving two or more intramolecular Heck coupling steps are covered in **Sect. IV.3**.

B. CYCLIZATION OF 2-HALO-1,($n-1$)-ALKADIENES AND RELATED COMPOUNDS

B.i. General Remarks

By Pd-catalyzed intramolecular coupling of 2-halo-1,($n-1$)-alkadienes and related compounds, all ring sizes from three- to nine-membered are attainable, either by *exo–trig* for three- to nine- or *endo–trig* cyclizations for six- to nine-membered rings (**Table 1**).[1] Applications toward the construction of larger rings (sizes 13–24) have been demonstrated for substrates on solid support in combinatorial syntheses (see also **Sect.X.3**),[3] by employing slow addition of the substrate and/or high dilution techniques.[4]

B.ii. Synthesis of Cyclopropanes

The synthesis of cyclopropanes by simple cyclization of 2-halo-1,4-pentadienes has not been achieved, presumably because the product 1,2-dimethylenecyclopropane would not be stable under the reaction conditions necessary for ring closure. However, the formation of bicyclo[n.1.0]alkanes from certain 2-halo-1,3-pentadienes (**Sect. IV.2.2.1.C.iii.a**) or by a cascade reaction (**Sect. IV.3.1**) has been achieved.

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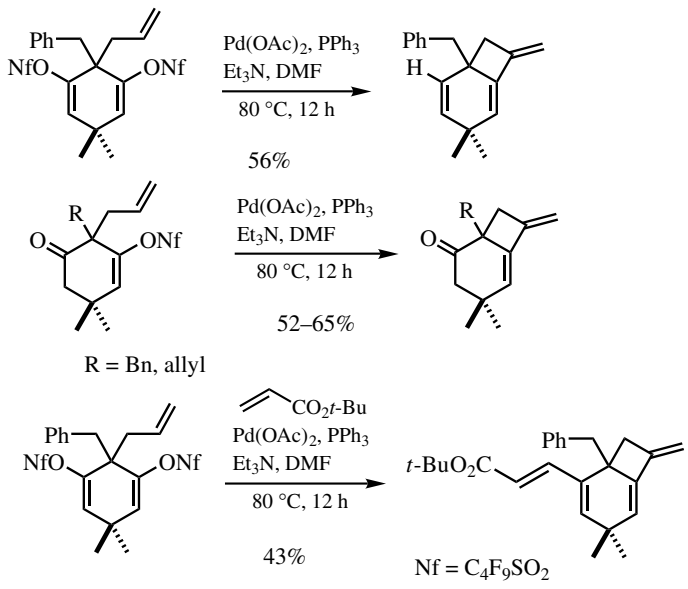
TABLE 1. Examples of Ring Sizes Achieved by Intramolecular Heck Reactions

Ring Size	Reference for *endo-trig(dig)*	Reference for *exo-trig(dig)*
3		[5]–[7][a]
4		[8],[10]
5		[4],[12]–[35]
6	[14],[36]–[38],[80]	[13],[16],[23],[27],[38],[39]–[53]
7	[38],[54]–[57],[80]	[16],[58]–[62]
8	[42],[54,[55],[59],[63]	[60],[61],[64],[65]
9	[54],[55]	[66][b]
10–15	[4],[66] (13)	[66] (11,12)[b], [67] (12–15)[c]
16–19	[68] (16), [69] (16, 18)	[66] (18)[b], [67] (16, 17)[c]
>19	[66] (21), [69] (20, 22), [3] (20–24), [4] (26)	

[a]The formation of three-membered rings is reversible: Compare Ref. [38c].
[b]With allene coupling partners instead of alkenes.
[c]Heck–Stille cascade.

B.iii Synthesis of Cyclobutanes: Cyclization of 2-Halo-1,4-hexadienes and Related Compounds

The cyclization of simple 2-halo-1,5-hexadienes to yield 1,2-dimethylenecyclobutanes has not been achieved so far.[34] Presumably, a rapid Cope rearrangement of the starting 1,5-hexadiene may inhibit such a process or ring-opening polymerization of the initially formed 1,2-dimethylenecyclobutane derivative may prevent its isolation. However, when the functionalized double bond is incorporated in a six-membered ring, cyclization with a tethered alkenyl group to give an 8-methylenebicyclo[4.2.0]oct-1-ene derivative does occurs. Starting from dimedone, novel cyclohexa-1,4-diene-1,5-diyl bis(nonafluorobutanesulfonates) have been prepared and cyclized under palladium catalysis to cleanly give bicyclo[4.2.0]octadienes and bicyclo[4.2.0]octenones, respectively, by unprecedented 4-*exo-trig* processes (**Scheme 1**). In the presence of a chiral



Scheme 1

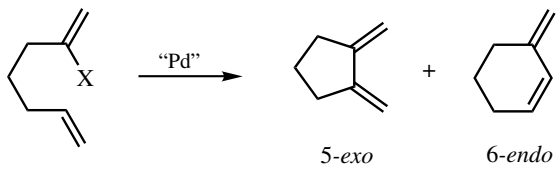
catalyst the BINAP ligand furnished the products with modest asymmetric induction (up 53% ee).[10]

B.iv. Synthesis of Cyclopentanes: Cyclization of 2-Halo-1,6-heptadienes and Related Compounds

Intramolecular Heck reactions have frequently been used for the synthesis of cyclopentanoid structures. In nearly all cases reported so far, the ring closure occurs as a 5-*exo* process (for an exception, see **Table 4**, entry 6), for which 2-halo-1,6-heptadienes and related compounds are the appropriate starting materials. In some cases, however, these substrates cyclize by a 6-*endo* mode to give cyclohexane derivatives (see **Sect. IV.2.2.1.B.v**).

Simple open-chain 2-bromoheptadienes have frequently been used as substrates to generate 1,2-dimethylenecyclopentanes (**Tables 2** and **3**), which in turn have served as valuable starting materials in Diels–Alder cycloadditions. It has turned out to be even more favorable to carry out the intramolecular Heck reaction and subsequent Diels–Alder reaction as a domino-type sequence in a single operation (see **Table 6**). In the presence of secondary amines, aminoalkylcyclopentanes are produced (**Sect. IV.3.2**).

Cycloalkenyl groups as acceptors in the carbopalladation step have frequently been employed to form bicyclic systems (**Table 3**, entries 2, 5, 6; **Table 4**, entries 2, 3, 5, 12). These developments have contributed toward applications in the total synthesis of natural products as, for example, aphidicolin (**Table 3**, entry 5; see also **Table 9**, entry 9). [17],[18] In some cases, the formation of 6-*endo* products (**Scheme 2**) and/or double bond isomers can be prevented by using 2,6-dihaloheptadienes rather than the monohalodiene substrates (see **Table 2**, entry 8).[31]



Scheme 2

Especially under classical Heck conditions, that is, in the presence of PPh_3, the coupling of an *o*-halostyrene formed in the first two coupling steps of an *o*-dihalobenzene derivative may yield alkylideneindane and alkylindene derivatives by 5-*exo-trig* cyclization of the intermediate *o*-alkenyl(phenylethyl)palladium (**Scheme 3**)

This side reaction played a dominant role in the attempted sixfold Heck coupling of hexabromobenzene with styrenes and led to mixtures of various isomers of the expected hexakisstyrylbenzene derivatives.[75] Sixfold Suzuki and Stille coupling reactions of hexabromobenzene, however, worked perfectly well, to give hexakisalkenylbenzene derivatives in high yields.

Five-membered ring closure has also been observed upon Pd-catalyzed coupling of *o*-halostyrene derivatives with alkenes.[19] 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. This reaction mode for the alostyrene is observed especially under Jeffery conditions when the alkene is ethylene, propene, or an

TABLE 2. Synthesis of Cyclopentanes: Cyclization of Open-Chain 2-Halo-1,6-heptadienes and Related Compounds

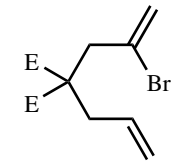
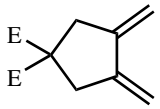
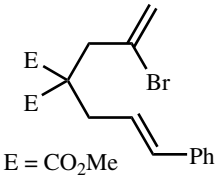
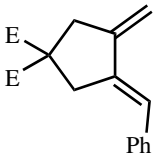
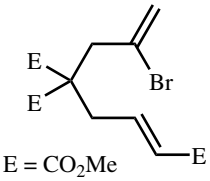
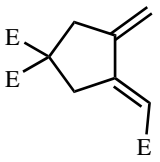
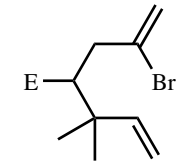
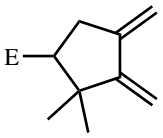
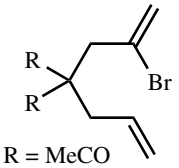
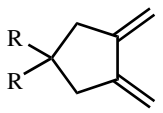
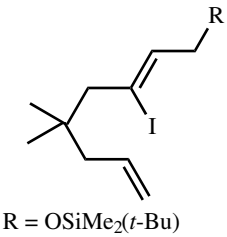
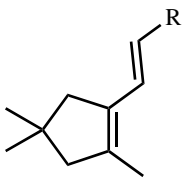
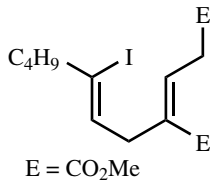
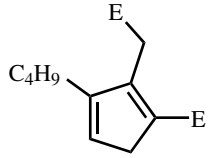
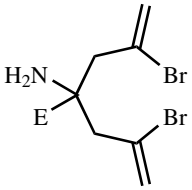
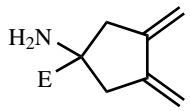
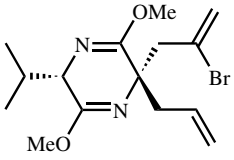
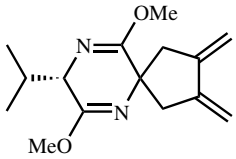
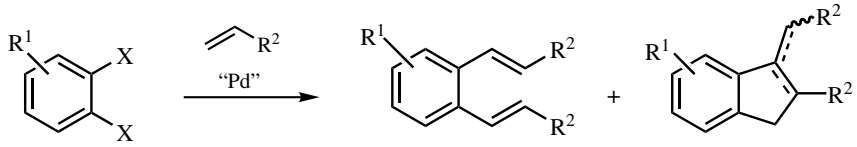
Entry	Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)	Reference
1	 E = CO_2Et		$Pd(OAc)_2$, PPh_3, K_2CO_3, MeCN, 80 °C, 3.5 h	92	[34]
			$Pd(OAc)_2$, PPh_3, MeCN, 80 °C, 75 min	90	[35]
2	 E = CO_2Me		$Pd(OAc)_2$, PPh_3, MeCN, 80 °C, 6 h	45	[70]
			$Pd(OAc)_2$, PPh_3, K_2CO_3, MeCN, 30 °C, 96 h	88	[33]
3	 E = CO_2Me		$Pd(OAc)_2$, PPh_3, K_2CO_3, MeCN, 30 °C, 35 h	45	[33]
4	 E = CO_2Me		$Pd(OAc)_2$, PPh_3, K_2CO_3, MeCN, 80 °C, 12 h	74	[33]
5	 R = MeCO		$Pd(OAc)_2$, PPh_3, K_2CO_3, MeCN, 80 °C, 2.3 h	55 (19)[a]	[32],[33]
6	 R = $OSiMe_2(t\text{-Bu})$		$Pd(PPh_3)_4$, Et_3N, MeCN/THF	68	[26]

TABLE 2. (*Continued*)

Entry	Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)	Reference
7	 E = CO_2Me		$Pd(PPh_3)_4$, Et_3N, MeCN, 100 °C, 16 h	63	[26]
8	 E = CO_2Et		$Pd(PPh_3)_4$, Ph_2P-C_6H_4 polystyrene, K_2CO_3, MeCN, 135 °C (sealed tube), 46 h	68	[31]
9			$Pd(PPh_3)_4$, K_2CO_3, MeCN, 80 °C, 48 h	51 (1:1.1)[b]	[30]

[a] Yield of the corresponding cyclohexene derivative formed by a 6-*endo* process (in parentheses).
[b] Mixture of double bond positional isomers (ratio in parentheses).



Scheme 3

alkenyl ether (R^2 = H, Me or OR) (**Scheme 4**).[19] Under the same conditions, however, *o*-dibromobenzene gives very high yields of *o*-dialkenylbenzene derivatives (see **Sect. IV.2.1.2**).

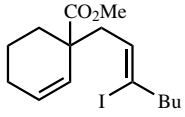
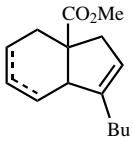
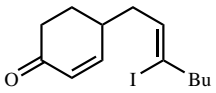
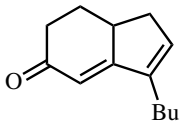
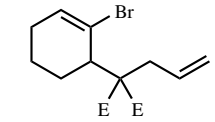
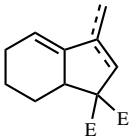
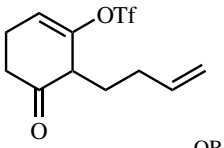
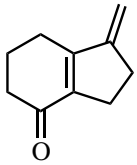
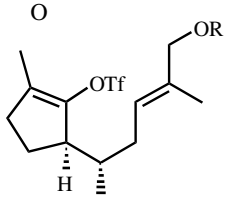
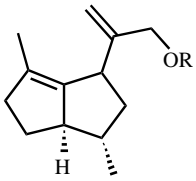
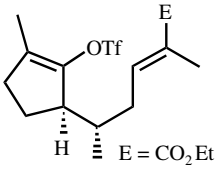
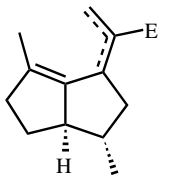
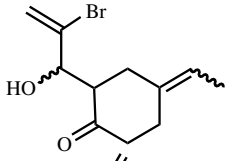
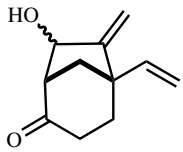
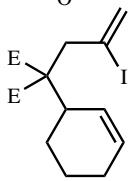
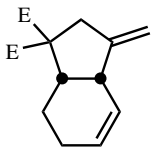
When the β-hydride elimination in the intermediate is retarded or even impossible, as in the carbopalladation products of alkynes or norbornene, the respective cyclopentannelation products are formed in higher yields (**Scheme 5**).[19],[20]

Benzyl halides and other benzyl esters can be coupled under Heck conditions, and the pioneering work of Heck and co-workers on such intermolecular couplings has been extended by Negishi and co-workers to intramolecular cases to give indane derivatives (**Table 5**).[16]

Similarly, acid chlorides have been found to undergo an oxidative addition to palladium(0) species and the intermediates to cyclize, if a vicinal allyl group is present, to give α-methyleneindanone derivatives. As a stoichiometric reaction, this cyclization has been demonstrated as early as 1985 by Tour and Negishi (**Scheme 6**).[21]

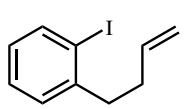
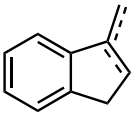
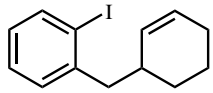
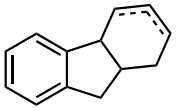
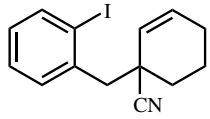
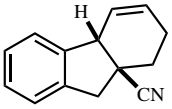
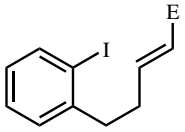
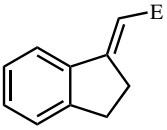
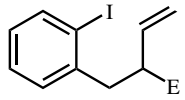
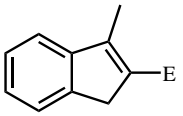
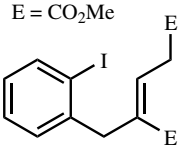
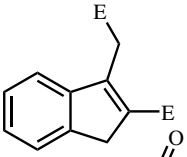
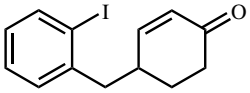
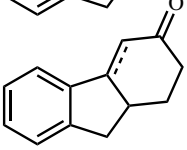
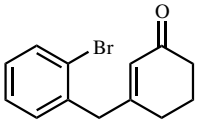
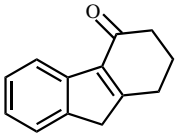
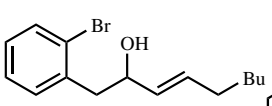
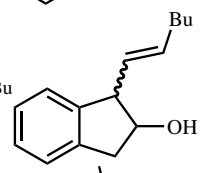
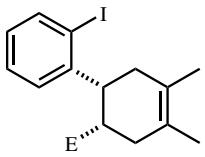
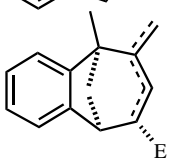
The intramolecular Heck reaction followed by a Diels–Alder cycloaddition[33] leading to bicyclo[4.3.0]nonene derivatives has been developed into a one-pot cascade reaction.[22],[23] Various 2-bromo-1,6-heptadienes including systems with heteroatoms in the tether between the double bonds were cyclized under palladium catalysis producing vicinal exodimethylenecycloalkanes, which reacted with dienophiles (either present

TABLE 3. Sythesis of Cyclopentanes: Cyclization of Monocyclic 2-Halo-1,6-heptadienes and Related Compounds

Entry	Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)
1			$Pd(PPh_3)_4$, MeCN/THF, 100 °C, 6 h	73
2			$Pd(PPh_3)_4$, MeCN/THF, 100 °C, 20 h	68
3	 E = CO_2Et		$Pd(OAc)_2$, PPh_3, K_2CO_3, Et_4NCl, 80 °C, 1 h	55[a]
4			$Pd(OAc)_2$, PPh_3, Et_3N, MeCN, 70 °C	88
5	 R = $SiMe_2t$-Bu		$Pd(PPh_3)_4$, LiCl, Li_2CO_3, THF, reflux, 3 h	91
6			$Pd(PPh_3)_4$, LiCl, Li_2CO_3, THF, reflux, 3 h	98 (5:1)[b]
7			$Pd(OAc)_2$, $P(o\text{-Tol})_3$, K_2CO_3, MeCN, reflux, 2 h	90
8		 E = CO_2Me	$PdCl_2$, sulfonated triphenylphosphine, $(i\text{-Pr})_2NEt$, $MeCN/H_2O$ 6:1, 70 °C, 12 h	68

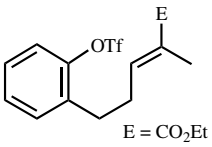
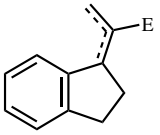
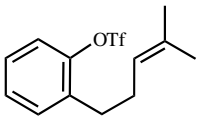
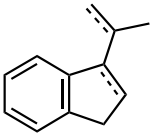
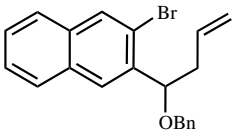
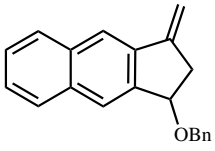
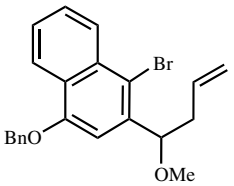
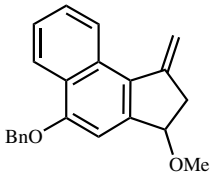
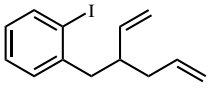
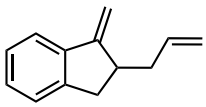
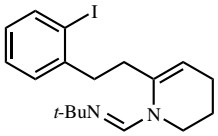
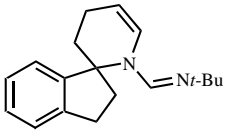
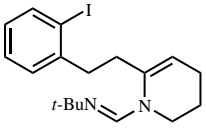
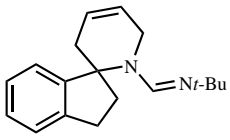
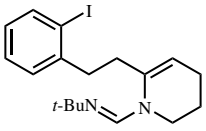
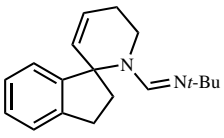
[a]Mixture of regioisomers, depending on type and amount of added base.
[b]Mixture of isomers.

TABLE 4. Synthesis of Indanes: Cyclization of 1-Halo-2-butenylarenes and Related Compounds

Entry	Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)	Reference
1			$Pd(PPh_3)_2Cl_2$, Et_3N, MeCN/PhH (1:1), 100 °C, 12 h	89 (60:40)[a]	[21]
2			$Pd(PPh_3)_4$, MeCN/THF, 60 °C, 24 h	80	[27]
3			$Pd(OAc)_2$, PPh_3, Ag_2CO_3, MeCN, 80 °C, 72 h	62	[27]
			$Pd(OAc)_2$, *n*-Bu_4NCl, KOAc, DMF, 25 °C, 25 h	77 (5.25:1)[a]	[27]
4			$Pd(PPh_3)_4$, MeCN/PhH, 60 °C, 24 h	71	[26]
5			$Pd(PPh_3)_4$, Et_3N, MeCN, 100 °C, 16 h	50	[26]
6			$Pd(PPh_3)_4$, Et_3N, MeCN, 100 °C, 16 h	65	[26]
7			$Pd(PPh_3)_4$, MeCN/THF, 100 °C,16 h	50 (30)[b]	[25]
8			$Pd(OAc)_2(PPh_3)_2$ DMF, 80 °C, 36 h	68	[26]
9			$Pd(OAc)_2$, PPh_3 MeCN, 80 °C, 24 h	86	[24]
10			$Pd(OAc)_2$, TlOAc or AgOAc, anisole, 120–148 °C	80[c]	[29]

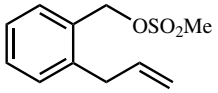
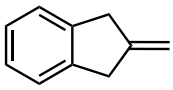
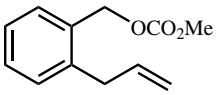
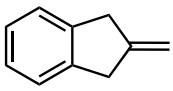
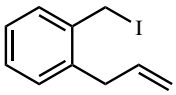
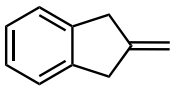
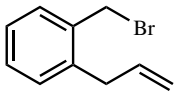
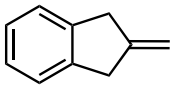
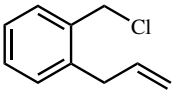
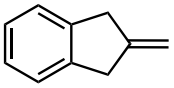
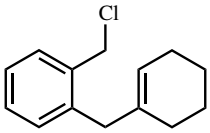
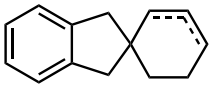
(*Continued*)

TABLE 4. (*Continued*)

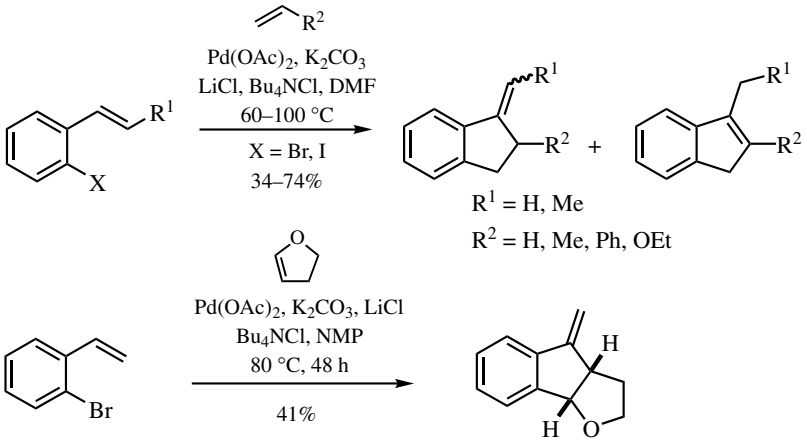
Entry	Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)	Reference
11			$Pd(PPh_3)_4$, LiCl, Et_3N, THF, 90 °C, 3 h	80[a] (1.5:1)	[28]
12			$Pd(PPh_3)_4$, LiCl, Et_3N, THF, 90 °C, 3 h	72[a] (6:1)	[28]
13			$Pd(OAc)_2$, Ag_2CO_3, dppp, MeCN, 80 °C, 2 h	96	[71],[72]
14			$Pd(OAc)_2$, Ag_2CO_3, dppp, MeCN, 80 °C, 2 h	96	[71],[72]
15			$Pd(OAc)_2$, PPh_3, Ag_2CO_3, MeCN, reflux, 24 h	67	[73]
16			$Pd(OAc)_2$, K_2CO_3, MeCN, 100 °C, 168 h	54	[74]
17			$Pd(OAc)_2$, (+)-BINAP, Et_3N, cyclohexene, MeCN, 60 °C, 3 h	54	[74]
18			$Pd(OAc)_2$, TlOAc, Et_3N, MeCN, 80 °C, 17 h	79	[74]

[a] Mixture of double bond isomers (ratio in parentheses).
[b] Yield of the corresponding cyclohexane derivative, formed by 6-*endo* process.
[c] Mixture of double bond positional isomers.

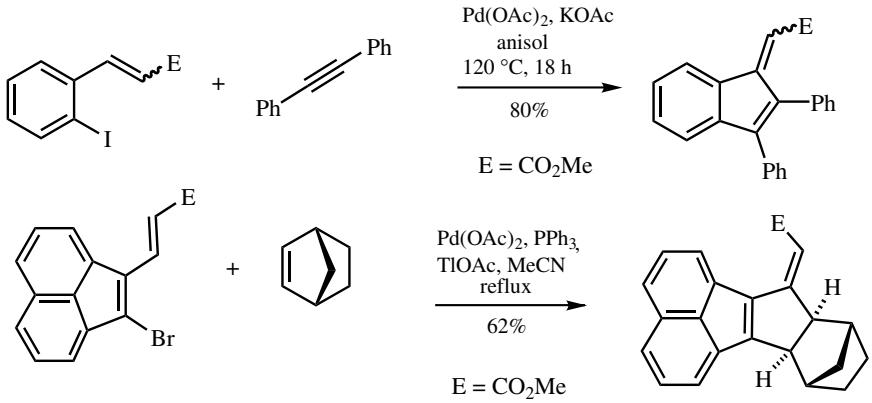
TABLE 5. Synthesis of Indanes: Cyclization of 1-Halomethyl-2-propenylarenes and Related Compound[16]

Entry	Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)
1			$Pd(PPh_3)_2$, Et_3N, MeCN, reflux, 1 h	60[a]
2			$Pd(PPh_3)_2$, Et_3N, MeCN, reflux, 5 d	26 (23)[b]
3			$Pd(PPh_3)_2$, Et_3N, MeCN, reflux, 0.5 h	64 (18)[b]
4			$Pd(PPh_3)_2$, Et_3N, MeCN, reflux, 0.5 h	82[a]
5			$Pd(PPh_3)_2$, Et_3N, MeCN, reflux, 1 h	82[a]
6			$Pd(PPh_3)_2$, Et_3N, MeCN, reflux, 24 h	60 (70:30)[c]

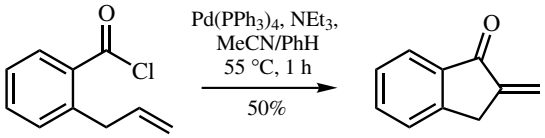
[a] The isomeric 2-methylindene was produced in 1% yield.
[b] Yield of the isomeric compound, 2-methylindene, in parentheses.
[c] Ratio of double bond positional isomers in parentheses.



Scheme 4

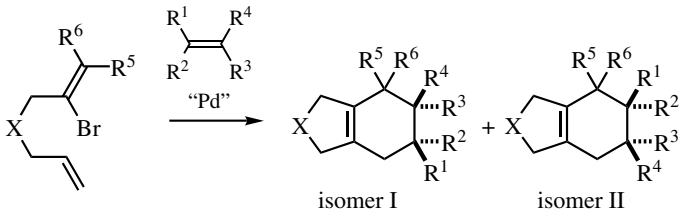


Scheme 5

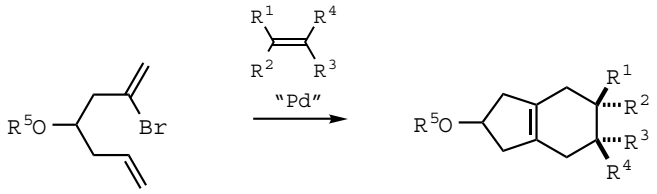


Scheme 6

during the cyclization or added afterwards in a one-pot process) to give bicyclo[4.3.0]nonene derivatives and heterocyclic analogs in good to excellent yields (**Schemes 7** and **8**, **Tables 6** and **7**). While methyl 2-chloro-2-cyclopropylideneacetate and methyl 2-cyclopropylideneacetate as the dienophiles gave the corresponding five-membered ring annelated spiro[2.5]octene derivatives in very good yields in both the one-step and the two-step procedure (**Table 6**, entries 13 and 14), the highly strained methyl dimethylcyclopropenecarboxylate and 1,2-dicyanocyclobut-1-ene gave the expected tricyclic products in only moderate yields (**Table 6**, entries 16 and 17). The yield of the latter reaction could be increased by performing the second step under high pressure



Scheme 7



Scheme 8

TABLE 6. Synthesis of Hydroindanes: One-Pot Cyclization of 2-Bromo-1,6-heptadienes and Subsequent One-Pot Diels-Alder Reaction (see Scheme 7)[22],23]

Entry	R^5	R^6	X	R^1	R^2	R^3	R^4	Method[a]	One Step (Isomer)	Two Step (Isomer)
1	H	H	$C(CO_2Et)_2$	CN	H	H	H	A	83	70
2	H	H	$C(CO_2Et)_2$	COMe	H	H	H	A	81	70
3	H	H	$C(CO_2Et)_2$	CO_2Me	H	H	H	A	93	60
4	H	H	$C(CO_2Et)_2$	CO_2R*[b]	H	H	H	A	–[d]	55
5	H	H	$C(CO_2Et)_2$	COX*[c]	H	H	H	A	–[d]	52
6	H	H	$C(CO_2Et)_2$	CN	Cl	H	H	A	74	–
7	H	H	$C(CO_2Et)_2$	CO_2Me	H	CO_2Me	H	A	85	–
8	H	H	$C(CO_2Et)_2$	CO_2Et	H	CO_2Et	H	B	88	–
9	H	H	$C(CO_2Et)_2$	CO_2Et	H	CO_2Et	H	A	94	–
10	H	H	$C(CO_2Et)_2$	CO_2Me	H	H	CO_2Me	A	93	–
11	H	H	$C(CO_2Et)_2$	CN	CN	CN	CN	A	–	79
12	H	H	$C(CO_2Et)_2$	CO_2Et	CO_2Et	CO_2Et	CO_2Et	A	78	48
13	H	H	$C(CO_2Et)_2$	$-CH_2-CH_2-$		CO_2Me	H	A	83	79
14	H	H	$C(CO_2Et)_2$	$-CH_2-CH_2-$		CO_2Me	Cl	A	83	61
15	H	H	$C(CO_2Et)_2$	H	$-CH_2-CH_2-CO-$		H	A	–	30[e]
16	H	H	$C(CO_2Et)_2$	CN	$-CH_2-CH_2-$		CN	A	–	71[f]
17	H	H	$C(CO_2Et)_2$	H	$-C(CH_2)_2-$		CO_2Me	A	–	48
18	H	H	$C(CO_2Et)_2$		$EtO_2C-C\equiv C-CO_2Et$			A	–	94
19	H	H	$C(CO_2Et)_2$		$EtO_2C-N=N-CO_2Et$			A	–	78
20	H	H	$C(CO_2Et)_2$		1,4-benzoquinone			A	43	–
21	H	H	$C(CO_2Et)_2$		1,4-benzoquinone			A	71	–
22	H	H	$C(CO_2Et)_2$		1,4-naphthoquinone			A	78	–
23	H	Me	$C(CO_2Et)_2$	CO_2Me	H	H	H	A	60 (II)	–
24	Me	H	$C(CO_2Et)_2$	CO_2Me	H	H	H	C	48[g] (II)	–

(*Continued*)

TABLE 6. (*Continued*)

Entry	R^5	R^6	X	R^1	R^2	R^3	R^4	Method[a]	One Step (Isomer)	Two Step (Isomer)
25	$-CH_2$-CH_2-		$C(CO_2Et)_2$	CO_2t-Bu	H	H	H	A	68 (I)	–
26	$-CH_2$-CH_2-		$C(CO_2Et)_2$	CO_2X*[c]	H	H	H	A	–[d]	57 (I)
27	$-CH_2$-CH_2-CH_2-		$C(CO_2Et)_2$	CO_2Me	H	H	H	C	18 + 32[h] (I + II)	–
28	$-(CH_2)_4-$		$C(CO_2Et)_2$	CO_2Me	H	H	H	C	43[i] (II)	–
29	H	H	NCHO	CO_2t-Bu	H	H	H	A	54	–
30	H	H	NCHO	CO_2t-Bu	H	H	CO_2t-Bu	A	56	–
31	H	H	NCHO	CN	H	H	H	A	63	–
32	H	H	NCHO	CN	Cl	H	H	A	44	–
33	H	H	NCOMe	CO_2Me	H	H	H	A	54	–
34	H	H	NCOMe	CO_2t-Bu	H	H	H	A	62	–
35	H	H	NCOMe	CO_2t-Bu	H	H	CO_2t-Bu	A	55	–
36	H	H	NCOMe	CN	H	H	H	A	60	–
37	H	H	NCOMe	CN	Cl	H	H	A	46	–
38	H	H	NBoc	CO_2Me	H	H	H	A	45	–
39	H	H	NBn	CO_2Me	H	H	H	A	46	–
40	H	H	NTs	CO_2Me	H	H	H	A	48	–
41	H	H	NTs	CO_2t-Bu	H	H	H	A	51	–
42	H	H	NTs	CN	H	H	H	A	43	–
43	H	H	NTs	CN	Cl	H	H	A	41	–
44	H	H	NNs	CO_2Me	H	H	H	A	48	–
45	H	H	NNs	CO_2t-Bu	H	H	H	A	73	–
46	H	H	NCHO	CO_2Me	H	$-(CH_2$-$CH_2)-$		A	41	–
47	H	H	NCHO	CO_2Me	Cl	$-(CH_2$-$CH_2)-$		A	55	–

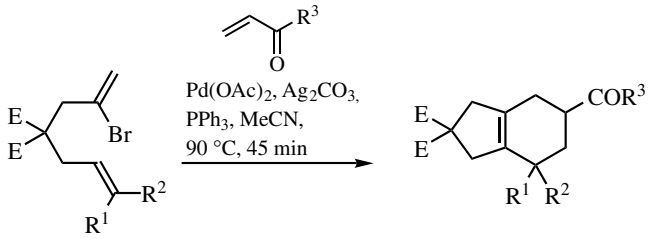
48	H	H	NCOMe	CO_2Me	Cl		$-(CH_2\text{-}CH_2)-$		A	68	–
49	H	H	NBoc	CO_2Me	Cl		$-(CH_2\text{-}CH_2)-$		A	43	–
50	H	H	NTs	CO_2Me	Cl		$-(CH_2\text{-}CH_2)-$		A	44	–
51	Me	H	NBn	CO_2Me	H	H		H	A	41[j] (I + II)	–
52	H	H	O	CO_2Me	H	H		H	A	42	–
53	Me	H	O	CO_2Me	H	H		H	A	55[k] (I + II)	–

[a] A: $Pd(OAc)_2$, Ag_2CO_3, PPh_3. B: $Pd(OAc)_2$, Ag_2CO_3, dmphen. C: $Pd(OAc)_2$, K_2CO_3, PPh_3.
[b] R* = (*R*)-myrtenyl.
[c] X* = camphorsultam.
[d] Not carried out.
[e] In the presence of $AlCl_3$.
[f] At 10 kbar, 28% yield at ambient pressure.
[g] Together with 24% of isomerized 1,3-diene.
[h] Together with 15% of isomerized starting material.
[i] Together with 45% of the isomerized intermediate diene.
[j] As a 1:5.8 mixture of diastereomers and 16:84 mixture of regioisomers I and II.
[k] As a 1:4.2 mixture of diastereomers and 14:86 mixture of regioisomers I and II.

TABLE 7. Synthesis of Hydroindanes: Cyclization of 2-Bromo-1,6-heptadienes and Subsequent One-Pot Diels–Alder Reaction[23]

Entry	R^2	R^2	R^3	R^4	R^5	One Step	Two Step
1	CO_2Me	H	H	H	H	87	—
2	CO_2Me	H	H	H	COMe	87	—
3	CO_2H	H	H	H	TBDMS	77	—
4	CO_2t-Bu	H	H	H	TBDMS	73	—
5	CO_2Me	H	H	CO_2Me	TBDMS	80	—
6	CO_2Me	H	H	H	THP	77	—
7	CO_2Me	Me	H	H	THP	86	87
8	CO_2Me	H	H	H	TBDMS	56	67

(10 kbar). Reaction of the bromodiene with chiral, nonracemic dienophiles such as (*R*)-myrtenyl acrylate and *N*-acryloyl camphorsultam according to the two-step procedure gave the correspondingly substituted bicycles with a diastereomeric excess of 82% and >95%, respectively (**Table 6**, entries 4 and 5). When 0.5 equiv of *p*-benzoquinone was used with the 2-bromohepta-1,6-diene, a linearly annelated pentacycle was isolated in 71% yield along with a trace of the tricyclic monoadduct (**Table 6**, entries 20 and 21) while 1,4-naphthoquinone as a dienophile led to a tetracyclic system (**Table 6**, entry 22). When (*E*)/(*Z*)-2-bromo-1,6-octadienes, which correspond to the parent 2-bromohepta-1,6-diene with a methyl group on the alkene moiety, were treated in the usual manner [$Pd(OAc)_2$, PPh_3, Ag_2CO_3 plus a suitable dienophile], the expected bicycles were isolated only in moderate yields (24–35%) because a competing β-hydride elimination from the methyl group in the intermediate alkylpalladium halide after 5-*exo-trig* carbopalladation yields a 1,4-diene rather than the desired 1,3-diene (**Scheme 9**). In addition, 1,6-heptadienes with a methylenecyclopropane terminator or starter were cyclized under Pd catalysis in the presence of methyl vinyl ketone and methyl acrylate (**Scheme 9**) and other dienophiles to give spirocyclopropane-annelated bicyclo[4.3.0]nonenes as single regioisomers in good yields (**Table 6**, entries 25 and 26; **Scheme 7**). These are the first intramolecular Pd-catalyzed coupling reactions with methylenecyclopropane moieties, which occur without opening of the three-membered ring. When Trost's protocol for the cycloisomerization of 1,6-enynes was applied to the enyne with a methylenecyclopropane terminator, neither the exocyclic diene nor its cycloadduct—in the presence of methyl acrylate—was observed. The higher homologues of the 1,6-diene with a bromomethylenecyclobutane and a bromomethylenecyclopentane, respectively, instead of a bromomethylenecyclopropane starter, did not cyclize when treated with the $Pd(OAc)_2/Ag_2CO_3$ system in the presence of a variety of ligands (PPh_3, dppe, dppf, 2,9-dimethyl-1,10-phenanthroline) or without added ligands. Surprisingly, when Ag_2CO_3 was replaced by K_2CO_3, both compounds as well as the (*Z*)-substituted and the 1,1-dimethylhepta-1,6-dienes, which did not react under the previously favored conditions, cyclized smoothly in a 5-*exo-trig* mode (**Table 6**, entries 24, 27 and 28). One equivalent of silver salt in relation to the added amount of palladium catalyst was sufficient to block the Heck reaction. The rationale of these unprecedented experimental results and the role of silver salts in this process are not clear at present. While the methylenecyclopropane derivative as well as the methylenecyclopentane derivative each yielded only one regioisomer, respectively, in the Diels–Alder reaction with methyl acrylate, the corresponding methylenecyclobutane compound gave two isomers in a ratio of about 1:1.7.

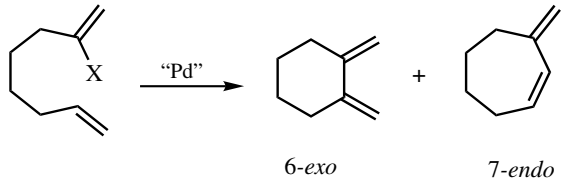


R^1	R^2	R^3	Yield (%)
Me	Me	OMe	24
$-(CH_2)_2-$		OMe	86
$-(CH_2)_2-$		Me	86

Scheme 9

B.v. Synthesis of Cyclohexanes: Cyclization of 2-Halo-1,7-octadienes and Related Compounds

The syntheses of cyclohexane derivatives by 6-*exo*-cyclizations of 2-halo-1,7-octadienes and 1-halo-1,6-heptadienes are well documented, yet the formation of seven-membered rings during these cyclizations has also been observed (**Scheme 10**). This type of ring closure to cyclohexane derivatives has been applied in various total syntheses of natural products and been further elaborated applying chiral ligands in the catalysts to enable an enantioselective control (**Tables 8** and **9**).

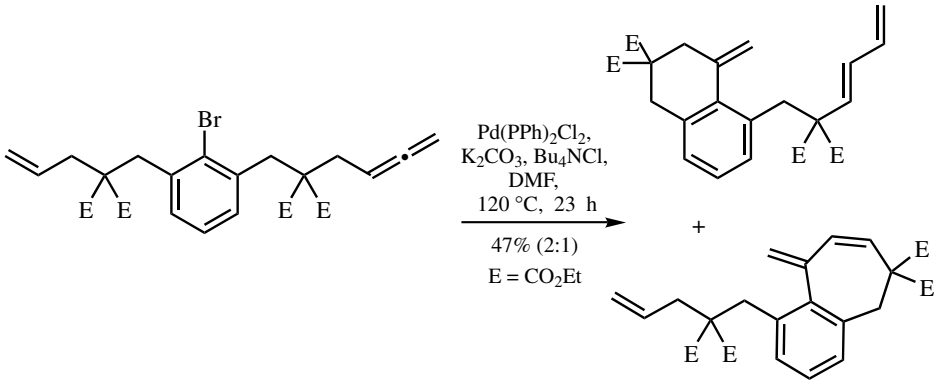


Scheme 10

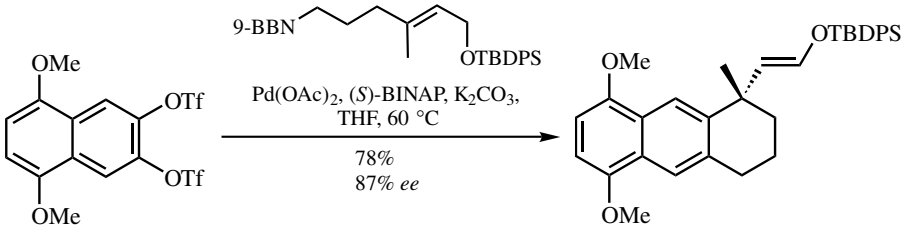
An interesting example concerning the competition between six- and seven-membered ring formation has been provided by Ma and Negishi (**Scheme 11**).[66] At least when an allenyl group competes with an ethenyl group, seven-membered ring formation occurs with approximately the same rate as six-membered ring closure.

The first reported cascade consisting of an intermolecular Suzuki cross-coupling and a subsequent intramolecular asymmetric Heck reaction involving a 6-*exo-trig* cyclization[46] has been developed as a key step in an elegant access to halenaquinone, the oxidation product of halenaquinol, a marine natural product with interesting antibiotic, cardiotonic, and protein kinase inhibitory activities (**Scheme 12**). The two-step process consisting of a Suzuki coupling and a subsequent Heck cyclization has been demonstrated to be similarly efficient.[53]

While the cyclization of 2-halo-1,6-heptadienes under standard Heck conditions leads to the formation of five-membered rings, predominant six-membered ring formation by a formal 6-*endo-trig* process was observed in an aqueous solvent mixture comprising a catalyst system with a water-soluble sulfonated triphenylphosphine ligand. However, the methylenecyclohexene derivative was obtained in 30% yield only



Scheme 11



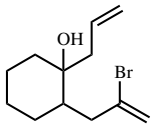
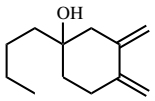
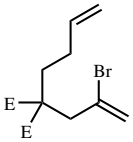
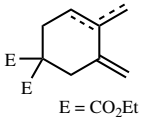
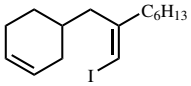
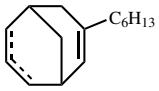
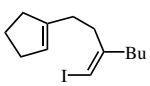
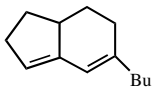
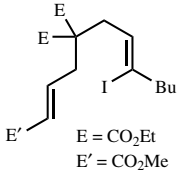
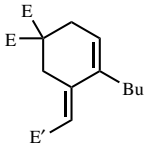
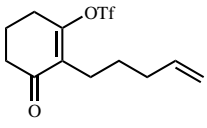
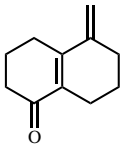
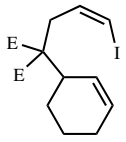
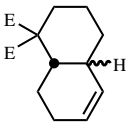
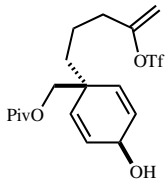
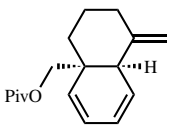
Scheme 12

(**Table 10**, entry 2). The 6-*endo-trig* cyclization has been discussed as a result of a sequence of a 5-*exo-trig*, 3-*exo-trig*, and *retro*-3-*exo-trig* (cyclopropylmethyl to homoallyl rearrangement) cyclizations (**Scheme 13** and **Table 10**). This rearrangement cascade has unquestionably been poven for some examples.[38] Since the process is reversible, it is difficult to state whether the cyclopropyl intermediate has been formed in every single case, see e.g.[24]

A six-membered ring formation has also been observed in the cyclization of 2-bromo-1,7-heptadienes with (1′-methylmethylene)cyclopropyl end groups (**Scheme 14**). Most probably, the six-membered ring intermediate **C** is not formed by a 6-*endo-trig* carbopalladation of the first formed alkenylpalladium bromide, but by a sequence of 5-*exo-trig*, 3-*exo-trig* carbopalladation to give **B** via **A**, and subsequent cyclopropylmethyl- to homoallylpalladium bromide rearrangement. Intermediate **C** would then undergo the same rearrangement once more, and the resulting **D** finally would undergo β-hydride elimination to furnish a cross-conjugated triene, a so-called dendralene. The same products are also obtained by a Pd-catalyzed cycloisomerization of a terminal acetylene with a (1′-methylmethylene)cyclopropyl group at the other end. The same eneynes, when treated with iodobenzene under Heck conditions, yield phenyl-substituted dendralenes in addition to the cross-coupling product of iodobenzene and the eneyne (**Scheme 14**).[80]

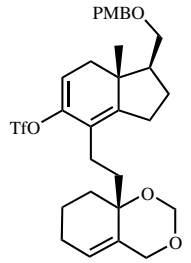
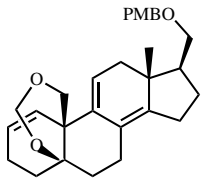
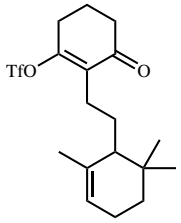
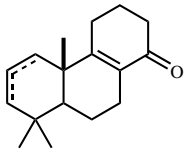
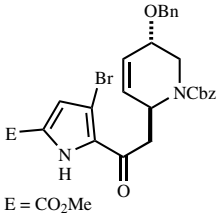
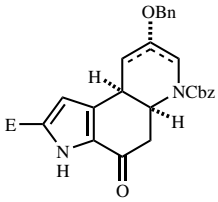
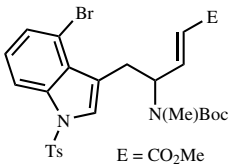
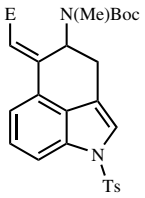
The cyclization of *o*-butenylbenzyl halides proceeds by a 6-*exo-trig* carbopalladation to yield 2-methylenetetraline (**Scheme 15**).[16]

TABLE 8. Synthesis of Cyclohexanes: Cyclization of 2-Halo-1,7-octadienes, 1-Halo-1,6-heptadienes, and Related Compounds by a 6-*exo* Process

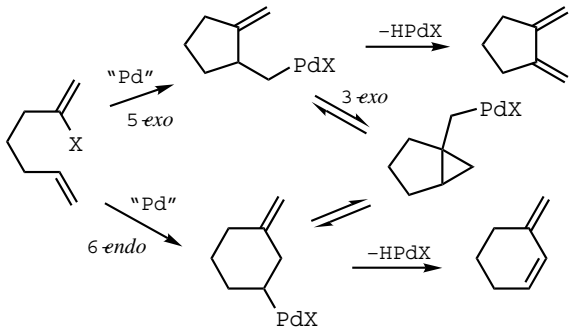
Entry	Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)	Reference
1			$Pd(OAc_2)$, PPh_3, MeCN, 80 °C, 23 h	67 (2:1)[a]	[32],[33]
2			$Pd(OAc_2)$, PPh_3, K_2CO_3, MeCN, 80 °C, 4 h	86 (4:1)[a]	[32] (cf. [34])
3			$Pd(PPh_3)_4$, Et_3N, MeCN/THF, reflux, 2 h	70 (9:1)[a]	[27]
			$Pd(PPh_3)_4$, NaOAc, MeCN/THF, reflux, 2 h	97 (GLC)[b]	[27]
4			$Pd(PPh_3)_4$, Et_3N, MeCN/THF, reflux, 1 h	70 (7:3)[a]	[27]
5			$Pd(PPh_3)_4$, Et_3N, MeCN, reflux, 1.5 h	91	[26]
6			$Pd(OAc_2)$, PPh_3 Et_3N, MeCN, 70 °C, 12 h	80	[9]
7			$PdCl_2$, sulfonated triphenylphosphine, $(i\text{-}Pr)_2NEt$, $MeCN/H_2O$ 6:1, 70 °C, 12 h	80[c]	[37]
8			$Pd(OAc)_2$, (*R*)-BINAP, *t*-BuOH, K_2CO_3, $ClCH_2CH_2Cl$, 60 °C, 42 h	76 (86% ee)	[52]

(*Continued*)

TABLE 8. (*Continued*)

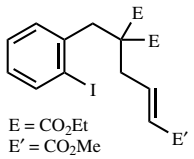
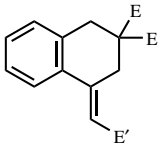
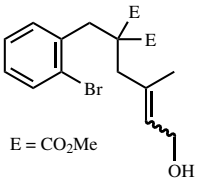
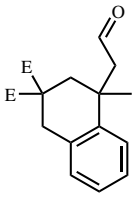
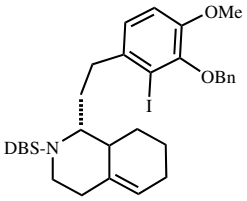
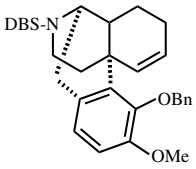
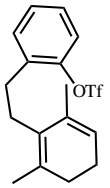
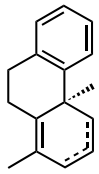
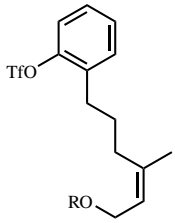
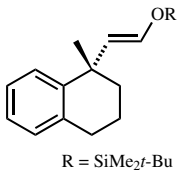
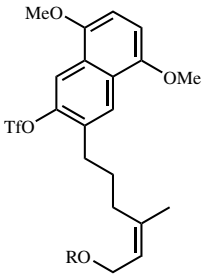
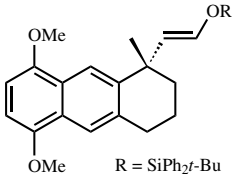
Entry	Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)	Reference
9			$Pd_2(dba)_3$, dppb, KOAc, DMA, 75 °C	65–70	[47]
10			$Pd(OAc)_2$, PPh_3, Et_3N, MeCN, 70 °C, 30 h	95 (3:1)[a]	[51]
11			$Pd(OAc)_2$, P(*o*-Tol)$_3$, Et_3N, MeCN, 110 °C, 26 h	>90 (7:1)[a]	[50]
12			$PdCl_2$, dppp, Ag_3PO_4, $CaCO_3$, DMF, 100 °C, 5 h	77	[49]

[a] Mixture of double bond positional isomers.
[b] Purity according to gas chromatography.
[c] Equimolar mixture of *cis*- and *trans*-fused products.



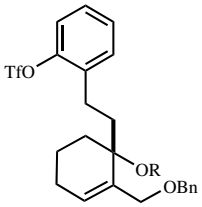
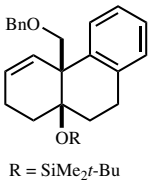
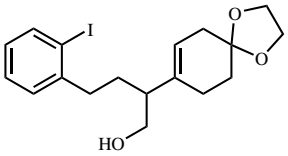
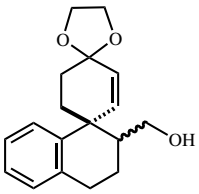
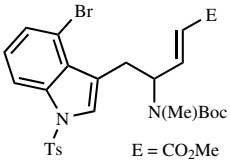
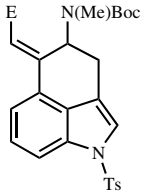
Scheme 13

TABLE 9. Synthesis of Tetralines: Cyclization of 1-Halo-2-pentenylarenes and Related Compounds

Entry	Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)	Reference
1			$Pd(PPh_3)_4$, Et_3N, MeCN, 50–100 °C	82	[26]
2			$Pd(OAc)_2$, PPh_3, Et_3N, MeCN, 80 °C, 48 h	62	[24]
3			$Pd(OTfa)_2(PPh_3)_2$, PMP, toluene, 120 °C, 42 h	60	[76]
4			$Pd(OAc)_2$, (*R*)-BINAP, K_2CO_3, toluene, 80 °C, 72 h	71[a] (95% *ee*)[b]	[77]
5			$Pd(OAc)_2$ (*R*)-BINAP, K_2CO_3, THF, 50 °C, 50h	85 (87%) *ee*	[84]
6			$Pd(OAc)_2$, (*S*)-BINAP, K_2CO_3, THF, 60 °C, 22 h	78 (87% *ee*)	[46],[79], [85]

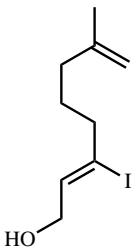
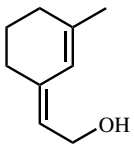
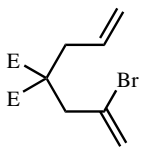
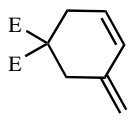
(*Continued*)

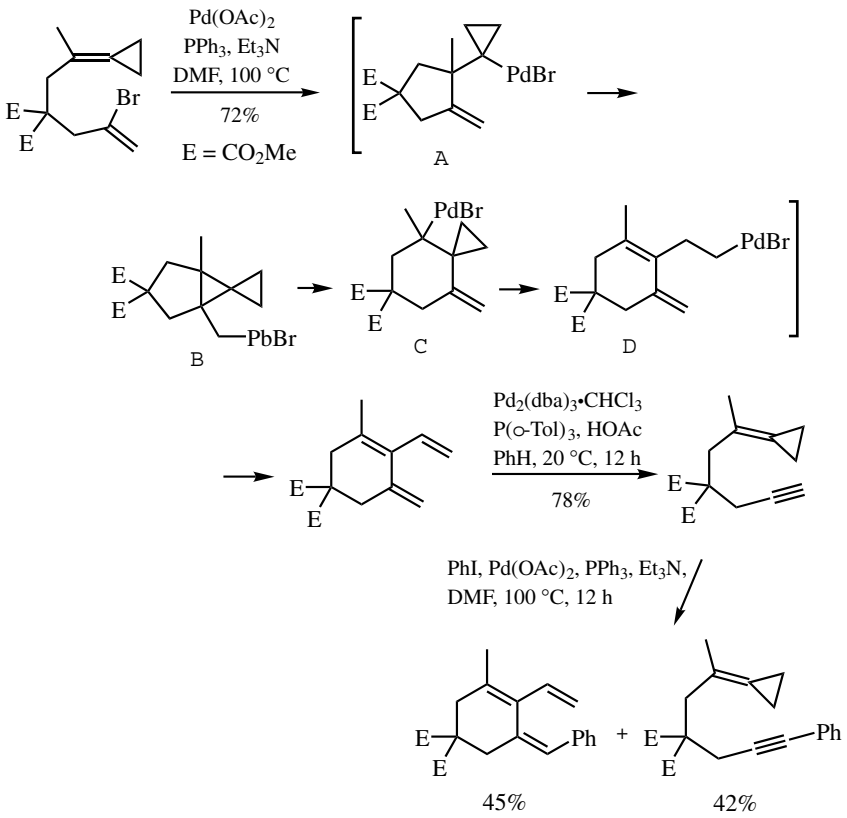
TABLE 9. (*Continued*)

Entry	Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)	Reference
7		 R = $SiMe_2t$-Bu	Pd(dppb), KOAc, DMA, 120 °C, 30 h	65	[47]
8			$Pd(OAc)_2$, PPh_3, Ag_2CO_3, *t*-BuOMe, reflux, 15 h	67	[48]
9	 E = CO_2Me		$PdCl_2$, dppp, Ag_3PO_4, $CaCO_3$, DMF, 100 °C, 5 h	77	[49]

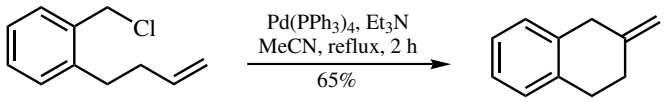
[a] Mixture of double bond positional isomers.
[b] Determined by HPLC analysis of an oxidation product.

TABLE 10. Synthesis of Cyclohexanes: Cyclization of 2-Halo-1,6-heptadienes by a Formal 6-*endo-trig* Process

Entry	Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)	Reference
1			$PdCl_2$, Et_2NH, Et_3N, DMF, 80 °C, 8 h	69	[38]
2		 E = CO_2Me	$PdCl_2$, sulfonated triphenylphosphine, $(i\text{-}Pr)_2NEt$, Ag_2CO_3, $MeCN/H_2O$ 6:1, 90 °C, 24 h	30	[37]



Scheme 14



Scheme 15

B.vi. Synthesis of Cycloheptanes: Cyclization of 2-Halo-1,8-nonadienes and Related Compounds

Several 7-*exo-trig* cyclizations of 2-halo-1,8-nonadiene systems have been reported over the last decade; however, a substantial fraction of 8-*endo-trig* cyclization product has been observed in these cases (**Scheme 16**, **Table 11**).

This type of 7-*exo-trig* cyclization between an iodofurane moiety and a tethered cyclohexenone system served as a key step in the total syntheses of the squalene synthase inhibitors CP-225,917 and CP-263,114 (**Scheme 17**). Crucial at this point was the fact that the *syn*-β-hydride elimination was essential to install the correct double bond pattern.[62] The formation of cycloheptanes via a 7-*endo-trig* process might be envisaged as a sequence of a 6-*exo-trig*, 3-*exo-trig*, and *retro*-3-*exo-trig* process related to the formal 6-*endo* cyclization. This sequence ought to be the major pathway for disubstituted alkenes as acceptor alkene moieties whereas electron deficient alkenes like α,β-unsaturated ketones are added in the 7-*endo* mode (**Table 12**).

TABLE 11. Synthesis of Cycloheptanes: Cyclization of Halo-1,7-octadienes and Related Compounds. E=CO_2Me, E′=CO_2Et

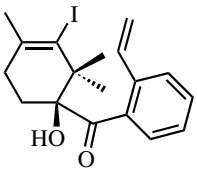
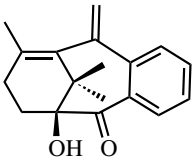
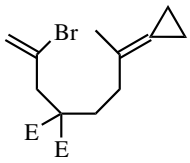
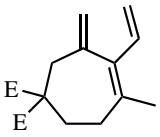
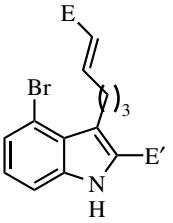
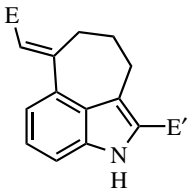
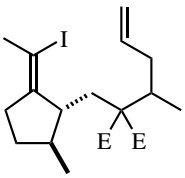
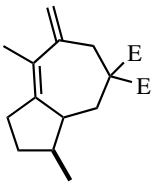
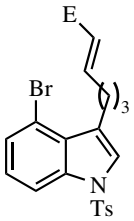
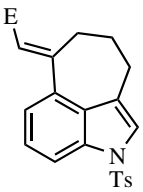
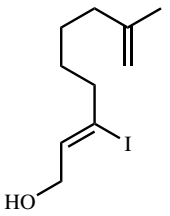
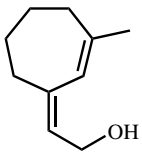
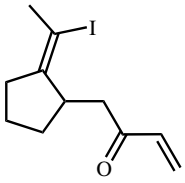
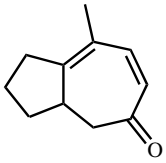
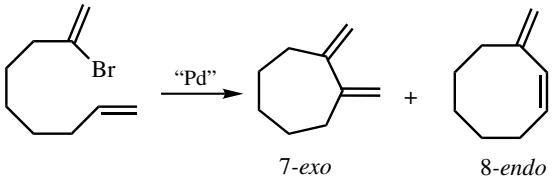
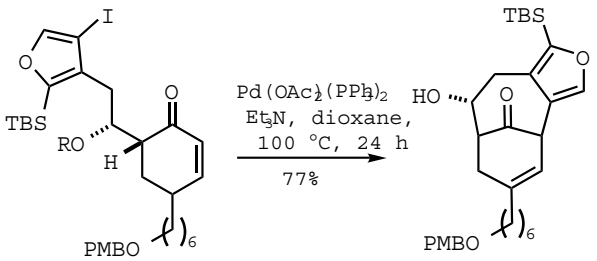
Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)	Reference
		$Pd(PPh_3)_2(OAc)_2$, Et_3N, THF, 70 °C	52	[61]
		$Pd(OAc)_2$, Et_3N, PPh_3 DMF, 100 °C, 12 h	53	[80]
		$Pd(PPh_3)Cl_2$, Et_3N, DMF, 100 °C, 7 h	49	[86]
		$Pd(PPh_3)_4$, Et_3N, MeCN, reflux, 10 h	80	[57]
		$Pd(PPh_3)Cl_2$, Et_3N, DMF, 100 °C, 7 h	67	[86]

TABLE 12. Synthesis of Cycloheptanes: Cyclization of Halo-1,6-octadienes

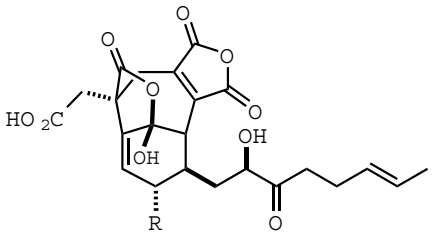
Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)	Reference
		$PdCl_2$, Et_2NH, Et_3N, DMF, 80 C, 8 h	68	[38]
		$Pd(OAc)_2$, K_2CO_3, n-Bu_4NCl, DMF, 23 C, 12 h	53	[57]



Scheme 16



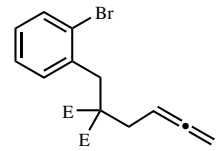
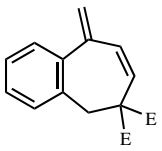
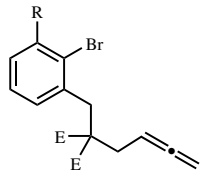
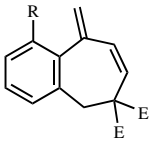
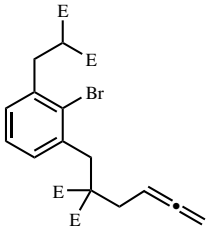
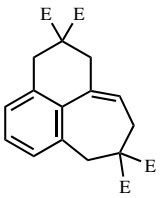
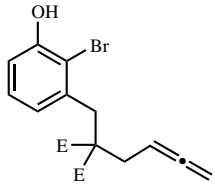
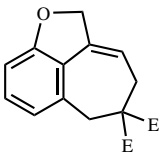
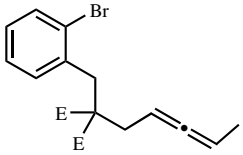
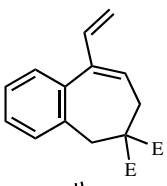
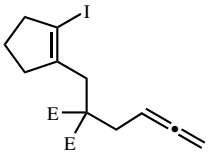
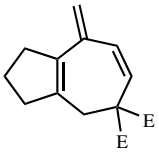
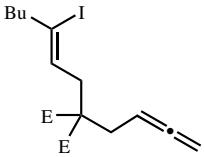
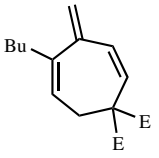
TBS = $SiMe_2$-t-Bu PMB = p-$MeOC_6H_4CH_2$



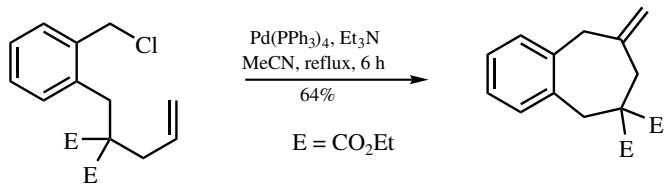
CP-225,917

Scheme 17

TABLE 13. Synthesis of Cycloheptanes: Cyclization of 1-Halo-2-(penta-4,5-dienyl)benzene Derivative: E = CO_2Et

Entry	Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)	Reference
1			$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 8C, 4 h	65	[66]
2	 R = $CH_2C(CO_2Et)_2CH_2Allyl$ or $CH_2C(CO_2Et)_2(CH_2)C{\equiv}CMe$		$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 8C, 4 h	65	[66]
3			$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 110–120 8C, 4 h	40	[66]
4			$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 110–120 8C, 4 h	20	[66]
5			$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 8C, 22 h	58	[66]
6			$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 8C, 4 h	58	[66]
7			$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 8C, 3 h	66	[66]

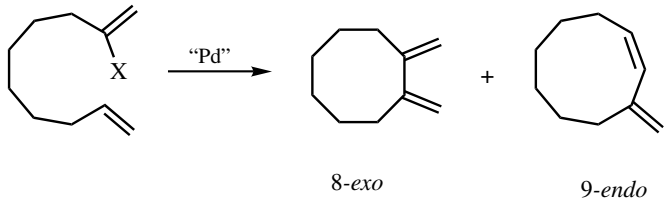
Seven-membered rings are also formed by a Pd-catalyzed 7-*exo-trig* cyclization of benzyl halides with an *ortho*-tethered 4′-pentenyl group as reported by Negishi and co-workers (**Scheme 18**).[16]



Scheme 18

B.vii. Synthesis of Cyclooctanes: Cyclization of 2-Halo-1,8-decadienes and Related Compounds

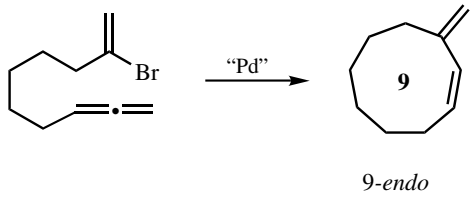
In their studies toward the total synthesis of Taxol®, Danishefsky and co-workers have focused their attention on the formation of eight-membered rings by an intramolecular Heck reaction proceeding by an 8-*exo-trig* cyclization of a 2-halo-1,8-decadiene system (**Scheme 19**, **Table 14**).



Scheme 19

B.viii. Synthesis of Cyclononanes and Larger Ring Systems: Cyclization of 2-Halo-1,*n*-decadienes and Related Compounds

The possibility of forming cyclononanes and larger rings by Pd-catalyzed intramolecular cross-coupling reactions has been investigated to a far lesser extent than that of the smaller rings. Very good yields have been reported for the cyclization of 2-bromo-1,8,9-trienes in which allenyl groups serve as terminators and/or with the aid of high dilution techniques (**Scheme 20**, **Table 15**).



Scheme 20

TABLE 14. Synthesis of Cyclooctanes: Cyclization of 2-Halo-1,8-nonadienes and Related Compounds

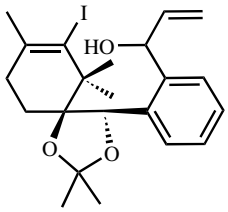
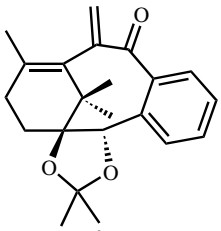
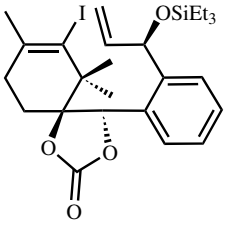
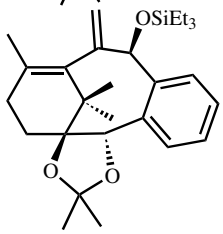
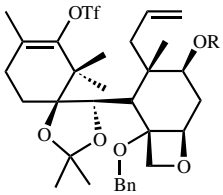
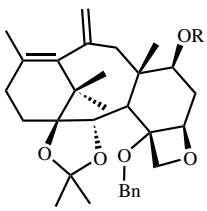
Entry	Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)	Reference
1			$Pd(OAc)_2$, K_2CO_3, 80 °C, 46 h	80	[61]
2			$Pd(PPh_3)_4$, K_2CO_3, MeCN, 90 °C, 72 h	70	[65]
3	 R = $SiMe_2t$-Bu		$Pd(PPh_3)_4$, K_2CO_3, MeCN, MS, 90 °C	49	[60]

TABLE 15. Synthesis of Cyclononanes and Larger Rings: Cyclization of 2-Halo-1,9,10-decatrienes and Related Compound: E = CO_2Et

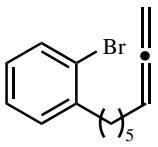
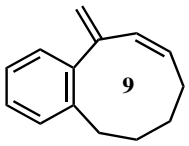
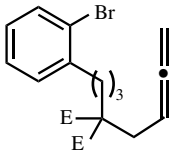
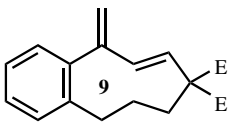
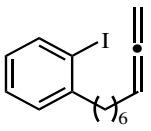
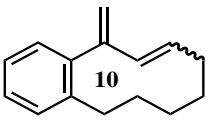
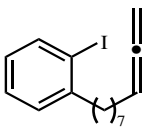
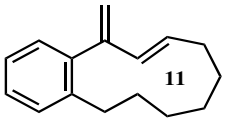
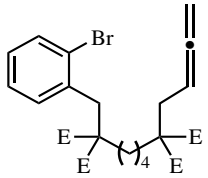
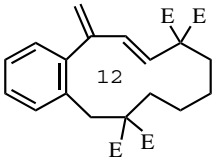
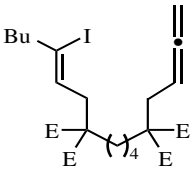
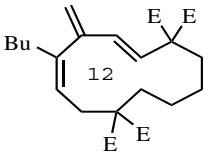
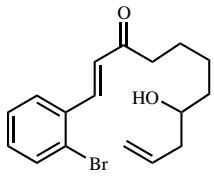
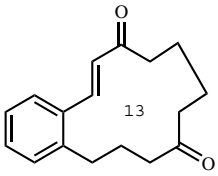
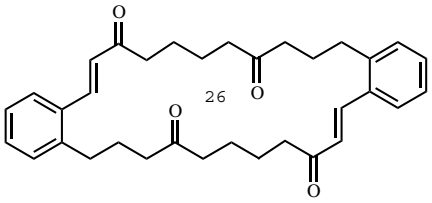
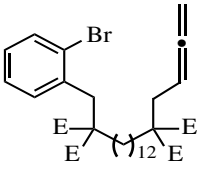
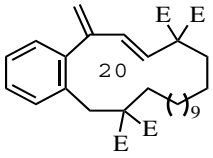
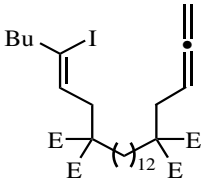
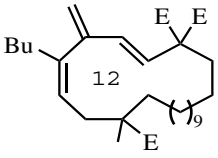
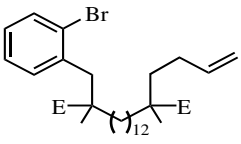
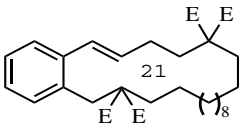
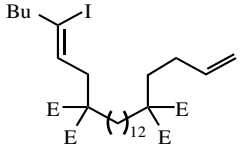
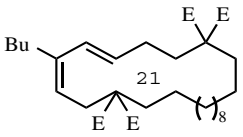
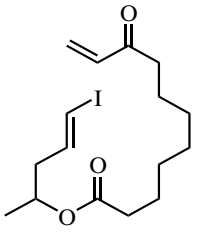
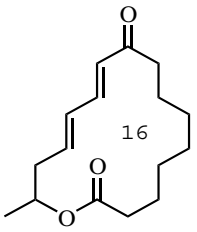
Entry	Starting Material	Product	Ring Size	Catalyst, Solvent, Temperature	Yield (%)	Reference
1			9	$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 8C, 12 h	55	[66]
2			9	$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 8C, 12 h	62	[66]
3			10	$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 8C, 12 h	47 (E/Z = 73:27)	[66]
4			11	$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 8C, 12 h	40	[66]

TABLE 15. (*Continued*)

Entry	Starting Material	Product	Ring Size	Catalyst, Solvent, Temperature	Yield (%)	Reference
5			12	$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 °C, 12 h	50	[66]
6			12	$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 °C, 12 h	27	[66]
7			13/26	$Pd(OAc)_2$, $EtNiPr_2$, LiCl, (8 mmol L^{21}) DMF, 80 °C, 2 d	61/17	[4]
						
8			20	$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 °C, 12 h	86	[66]
9			20	$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 °C, 12 h	47[a]	[66]
10			21	$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 °C, 12 h	66	[66]

(*Continued*)

TABLE 15. (*Continued*)

Entry	Starting Material	Product	Ring Size	Catalyst, Solvent, Temperature	Yield (%)	Reference
11			21	$Pd(PPh_3)_2Cl_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, DMF, 120 °C, 12 h	15	[66]
12			16	$Pd(MeCN)_2Cl_2$, Et_3N, MeCN, 25 °C, 11 h	55	[68]

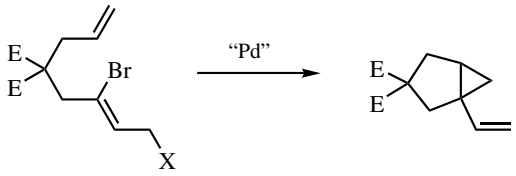
[a]Yield determined by NMR spectroscopy with an internal standard.

C. SYNTHESIS OF BICYCLIC SYSTEMS

C.i. Cyclization of 8-Substituted 6-Halo-1,6-octadienes and Related Compounds with an Additional Leaving Group

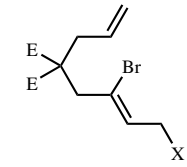
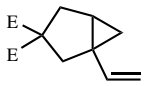
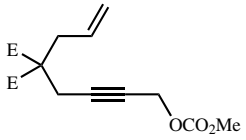
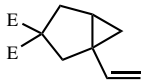
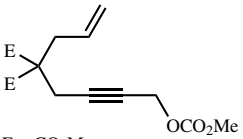
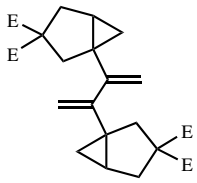
Starting from 6,8-disubstituted 1,6-octadienes having two leaving groups in a 1,3-relationship, Pd-catalyzed cyclization leads to the formation of bicyclic vinylcyclopropanes (**Scheme 21**).[78] The insertion of palladium into the vinylic carbon–halogen bond is regarded as the first step. The thus formed intermediate might rearrange to a palladium–carbene complex, which in turn cyclopropanates the other double bond. Alternatively, the alkenylpalladium halide carbopalladates the other double bond and a 3-*exo-trig* cyclization with subsequent elimination of a palladium(II) salt follows up to form the bicyclic system. Besides bromoallyl esters, propargyl carbonates with an alkenyl tether can also serve as starting materials; however, the presence of sodium formate and Et_4NBr is required to suppress the formation of dehydrodimers (**Table 16**). Propargyl carbonates have also been used in a domino carbocyclization–methylation sequence by means of zincates as nucleophiles (**Sect. IV.3.2**).

Similar approaches to ethenylcyclopropanes from open-chain halodienes or haloenynes have been published by the groups of Oppolzer and Grigg. However, these cascades proceed with a different termination (zincates).[80]–[82]



Scheme 21

TABLE 16. Synthesis of Bicyclo[3.1.0]hexanes: Cyclization of 6-Halo-1,6-octadienes and 1,6-Octenynes[78]

Entry	Starting Material	Product	Catalyst, Solvent, Temperature	Yield (%)
1	 X = OAc, $OCOCF_3$, OCO_2Et	 E = CO_2Me	$Pd(OAc)_2$, PPh_3, Et_3N, MeCN, 85 C, 5–6 h	22–34[a]
2		 E = CO_2Me	$Pd(OAc)_2$, PPh_3, Et_3N, NaO_2CH, Et_4NBr, MeCN, 85 C, 2 h	68
3	 E = CO_2Me		$Pd(OAc)_2$, PPh_3, Et_3N, MeCN, 85 C, 1.5 h	36

[a]The influences of different bases and ligands lead to byproducts and different product compositions.

D. OTHER METHODS

Intramolecular Heck reactions leading to carbocycles involving domino, tandem, or cascade reactions terminated with tethered alkenes and other nucleophiles will be covered in **Sect. IV.3.1** and **V.3.2**, respectively.

E. SUMMARY

1. Various ring sizes (4 to 21 carbon atoms) have been achieved by intramolecular Heck reactions.

2. All formations of four- and five- as well as most of the 6-membered rings proceed via an *n-exo-trig* carbopalladation, while the formation of larger rings has mostly been achieved by *n-endo-trig* processes.

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