Thermal Reactions of Dipolar Trimethylenemethane Species

EIICHI NAKAMURA*,† AND SHIGERU YAMAGO‡
Department of Chemistry, The University of Tokyo, Bunkyo-ku, Tokyo 113-0033, Japan, and Department of Synthetic Chemistry and Biological Chemistry, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

Received September 24, 2001

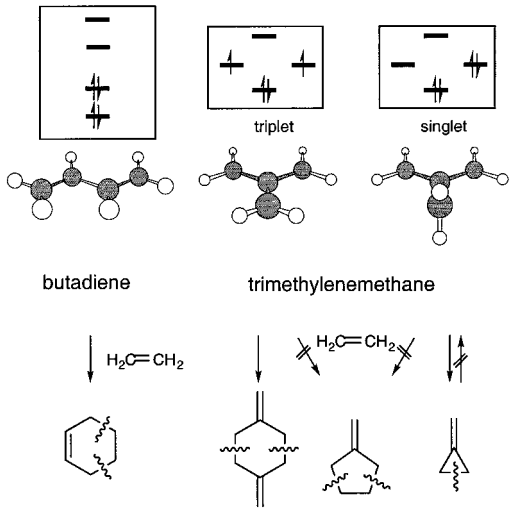
ABSTRACT
Installation of two alkoxy groups on a terminal methylene of trimethylenemethane (TMM) dramatically alters the electronic state and the reactivities of the TMM. Thermolysis of a 1,1-dialkoxy-2-methylenecyclopropane generates such a TMM, which exhibits a marked singlet dipolar character. It undergoes [3 + 2] cycloadditions to a variety of electron-deficient unsaturated compounds including alkenes, alkynes, oximes, carbonyl compounds, and fullerenes and reacts with active methelene compounds and organozinc reagents as a 1,3-dipolar synthon.

1. Introduction

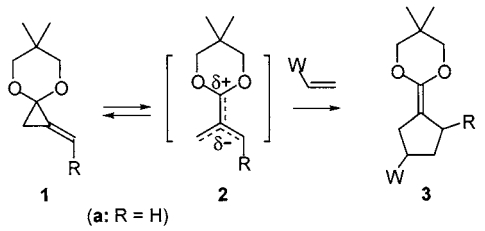
Thermal cycloaddition reactions[1] that produce complex carbon frameworks in a single step without additional reagents are versatile synthetic protocols owing to their operational simplicity as well as to their "green" character. The latter point may become even more important since common metal catalysts such as palladium or platinum might someday be banned due to environmental problems.[2]

An archetypal cycloaddition reaction is the Diels−Alder reaction between a four π-electron 1,3-diene and a two π-electron olefin. Chemists have successfully "played the 6π-electron game" to synthesize a diverse array of chemical structures.[3] The reactants couple with each other under thermal conditions, and there is no loss of atoms in the reaction. Building a similar six π-electron system for a [3 + 2] synthesis of cyclopentanes is more difficult owing to the limited availability of suitable four-electron/three-carbon candidates.[4,5] Trimethylenemethane (TMM) is one of the rare kinds of such reactants. In this Account, we describe the chemistry of a dialkoxy trimethylenemethane (**2**) that can be generated easily and cleanly from a 1,1-dialkoxy-2-methylenecyclopropane (DMCP, **1**). This TMM species has been shown to be useful for the [3 + 2] synthesis of five-membered rings (**3**) (eq 1) as well as for other synthetic transformations.

Scheme 1. C_4H_6 Isomers: Conformations, Electronic States, and Reactivities[a]



[a] Newly forming bonds are marked with wavy lines.



(1)

2. Nature of TMM Intermediates

1,3-Butadiene and TMM share the same molecular formula C_4H_6 and possess four π-electrons (Scheme 1). In their most stable electronic configurations, both are planar, but their electronic states differ. Butadiene is a closed-shell singlet, and planar TMM (D_{3h}) is a ground-state triplet because of the presence of degenerate orbitals.[6] Butadiene smoothly reacts with an alkene in the Diels−Alder fashion. Triplet TMM, on the other hand, does not react with an alkene but instead undergoes homocoupling to give a dimer: with appropriate substitution, it undergoes [3 + 2] cycloaddition to olefins expectedly with loss of the stereochemical integrity of the olefin.[7] There is also a singlet TMM species. While this TMM can potentially undergo cycloaddition to an alkene, intramolecular C−C bond formation overrides the intermolecular reaction to give, irreversibly, a methylenecyclopropane.

A route to singlet TMM intermediates was developed some time ago by Berson,[7] who utilized thermal or

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), and The Nagoya Medal of Organic Chemistry (2001). 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.

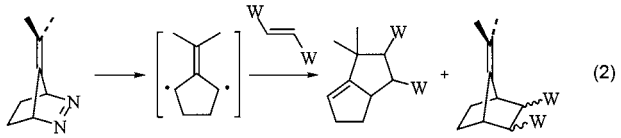
Shigeru Yamago received his B.S. and Ph.D in chemistry from Tokyo Institute of Technology in 1986 and 1991, respectively, and then he immediately joined the same institute as Assistant Professor. In 1995, he moved to Kyoto University, where he is currently Associate Professor in the Department of Synthetic Chemistry and Biological Chemistry. He has been honored with an Incentive Award in Synthetic Organic Chemistry from Japan (2001). His major current research interests are synthetic radical chemistry and carbohydrate chemistry.

* To whom correspondence should be addressed. Tel and fax: +81-3-5800-6889. E-mail: nakamura@chem.s.u-tokyo.ac.jp.
† University of Tokyo.
‡ Kyoto University.

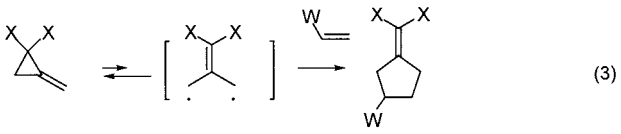
10.1021/ar0100935 CCC: $22.00
Published on Web 06/13/2002

photochemical decomposition of a five-membered alkylidene diazene, in which a TMM intermediate and dinitrogen are irreversibly generated (eq 2). The method has been proven to be useful for intramolecular cycloadditions.[8] Intermolecular reactions have also been carried out for electron-deficient olefins but less efficiently.[9] Dimerization of the TMM species generated irreversibly from the diazene precursor competes with the cycloaddition with the olefin in an intermolecular reaction.

A potentially attractive alternative route to singlet TMM species is the thermolysis of a methylenecylopropane (eq 3), which may reversibly generate a closed-shell singlet TMM. This idea has proven not to work because of kinetic and thermodynamic problems. First, methylenecyclopropane resists ring cleavage (E_a = 42 kcal/mol for X = D).[10] Second, even when the energy barrier of ring cleavage may be lowered by installation of aryl groups (E_a = 23 kcal/mol for X = Ph),[11] [3 + 2] cycloaddition to olefins does not take place[12] possibly due to insufficient equilibrium concentration of the TMM species. Until our first report in 1989,[5,13] The methylenecyclopropane route to free TMM species has met with only limited synthetic success because of the problems of the synthesis and handling of the starting materials: methylenecyclopropanes substituted with fluorine atoms[14] or incorporated into a highly strained bicyclo[2.1.0]pentane skeleton have been found to give the desired [3 + 2] cycloadducts.[15]



(2)



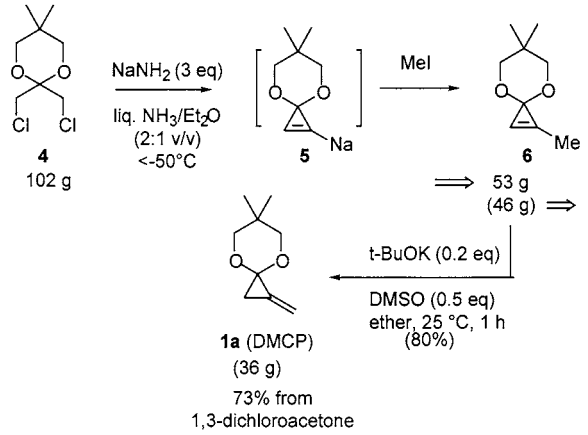
(3)

Sometime ago, we conjectured that the placement of two alkoxy groups on the methylenecyclopropane ring groups (**1** in eq 1) might be powerful enough both to solve the kinetics of the ring opening and to stabilize the resulting closed-shell singlet TMM by lifting the orbital degeneracy of the TMM. This thought was first expressed by Berson in 1976[16] and was in fact found to be the case: thermolysis of the DMCP (**1**) took place readily around 60−80 °C and generated a well-behaved closed-shell singlet TMM intermediate **2** that acts as a nucleophilic dipolar reagent in various reactions.[13] In the following sections, we describe the mechanism and synthetic applications of these reactions.

3. Generation of Dipolar TMM from Methylenecyclopropane

3.1. Synthesis of TMM Precursors. The key to enter into the "6π game" of the dipolar TMM was the development of a large-scale preparation of DMCP (**1**). This was

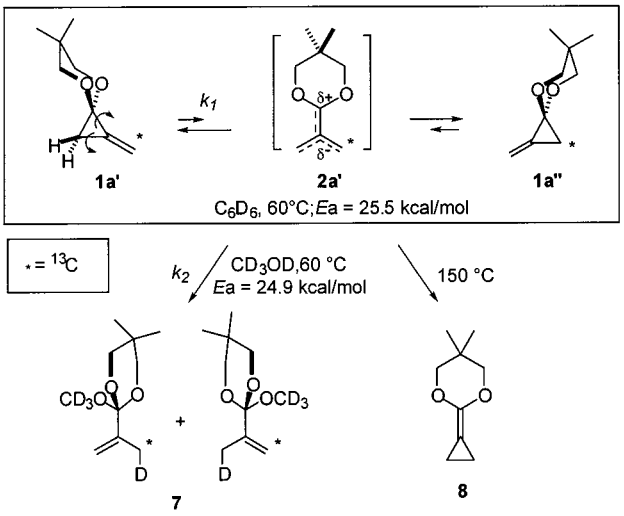
Scheme 2. Preparation of 1,1-Dialkoxy-2-methylenecyclopropane (DMCP) 1a



achieved in three steps as illustrated in Scheme 2.[17] Commercially available 1,3-dichloro-2-propanone is first converted quantitatively to its acetal **4**, which is then cyclized with $NaNH_2$ to form a sodiocyclopropene intermediate **5**. This is trapped in situ with MeI (or with another alkyl halide) to give the cyclopropenone acetal **6**.[18] Base treatment of this strained molecule causes smooth isomerization to the less strained DMCP **1a**, which can be isolated pure by distillation (or by chromatography for higher analogues). It can be stored in a capped bottle without appreciable decomposition and is stable for hours even in a hot toluene solution. The merits of the use of neopentyl glycol protection include the low cost and the moderate temperature (80 °C) required for the generation of the dipolar TMM from **1a**. Other acetals, for instance, the acetal derived from *dl*-2,4-hexanediol form dipolar TMM much more easily, even at room temperature.

3.2. Thermal Generation and Properties of Dipolar TMM from DMCP (1).[19] The remarkable heat stability of the DMCP **1a** cast doubt on the feasibility of thermal cycloaddition chemistry with this compound. However, isotope labeling experiments provided firm evidence of reversible TMM generation from DMCP **1a**; namely, the reaction of ^{13}C-labeled DMCP (**1a′**) smoothly equilibrated to its isomer **1a″** via ^{13}C-labeled TMM **2′**. Thus, despite the apparent stability, we found that **1a′** rearranges, even at room temperature, to **1a″**, which now bears the ^{13}C label on the ring carbon (Scheme 3). The isomerization proceeded with an appreciable rate at 50−70 °C, producing a 1:1 mixture of **1a′** and **1a″**. The first-order rate constant (k) of the scrambling reaction (60 °C, 0.30 M C_6D_6) was 9.6×10^{-5} s^{-1}, and the activation energy (E_a) was 25.5 kcal/mol. The rate (60 °C) increased 191 times as the solvent was changed from C_6D_{12} to DMSO-d_6, suggesting a relatively polar transition state. Notably, no side reactions took place under these conditions, and **1a′**/**1a″** could be quantitatively recovered. The rate of the rearrangement of **1a′** changed little in the presence of 1,4-dinitrobenzene (1 equiv, a radical trap) or under 1 atm of oxygen. Direct evidence for the formation of TMM **2a′** was obtained by solvolysis of **1a′** in CD_3OD at 40−60 °C to give an ortho ester **7** in quantitative yield. The deuterium atom

Scheme 3. Rapid Thermal Generation of a Symmetrical Intermediate 2a



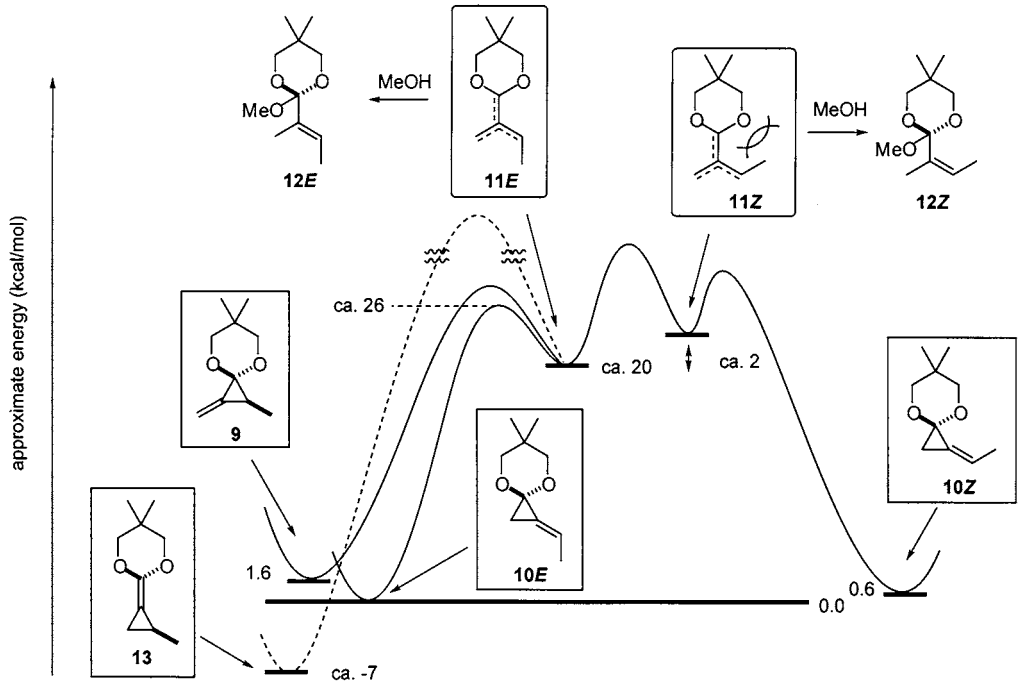
was specifically found on the allylic methyl group with complete scrambling of the ^{13}C label, while the label in the recovered starting material **1a′** stayed on the *exo*-methylene position throughout the time course of the methanolysis reaction. These experiments indicated that the symmetrical and zwitterionic intermediate **2a′** forms first and reacts with excess methanol faster than its recyclization to **1a′** or **1a″**. We also noted that, above 150 °C, there exists an alternative, irreversible ring closure pathway to dimethyleneketene acetal **8**.

3.3. Planar TMM and Its *E*/*Z* Isomerism.[19] The dipolar TMM offers a rare chance to study the stereochemistry of substituted TMM species (Scheme 4). To generate methyl-substituted TMM, one can a priori consider three precursor cyclopropanes **9** and **10***E*,*Z*. When **9** was heated in methanol, we obtained an ortho ester of itaconate acid **12***E*, exclusively as *E*-isomer (>99%). The *E*-ethylidenecyclopropane (**10***E*) afforded the same *E*-isomer **12***E*, but **10***Z* afforded a 1:9 mixture of **12***E* and **12***Z*. These observations suggest that both the methyl and the acetal oxygen atoms lie in the TMM plane, thereby allowing steric interaction to destabilize the *Z*-TMM isomer (**11***Z*). The *Z* to *E* rotational barrier must be rather small since the rate of the isomerization of **11***Z* to **11***E* is comparable to that of the methanolysis reaction. Taken together with the theoretical analysis and the stereochemistry of the [3 + 2] cycloadditions (vide infra), we concluded that the TMM responsible for the methanolysis and the (concerted) cycloaddition chemistry is a planar species; that is, all substituents are located in the plane of the TMM framework.

Extended thermolysis of DMCP (**1**) at 150 °C led irreversibly to the fourth isomer, ketene acetal isomer **13**, which is about 7 kcal/mol more stable than the others (MP2-level model calculations) and acts as an energy sink of the complex equilibrium system. This ketene acetal serves as a useful surrogate of the enolate anion of a cyclopropane carboxylic esters (vide infra).

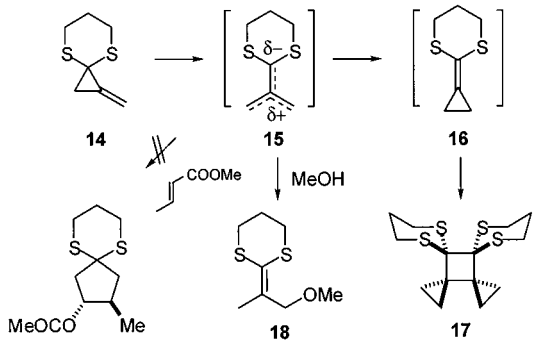
For comparison, a dialkylthiocyclopropane analogue **14** was prepared in five steps from epichlorohydrin, and the behavior of dialkylthio TMM intermediate **15** was studied.[20] The different reactivities of **1a** and **14** became immediately apparent upon attempted trapping of the TMM with methyl crotonate. The head-to-head dimer **17** formed in 70% yield, leaving the crotonate unchanged (Scheme 5). Dimer **17** is a [2 + 2] cycloadduct of dimethyleneketene dithioacetal **16** formed via the dialkylthio TMM **15**. Thermolysis in refluxing methanol afforded the

Scheme 4. Approximate Energy Profile of the Formation of Methyl-TMM Intermediates (11*E*,*Z*)[a]



[a] Energies in kcal/mol have been roughly estimated from experimental activation energies, equilibrium constants, and theoretical calculations.

Scheme 5. Generation and Reactions of Dialkylthio TMM



methanol adduct **18**, which suggests that the dithio TMM **15** has polarity opposite to that of the dialkoxy TMM **2**.

3.4. Electronic State of Dialkoxy TMM. Four electron/four orbital CASSCF calculations were carried out for the singlet state of dihydroxyl TMM[16,19,21] in various conformations to determine the geometry and the properties of the reactive intermediate (Figure 1). All three stable conformers, the closed-shell C_2-planar (**i**), the C_2-bisected (**ii**), and the C_s-bisected conformers (**iii**), have comparable energies, but, perhaps in fortuitous agreement with the experiments, the planar TMM **i** is the most stable TMM species. Although **ii** and **iii** are pure diradicals by symmetry, **i** is a closed-shell singlet species. Charge analysis shows that **i** is polarized enough to act as a four-electron donor and is expected to be responsible for the alcoholysis and the cycloaddition chemistry. It is likely to be of interest for theoreticians to study the details of the reaction paths of the cycloaddition reactions.

4. Concerted [3 + 2] Cycloaddition Reactions

4.1. Reactivitiy and Stereospecificity.[22−24] A general and efficient synthesis of substituted carbocycles has been achieved by thermal [3 + 2] cycloadditions of the dipolar TMM with electron-deficient alkenes and alkynes (Scheme 6). A variety of olefins substituted with a single electron-withdrawing group reacted at 60−80 °C with retention of the olefin geometry to give the ketene acetal of cyclopentane carboxylic acid ester. The ketene acetal functionality found in the products can be transformed to an ester (hydrolysis), an acetal (hydrogenation), a ketone (ozonolysis), and other useful functional groups.

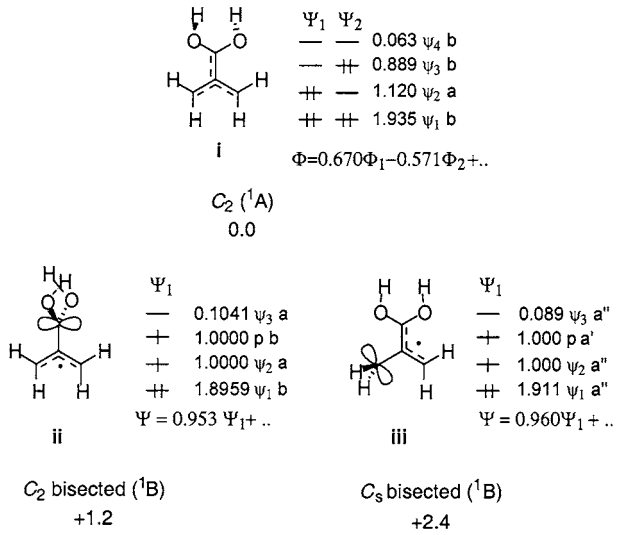
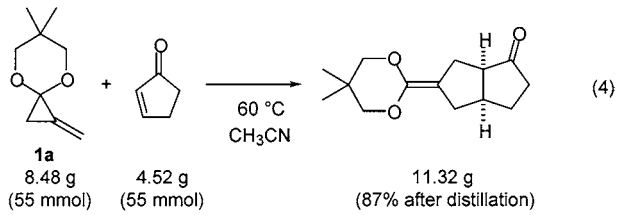


FIGURE 1. Energies (kcal/mol) and electronic configurations of singlet dihydroxy TMM obtained by MCQDPT2/6-31G(d)/6-31G(d)//CASSCF(4,4)/6-31G(d) (CASSCF(4,4)/6-31G(d)).

How fast is the cycloaddition relative to the ring closure of the TMM **2** back to the cyclopropane **1**? To answer this question, the [3 + 2] cycloaddition to dimethyl fumarate (used as solvent) was carried out with the ^{13}C-labeled DMCP **1′**. The rate of the scrambling of the label was found to be comparable to that of the cycloaddition. Therefore, the TMM **2** experiences rapid equilibrium with the cyclopropane **1** before undergoing cycloaddition to the olefin acceptor.

Alkynes are less reactive than olefins bearing the same electron-withdrawing group, and the cycloaddition requires heating at ca. 100 °C. The successful use of alkynes for the cycloaddition is noteworthy, since they are poor substrates for the diazene route.[25] Cycloaddition also took place smoothly with *O*-alkyloximes providing pyrrolidines. Unactivated olefins including norbornene and electron-rich olefins such as enol silyl ethers proved unreactive.

The reaction below illustrates a preparative scale synthesis of a bicyclo[3.3.0]octane by this route (eq 4).[17] The TMM species, generated in a minute amount, reacts with the C=C compound or reverts to the cyclopropane precursor, and therefore few side reactions took place. The thermal cycloaddition reaction can be performed with a 1:1 stoichiometry of the two reactants. The reaction does not require the use of solvent and tolerates the use of a variety of aprotic solvents (e.g., hydrocarbon, ether, haloalkane, nitrile, DMSO, etc.). Because of the more rapid formation of the dipolar TMM (vide supra), the reaction proceeds faster in polar solvents, which however give lower endo-stereochemistry (vide infra). One synthetically attractive property of the reaction is that rigorous exclusion of oxygen or moisture is unnecessary.

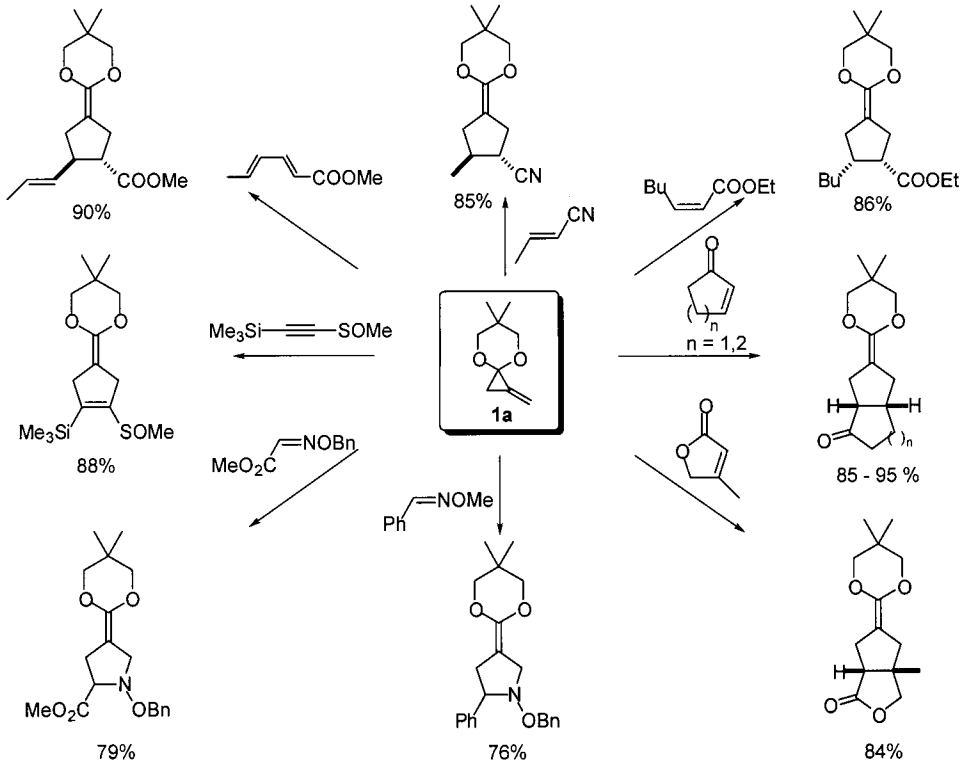


(4)

4.2. Concerted Endo-Cycloaddition.[26] Stereochemistry provides information concerning the mechanism of cycloaddition reactions. The concerted nature of the [3 + 2] cycloaddition of the dipolar TMM to β-substituted α,β-unsaturated esters was supported by independent lines of evidence. For instance, methyl (*Z*)-2-heptenoate reacts six times slower than the corresponding *E*-isomer. Both of the factors are signatures of concerted cycloaddition.[27]

The reaction of the dipolar TMM with an α,β-unsaturated ester takes place through an endo transition state. The reaction of methyl-substituted DMCP **10***E* and dimethyl maleate in an aprotic solvent at 80−120 °C for 20−

Scheme 6. Concerted [3 + 2] Cycloadditions of Singlet TMM[a]



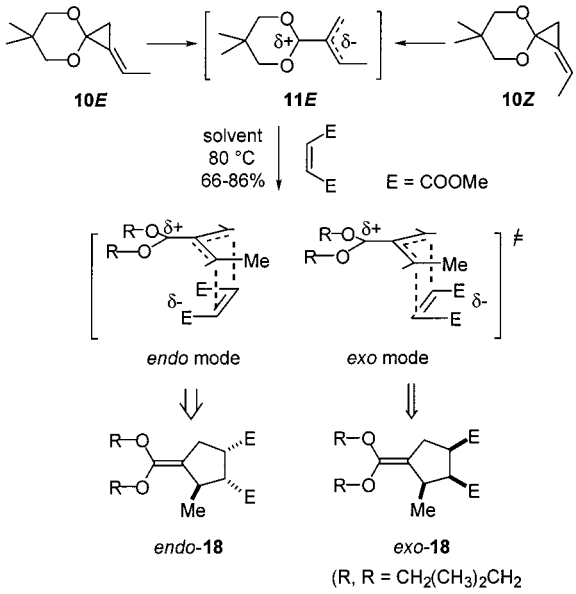
[a] Yields refer to typical isolated yields based on electrophiles.

75 h under nitrogen gives a [3 + 2] cycloaddition product **18** with moderate to high endo-stereoselectivity (Scheme 7). The *E*-stereochemistry of the TMM intermediate **11***E* generated from the *E*-precursor **10***E*, combined with the product stereochemistry, indicates that the reaction proceeds through an endo-transition state, as shown in Scheme 7. The endo-stereoselectivity erodes from 97:3 to 73:27 upon changing the solvent from a nonpolar to a polar one ($\epsilon = 1.9$ to 46.6), suggesting that the stereocontrol is achieved through electrostatic interactions in the transition state. Note however that the endo rule may be overridden by the geometrical constraints of an intramolecular reaction (vide infra).

Interestingly, the corresponding *Z*-DMCP **10***Z* from slightly slower to give the cycloadducts of the same isomer composition obtained with **10***E*. Apparently, the *Z*-TMM (**11***Z*) generated from **10***Z* isomerized to the *E*-TMM (**11***E*) before reaction with the olefin. The lack of reactivity (or very short lifetime before isomerization) of *Z*-TMM is synthetically advantageous, since the *Z*-DMCP **10***Z*, which often forms as a minor product in the preparation and may be difficult to separate from the *E*-isomer, converges to the same cycloadduct.

For unsymmetrical olefins, a regiochemical issue arises (Scheme 8). When the substituents both on the alkene acceptors and on the TMMs are small (e.g., $R^1 = R^2 = CH_3$), a 1:1 regioisomeric mixture forms. However, if *either one* of those are bulkier (e.g., isopropyl or *tert*-butyl group), excellent regiocontrol results (Scheme 8). Assuming the endo transition state, one can account for the origin of the regiocontrol primarily with the steric effects of the substituents.

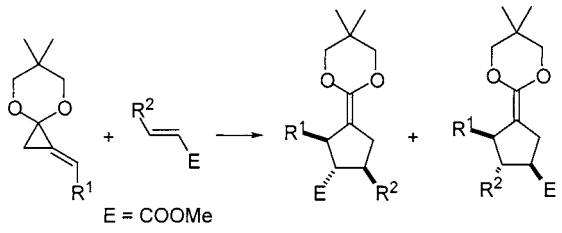
Scheme 7. Solvent-Dependent Endo Selectivity



Solvent	ε	*endo*:*exo*
octane	1.9	97:3
benzene	2.3	95:5
toluene	2.6	97:3
DME	7.2	92:8
1,2-dichloroethane	10.4	92:8
DMF	36.7	80:20
acetonitrile	37.5	80:20
DMSO-d_6	46.6	73:27

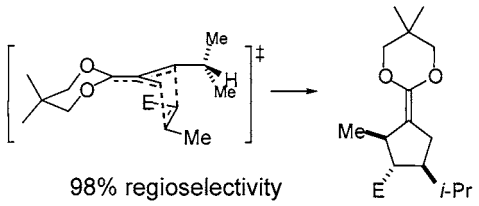
The cycloaddition to *O*-alkyloximes also shows a sign of concertedness.[23] For instance, the TMM **2** reacts with

Scheme 8. Regio- and Stereoselective Cycloaddition

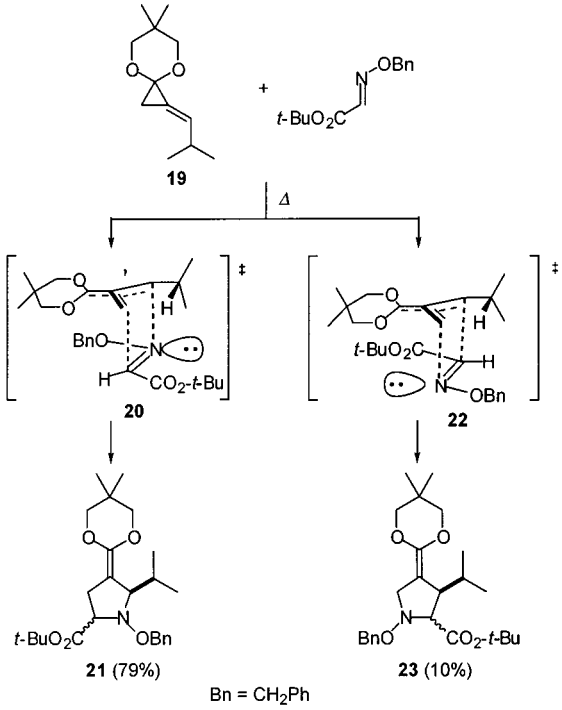


R^1	R^2	yield	ratio
Me	Me	81	50:50
i-Pr	Me	71	98:2
Me	*t*-Bu	89	>97:3

a proposed transition state for R^1 = *i*-Pr, R^2 = Me

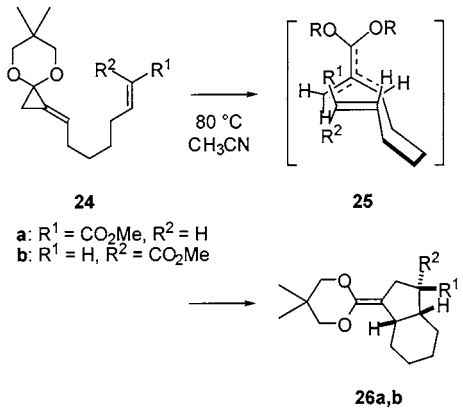


Scheme 9. Stereoselective Synthesis of Substituted Pyrrolidines



the anti-isomer of *O*-methoxime of 2-furaldehyde in CD_3CN 67 times faster than with the syn-isomer. The stereochemistry of the cycloaddition appears to be controlled largely by steric effects. The reaction of *E*-isobutylidenecyclopropane **19** with *anti*-*O*-benzyloxime of *tert*-butyl glyoxylate afforded cycloadduct **21** as the major product and cycloadduct **23** as the minor product. The product structure combined with the *E*-geometry of both reactants suggested that the major product formed through the transition state **20** and the minor through **22**. The origin of the 8:1 preference of **21** over **23** may be ascribed to the smaller magnitude of the lone pair−isopropyl interaction than that with a hydrogen atom as shown in Scheme 9.

4.3. Intramolecular [3 + 2] Cycloadditions.[28] Intramolecular studies provided unexpectedly rich mechanistic information. When the dienyl substrate **24** bearing a four-methylene tether connected to *E*-unsaturated ester (**24a**; $R^1 = CO_2Me$, $R^2 = H$) was heated in acetonitrile at 80 °C, the cycloaddition took place smoothly to give the expected bicyclo[4.3.0]nonane cycloadduct **26a** (eq 5). The olefin geometry is retained, and the ring fusion is cis in accordance with the endo transition state (i.e., R^1 closer to the acetal group). The reaction of the *Z*-unsaturated ester **24b** ($R^1 = H$, $R^2 = CO_2Me$) also gave a single diastereomer **26b** with retention of the olefin geometry. Here, the endo rule no longer holds: Presumably, the conformational constraint of bicyclic ring formation[29] compete with endo selection and overrides it.

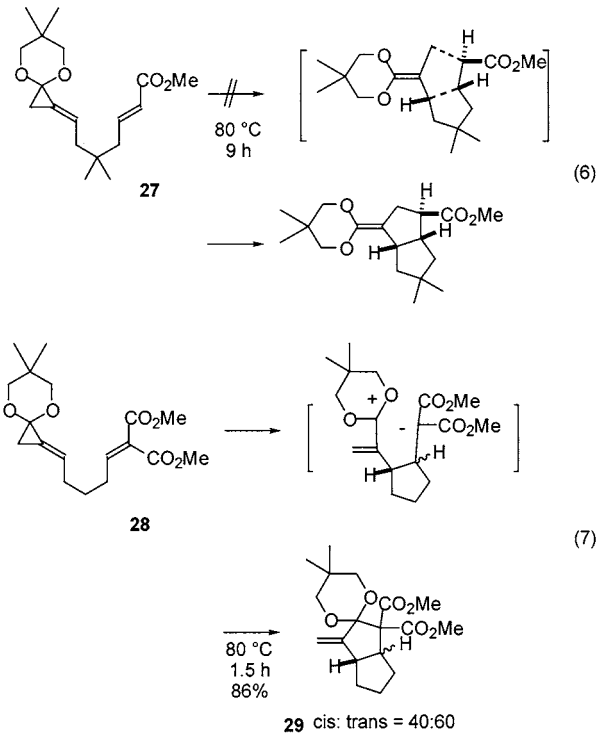


(5)

A surprise came when we attempted to form a bicyclo[3.3.0]octane ring with a lower homologue **27** (eq 6).[21] This substrate failed to cyclize and returned the starting material. Molecular models of the [3.3.0] system indicated that the geometry required for concerted cycloaddition leading to either cis- or trans-fused bicyclo[3.3.0]octane is significantly strained. In sharp contrast, an alkylidene malonate substrate **28** with the same tether took place smoothly to give the [3.3.0]cycloadduct **29** now as a 1:1 cis/trans fused mixture (eq 7).[30] The trans-fused product is so strained that the C−C bond flanked by the acetal and the ester groups undergoes hydrolytic cleavage on silica gel. This difference reflects the mechanistic crossover from the concerted to a stepwise reaction.

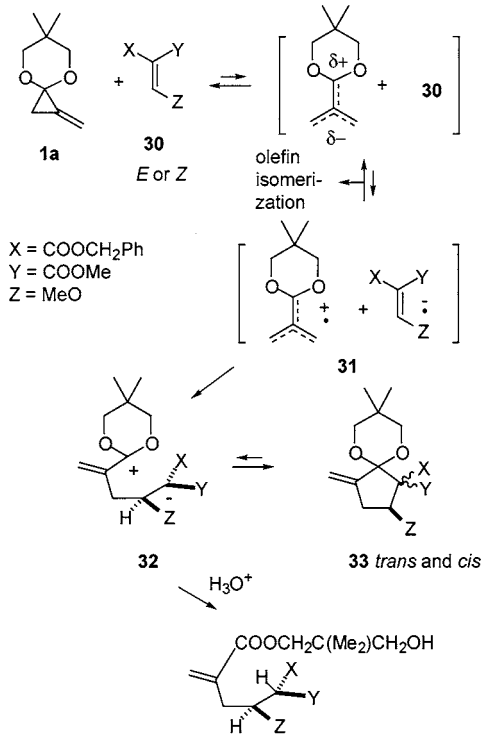
5. Stepwise [3 + 2] Cycloaddition Reactions

Stepwise cycloaddition of the dipolar TMM occurs with highly electron-deficient substrates (e.g., **30**) to produce predominantly an α-alkylidene acetal (e.g., **33**) instead of the ketene acetal that is formed in the concerted cycloaddition (compare Scheme 10 with Scheme 6).[31] Detailed studies on the reaction of **1a** with *E*- and *Z*-isomers of benzyl methyl *β*-(methoxy)methylenemalonate (**30**) showed, among other results, (1) rapid and nonstereospecific cycloaddition and (2) slow isomerization of the starting olefin during reaction, which does not take place in the



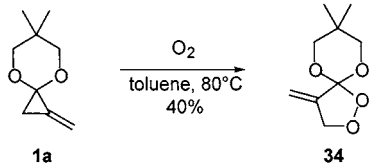
absence of **1a**. The reaction is therefore considered to proceed in a stepwise manner: TMM **2a** is formed first and donates one electron to **30** to generate a radical ion pair **31**. Radical coupling gives a zwitterionic intermediate **32** where the positive and negative charge reside at the centers that allow the most effective stabilization. Ring closure of **32** gives the cyclopentane **33**. It is interesting to note that the C−C bond flanked by the acetal and the ester groups in **33** is easily hydrolyzed by water probably via the zwitterion **32**.

Scheme 10. Single Electron Transfer Initiated Stepwise Cycloaddition



Roughly speaking, an olefin whose reduction potential is less negative than about −1.8 V (vs SCE) reacts through this mechanism. Interestingly, the dipolar TMM **1a** reacts with these olefins faster than with MeOH, water,[32] or acetic acid. Carbonyl compounds,[33] acyl imines[34] and fullerenes react, probably also in a stepwise manner, to give the *exo*-methylene acetals as the major product. The results are summarized in Scheme 11.

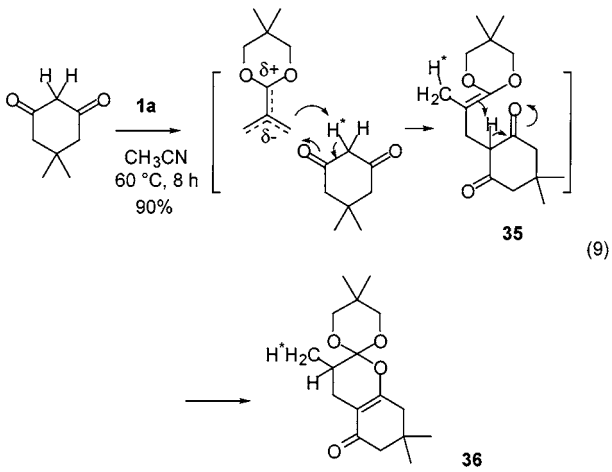
The DMCP **1a** reacts slowly with molecular oxygen even under the conditions where methyl acrylate undergoes rapid cycloaddition. Only after bubbling oxygen for 24 h at 80 °C into a toluene solution containing **1a** does it afford an unstable peroxide **34** in 40% yield (eq 8).[35] In no cases did we observe CIDNP signals in the heated solution of **1a**.[36] These and other observations strongly suggest that triplet TMM species is not generated in any systems described in this Account.



(8)

6. Other Reactions

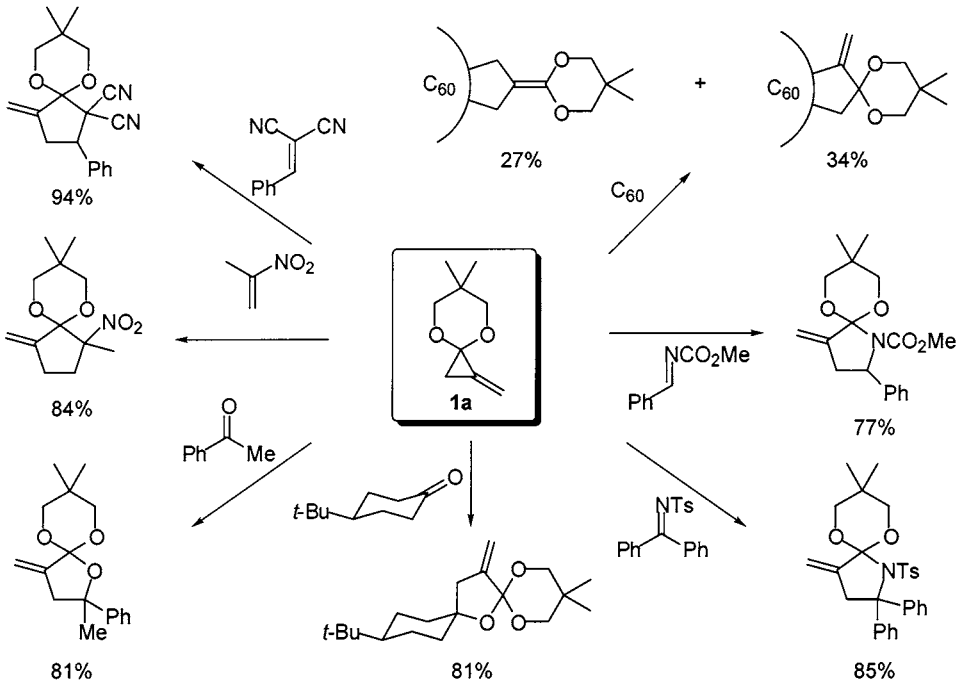
6.1. Formal [3 + 3] Cycloaddition with Active Methylene Compounds.[37] As described in a previous section, the dipolar TMM reacts with MeOH to form a new C−O bond. We thus conjectured that an active methylene compound may also react to form a new C−C bond (eq 9). The reality was a little more complicated: When we heated an equimolar mixture of DMCP and dimedone, we obtained a dihydropyran derivative **35**, as the result of a formal [3 + 3] cycloaddition of the TMM to an enol. The reaction involves two sequential proton transfers revealed by deuterium-labeling.



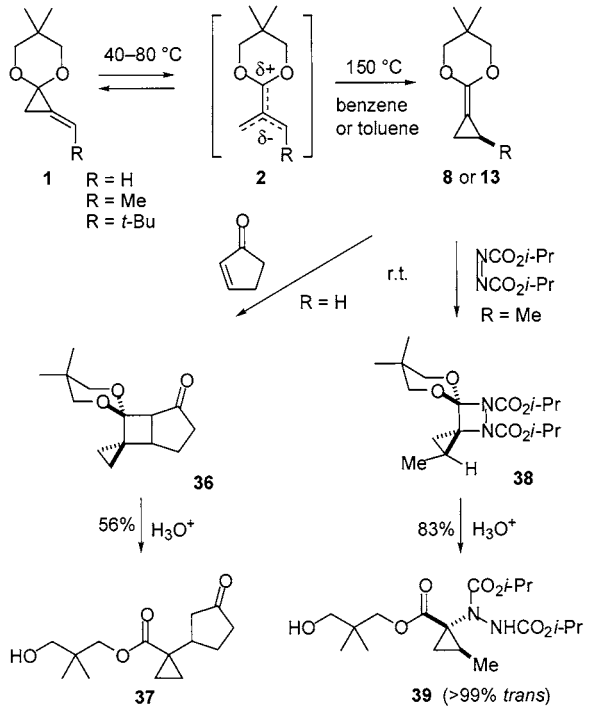
(9)

6.2. [2 + 2] Cycloaddition of Dimethyleneketene Acetal.[38,39] High-temperature thermolysis of DMCP **1** produces the dimethyleneketene acetal **8** or **13** (Scheme 12; see also Schemes 3 and 4), which is hydrolytically

Scheme 11. Stepwise [3 + 2] Cycloaddition Reactions and the Major Products

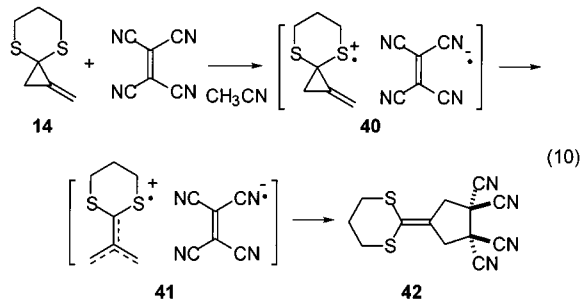


Scheme 12. Formation and Reactions of Dimethyleneketene Acetals



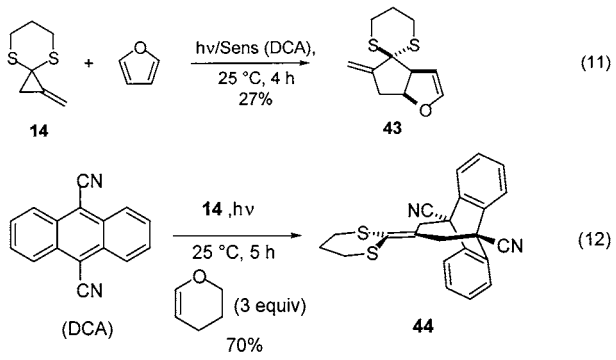
unstable. This highly strained ketene acetal serves as a useful surrogate of the enolate anion of an alkyl cyclopropanecarboxylate, which is difficult to generate from the parent ester. The ketene acetal **8** undergoes smooth [2 + 2] cycloaddition to an electron-deficient olefin, a dialkyl azodicarboxylate, and C_{60}. These reactions are apparently stepwise reactions. The cyclobutane ring **36** formed by the reaction with an enone undergoes remarkably facile C−C bond hydrolysis (wet silica gel) to give the formal Michael addition product **37**. The diazacyclobutane **38** formed by the [2 + 2] cycloaddition with *i*-$PrO_2CN{=}NCO_2$*i*-Pr also hydrolyzes to give cyclopropane amino acid **39** with high diastereoselectivity.

6.3. Cycloaddition of Dialkylthio TMM Analogue. As described in section 3.3, the dialkylthiocyclopropane **14** generates an intermediate which does not undergo cycloaddition to methyl crotonate (Scheme 5). However, cycloaddition reactions with highly electron deficient olefinic substrates do take place via radical ion pairs **40** and **41** (eq 10).[20] Thus, a mixture of the dithiomethylenecyclopropane and tetracyanoethylene afforded the ketene dithioacetal cycloadduct **42** in 87% yield when heated at 60 °C.

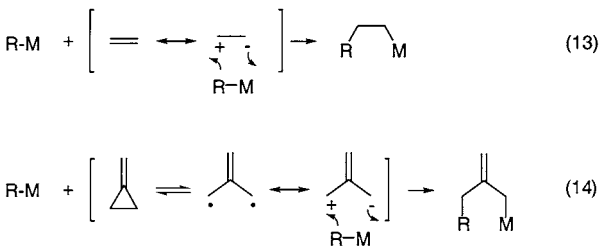


Unlike the acetal counterpart **1**, the thioacetal **14** undergoes [3 + 2] cycloaddition with furan upon irradiation with UV light in the presence of 30 mol % 9,10-dicyanoanthracene (DCA) as a photoelectron-transfer agent (eq 11). The product is an oxabicyclo[3.3.0]octene **43**. It also undergoes a [3 + 4] cycloaddition with DCA to give an adduct **44** in the presence of an excess 2,3-dihydropyran (eq 12). The mechanism of these intriguing photochemical reactions is unclear.

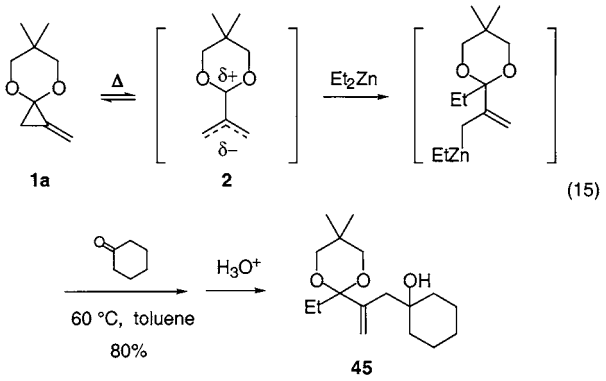
6.4. Carbozincation of Dipolar Trimethylenemethane.[40] Addition of an organozinc reagent across an olefin is a



well-established method for the synthesis of functionalized organozinc reagents (eq 13).[41,42] In a similar way, one would expect that an organometallic reagent undergoes addition to a trimethylenemethane intermediate (eq 14). Ideally, one may hope that methylenecyclopropane undergoes ring opening to generate a TMM that reacts with an organozinc reagent to generate an allylic zinc reagent. This straightforward scheme so far never produced any fruitful experimental outcome. We conjectured that our dipolar TMM may react even with an organometallic reagent to provide a new entry to functionalized organometallics, on which we carried out some pioneering studies.[43]



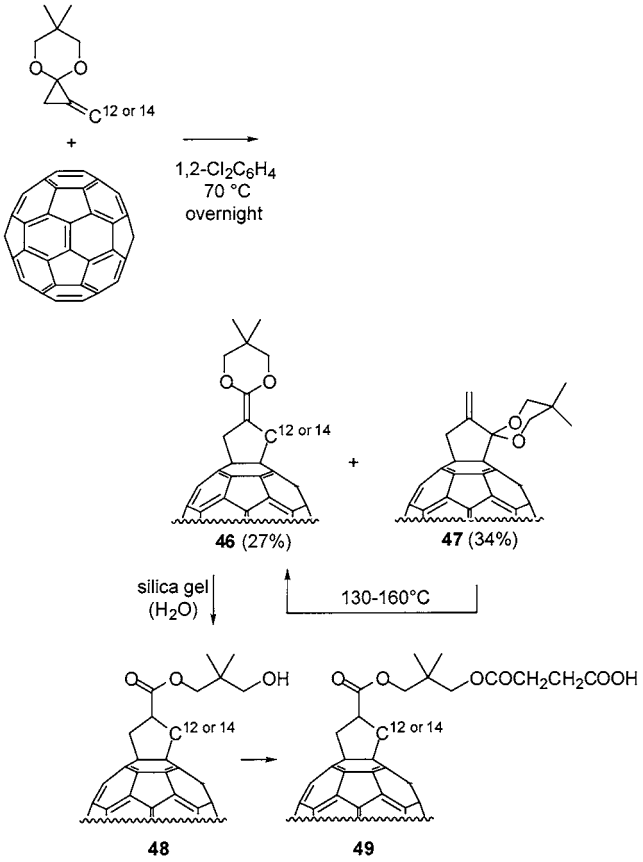
We found that it is feasible to add R_2Zn across the dipolar TMM to generate a functionalized allylic zinc reagent, which can be trapped in situ with a carbonyl compound. For instance, the coupling of **1a**, Et_2Zn, and cyclohexanone afforded the product **45** in 80% isolated yield. There also formed a small amount of the acetal of an α-methylene-γ-lactone (6%), the product of direct [3 + 2] cycloaddition between TMM **2a** and the ketone.



7. Application to Fullerene Functionalization

The high reactivity of the dipolar TMM toward C_{60} provided a unique opportunity to investigate the biological

Scheme 13. Synthesis of Water-Soluble Organofullerenes

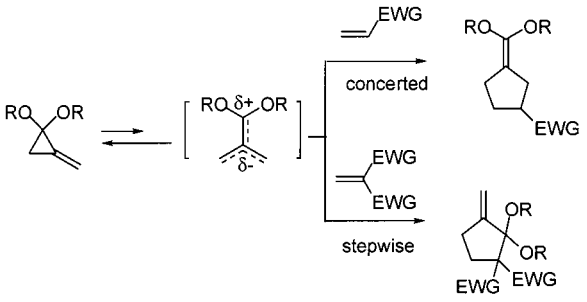


behavior of water-soluble fullerenes.[44] The [3 + 2] cycloaddition between **1a** and C_{60} afforded a mixture of ketene acetal and exomethylene products **46** and **47**,[45,46] the latter isomerizing to the former upon heating at higher temperature (Scheme 13). Silica gel hydrolysis of **46** afforded the alcohol **48**, which was then converted to the succinate **49**. This succinate ester was found to cut double-stranded DNA or to inhibit growth of mammalian cells upon visible light irradiation.[47,48] Inhibition of enzyme activity including that of HIV protease was also noted.[49] When $^{14}CH_3I$ was used en route to the DMCP (cf. Scheme 3), radiolabeled dipolar TMM could be generated. The labeled succinate **49** provided the first information on the pharmacokinetic behavior or water-soluble fullerenes.[50] Notable observations made in this study included (1) the pharmacokinetic behavior of water-soluble fullerene being similar to that of a hydrophobic steroid, (2) the very low level of acute toxicity, and (3) the ability of fullerene go through blood brain barrier, paving a way to the recent development of fullerene biology.[51,52]

8. Conclusion

The synthetic viability of thermal generation of a dipolar TMM species from methylenecyclopropanes has been established for the first time by the use of DMCP **1** as summarized in Scheme 14. The synthesis of the staring material **1** can be achieved on a large scale using inexpensive commercially available compounds, 1,3-dichloro-2-propanone, neopentyl glycol, sodium amide, and am-

Scheme 14. Concerted and Stepwise [3 + 2] Cycloaddition Reactions of Dipolar TMM



monia (solvent). The compound by remains unchanged upon moderate heating but reacts smoothly in the presence of an appropriate electrophile to render the present cycloaddition chemistry an attractive as a synthetic method.

This new route to reactive dipolar TMM species has an intellectually pleasing character for its own sake: the singlet TMM intermediate is reversibly generated in a spectroscopically undetectable amount from DMCP, and therefore, if the molecule fails to react with a suitable olefinic partner, it simply cyclizes back to the starting cyclopropane. Since the concentration of the TMM species is kept very low, dimerization reaction is effectively suppressed.

The installation of the two alkoxy groups onto TMM has a large impact on reactivity of the TMM, the magnitude of which is comparable to the effects of alkoxy substituents on ethylene (cf. ethylene vs enol silyl ether). The dialkoxy group lowers the activation energy of the cyclopropane ring cleavage from about 40 to about 20 kcal/mol. For reasons yet unclear, the *gem*-dialkoxy substitution suppresses intervention of triplet TMM. Radical character observed in some reactions has been ascribed to single electron-transfer mechanisms rather than the triplet TMM. The *gem*-alkoxy TMM is a dipolar species that acts as a nucleophilic 1,3-dipole. Note however that "dipolar" does not necessarily means "zwitterionic", as the TMM is rather unreactive toward highly polarized proton sources such as MeOH or water. Experiments and theory suggest that this TMM shows its dipolar character only in its planar conformation.

The [3 + 2] cycloaddition of the TMM to an electron-deficient olefin such as an α,β-unsaturated carbonyl compound conforms to an endo-rule, where attractive interaction between the acetal carbon in the TMM and the carbonyl group in the electrophile controls the stereoselectivity. Finally, the ketene acetal and the α-methylenecarbonyl functionality in the products are attractive for further synthetic elaboration. One application that we have found uniquely effective is the study of on the biological activity of fullerenes, which is currently developed into a new gene delivery system.[53,54]

This Account is dedicated to the memory of the late Satoshi Ejiri, with whom we shared the most exciting period of the research. We thank our collaborators listed in the references, in particular, Dr. Masaharu Nakamura, for their experimental and intellectual contributions, without which this work could never be completed. Collaboration with Prof. Keiji Morokuma was vital for the theoretical understanding of the complex chemistry of trimethylenemethane species. Financial support from Monbu Kagakusho for the whole period of the research (Grant-in-Aid for Scientific Research, Specially Promoted Research) is gratefully acknowledged. Continued support on the computer time from the Institute for Molecular Science is gratefully acknowledged.

References

(1) Cf.: *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vols. 4 and 5.
(2) Cf.: Barbante, C.; Veysseyre, A.; Ferrari, C.; Van De Velde, K.; Morel, C.; Capodaglio, G.; Cescon, P.; Scarponi, G.; Boutron, C. Greenland snow evidence of large scale atmospheric contamination for platinum, palladium, and rhodium. *Environ. Sci. Technol.* **2001**, *35*, 835−839.
(3) Cf.: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976. See also ref 1.
(4) (1) Boger, D. L.; Brotherton, C. E. *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, p 147. (b) Tokuyama, H.; Isaka, M.; Nakamura, E. Thermal Reactions of Substituted Cyclopropenone Acetals. Regio- and Stereochemistry of Vinylcarbene Formation and Low-Temperature [3 + 2] Cycloaddition. *J. Am. Chem. Soc.* **1992**, *114*, 5523−5530.
(5) (a) Nakamura, E. Thermal [3 + 2] Cycloadditions−"A 6π Game". In *Organic Synthesis in Japan. Past, Present and Future*; Noyori, R., Ed.; Tokyo Kagaku Dojin: Tokyo, 1992; pp 275−282. (b) Yamago, S.; Nakamura, E. [3 + 2] Cycloaddition of Trimethylenemethane and Its Equivalents. *Org. React.*, in press.
(6) Dowd, P. Trimethylenemethane. *Acc. Chem. Res.* **1972**, *5*, 242−248.
(7) Berson, J. A. The Chemistry of Trimethylenemethanes, a New Class of Biradical Reactive Intermediates. *Acc. Chem. Res.* **1978**, *11*, 446−453.
(8) Allan, A. M.; Carroll, G. L.; Little, R. D. The Versatile Trimethylenemethane Diyl; Diyl Trapping Reactions-Retrospective and New Modes Reactivity. *Eur. J. Org. Chem.* **1998**, 1−12. Little, R. D. Diyl Trapping and Electroreductive Cyclization Reactions. *Chem. Rev.* **1996**, *96*, 93−114. Little, R. D. The Intramolecular Diyl Trapping Reaction. A Useful Tool for Organic Synthesis. *Chem. Rev.* **1986**, *86*, 875−884.
(9) Little, R. D.; Bukhari, A.; Venegas, M. G. A New Route to Linearly Fused Tricyclopentanoids. Diyl Trapping Reactions in Organic Synthesis. *Tetrahedron Lett.* **1979**, *4*, 305−308.
(10) LeFevre, G. N.; Crawford, R. J. Kinetics of Some Methylenecyclopropane Rearrangements. *J. Org. Chem.* **1986**, *51*, 747−749. Kirmse, W.; Murawski, H.-R. Thermal Rearrangement of 1-Alkoxy-2-methylenecycloproanes. *J. Chem. Soc., Chem. Commun.* **1977**, 122−123.
(11) Gilbert, J. C.; Butler, J. R. Degeneracy in the Methylenecyclopropane Rearrangement. *J. Am. Chem. Soc.* **1970**, *92*, 2168−2169.
(12) Noyori, R.; Hayashi, N.; Kato, M. Reaction of Methylenecyclopropanes with Tetracyanoethylene. A New Cycloaddition Involving Three- and Four-Carbon Units. *J. Am. Chem. Soc.* **1971**, *93*, 4948−4950.
(13) Yamago, S.; Nakamura, E. Use of Methylenecyclopropanone Ketals for Cyclopentane Synthesis. A New Efficient Thermal [3 + 2] Cycloaddition. *J. Am. Chem. Soc.* **1989**, *111*, 7285−7286.
(14) Dolbier, J. W. R., Jr.; Burkholder, C. R. The Bimolecular Reactions of Trimethylenemethane Diradicals with Acrylonitrile and Molecular Oxygen. *Tetrahedon* **1985**, *41*, 297−307.
(15) Rule, M.; Mondo, J. A.; Berson, J. A. Synthesis and Thermolysis of 5-Alkylidenebicyclo[2.1.0]pentanes. Generation and Dimerization of Trimethylenemethane Triplet Biradicals by Bond Rupture of Strained Hydrocarbons. *J. Am. Chem. Soc.* **1982**, *104*, 2209−2216. Mazur, M. R.; Berson, J. A. Formal Kinetic Proof of Reversible Unimolecular Transformation to a Biradical as an Obligatory First Step in the Mechanism of Cycloaddition of 5-Isopropylidenebicyclo[2.1.0]pentane to Olefins. *J. Am. Chem. Soc.* **1982**, *104*, 2217−2222. Mazur, M. R.; Berson, J. A. Identification of a Biradical as the Reactive Form of the 2-Isopropyridenecyclopentane-1,3-diyl Singlet Species. *J. Am. Chem. Soc.* **1981**, *103*, 684−686.
(16) Carpenter, B. K.; Little, R. D.; Berson, J. A. The Influence of Substituents on the Molecular Orbital Energies and Ground Electronic States of Substituted Trimethylenemethanes. *J. Am. Chem. Soc.* **1976**, *98*, 5723−5725. Platz, M. S.; McBride, J. M.; Little, R. D.; Harrison, J. J.; Shaw, A.; Potter, S. E.; Berson, J. A. Triplet Ground States of Trimethylenemethanes. *J. Am. Chem.*

Soc. **1976**, *98*, 5725−5726. Siemionko, R.; Shaw, A.; O'Connell, G.; Little, R. D.; Carpenter, B. K.; Shen, L.; Berson, J. A. Frontier Orbital Control of Regiospecificity in Sinlget Cycloadditions of 2-Methylenecyclopenta-1,3-Diyls. *Tetrahedron Lett.* **1978**, 3529.
(17) Nakamura, M.; Wang, X. Q.; Isaka, M.; Yamago, S.; Nakamura, E. Synthesis and [3 + 2] Cycloaddition of 2,2-Dialkoxy-1-methylenecylopropane: 6,6-Dimethyl-4,8-dioxa-1-methylenespiro[2.5]-octane. *Org. Synth.*, submitted for publication.
(18) Isaka, M.; Matsuzawa, S.; Yamago, S.; Ejiri, S.; Miyachi, Y.; Nakamura, E. Applications of Metalated Cyclopropenone Ketals in a General Synthesis of Cyclopropenones. An Efficient Synthesis of the Antibiotic Penitricin. *J. Org. Chem.* **1989**, *54*, 4727−4729. Isaka, M.; Ejiri, S.; Nakamura, E. General Synthesis of Cyclopropenones and Their Acetals. *Tetrahedron* **1992**, *48*, 2045−2057.
(19) Nakamura, E.; Yamago, S.; Ejiri, S.; Dorigo, A. E.; Morokuma, K. Reversible Generation of Trimethylenemethanes by Mild Thermolysis of Dialkoxy Methylenecyclopropanes. *J. Am. Chem. Soc.* **1991**, *113*, 3183−3184.
(20) Nakamura, M.; Toganoh, M.; Ohara, H.; Nakamura, E. Cycloaddition Reactions of Trimethylenemethane Radical Cation Generated from Methylenecyclopropanone Thioacetal. *Org. Lett.* **1999**, *1*, 7−10.
(21) Mori, S.; Nakamura, E. Unpublished results.
(22) Yamago, S.; Ejiri, S.; Nakamura, E. A Concise Synthetic Route to Cyclopentenes by [3 + 2] Cycloaddition of Dipolar Trimethylenemethane to Acetylenes. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2154−2156.
(23) Yamago, S.; Nakamura, M.; Wang, X. Q.; Yanagawa, M.; Tokumitsu, S.; Nakamura, E. Thermal Hetero [3 + 2] Cycloaddition of Dipolar Trimethylenemethane to *O*-Alkyloximes. Straightforward Synthetic Route to Substituted Pyrrolidines and Prolines. *J. Org. Chem.* **1998**, *63*, 1694−1703.
(24) Rosenstock, B.; Gais, H.-J.; Herrmann, E.; Raabe, G.; Binger, P.; Freund, A.; Wedemann, P.; Krüger, C.; Lindner, J. Formal Asymmetric Synthesis of Pentalenolactone E and Pentalenolactone F 1. Retrosynthesis and π-Facil Differentiation in Palladium-Catalyzed and Dipolar [3 + 2]-Cycloaddition Reactions of Bicyclic Alkenes: Evidence for Electrostatic Control of Stereochemistry. *Eur. J. Org. Chem.* **1998**, 257−273.
(25) Little, R. D.; Bode, H.; Stone, K. J.; Wallquist, O.; Dannecker, R. Use of Heteroatom-Containing π Systems as Diylophiles in the Intermolecular 1,3-Diyl Trapping Reaction. Construction of Heterocycles *J. Org. Chem.* **1985**, *50*, 2400−2401.
(26) Ejiri, S.; Yamago, S.; Nakamura, E. Regio- and *endo*-Stereoselective [3 + 2] Cycloaddition of Trimethylenemethane to Electron-Deficient Olefin. *J. Am. Chem. Soc.* **1992**, *114*, 8707−8708.
(27) Trost, B. M.; Miller, M. L. Criteria for Concertedness in Cycloadditions. *J. Am. Chem. Soc.* **1988**, *110*, 3687−3689.
(28) Nakamura, M.; Toganoh, M.; Wang, X. Q.; Yamago, S.; Nakamura, E. Intramolecular [3 + 2] Cycloaddition Reaction of Dipolar Trimethylenemethane. *Chem. Lett.* **2000**, 664−665.
(29) Roush, W. R. Intramolecular Diels−Alder Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, pp 513−550.
(30) Yamada, T.; Uekusa, H.; Ohashi, Y.; Yamago, S.; Wang, X. Q.; Nakamura, E. *Acta Crystallogr.* **1995**, *C51*, 1137−1139.
(31) Yamago, S.; Ejiri, S.; Nakamura, M.; Nakamura, E. A Single Electron-Transfer Pathway in the [3 + 2] Cycloaddition of Dipolar Trimethylenemethane with Olefins. *J. Am. Chem. Soc.* **1993**, *115*, 5344−5345.
(32) Little, R. D.; Brown, L. M.; Masjedizadeh, M. R. Expression of Dipolar Character in Diyl Trapping Chemistry. *J. Am. Chem. Soc.* **1992**, *114*, 1−3075.
(33) Yamago, S.; Nakamura, E. Thermal Hetero [3 + 2] Cycloaddition Approach to Functionalized Tetrahydrofurans. *J. Org. Chem.* **1990**, *55*, 5553−5555.
(34) Yamago, S.; Yanagawa, M. Nakamura, E. Thermal Hetero [3 + 2] Cycloaddition of Dipolar Trimethylenemethane to N-Sulfonyl and N-Acyl Imines. Synthesis of γ-Amino Acid Derivatives. *Chem. Lett.* **1999**, 879−880.
(35) Cf.: Wilson, R. M.; Geiser, F. Biradical Trapping: The Formation of Bicyclic Peroxides via the Thermal and Photodecomposition of Azo Compounds in the Presence of Oxygen. *J. Am. Chem. Soc.* **1978**, *100*, 2225−2226.
(36) Corwin, L. R.; McDaniel, D. M.; Bushby, R. J.; Berson, J. A. Dimerization and Cycloaddition Reactions of Trimethylenemethane Derivative, 2-Isopropylidenecyclopenta-1,3-Diyl. Mechanistic Separation of Triplet and Singlet Reactions. *J. Am. Chem. Soc.* **1980**, *102*, 276−288.
(37) Nakamura, M.; Yoshikai, N.; Toganoh, M.; Nakamura, E. [3 + 3] Cycloaddition Reaction of Dipolar Trimethylenemethane with Active Methylene Compound. *Synlett* **2001**, 1030−1033 (Noyori Special Issue).
(38) Yamago, S.; Takeichi, A.; Nakamura, E. Synthesis and [2 + 2] Cycloaddition of Dimethyleneketene Acetals. Reaction with C_{60} and Facile Hydrolysis of the C═C Bond Connected to C_{60}. *J. Am. Chem. Soc.* **1994**, *116*, 1123−1124.
(39) Yamago, S.; Takeichi, A.; Nakamura, E. Synthesis of Dimethyleneketene Acetals and Their [2 + 2] Cycloaddition to Olefins and [60]Fullerene as Cyclopropanecarboxylate Synthons. *Synthesis* **1996**, 1380−1388.
(40) Nakamura, M.; Yoshikai, N.; Nakamura, E. Carbozincation of Dipolar Trimethylenemethane. A New Route to Functionalized Organozinc Reagents. *Chem. Lett.* **2002**, 146−147.
(41) Nakamura, E. *Organometallics in Synthesis, A Manual*, 2nd ed.; Schlosser, M., Ed.; John Wiley & Sons: New York, 2002.
(42) (a) Nakamura, M.; Hara, K.; Hatakeyama, T.; Nakamura, E. Regioselective Allylzincation of Alkenylboronate. *Org. Lett.* **2001**, *3*, 3137−3140. (b) Nakamura, E.; Kubota, K.; Sakata, G. Addition of Zincated Hydrazone with Vinyl Grignard Reagent. Ketone Synthesis by Four-Component Coupling. *J. Am. Chem. Soc.* **1997**, *119*, 5457−5459. (c) Kubota, K.; Nakamura, E. Addition of Azaenolate to Simple Unactivated Olefin. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2491−2493.
(43) Kuwajima, I.; Nakamura, E. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: London, 1991; Vol. 2, Chapter 1.14.
(44) Tokuyama, H.; Yamago, S.; Nakamura, E.; Shiraki, T.; Sugiura, Y. Photoinduced Biochemical Activity of Fullerene Carboxylic Acid. *J. Am. Chem. Soc.* **1993**, *115*, 7918−7919.
(45) Prato, M.; Suzuki, T.; Foroudian, H.; Li, Q.; Khemani, K.; Wudl, F.; Leonetti, J.; Little, R. D.; White, T.; Rickborn, B.; Yamago, S.; Nakamura, E. [3 + 2] and [4 + 2] Cycloadditions of C_{60}. *J. Am. Chem. Soc.* **1993**, *115*, 1594−1595.
(46) Yamago, S.; Nakamura, E. Cycloaddition of Dipolar Trimethylenemethane to C_{70} Promoted by a Trace Amount of Water. *Chem. Lett.* **1996**, 395−396.
(47) Yamago, S.; Tokuyama, H.; Nakamura, E.; Prato, M.; Wudl, F. Chemical Derivatization of Organofullerenes through Oxidation, Reduction, C-O and C−C Bond Forming Reactions. *J. Org. Chem.* **1993**, *58*, 4796−4798.
(48) Irie, K.; Nakamura, Y,; Ohigashi, H.; Tokuyama, H.; Yamago, S.; Nakamura, E. Photocytotoxicity of Water-soluble Fullerene Derivatives. *Biosci. Biotech. Biochem.* **1996**, *60*, 1359−1361.
(49) Nakamura, E.; Tokuyama, H.; Yamago, S.; Shiraki, T.; Sugiura, Y. Biological Activity of Water-Soluble Fullerenes. Structural Dependence of DNA Cleavage, Cytotoxicity and Enzyme Inhibitory Activities. *Bull. Soc. Chem. Jpn.* **1996**, *69*, 2143−2151.
(50) Yamago, S.; Tokuyama, H.; Nakamura, E.; Kikuchi, K.; Kananishi, S.; Sueki, K.; Nakahara, H.; Enomoto, S.; Ambe, F. In vivo Biological Behavior of Water-Miscible Fullerenes. ^{14}C-Labeling, Absorption, Distribution, Excretion and Acute Toxicity. *Chem. Biol.* **1995**, *2*, 385−389.
(51) Yamago, S.; Tokuyama, H.; Nakamura, E.; Prato, M.; Wudl, F. Synthesis of Organic Derivatives of Fullerenes. *Trans. Mater. Res. Soc. Jpn.* **1994**, *14B*, 1169−1172.
(52) Zhou, S.; Burger, C.; Chu, B.; Sawamura, M.; Nagahama, N.; Toganoh, M.; Hackler, U. E.; Isobe, H.; Nakamura, E. Spherical Bilayer Vesicles of Fullerene Based Surfactants in Water: A Laser Light Scattering Study. *Science* **2001**, *291*, 1944−1947.
(53) Nakamura, E.; Isobe, H.; Tomita, N.; Sawamura, M.; Jinno, S.; Okayama, H. Functionalized Fullerene as a New Artificial Vector for Transfection. *Angew. Chem., Int. Ed.* **2000**, *39*, 4254−4257.
(54) Isobe, H.; Sugiyama, S.; Fukui, K-i.; Iwasawa, Y.; Nakamura, E. Atomic Force Microscope Studies on Condensation of Plasmid DNA with Functionalized Fullerene. *Angew. Chem., Int. Ed.* **2001**, *40*, 3364−3367.

AR0100935