EFFICIENT SYNTHESIS OF HETEROCYCLES USING HIGHLY ELECTROPHILIC ETHENETRICARBOXYLATES

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Abstract – The synthesis of heterocyclic compounds utilizing highly electrophilic ethenetricarboxylates is described. Ethenetricarboxylate is a member of methylenemalonates and more reactive than frequently used alkylidenemalonates by the electron-withdrawing effect of 2-carboxyl group. They are utilized as efficient Michael acceptors or electron-deficient C=C components. Lewis acids also promote the reactions of ethenetricarboxylate derivatives efficiently. The intermolecular and intramolecular reactions of ethenetricarboxylates towards synthesis of heterocycles are presented.

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1. INTRODUCTION
Heterocycles have a great importance in biology and industry. The development of new efficient methods to synthesize heterocycles is considerable interest. In our research to date, we have shown various synthetic utility of ethenetricarboxylate derivatives. The present review deals with the application of ethenetricarboxylates to synthesize heterocycles.

Arylidene, alkylidene and methylenemalonates 1 can serve as electrophilic partners in the Michael and cycloaddition reactions (Scheme 1).\(^1\) Ethenetricarboxylate is a member of these compounds and it is not as unstable as the parent methylenemalonates 1 (R^2 = H) and more reactive than arylidene, and alkylidenemalonates 1 (R^2 = Ar, R) by the electron-withdrawing effect of 2-carboxyl group. Furthermore, ethenetricarboxylates allow for the facile derivatization at 2-carboxyl group.

Ethenetricarboxylic acid diester 3 is considered to be a useful compound bearing two reactive sites: a CO_2H group and electrophilic C=C component. A few examples of 2-carbonyl group substituted analogues 2 (Y = R) are also included in this review.

\[
\begin{align*}
\text{Scheme 1}
\end{align*}
\]
Lewis acids promote the reactions of ethenetricarboxylate derivatives efficiently. Nucleophiles could undergo conjugate additions and the further bond-forming reactions. Thus, owing to the high reactivity of $\text{C}=$ $\text{C}$ bond, they are susceptible for various cycloadditions reactions and intramolecular cyclization reactions leading to heterocycles.

2. SYNTHESIS OF ETHENETRICARBOXYLATES

Although various preparation methods for ethenetricarboxylate triesters 2 have been reported,$^2$ they are conveniently prepared by the reaction of ketomalonate with the corresponding (triphenylphosphoranylidne)acetates by Wittig reactions (Scheme 2).$^3$

![Scheme 2]

Ethenetricarboxylic acid diester 3 is prepared from 2-tert-butyl ethenetricarboxylate 2 ($Y = \text{O}^\text{t}$$\text{Bu}$) upon treatment with $\text{CF}_3\text{CO}_2\text{H}$.$^{2a}$ Amides 2 ($Y = \text{NRR}'$) are prepared by the condensation reaction of 3 with the corresponding amines in the presence of condensation reagents such as HOBt/EDCI/Et$_3$N (Scheme 2).$^4$ Esters ($Y = \text{OR}$) can also be prepared by the reaction with the alcohols, for example, under Mitsunobu conditions$^5$ or by EDCI/DMAP or EDCI/HOBt condensations.$^6$

Other 2-carbonyl group substituted derivatives such as acetylmethylidene and benzoylethylidene-malonates are also prepared by Wittig reactions.$^{1e,f,2}$ The following method to prepare various aroylmethylidenemalonates 2 ($Y = \text{Ar}$) from easily accessible $\text{trans}$-$2$-aryl-$3$-nitro-cyclopropane-$1,1$-dicarboxylates 4 was reported by Selvi and Srinivasan.$^8$

Treatment of $\text{trans}$-$2$-aryl-$3$-nitro-cyclopropane-$1,1$-dicarboxylates 4 with $\text{BF}_3\cdot\text{OEt}_2$ afforded aroylmethylidenemalonates 2 ($Y = \text{Ar}$) (Scheme 3).

![Scheme 3]
The mechanism shown in Scheme 4 for the formation of aroylmethyldenedmalonates 2 (Y = Ar) from the nitrocyclopropanes 4 was proposed. Ring-opening for the cyclopropanes upon coordination of the Lewis acid to the malonyl and nitro moieties is followed due to more resonance stabilization offered to the carbanion by the malonyl unit. The zwitter ionic intermediate B generated eliminates the nitro group to give the ion-pair C, which, upon recombination, yields the nitro compound D. The Nef reaction of D in the presence of BF₃·OEt₂ furnishes the product 2 (Y = Ar). It was presumed that the Nef reaction took place via nitronic acid−BF₃ complex E, oxaziridine F, and hydroxynitroso intermediate G.

Scheme 4. Mechanism for the formation of 2 (Y = Ar) from 4

3. CYCLOADDITION REACTIONS
3-1. Lewis Acid-Catalyzed Cycloaddition Reactions
3-1-1. Lewis Acid-Promoted Conjugate Addition-Cyclization Reactions with Propargylamines and Alcohols
Methylenetetrahydrofurans and methylenepyrrolidines are potentially useful as their synthetic intermediates and the skeletons also appear in natural products. Propargyl alcohols and amines have been effectively utilized in one-pot formal [3+2] cycloadditions to lead to methylenetetrahydrofurans and methylenepyrrolidines.

We have reported zinc- and indium-promoted conjugate addition-cyclization reaction to afford methylenepyrrolidines and methylenetetrahydrofurans. Triester 2a (Y = O'Bu) and N-methylpropargylamine (5a) reacted in the presence of ZnBr₂ (1.2 equiv) in CH₂Cl₂ at room temperature overnight to afford five-membered proline derivative 6a (Y = O'Bu, R = Me) in 81% yield (Scheme 5). Catalytic conditions using InBr₃–Et₃N (0.2 equiv) in CH₂ClCH₂Cl at 80 °C for 4 h gave the cyclized product 6a in 74% yield. The reaction of 2a and N-propargylamine 5b in the presence of catalytic InBr₃–Et₃N (0.2 equiv) at 80 °C for 4 h gave a proline derivative 6b (Y = O'Bu, R=H) in 75% yield.
The reaction conditions for the indium bromide catalysis (0.2 equiv InBr$_3$–Et$_3$N, in CH$_2$ClCH$_2$Cl, 80 °C, 4 h) were also shown to be applicable to various ethenetricarboxylates 2. In addition to various esters 2b,c (Y = OEt, OCH$_2$Ph), amide 2d (Y = NMeCH$_2$C≡CH) and ketone derivatives 2e (Y = Ph) also gave the novel proline analogs 6 in 45–69% yields.

The reaction conditions for the zinc and indium catalysis were also suitable for methyltetrahydrofuran formation. The reactions of ethenetricarboxylate 2 with propargyl alcohol 7 in the presence of catalytic amount of InBr$_3$–Et$_3$N gave methylenetetrahydrofuran 8 (Y = OEt) in 73% yield. The reaction of 2e,f with 7 in the presence of InBr$_3$ gave cyclized product 8 in 78–88% yield (Scheme 6).

Stoichiometric use of propargyl alcohol 7 is sufficient to lead to satisfactory yields, in contrast to the reaction of diethyl benzylidenemalonate (1a (R$^1$ = Et, R$^2$ = Ph) in Scheme 1). These results arise from the higher reactivity of 2 towards propargyl alcohol and propargyl amines than that of 1a. The reaction of ketone derivative 2e or piperidine amide 2f with 7 also gave methylenetetrahydrofurans 8 in 78–88% yield.
Reaction of 2b and 2e in the presence of ZnBr₂ (0.2 equiv) gave 8 in good yields (Y = OEt, 81%; Y = Ph, 89%). Use of AlCl₃ and SnCl₄ gave a small amount of 8, accompanied by the noncylized adduct and starting material 2.

A Lewis acid catalyzed cyclization of ethenetricarboxylate derivatives was applied to that with γ-substituted propargyl alcohols. Reaction of 2 and 3-silyl-2-propyn-1-ols 9 in the presence of a catalytic amount of ZnBr₂ (0.2 equiv) in ClCH₂CH₂Cl or toluene at 80–110 °C gave (Z)-silyl-substituted methylenetetrahydrofurans 10 stereoselectively (Scheme 7). Reaction of 2 with various silyl groups such as TMS-, PhMe₂Si-, Ph₂MeSi-, Ph₃Si-, CH₂=CHMe₂Si-, and PhCH₂Me₂Si-substituted propargyl alcohols gave cyclized products 10 in 53–92% yield. The reaction of less reactive diethyl benzylidemalonate 1a with 9 (SiR₃ = TMS, SiMe₂Ph) in the presence of ZnBr₂ also gave cycloadducts in 63–68% yields.

Scheme 7

Ester-substituted propargyl alcohols were expected to be highly activated in the electrophilic acetylene moiety. Reaction of 2b,e and methyl 4-hydroxy-2-butynoate (11) in the presence of a catalytic amount of ZnX₂, InCl₃, FeCl₃ and AlCl₃ (0.2 equiv) gave the Z-ester-substituted methylenetetrahydrofurans 12 stereoselectively in 52–98% yield. On the other hand, reaction of 2 and 11 in the presence of SnCl₄ at room temperature in CH₂Cl₂ gave the E-isomer 13 exclusively in 49–74% yield.

Scheme 8
The reaction of triethyl ethenetricarboxylate 2b and \( \gamma \)-CF\(_3\)-substituted propargyl alcohols 14 in the presence of ZnBr\(_2\) (0.2 equiv) at 110 °C in toluene gave 15 in 66–85% yield, as diastereomer mixtures in a 1:1 to 1:1.3 ratio, respectively (Scheme 9).\(^{13}\) The CF\(_3\) group activates alkyne as an electron-withdrawing group. For the geometry of the alkene moiety, Z-CF\(_3\)-substituted methylenetetrahydrofurans were obtained selectively. The reaction of 2b and 1-(3,3,3-trifluoroprop-1-ynyl)cyclohexanol 14f with ZnBr\(_2\) (0.2 equiv) gave 15f in lower yield (32%), probably due to steric hindrance in the initial addition step.

**Scheme 9**

The probable mechanism for formation of the five-membered ring is shown in Scheme 10. Conjugate addition of nitrogen or oxygen of propargylic substrates to zinc- (or indium-) coordinated 2 in the diester moiety and proton transfer give intermediate A. The use of highly electrophilic ethenetricarboxylates 2 may be effective in the first conjugate-addition step. Zinc (or indium) transfer to alkyne leads to intermediate B, and the following cyclization gives C. Protonation of the sp\(^2\) carbon in the intermediate C.

**Scheme 10.** Proposed mechanism for the reaction of 2 and propargyl amines and alcohols with MX\(_n\) (M = Zn, In)
by the generated proton and zinc (or indium) coordination to the diester moiety give the more stable intermediate D. The intermediate D furnishes the five-membered rings along with the release of the zinc (or indium) catalyst. The facile cyclization by zinc (or indium) Lewis acid can be explained by the dual activation ability of the carbonyl and alkyne moieties. DFT calculations support the proposed mechanism involving the effective zinc chelate for C-C bond formation.

The proposed mechanism is in agreement with the observed Z selectivity for the zinc Lewis acid promoted reaction of 2 and γ-substituted propargyl alcohols: γ-silicon substituted propargyl alcohols 9, 4-hydroxy-2-butynoate (11), and γ-CF₃-substituted propargyl alcohols 14. Thus, the alkenyl zinc intermediate C in Scheme 10 retains the configuration.

The observed E selectivity for SnCl₄ can be explained as shown in Scheme 11. Initial adduct E, which is the same type as intermediate A in Scheme 10, would transform to intermediate F, not a B-type intermediate in Scheme 10, because the harder Sn⁴⁺ may prefer carbonyl oxygen to carbon. Ring closure may occur from the intermediate F leading to intermediate G. Intermolecular proton- (or protonation by liberated H⁺) from outside would lead to Sn-diester chelate intermediate H.

On the other hand, reaction of γ-trifluoromethyl-α-aryl propargyl alcohols 14 with 2b in the presence of 1 equiv of SnCl₄ gave cyclobutane derivatives 16 in 29–49% yield (Scheme 12). Formation of cyclobutane 16a arises from the [2+2] cycloaddition between ethenetricarboxylate 2b and chloroallene 17, which is produced by the reaction of propargyl alcohol 14a and SnCl₄.
3-1-2. Lewis Acid-Catalyzed Reactions Leading to Quinoline Derivatives

Quinolines are an important class of compounds found in many naturally occurring and synthetic molecules possessing a variety of biological activities. The development of new efficient synthetic strategies for the construction of quinolines is of considerable importance from the viewpoint of the medicinal and organic chemistry.

We have examined the reaction of ethenetricarboxylates 2 or 3a and 2-ethynylanilines 18 as the one-carbon homologues for propargylamines 5 in the presence of zinc Lewis acids. The ZnBr₂ and Zn(OTf)₂ catalyzed reaction of tert-butyl ester 2a and 18a in ClCH₂CH₂Cl at 80 °C gave an unexpected compound 19a as a major isolable product in 35 and 50% yields, respectively (Scheme 13). Interestingly, the ZnBr₂ and Zn(OTf)₂ catalyzed reaction of 2a and 18b also gave 19a in 38 and 58% yields, respectively. Apparently, tBu and TMS groups were lost under the reaction conditions.
Furthermore, reactions between a substrate bearing a free CO$_2$H 3a and 2-ethynylaniline 18a gave 19a in 43–58% yield. The reaction of various 2-ethynylaniline derivatives 18c was also examined and they gave the bridged quinolone products 19. 4-CN-Derivative 18c (Z = 4-CN) gave the product 19 (Z = 4-CN) in up to 85% yield.

The reaction of 2a with 2'-aminoacetophenone 20 also gave the bridged tetrahydroquinoline derivative 19a (Scheme 14). It is supposed that the initially formed Michael-aldol-type product X undergoes further ring closure, giving the bridged tetrahydroquinoline 19a.

2-Aminobenzaldehydes 21 are expected to be more reactive than 2' -aminoacetophenone 20. Zinc triflate-catalyzed reaction of 2a with 2-aminobenzaldehydes 21 at 80 °C in ClCH$_2$CH$_2$Cl gave bridged quinoline derivatives 22 in 15–95% yield (Scheme 15), similar to the reaction of 2a and 2'-aminoacetophenone 20. On the other hand, the reaction of 2a or 2b and 21 with Zn(OTf)$_2$ (0.2 equiv) at room temperature in CH$_2$Cl$_2$ gave hydroxyquinoline derivatives 23 in 38–90% yield. The major isolated diastereoisomers obtained for the hydroxyquinoline derivatives 23 have 1,3-cis stereochemistry, probably due to the stable diequatrial (OH and CO$_2$R) conformation of six-membered ring products. The reaction of diethyl benzylidenemalonate (1a) with 21 (Z = H, 5-Cl) gave a complex mixture including the starting benzylidene malonate 1a.
Heating **23** (R = 'Bu) with zinc trflate (0.2 equiv) at 80 °C in ClCH₂CH₂Cl gave bridged quinoline derivatives **22** in 75–96% yield.

DFT calculations support the proposed reaction mechanism shown in Schemes 16 and 17 to give the same bridged quinoline product from 2-ethynylaniline **18** and 2'-aminoacetophenone **20**. The zinc coordination of both diester and alkyne was found in **E₁**, transition state **TS₁** and the resulting intermediate **E₂** for the first cyclization step. Then, a proton and zinc change places to give the intermediate **E₃**. Protonation to the alkene moiety of **E₃** and zinc transfer may give the benzylic cation intermediate **E₄**. This stable intermediate **E₄** may be the same intermediate as that from 2'-aminoacetophenone **20** in Scheme 17. The ring closure transition state **TS₂** by zinc carboxylate moiety was obtained and the second ring closing step may be a facile process.

The proposed reaction mechanism for 2'-aminoacetophenone **20** is shown in Scheme 17. The zinc coordination of both the diester and acetyl moiety was found in the precursor **A₁**, transition state **TS₁A**, and the resulting intermediate **A₂** for the first cyclization step. Proton transfer from **A₂** leads to the intermediate **A₃**, which is shown as **X** in Scheme 13. Successive proton, zinc, and water transfers occur to
give the same intermediate A5 as that of ethynylaniline apart from the eliminated water, E4 in Scheme 16. Then, the second ring closure takes place, similar to the reaction of ethynylaniline 18a to give the bridged tetrahydroquinoline derivative 19a. DFT calculations support the proposed reaction mechanisms for the reactions of ethynylaniline 18a and 2'-aminoacetophenone 20.

The reaction mechanism for 2-aminobenzaldehyde 21a is also proposed in Scheme 17. DFT calculations suggest the facile first ring closure (TS1B < TS1A) and the stability of the formed hydroxyquinoline intermediates B2 and B3 compared with those of the corresponding 2'-aminoacetophenone intermediates A2 and A3 may explain the isolation of the hydroxyquinoline products 23.

Scheme 17. Proposed mechanism for the reaction of 2/3a and 2'-aminoacetophenone (20)/2-aminobenzaldehyde (21a) with Zn(OTf)2 and B3LYP/6-31G* calculated energies.

3-1.3. Lewis Acid-Promoted Cyclization Reactions with Aminoacetals Leading to Nitrogen-Containing Heterocycles

We have reported that Lewis acid-catalyzed cyclization of aminoacetals (24) and triethyl ethenetricarboxylate (2b). The reaction of 3-aminopropionaldehyde diethyl acetal (24a) and 2b in the presence of 1 equivalent of TiCl4 at room temperature gave 4-ethoxy-piperidine-2,3,3-tricarboxylate 25a (R1 = Et) in 92% yield with 2,4-diastereomer ratio 1:1 (Scheme 18). The reaction in the presence of 3 equivalents of TiCl4 gave 2,4-trans-piperidine derivative 25a (R1 = Et) in 86% yield predominantly. The reaction of aminoacetalddehyde diethyl/dimethyl acetals 24b,c and 2b with 3 equivalents of TiCl4 gave 2,4-trans-4-pyrrolidine-2,3,3-tricarboxylates (26a,b) predominantly.
The probable mechanism for formation of the nitrogen-containing six-membered ring is shown in Scheme 19. Conjugate addition of nitrogen of $24a$ to ethenetricaboxylate $2b$ gives an adduct $27$, which is coordinated with TiCl$_4$. TiCl$_4$-promoted abstraction of EtO$^-$ from acetal moiety gives an oxonium intermediate $A$. The electrophilic oxonium moiety in the intermediate $A$ reacts at the generated nucleophilic malonate carbon, to gives the cyclized product $25a$.

The stereochemistry of the nitrogen-containing ring is likely to be under thermodynamic control in the presence of TiCl$_4$ at room temperature. The TiCl$_4$ coordination diastereomers formed during complexation of the cyclized products may vary in stability by steric effects of multiple substituents and their TiCl$_4$ coordination. For six-membered ring formation of $25$, when 3 equivalents of TiCl$_4$ were used, 2,4-trans diastereomer formation is preferred.
3-1-4. Lewis Acid-Promoted Reactions with Allenes: Synthesis of γ-Lactones via Conjugate Addition/Cyclization Reaction

We have reported that the reaction of arylallenes and ethenetricarboxylate triesters 2 with SnCl₄ gave indene derivatives efficiently, via a conjugate addition/Friedel-Crafts cyclization reaction.¹² The reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate (3a) and allene 28a in the presence of SnCl₄ (1 equiv) at room temperature gave indene derivative 29 in 17% yield along with a complex mixture. Interestingly, the reactions of 3a and 28a at -78 °C and subsequent treatment with Et₃N gave γ-lactone 30a in 55% yield (Scheme 20).

The reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate (3a) and various aryl and alkyl allenes 31 in the presence of SnCl₄ at -78 °C or room temperature gave exomethylene γ-lactones 32 and/or the conjugated isomers, α,β-unsaturated-γ-lactones 33 after usual work-up (Scheme 21). The exomethylene γ-lactones 32 are unstable to distillation or column chromatography and difficult to be purified. Treatment of γ-lactones 32 or the mixture of 33 and 32 with Et₃N gave γ-lactones 33.

Scheme 20

Scheme 21
Next, the reactions of triethyl ethenetricarboxylate (2b) and alkylallenes 31d,e,f in the presence of SnCl₄ was examined. The reaction of 1,1-dialkylallenes 31 at room temperature also gave γ-lactones with better yields than the reaction of 3a and 31d,e,f, in 49–82% yield (Scheme 22). One ethyl group is lost in the reaction. 3b

![Scheme 22](image)

Formation of γ-lactones from 3a/2b and 31 may proceed through the common allylic cation intermediate A (Scheme 23). Formation of intermediate B may be reversible. The reaction of 3a and arylarenes 31a–c at lower temperature leads to γ-lactones 32 and 33. At higher temperature the equilibrium moves to the stable C-C bond formation through a Friedel-Crafts reaction in the case of arylallenes.

![Scheme 23](image)

3-2. Palladium-Catalyzed Cyclocarbonylation
Okuro and Alper reported that palladium-catalyzed intermolecular cyclocarbonylation of 2-iodoanilines 34 with triethyl ester 2b gave 2,3,3-triethoxycarbonyl-2,3-dihydro-4(1H)-quinolinone derivatives 35 in 26–90% yields (Scheme 24). 3b They initially tried several reactions of 2-idoaniline 34 with diethyl
benzylidenemalonate 1a. The expected reaction, however, did not take place, and 1a was recovered unchanged. A possible reaction mechanism for the formation of 35 is shown in Scheme 25. Michael addition between 2-iodoaniline (34) and triethyl ester 2b can give the initial Michael adduct 36. The phosphine ligated Pd(0) species, then undergoes oxidative addition to the C-I bond of 36, followed by insertion of carbon monoxide to produce an aroylpalladium intermediate A. Nucleophilic attack of the internal malonate anion on the aroylpalladium intermediate A completes the catalytic cycle affording 4(1H)-quinolinones 35 and regenerates the Pd(0) species.
3-3. Cycloaddition Reactions without Catalysts
3-3-1. Reaction with Electron-Rich Alkenes

Hall Jr. and his coworkers reported that an inverse electron demand hetero Diels-Alder reaction of trimethyl ethenetricarboxylate 2g with electron-rich alkenes 37 (R = OR, SR, Aryl) gave 6-alkoxy-3,4-dihydro-2H-pyrans (Scheme 26). For the reaction of 2g and phenyl vinyl sulfide 37c, [2+2] cycloadduct is formed in the presence of Lewis acids (ZnCl2 or ethereal LiClO4).

We have studied the reaction of the Huisgen zwitterions, derived from triphenylphosphine and azodicarboxylates with ethenetricarboxylates 2. The reaction of dialkyl azodicarboxylates 39 and triphenylphosphine leads to the formation of Huisgen zwitterions A (Scheme 27), which plays an important role in the Mitsunobu reaction. Brunn and Huisgen reported that the cycloaddition reaction of the zwitterion A with dimethyl acetylenecarboxylate afforded pyrazoles. The reactions of the zwitterion and allenes, phenyl isocyanate, phenylisothiocyanate or ketone derivatives leading to various nitrogen-containing heterocycles have been reported. Few cycloaddition reactions of the zwitterion and alkenes leading to pyrazolines have been reported.

The reaction of ethenetricarboxylate 2a (R = O'Bu) and diethyl azodicarboxylate 39a with 1 equivalent of PPh3 in ether at room temperature for 18 h gave pyrazoline 40a (R = O'Bu) in 85% yield and quantitative triphenylphosphine oxide. Reaction of various ethenetricarboxylates 2 and diethyl azodicarboxylate 39a with PPh3 gave pyrazolines 40 efficiently (Scheme 27). The reaction of less reactive diethyl ethyldienemalonate (1b) and 39a with PPh3 at room temperature in ether, 80 °C in benzene and 110 °C in toluene for 18 h gave the cycloadduct in 36–44% yield, along with the remained starting material 1b. The reactions of diethyl benzylidenemalonate (1a) and 39a with PPh3 gave an inseparable mixture possibly containing cycloadduct with the starting alkene 1a at room temperature and higher temperatures.
The formation of the pyrazoline ring may undergo similar to the reaction of zwitterions A and dimethyl acetylenedicarboxylate or allenic esters.\textsuperscript{24,25} To clarify the mechanisms for pyrazoline formation, we carried out DFT calculations for the cyclization reactions of the model compounds, trimethyl ethenetricarboxylate 2g, dimethyl azodicarboxylate 39 (R = Me), and trimethylphosphine (Scheme 28). The structures of intermediates and transition states (TS) were optimized by B3LYP/6-31G* calculations.

Scheme 28. Proposed mechanism for the reaction of model compounds 2g, 39 (R = Me) and trimethylphosphine and B3LYP/6-31G* calculated Gibbs free energies ($T = 298.15$ K and $P = 1$ atm).
Conjugate addition of nitrogen of the zwitterion A (generated from 39 (R = Me) and trimethylphosphine) to ethenetricaboxylate 2g gives the stable intermediate Int1 (ΔG° = -1.57 kcal/mol). The use of highly electrophilic ethenetricarboxylates 2 may facilitate this addition step. The ring closure by a nucleophilic attack of the generated malonate anion to the ester group of the azoester gives betaine intermediate Int2. The intermediate Int2 transforms to the oxaphosphetane intermediate Int4. Elimination of the phosphine oxide from Int3 via a process similar to the Wittig reaction gives the cyclized product 40a.

3-3-3. Reaction of Ethenetricarboxylic Acid Diester with Amino Alcohols
We have examined reactions of 3a and reagents with oxygen and nitrogen nucleophilic moieties. The reaction of 3a with 2-aminoalcohols 41 in the presence of EDCI and HOBt in one pot gave N,O-containing heterocyclic compounds 42, regioselectively. In addition to various 2-aminoalcohols, the reaction of 3a with symmetric secondary 1,2- and 1,3-diamines, 2-aminophenols, 2-hydroxymethylaniline, and pyrocatechol in the presence of EDCI and HOBt in THF gave cyclized products 43–46 as major products (Scheme 29).

The stepwise methods involving N-Boc protected aminoesters or O-TBS protected amides also afforded the regioisomeric 1,4-oxazine derivatives, respectively.6
3-3-4. Reaction of Ethenetricarboxylic Acid Diester with Carbodiimides

Volonterio and Zanda reported that the reaction of ethenetricarboxylic acid diester 3a and carbodiimides 47 in the absence of a nucleophile gave N,N-disubstituted hydantoins 50 in good yields (Scheme 30). Strongly activated acid 3a reacted smoothly (5 min) with N-dialkylcarbodiimides 47a–d in CH₂Cl₂ at room temperature. Even sterically hindered tert-butylcarbodiimide 47 (R = R¹ = tBu) gave 50 in 64% yield.²⁸

This process is likely to take place through the putative 2-imino-oxazolin-5-one intermediate 49, which in turn is formed by intramolecular aza-Michael addition of the unsaturated O-acrylisourea 48.

![Scheme 30](image)

On the other hand, we have used EDCI/HOBt conditions in the presence of amines to prepare amides of ethenetricarboxylates as major products in many examples (Scheme 2). Formation of HOBt activated ester may facilitate amide formation.

3-3-5. Reaction of Aroylmethylene Malonates with Diamines

Selvi and Srinivasan reported that the cyclocondensation of aroylmethylene malonates 2e,h with acetamidine hydrochloride 51 in the presence of triethylamine in CH₂Cl₂ gave the imidazole derivatives 52 after monodecarbethoxylation of the malonyl unit (Scheme 31).⁸ Treatment of 2e,i,j with ortho-phenylenediamines 53 in ethanol afforded quinoxalines 54 in 90–97% yield with the loss of the malonyl unit. Similarly, the reaction of 2e,i with o-aminothiophenol 55 furnished benzo[1,4]thiazine derivatives 56.
4. CYCLIZATION REACTIONS OF FUNCTIONALIZED ETHENETRICARBOXYLATES

4-1. Lewis Acid-Promoted Intramolecular Cyclization Reactions of Esters and Amides

4-1-1. Lewis Acid-Promoted Intramolecular Cyclization Reactions of Alkynyl Esters and Amides

Snider and Roush reported an example of cyclization of propargylic esters of ethenetricarboxylic acid 57 in the presence of FeCl₃ to give chlorinated \( \gamma \)-lactones (Scheme 32). ²h

We have reported that reactions of enynes with three carboxyl groups (59) in the presence of halogen-ligand Lewis acids gave cyclized products with halide incorporation (60) with high generality. ³f

The reaction of 59a with ZnBr₂ (1.2 equiv)-THF (1.0 equiv) or FeCl₃ (1.2 equiv) at -40 °C in CH₂Cl₂ and
subsequent workup with H_2O gave the cyclized HBr and HCl adducts 60 in 52–98% yield (Scheme 33). The reaction gave the (Z)-olefin products stereoselectively. Reaction of 59b in the presence of ZnX_2 (X = Br, I) or FeCl_3 at room temperature gave cyclized products 60b.

Reaction of the phenylsubstituted alkyne amide 59c (R_1 = Ph) with ZnBr_2·THF in CH_2Cl_2 at -40 °C gave the brominated γ-lactam 60c (Z = NMe, R_1 = Ph, X = Br) in 84% yield. Zinc chloride and zinc iodide promoted reactions also gave the corresponding halogenated γ-lactams in good yields. Reaction of n-propyl-substituted alkyne 59c (R_1 = n-Pr) with FeCl_3 or zinc halides in CH_2Cl_2 proceeded at room temperature.

Facile isomerization and dehydrohalogenation of five-membered products 60a (Z = O) and 60b (Z = O) by Al_2O_3 or Et_3N were also observed (Scheme 34); this process introduces conjugated moieties into the products. 22

Next, we have shown that zinc halide-promoted cyclization of enynes with a terminal acetylenic moiety 59d afforded alcohol incorporated six-membered rings 63 in the presence of an alcohol as the main products in 41–75% yield (Scheme 35). 30 Methanol, ethanol, benzyl alcohol, and allyl alcohol worked efficiently as nucleophiles.
The probable mechanism for formation of these six-membered rings 63 can be shown in Scheme 36, similar to the intermolecular reaction in Section 3-1-1. Conjugate addition of oxygen of alcohol to zinc-coordinated A in the diester moiety and proton transfer gives intermediate B. Zinc coordination to alkyne leads to intermediate C, and the following cyclization gives D. Protonation of the sp^2 carbon in the intermediate D by the generated proton gives the intermediate E. The intermediate E furnishes the six-membered rings 63 along with the release of the zinc Lewis acid.

4-1-2. Lewis Acid-Promoted Intramolecular Cyclization Reactions of Alkenyl and Allenyl Esters and Amides

Snider and Roush reported that Lewis acid-promoted intramolecular reactions of alkenyl ethenetricarboxylates 64 gave chlorinated γ-lactones 65 (Scheme 37).^{3b}
We have studied Lewis acid-promoted intramolecular reactions of alkenyl ethenetetracarboxylates and the corresponding amides in detail. Reaction of allyl ethenetetracarboxylates and the amides 64 with Lewis acids (1-2 equiv) such as TiCl₄, TiBr₄, AlCl₃ and AlBr₃ gave 3,4-trans halogenomethyl γ-lactone and γ-lactam derivatives 65 stereoselectively in high yields (Scheme 38). The 3,4-stereochemistry of 65 was determined by NOE experiments.

We have also examined the reaction of (E)/(Z)-2-butyl esters 64OE/Z with Lewis acid. The (E)/(Z)-2-butyl dimethyl esters 64OE/Z (R = Me) are the substrate which Snider and Roush reported.
The reaction with 1 equivalent of AlCl₃ or FeCl₃ at room temperature overnight gave chloro-substituted γ-lactones 65h,i as major products. The 3,4-cis stereochemistry was suggested for 65h,i (R = Me) by Snider and Roush based on coupling constants[3b] and we have assigned the stereochemistry as 3,4-trans based on NOE.[4] The relative configurations of CHClMe to C-3, C-4 for diastereomers 65h,i were deduced as shown in Scheme 39 by the proposed reaction mechanism (see Scheme 41).

Reaction of (E)/(Z)-2-alkenyl amides 64NE/Z with ZnI₂ gave 3,4-trans γ-lactam diastereomers 65Na or 65Nb stereospecifically, along with the ene adducts (see Section 4-2-1). The 3,4-trans stereochemistry of both 65Na and 65Nb was determined by NOEs. The relative configurations of CHI(CH₂R) to C-3, C-4 for diastereomers 65Na and 65Nb could be deduced as shown in Scheme 40, respectively, similar to the oxygen analogues discussed below.

The proposed reaction mechanism to give the halogenated five-membered heterocycles 65 is shown in Scheme 41.
The structures of the intermediates and transition states of model compounds (the corresponding methyl ester 64m and Al₂Cl₆) were calculated using B3LYP/6-31G*. The reaction may proceed stereospecifically via the concerted Cl-C bond formation by intermolecular Cl anti attack and C-C bond formation. Protonation and removal of AlCl₂OH yield the product 65. The relative configuration of CHClMe to C-3, C-4 for diastereomers, 65h,i and 65Na,b could be deduced as by the similar reaction mechanism for the reaction of 64a.¹⁴

Next, we have studied Lewis acid-promoted intramolecular reactions of allenyl ethenetricarboxylates and the corresponding amides. The reaction of allenyl ethenetricarboxylates 66a,b with 1 equivalent of various Lewis acid such as AlCl₃ and AlBr₃ in CH₂Cl₂ at room temperature gave 3,4-trans haloalkenyl γ-lactone derivatives 67 stereoselectively (Scheme 42).³¹

Reaction of allenyl amides (68b) with AlCl₃, ZnCl₂, ZnBr₂, and ZnI₂ at room temperature gave 3,4-trans γ-lactams 69 in 55–76% yield (Scheme 43). The 3,4-trans stereochemistry was determined by NOEs.

Furthermore, we have examined Lewis acid-promoted reactions of 2-substituted 2-alkenyl esters of ethenetricarboxylate 70.³² Interestingly the six-membered ring formation from 70 was found. Thus, the reaction of the substrates 70a,b,c, with AlCl₃ (1 equiv) gave chlorinated 2-oxotetrahydro-2H-pyrans
71a, b, c in 55–70 yield as the major products (Scheme 44). However, the reaction of 70d with AlCl3 or FeCl3 gave a complex mixture.

![Chemical structure of 70a, 70b, 70c, 70d, 71a, 71b, 71c, 71d]

**Scheme 44**

The reaction of allenyl ester was examined as the extension for six-membered ring formation of the ester analog. The reaction of 2-methylbuta-2,3-dienyl ethenetricarboxylate 72 with 1 equivalent of various Lewis acids such as AlCl3, SnCl4, EtAlCl2, TiCl4, and FeCl3 in CH2Cl2 at room temperature gave δ-lactone 73 as a major product along with a small amount of γ-lactone 74 (Scheme 45). Use of TiCl4 gave δ-lactone 73 (46%) and γ-lactone 74 (30%).

![Chemical structure of 72, 73, 74]

**Scheme 45**

The reaction of ethenetricarboxylate 2-methyl-2-propenyl amide 75a with AlCl3 (1 equiv) at room temperature gave 2-oxo-5,6-dehydropiperidine 76a in 68% yield as a major product. The reaction of 2-methyl-2-propenyl amides of ethenetricarboxylate 75a–c with a catalytic amount of AlCl3 (0.2 equiv) at room temperature or 80 °C gave 2-oxo-5,6-dehydropiperidines 76a–c in 59–70% yield as major products (Scheme 46). The reaction of 3a with EtAlCl2 or FeCl3 (0.2 equiv) also gave 76a as a major product in 49% and 67% yields, respectively. The reaction of 2-phenyl-2-propenyl amide 75f gave 76f as an isolable
product in 34% yield. The lower yield of 76f possibly results from side reactions at Ph moiety and steric reasons. Six-membered rings were formed similar to the corresponding esters, but the elimination products 76 were obtained selectively, instead of the substitution products 77 corresponding to the compound 71 in Scheme 44.

![Scheme 44](image)

Scheme 44

4-1-3. Lewis Acid-Promoted Intramolecular Cyclization Reactions of Aromatic Esters and Amides

We have shown that a cyclization reaction of ethenetricarboxylate derivative aromatic compounds in the presence of various Lewis acids gave benzo-annulated cyclic compounds such as oxindole and benzofuran derivatives via Friedel-Crafts intramolecular Michael addition in high yields. For example, the reaction of diethyl 2-[(N-methyl-N-phenylcarbamoyl)methylene]malonate (78a, R₁ = R² = R³ = H) in the presence of ZnCl₂ at room temperature gave diethyl 2-(1-methyl-2-oxindolin-3-yl)malonate (79a) in 98% yield (Scheme 47). The reactions also proceeded with a catalytic amount of a Lewis acid such as AlCl₃, ZnCl₂, ZnBr₂, Sc(OTf)₃, or InBr₃. Reaction of substrates with various alkyl groups on nitrogen proceeded to give oxindole derivatives. Interesting regioselectivity was observed for meta halogen substrates. Dimethoxyisoquinoline analogs were also obtained by this reaction using a catalytic Lewis acid.

![Scheme 47](image)

Scheme 47
The reaction of triester substrates was also examined. The reaction of 1,1-diethyl 2-phenyl ethene-1,1,2-tricarboxylate (80a) with ZnBr₂ in CH₂Cl₂ at room temperature did not proceed, however, reaction with the stronger Lewis acid FeCl₃ (1.2 equiv) gave diethyl 2-oxobenzofuran 81 in 65% yield (Scheme 48). Substrates without OMe at the meta-position of the phenyl ring did not react with ZnX₂ but reacted with FeCl₃. On the other hand, the reaction of m-methoxyphenyl esters 80b–d with ZnCl₂ or Sc(OTf)₃ gave 2-oxobenzofuran derivatives 81 in high yields and regioselectivity.

4-1-4. Lewis Acid-Promoted Cyclization Reactions of 2-tert-Butyl Ester

We have reported that a novel cyclization of 1,1-diethyl 2-tert-butyl ethenetricarboxylate (2a) in the presence of a Lewis acid afforded a 5,5-dimethyl-γ-lactone derivative 82a (Scheme 49).³c

It was suggested that the formation of γ-lactone 2a probably proceeds by Lewis acid-catalyzed generation of isobutylene driven by activation of the tert-butyl ester, followed by elimination. Addition of isobutylene to the double bond of ethenetricarboxylate 2a (activated by Lewis acid chelation to two carboxyl ester groups), followed by ring closure of carboxyl group to the stable tertiary carbocation thus generated, delivers product 82a (Scheme 50).
To obtain information on the mechanism, the reaction of 1a with 2-methyl-2-butene (1.0 equiv for 2a) with SnCl₄ (1.2 equiv for 2a) in CH₂Cl₂ was examined. The reaction gave a mixture of 82b (3:1 diastereomer mixture, 71%) and 82a (29%) (Scheme 51). Furthermore, the reaction of a 1:1 mixture of 2k and 2l with SnCl₄ gave 82a (17%), 82c (21%), 82b (30%), and 82d (21%), respectively. These results demonstrate that the reaction of carboxylic acids and alkenes generated in situ proceeds not in an intramolecular but rather in an intermolecular manner.

Lewis acid-promoted intermolecular reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate (3a) and various alkenes such as 2-methyl-2-butene and 2,3-dimethyl-2-butene to afford highly functionalized γ-lactones were also developed.³
4-2. Thermal Cyclizations Including Sequential Reactions

4-2-1. Ene Reactions

Kelly reported that the reaction of the mixed anhydride 83 and dienol 84 in the presence of pyridine underwent an intramolecular ene reaction directly at 25 °C via norbornadienylmethyl ethenetricarboxylate 85 (Scheme 52). Steric (strain relief) and electronic effects (tetra-substituted electron-rich double bond) may make this example a facile ene reaction.

\[
\text{MeO}_2\text{C} - \text{CO}_2\text{Me} + \text{OH} \quad \xrightarrow{25 \degree \text{C}} \quad \text{CO}_2\text{Me} - \text{CO}_2\text{Me}
\]

Scheme 52

Snider et al. reported that treatment of 64OE/Z (R = Me) at 135 °C for 200 h gave ene products 87 along with the hetero Diels-Alder adduct as described in the next section 4-2-2. The 3-methyl-2-butenyl ester 64OX is slightly more reactive than 64OE/Z (R = Me), giving a 70:30 mixture of ene adduct 88 and hetero Diels-Alder adduct described in the next section at 85 °C for 112 h. On the other hand, heating 64OX at 120 °C for 30 h gives 88 in 95% yield (Scheme 53).

\[
\text{MeO}_2\text{C} - \text{CO}_2\text{Me} \quad \xrightarrow{135 \degree \text{C} \quad 200 \text{h}} \quad \text{MeO}_2\text{C} - \text{CO}_2\text{Me}
\]

Scheme 53

We have reported that the ene cyclization of Z-alkenyl amides 64NZ proceeds stereoselectively (Scheme 54). At room temperature or 80 °C, (Z)-amides 64NZ were transformed to 3,4-cis ene adducts 89. The
$t_{1/2}$ of $64NZ$ ($R = H$) is approximately 90 h in CDCl$_3$ at 24 °C. ($E$)-amides $64NE$ were transformed to 3,4-cis and trans ene adduct mixtures $89$ at room temperature or 80 °C.

Scheme 54

The stereochemistry of cyclized products $89$ from alkenyl amides $64N$ can be explained by a concerted ene reaction mechanism discussed in references.$^{2c,34}$ Transition state for formation of the 3,4-trans substituted product $89$ from the Z-alkene $64NZ$ is sterically impossible. Thermal reaction of Z-alkene gave 3,4-cis product $89$ stereoselectively. On the other hand, thermal reaction of $E$-alkene $64NE$ gave a mixture of 3,4-cis and trans diastereomers $89$ via two transition states.$^{4b}$

Attempted preparation of amide precursor $N$-benzyl-$N$-(3-methyl-2-butenyl)amide $91$ led directly to ene-cyclized product $92$ with 3:1 trans/cis diastereomeric ratio in 50% yield (Scheme 55).

Scheme 55

The ene cyclization of amides $64NE/Z$ proceeds at lower temperature than oxygen derivatives $64OE/Z$. The conformations of $E$ and $Z$ esters $64OE/Z$ ($R = Me$) and model compounds of amide substrates $64NE/Z$ were calculated. The $s$-cis and $s$-trans conformations about the 2-ester or amide carbonyl moiety are shown in Scheme 56. $E$ ester $64OE$ and $Z$ esters $64OZ$ are 7.48 and 7.44 kcal/mol more stable in $s$-cis conformation, respectively, probably because of the steric repulsion. On the other hand, the energy differences of $s$-cis and $s$-trans conformations of dimethyl ester amides are small. In order to cyclize, they
must have s-trans conformations. The rate enhancement observed with the ene reaction of amides probably originates from higher ratio of the reactive conformer.\textsuperscript{35,\textdagger}

Scheme 56. Conformational isomers of ester 64OE/Z (R = Me) and model compounds of amide substrates 64NE/Z. Relative Gibbs free energies \((T = 298.15 \text{ K and } P = 1 \text{ atm})\) for s-cis E/Z conformational isomers are obtained by B3LYP/6-311+G(d,p) SCRF = (PCM, solvent = CH\textsubscript{2}Cl\textsubscript{2}) \textbackslash B3LYP/6-31G* and they are relative to O s-trans and N s-trans models, respectively.

4-2-2. Diels-Alder Reactions

Snider et al. described reversible formation of hetero Diels-Alder adducts as biproducts of ene adducts as described in the previous section, on treatment of allylic ethenetricarboxylates 64 (Scheme 57).\textsuperscript{3e}

Snider et al. also reported that heating cinnamyl triester 96 in benzene-d\textsubscript{6} at 85 °C led to a ~2:1 mixture of 96 and hetero Diels-Alder adduct 97. On raising the temperature to 115 °C the equilibrium shifts, giving a
8:1 mixture. Lowering the temperature to 80 °C reestablishes the 2:1 equilibrium. Thus, the hetero Diels-Alder reaction is reversible and thermodynamically unfavored at high temperature (Scheme 58).

![Scheme 58](image)

We have reported that reaction of N-benzyl- or N-allyl-2-furylmethylamine 98 and 1,1-diethyl 2-hydrogen ethenetricarboxylate 3a in the presence of EDCI/HOBt/Et3N at room temperature led directly to an intramolecular Diels-Alder adducts 100 in 65–82% yield stereoselectively (Scheme 59). The intermediate 99 could not be observed under the reaction conditions of amide formation. The structure of 10-oxa-3-aza-tricyclo[5.2.1.01,5]dec-8-ene 100 was determined by X-ray analysis.

![Scheme 59](image)

5. CONCLUSION
The synthesis of heterocyclic compounds utilizing highly electrophilic ethenetricarboxylates are described based, in part, on research conducted in our group. Intermolecular and intramolecular reactions of ethenetricarboxylates towards heterocycles were presented. Owing to the three carbonyl groups, ethenetricarboxylates are utilized as reactive Michael acceptors or electron-deficient C=C components. Lewis acids also promote the reactions of ethenetricarboxylate derivatives efficiently. The high functionalization of the products may be useful for further elaboration.

REFERENCES


**Professor Shoko Yamazaki** was born in Osaka, Japan. She studied chemistry at Osaka University and received her Ph.D. in 1986 under the supervision of Prof. Ichiro Murata. From 1985, she was an assistant lecturer at Nara University of Education. She joined the group of Professor Barry M. Trost as a visiting researcher at Stanford University (USA) in 1987–1988. She became an assistant Professor of Nara University of Education in 1989 and since 2003, a full Professor of Nara University of Education. She was the recipient of Kansai Branch Award of The Society of Synthetic Organic Chemistry, Japan in 2008. Her current main research interests are the development of new organic synthetic reactions.