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Bicyclopropylidene. A unique tetrasubstituted alkene and versatile C_6-building block for organic synthesis*

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Abstract: Bicyclopropylidene (**4**), now readily available in preparatively viable quantities, is evolving as a useful C_6 building block for organic synthesis due to its enhanced reactivity at the C–H, the C=C, as well as both types of C–C single bonds. Monosubstituted derivatives are accessible by deprotonation/electrophilic substitution. Di- and tetrasubstituted bicyclopropylidenes are best made by copper-mediated reductive dimerization of bromolithiocarbenoids. The 1,3-dipolar cycloadducts of nitrones rearrange to spirocyclopropanated piperidones, palladium-catalyzed codimerizations with acrylates occur with opening of one of the rings to yield precursors to bicyclo[3.3.0]octene and bicyclo[5.3.0]decene skeletons. Silicon-heteroatom bonds can be added across the double bond of **4** under palladium catalysis just like across a C≡C triple bond, and carbopalladation of the double bond in **4** occurs more rapidly than that in an acrylate. A variety of new three-component reactions of **4** with alkenyl as well as aryl halides and dienophiles have been developed and extended to be carried out in a combinatorial sense, even on a polymer support, with an additional dimension added in the cleavage step. Most of the reported reactions of bicyclopropylidene (**4**) proceed with good to excellent yields.

When first conceived [1], bicyclopropylidene (**4**) was simply an exotic molecule and of interest to physically oriented organic chemists, who were curious to learn something about the type of bonding in such an arrangement of two cyclopropyl groups with a double bond in common. The first two syntheses [1] did not even provide enough of this compound to perform a full spectroscopic and structural characterization. Although more productive, even the second-generation synthesis is only of historical interest [2]. The third-generation approach [3] did make this highly strained alkene available in large enough quantities to thoroughly study its physical properties, for a broad screening of its chemistry, however, this method, in spite of several improvements over the years, had the significant disadvantage of being too tedious. The real breakthrough that made this compound available in preparatively viable quantities (Scheme 1), came with the advent of the Kulinkovich reaction [4] (e. g., the transformation of a carboxylic acid ester to a cyclopropanol with the ethylmagnesium bromide/titanium tetraisopropoxide reagent). This reaction, applied to methyl cyclopropanecarboxylate (**1**), gave the key precursor to **4**, the cyclopropylcyclopropanol (**2**) in quantitative yield. This alcohol can conveniently be converted to the bromide (**3**), which in turn is dehydrobrominated with potassium *tert*-butoxide to bicyclopropylidene

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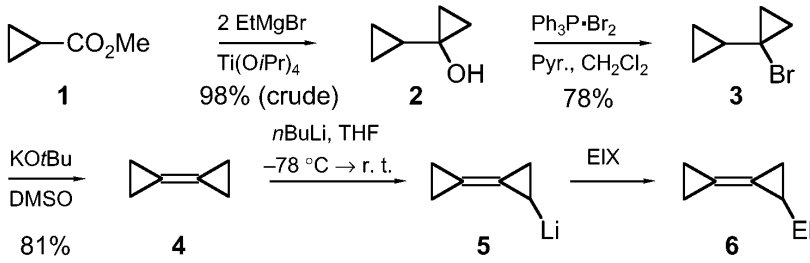


ElX	El	%	ElX	El	%
Me_3SiCl	$SiMe_3$	85	1) CO_2 2) H_2O	CO_2H	95
PhSSPh	SPh	77	Me_2CO	CMe_2OH	50
C_2Cl_6	Cl	73	H_2CO	CHO	73
Br⌒Br	Br	65	AcCl	COMe	71
*n*BuI	*n*Bu	72	⌒Br	⌒	50

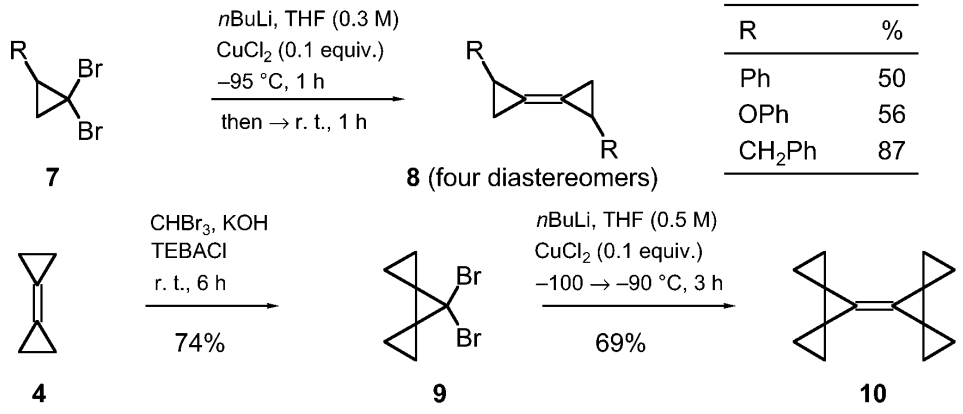
Scheme 1 Versatile synthesis of bicyclopropylidene and monosubstituted derivatives [5–9].

(**4**) [5]. This sequence of three steps can easily be carried out in one week, starting from 100 g of the ester **1** one can obtain up to 50 g of the alkene.

Substituted bicyclopropylidenes **6** can conveniently be prepared by deprotonation of the alkene with butyllithium and subsequent electrophilic substitution with a wide variety of electrophiles [6–9]. The carboxylation with carbon dioxide works particularly well [6] and yields bicyclopropylidenecarboxylic acid, which can be optically resolved to give the enantiomerically pure carboxylic acid, the key starting material to derivatives with which many of the reactions can be carried out in an enantioselective mode [10].

Bicyclopropylidene (4) is characterized by a relatively high-lying highest occupied molecular orbital (HOMO), as expressed by its lowest ionization event observed in the photoelectron spectrum at 8.93 eV [11], which is significantly lower than that of methylenecyclopropane. Although the ionization energy is not as low as that of tetramethylethylene, bicyclopropylidene (4) is significantly more reactive in any sort of addition across its double bond than tetramethylethylene, which is in part due to decreased steric congestion, but mainly to a difference in hybridization of the two carbon atoms making up the double bond. As expressed by the significant shortening of this bond between two almost sp-hybridized carbon atoms [12], it is comparable to the central double bond in 1,2,3-butatriene, or, in another description, approaching the properties of an acetylenic triple bond. The overall reactivities of bicyclopropylidene (**4**) are characterized by four features: There is an enhanced kinetic acidity, expressed by the facile deprotonation of one of the four identical methylene groups, there is a drastically enhanced reactivity of the double bond, and there are reactions, in which the single bond adjacent to the double bond or the single bond opposite the double bond are opened up. In addition, there are a number of combinations of these reactivities.

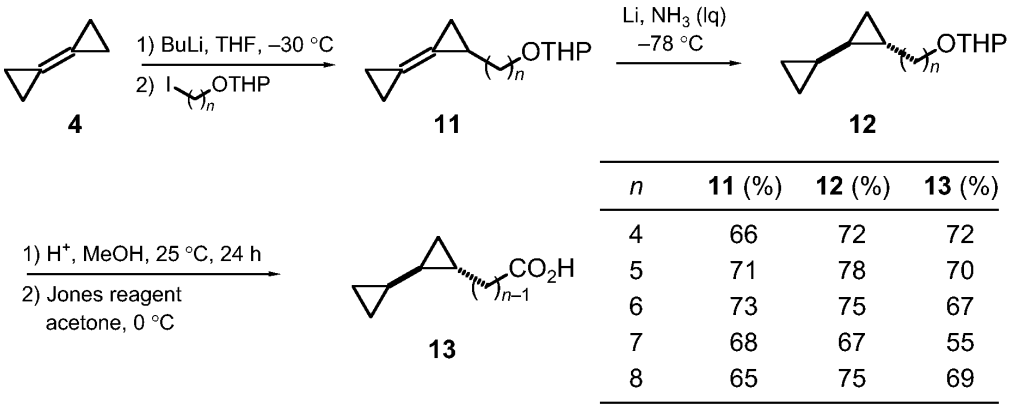
Di- or tetrasubstituted bicyclopropylidene derivatives are most easily accessible by a copper-mediated reductive dimerization of cyclopropylidenoids, generated from substituted dibromocyclopropanes **7** by bromine–lithium exchange in the presence of cupric chloride. This method, developed by Neuenschwander *et al.* [13], yields mixtures of diastereomers, however, in some cases with a significant diastereoselectivity (Scheme 2). This reductive dimerization could even be applied to the dibromocarbene adduct **9** of bicyclopropylidene (**4**) to give the second-generation bicyclopropylidene **10**, the perspirocyclopropanated analog of the parent alkene (Scheme 2) [14].



R	%
Ph	50
OPh	56
CH_2Ph	87

Scheme 2 Versatile synthesis of di- and tetrasubstituted bicyclopropylidenes, including the second-generation bicyclopropylidene **10** [13,14].

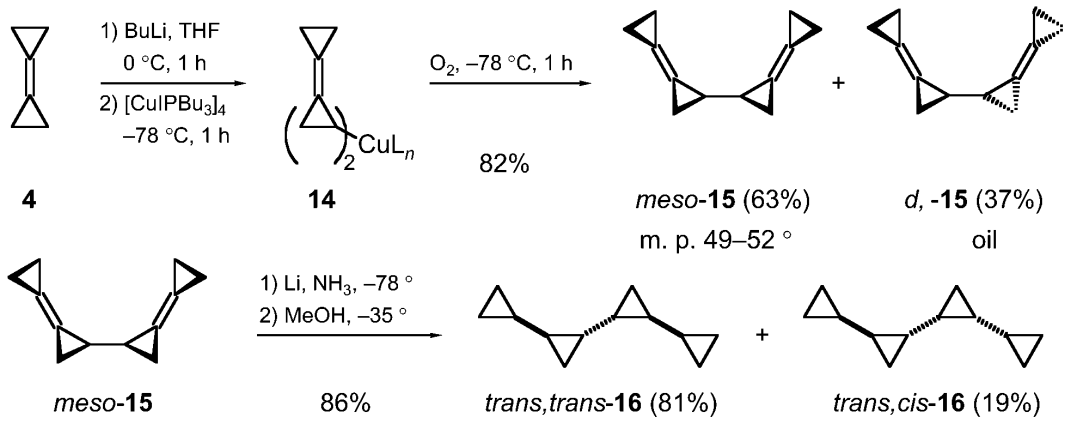
The deprotonation-electrophilic substitution sequence was used to access bicyclopropyl-terminated fatty acids (**13**) (Scheme 3) [8,15]. It is quite remarkable that the double bond in the bicyclopropylidene moiety can easily be reduced under Birch conditions [14,15]. The biological activity, as well as the metabolism, of these bicyclopropyl-terminated fatty acids **13** were studied [8,15].



n	**11** (%)	**12** (%)	**13** (%)
4	66	72	72
5	71	78	70
6	73	75	67
7	68	67	55
8	65	75	69

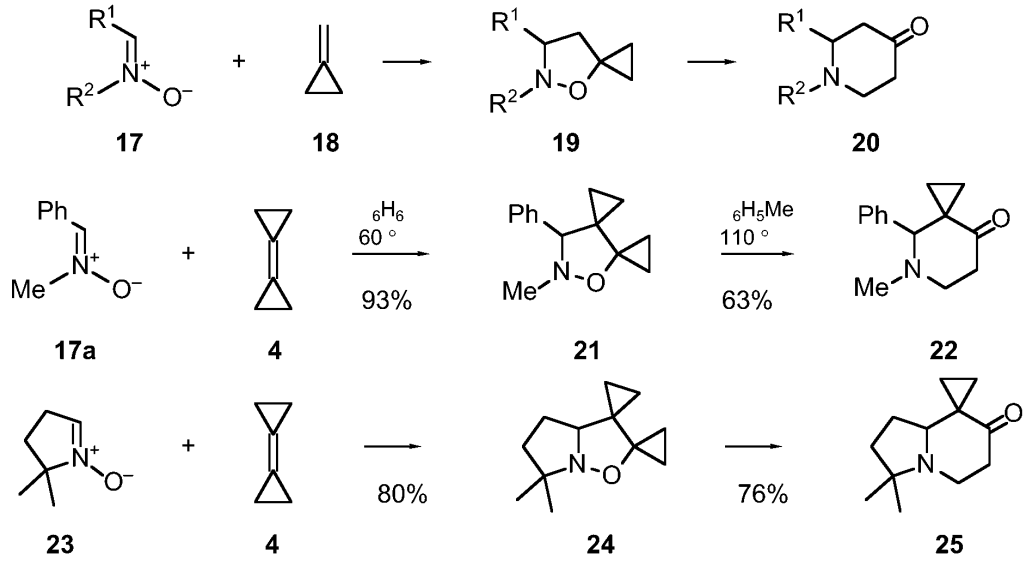
Scheme 3 Facile preparation of bicyclopropyl-substituted fatty acids [8,15].

Bicyclopropylidene (**4**) could also be converted to a higher-order cuprate **14** by treatment of its lithium derivative with a cuprous iodide phosphine complex, and this cuprate **14** upon oxidation with oxygen gave two diastereomeric bisbicyclopropylidenyls *meso*- and *d,l*-**15** (Scheme 4) [14]. The *meso*-diastereomer *meso*-**15** crystallized out and could be purified very easily, while the purification of the *d,l*-diastereomer *d,l*-**15** was a little more tedious. Birch reduction of these interesting 1,5-dienes **15** led to all four possible diastereomeric quatercyclopropyls **16** (e. g., the *meso*-isomer *meso*-**15** yielded predominantly the *all-trans*-**16** along with the *trans,cis*-isomer *trans,cis*-**16)** [14]. These quatercyclopropyls were prepared in order to study their conformational behavior in order to possibly contribute to an understanding of the biological activity of the intriguing natural products containing fatty acid residues with four or even five consecutive cyclopropyl groups [16].



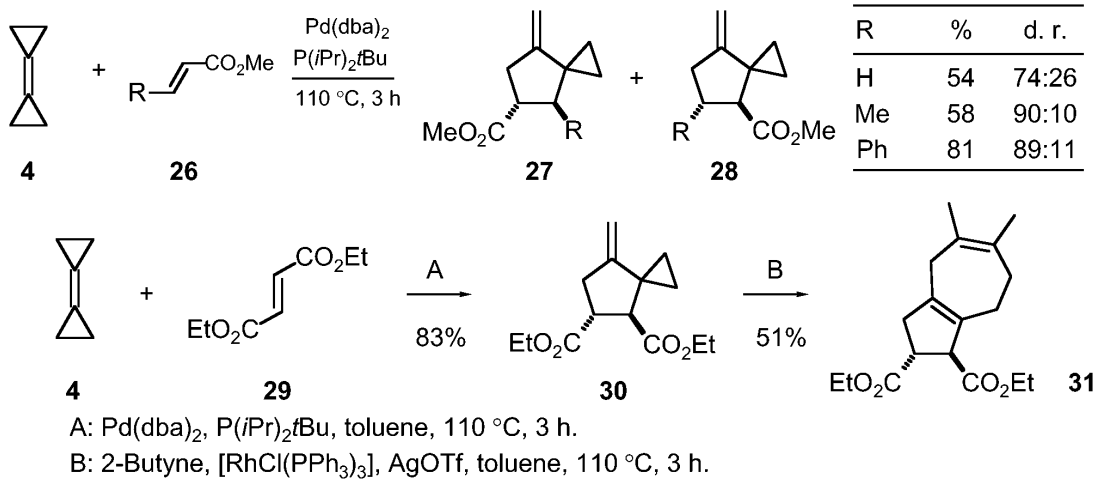
Scheme 4 Bis(bicyclopropylidenyl) **15**: an interesting 1,5-diene and an access to quatercyclopropyls **16** [14].

Brandi *et al.* have developed the 1,3-dipolar cycloaddition of nitrones **17** to methylenecyclopropane **18** and their thermal rearrangement in which the N–O bond opens up with an ensuing oxacyclopropylcarbinyl to oxahomoallyl radical rearrangement, and subsequent reclosure to piperidones **20**. The same nitrone addition applied to bicyclopropylidene (**4**) yields oxazolidines **21** with two annelated spirocyclopropane rings, and these, upon heating, yield piperidones **22** with annelated spirocyclopropane groups very efficiently (Scheme 5) [17,18]. Compounds of this kind, made by 1,3-dipolar cycloadditions of appropriately substituted cyclic nitrones **23** lead to aza analogs **25** containing the skeleton and the major functionalities of the cytotoxic illudines and ptaquilosides (Scheme 5) [18]. In fact, some of the derivatives made by this route showed DNA-cleaving abilities.



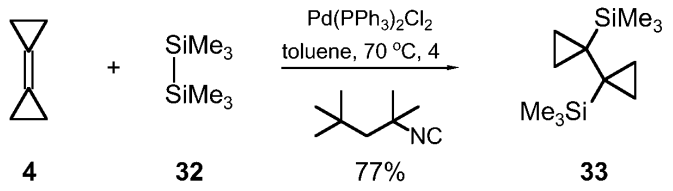
Scheme 5 Nitrone cycloadditions to methylenecyclopropane and bicyclopropylidene [17,18].

It is particularly interesting that bicyclopropylidene (**4**) can undergo cocyclizations with acceptor-substituted alkenes **26** under palladium catalysis. With methyl acrylate, methyl crotonate, and methyl cinnamate, two regioisomers **27** and **28** were obtained, but the latter two cocyclizations occurred with a regioselectivity of 9:1 (Scheme 6) [19]. The formation of regioisomers can easily be avoided by using a symmetrically disubstituted substrate like diethyl fumarate (**29**). These formal cycloadditions occur with ring opening of one of the two cyclopropyl groups in bicyclopropylidene yielding methylenespiro-[2.4]heptane derivatives **27**, **28**, and **30** with an exocyclic vinylcyclopropane unit. These adducts do undergo a clean thermal rearrangement to yield bicyclo[3.3.0]octene derivatives. An even more interesting use of the exocyclic vinylcyclopropane unit in the adduct **30** is by rhodium-catalyzed cocyclization with an alkyne such as 2-butyne to yield a seven-membered ring annelation product **31** (Scheme 6) [19]. The creation of such five-seven-ring combinations may be applicable in terpene total synthesis.

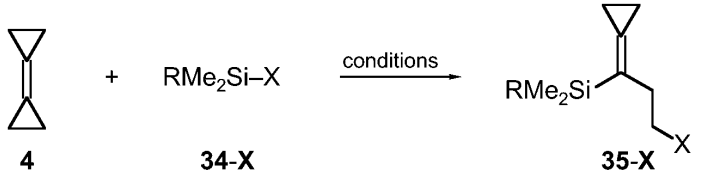


Scheme 6 Pd(0)-catalyzed formal [3+2] cycloadditions of bicyclopropylidene (**4**) with alkenes and Rh(I)-catalyzed intermolecular formal [5+2] cycloaddition of the resulting vinylcyclopropane [19].

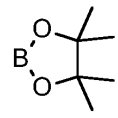
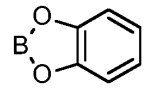
The analogy of the double bond in bicyclopropylidene (**4**) and a triple bond is particularly well documented by the fact that silicon–silicon bonds can be added to this double bond under palladium catalysis (Scheme 7) [20]. Such additions of disilanes have previously been observed and developed as a synthetic method by Ito *et al.* only for triple bonds [21]. While hexamethyldisilane **32** under palladium catalysis in the presence of isooctylisonitrile yields bistrimethylsilylbicyclopropyl **33** with retention of both three-membered rings, the addition of difluorotetramethyldisilane in the absence of the isonitrile ligand yields an adduct **35** with a homoallylsilane moiety. The same reaction mode was observed with dimethylphenylsilylboranes and trimethylsilylstannanes (Scheme 7) [20]. These palladium-catalyzed additions of silane derivatives **34** to bicyclopropylidene open up routes to a variety of building blocks **35**-**X** containing a methylenecyclopropane end group which has been found to be benificial for many intramolecular reactions [22]. Particularly versatile, in this respect, is the addition of trimethylsilyl cyanide **34**-**CN**, which occurs with the same type of ring opening to yield a trimethylsilyl-substituted 4-cyclopropylidenebutyronitrile **35**-**CN** that can readily be converted to a number of functionally substituted methylenecyclopropane derivatives with a cyrboxylic acid, an aldehyde, or an amino terminus [20].



4 **32** 77% **33**



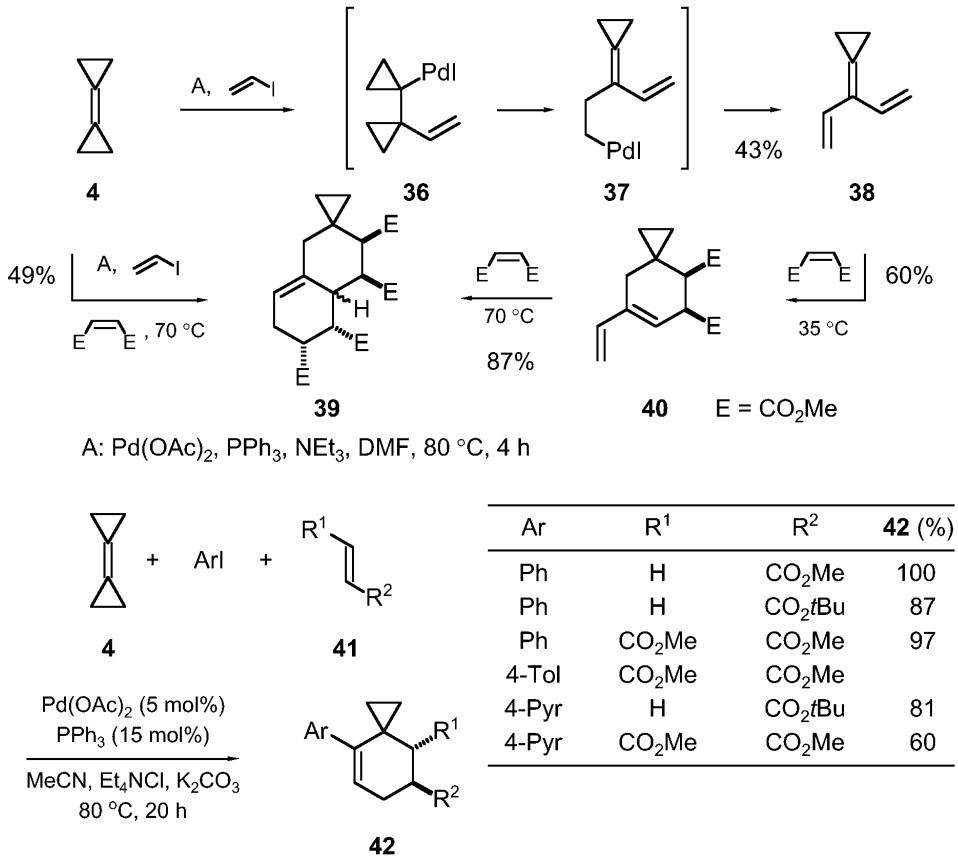
4 **34-X** **35-X**

R	Conditions	X	**35-X** (%)
F	$Pd(PPh_3)_2Cl_2$, C_6H_6, 70 °C, 12 h	$SiMe_2F$	55
Ph	$Pd(OAc)_2$,  NC, Tol, 130 °C, 3		71
Ph	$Pd(OAc)_2$,  NC, Tol, 130 °C, 5		54
Me	$Pd(PPh_3)_4$, Et_2O, 50 °C, 3	$SnBu_3$	61
Me	$Pd(PPh_3)_4$, Et_2O, 50 °C, 4	$SnMe_3$	92
Me	$PdCl_2$, Tol, 100 °C, 14	CN	68

Scheme 7 Pd-catalyzed addition of disilanes, silylboranes, -stannanes and cyanide to bicyclopropylidene (**4**) [20].

It is particularly remarkable that bicyclopropylidene (**4**) undergoes Heck-type coupling reactions with alkenyl and aryl halides. Under typical Heck reaction conditions, it reacts with vinyl iodide in the presence of a dienophile such as dimethyl maleate to yield a spirocyclopropane-annelated bicyclo[4.4.0]decene skeleton **39** in a single operation (Scheme 8) [23].

The coupling reaction apparently proceeds in the typical manner starting with a carbopalladation of bicyclopropylidene (**4**) by the initially formed vinylpalladium iodide, the resulting intermediate **36** has the feature of a cyclopropylmethylpalladium iodide which rapidly opens up to a homoallylpalladium iodide moiety **37**, and β-hydride elimination ensues to give a cross-conjugated triene **38** (Scheme 8) [23–25]. This can, in fact, be isolated, when the reaction is performed in the absence of a dienophile and reacted separately with dimethyl maleate at 35 °C to selectively yield a vinyl-substituted spiro[2.5]octene derivative **40**, which in turn can react at elevated temperature (70 °C) to the product **39** obtained in the one-pot sequential reaction. This multicomponent reaction offers itself for combinatorial synthesis [24a]. Not only alkenyl halides, but a large variety of aryl halides can be employed in this three-component reaction with bicyclopropylidene (**4**) to give aryl-substituted spiro[2.5]octene derivatives **42** (Scheme 8) [23–25].

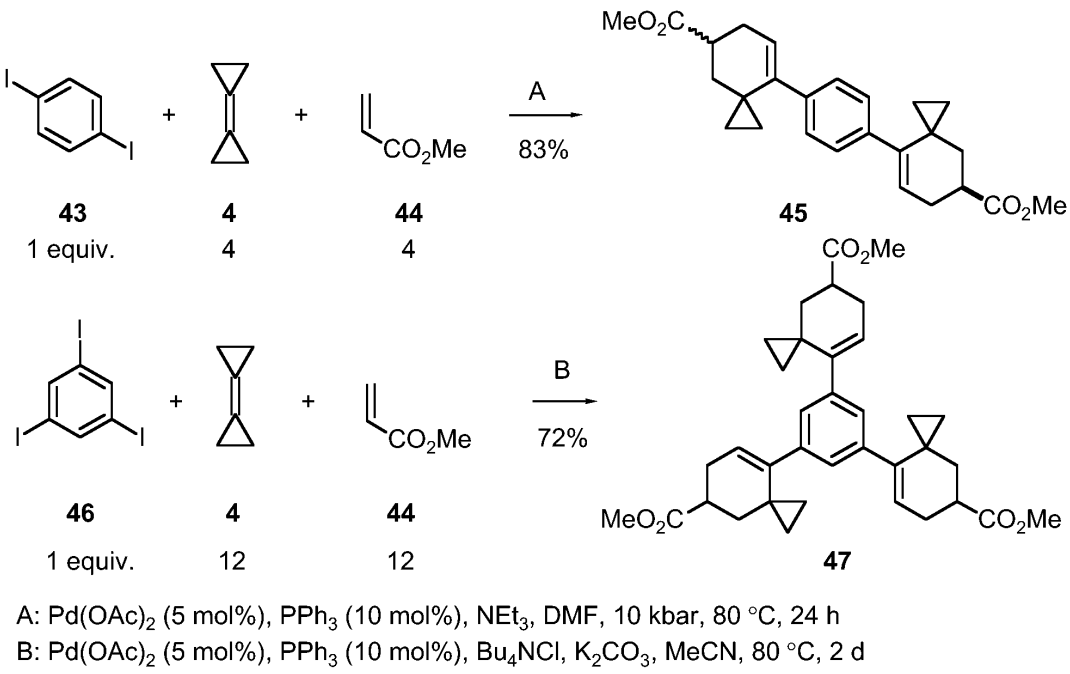


Ar	R^1	R^2	**42** (%)
Ph	H	CO_2Me	100
Ph	H	CO_2tBu	87
Ph	CO_2Me	CO_2Me	97
4-Tol	CO_2Me	CO_2Me	
4-Pyr	H	CO_2tBu	81
4-Pyr	CO_2Me	CO_2Me	60

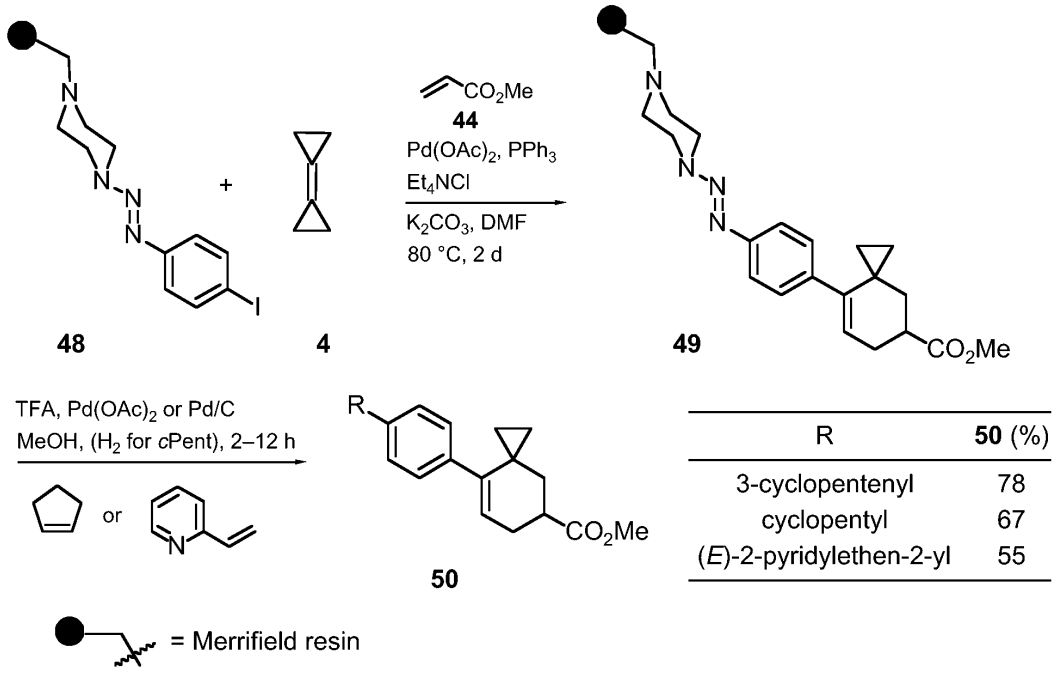
Scheme 8 An inter-intermolecular domino of Heck and Diels–Alder reactions [23–25].

In many cases, the yields are between 80 and 95% or virtually quantitative. This three-component reaction has been carried out on a robotic system to make several small-molecule libraries of 96 components each with the given skeleton [24a,25]. The coupling–cycloaddition sequence can be carried out twice, for example, with *p*-diiodobenzene (**43**), bicyclopropylidene (**4**), and methyl acrylate (**44**) to give the biscoupling-biscycloaddition product **45** as a single diastereomer, as proved by an X-ray crystal structure analysis (Scheme 9) [25]. The yield has been as high as 83%, when high pressure was applied to accelerate the Heck coupling as well as the cycloaddition, but even without applying high pressure, the yield was 64%. Even a threefold coupling and threefold cycloaddition occurred very cleanly with 1,3,5-triiodobenzene (**46**) to give the corresponding product **47** in a surprising 72% yield (Scheme 9) [25].

The combinatorial aspect can be extended further by running the reaction on a solid support. Making use of the triazene-linker methodology developed by Bräse *et al.* [e. g., starting with an aryl iodide bound via a triazene-linker to a Merrifield resin (**48**)], the three-component reaction gave the coupling–cycloaddition product **49** in good yield (Scheme 10) [24a]. The triazene-linker has two favorable features: It can be cleaved off without leaving a trace by treatment with trifluoroacetic acid, or else the intermediate diazonium ion generated under these conditions can undergo a further Heck-type coupling. This then offers another dimension in the combinatorial scheme, in that a variety of alkenes can be coupled upon cleaving the product off the linker. In the current case, this has been demonstrated with cyclopentene and 2-vinylpyridine (Scheme 10) [24a].

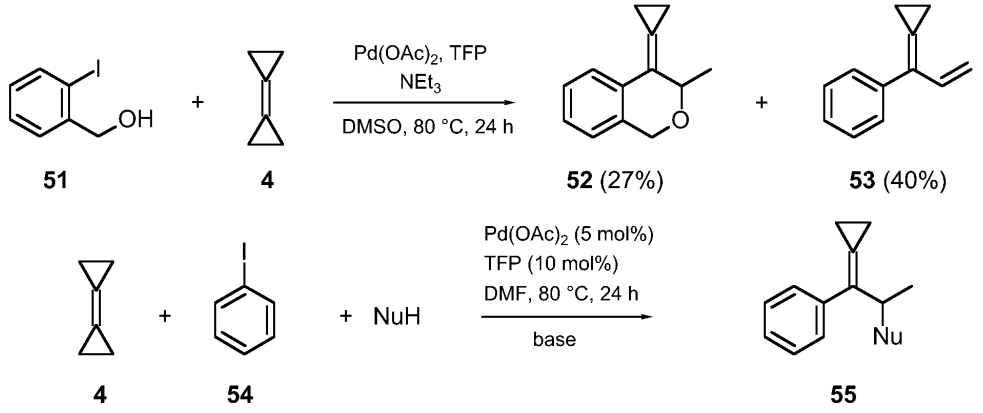


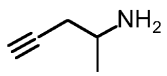
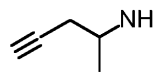
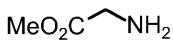
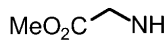
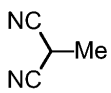
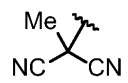
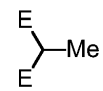
Scheme 9 An inter-intermolecular domino of Heck and Diels–Alder reactions—up to nine new C–C bonds in a single operation [25].

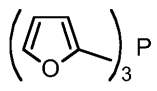


Scheme 10 Combination of cross-coupling, Diels–Alder reaction and cross-coupling with a combinatorial potential [24a].

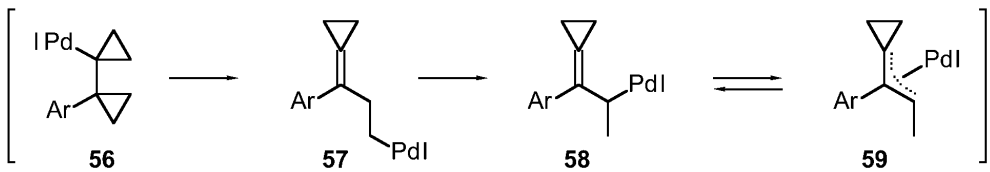
Yet another reaction mode was observed, when *o*-iodobenzyl alcohol (**51**) was coupled to bicyclopropylidene (**4**), which gave a benzodihydropyran derivative **52**, apparently arising from an intramolecular trapping of a π-allylpalladium intermediate. This reaction mode is favored by electron-rich ligands like trisfurylphosphine (TFP), which are known to retard β-hydride elimination reactions. Thus, the intermediate **57** formed by ring opening of the primary carbopalladation product **56**, would not undergo β-hydride elimination but rearrangement to a σ-allylpalladium species **58**, and this—although it would certainly be in a equilibrium with a π-allylpalladium species **59**—would selectively be attacked by nucleophiles at the sterically less congested position (Scheme 11) [25].



NuH	Base	Nu	**55** (%)
LiOA	—	OA	50
$BnNH_2$	—	BnNH	60
i$BuNH_2$	—	*i*BuNH	85
t$BuNH_2$	—	*t*BuNH	95
	NEt_3		38
	NEt_3		63
	NEt_3		77
	NEt_3		57

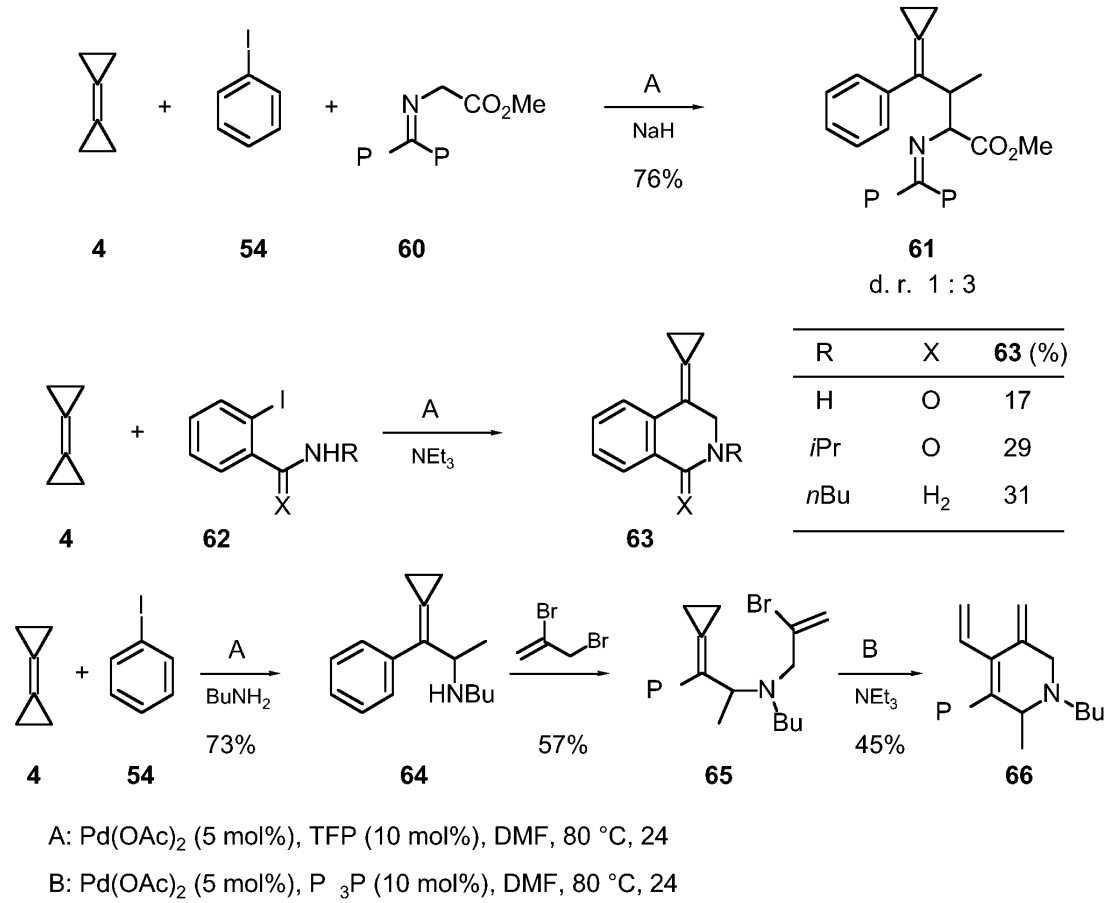
TFP = 

E = CO_2Et



Scheme 11 Domino reaction of bicyclopropylidene involving a α-homoallyl- to π-allylpalladium rearrangement [24b,25].

This reaction mode again can be utilized in a combinatorial sense with a large variety of aryl halides and a wide range of nucleophiles, including carbon nucleophiles, to give aryl-substituted methylenecyclopropane derivatives with a wealth of substituents [25]. For example, amino acid derivatives **60** can be offered as nucleophiles to give a range of products **61** which can be further elaborated upon. This reaction mode can also be carried out in an intramolecular fashion, yet the yields of compounds **63** in this intramolecular version definitely need further improvement (Scheme 12) [25]. One example for further elaboration is demonstrated by the use of the coupling-substitution product of bicyclopropylidene (**4**), iodobenzene (**54**), and butylamine, which was used to substitute the allylic bromide in 2,3-dibromopropene. The bromodiene **65** formed in this reaction was subjected to Heck coupling conditions and gave a cross-conjugated triene **66** that would be set up for domino Diels–Alder cycloadditions as demonstrated before with such trienes (Scheme 12) [25].



R	X	**63** (%)
H	O	17
*i*Pr	O	29
*n*Bu	H_2	31

A: $Pd(OAc)_2$ (5 mol%), TFP (10 mol%), DMF, 80 °C, 24

B: $Pd(OAc)_2$ (5 mol%), P_3P (10 mol%), DMF, 80 °C, 24

Scheme 12 Bicyclopropylidene: more three-component reactions and yet another dimension [25].

It is obvious that the highly compact multifunctional building block bicyclopropylidene (**4**) opens up a variety of elegant routes to a range of skeletons, most of which do contain one remaining cyclopropane ring [9]. The high reactivity of **4** in transition-metal catalyzed transformations undoubtedly relates to the fact that it is a particularly good ligand for transition metals, as demonstrated by the isolation and characterization of a stable cobalt complex as well as a titanium complex [26]. This feature of bicyclopropylidene will certainly be utilized much more with other transition metals in near future.

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