Cyclopropenone Acetals—Synthesis and Reactions

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Contents

I. Introduction

Having a simple appearance outside, yet full of wonder inside, cyclopropenone seems like a miniature carved ivory altarpiece in a Chinese curio box. The acetal of cyclopropenone looks much less fancy, because of a lack of the aromaticity that characterizes the parent ketone. However, this compound is attracting the attention of chemists because of its synthetic utility, not to mention its ability to produce cyclopropenone upon hydrolysis of the acetal moiety. The first stage in the development of the chemistry of cyclopropenone acetal (hereafter called CPA) began in 1959, when it was first described in the literature.[1] Over the next 20 years, the compound was primarily regarded as being associated with the corresponding ketone. The second development was brought about in the mid-1980s by Boger, who discovered the unexpectedly high synthetic potential of CPA.[2] In a series of publications, he demonstrated that CPA is useful for the construction of a variety of carbocyclic and heterocyclic structures. The third stage of development arose from a report by Nakamura that showed that 2-metalated CPA could be generated and trapped with an electrophile.[3] This synthetic method made available a diverse array of acetals of 2,3-disubstituted cyclopropenones and their corresponding cyclopropenones, and as a result, new synthetic utilities of CPA have emerged. Among a variety of developments made in the past 10 years, have been (i) the addition of organometallics across the strained double bond, (ii) the synthesis of cyclopropenone-bearing complex side chains, and (iii) the discovery of the biological activities of fullerenes.

The present paper represents the first comprehensive review specifically focusing on the chemistry of CPAs and their analogues (e.g., nitrogen and sulfur analogues of the acetal) and covers all the experimental data reported before May 2002 on the chemistry of these compounds. Although the chemistry of CPA has been partially addressed in various reviews on strained rings,[4,5] cycloadditions,[6−10] and organometallic chemistry,[11−15] we do not intend to avoid any overlaps, so that this work will be the most comprehensive available.

II. Synthesis of CPA and Its Derivatives

A. Historical Overview of the Synthesis of CPA

The earlier studies on cyclopropenone and CPA were driven by curiosity about the basic physical and chemical properties of these peculiar-looking molecules. Interest was led by the pioneering work of Breslow and Vol'pin, who reported independently the first synthesis of diphenylcyclopropenone **2** in 1959.[1,16] 3,3-Dimethoxy-1,2-diphenylcyclopropene **1** was used as an intermediate during the first cyclopropenone synthesis by Breslow.[1] Synthesis of a variety of substituted cyclopropenones (Scheme 1),[17−19] which later proved to serve as intermediates for the syn-

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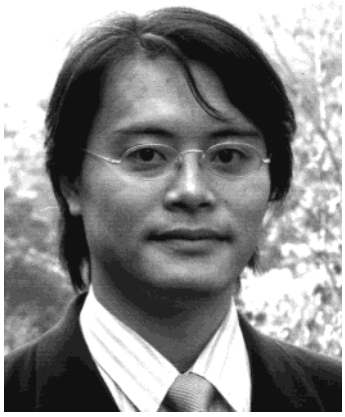
Eiichi Nakamura received degrees from Tokyo Institute of Technology (B.S. and Ph.D. in chemistry). After postdoctoral work at Columbia, he came back to his Alma Mater and was promoted to the rank of professor. In 1995, he moved to the University of Tokyo. He has been honored with The Chemical Society of Japan Award for Young Chemists (1984), The Japan IBM Prize (1993), Elected Fellow of the American Association for the Advancement of Science (1998), The Nagoya Medal of Organic Chemistry (2001), and the Chemical Society of Japan Award (2003). He is currently serving as associate editor of *Organic Letters*. His research field includes synthetic, organometallic, bioorganic, and computational/theoretical chemistry, all of which focus on reactive intermediates.



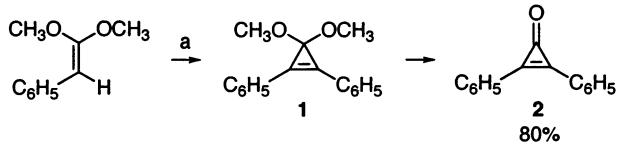
Hiroyuki Isobe was born in Tokyo, Japan, in 1970. He received his B.S. and M.S. degrees from Tokyo Institute of Technology and received his Ph.D. degree in 1999 from The University of Tokyo. During that time he shortly joined Professor Daniel Kahne's group at Princeton University as a visiting researcher (1996). In 1998, he became an assistant professor of The University of Tokyo. He received the first IUPAC Prize for Young Chemists in 2000 and the first Young Scientist's Research Award in Natural Product Chemistry in 2001. His current research interests include synthesis of nanometer-size organic compounds and development of their functions in bioorganic and material chemistry.

thesis of their acetals,[20−22] were developed, and these finally culminated in the synthesis of the cyclopropenone **3** (Scheme 2).[23−25]

In 1972, Butler and Baucom reported on the synthesis of cyclopropenone dimethyl acetal **4** with the aid of a base-promoted three-membered-ring formation reaction of 1-bromo-2,2-dimethoxy-3-chloropropane, which was later improved by Breslow (Scheme 3).[26,27] Butler's synthesis utilized commercially available 2,3-dichloropropene, which was first converted to 1-bromo-3-chloro-2,2-dimethoxypropane by treatment with *N*-bromosuccinimide in methanol. Subsequent dehydrohalogenation with 2 equiv of potassium amide gave **4** in a 50% yield (Scheme 3). The cyclization reaction of an α,α′-dihalopropanone

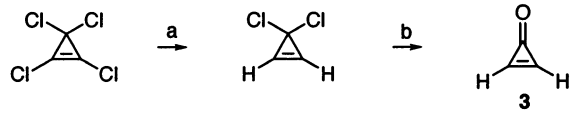
Masaharu Nakamura received Ph.D. degree from Tokyo Institute of Technology in 1996 and became assistant professor at The University of Tokyo. After postdoctoral work at Harvard, he was promoted to lecturer. He has been honored with The Chemical Society of Japan Award for Young Chemists (2000). His research field includes synthetic, organometallic, and computational/theoretical chemistry, all of which focus on the invention of new molecular transformation processes.

Scheme 1[a]



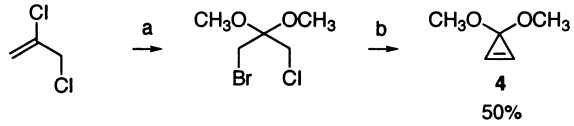
[a] (a) $C_6H_5CHCl_2$, $(CH_3)_3COK$.

Scheme 2[a]



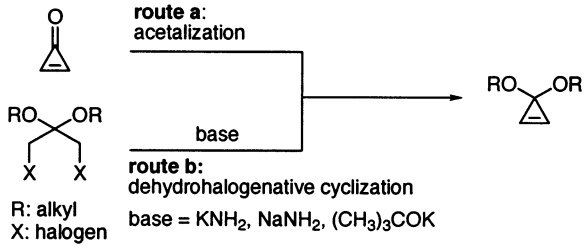
[a] (a) $(C_4H_9)_3SnH$, (b) H_2O.

Scheme 3[a]



[a] (a) *N*-bromosuccinimide, CH_3OH; (b) KNH_2, NH_3.

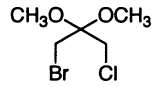
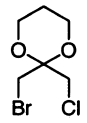
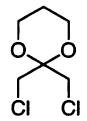
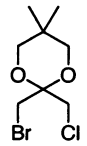
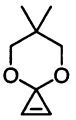
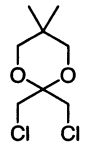
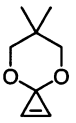
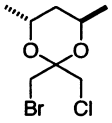
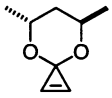
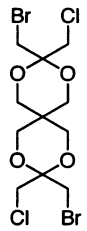
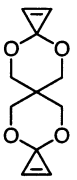
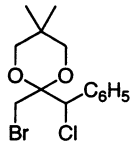
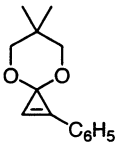
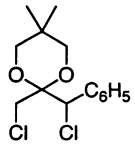
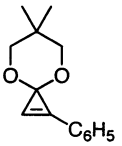
Scheme 4



acetal was further improved by Breslow,[27] Boger,[28] and Nakamura[3,29] and this has become a versatile method for the preparation of a variety of CPAs.

There are two commonly used synthetic routes to produce CPAs, as shown in Scheme 4: acetalization of cyclopropenone (route a) and the cyclization of 1,3-dihalo-2-propanone acetals (route b). Cyclopropanone is strained and is very unstable. It rapidly reacts with water or an alcohol to give a geminal diol or a hemiacetal.[30] On the other hand, the 2π-electron

Table 1. Preparation of CPAs via Base-Promoted Cyclization (Scheme 4, Route b)

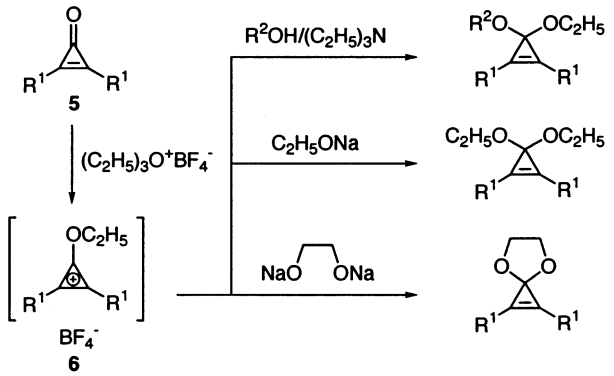
entry	substrate	CPA	yield	ref.
1[a]			40-65%	26
2[a]			55-70%	27
3[b]			69%	28
4[b]			40-55%	79
5[b]			85%	28
6[a]			85%	59
7[a]			95%	33
8[c]			70%	32
9[b]			73%	28

[a] −50 °C, KNH_2/NH_3. [b] −50 °C, $NaNH_2/NH_3$. [c] $(CH_3)_3COK$, THF/DMI.

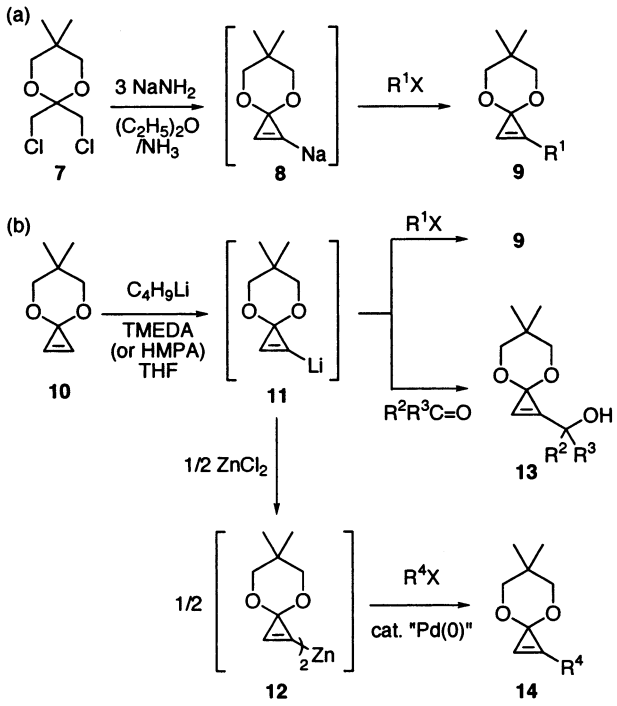
cyclopropenone is stable, as is the cyclopropenium cation, which is a genuine 2π-aromatic compound.[31] Hence, the acetalization route requires rather harsh reaction conditions. For example, cyclopropenone **5** is first converted to cyclopropenium ion **6** by treatment with triethyloxonium fluoroborate. This is then treated with an alcohol under basic conditions (Scheme 5).[22,32] Route b has a number of advantages over route a in terms of its simplicity and its broader applicability.

As summarized in Table 1, the base-promoted cyclization reaction (Scheme 4, route b) provides a variety of CPAs in good to excellent yield.[3,26−28,33] The cyclic acetal analogues in entries 2−9 are generally more stable and easier to handle than the cyclopropenone dimethyl acetal **4** of entry 1.[34]

Scheme 5



Scheme 6



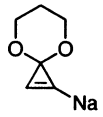
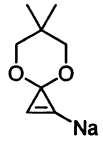
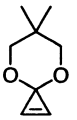
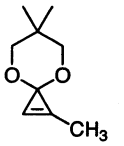
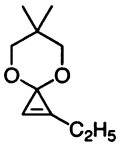
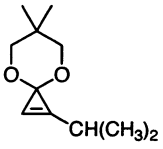
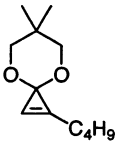
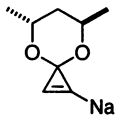
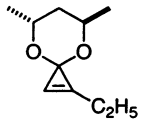
R^1 = alkyl; R^2 = H, alkyl, aryl; R^3 = H, alkyl, aryl; R^4 = aryl, alkenyl

B. Generation of Metalated CPAs and Their Application to the Synthesis of Functionalized Analogues

In 1989, Nakamura et al. reported a general synthetic protocol for the synthesis of functionalized CPAs (Scheme 6).[3,29] Their key discovery was that the vinylic proton of CPA **10** that was prepared in situ could be deprotonated, and the resulting metalated CPA **8** could react with a variety of electrophiles. Alkyl-, aryl-, and vinyl-substituted cyclopropenones have been prepared by the electrophilic trapping of a metalated CPA followed by acid hydrolysis of the acetal.[3,35]

In the Nakamura procedure (Scheme 6a), a cyclic acetal of commercially available 1,3-dichloro-2-propanone **7** was used instead of the 1-bromo-3-chloro-2-propanone acetal in Butler's original procedure (Scheme 3). The acetal was treated with 3 equiv of

Table 2. Electrophilic Trapping of Sodio-CPA (Ref 29)

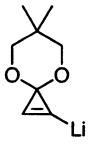
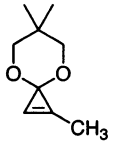
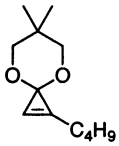
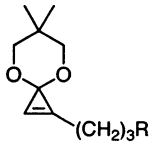
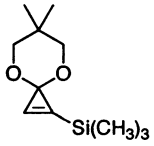
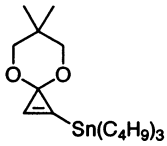
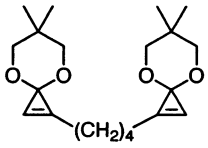
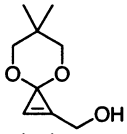
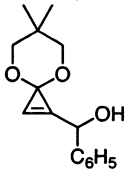
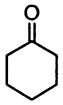
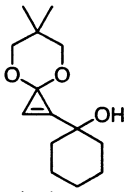
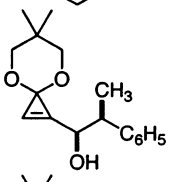
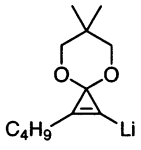
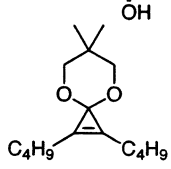
entry	substrate	electrophile	product	yield[a]
1		NH_4Cl		69%
2		NH_4Cl		85%
3		CH_3I		72%
4		C_2H_5Br		71%
5		$(CH_3)_2CHBr$		24%
6		C_4H_9I		77%
7		C_2H_5I		75%

[a] Yield is based on 1,3-dichloro-2-propanone acetal (Scheme 6a).

sodium amide, which effected the cyclization and in situ metalation of the CPA to obtain the sodio-CPA **8** (Scheme 6a). The sodium compound **8** in liquid ammonia reacted with an alkyl halide to afford alkyl derivative **9**. Deprotonation of the vinylic proton of CPA **10** with butyllithium generated lithio-CPA **11**, which reacted with a much broader range of electrophiles, including carbonyl compounds (Scheme 6b). The lithio derivative **11** was treated with 0.5 equiv of anhydrous zinc chloride to obtain the corresponding dicyclopropenyl zinc compound **12**, which underwent a palladium-catalyzed Csp^2-Csp^2 bond formation reaction (Scheme 6b).

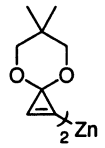
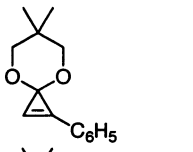
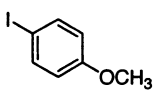
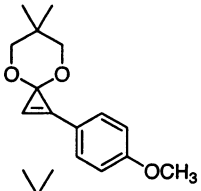
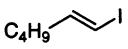
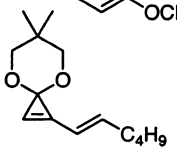
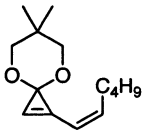
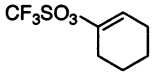
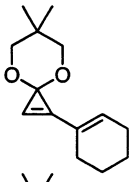
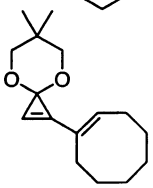
Tables 2−4 summarize the reactions of the metalated CPAs with various electrophiles. The sodio and lithio derivatives, **8** and **11**, produced an alkylated and a hydroxymethylated CPA upon reaction with an alkyl halide and a carbonyl compound, respectively (Tables 2 and 3). Disubstituted CPAs were synthesized by repetition of the metalation/alkylation sequence on a monosubstituted CPA (entry 11 of Table 3). Paquette showed the utility of the cyclopropenylmetal compounds in a complex molecule synthesis. The reaction of lithio-CPA **11** with a squarate ester gave the polycyclic molecule **15**, where

Table 3. Electrophilic Trapping of Lithio-CPA

entry	substrate	electrophile[a]	product	yield[b] [ref.]
1		CH_3I		85% [3]
2		C_4H_9Br		91% [3]
3		$R(CH_2)_3I$		76% [3]
4		$(CH_3)_3SiCl$		75% [34]
5		$(C_4H_9)_3SnCl$		73% [34]
6		$I(CH_2)_4I$		82% [3]
7		HCHO		51% [3]
8		C_6H_5CHO		93% [3]
9				92% [3]
10		$C_6H_5CH(CH_3)CHO$		82% [34]
11		C_4H_9I		57% [34]

[a] R = trimethylsilylethynyl. [b] Yield is based on cyclopropenone acetal (Scheme 6b).

Table 4. Electrophilic Trapping of Zincio-CPA (Ref 3)

entry	substrate	electrophile	product	yield[a]
1				73%
2				79%
3				93%
4				87%
5				83%
6				95%

[a] Yield is based on cyclopropenone acetal (Scheme 6b).

skeletal rearrangement reactions were driven by the release of ring strain of the starting materials (Scheme 7).[36]

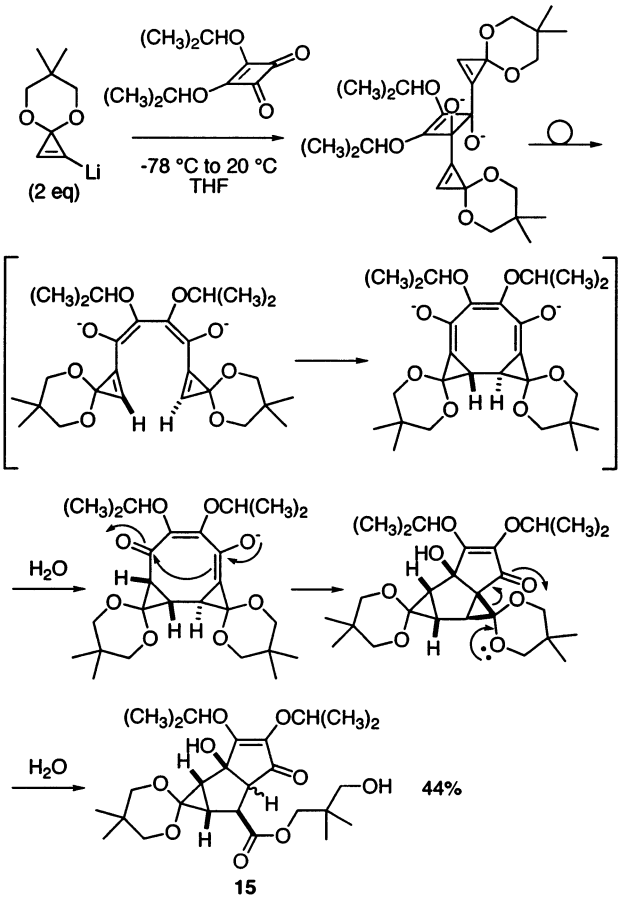
Transmetalation of the lithio-CPA **11** provides various metallo-CPA derivatives. As shown in Table 4, an alkenyl halide or triflate and an aryl halide can react with the zincio derivative **13** to give alkenyl- and aryl-substituted CPAs **14**, which are the key intermediates in the synthesis of biologically active cyclopropenone derivatives (see section III.B).[37−39] A cerium compound has been prepared by treatment of **11** with cerium trichloride and this was utilized in the addition reaction of α-amino aldehydes to synthesize the cyclopropenone-containing amino acid mimic (Scheme 8).[40]

III. Hydrolysis of the Acetal Moiety and Synthesis of Cyclopropenone Derivatives

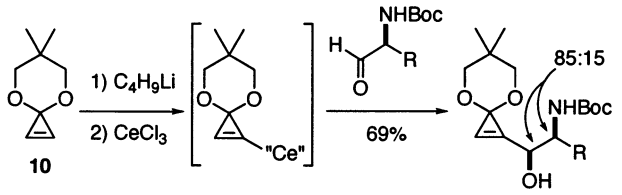
A. Hydrolysis

CPAs can be readily hydrolyzed to the corresponding cyclopropenones under a variety of aqueous acidic conditions (e.g., aq HCl, aq H_2SO_4, and aq $HClO_4$). Owing to the interest in the intermediary oxocarbenium ion, mechanistic studies have been carried out on the acid-catalyzed hydrolysis reaction of CPAs.[41,42]

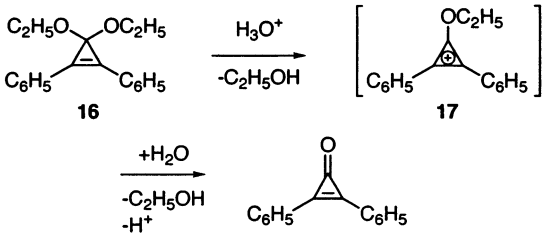
Scheme 7



Scheme 8



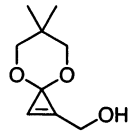
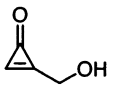
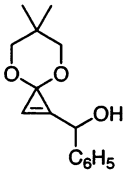
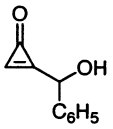
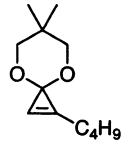
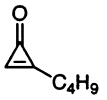
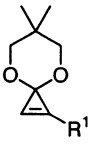
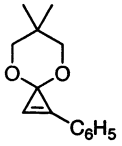
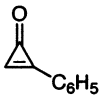
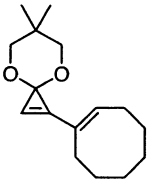
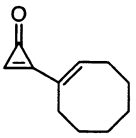
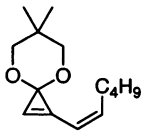
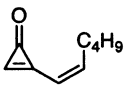
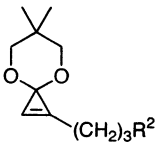
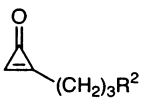
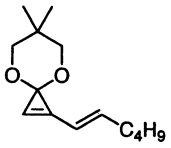
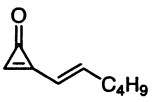
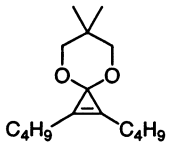
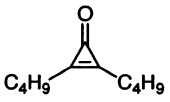
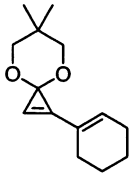
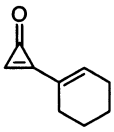
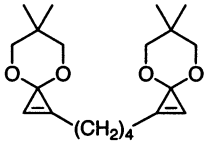
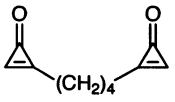
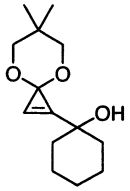
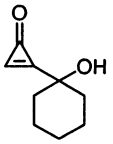
Scheme 9



McGarrity studied the hydrolysis of 1,1-diethoxy-2,3-diphenylcycloprop-2-ene **16** in aqueous acetone using a rapid injection NMR technique to observe the formation of the cyclopropenium intermediate **17**, which has a half-life of ca. 400 ms (Scheme 9).

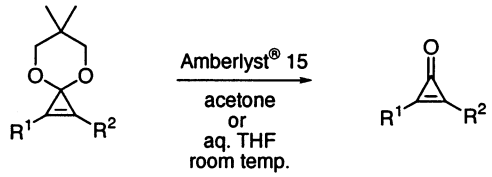
The flexible synthesis of functionalized CPAs combined with a mild and selective hydrolysis of the acetal moiety affords a variety of functionalized cyclopropenones. A convenient method for the hydrolysis of CPAs is the use of Amberlyst 15 in acetone or aqueous THF at ambient temperature (Scheme 10,

Table 5. Hydrolysis of CPA (Ref 3)

entry	CPA[b]	product	yield	entry	CPA[b]	product	yield
1			71%	8			88%
2			93%	9			92%
3			93%	10			92%
4			99%	11			96%
5			84%	12			91%
6			80%	13			78%
7			91%				

[a] Amberlyst 15, H_2O, room temp. [b] R^1 = 4-methoxyphenyl. R^2 = trimethylsilylethynyl.

Scheme 10



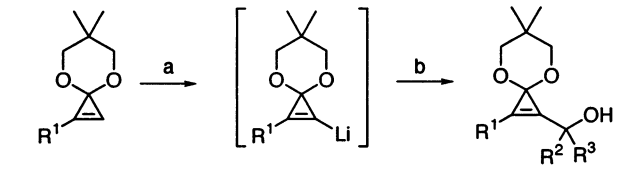
R^1 = H, alkyl, alkenyl, aryl, etc.; R^2 = H, alkyl, alkenyl, aryl, etc.

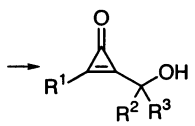
Table 5). These conditions have proved to be especially useful for the synthesis of water-soluble cyclopropenones, such as penitricin **18** (where R^1 = H and R^2 = CH_2OH), and its congeners.[37,38]

B. Application to the Synthesis of Biologically Active Compounds

The above-mentioned sequential transformations of CPA to a functionalized cyclopropenone have enabled the synthesis and exploration of a series of biologically active molecules that possess a cyclopropenone moiety such as penitricin (**18**). As summarized in Scheme 11, a variety of cyclopropenone-containing synthetic molecules have been synthesized and they have shown considerable biological activity. For example, the penitricin analogues of compounds **19**, **20**, and **21** show antimicrobial activity comparable to penitricin against Gram-positive bacteria. The phenyl-substituted analogue **22** shows high cytotoxicity against the HeLa S3 cell line (ED_{50} =

Scheme 11[a]

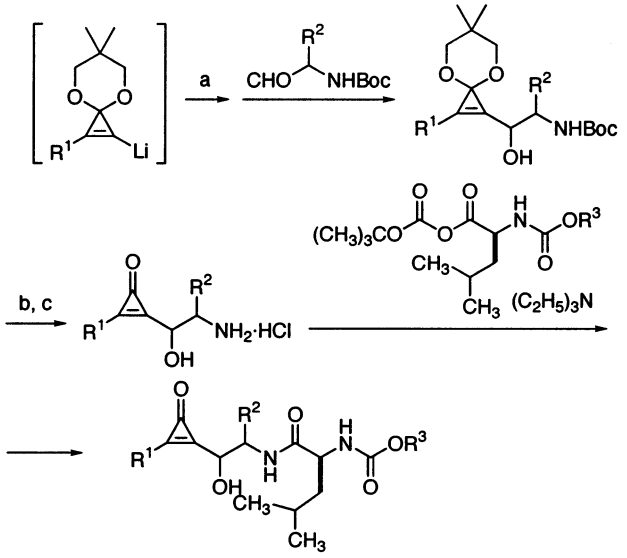




$R^1 = R^2 = R^3$ = H: penitricin **18**, 36%
$R^1 = R^2$ = H, $R^3 = C_2H_5$: **19**, 65%
R^1, R^2 = H, $R^3 = C_7H_{15}$: **20**, 68%
R^1 = H, R^2,R^3 = -$(CH_2)_5$-: **21**, 84%
$R^1 = C_6H_5$, R^2 = H, $R^3 = C_5H_{11}$: **22**, 69%

[a] (a) C_4H_9Li/TMEDA/THF; (b) R^2COR^3 then H_2O; (c) Amberlyst 15, acetone or aq THF.

Scheme 12[a]



R^1 = H, CH_3, $CHCH_3(CH_2CH_3)$, (*Z*)-1-hexenyl, C_6H_5, 4-fluorophenyl, 2-tolyl,5-trimethylsilyl-2-thienyl; R^2 = $CH(CH_3)_2$, C_4H_9; R^3 = cyclohexylmethyl or benzyl

[a] (a) $CeCl_3$; (b) Amberlyst 15, 2,6-di-*tert*-butylpyridine, or 0.1 N H_2SO_4, or 0.1 N HCl; (c) $TsOH·H_2O$ or 3 N HCl.

2.00 μg/mL).[38] A variety of cyclopropenone-containing cysteine proteinase inhibitors have also been synthesized by sequential transformation, and their inhibitory mechanism has been studied (Scheme 12).[39,37]

The alutacenoic acids **23** and **24**, which are isolated as fungal metabolites from *Eupenicillium alutaceum* Scott, have been proven to be potent specific inhibitors of factor XIIIa (IC_{50} = 1.9 and 0.61 μM, respectively). As shown in Scheme 13, synthesis of these natural products and their analogues has been achieved using the sequential transformation from a CPA (Scheme 13a), leading to the discovery of a phenethyl amide compound (**25**) that shows an improved inhibitory potency of 26 nM (Scheme 13b).[43]

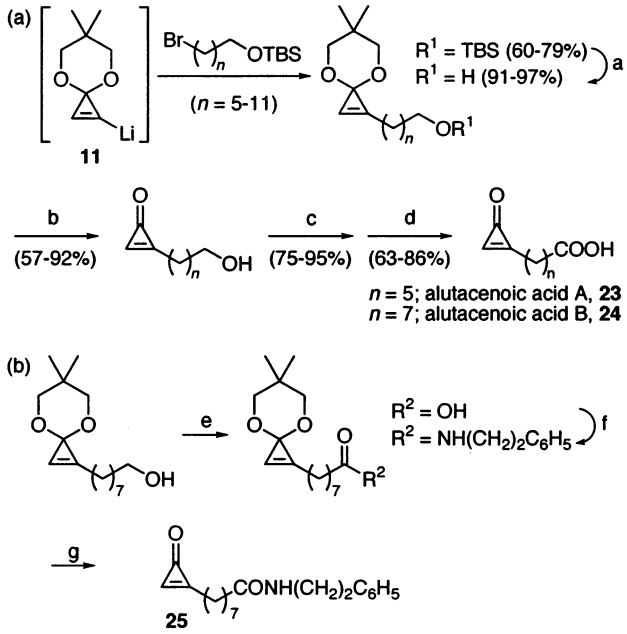
IV. Reactions of the C–C Double Bond

A. Isomerization to 2-Alkylidenecyclopropan-1-one Acetal

Although both cyclopropene and methylenecyclopropane are strained, the latter compound is less strained than the former. Thus, the strain in cyclopropene is 52 kcal/mol and that in methylenecyclopropane is 41.0 kcal/mol.[44] Owing to this difference, isomerization of methylcyclopropene to methylenecyclopropane is exothermic by 10.3 kcal/mol.[45] A variety of substituted CPAs possessing a primary alkyl group at the 2-position therefore undergo base-mediated isomerization to 2-alkylidenecyclopropanone acetals **26** (Scheme 14).

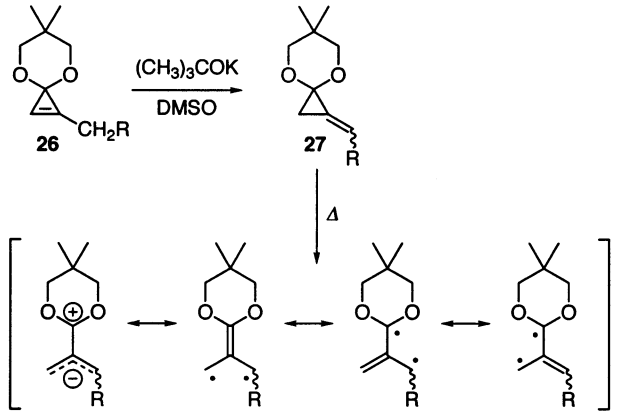
The 2-alkylidenecyclopropan-1-one acetal **27** is a useful precursor of dialkoxy trimethylenemethane (TMM). Mild thermolysis of **27** in the presence of an electrophile generates the TMM, which undergoes a [3 + 2] cycloaddition and other in situ reactions with the electrophile. The electrophiles include electron-

Scheme 13[a]



[a] (a) $(C_4H_9)_4NF$, CH_3COOH, THF; (b) Amberlyst 15, aq THF; (c) Swern oxidation; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene; (e) TEMPO, KBr, Aliquat 336, NaClO, $NaHCO_3$, CH_2Cl_2; (f) 1,1-carbonyldiimidazole, phenethylamine, CH_2Cl_2; (g) Amberlyst 15, aq THF.

Scheme 14

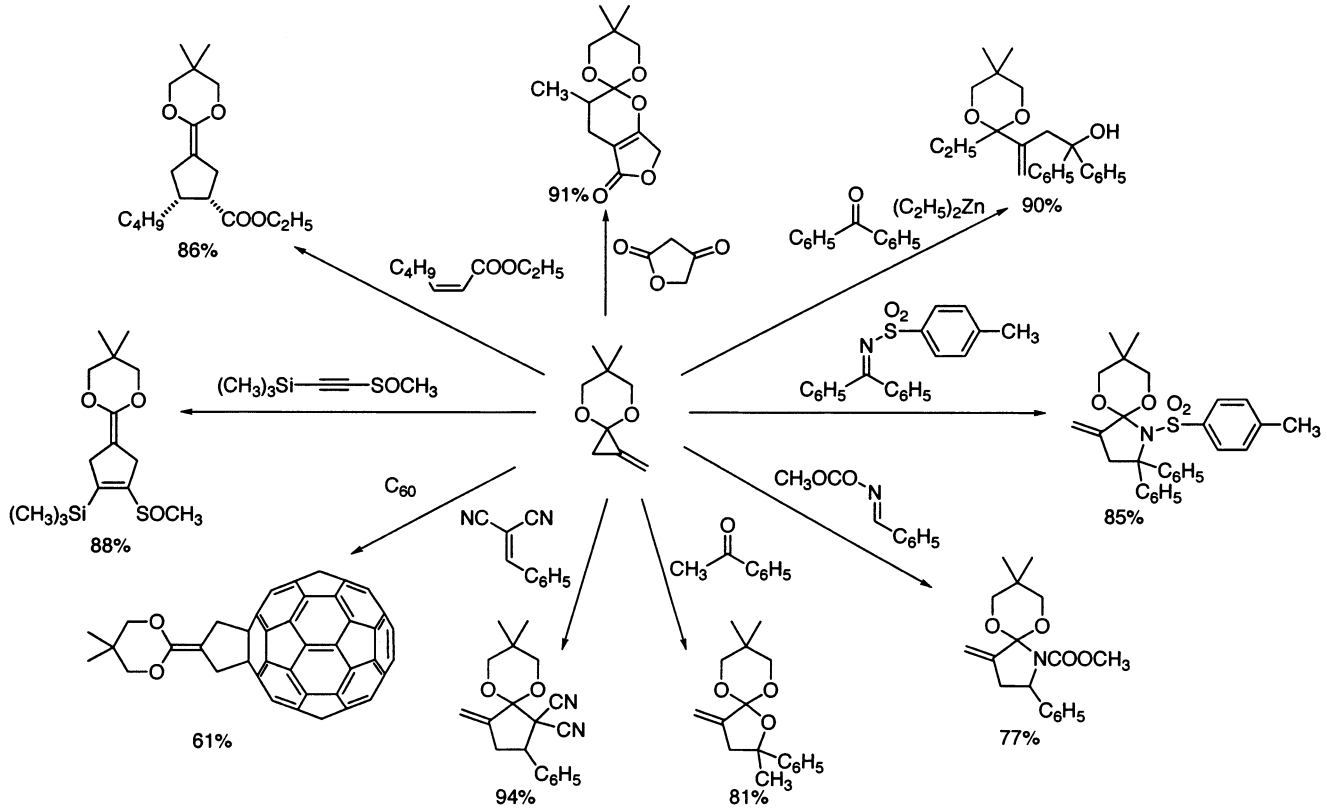


deficient alkenes,[46,47,48] alkynes,[49] carbonyl compounds,[50] imines,[51] [60]fullerene (C_{60}),[52] active methylene compounds,[53] and organozinc compounds[54] (Scheme 15). The reactivity of TMM has recently been reviewed.[55,56]

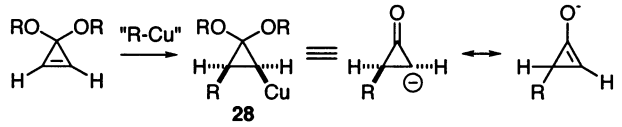
B. Addition to the C–C Double Bond

The highly strained double bond of a CPA serves as a good acceptor for the addition of a neutral or an anionic reagent. In 1988, Nakamura et al. discovered that a *cis* addition of an organocopper reagent across the strained double bond proceeds in high yield.[57] A series of studies on the addition of organolithium, organomagnesium, and organozinc reagents proved that the carbometalation reaction was useful for selective organic synthesis (see section IV.B.1). Neutral nucleophiles, such as an amine, a carbon radical, or a tin radical also undergo facile addition across the double bond (see section IV.B.2). CPA can also serve as an excellent acceptor of dienes to provide

Scheme 15



Scheme 16



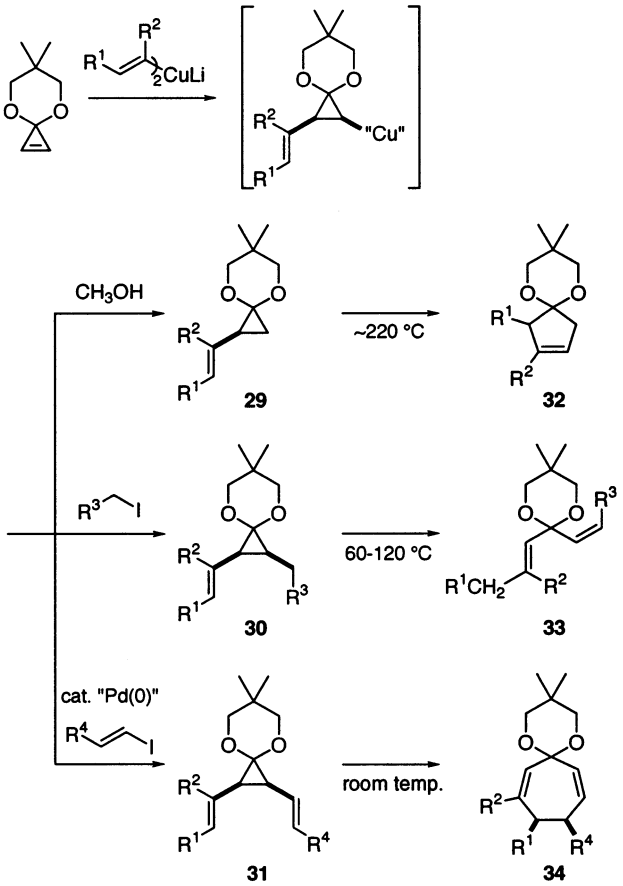
[2 + 4] cycloadducts, which can be subjected to further synthetic elaboration (see section IV.B.3).[58]

1. Addition of Organometallics

A CPA reacts with an organocopper reagent to produce a metalated cyclopropanone acetal. This then reacts with a variety of electrophiles to afford substituted cyclopropanone acetals. The organocopper intermediate **28** serves as a synthon of cyclopropanone enolate, which, by itself, does not exist as a stable intermediate (Scheme 16).[57]

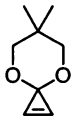
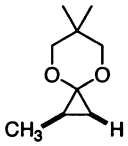
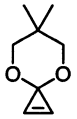
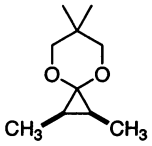
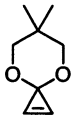
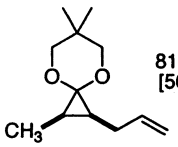
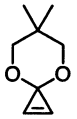
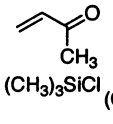
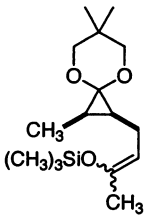
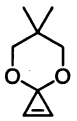
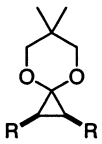
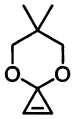
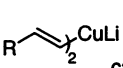
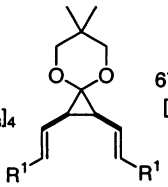
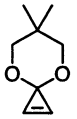
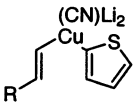
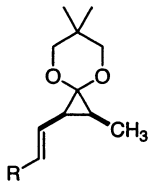
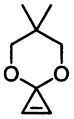
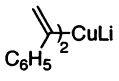
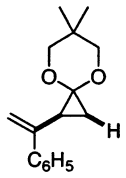
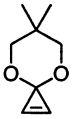
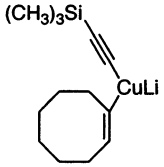
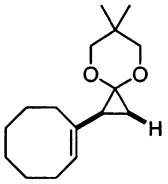
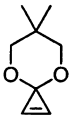
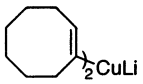
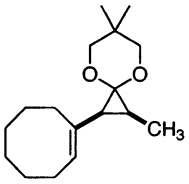
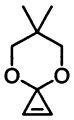
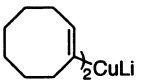
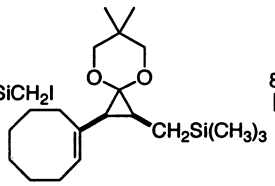
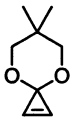
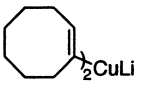
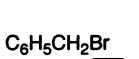
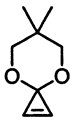
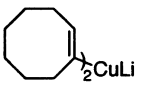
Table 6 summarizes the carbocupration reactions of various CPAs and electrophilic trapping of the resulting organocopper reagent **28**. The substituted cyclopropanone acetals, synthesized using this method, can be used as synthetic intermediates for stereoselective synthesis of cyclic and acyclic compounds. For example, addition of a vinyl cuprate to a CPA followed by trapping with water, an alkyl halide, or a vinyl iodide in the presence of a Pd(0) catalyst provides the corresponding vinyl-substituted cyclopropanone acetals **29**−**31** (Scheme 17). These cyclopropane derivatives thermally rearrange to the cyclopentenone acetal **32**, the divinyl ketone acetal **33**, and the cycloheptadienone acetal **34**, respectively, through vinylcyclopropane rearrangement, homo-1,5-sigmatropic hydrogen shift, and divinylcyclopropane rearrangement (Scheme 17).[57,59,60]

Scheme 17



Regio- and stereoselective carbocupration of the substituted CPA **35** derived from a chiral 2,4-pentanediol can be used for asymmetric synthesis of a

Table 6. Carbocupration of CPA

entry	CPA	RM[a]	electrophile	product	yield [ref.]
1		$(CH_3)_2CuLi$	H^+		71% [56]
2		$(CH_3)_2CuLi$	CH_3I		88% [56]
3		$(CH_3)_2CuLi$			81% [56]
4		$(CH_3)_2CuLi$			65% [56]
5		R_2CuLi	RI		72% [56]
6		 cat. $Pd[P(C_6H_5)_3]_4$			67%[b] [56]
7			CH_3I		89% [57]
8			H^+		78% [56]
9			H^+		72% [56]
10			CH_3I		79% [57]
11					84% [57]
12					90% [57]
13					68% [57]

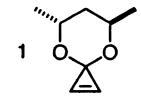
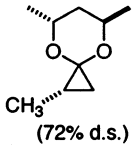
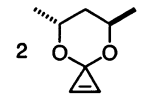
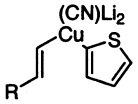
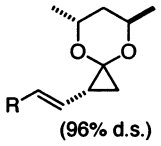
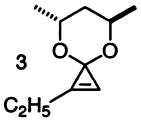
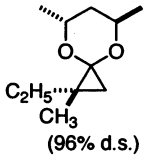
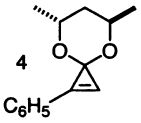
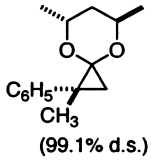
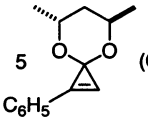
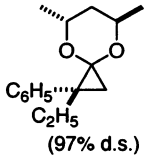
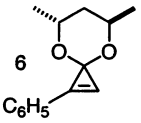
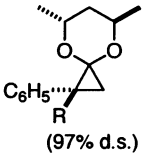
[a] R = C_4H_9. [b] Yield was determined after thermal conversion to 4,5-*cis*-dibutylcyclo-heptadienone acetal.

quaternary carbon center (Table 7).[61] Thus, the addition of dimethyl cuprate to CPA **35** followed by trapping of the resulting cyclopropyl cuprate with benzoyl chloride in the presence of a Pd(0) catalyst produces the cyclopropyl ketone derivative **36** as a single isomer. The ketone can be transformed to the γ-keto acid **37** by sequential treatment of the keto acetal with aqueous HCl, PCC, and K_2CO_3 (Scheme 18).

An allylic lithium reagent bearing an alkoxy substituent (**38**) can react with a CPA to produce an alkoxyallylated cyclopropanone acetal with a high stereo- and regioselectivity (Scheme 19, Table 8).[62] The regiochemistry of the α- or γ-addition of the allylic lithium reagent depends strongly on the structure of the lithium reagent. For example, carbon−carbon bond formation takes place at the α-position using a β-,γ- or an α-,γ- disubstituted allylic lithium reagent (entries 1−5), while a monosubstituted alkoxyallylic lithium reagent mainly gives a γ-adduct (entry 6).

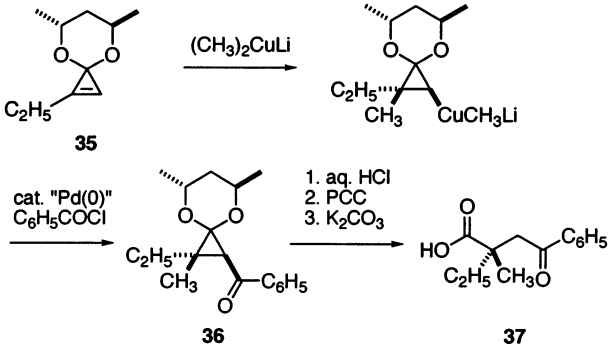
Addition of the alkoxyallylic zinc reagent **39** to the CPA **10** proceeds in high yield with high γ-selectivity (Scheme 20). Almost perfect stereocontrol of the

Table 7. Carbocupration of Chiral CPA (Ref 61)

entry	CPA	RM[a]	electrophile	product	yield
1		$(CH_3)_2CuLi$	H^+	 (72% d.s.)	77%
2			H^+	 (96% d.s.)	84%
3		$(CH_3)_2CuLi$	H^+	 (96% d.s.)	89%
4		$(CH_3)_2CuLi$	H^+	 (99.1% d.s.)	65%
5		$(C_2H_5)_2CuMgBr$	H^+	 (97% d.s.)	80%
6		R_2CuLi	H^+	 (97% d.s.)	81%

[a] R = C_4H_9.

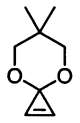
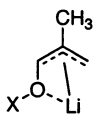
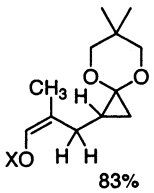
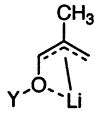
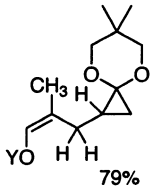
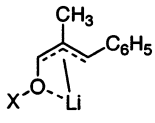
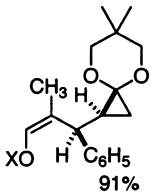
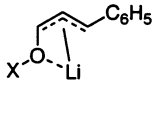
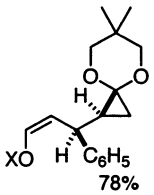
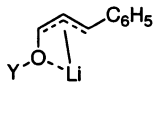
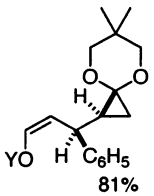
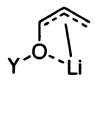
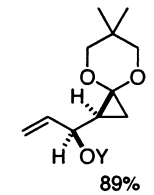
Scheme 18



allylzincation combined with a high regioselectivity results in the exclusive formation of one diastereomer (Table 9). Opposite to the case with lithium, the regioselectivity does not depend on the structure of the allylic metal reagent.

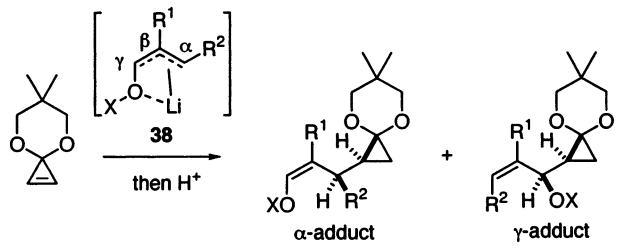
Addition of an allylic zinc reagent bearing an alkyl substituent also proceeds with a high regio- and diastereoselectivity to give a variety of substituted cyclopropanone acetals (Table 10). Installation of a bulky dummy ligand on the zinc atom is mandatory to achieve a high stereoselectivity (entries 1−3). The C_2 chiral CPA **40** undergoes stereoselective reaction

Table 8. Addition of Alkoxyallylic Lithium Reagent (Ref 62)

entry	CPA	allylic lithium[a]	product yield	ds regio (α:γ)
1			 83%	- 96:4
2			 79%	- 96:4
3			 91%	>97% ds >99:1
4			 78%	>97% ds 96:4
5			 81%	>97% ds 88:12
6			 89%	>97% ds 9:91

[a] X = methoxymethyl, Y = 4-methoxyphenyl. [b] Regioselectivity.

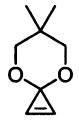
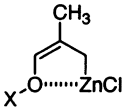
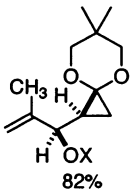
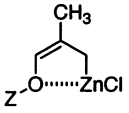
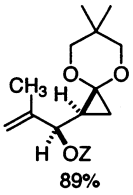
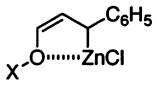
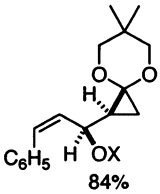
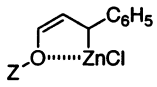
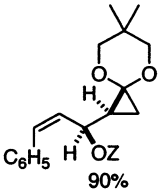
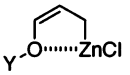
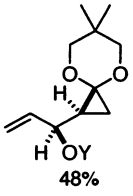
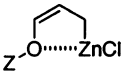
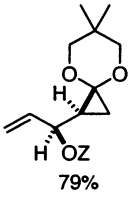
Scheme 19



R^1 = H, CH_3, C_6H_5; R^2 = H, CH_3, C_6H_5;
X = CH_2OCH_3, 4-methoxyphenyl

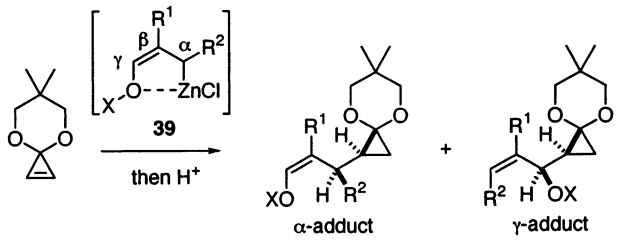
with various allylic zinc reagents to give optically active compounds (entries 4 and 5). The allylzincation of a CPA bearing a group 14 substituent gives a *trans*-2,3-disubstituted cyclopropanone acetal in high

Table 9. Addition of Alkoxyallylic Zinc Reagent to CPA (Ref 62)

entry	CPA	allylic zinc[a]	product yield	ds regio (α:γ)
1			 82%	>97% ds 6:94
2			 89%	>97% ds >3:97
3			 84%	>97% ds 20:80
4			 90%	>97% ds 18:82
5			 48%	>97% ds >3:97
6			 79%	>97% ds >3:97

[a] X = methoxymethyl, Y = 1-methyl-1-methoxymethyl, Z = 4-methoxyphenyl.

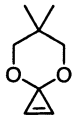
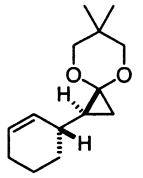
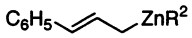
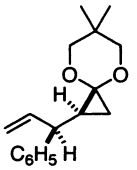
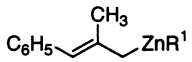
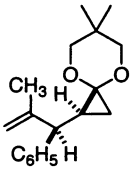
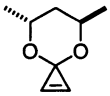
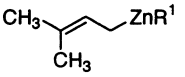
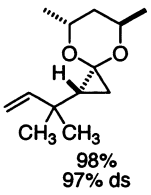
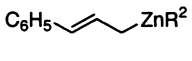
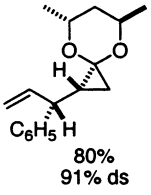
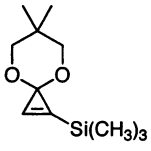
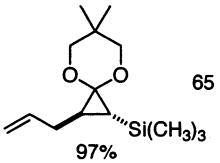
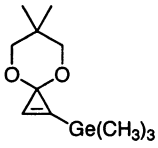
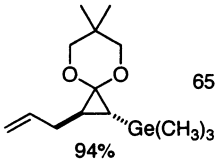
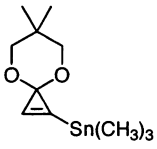
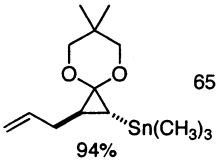
Scheme 20



R^1 = H, CH_3, C_6H_5; R^2 = H, CH_3, C_6H_5;
X = CH_2OCH_3, 4-methoxyphenyl, $CH(CH_3)OCH_3$

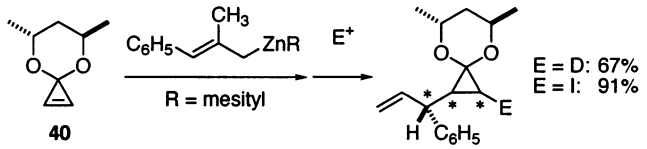
yield, owing to the directing effect of the group 14 substituent (entries 6−8).[63] As described above, an allylic zinc and an allylic lithium reagent also show a high reactivity toward the olefinic double bond of a CPA to give cyclopropylzinc and a lithium compound, respectively, which can be trapped with an electrophile. Addition of a variety of allylic zinc reagents to an optically active CPA proceeds in such

Table 10. Addition of an Allylic Zinc Reagent to CPA

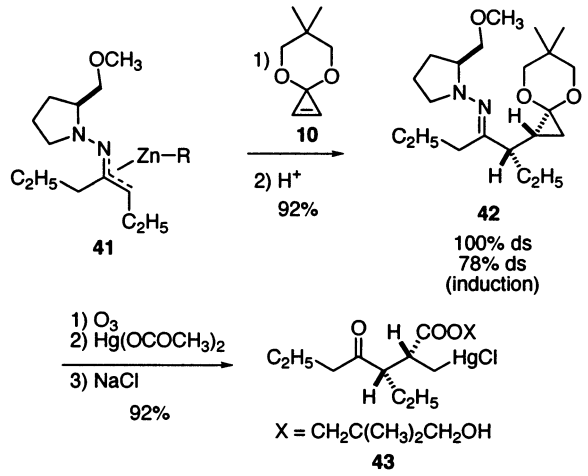
entry	CPA	allylic zinc[a]	product[b] yield ds	ref.
1			 85% 98.5% ds	62
2			 70% 96% ds	62
3			 79% 96% ds	62
4			 98% 97% ds	62
5			 80% 91% ds	62
6			 97%	65
7			 94%	65
8			 94%	65

[a] R^1 = $C(CH_3)_3$, R^2 = mesityl. [b] After hydrolysis.

Scheme 21



Scheme 22



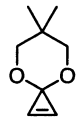
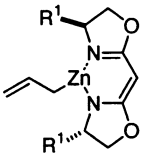
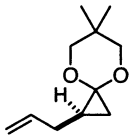
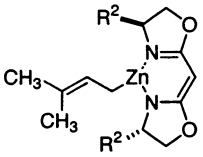
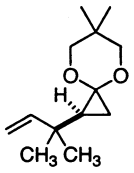
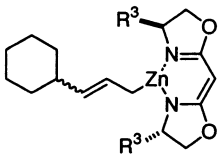
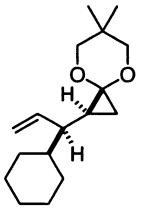
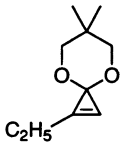
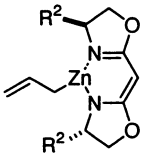
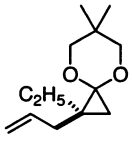
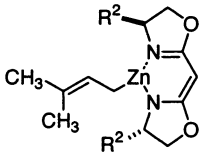
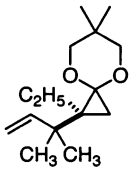
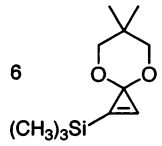
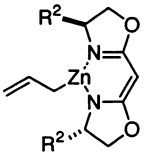
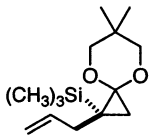
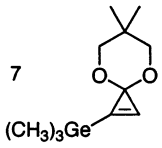
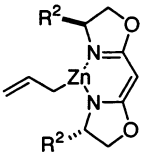
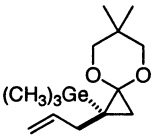
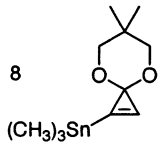
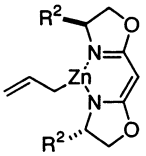
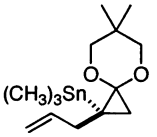
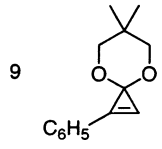
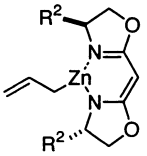
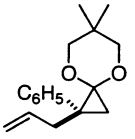
a manner that construction of three newly formed stereogenic centers can be controlled to within >90% net selectivity (Scheme 21).[64]

An allylic zinc reagent possessing a chiral anionic bisoxazoline ligand provided the first example of an enantioselective olefin carbometalation reaction that proceeds with a high enantioselectivity. The allylzincation reaction proceeds with an asymmetric induction of 95.0−99.5% ee (entries 1−3 in Table 11).[65,66] The allylzincation reaction of substituted CPAs possessing an ethyl or a phenyl substituent provides a method for the enantioselective construction of a quaternary carbon center with high regio- and stereocontrol (entries 4, 5, and 9). Substituted CPAs bearing a trialkylsilyl, trialkylgermyl, or a trialkylstannyl substituent react with an optically active allylzinc reagent to generate a quaternary chiral center with 97.0−99.8% ee (entries 6−8). The inherent regioselectivity of the allylzincation of group 14-substituted cyclopropenes is such that a 2,3-disubstituted cyclopropanone acetal is formed as the main product, owing to the anion stabilizing effect of these groups. Introduction of a chiral bulky ligand on the zinc atom overwhelms the inherent regioselectivity to give a 2,2-disubstituted cyclopropanone acetal, representing a unique example of ligand control on regioselectivity in an addition reaction.[67]

A zinc enolate or a zincated hydrazone reacts with cyclopropanone acetal in a highly diastereoselective manner to afford a β-cyclopropyl carbonyl derivative (Table 12).[68] The addition of the chiral zincated hydrazone **41** to the CPA **10** yields optically active product **42** in a high yield. The ring-opening reaction of the cyclopropane produces highly functionalized metal homoenolate species **42** in an optically active form (Scheme 22).

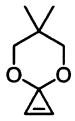
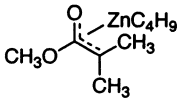
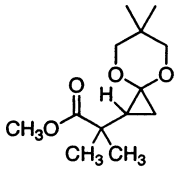
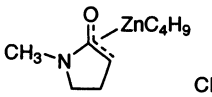
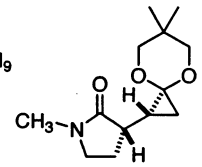
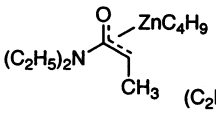
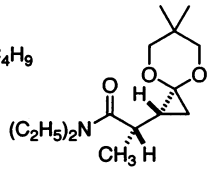
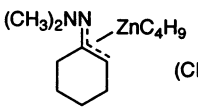
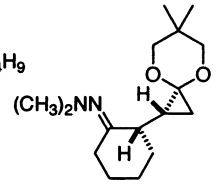
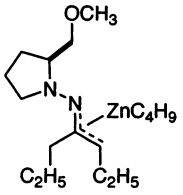
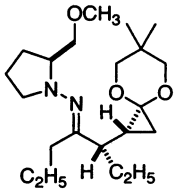
In the presence of a catalytic amount of an inorganic iron salt, a variety of Grignard reagents and organozinc reagents can add to the double bond of a CPA. Table 13 summarizes the addition and the electrophilic trapping of the resulting cyclopropyl-

Table 11. Addition of a Chiral Allylic Zinc Reagent to CPA (Refs 65 and 66)

entry	CPA	allylic zinc[a]	major product[b]	yield ee, ds [ref.]
1				89% >98% ee [63, 64]
2				96% 98% ee [63, 64]
3				58% 97% ee 81% ds [63]
3				95% >98% ee [65]
5				93% >99.5% ee [65]
6				83% 97.8% ee [65]
7				96% 99.6% ee [65]
8				83% 99.8% ee [65]
9				98% >98% ee [65]

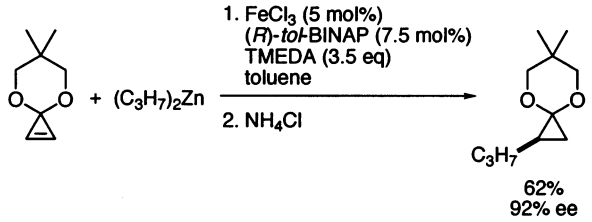
[a] $R^1 = CH(CH_3)_3$, $R^2 = C_6H_5$, $R^3 = C(CH_3)_3$. [b] After hydrolysis.

Table 12. Addition of Zinc Enolate and Zincated Hydrazone (Ref 68)

entry	CPA	zinc reagent	major product[a]	yield[b] ds[c]
1				97% -
2				82% 96% ds
3				64% 87% ds
4				100% 96% ds
5				92% 100% ds (78% ds)[d]

[a] After hydrolysis. [b] Yield is based on CPA. [c] Diastereoselectivity as to the newly formed carbon−carbon bond. [d] The value refers to the selectivity relative to the chiral auxiliary.

Scheme 23

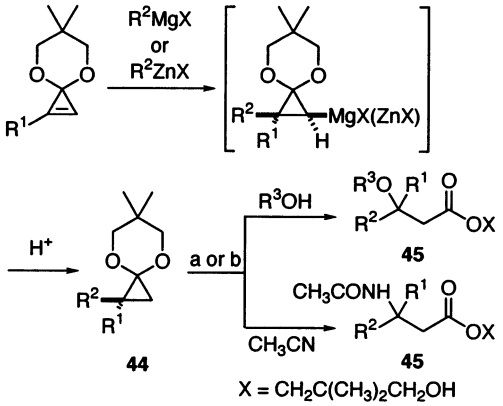


(*R*)-*tol*-BINAP = (*R*)-2,2'-bis[bis(4-methylphenyl)phosphino]-1,1'-binaphtyl

metal intermediate. The reaction in the presence of optically active tol-BINAP provided the first example of catalytic enantioselective C−C bond formation by iron catalysis. This reaction takes place with an enantiomeric excess as high as 92% ee (Scheme 23).[69]

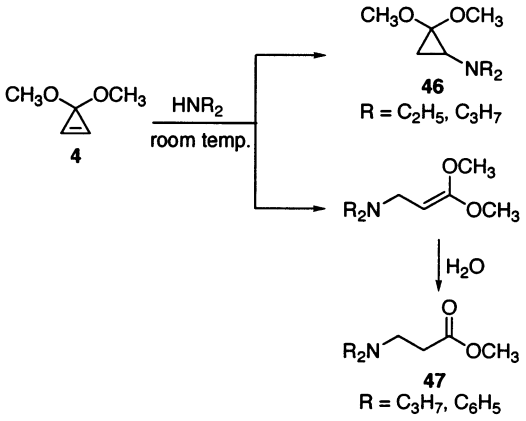
The oxidative cleavage of the cyclopropane ring of the carbometalation product **44** in the presence of a nucleophile provides a variety of propionate derivatives **45** (Scheme 24 and Table 14). An equimolar amount of MnO_2 or PbO_2 affects the ring-opening reaction of the substituted cyclopropanone acetal under acidic conditions.[70]

Scheme 24[a]

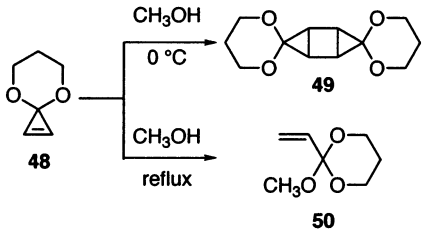


[a] MnO_2/CF_3SO_3H; (b) PbO_2/CF_3SO_3H.

Scheme 25



Scheme 26

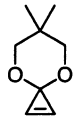
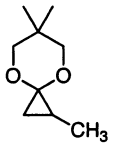
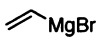
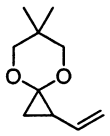
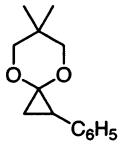
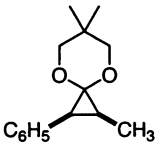
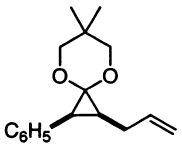
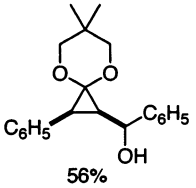
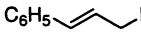
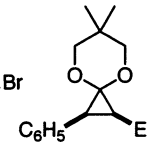
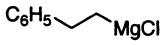
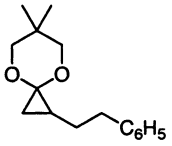
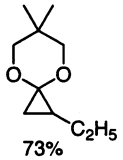
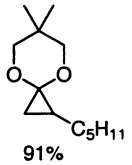
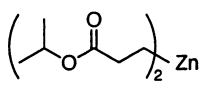
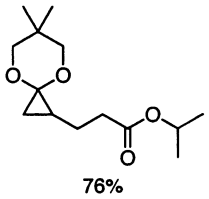


2. Addition of Neutral Nucleophiles

A neutral nucleophile, such as an amine and a radical, can add to the strained double bond of a CPA. Butler et al. reported that the addition of a secondary amine to cyclopropenone dimethyl acetal **4** gives an aminocyclopropane compound or a β-alanine derivative, depending on the structure of the amine (Scheme 25).[71] This stands in marked contrast to the reaction of an alcohol, which gives the [2 + 2] dimer **49** of CPA **48** at 0 °C or an ortho ester of acrolein **50** under reflux conditions (Scheme 26).[34]

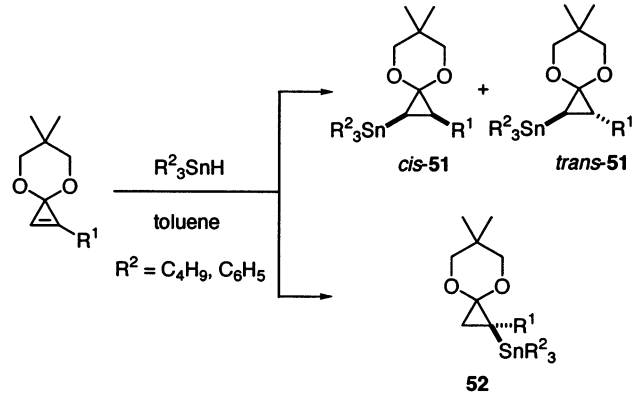
The hydrostannation of a CPA with a trialkyltin or triaryltin hydride readily takes place in the presence of a radical initiator, such as AIBN or triethylborane, to afford the stannylcyclopropanone acetals **51** or **52** in high yield (Scheme 27). While the reaction is generally conducted using a radical initiator under ordinary thermal conditions, the reaction can also be driven sonochemically.[72] As summarized in Table 15, the radical addition to a substituted CPA takes place regio- and stereoselectively, regardless

Table 13. Iron-Catalyzed Carbomagnesation and Carbozincation of CPA (Ref 69)

entry	CPA	R-metal	electrophile	product[a] yield
1		CH_3MgBr	H^+	 66%
2			H^+	 75%
4		C_6H_5MgBr	H^+	 96%
5			CH_3I	 90%
6				 85%
7			C_6H_5CHO	 56%
8				 75%
9			H^+	 85%
10		$(C_2H_5)_2Zn$	H^+	 73%
11		$(C_5H_{11})_2Zn$	H^+	 91%
12			H^+	 76%

[a] E = *trans*-cinnamyl.

Scheme 27



of the substituent of the CPA, to afford a *cis* disubstituted cyclopropanone acetal (**51** or **52**).

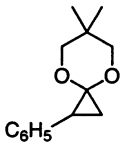
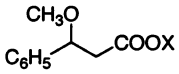
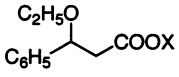
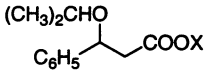
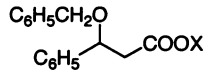
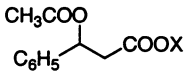
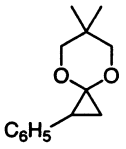
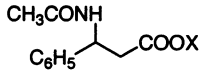
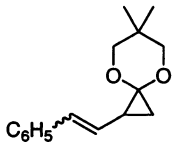
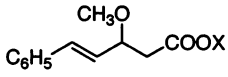
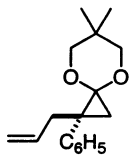
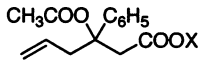
Comparison of the reactivity of the strained double bond with that of acetylene for an intermolecular competitive experiment showed that the tin radical reacted with the strained double bond rather than with an acetylenic triple bond (**53** vs **54**, Scheme 28).[73] On the other hand, an intramolecular competitive experiment using CPA **55** revealed that the strained double bond and acetylenic triple bond are equally reactive toward the triphenylstannyl radical under kinetically controlled conditions, indicating that the radical addition to a CPA (path a) is thermodynamically more favorable than that to an alkyne (path b, Scheme 29).

The intermolecular addition of an electrophilic alkyl radical to CPA **10** proceeds under photochemical conditions. Thus, the visible-light irradiation (from a 250-W Xenofot sunlamp) of a benzene solution containing a mixture of a xanthate and a CPA gives the expected adduct **56** in a 46% yield (Scheme 30).[74]

3. Diels–Alder Reaction

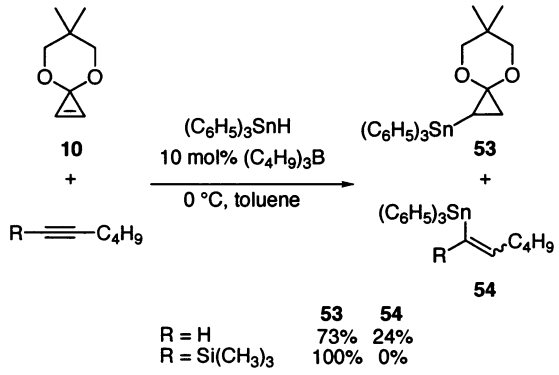
Butler and co-workers described the first example of the Diels−Alder reaction of cyclopropenone di-

Table 14. Oxidative Ring-Opening Reactions of Substituted Cyclopropanone Acetals (Ref 70)

entry	intermediate	nucleophile	product[a]	yield
1[b] 2[c]		CH_3OH		80% 71%
3[b]		C_2H_5OH		83%
4[b]		$(CH_3)_2CHOH$		81%
5[b]		$C_6H_5CH_2OH$		78%
6[d]		CH_3COOH		84%
7[b] 8[c]		CH_3CN		77% 78%
9[c]		CH_3OH		63%
10[d]		CH_3COOH		67%

[a] X = $CH_2C(CH_3)_2CH_2OH$. [b] PbO_2/CF_3SO_3H. [c] MnO_2/CF_3SO_3H. [d] PbO_2/none.

Scheme 28

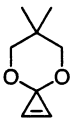
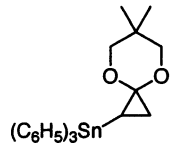
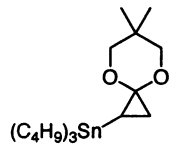
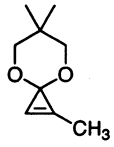
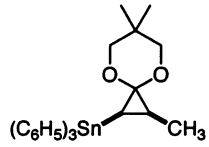
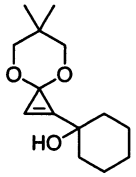
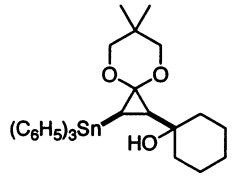
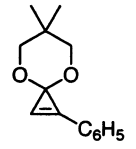
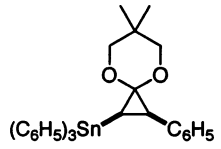
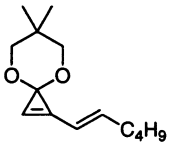
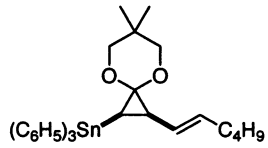
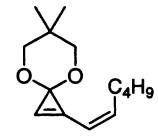
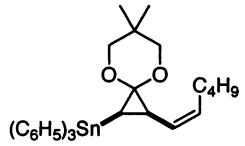
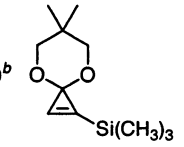
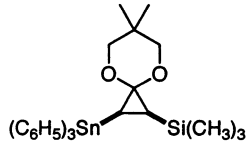


methylacetal **4** with 1,3-diphenylisobenzofuran,[26] and, thereafter, with 1,3-butadiene, isoprene, 2,3-dimethyl-1,3-dimethyl-1,3-butadiene, and 1-methoxy-1,3-butadiene (entries 1−4 in Table 16).[71] Because of the thermal instability of cyclopropenone dimethyl acetal, all the reactions were carried out at ambient temperature and so required a prolonged reaction period of from 9 days to 4 weeks.

In 1986, Boger et al. reported the [2 + 4] cycloaddition reactions of cyclic CPA **48** with various electron-deficient, electron-rich, and neutral dienes and illustrated the feasibility of normal and inverse electron-demand Diels−Alder reactions. The results are summarized in Table 16.

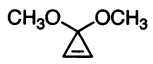
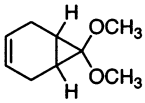
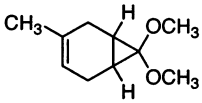
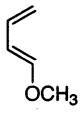
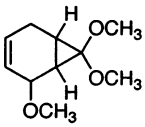
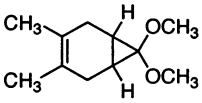
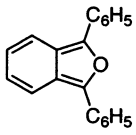
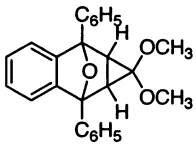
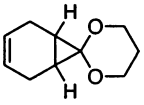
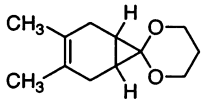
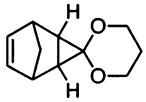
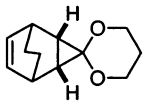
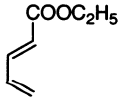
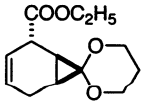
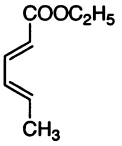
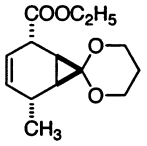
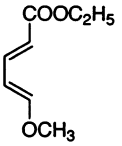
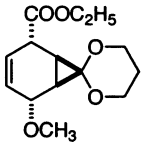
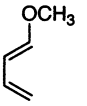
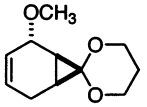
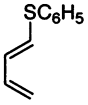
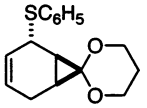
Neutral dienes were found to participate in productive [2 + 4] cycloaddition reactions with neat CPAs under thermal conditions at 25−35 °C and in methylene chloride, benzene, or acetonitrile (see entries 6−10 and 13−15) or were pressure-promoted (at 0.6 GPa, neat or in methylene chloride at 25 °C; see entries 11, 12, and 16) at a rate that was

Table 15. Tin Radical Addition (Ref 73)

entry	CPA	product	yield (*cis*:*trans*) [51:52]
1[a] 2[b] 3[c]			99% 100% 83%
4[b]			64%
5[a]			90% [7:3]
6[b]			99% (87:13) [>99:1]
7[b]			96% (85:15) [>98:2]
8[b]			68% [>98:2]
9[b]			92% (88:12) [>98:2]
10[b]			100% (95:5) [>99:1]

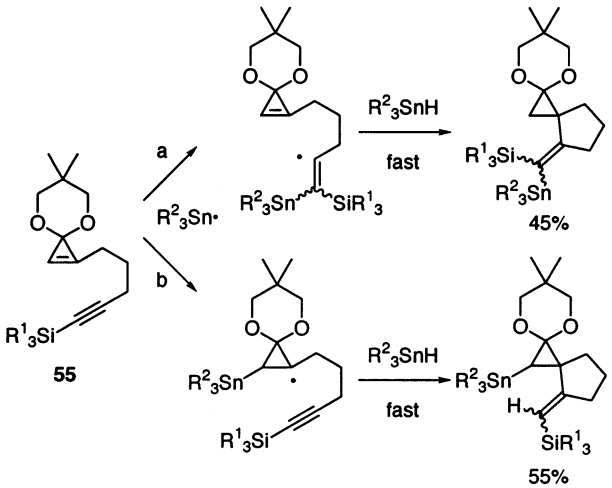
[a] 10 mol% AIBN. [b] 10 mol% $(C_4H_9)_3B$ or $(C_2H_5)_3B$. [c] Ultrasound irradiation.

Table 16. Diels–Alder Reaction of CPA with Diene

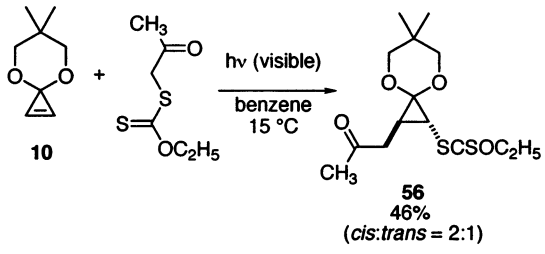
entry	CPA	substrate	product[a]	yield [ref.]
1[b]				90% [69]
2[b]				93% [69]
3[b]				41% [69]
4[b]				30% [69]
5[c]				30% [25]
6[b]				69% [74]
7[d]				57%
8[e]				44%
9[f]				28%
10[g]				23%
11[h]				83%
12[j]				96% [74]
13[d]				57%
14[k]				48% [74]
15[d]				57% [74]
			end:exo = 1:1	
16[i]				25% [74]
17[d] 18[j]				65% 56% [74]
19[d]				46%
20[h]				45%
21[k]				70%
22[l]				62%
23[m]				41% [74]
24[d]				80% [74]
25[d]				72%
26[n]				56% [74]
27[d]				33% [74]

[a] The stereochemistry of the product was not detemined for entries 3 and 5. [b] Room temp. neat. [c] Room temp. CCl_4. [d] 25 °C, neat. [e] 25 °C, CH_2Cl_2. [f] 25 °C, benzene. [g] 25 °C, CH_3CN. [h] 25 °C, 0.6 GPa, CH_2Cl_2. [i] 25 °C, 0.6 GPa, neat. [j] 75 °C, benzene. [k] 35 °C, neat. [l] 35 °C, heptane. [m] 35 °C, benzene. [n] 80 °C, benzene.

Scheme 29



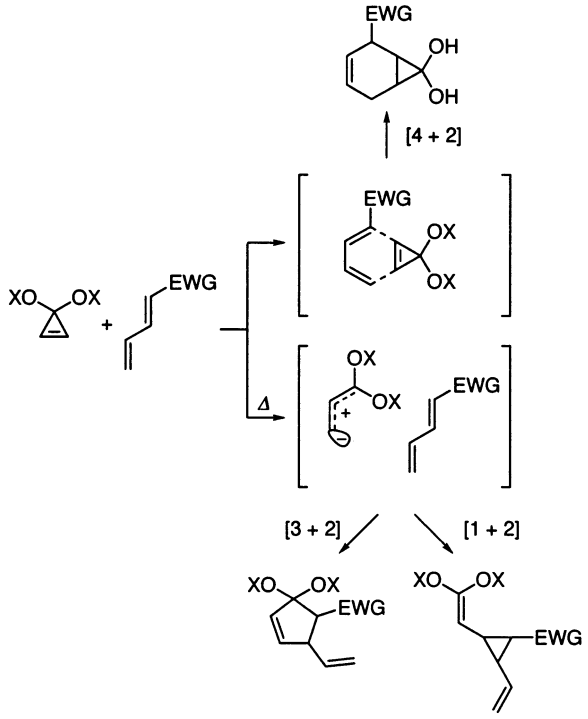
Scheme 30



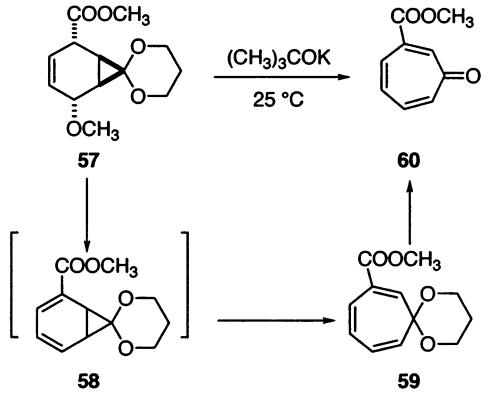
qualitatively slower than the rate exhibited by the electron-rich or electron-deficient dienes. The Diels–Alder reactions of **48** were found to proceed at a much faster rate than that of compound **4** reported previously by Butler.

The reaction with an electron-deficient diene proceeded smoothly under mild conditions (25–35 °C,

Scheme 31



Scheme 32

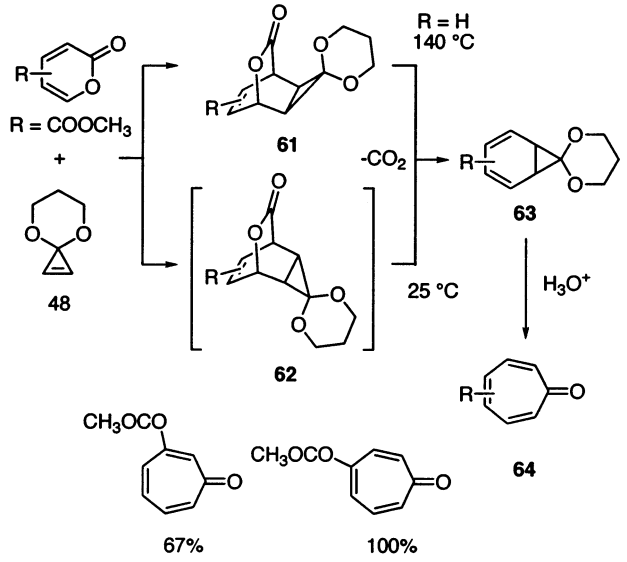


neat) to provide the expected [2 + 4] cycloaddition product. Similarly, the reaction of 1-methoxy-1,3-butadiene with a CPA (25 °C/neat or 80 °C/benzene) provided the [2 + 4] cycloaddition product at a rate comparable to that observed with the electron-deficient dienes.

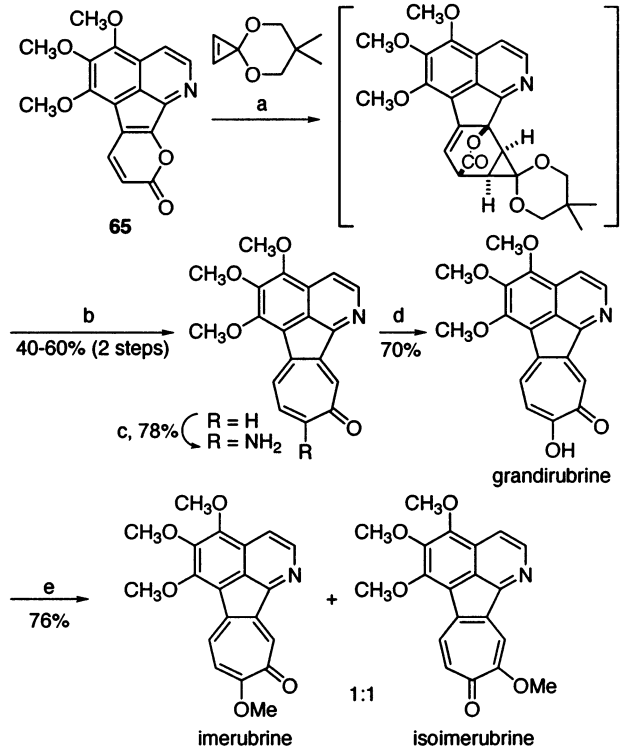
In the thermal reaction of CPA **48** with methyl 2,4-pentadienoate, three a priori thermal reaction pathways are possible: (i) [1 + 2], (ii) [3 + 2], and (iii) [2 + 4] cycloaddition pathways (Scheme 31). Experimentally, the [2 + 4] cycloadduct has been isolated as the exclusive product. As detailed in the following section, the course of the thermal reaction of a CPA with a diene depends heavily on the nature of the diene.

The above-mentioned inverse electron-demand Diels–Alder reaction of CPA provides a synthetic route for substituted tropones (Scheme 32).[75,76] Cyclic electron-deficient enophiles, as well as the acyclic enophiles in Table 16, react with CPA in good yield (47–70%) to afford the corresponding Diels–Alder adduct. Treatment of the cycloadduct between **57** and

Scheme 33



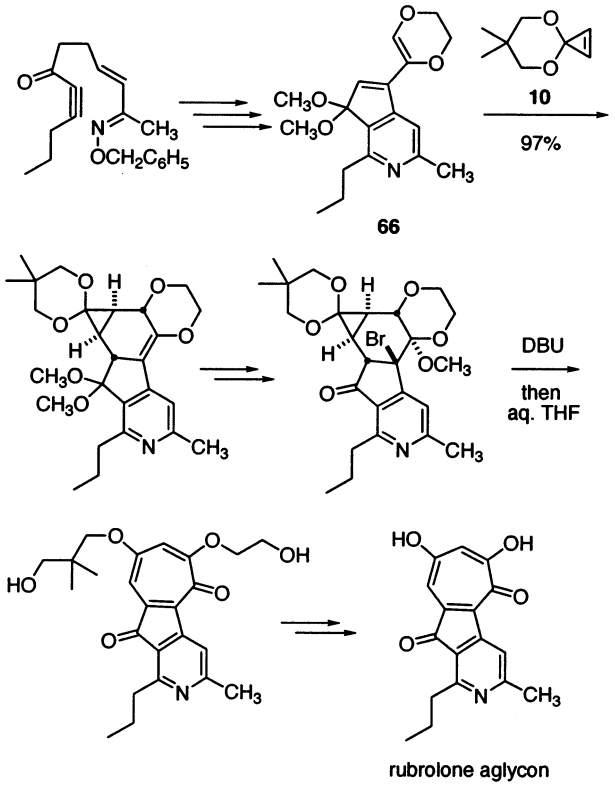
Scheme 34[a]



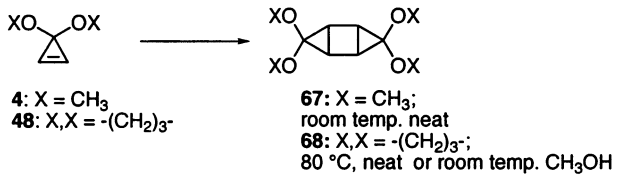
[a] (a) 1.2 GPa, $CHCl_3$/pyridine; (b) HCl/$CH_3CO_2C_2H_5$; (c) H_2N-NH_2; (d) KOH/CH_3OH; (e) $(CH_3)_3SiCHN_2$.

4-methoxy-1,3-butadiene-1-carboxylate with *t*-BuOK produces a norcaradiene intermediate **58**, which can be converted to cycloheptatrienone **60** upon loss of CH_3OH and thermal rearrangement followed by acidic hydrolysis. The reaction of α-pyrone with **48** under high pressure gives a mixture of the *exo*- and *endo*-cycloadduct in a high yield. The *endo* adduct **62** undergoes cheletropic loss of carbon dioxide at room temperature to give norcaradiene intermediate **63**, whereas the *exo* isomer **61** requires a higher temperature (140 °C) for this transformation to occur. Hydrolysis of the acetal intermediate **63** during purification on silica gel gives the tropone **64** in good yield (Scheme 33).

Scheme 35



Scheme 36



The Diels−Alder reaction between CPA and α-pyrone was applied to a concise total synthesis of grandirubrine and related compounds, where the pressure-promoted [2 + 4] cycloaddition between CPA **10** and **65** followed by the release of CO_2 gave the corresponding tropone intermediate in good yield (Scheme 34).[77] Boger also achieved an efficient total synthesis of the rubrolone aglycon, which represents the unique azuleno[2,3-*c*]pyridine-2,5,13-trione structure, based on a key Diels−Alder reaction between CPA **10** and the diene compound **66** (Scheme 35).[78,79]

C. Oligomerization and Polymerization

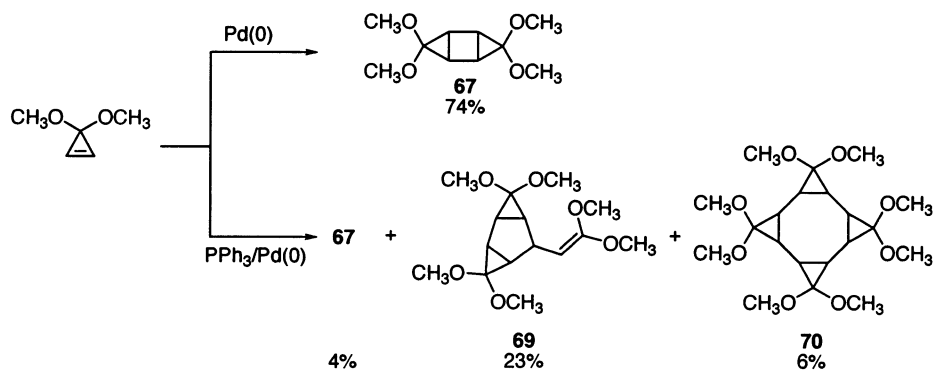
Dimerization of CPA **4** proceeds at ambient temperature to afford 3,3,6,6-tetramethoxytricyclo-[3.1.0.0^{2,4}]hexane **67** in high yield under thermal conditions, while cyclic acetal **48** dimerizes to give **68** at an elevated temperature (80 °C) or at ambient temperature in methanol (Scheme 36).[26,34] Catalysis by a transition metal, such as palladium or nickel, alters the reaction course to provide a variety of cyclic oligomers and adducts. Thus, $Pd(dba)_2$, a phosphine-free Pd catalyst, gives the CPA dimer **67** as the major product in a 74% yield, whereas the use of $Pd(dba)_2$ in the presence of triphenylphosphine affords the trimer **69** in 23% yield, with the formation of the dimer **67** (4%) and the tetramer **70** (6%) as byproducts (Scheme 37).[80] Thermal conversion of 3,3,6,6-tetramethoxytricyclo[3.1.0.0^{2,4}]hexane **67** to quinone diacetal derivative **71** can occur (Scheme 38).

The CPAs can undergo ring-opening polymerization under cationic conditions.[81,82] Among a variety of initiators that have been examined, bromine has been found to be a good initiator and gives polymers with M_N values of about 10 000. On the other hand, copolymerization of a CPA with a variety of olefins, such as acrylonitrile, styrene, *N*-vinylpyrrolidone, or 2-vinylpyridine, proceeds via radical initiation.[83] The existence of a charge-transfer complex between the CPA **10** and *N*-vinylpyrrolidone and its participation in copolymerization was suggested by Butler, wherein the 2:1 copolymer **72** forms, irrespective of the initial monomer feed ratio (Scheme 39).[84]

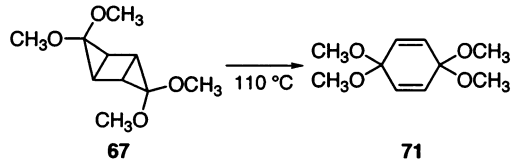
D. Coordination and Ring Cleavage with a Transition Metal Complex

The strained double bond of CPA readily coordinates to a variety of transition metal complexes. The formation of an η^2-olefin complex between the low-valent titanium complex **73** and the CPA **48** takes place via a ligand exchange reaction, indicating a high coordination ability of the olefinic double bond of CPAs (Scheme 40).[85] Reaction of cobalt chloride complex **74** with CPA **4** gives the cyclopropene complex **75** in 78% yield and vinylcarbene complex **76** side product, which was not fully characterized (Scheme 41).[86] The reaction of tungsten imido complex **77** with the CPA **48** in ether gives η^2-olefin complex **78** in fair to excellent yield, depending on the structure of the phosphine ligand and the imido

Scheme 37

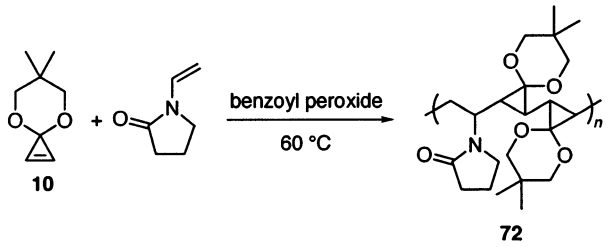


Scheme 38



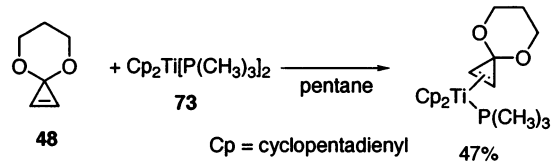
67 71

Scheme 39



10 72

Scheme 40

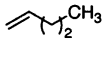
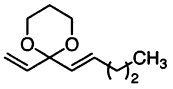
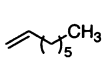
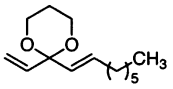
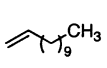
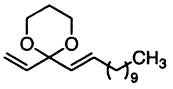
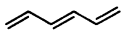
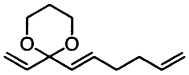
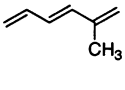
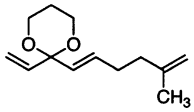
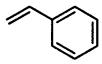
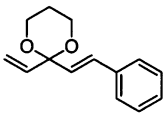
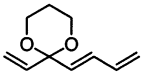
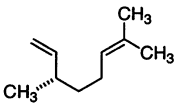
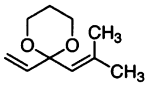
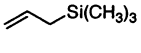
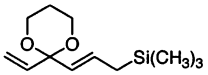
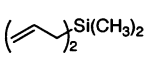
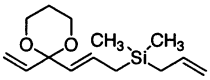
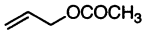
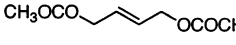


48

ligand (Scheme 42).[87] The olefin complexes that form with the trimethyl phosphite ligands undergo partial decomposition to a vinylalkylidene complex in CD_2Cl_2 solution at room temperature, as described in section V.B.

The ring-opening-metathesis reaction of a CPA with a terminal alkene takes place in the presence of a catalytic amount of Grubbs' catalyst $[Cl_2(Cy_3P)_2Ru{=}CHPh]$ to afford a variety of 1,4-divinyl ketone acetals **79** in good yield (Scheme 43 and Table 17). A selective cross-metathesis reaction dominates when a slight excess of the terminal olefin substrate is used, and no competitive ring-opening polymerization is observed.[88]

Table 17. Ring-Opening Metathesis of CPA (Ref 88)

entry	CPA	substrate	product	yield (*E*:*Z*)
1[a]				83% (87:13)
2[b]				79% (86:14)
3[b]				69% (82:18)
4[b]				32% (86:14)
5[b]				76% (85:15)
6[b]				76% (85:15)
7[c]				86% (96:4)
8[b]				52%
9[a]				86% (95:5)
10[a]				86% (95:5)
11[a]				78%

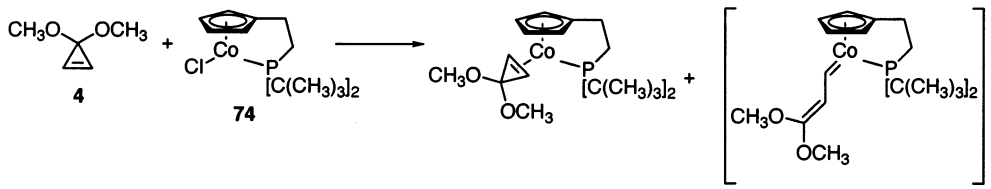
[a] Room temp. [b] 80 °C. [c] 0 °C.

V. Reactions Resulting in C–C σ-Bond Cleavage

A. Thermal Reactions

There have been reports of a number of reactions of CPAs that result in the cleavage of the strained C−C σ-bond under thermal conditions. This reaction generates two isomeric vinylcarbene intermediates (Scheme 44), depending on the regioselectivity of the C−C bond cleavage (i.e., bond a or b). The bond cleavage initially produces *syn* isomers that may isomerize to the corresponding *anti* isomers. A theoretical study at the MP2 perturbation theory level shows that the vinylcarbene intermediate (where R^1, R^2, and R^3 = H) is the most stable in its π-delocalized singlet vinylcarbene form.[6,89] The reactivity profiles reported to date are consistent with such a π-delocalized singlet species that can react either as a 1,1-dipole or as a 1,3-dipole. The following sections summarize the insertion, cheletropic [1 + 2] cycloaddition, [3 + 2] cycloaddition, and [3 + 4] cycloaddition reactions under thermal conditions.

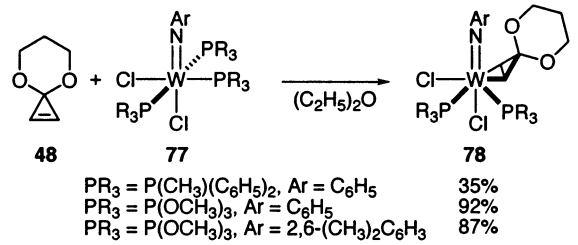
Scheme 41



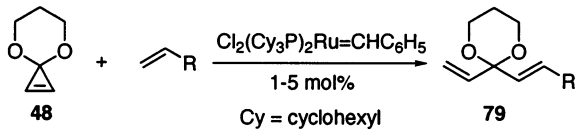
4 74 75 76

93% (5:1) not completely characterized

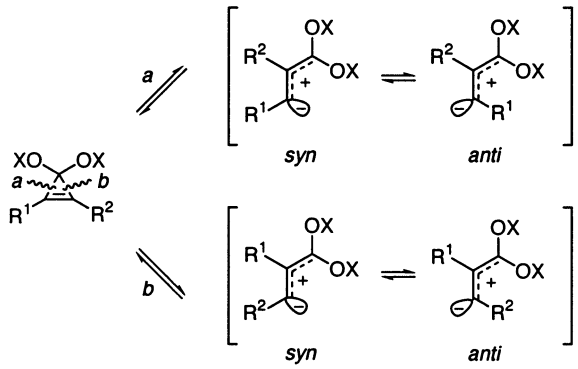
Scheme 42



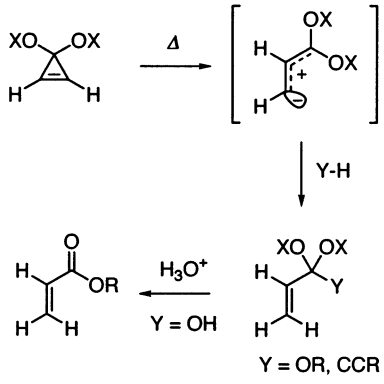
Scheme 43



Scheme 44



Scheme 45

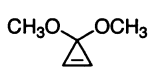
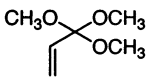
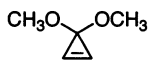
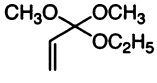
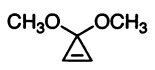
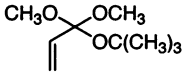
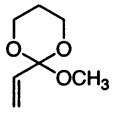
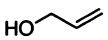
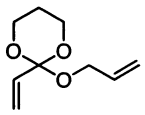
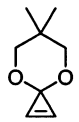
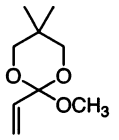
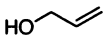
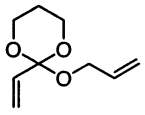
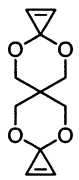
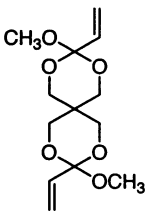
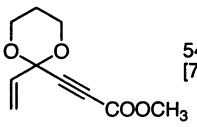


1. Insertion Reactions

An intermolecular insertion reaction of the vinylcarbene intermediate has been reported for an unsubstituted CPA (Scheme 45). The insertion reactions of the vinylcarbene intermediate to an acidic O−H or C−H bond are summarized in Table 18. The insertion reaction to an O−H bond of an alcohol produces the corresponding orthoacrylate (entries 1−6),[34] and the insertion reaction to an alkynyl C−H bond produces a ketoalkyne (entry 7).[75]

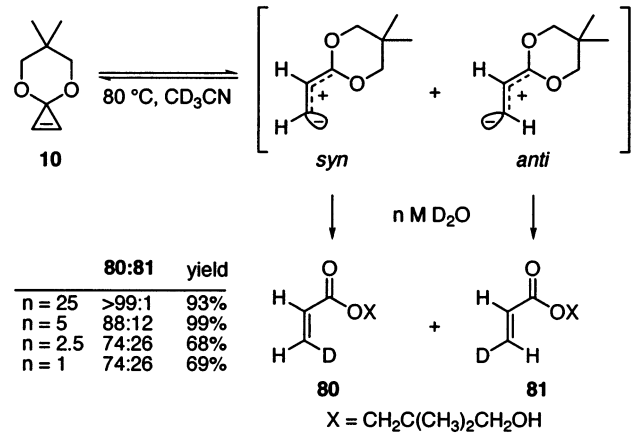
The insertion reaction of the vinylcarbene intermediate with water has been studied in detail, which has provided experimental information on the nature of the reactive intermediates.[90] The reaction with water gives an acrylate ester after hydrolysis of the thermodynamically labile orthoacrylate (Scheme 45, Y = OH). The reaction of unsubstituted CPA **10** with excess D_2O (25 M D_2O in CH_3CN) proceeds quantitatively to give the monodeuterated product **80** in a completely regioselective and *Z*-stereoselective manner via the *syn*-vinylcarbene intermediate (Scheme 46). When the D_2O concentration was reduced to 5 and 1 M, the stereospecificity decreased to 88% and to 74%, respectively. The loss of the stereospecificity is due to isomerization of the *syn*-vinylcarbene to form the geometrical *anti* isomer before the reaction

Table 18. Insertion Reaction of the Vinylcarbene Intermediate with Alcohol and Alkyne

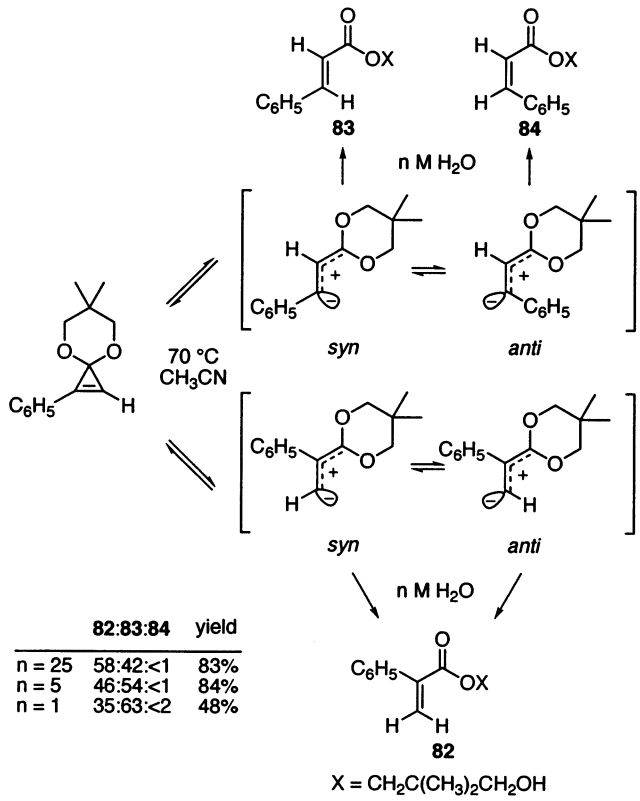
entry	CPA	substrate	product	yield [ref.]
1[a]		CH_3OH		73% [33]
2[a]		C_2H_5OH		30% [33]
3[a]		$(CH_3)_3COH$		68% [33]
4[b]		CH_3OH		65% [33]
5[c]				28% [33]
6[b]		CH_3OH		59% [33]
7[c]				40% [33]
8[b]		CH_3OH		55% [33]
9[d]				54% [73]

[a] 0 °C, CH_3OH. [b] Reflux, CH_3OH. [c] Room temp. CH_2Cl_2. [d] 80 °C, benzene.

Scheme 46



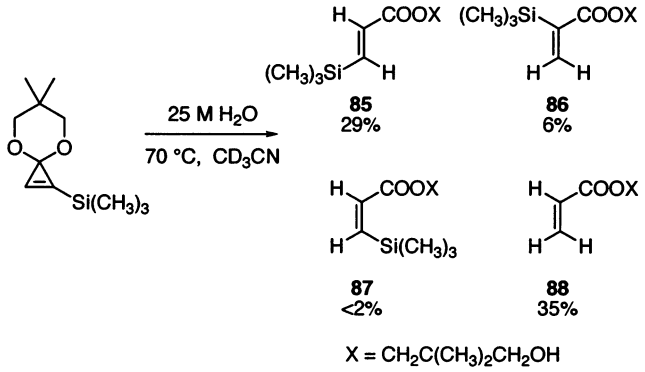
Scheme 47



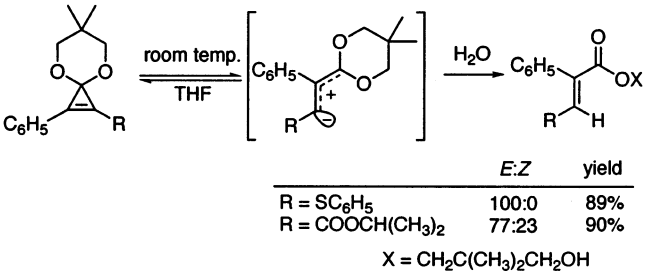
with water, which in turn suggests that the 25 M D_2O kinetically quenches the carbene that was initially generated.

An alkyl substituent retards the ring-cleavage reaction, and thus, the ethyl-substituted CPA does not react at 70 °C, and at 100 °C it gives a complex mixture.[90] On the other hand, the phenyl-substituted CPA generates the vinylcarbene more readily. In the kinetic quenching conditions of 25 M D_2O, the reaction of phenyl-substituted CPA gives a 58:42 isomeric mixture of **82** and **83** in an 83% yield (Scheme 47). The isomer ratio changes as the water concentration is reduced. The hydrolysis of a silyl-substituted CPA at 70 °C in 25 M H_2O is a fast reaction but is complicated by desilylation (Scheme 48). Among the expected ring-opening products that account for ca. 35% of all the products, the terminal silyl-substituted *E*-isomer **85** predominates over isomer **86**. With a

Scheme 48



Scheme 49



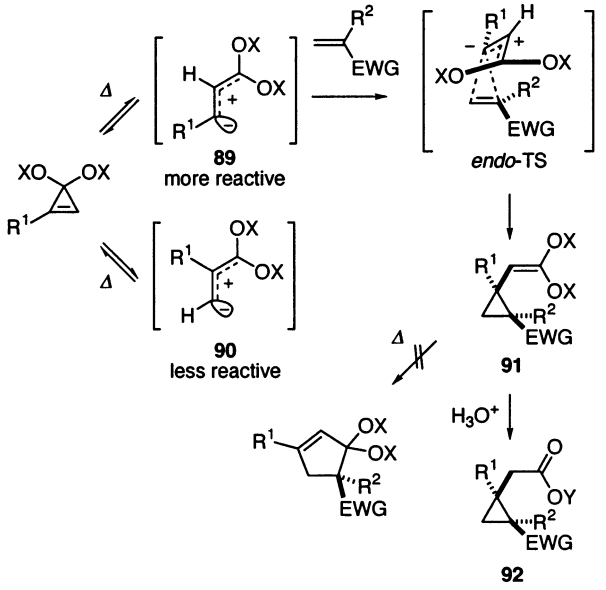
substituent of a more pronounced electron-withdrawing character, such as SPh and COOR, the carbene is generated, and this reacts with water at room temperature in a completely regioselective manner to give predominantly *E*-isomers (Scheme 49).

The hydration experiments provide useful experimental information on the stereochemistry of the cyclopropene-to-vinylcarbene conversion reaction. The reaction in a high water concentration indicates that the ring-opening reaction takes place by retaining the olefin geometry, because the carbene is protonated immediately as it forms. The loss of stereochemistry under low water concentration indicates a relatively low barrier for stereochemical isomerization of the singlet vinylcarbene (Scheme 44). The *syn*- and *anti*-vinylcarbene isomers are of nearly equal energy, as determined by single determinant ab initio calculations.[6] A CPA that bears a group having a strong electron-withdrawing character reacts via a single regioisomeric carbene (Scheme 49), whereas a CPA that bears a group with a less pronounced electronic character exhibits a less defined regiochemistry (Schemes 46−48).

2. [1 + 2] Cycloaddition Reactions

The singlet π-delocalized vinylcarbene intermediate exhibits a nucleophilic carbene character and participates in a [1 + 2] cycloaddition reaction with an electron-deficient olefin.[6,75,91,92] Thus, from the initial studies of Boger, and following on from the studies of Nakamura defining the synthetic utility of CPAs, these were shown to serve as a viable source of substituted carbenes that undergo stereoselective [1 + 2] cycloaddition reactions with olefins bearing a single electron-withdrawing group. The reaction produces cyclopropyl ketene acetal **89**, which upon hydrolysis produces cyclopropane carboxylic ester **90**

Scheme 50

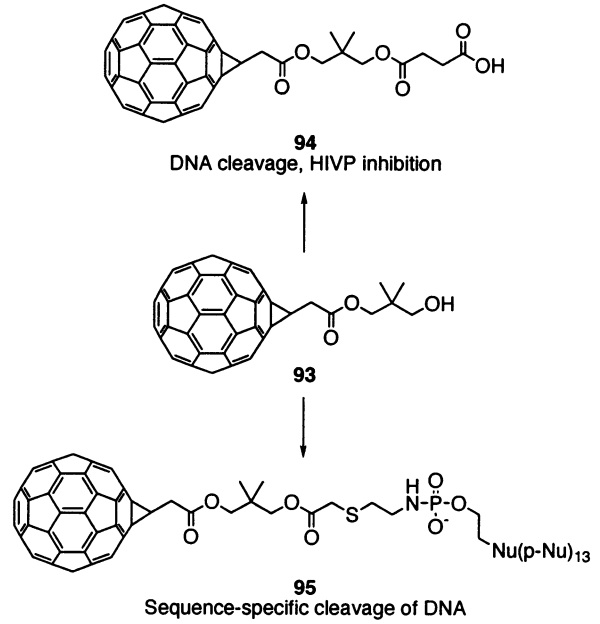


(Scheme 50). The ketene acetal is thermally stable and does not undergo vinylcyclopropane rearrangement.

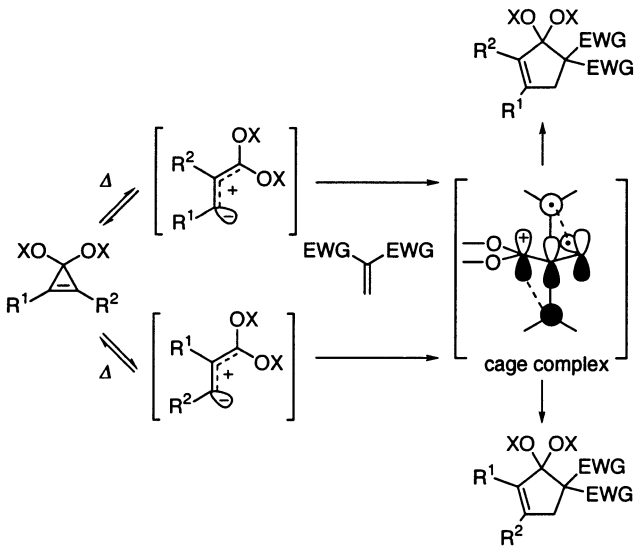
The results of the [1 + 2] cycloaddition reactions are summarized in Table 19. The [1 + 2] reaction affords the thermodynamically less stable *cis*-substituted cyclopropane. Although the rate of the reaction is virtually unaffected, the stereoselectivity decreases with increasing solvent polarity (entries 4−6 and 9−12). This observation suggests that the *cis*-selectivity is the result of the stabilizing interaction between the substrate's electron-withdrawing substituent and the cationic end of the reacting π-delocalized singlet vinylcarbene (Scheme 50). This *endo* effect is consistent with a stable transition state for a nonlinear, cheletropic [$_{\pi}2_{s} + _{\omega}2_{a}$] cycloaddition.[6] The substituent, X, of the acetal moiety affects the stereoselectivity of the cycloaddition. A higher stereoselectivity is shown by 1,3-propanediyl acetal than diethyl and 2,2-dimethyl-1,3-propanediyl acetals (entries 3, 18, and 22). This effect of the *gem*-dimethyl group on the 2,2-dimethyl-1,3-propanediyl acetal is consistent with the *endo* transition state (Scheme 50), wherein the acetal group is located in a sterically encumbered position.

The reaction of substituted CPAs proceeds regioselectively (>94%) via the regioisomer **89** (Scheme 50) to give **92** as the sole product in favor of the C−C bond cleavage at the substituted terminal (entries 3, 17−21, 24, and 25).[92] On the other hand, in the presence of excess olefin, the reaction of ethyl-substituted CPA produces a regioisomeric mixture of products (~7:3). It is suggested that the observed regiochemistry of the [1 + 2] cycloaddition reflects the kinetic reactivities of **89** and **90**. The preferential [1 + 2] cycloaddition of ethyl-substituted CPA via isomer **89** stands in contrast to the [3 + 2] cycloaddition of the same cyclopropene, which proceeds predominantly via isomer **90** (see section V.A.3), suggesting a significant mechanistic difference between the [1 + 2] and the [3 + 2] cycloaddition reactions.

Scheme 51



Scheme 52

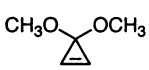
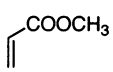
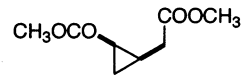
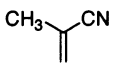
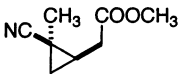
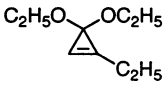
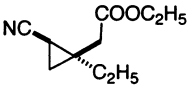
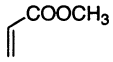
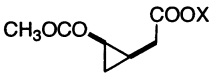
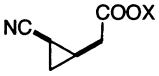
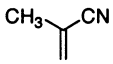
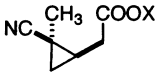
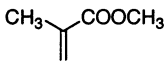
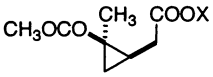
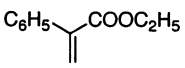
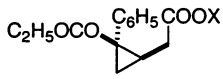
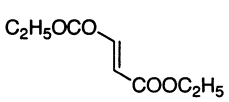
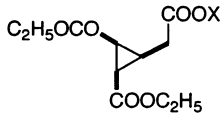
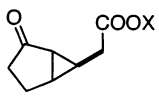
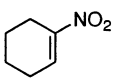
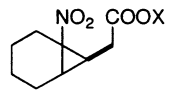


The [1 + 2] cycloaddition reaction of CPA takes place with C_{60} to afford a methanofullerene (entry 23 in Table 19).[93,94] Interestingly, the [3 + 2] cycloaddition reaction takes place predominately when the reaction is carried out above 140 °C (see section V.A.3). Water-soluble fullerenes have been synthesized by conversion of the methanofullerene **93** to carboxylic acid **94** and oligonucleotide conjugate **95** (Scheme 51). The carboxylic acid **94** exhibits photoinduced DNA cleavage and enzyme inhibition activity.[95,96] This compound has been tested for acute toxicity and shown to be nontoxic (LD_{50} > 500 mg/kg).[97] The oligonucleotide conjugate **95**, synthesized from **93**, specifically cleaves a DNA sequence upon complexation with its complementary double-strand DNA.[98]

3. [3 + 2] Cycloaddition Reactions with Olefins

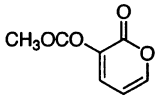
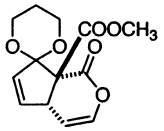
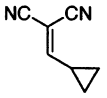
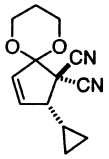
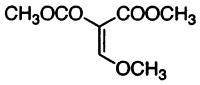
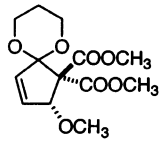
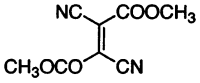
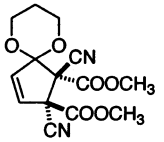
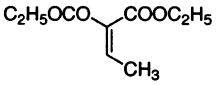
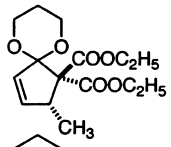
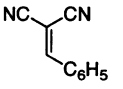
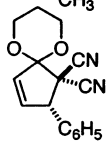
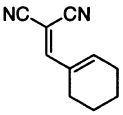
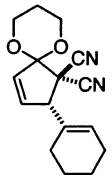
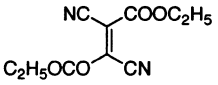
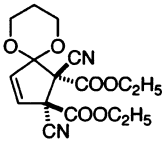
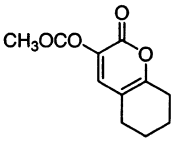
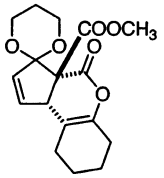
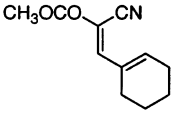
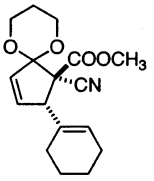
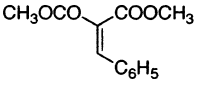
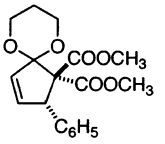
The [3 + 2] cycloaddition reaction of the singlet vinylcarbene with an electron-deficient olefin under

Table 19. Thermal [1 + 2] Cycloaddition Reaction of Vinylcarbene Intermediate with Olefin

entry	CPA	substrate	product[a]	yield (*cis*:*trans*)	ref.
1[b]				49% (85:15)	73, 89, 90
2[b]				63% (5:1)	73, 89
3[b]				68%[c] (84:16)	90
4[b]				69% (95:5)	
5[d]				72% (60:40)	73, 89, 90
6[e]				69% (35:65)	
7[b]				65% (10:1)	73, 89
8[b]				80% (9:1)	73, 89
9[b]				49% (1:1)	
10[d]				49% (2:3)	73, 89
11[e]				50% (2:3)	
12[f]				trace	
13[b]				40% (1:1)	73, 89
14[b]				36% (100:0)	73, 89
15[b]				13-36% (ND[g])	73
16[b]				24% (ND[g])	73

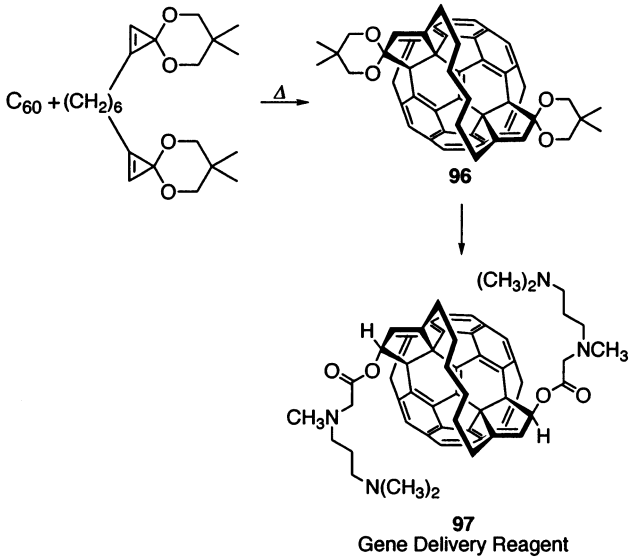
[a] X = $(CH_2)_3OH$, Y = $CH_2C(CH_3)_2CH_2OH$. [b] 80 °C−160 °C, benzene or toluene. [c] The reaction proceeds regioselectively (>92%) via intermediate **89** (Scheme 50). [d] 75 °C, CH_3CN. [e] 75 °C, DMF. [f] 75 °C, CH_3NO_2. [g] Not determined. [h] 80 °C, 1,4-$Cl_2C_6H_4$.

Table 20. Thermal [3 + 2] Cycloaddition Reaction of the Vinylcarbene Intermediate with Olefin

entry	CPA	substrate	product	yield	ref.
1[a]				60%	73
2[a]				89%	97
3[a] 4[b] 5[c] 6[d] 7[e]				95-100% 85% 82% 73% 61%	73
8[a]				30%	97
9[a]				57%	73
10[a]				86%	73
11[a]				62%	73
12[a]				66%	97
13[a]				42%	73
14[a]				58% *trans:cis* = 9:1	73
15[a]				60%	73

[a] 75-80 °C, benzene or toluene. [b] 75 °C, acetonitrile. [c] 75 °C, DMF. [d] 75 °C, nitrobenzene. [e] 75 °C, pyridine. [f] 80 °C, neat. [g] 150 °C, toluene. [h] 150 °C, 1,2-$Cl_2C_6H_4$. [i] 120 °C, toluene. [j] 170 °C, 1,2-$Cl_2C_6H_4$. [k] 0−25 °C, THF. [l] The starting olefin and the product consisted of a single isomer. Stereochemistry has not been assigned.

Scheme 53

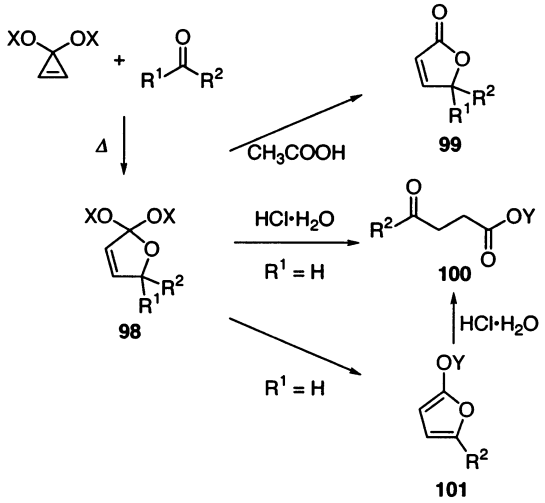


mild thermal conditions is unique, in that the reaction represents a rare example of an all-carbon thermal [3 + 2] cycloaddition reaction (see Scheme 52).[2,6,58,75,90,99] The reaction was first discovered by Boger[2] and was subsequently shown by his group to proceed via a single electron transfer between the vinylcarbene intermediate and the olefin to give the cyclopentenone acetal.[99] The [3 + 2] cycloaddition reaction of a CPA with an electron-deficient olefin containing two geminal electron-withdrawing substituents and dienes is summarized in Table 20.

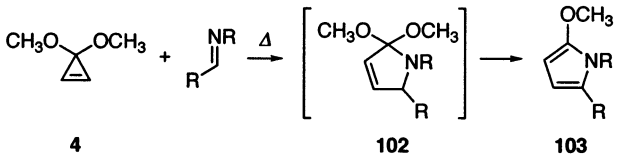
The [3 + 2] cycloaddition reaction proceeds smoothly in an aromatic solvent to exclusively form the cyclopentenone acetal without showing any evidence of a transient intermediate. The rate and stereoselectivity of the reaction do not depend on the solvent polarity (entries 3−7, 25, and 26). The [3 + 2] cycloaddition reaction with an *E*- or a *Z*-olefinic substrate proceeds with partial loss of the olefin geometry (entries 14, 21, and 22). The reaction with a diene substrate (entries 14, 23, and 24) predominantly affords a single [3 + 2] cycloadduct. The reaction mechanism of the [3 + 2] cycloaddition has been shown to involve a single electron transfer that provides an intermediate cage carbene-derived radical cation and substrate radical anion, a radical combination, and a final zwitterion collapse.[6] Among various substrates examined to date, C_{60} is the only substrate that participates in both the [1 + 2] and the [3 + 2] cycloaddition reactions.[93,94,100] As mentioned above, low temperatures favor [1 + 2] cycloaddition, and high temperatures (>140 °C) favor the [3 + 2] cycloaddition (entries 23 and 25). The origin of this temperature-dependent dichotomy is presently unknown.

The [3 + 2] cycloaddition reaction with C_{60} has been applied to the synthesis of a gene delivery reagent (**97**) (transfection reagent). The tether-directed double cycloaddition reaction with C_{60} affords a C_2 symmetric cycloadduct **96**,[101−103] which has been converted to the two-handed fullerene **97** bearing an amine residue (Scheme 53). This tetramine exhibits a transfection capability comparable to that of commonly used transfection reagents.[104−106]

Scheme 54



Scheme 55



4. [3 + 2] Cycloaddition Reactions with Carbonyl and Related Compounds

The reaction pathway of a CPA with a carbonyl compound is outlined in Scheme 54. The cycloaddition reaction of the π-delocalized vinylcarbene with a ketone proceeds in a formal [3 + 2] manner to afford the ortho ester **98** (entries 3 and 9 in Table 21).[6,75,107] Acidic workup of the reaction mixture affords butenolide **99** (entries 4, 8, 10, and 11). The reaction with an aldehyde gives γ-keto ester **100** (entries 2, 5, 7, and 12) or furan **101** (entries 1 and 6), depending on the workup conditions. The cycloaddition reaction with an imine does not take place.

The cycloaddition reaction with a C−N double bond has been reported only for a triazine.[108] The reaction gives pyrrole derivative **103** after elimination of methanol from the initial [3 + 2] cycloadduct **102** (Scheme 55 and Table 22).

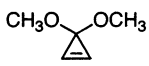
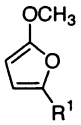
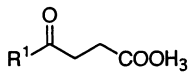
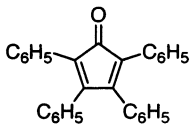
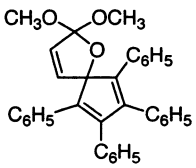
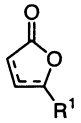
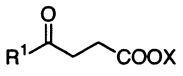
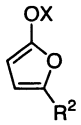
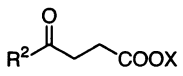
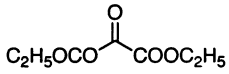
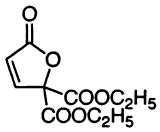
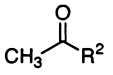
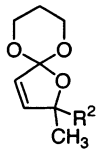
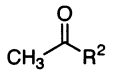
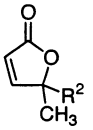
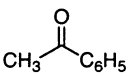
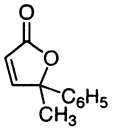
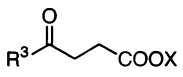
5. [3 + 4] Cycloaddition Reactions

The cycloaddition reaction of the vinylcarbene intermediate with α-pyrones proceeds in a [3 + 4] manner (Schemes 56−58).[75,109] A mild aqueous acid treatment of the [3 + 4] cycloadduct **104** produces bicyclolactone **105**, which is converted to cycloheptatrienone **106** (tropone) upon thermolysis (Scheme 56). This reaction has been utilized as a key reaction in the formal total synthesis of the natural product colchicine (Scheme 58).[110,111]

B. Metal-Catalyzed Reactions

Cleavage of the C−C σ-bond of CPA can be accelerated by various metal complexes, most likely by the formation of a metal−carbene complex.[112] In some

Table 21. Thermal [3 + 2] Cycloaddition Reaction of the Vinylcarbene Intermediate with Carbonyl Compound

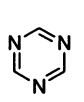
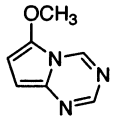
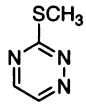
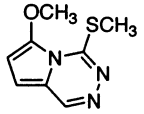
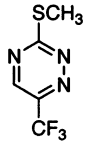
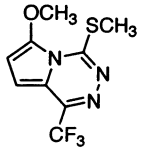
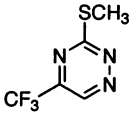
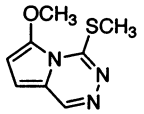
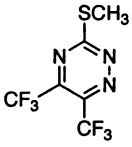
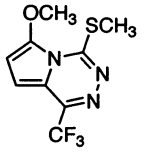
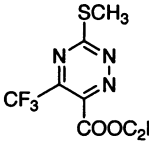
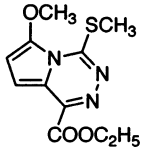
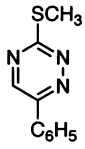
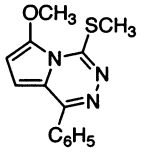
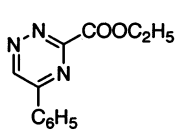
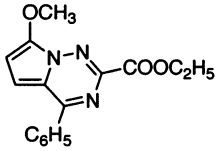
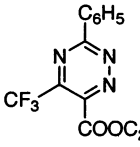
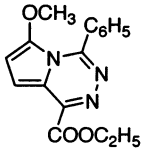
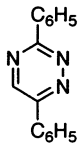
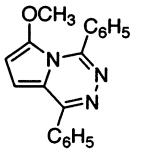
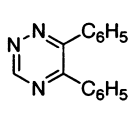
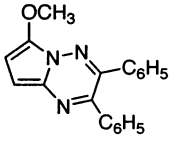
entry	CPA	substrate[a]	product[a, b]	yield	ref.
1[c]				30%	73
2[d]				49%	73
3[e]				13%	69
4[f]				38%	73
5[d]				53%	73
6[c]				45%	73
7[d]				44%	73
8[c]				13%	73
9[c]				22%	73
10[f]				31%	73
11[c]				15%	73
12[d]				28%	73

[a] R^1 = 3,4-dichlorophenyl. R^2 = 4-nitrophenyl. R^3 = 4-methoxyphenyl. [b] X = $(CH_2)_3OH$. [c] (i) 80 °C, heptane; (ii) SiO_2. [d] (i) 80 °C, heptane; (ii) HCl/H_2O. [e] Reflux, THF. [f] (i) 80 °C, heptane; (ii) CH_3COOH/H_2O.

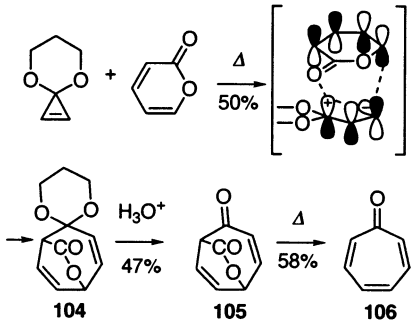
cases, the metal−carbene complexes have been isolated and characterized.

A Ni(0)-catalyzed [1 + 2] cycloaddition of CPA with methyl acrylate mainly gives the thermodynamically

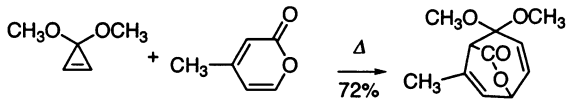
Table 22. Thermal [3 + 2] Cycloaddition Reaction of the Vinylcarbene Intermediate from Cyclopropenone Dimethyl Acetal 4 with Triazine (Ref 108)

substrate	product	yield
		25%
		21%
		20%
		34%
		28%
		27%
		17%
		27%
		35%
		51%
		28%

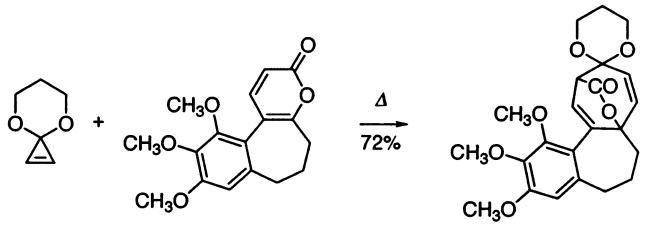
Scheme 56



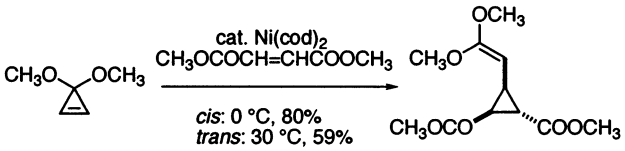
Scheme 57



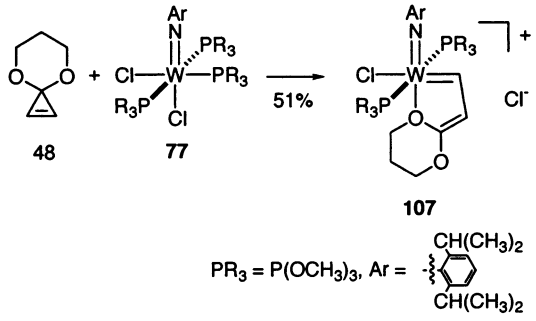
Scheme 58



Scheme 59



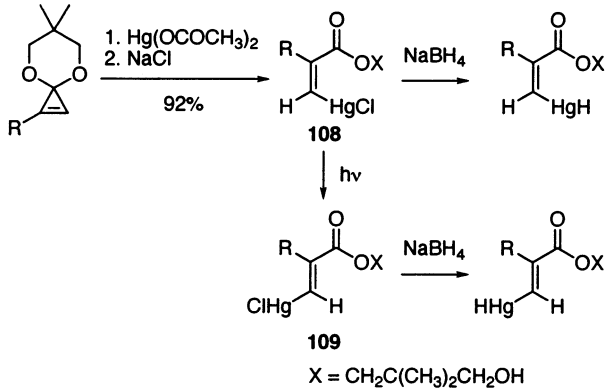
Scheme 60



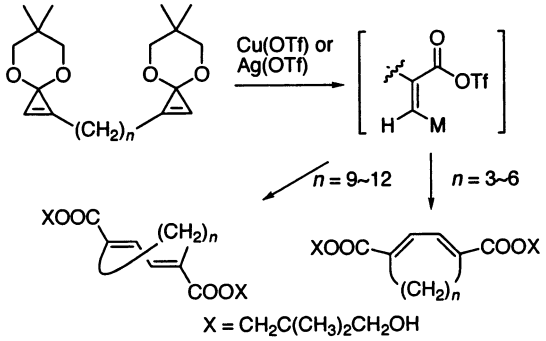
stable 1,2-*trans* substituted cyclopropane (Scheme 59).[80] Thus, the stereoselectivity is opposite to the one observed in the thermal reaction (see section V.A.2). The reaction of the cyclopropenone dimethyl acetal with dimethyl fumarate or maleate in the presence of a catalytic amount of $Ni(cod)_2$ affords the *trans*-cyclopropane derivative with respect to the ester groups. The loss of stereochemistry of the substrate is due to the stepwise nature of the cycloaddition of the nickel vinylcarbene complex with the olefin.

The reaction of arylimido tungsten complex **77** with CPA **48** results in the formation and isolation of vinylcarbene complex **107** (Scheme 60).[87] Sterically, the bulky arylimido group or ligand on the tungsten metal favors the formation of the vinylcarbene complex over the corresponding η^2-complex (cf. section

Scheme 61



Scheme 62



IV.D). Vinylcarbene complexes are also formed in the reaction with an oxo tungsten complex.[113]

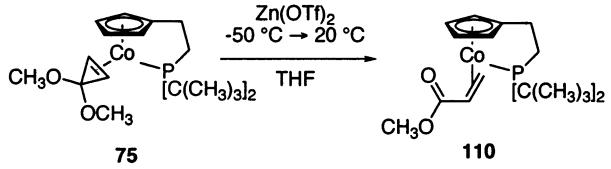
When the ring-opening reaction is caused by a Lewis acid metal, such as mercury, copper, silver, or cobalt, the reaction generates a vinylmetal compound instead of a carbene complex. A ring-opening reaction of CPA with $Hg(OAc)_2$, followed by treatment with aqueous NaCl solution, produces *Z*-olefinic mercury chloride **108** in a stereoselective manner (Scheme 61).[114] The bond cleavage takes place exclusively on the less substituted side of the CPA. The mercury chloride can be converted to a mercury hydride that has an unusual thermal stability by reduction with $NaBH_4$. The geometrical isomer can also be obtained by photochemical conversion to compound **109**.

The intramolecular dimerization reaction of CPA provides an unusually effective route to medium-sized and macrocyclic rings. Intramolecular Csp^2–Csp^2 bond formation takes place with the aid of CuOTf or AgOTf (Scheme 62).[115] Carbocycles with different ring size can be obtained by changing the length of the methylene tether between two cyclopropene rings. Interestingly, medium rings are formed with exclusive *E*,*E*-configuration, and larger ones are formed with exclusive *Z*,*Z*-configuration. Similar vinylmetal species take part in the reaction, leading to the formation of the cobalt η^2-complex **110** (Scheme 63).[116]

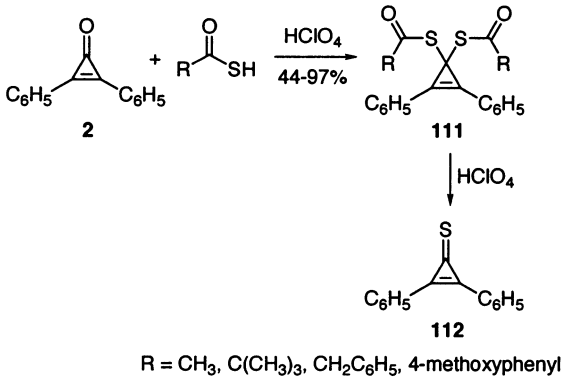
VI. Miscellaneous Analogues

This final section describes the synthesis of cyclopropenes bearing two geminal heterosubstituents. Starting from cyclopropenone or its analogue, a series of CPA analogues have been synthesized. Reaction

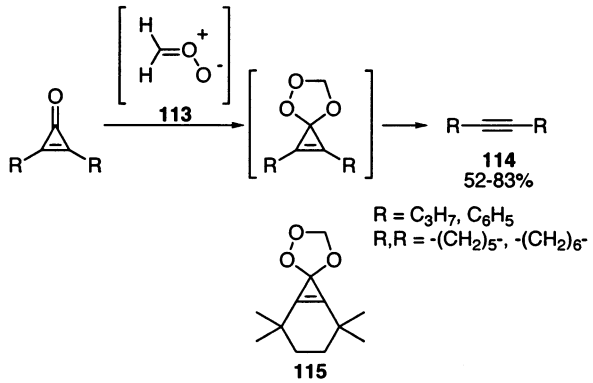
Scheme 63



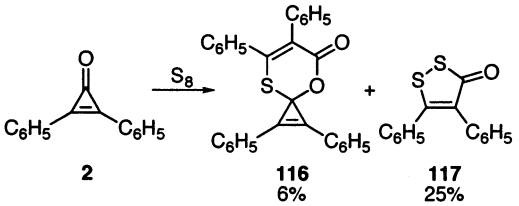
Scheme 64



Scheme 65



Scheme 66

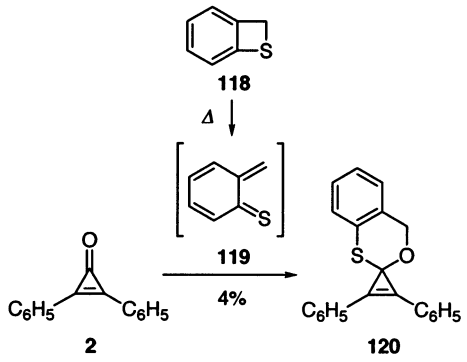


of diphenylcyclopropenone **2** with thioacetic acid produces the corresponding bisacylthiocyclopropene **111** in good to moderate yields (Scheme 64).[117] Bisacylthiocyclopropene **111** has been converted to cyclopropenethione **112** under acidic conditions.[117,118]

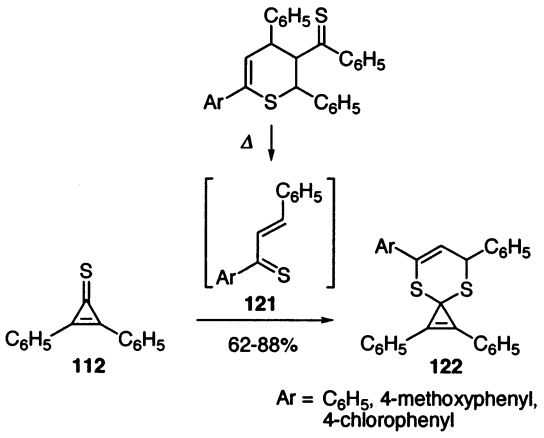
A range of analogues has been synthesized by cycloaddition reactions at the C=O or the C=S bond of cyclopropenone and congeners. The reaction of cyclopropenone with formaldehyde *O*-oxide **113** affords alkyne **114** via a spiroozonide (Scheme 65). The spiroozonide **115** has been isolated with a sterically hindered cyclopropenone.[119]

Reaction of sulfur (S_8) with **2** affords analogue **116** as a minor product in a 6% yield (Scheme 66).[120] The major product of 1,2-dithioleone **117** is obtained by the ring-opening reaction of **2** with sulfur, and a further cycloaddition reaction of **2** with **117** affords the CPA analogue **116**. The [2 + 4] cycloaddition

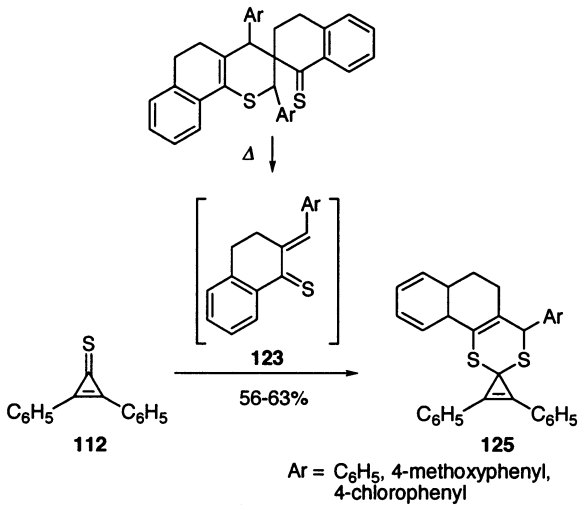
Scheme 67



Scheme 68



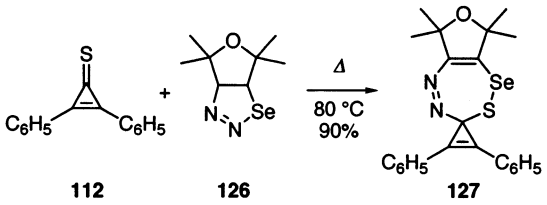
Scheme 69



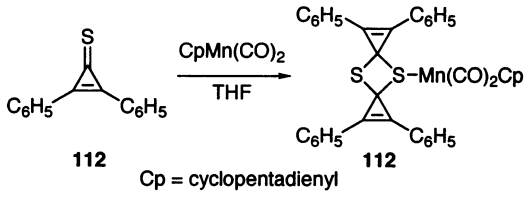
reaction of an α,β-unsaturated thione with a cyclopropenone gives a monothioacetal. The *o*-thiobenzoquinone **119** thermally generated from the benzothiete **118** reacts with **2** to give monothioacetal **120** in a 4% yield (Scheme 67).[121] A similar [2 + 4] cycloaddition reaction of thioketone **112** with α,β-unsaturated thiones **122** and **124** takes place to give dithioacetals **122** and **125**, respectively (Schemes 68 and 69).[122]

A formal [2 + 5] cycloaddition reaction between the C=S bond of thioketone **112** and selenadiazole **126** can take place (Scheme 70).[123,124] The reaction occurs upon heating the mixture in benzene to give seven-membered ring product **127** in a 90% yield.

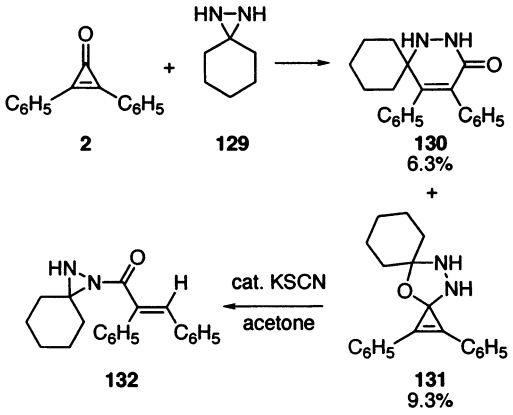
Scheme 70



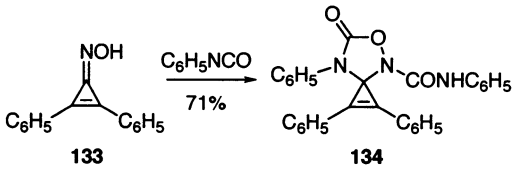
Scheme 71



Scheme 72



Scheme 73



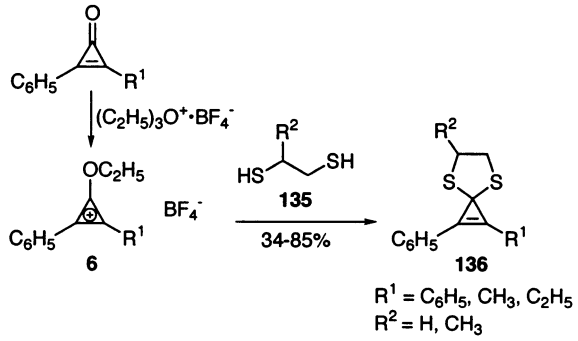
A [2 + 2] dimerization reaction of thioketone **112** results in the formation of a dithietane. Upon treatment of **112** with $CpMn(CO)_2$ in THF, the dithietane−manganese complex **128** is obtained in a 5% yield (Scheme 71).[125]

Along with ring-opened product **130**, hemiaminal ether **131** has been obtained by the [2 + 3] cycloaddition reaction of **2** with diaziridine **129** (Scheme 72).[126] The hemiaminal ether **131** is thermally labile, and a ring-opening reaction gives acrylamide **132**. Thiocyanate catalyzes the conversion of **131** to **132**.

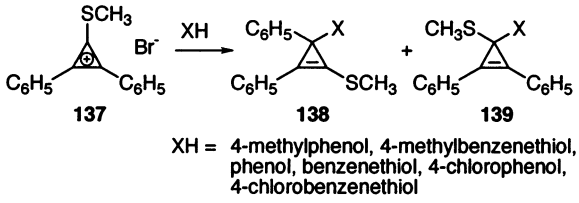
The reaction of the cyclopropenone oxime **133** with an isocyanate gives an aminal derivative **134** (Scheme 73).[127] The reaction of **133** with an isocyanate was first reported in 1987.[128,129] However, the structure of the product was erroneously identified initially and later correctly identified to be **134** from X-ray crystallographic analysis.[127] The cycloadduct **134** is formed by the [3 + 2] cycloaddition of the nitrone intermediate with isocyanate.

Heteroacetals can also be prepared from cyclopropenium salts. The same synthetic route utilized for the preparation of CPAs (see section II.A) has also

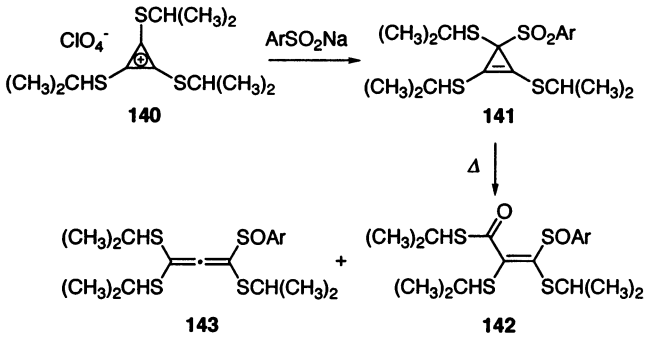
Scheme 74



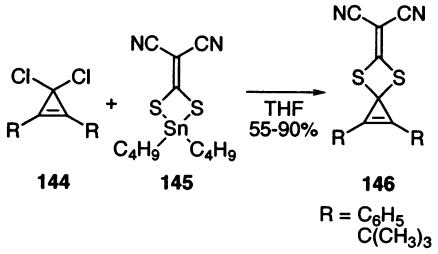
Scheme 75



Scheme 76



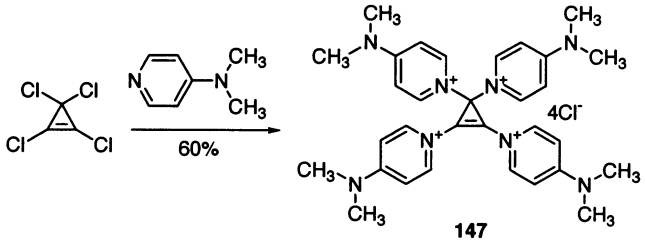
Scheme 77



been applied to the preparation of dithioacetals (Scheme 74).[22] The reaction of 1,2-dithiol **135** with ethoxycyclopropenium salt **6** gives the corresponding dithioacetal **136** in good to moderate yields. The monoacetal **138** and dithioacetal **139** have been spectroscopically detected in the reaction of the thiocyclopropenium salt **137** with an alcohol or thiol (Scheme 75).[130] The reaction of an arylsufinate with cyclopropenium **140** affords α,β-unsaturated ester **142** and allene **143** (Scheme 76).[131] Dithio analogue **141** has been isolated and identified as an intermediate in this reaction.

A nucleophilic substitution reaction of dichlorocyclopropene produces CPA analogues. The reaction of a diphenyl and di-*tert*-butyl dichlorocyclopropene **144** with **145** gives the corresponding dithietane derivative **146** in moderate yield (Scheme 77).[132] The substitution reaction of tetrachlorocyclopropene with

Scheme 78



N,*N*-(dimethylamino)pyridine gives ionic cyclopropene **147** in a 60% yield (Scheme 78).[133−136]

VII. Summary

In the foregoing sections, we have compiled all the literature examples of the synthesis and reactions of CPAs. Although the total number of CPA-related references was only 14 up until 1980, about 20 papers have been published in the 1980s, and over 70 papers after 1990. The initial interest in CPAs exclusively focused on the chemistry related to cyclopropenones. After being a subject of study for a long time, the literature on CPAs now covers a variety of fields, extending to organometallic, inorganic, and bioorganic chemistry. During the present survey of this field, we noted that a number of seemingly obvious possibilities still remain unexplored, and a variety of areas for new research initiatives are left unattended. It is our hope that the present review will foster new interest in these in the mind of the reader.

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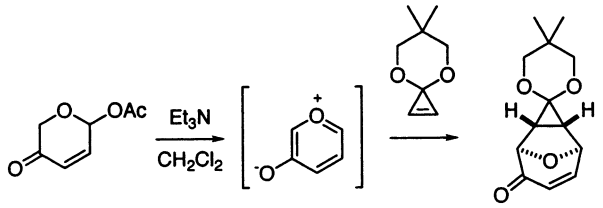

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