Transition Metal-Catalyzed Reactions of Methylenecyclopropanes

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Abstract: The transition metal-catalyzed formal [3+2] cycloaddition of methylenecyclopropanes with unsaturated compounds X=Y, such as alkenes, aldehydes, and imines, gives five-membered carbocycles or heterocycles. The Heck-type reaction of R-Pd-X with the exomethylene part of methylenecyclopropanes gives the corresponding cyclopropylcarbinylpalladium complexes which undergo further transformations through typical palladium reactions such as β-hydride elimination or reductive elimination of Pd(0). Hydrostannation, hydrosilylation, hydrocarbonation, hydroamination, and hydroalkoxylation of methylenecyclopropanes proceed through the addition of the metal hydrides (H-M) and pronucleophiles (H-Nu) to the olefinic part, and the resulting intermediates are converted to the allylic products in which the homologation by three carbon atoms takes place from M and Nu, respectively. Bismetallation produces 1,3-bimetallic derivatives through metallacyclobutane intermediates.

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4 Addition of Metal Hydrides (H-M) and Pronucleophiles (H-Nu)
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Keywords: catalytic reaction; hydroamination; hydrocarbonation; methylenecyclopropane; transition metals (late).

1 Introduction

Over the last decade, the examples of methylenecyclopropane derivatives applied to synthetic transformations have brought about mounting interest in this area of study. The attractive feature of these compounds is their surprising stability, accompanied by a high level of strain, conferring on them an otherwise unattainable chemical reactivity.[1] Since the 1970's, the chemistry of methylenecyclopropanes in the presence of transition metal catalysts has been explored.[2] The reaction course of methylenecyclopropanes with transition metal catalysts is categorized into the following four patterns. When the cyclopropane ring of methylenecyclopropane **1a** reacts with transition metal catalysts, there are two different types of the reaction pattern; the insertion of ***M*** into the distal bond (C-3/C-4) gives **2**, whereas that into the proximal bond (C-2/C-3) provides **3** (Figure 1). When the exomethylene part of **1a** reacts with organotransition metallics (R-ML_n), there are two different types of the addition pattern; the addition of ***M*** to C-1 gives the anti-Markovnikov product **4**, whereas that to C-2 affords the Markovnikov product **5.** The organometallic intermediates **2–5** undergo further rearrangements and/or reactions with substrates, giving the final products.

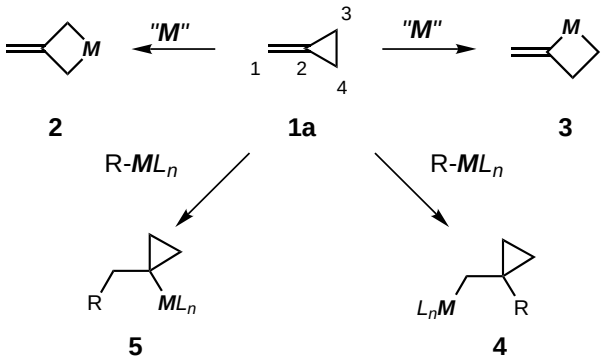

Figure 1. Methylenecyclopropane **1a.**

In this review, we summarize (a) the transition metal-catalyzed reactions of methylenecyclopropanes with unsaturated compounds (X=Y), that is [3+2] cycloadditions, (b) Heck-type reactions with R-Pd-X, (c) the additions of metal hydrides (H-M) and pronucleophiles (H-Nu), and (d) the additions of bis-metallic compounds.

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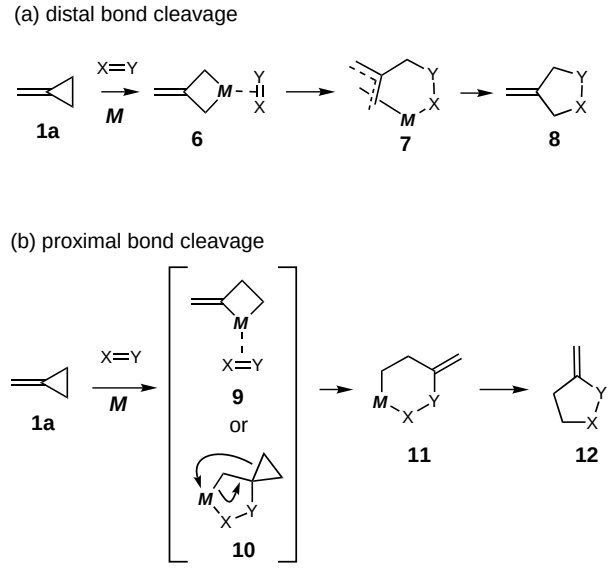
Itaru Nakamura was born in Sapporo, Japan, in 1973. He received his M.Sc. (1998) and Ph. D. (2001) degrees from Tohoku University working under the direction of Professor Y. Yamamoto. He was appointed as a Research Associate at Tohoku University in 2001. His current research interest is focused on the development of new transition metal-catalyzed reactions.

Yoshinori Yamamoto was born in Kobe, Japan, in 1942. He received his M.Sc. (1967) and Ph. D. (1970) degrees from Osaka University, Japan. He was appointed as an Instructor at Osaka University in 1970. While he was working as an Instructor at Osaka University, he went to Professor H. C. Brown's research group at Purdue University, as a Postdoctoral Associate (1970 – 1972). In 1977 he was appointed as an Associate Professor at Kyoto University, Japan where he remained until 1985. In 1986 he moved to Tohoku University to take up his present position, Professor of Chemistry. He also holds a Professorship at IMRAM, Tohoku University and a visiting Professorship at Kyushu University. He was a recipient of the Chemical Society of Japan Award for Young Chemists in 1976. More recently, he was awarded the Chemical Society of Japan Award (1995). He is the Regional Editor of Tetrahedron Letters and Volume Editor of Science of Synthesis. He is the President of the International Society of Heterocyclic Chemistry (2000 – 2001). He has a wide range of research interests in synthetic organic and organometallic chemistry. His recent work focussed on the use of transition metal complexes as catalytic reagents in organic synthesis and synthesis of complex natural products.

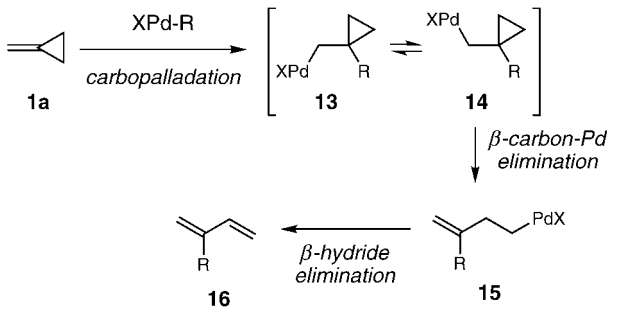
In the catalytic [3 + 2] cycloaddition of methylenecyclopropanes, the cleavage of the cyclopropane ring takes place at either the proximal or the distal bond. The reaction involving distal bond cleavage proceeds through the formation of the metallacyclobutane species **6** followed by insertion of an X=Y multiple bond, as shown in **7**, giving the five-membered carbo- and heterocycles **8** (Scheme 1).[2] On the other hand, in the



Scheme 1. Catalytic formal [3 + 2] cycloaddition of methylenecyclopropanes (a) via distal bond cleavage (b) via proximal bond cleavage.

proximal bond cleavage, either direct attack of a catalyst to a proximal bond (**9**)[3] or formation of a metallacyclopentane (**10**) followed by β-carbon-metal elimination takes place, giving alternative five-membered carbo- and heterocycles **12** via the metallacycle intermediate **11**.[4] The mode of ring opening mainly depends on the choice of catalysts. For example, the cycloadditions catalyzed by naked nickel catalysts prefer the proximal bond cleavage.[5]

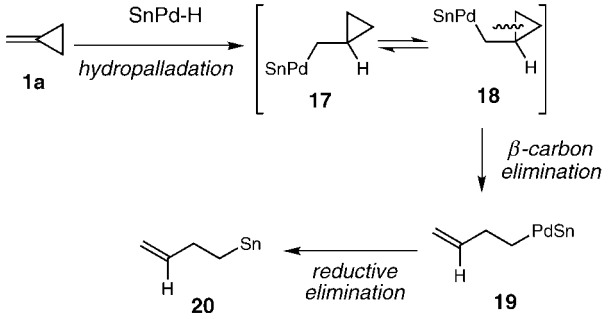
The palladium-catalyzed Heck-type reaction of methylenecyclopropanes predominantly proceeds through proximal bond cleavage. At the beginning of this reaction, the carbopalladation of the olefinic moiety of methylenecyclopropane **1a** by the R-Pd-X species takes place to form the cyclopropylcarbinylpalladium complex **13** (Scheme 2). The β-carbon-Pd elimination leads to the homoallylpalladium species **15** and subsequent β-hydrogen elimination gives the 2-alkylated diene **16.** On the way to **16** from **15**, a π-allylpalladium intermediate intervenes[6] which may undergo the Tsuji–Trost-type



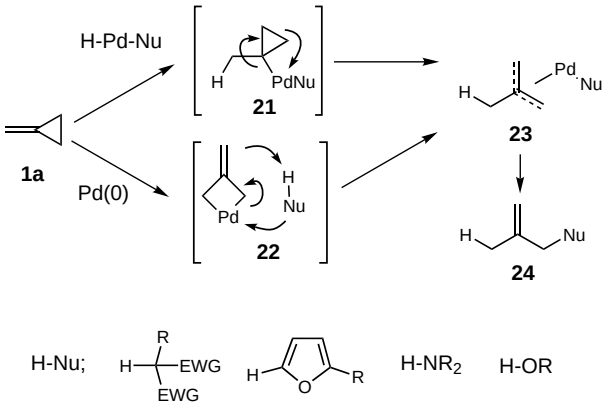
Scheme 2. Palladium-catalyzed Heck-type reaction with methylenecyclopropanes.

reaction if an appropriate nucleophile is present in the reaction system.

In the reaction of methylenecyclopropanes with metal hydrides and pronucleophiles, the selectivity of bond cleavage is mainly dependent on the substrates. The addition of metal hydride species (H-M), such as stannyl hydride (H-SnR_3), and hydrosilanes (H-SiR_3), predominantly proceeds through proximal bond cleavage. For example, in the hydrostannation reaction of **1a**, the insertion of Pd(0) into H-Sn bond takes place first, and then the resulting H-Pd-Sn species undergoes the anti-Markovnikov hydropalladation to give **17** (Scheme 3). The β-carbon-Pd elimination followed by reductive elimination of Pd(0) from **19** leads to the homoallylstannane **20**. The addition of a boron-boron bond (B-B) also proceeds through proximal bond cleavage. On the contrary, the palladium-catalyzed addition of pronucleophiles (H-Nu), such as carbo-pronucleophiles H-$C(EWG)_nR_{3-n}$, amines H-NR_2, and alcohols H-OR, mainly proceeds through distal bond cleavage. There are two mechanistic possibilities in this type of reaction. The first possibility is that the H-Pd-Nu species formed from Pd(0) and H-Nu adds to a carbon-carbon double bond of methylenecyclopropane **1a** in the manner of Markovnikov hydropalladation, giving the cyclopropylpalladium species **21**, which undergoes the β-carbon-Pd elimination to give the π-allylpalladium **23** (Scheme 4). The usual Tsuji–Trost-type reaction of **23** affords the product **24**. The second possibility is that Pd(0) insertion into the distal bond of **1a** takes place to give the palladacyclobutane intermediate, which reacts with H-Nu as shown in **22** giving the same product **24** as obtained in the reaction through the hydropalladation mechanism.



Scheme 3. The mechanism of the palladium-catalyzed hydrostannation of methylenecyclopropanes.



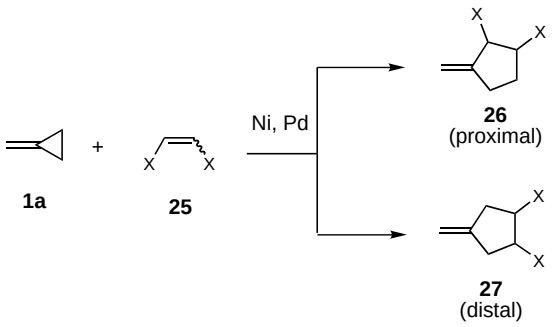
Scheme 4. Palladium-catalyzed addition of pronucleophiles to methylenecyclopropanes with distal bond cleavage.

2 [3 + 2] Cycloadditions

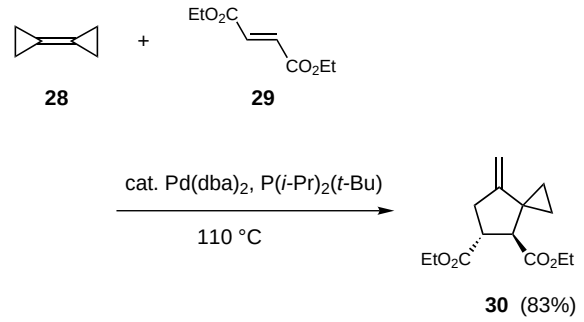
Transition metal-catalyzed formal [3 + 2] cycloaddition of methylenecyclopropanes with carbon-carbon multiple bonds **25** has been thoroughly investigated, and a wide variety of methylenecyclopropanes is utilized as a "three-carbon component". Nickel- and palladium-catalyzed intermolecular [3 + 2] cycloadditions with olefins were profoundly investigated by Noyori et al.,[3] Binger et al.,[2,4] and Trost et al.,[7] respectively (Scheme 5). Furthermore, this reaction was extended to intramolecular versions by Motherwell et al.,[8] Nakamura et al.,[9] and Lautens et al.,[10] respectively. Until today, this methodology has grown to be a powerful tool to construct five-membered carbocycles **26** and **27**. The chemistry of catalytic [3 + 2] cycloadditions of alkenes and alkynes has been extensively summarized in several excellent reviews,[5,11] and therefore will not be discussed further here.

Recently, de Meijere's group reported [3 + 2] cycloaddition of bicyclopropylidene **28** with olefins.[12] In the presence of catalytic amounts of $Pd(dba)_2$ and $(i\text{-}Pr)_2P(t\text{-}Bu)$, the reaction of bicyclopropylidene **28** and diethyl fumarate **29** produced the corresponding 4-methylenespiro[2.4]heptane derivative **30** in 83% yield (Scheme 6).

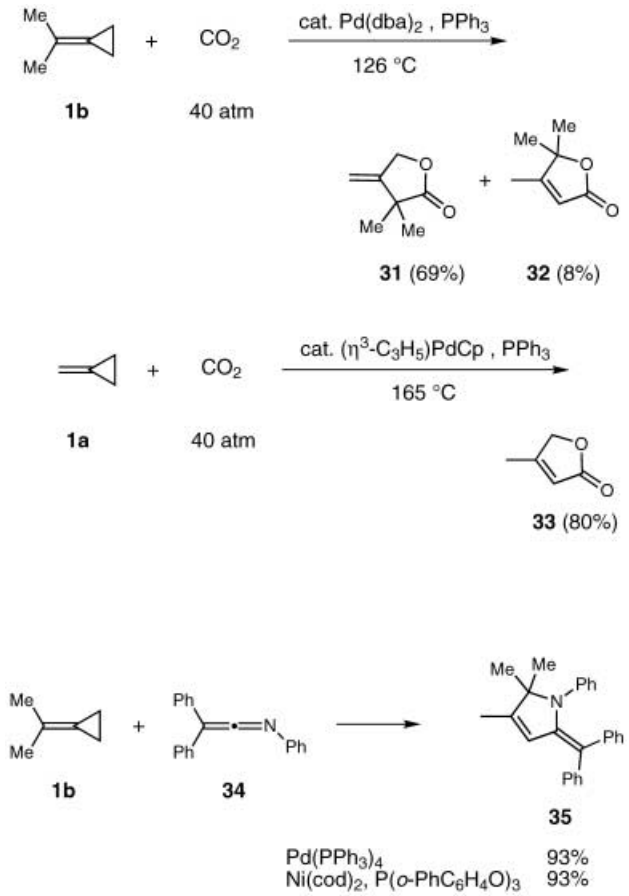
On the other hand, catalytic hetero [3 + 2] cycloadditions of methylenecyclopropanes with carbon-heteroatom double bonds were limited to the reaction with heterocumulenes, such as carbon dioxide and ketenimines (Scheme 7).[13-15] Inoue et al. previously reported that in the presence of catalytic amounts of $Pd(dba)_2$ and PPh_3, the reaction of isopropylidenecyclopropane **1b**



Scheme 5. Transition metal-catalyzed formal [3 + 2] cycloaddition of methylenecyclopropanes with olefins.



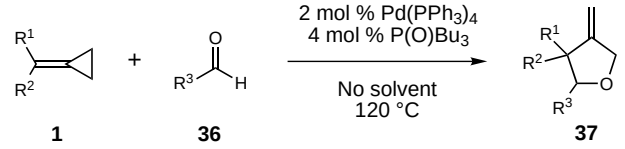
Scheme 6. Palladium-catalyzed [3 + 2] cycloaddition of bicyclopropylidene **28.**



Scheme 7. Palladium-catalyzed hetero [3 + 2] cycloaddition of methylenecyclopropanes with heterocumulenes.

with high pressure CO_2 produced the lactone **31** in 69% yield along with a small amount of **32**.[13] Binger's group also communicated the palladium-catalyzed [3 + 2] cycloaddition of methylenecyclopropane **1a** with carbon dioxide producing the lactone **33** in 80% yield.[14] On the other hand, Binger et al. reported that palladium and nickel catalysts promoted the hetero [3 + 2] cycloaddition of **1b** with ketenimine **34** and the corresponding pyrrolidine derivatives **35** were obtained in good yields.[15]

Recently, we found that the palladium-catalyzed hetero [3 + 2] cycloaddition of alkylidenecyclopropanes



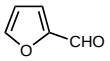
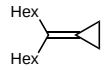
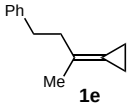
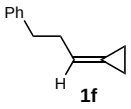
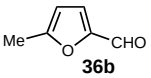
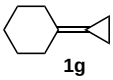
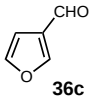
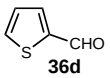
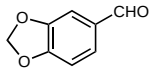
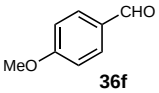
Scheme 8. Palladium-catalyzed [3 + 2] cycloaddition of alkylidenecyclopropanes with aldehydes.

1 with aldehydes **36** produces the multi-substituted tetrahydrofuran derivatives **37** in good to high yields (Scheme 8).[16] The results are summarized in Table 1. In the presence of catalytic amounts of $Pd(PPh_3)_4$ (2 mol %) and tributylphosphine oxide (4 mol %), the reaction of 1-butylpentylidenecyclopropane **1c** (0.5 mmol) with furfural **36a** (1.5 mmol) in the absence of solvent at 120 °C for 5 h gave the corresponding cycloadduct **37a** in 75% yield (entry 1). Without the palladium catalyst, the reaction of **1c** with **36a** did not proceed at all. The use of $Pd(dba)_2/PPh_3$ as a catalyst was less effective for producing **37a**, and $Pd_2(dba)_3 \cdot CHCl_3$, $Pd(OAc)_2$, allylpalladium chloride dimer and $Pt(PPh_3)_4$ were totally ineffective as catalysts. The reaction of **1c** with **36a** using traditional phosphine ligands, such as PPh_3, PBu_3, and $P(OPh)_3$, was slower than the reaction with $P(O)Bu_3$ and gave **37a** in lower yield. The use of THF solvent in the reaction of **1c** and **36a** gave **37a** in lower yield (36%). The reactions of 1-hexylheptylidenecyclopropane (**1d**), 1-methyl-3-phenyl-propylidenecyclopropane (**1e**), and 3-phenylpropylidenecyclopropane (**1f**) with **36a** afforded **37b**, **37c**, and **37d**, respectively (entries 2–4). The reaction of **1c** with 5-methylfurfural (**36b**) proceeded smoothly, and the corresponding cycloadduct **37e** was produced in 65% yield (entry 5). The spiro compound **37f** was obtained in 77% yield by the reaction of 2 equivalents of cyclohexylidenecyclopropane (**1g**) and **36b** (entry 6). Other examples are shown in Table 1.

A plausible mechanism is illustrated in Scheme 9. Oxidative addition of palladium(0) to a distal bond of the alkylidenecyclopropane **1** leads to the palladacyclobutane derivative **38**.[17] The addition of this σ-allylpalladium intermediate **38** to the aldehyde **36**, as shown in **39**, leads to the π-allylpalladium complex **40**. Reductive elimination of palladium(0) gives the [3 + 2] cycloadduct **37**.

Quite recently, we demonstrated that the palladium-catalyzed hetero [3 + 2] cycloaddition of **1c** with imines **41** gave the 3-methylenepyrrolidine derivatives **42** in good to high yields (Scheme 10).[18] The results are summarized in Table 2. In the presence of catalytic amounts of $Pd(PPh_3)_4$ and triphenylphosphine oxide, the reaction of **1c** with 2-furyl-*N*-tosylimine **41a**, 4-tolyl-*N*-tosylimine **41b**, and 4-anisyl-*N*-tosylimine **41c** proceeded smoothly and the corresponding cycloadducts **42a**, **42b**, and **42c** were obtained in 89, 91, and 94% yield, respectively (entries 1–3).

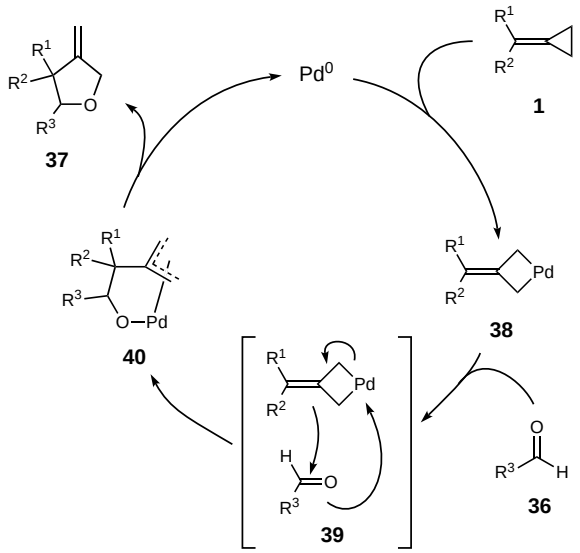
Table 1. Palladium-catalyzed [3 + 2] cycloaddition of alkylidenecyclopropanes **1** with aldehydes **36**.[a]

Entry	**1**	**36**	Time [h]	Yield of **37** [%][b]
1	 **1c**	 **36a**	5	**37a**, 75
2	 **1d**	**36a**	11	**37b**, 71
3	 **1e**	**36a**	16	**37c**, 86 (53:47)[c]
4	 **1f**	**36a**	20	**37d**, 42 (54:46)[c]
5	**1c**	 **36b**	6	**37e**, 65
6[d]	 **1g**	**36b**	20	**37f**, 77
7	**1c**	 **36c**	12	**37g**, 51
8	**1c**	 **36d**	19	**37h**, 64
9	**1c**	 **36e**	19	**37i**, 43
10[d]	**1c**	 **36f**	32	**37j**, 38

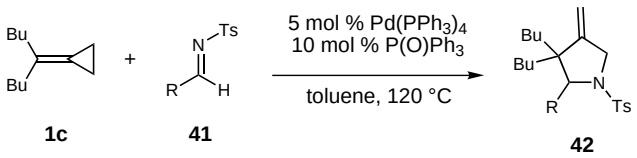
[a] The reaction of **1** (0.5 mmol) with **36** (1.5 mmol) wascarried out in the presence of 2 mol % of $Pd(PPh_3)_4$ and 4 mol % of tributylphosphine oxide without solvent at 120 °C.
[b] Isolated yield based on **1**.
[c] The diastereomeric ratio of **37**.
[d] Compound **1** (1 mmol) was treated with **36** (0.5 mmol), and the yield is based on **36**.

3 Heck-Type Reactions

Goré et al. for the first time reported palladium-catalyzed reactions of alkylidenecyclopropanes with alkenyl (or aryl) halides and with carbon nucleophiles.[19] In the presence of catalytic amounts of $Pd(dba)_2$ and dppe the reaction of methylenecyclopropane **1a** with 2-bromopropene **43** and the carbanion of dimethyl malonate **44** gave a 70:30 mixture of **45** and **46** in 55% yield (Scheme 11). This reaction proceeds through the carbopalladation by the R-Pd-Br species, formed by the oxidative insertion of Pd(0) into the C-Br bond of **43**, to an olefinic moiety of **1a**, giving the cyclopropylcarbinylpalladium intermediate **47**. The se-

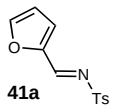
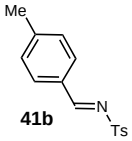
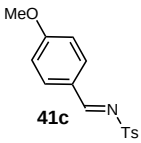


Scheme 9.

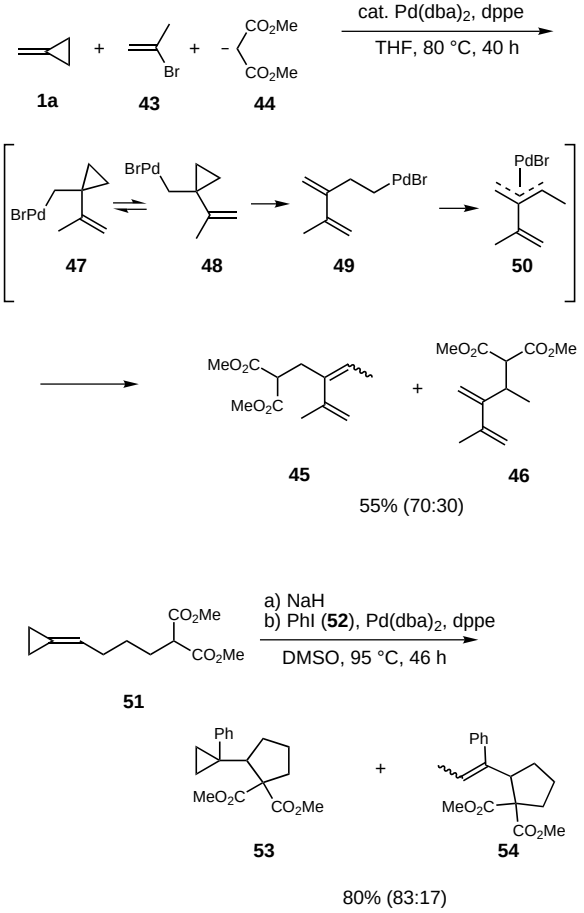


Scheme 10. Palladium-catalyzed [3 + 2] cycloaddition of alkylidenecyclopropanes with imines.

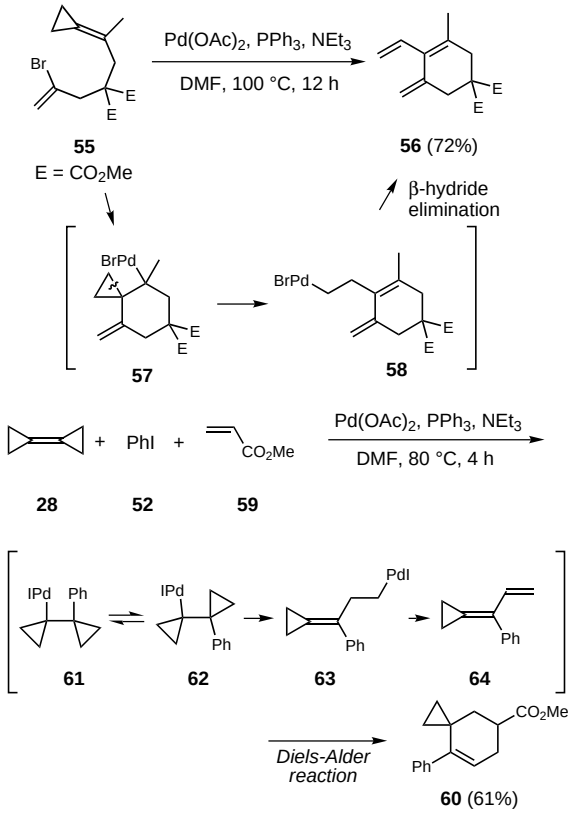
Table 2. Palladium-catalyzed [3 + 2] cycloaddition of an alkylidenecyclopropane **1** with imines **41**.[a]

Entry	**41**	Time [h]	Yield of **42** [%][b]
1	 **41a**	16	**42a**, 89
2	 **41b**	12	**42b**, 91
3	 **41c**	9	**42c**, 94

[a] The reaction of **1** (1.0 mmol) and **2** (0.5 mmol) was carried out in the presence of 5 mol % of $Pd(PPh_3)_4$ and 10 mol % of triphenylphosphine oxide in toluene at 120 °C.
[b] Isolated yield based on **41**.



Scheme 11. Palladium-catalyzed reaction of methylenecyclopropane with alkenyl or phenyl halides and anionic nucleophiles.



Scheme 12. Intra- and intermolecular palladium-catalyzed Heck-type reactions.

lective ring opening of a proximal cyclopropyl bond produces **49**, which is converted to the π-allylpalladium intermediate **50**. The nucleophilic addition of the carbon nucleophile **44** to **50** affords the products **45** and **46**. They extended this reaction to an intramolecular version. The reaction of **51** with iodobenzene **52** in the presence of palladium catalysts produced the bicyclic compound **53** as a major product along with a small amount of **54**.[20] Although the formation of **54** is understandable based on the reaction course shown above, **53** is produced through a different process; most probably PhPd(II)I coordinates to an olefinic bond of **51**, and the carbanion $^{-}CH(CO_2Me)_2$ attacks the resulting electron-deficient double bond to afford the cyclopentyl derivative having a PhPd(II)cyclopropyl moiety, and subsequent elimination of Pd(0) produces **53**.

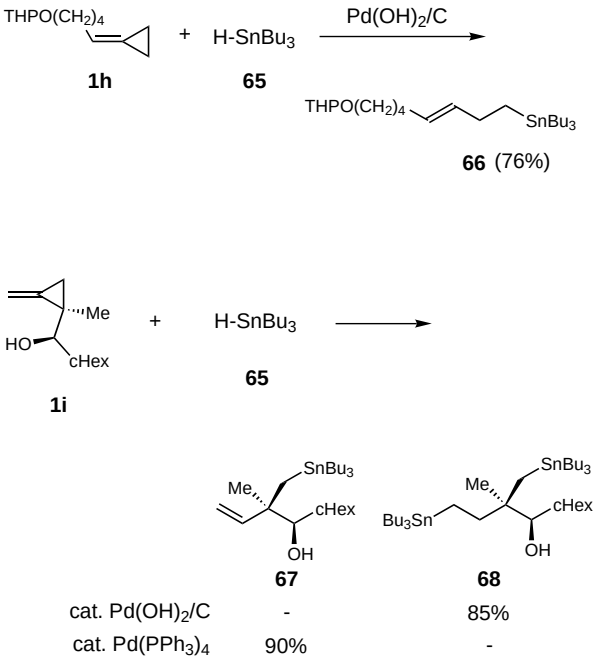
Meanwhile, de Meijere et al. recently reported the intramolecular Heck-type reaction of methylenecyclopropanes giving cross-conjugated trienes.[21,22] Under the typical Heck conditions ($Pd(OAc)_2$, PPh_3, NEt_3), **55** was converted to the [3]dendralene **56** in 72% yield (Scheme 12). In a similar manner as mentioned above, the reaction proceeds through **57** and **58**, and the β-hydride elimination gives the final product **56**. Under the same conditions, the reaction of bicyclopropylidene **28** with iodobenzene **52** and methyl acrylate **59** gave the spiro[2.5]octene **60** in 61% yield. The reaction proceeds in a similar manner (**61** to **64**), and the diene product **64** reacts with **59** to give the Diels–Alder product **60**.

4 Addition of Metal Hydrides (H-M) and Pronucleophiles (H-Nu)

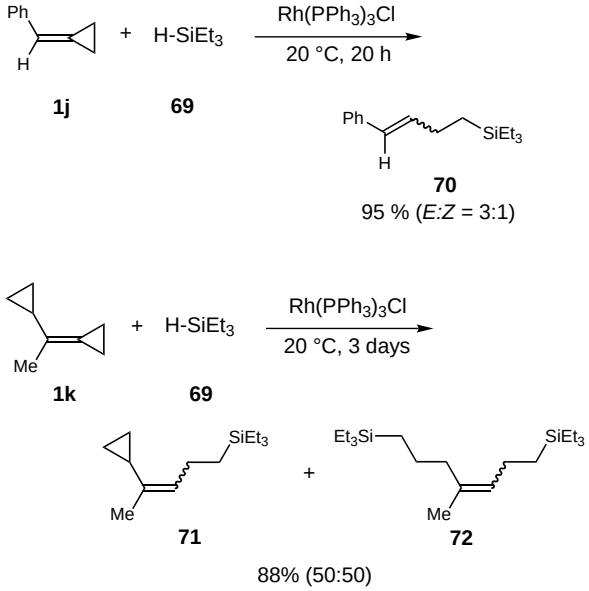
Catalytic addition of metal hydrides and pronucleophiles to carbon-carbon multiple bonds is of considerable interest because this methodology can introduce a functional group to unsaturated molecules in an atom-economic and ecological manner. 1,3-Dienes, allenes, 1,3-enynes, and alkynes have been used frequently as a reaction partner. In the last decade, methylenecyclopropanes came into the spotlight and several groups have reported catalytic addition reactions of H-M or H-Nu to methylenecyclopropanes.

4.1 Hydrostannation and Hydrosilylation

Recently, Lautens et al. reported the hydrostannation of methylenecyclopropanes catalyzed by palladium



Scheme 13. Palladium-catalyzed hydrostannation of methylenecyclopropanes.



Scheme 14. Rhodium-catalyzed hydrosilylation of methylenecyclopropanes.

(Scheme 13).[23] As explained in Scheme 3, the hydrostannation of the methylenecyclopropanes **1h** and **1i** exclusively proceeded through proximal bond cleavage. In the presence of palladium catalysts, the reaction of alkylidenecyclopropane **1h** with H-$SnBu_3$ **65** gave the homoallylstannane **66** in good yield. Meanwhile, in the reaction of methylenecyclopropanecarbinol **1i**, the choice of the palladium catalyst is very important. Under heterogeneous conditions with $Pd(OH)_2/C$ as a catalyst, the reaction of **1i** with H-$SnBu_3$ **65** gave the diorganostannane **68**, while homoallylstannane **67** was obtained in the presence of $Pd(PPh_3)_4$ as a catalyst.

Beletskaya et al. investigated the rhodium-catalyzed hydrosilylation of methylenecyclopropanes.[24] The reaction of benzylidenecyclopropane **1j** with triethylsilane **69** in the presence of 0.1 mol % of $Rh(PPh_3)_3Cl$ at 20 °C produced the corresponding homoallylsilane **70** in 95% yield (Scheme 14). Here again, a proximal bond cleavage takes place (see Scheme 3). The reaction of **1k** containing two reactive fragments, methylenecyclopropane and vinylcyclopropane moieties, led to a 1:1 mixture of mono- and disilylated olefins **71** and **72** in 88% yield.[25] The mono-silylation adduct **71** corresponds to the product formed via a proximal bond cleavage, and the disilylated one **72** is presumably formed by the ring opening of **71**.

4.2 Hydrocarbonation

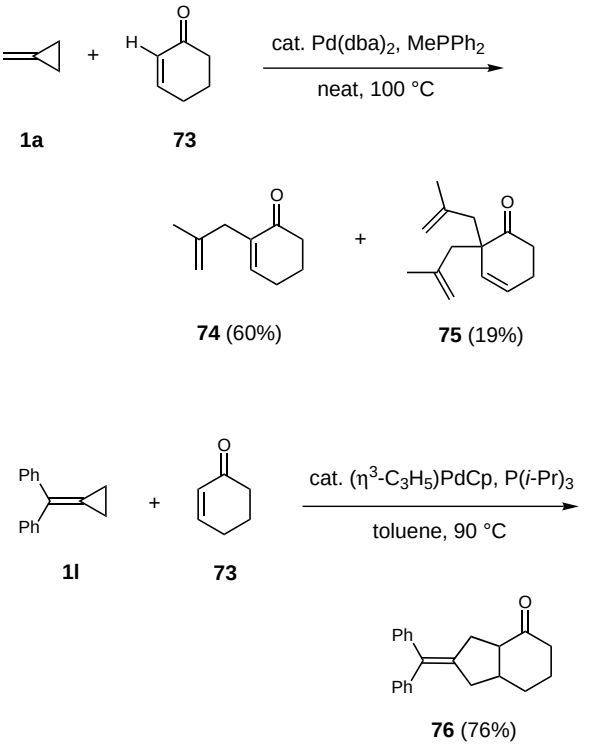
Recently, the hydrocarbonation of an unactivated C = C double bond with certain carbon pronucleophiles has been reported,[26-33] which presumably proceeds through the transition metal-catalyzed activation of a C-H bond of the carbon pronucleophiles such as active methynes and methylenes,[27-30] terminal alkynes,[31] aldehydes,[32] and aromatic compounds bearing an appropriate chelating element.[33] 1,3-Dienes,[27] 1,3-enynes,[28] allenes,[29] and alkynes[30] can be used as acceptors for these pronucleophiles. More recently, significant attention has been paid to methylenecyclopropanes as an alternative acceptor for pronucleophiles.

4.2.1 Addition of 2-Cyclohexen-1-ones

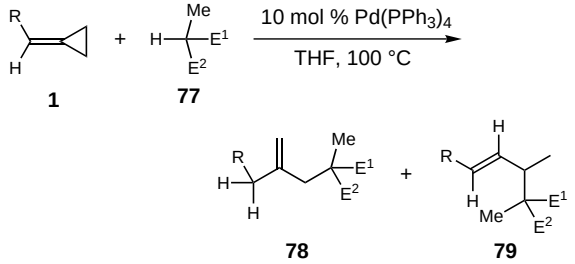
In 1979, the direct addition of a carbon-hydrogen bond at the α position of 2-cyclohexen-1-one to methylenecyclopropane was reported by Balavoine et al.[34] In the presence of catalytic amounts of $Pd(dba)_2$ and $MePPh_2$, the reaction of methylenecyclopropane **1a** and 2-cyclohexen-1-one **73** gave the monoalkylated product **74** in 60% yield along with the dialkylated product **75** in 19% yield (Scheme 15). In contrast, Binger's group reported that a catalytic amount of (η^3-allyl)(η^5-cyclopentadienyl)palladium and P(*i*-Pr)$_3$ promoted a typical [3 + 2] cycloaddition of **73** with diphenylmethylenecyclopropane **1l** smoothly giving the corresponding cycloadduct **76** in 76% yield.[35]

4.2.2 Addition of Active Methynes and Methylenes

We reported that the palladium-catalyzed reaction of the active methynes **77** with methylenecyclopropanes **1** affords either the hydrocarbonation products **78** or **79** in good to high yields, or in certain cases gives a mixture of



Scheme 15. Palladium-catalyzed addition of 2-cyclohexenone **73** to methylenecyclopropane **1a**.

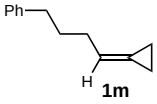
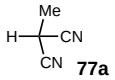
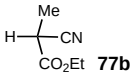
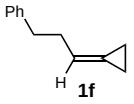
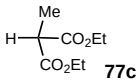
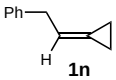


Scheme 16. Palladium-catalyzed hydrocarbonation of methylenecyclopropanes **1** with active methynes **77**.

78 and **79** (Scheme 16).[36] The product distribution depends upon the structure of substrates **1** and **77**.

The results are summarized in Table 3. The addition of methylmalononitrile **77a** to 4-phenyl-1-butenylidenecyclopropane **1m** proceeded smoothly in the presence of catalytic amounts of $Pd(PPh_3)_4$ in THF at 100 °C to give **78a** in 82% yield (entry 1). Other palladium catalysts, such as $PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3 \cdot CHCl_3/PPh_3$, gave the addition product in lower yields. The reaction of ethyl 2-cyanopropionate **77b** with **1m** gave **78b** in 95% yield (entry 2). Similarly, the ring opening of **1f** with **77b** or **77c** afforded **78c** or **78d**, respectively, in good yields (entries 3 and 4). The reaction of **77a** with **1f** gave **78e** in 75% yield along with small amounts (10%) of **79a** (entry 5). With 2-phenylethylidenecyclopropane **1n**, the reaction of **77a** afforded **78f** in 57% yield along with **79b** in 31% yield (entry 6). The reaction of benzylidenecyclopropane **1j** with **77a** or **77b** produced only **79c** or **79d** in 88 or 83% yield, respectively (entries 7 and 8). On the other hand, the reaction of **1j** with diethyl methylmalonate **77c** gave **78g** in 55% yield (entry 9). Accordingly, the mode of ring opening of methylenecyclopropanes depends upon both the structures of the pronucleophile and the substituent at the exomethylene carbon.

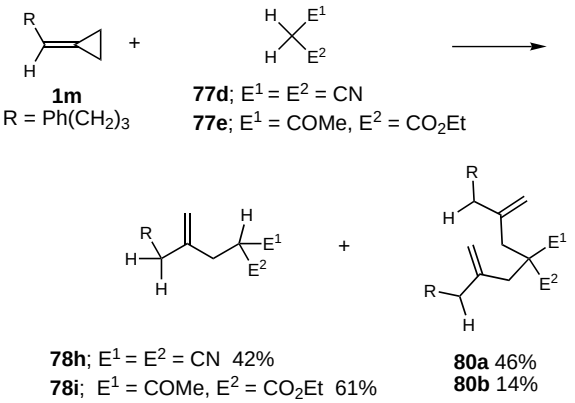
Table 3. Palladium-catalyzed addition of **77** to **1**.[a]

Entry	**1**	**77**	Yield of **78** [%]	Yield of **79** [%]
1	 **1m**	 **77a**	**78a**, 82	–
2	**1m**	 **77b**	**78b**, 95	–
3	 **1f**	**77b**	**78c**, 67	–
4	**1f**	 **77c**	**78d**, 70	–
5	**1f**	**77a**	**78e**, 75	**79a**, 10
6	 **1n**	**77a**	**78f**, 57	**79b**, 31
7	 **1j**	**77a**	–	**79c**, 88
8	**1j**	**77b**	–	**79d**, 83
9	**1j**	**77c**	**78g**, 55	–

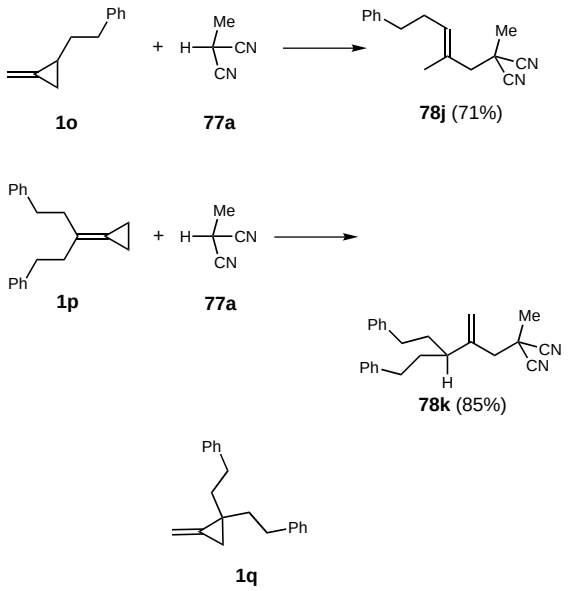
[a] The reaction of **77** (0.5 mmol) and **1** (1.0 mmol) was carried out in the presence of $Pd(PPh_3)_4$ (10 mol %) in THF at 100 °C for 2–3 days. All yields are of pure product isolated by column chromatography. The configuration of **79** was confirmed by the coupling constant between the olefinic protons (15.2–15.8 Hz).

In the reaction of active methylenes, both monoalkylation and dialkylation products were obtained (Scheme 17). The addition of malononitrile **77d** to **1m** gave ca. 1:1 mixture of the monoalkylation **78h** (42%) and the dialkylation product **80a** (46%), while the ketoester **77e** gave the corresponding monoalkylation product **78i** predominantly.

Our interest was then directed to the ring opening of methylenecyclopropanes **1o–q** which are mono-substituted at the cyclopropane ring or *gem*-disubstituted both at the exocyclic vinylic carbon and the cyclopropane ring (Scheme 18). The cyclopropane ring of **1o** opened at the distal position in the reaction with **77a** to provide **78j** in 71% yield along with small amounts of other isomers. In this reaction, **78e** was not obtained at all, while it was produced in the reaction of **1f** having a 2-phenylethyl



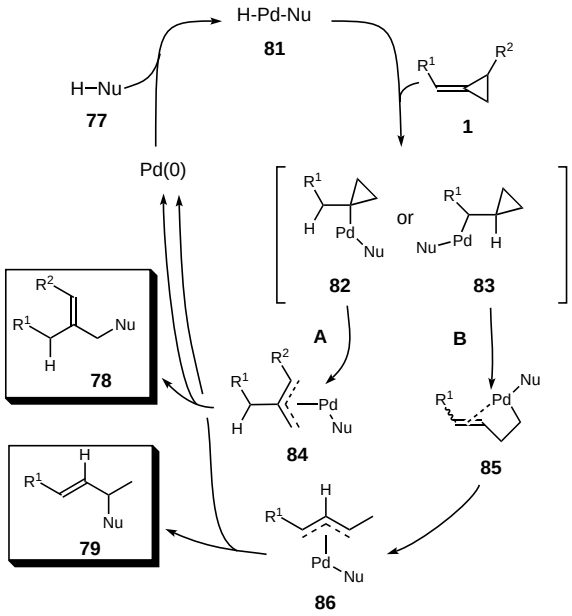
Scheme 17.



Scheme 18.

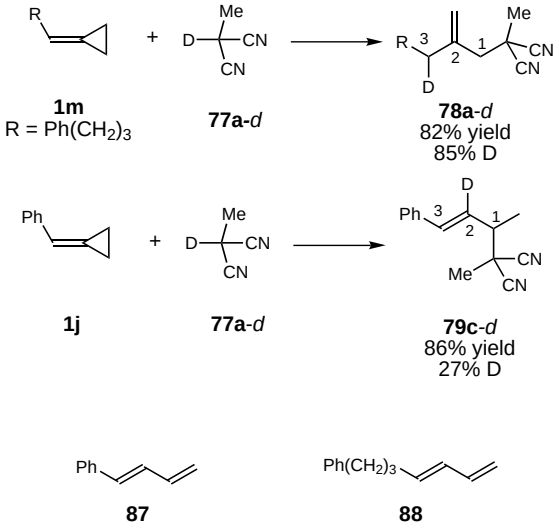
substituent at the exomethylene carbon. The reaction of **77a** with **1p** gave **78k** in 85% yield, but the reaction with **1q** did not afford the desired hydrocarbonation product at all.

A plausible mechanism for the ring opening of **1** with pronucleophiles **77** is shown in Scheme 19. Oxidative addition of the C-H bond of the pronucleophiles **77** to the Pd(0) species would generate the organopalladium hydride complex **81**. The hydropalladation of methylenecyclopropanes **1** with **81** would afford the alkylpalladium complexes **82** and/or **83**. The complex **82** would undergo rearrangement to the π-allylpalladium species **84** (route **A**) (see Scheme 4). The reductive elimination of Pd(0) from **84** would produce **78**. The palladium complex **83** would isomerize to the π-allylpalladium complex **86** *via* **85** (route **B**) (see Scheme 3). The reductive elimination would give **79** and Pd(0). Presumably, the reaction of **1j** with **77a** proceeded along route **B**, whereas the reaction of **1m** with **77a** went along route **A** (Table 3, entries 1 and 7).

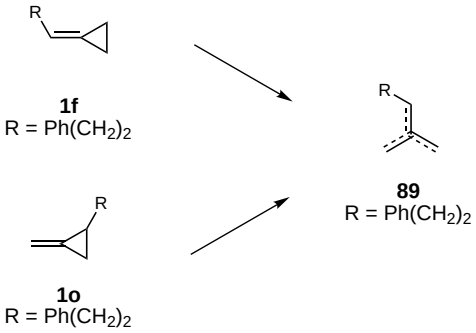


Scheme 19. A plausible mechanism for the reaction of **1** with **77** catalyzed by palladium.

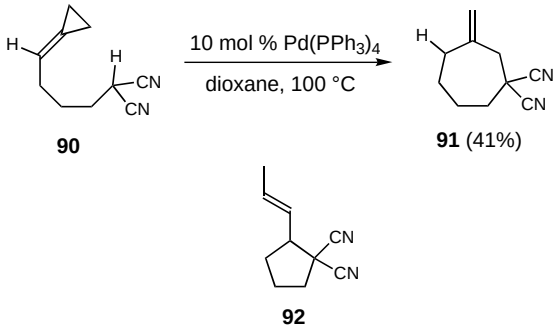
The reaction with deuterated methylmalononitrile **77a**-*d* substantiated the hydrocarbonation mechanism. The reaction of **77a**-*d* with **1m** under the same conditions as above gave **78a**-*d* in 82% yield in which the D-content at the C-3 position was 85% (Scheme 20). On the other hand, the reaction of **77a**-*d* with **1j** afforded **79c**-*d* in 86% yield in which the D-content at the C-2 position was 27%, and the other positions were not deuterated at all. The former observation is in good agreement with the proposed route **A**. The latter result supports the proposed route **B**, and the very low deuterium content at the C-2 position is presumably due to the intervention of



Scheme 20. The reaction of deuterated methylmalononitrile **77a**-*d*.



Scheme 21.

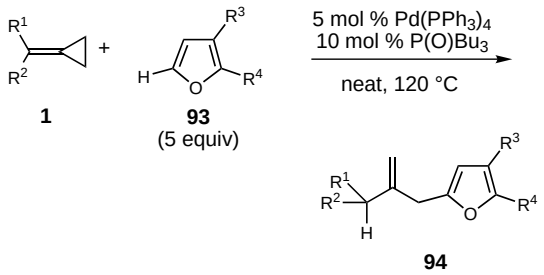


Scheme 22. The intramolecular hydrocarbonation of ω-cyclopropylidenealkylmalononitrile **90**.

the β-H-Pd elimination-addition process. We monitored the reaction of **1j** by using ^{1}H NMR spectroscopy and found that 1-phenyl-1,3-butadiene **87** was produced as an intermediate, its production reached a maximum after 25 h, and decreased along with the reaction progress. Formation of the 1,3-diene derivative **88** was not observed in the reaction of **1m**! The result clearly indicates that **87** is produced via the β-H-Pd elimination of **85** and the elimination-addition process occurs on the way from **85** to **86** in which loss of deuterium takes place.

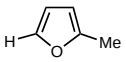
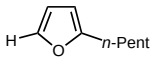
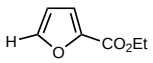
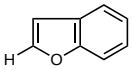
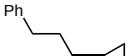
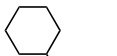
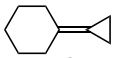
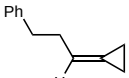
If the present hydrocarbonation reaction proceeds through a trimethylenemethane (TMM)-palladium complex **89**, the same product (or the same product ratio) should be obtained from **1f** and **1o** (Scheme 21).[37] However, the actual reactions afforded totally different results; only **78e** was obtained from the reaction of **1f**, whereas **78j** was produced predominantly from **1o**. Accordingly, it is not likely that the TMM-palladium complex **89** is an intermediate in the addition reactions of **77a** to **1f** and **1o**.

We carried out the intramolecular hydrocarbonation reaction of ω-cyclopropylidene-alkylmalononitrile **90**.[38] In the presence of a catalytic amount (10 mol %) of $Pd(PPh_3)_4$, the reaction of **90** produced the corresponding intramolecular hydrocarbonation product, the 7-membered carbocycle **91**, in 41% yield (Scheme 22). The chemical yield of **91** was not really good, but other products such as the 5-membered carbocycle **92** were not produced under the reaction conditions.



Scheme 23. Hydrofurylation of alkylidenecyclopropanes **1** catalyzed by palladium.

Table 4. Hydrofurylation of **1** catalyzed by palladium.[a]

Entry	**1**	**93**	Time [h]	Yield of **94** [%][b]
1	 **1c**	 **93a**	28	**94a**, 70
2	**1c**	 **93b**	34	**94b**, 70
3	**1c**	 **93c**	19	**94c**, 77
4	**1c**	 **93d**	21	**94d**, 63
5	 **1e**	**93a**	15	**94e**, 68
6	 **1r**	**93a**	39	**94f**, 74
7	 **1g**	**93a**	21	**94g**, 65
8	 **1f**	**93a**	17	**94h**, 43[c]

[a] The reaction of **1** (0.5 mmol) and **93** (2.5 mmol) was carried out in the presence of 5 mol % of $Pd(PPh_3)_4$ and 10 mol % of tributylphosphine oxide without solvent at 120 °C.

[b] Isolated yield based on **1**.

[c] As a byproduct, $PhCH_2CH=CH(CH_3)C=CH_2$ **95** was formed in 20% yield.

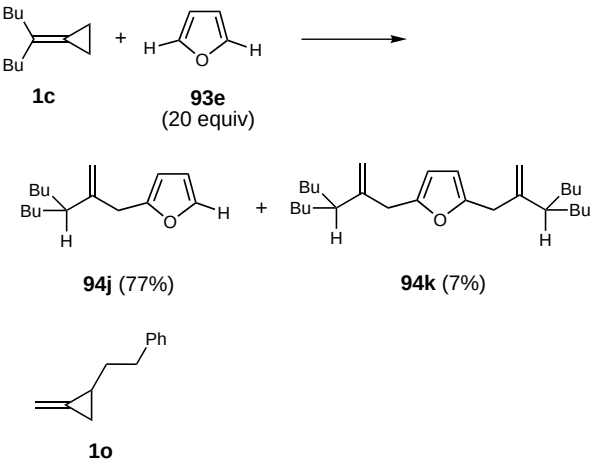
4.2.3 Addition of Furans (Hydrofurylation)

In continuation of our research on the hydrocarbonation reaction of pronucleophiles, we found that the carbon-hydrogen bond at the α-position of furan

derivatives **93** can undergo an addition to the double bond of alkylidenecyclopropanes **1** (i.e., a so-called *hydrofurylation*). Previously, the C-H activation of furans with $Rh_4(CO)_{12}$ as a catalyst had been reported,[39a] but a large excess of furans, significantly high CO pressures, and a very high reaction temperature were required. We have found that the palladium-catalyzed hydrofurylation of alkylidenecyclopropanes **1** affords 2-allylfuran derivatives **94** regioselectively in good to high yields under milder conditions (Scheme 23).[40]

The results are summarized in Table 4. The reaction of **1c** (0.5 mmol) and 2-methylfuran **93a** (2.5 mmol) in the presence of 5 mol % of $Pd(PPh_3)_4$ and 10 mol % of tributylphosphine oxide proceeded smoothly at 120 °C without solvent to give the corresponding 2-allylfuran derivative **94a** in 70% yield (entry 1). Other catalysts such as $Pd_2(dba)_3 \cdot CHCl_3$, $Pd(OAc)_2$, and $Pt(PPh_3)_4$ did not promote the reaction at all. The choice of phosphine ligands is very important. Among numerous phosphine ligands examined, *tributylphosphine oxide* gave the best result; the use of other ligands afforded unsatisfactory yields, and in the absence of tributylphosphine oxide the reaction was very slow. Perhaps, phosphine oxide promotes the generation of unsaturated palladium species, because this ligand is rather more labile than PPh_3. Normally, an excess of five equivalents of the respective furan was used. When three equivalents of **93a** was used, the yield of **94a** decreased to 63% yield. The reaction of **1c** with 2-pentylfuran **93b**, and ethyl 2-furoate **93c** gave **94b**, and **94c**, respectively, in good to high yields (entries 2 and 3). The reaction of benzofuran with **1c** produced **94d** in 63% (entry 4). The reaction of **1e**, 1-cyclohexylethylidenecyclopropane **1r**, and **1g** with **93a** produced **94e**, **94f**, and **94g** in 68, 74, and 65% yield, respectively (entries 5 – 7). The reaction of **1f** and **93a** gave **94h** in 43% yield along with 2-methyl-5-phenyl-1,3-pentadiene **95** (20%, entry 8).

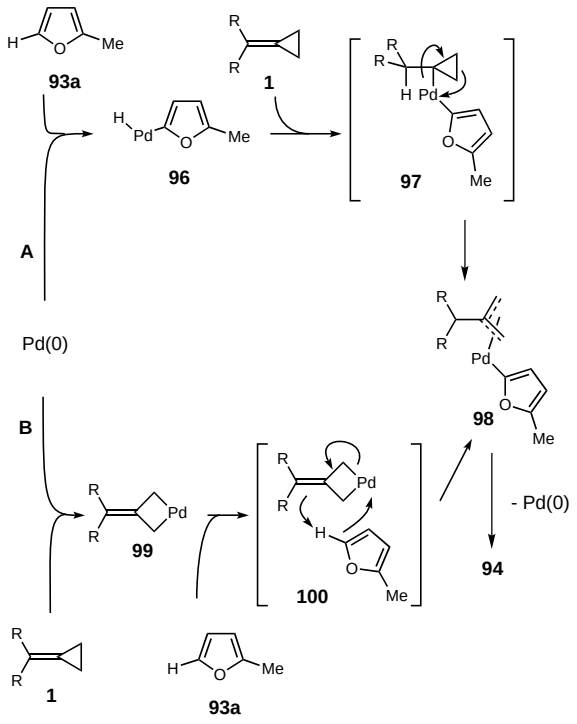
The reaction of **1c** with furan **93e** (20 equiv.) itself afforded the monoallylated furan **94j** in 77% yield along with a small amount (7%) of the diallylated furan **94k** (Scheme 24). The use of five equivalents of **93e** gave 64% of **94j** and 11% of **94k**. The reaction of the methylenecyclopropane **1o**, which had a substituent on the ring, with **93a** did not produce any adducts at all.



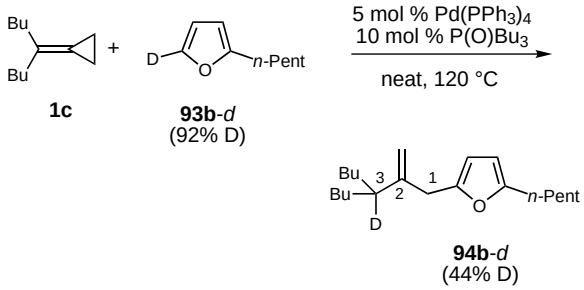
Scheme 24.

Plausible mechanisms for the hydrofurylation reaction are shown in Scheme 25. The oxidative addition of the carbon-hydrogen bond of furan **93a** to palladium(0) leads to the furylpalladium hydride complex **96** (route **A**). Hydropalladation of the double bond in **1** followed by cleavage of the distal bond of the cyclopropane ring would afford the π-allylpalladium intermediate **98**.[41] Reductive elimination of palladium(0) from **98** would give **94**. Because the C-H-acidity of the α-proton of furan is considerably lower than that of other pronucleophiles,[42] an alternative mechanism as shown in route **B** may be operative in the hydrofurylation reaction. Insertion of Pd(0) into the distal bond of **1** produces the palladacyclobutane intermediate **99**.[16,43] Since **99** is a sort of σ-allylpalladium species, a palladaene reaction with **93a** may take place as shown in **100**, giving the π-allylpalladium species **98**.

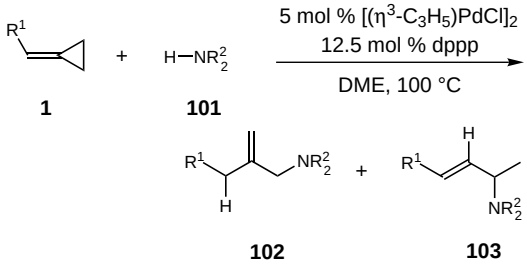
To know the fate of a hydrogen at the α-position of a furan, we carried out the reaction of 2-deuterio-5-pentylfuran **93b**-*d* (D content 92%) with **1c** under the same conditions as above. The mono-deuterated **94b**-*d*, in which the deuterium content at the C-3 position was 44%, was obtained in 66% yield (Scheme 26). No oligo-deuterated products and no mono-deuterated product, in which deuterium was attached to the carbon atoms other than C-3 position, were obtained at all. The formation of the C-3 deuterated product **94b**-*d* can be explained by both mechanisms (**A** and **B** in Scheme 25).



Scheme 25. A plausible mechanism for hydrofurylation of **1**.



Scheme 26.



Scheme 27. Palladium-catalyzed hydroamination of methylenecyclopropanes **1**.

Irrespective of the precise mechanism, we are now in a position to carry out the hydrofurylation reaction in good yields under reaction conditions which can be manipulated without using high temperatures and elevated pressures. The palladium-catalyzed hydrofurylation was also tried on diphenylacetylene instead of alkylidenecyclopropanes. However, no adducts were obtained, and the starting substrates were recovered, suggesting the hydropalladation mechanism (route **A**) seems to be not operative, but the hydrofurylation reaction proceeds most probably via route **B** (see Scheme 25). Furthermore, substitution on the methylenecyclopropane skeleton clearly influenced the yield of the hydrofurylation product. Disubstitution on the exomethylene of methylenecyclopropane gave higher yields than monosubstitution, and the substituent on the cyclopropane ring totally interrupted the hydrofurylation reaction. The substructure of oligo-substituted furans is often found in important natural products, such as furanocembranes,[44] furan fatty acids,[45] and calicogorgins.[46] The present methodology may be applicable to the synthesis of those furan derivatives.

4.3 Hydroamination

The formation of carbon-nitrogen bonds is one of the most important processes in organic synthesis. Especially, the addition of the nitrogen-hydrogen bond of amines to carbon-carbon multiple bonds, that is hydroamination, is an ideal and challenging method for this purpose.[47] The *intermolecular* hydroamination reactions catalyzed by titanium,[48] zirconium,[49] iridium,[50] rhodium,[51] lanthanide,[52] or actinide complexes[53] were reported by several groups. The catalytic cycle of these reactions involves the insertion process of a carbon-carbon double bond into the N-***M*** bond (Figure 2, Type I). On the other hand, the palladium catalyzed *intermolecular* hydroamination of 1,3-dienes,[54] allenes,[55] enynes,[56] propargylic compounds[57] and styrenes[58] proceeded through the insertion of the double bond to the H-***M*** bond (Type II).

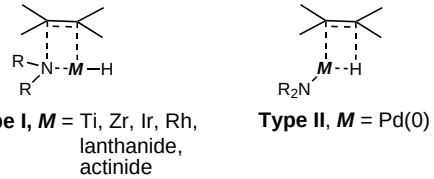


Figure 2. Transition metal-catalyzed hydroamination.

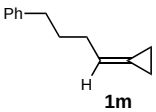
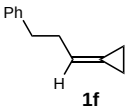
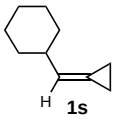
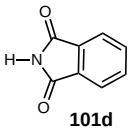
We recently reported that the palladium-catalyzed hydroamination of methylenecyclopropanes **1** mainly proceeds through a π-allylpalladium intermediate formed by distal bond cleavage (Scheme 27).[59]

The results are summarized in Table 5. The reaction of **1m** with dibenzylamine **101a** in the presence of a catalytic amount of allylpalladium chloride dimer (5 mol %) and 1,3-bis(diphenylphosphino)propane (dppp, 12.5 mol %) gave the corresponding hydroamination product **102a** in 91% yield (entry 1). The use of $Pd_2(dba)_3 \cdot CHCl_3$, $Pd(PPh_3)_4$, or $PdCl_2(PPh_3)_2$ as a catalyst gave **102a** in lower yields, and $Pd(OAc)_2$ did not promote the reaction at all. The reaction with pyrrolidine **101b** afforded the hydroamination product **102b** in good yield (entry 2). The carbamate **101c** reacted with **1m** very smoothly (entry 3). The reaction of **1f** with **101a** gave **102d** in 82% yield (entry 4), and the reaction of cyclohexylmethylenecyclopropane **1s** with **101a** afforded **102e** in 72% yield (entry 5). In the above reactions, not even a trace of product **103** could be detected. On the other hand, the reactions of **1j** lead exclusively to a different type of the hydroamination products **103**; **103a** was obtained from **101a** in 19% yield (entry 6) and **103b** in 84% yield from **101d** (entry 7).

The use of primary amines as nitrogen pronucleophiles also gave the corresponding alkylated products. In the reaction of benzylamine **101e** with **1m**, the dialkylated product **104a** was produced as a major product along with a small amount of the monoalkylated **102f.** However, the reaction of aniline **101f** led to only the monoalkylated product **102g** (Scheme 28). The reaction of the tetrasubstituted alkene **1e** with **101a** proceeded smoothly to give **102h** in 79% yield. The methylenecyclopropane **1o** having a substituent on the ring reacted with **101a** to give **102i**.

A proposed mechanism for the hydroamination of **1** with **101** is shown in Scheme 29. Oxidative addition of the nitrogen-hydrogen bond of amines onto the zerovalent palladium produces the hydridopalladium species **105**,[60] which would react with methylenecyclopro-

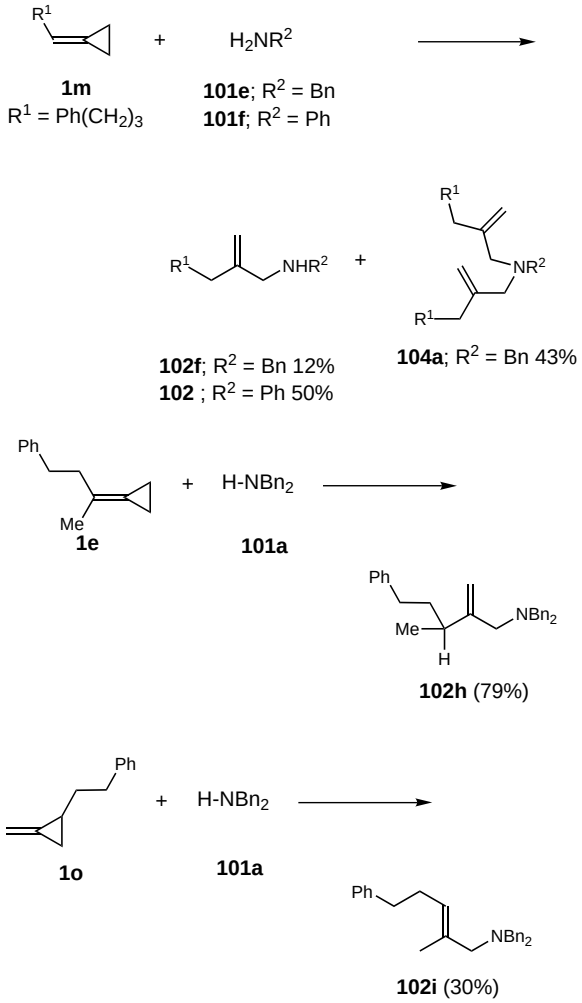
Table 5. Hydroamination of **1** catalyzed by palladium.[a]

Entry	**1**	**101**	Yield of **102** [%][b]	Yield of **103** [%][b]
1	 **1m**	H-NBn$_2$ **101a**	**102a**, 91	–
2	**1m**	 **101b**	**102b**, 64	–
3	**1m**	H-N(Boc)$_2$ **101c**	**102c**, 68	–
4	 **1f**	**101a**	**102d**, 82	–
5	 **1s**	**101a**	**102e**, 72	–
6	 **1j**	**101a**	–	**103a**, 19
7	**1j**	 **101d**	–	**103b**, 84

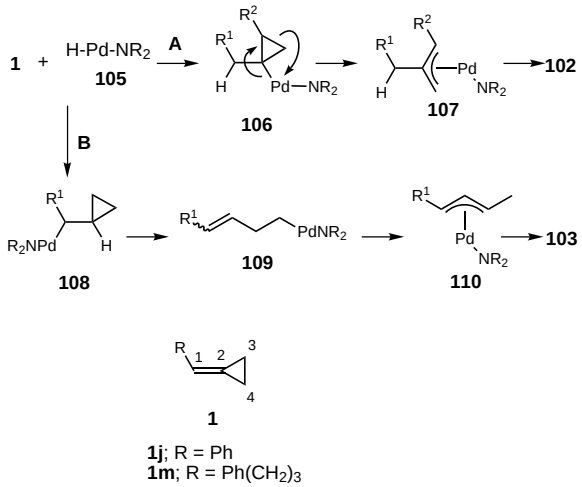
[a] The reaction of **1** (0.5 mmol) and **101** (1.0 mmol) was carried out in the presence of 5 mol % of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and 12.5 mol % of dppp in DME at 100 °C for 2 – 3 days.
[b] Isolated yield.
[c] The *trans* configuration of **103a** was confirmed by the coupling constant between the olefinic protons (16.2 Hz).

panes **1** in two different orientations; the Markovnikov hydropalladation (**A**) produces **106**, whereas the anti-Markovnikov hydropalladation (**B**) gives **108**.[41] The distal bond cleavage of **106** would afford the π-allylpalladium intermediate **107**, leading to **102** and Pd(0) upon reductive coupling. The proximal bond cleavage of **108** would give homoallylpalladium **109**,[61] which would undergo migration to π-allylpalladium **110**,[6] and subsequent reductive coupling would produce **103** and Pd(0).

The regioselectivity and reactivity of the hydroamination reaction were considerably affected by the substituent of methylenecyclopropanes. Alkyl substituents on the double bond tend to decrease the electron density at the C-1 carbon of **1** and the hydropalladation proceeds according to the Markovnikov type **106**. On the contrary, in the reaction of phenyl-substituted methylenecyclopropane **1j**, the phenyl group increases the electron density at the C-1 carbon and the hydropalladation proceeds with the anti-Markovnikov orientation **108**. AM1 calculations predicted higher negative charges on the C-1 carbon of **1j**, compared to the C-1 carbons of **1m**. On the other hand, the substituent on the cyclopropane ring decreased the reactivity toward the hydroamination reaction.



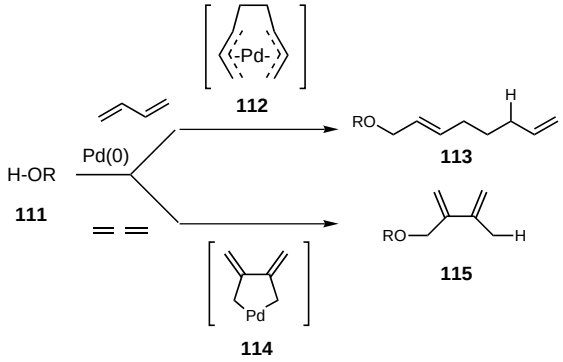
Scheme 28.



Scheme 29. A plausible mechanism for the hydroamination of **1**.

4.4 Hydroalkoxylation

The transition metal-catalyzed addition of alcohols **111** to unsaturated systems has not been widely investigated. Additions of alcohols to 1,3-dienes[62] or allenes,[63] presumably proceed via cyclic palladium intermediates **112** or **114**[63b] in which the dimerized diene is incorporated (Scheme 30). In these processes, the palladium activates the olefin for nucleophilic attack.

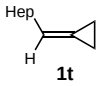
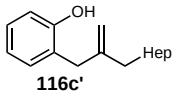
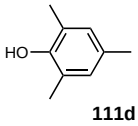
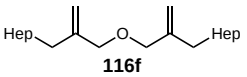
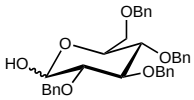
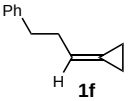
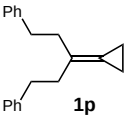


Scheme 30.

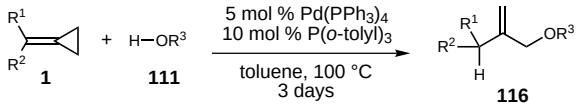
Recently, we demonstrated that the Pd-catalyzed addition of alcohols **111** to alkylidenecyclopropanes **1** proceeds in a way similar to the addition of amines, serving as a powerful tool in the synthesis of allylic ethers **116** (Scheme 31).[64]

The reaction proceeds with a wide range of alcohols **111** and with several different kinds of methylenecyclopropanes **1** (Table 6). In the presence of 5 mol % of $Pd(PPh_3)_4$ and 10 mol % of P(*o*-tolyl)$_3$ in toluene at 100 °C, the reaction of benzyl alcohol **111a** with **1t** afforded the allyl ether **116a** in 69% isolated yield (entry 1). 2,2,2-Trifluoroethanol **111b** also gave the hydroalkoxylated product **116b** (entry 2). The reaction

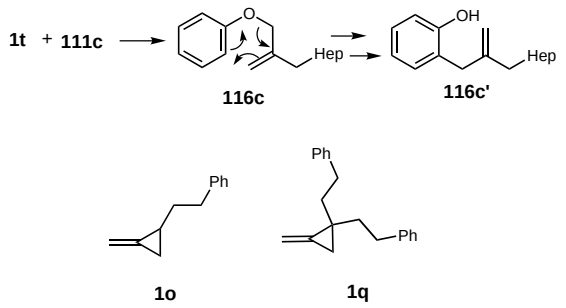
Table 6. Palladium-catalyzed addition of alcohols **111** to alkylidenecyclopropanes **1**.[a]

Entry	**1**	**111**	Yield of **116** [%][b]
1[c]	 **1t**	H-OBn **111a**	**116a**, 69
2	**1t**	H-OCH$_2$CF$_3$ **111b**	**116b**, 68
3[c]	**1t**	H-OPh **111c**	 **116c'** , 56[d]
4[e]	**1t**	 **111d**	**116d**, 67
5	**1t**	H-OSiEt$_3$ **111e**	**116e**, 49
6	**1t**	H$_2$O **111f**	 **116f** , 40
7	**1t**	H-O-*n*-Bu **111g**[f]	**116g**, 63
8	 **1c**	 **111h**	**116h**, 54
9	 **1f**	**111a**	**116i**, 67
10	 **1p**	**111a**	**116j**, 80

[a] Unless otherwise specified, all reactions were carried out on a 1:1 molar ratio.
[b] Isolated yields.
[c] Solvent used was toluene.
[d] See text.
[e] The reaction was carried out at 70 °C.
[f] The alcohol was used as the solvent.



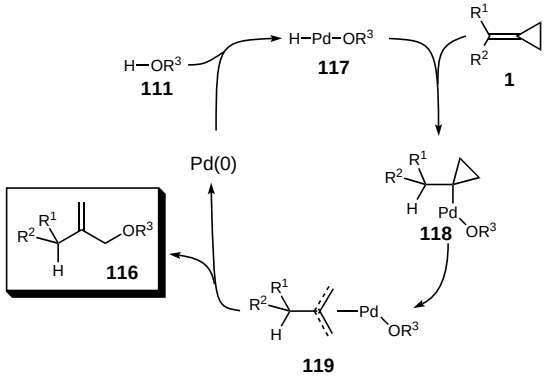
Scheme 31. Hydroalkoxylation of methylenecyclopropanes **1** catalyzed by palladium.



Scheme 32.

of phenol **111c** with **1t** also proceeded smoothly (entry 3), but the initial product **116c** (Scheme 32) underwent further Claisen rearrangement to afford **116c'**. When the reaction was performed at 70 °C for 6 h, **116c** was isolated in 32% yield along with **116c'** and the starting material. 2,4,6-Trimethylphenol **111d** gave **116d** (entry 4) efficiently. The use of triethylsilanol **111e** as a pronucleophile also afforded the hydroalkoxylated product **116e** in moderate yield (entry 5). Moreover, water **111f** could effectively act as an oxygen pronucleophile to give **116f** by addition of both O-H bonds to a molecule each of **1t** (entry 6). It is noteworthy that water as a substrate does not render the palladium catalyst inactive. An aliphatic alcohol such as *n*-butanol **111g** likewise underwent the hydroalkoxylation reaction to afford **116g** (entry 7). The reaction, however, required an excess amount of the alcohol. When 1 equiv. of **111g** was used in the reaction with **1t** in THF, **116g** was produced in poor yield indicating that the nucleophilicity of a normal aliphatic alcohol is lower than that of **111a – 111f**. Moreover, the protected sugar **111h**, 2,3,4,6-tetra-*o*-benzyl-D-glucopyranose, also underwent hydroglycosylation reaction with **1c** to give **116h** (entry 8). The methylenecyclopropanes **1e** and **1p** with a 2-phenethyl substituent at the exocyclic methylene carbon atom also underwent hydroalkoxylation reactions with **111a** to give **116i** and **116j**, respectively (entries 9 and 10). However, the reactions of **1o** and **1q** with either **111a** or **111b** did not give the desired hydroalkoxylation products at all, probably due to steric and electronic factors.

The examples shown in Table 6 indicate that the reaction shows excellent chemoselectivity in that the regioselective distal bond cleavage of the cyclopropane ring occurs (see Scheme 33). The facile addition of phenols, silanols, as well as a wide range of alcohols to the alkylidenecyclopropanes proceeds smoothly. In the case of phenolic OH, the reaction of **111d** with **1t** proceeds very well even at 70 °C. Moreover, the



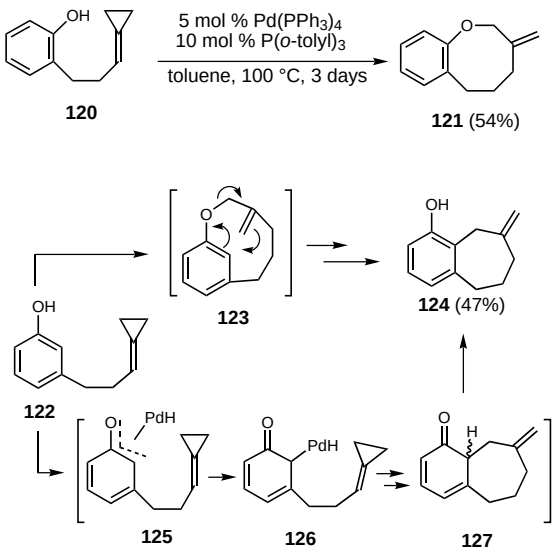
Scheme 33. A plausible mechanism for hydroalkoxylation of **1**.

formation of **116c** and **116c'** was observed within 6 h suggesting the high reactivity of phenolic OH towards **111a.** The higher cationic property of the Pd in the H-Pd-OPh complex makes it more reactive toward alkylidenecyclopropanes compared to the H-Pd-OR complexes for alcoholic hydroxy groups. Steric factors also contribute to the observed chemoselectivity and reactivity.

A plausible mechanism for this hydroalkoxylation reaction is illustrated in Scheme 33. As already mentioned in the case of H-C and H-N, oxidative addition of H-OR to Pd(0) produces the highly reactive H-Pd-OR complex **117**.[65] Hydropalladation of the alkylidenecyclopropane **1** would give the intermediate **118** which upon distal bond cleavage would afford the π-allyl complex **119**. Reductive elimination regenerates the Pd(0) and **116** is produced. Other products arising from the possible cleavage of the proximal cyclopropyl bond were never observed.

Further, we examined the intramolecular version of the addition of alcohols to alkylidenecyclopropanes.[66] In the reaction of the phenol-tethered alkylidenecyclopropane **120**, facile cyclization was observed affording the 8-membered exomethylene ether ring (**121**) in 54% yield in high regioselectivity (Scheme 34). In the case of **122**, cyclization also proceeded, but presumably the initial hydroalkoxylation product **123** underwent further Claisen rearrangement to give 47% of **124**. Alternatively, π-oxoallyl palladium complex **125** could have been formed to give **126** which upon intramolecular hydropalladation would lead to **127**, and subsequent rearrangements would give **124**.

This type of transformation via catalytic process had not been known previously and thus the present development provides a further example for the utility of palladium as an efficient catalyst in the addition of alcohol pronucleophiles to nonconjugated unsaturated systems. The excellent regioselectivity and the wide range of alcohols that can serve as pronucleophiles provide a new and efficient route to a variety of allyl ethers.



Scheme 34. Intramolecular hydroalkoxylation of methylenecyclopropanes.

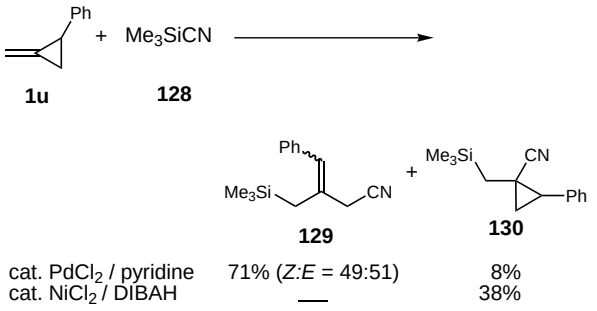
5 Bismetallation

Catalytic bismetallation is of current interest because this process is an attractive methodology to introduce two metal atoms into a carbon framework by addition to carbon-carbon multiple bonds directly.[67] Alkynes, alkenes, 1,3-dienes, and allenes have been used for catalytic bismetallation.[68] More recently, methylenecyclopropanes have been utilized as an acceptor because of their unique structural characteristics.

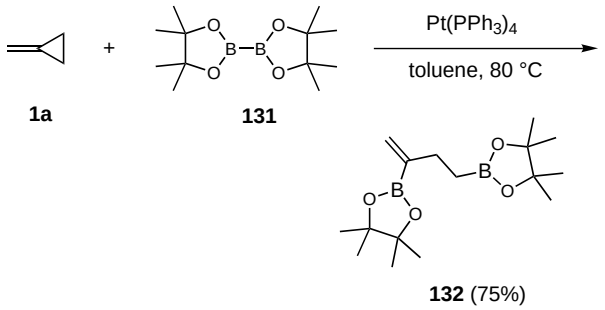
Chatani et al. reported the palladium- and nickel-catalyzed reaction of methylenecyclopropanes with trimethylsilyl cyanide **128**.[69] The reaction of **1u** with **128** in the presence of $PdCl_2$/pyridine gave the allylsilane **129** as the major product. In contrast, when a Ni(0) catalyst, generated by reduction of $NiCl_2$ with DIBAH (*i*-Bu_2AlH), was used as a catalyst instead of the Pd-catalyst, the major product was **130** (Scheme 35).

Recently, Miyaura et al. reported diboration of methylenecyclopropanes catalyzed by platinum.[70] When methylenecyclopropane **1a** was treated with bis(pinacolato)diboron **131** in toluene at 80 °C for 5 h in the presence of 3 mol % of $Pt(PPh_3)_4$, the corresponding ring-opened diboration product **132** was obtained in 75% yield, as a single isomer (Scheme 36). This reaction proceeds predominantly through cleavage of the proximal bond of the cyclopropane ring.

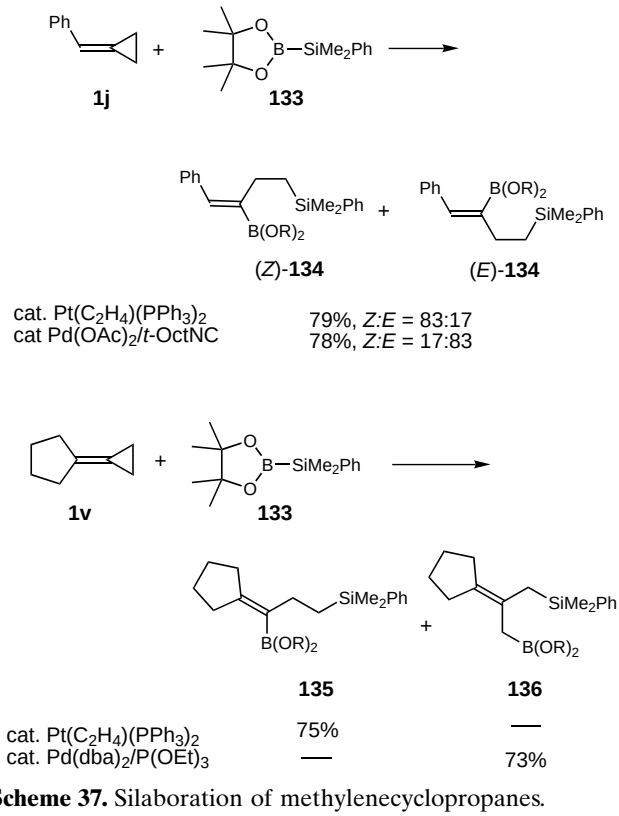
Quite recently, Ito et al. reported palladium- and platinum-catalyzed silaboration of methylenecyclopropanes.[71] In the reaction of **1j** with the silylborane **133** under platinum catalysis, (*Z*)-**134** was obtained selectively via a cleavage of the proximal C-C bond *trans* to the phenyl group, while under palladium catalysis, the corresponding (*E*)-configurated product was formed predominantly via the proximal *cis* C-C bond cleavage



Scheme 35. Nickel- and palladium-catalyzed addition of trimethylsilyl cyanide **128** to methylenecyclopropanes.

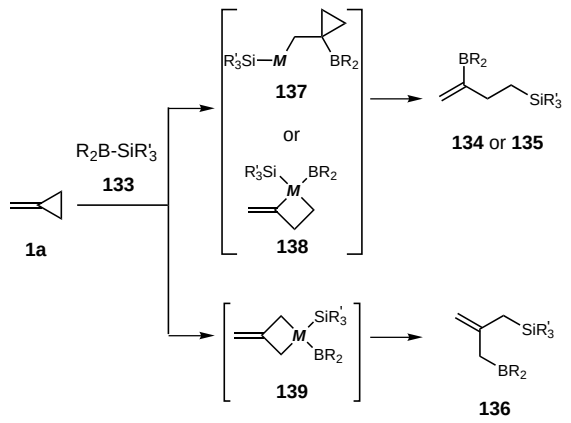


Scheme 36. Diboration of methylenecyclopropanes catalyzed by platinum.

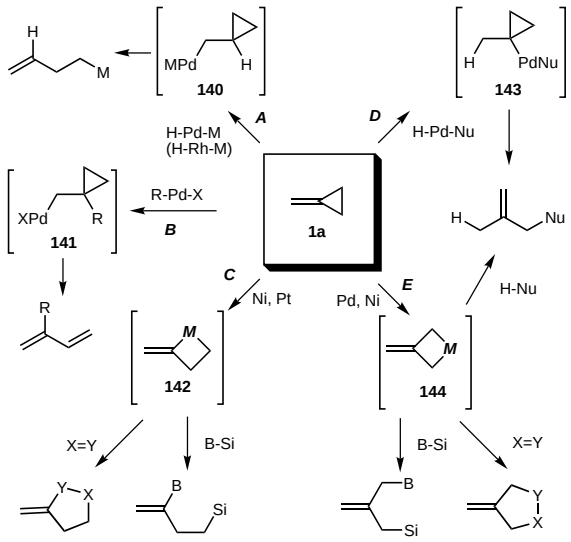


Scheme 37. Silaboration of methylenecyclopropanes.

(Scheme 37). On the other hand, **1v** reacted with **133** in the presence of the platinum catalyst resulting in the selective formation of the alkenylborane **135**. On the



Scheme 38.



Scheme 39. Transition metal-catalyzed reactions of methylenecyclopropane **1a**.

contrary, the reaction using a catalytic amount of $Pd(dba)_2$ and $P(OEt)_3$ proceeded through the distal bond cleavage, and the corresponding silaboration product **136** was obtained in 73% yield.

The catalytic silaboration involving proximal bond cleavage may proceed through the formation of either the cyclopropylcarbinylpalladium species **137** or the metallacyclobutane intermediate **138** (Scheme 38). On the other hand, distal bond cleavage must occur through the formation of alternative metallacyclopropane species **139**.

6 Conclusion

The various reaction pathways of methylenecyclopropanes are summarized in Scheme 39. Proximal bond cleavage proceeds through the cyclopropylcarbinylpalladium species **140** or **141** formed by the addition of H-Pd or R-Pd intermediates to the double bond in the methylenecyclopropane **1a** (paths A and B). Oxidative addition of the proximal bond to the transition metal catalysts leading to **142** can also be a key process to cleave a proximal bond (path C). On the other hand, distal bond cleavage proceeds through Markovnikov hydropalladation of H-Pd-Nu complex **143** (path D) or the formation of palladacyclobutane species **144** (path E). The selectivity of the respective ring-opening position depends on the combination of substrates and catalysts. While it is not clear what is the crucial factor to determine the mode of ring opening, the difference of the ease of oxidative addition of a substrate to a transition metal complex plays an important role. Substituents on the methylenecyclopropane skeleton often affect the reactivity and the regioselectivity. Especially in the reaction with less reactive pronucleophiles, such as furans, amines and alcohols, disubstitution on the olefinic moiety of methylenecyclopropane gives the ring opening products in higher yields than monosubstitution, and substitution on the cyclopropane ring tends to decrease the addition of pronucleophiles.

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