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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.

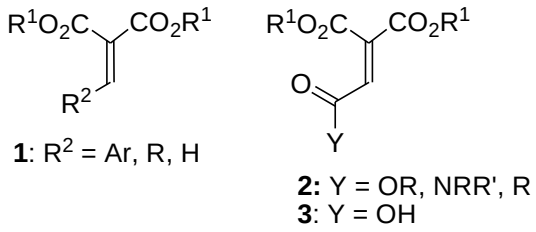
CONTENTS

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.

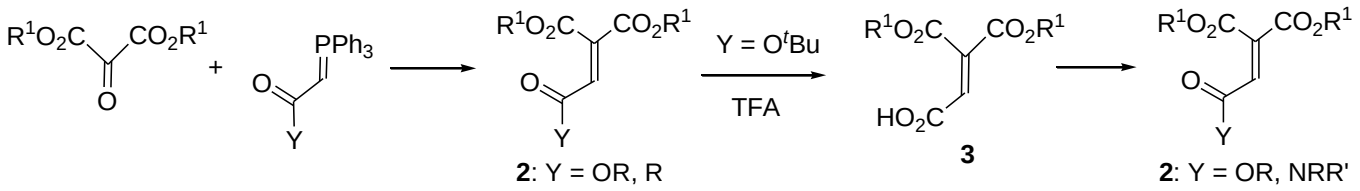


Scheme 1

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 C=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 ketomalonates with the corresponding (triphenylphosphoranylidne)acetates by Wittig reactions (Scheme 2).[3]

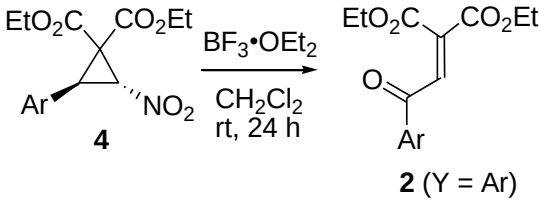


Scheme 2

Ethenetricarboxylic acid diester **3** is prepared from 2-*tert*-butyl ethenetricarboxylate **2** (Y = O^{t}Bu) upon treatment with CF_3CO_2H.[2a] Amides **2** (Y = NRR') are prepared by the condensation reaction of **3** with the corresponding amines in the presence of condensation reagents such as HOBt/EDCI/Et_3N (Scheme 2).[4] Esters (Y = 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]

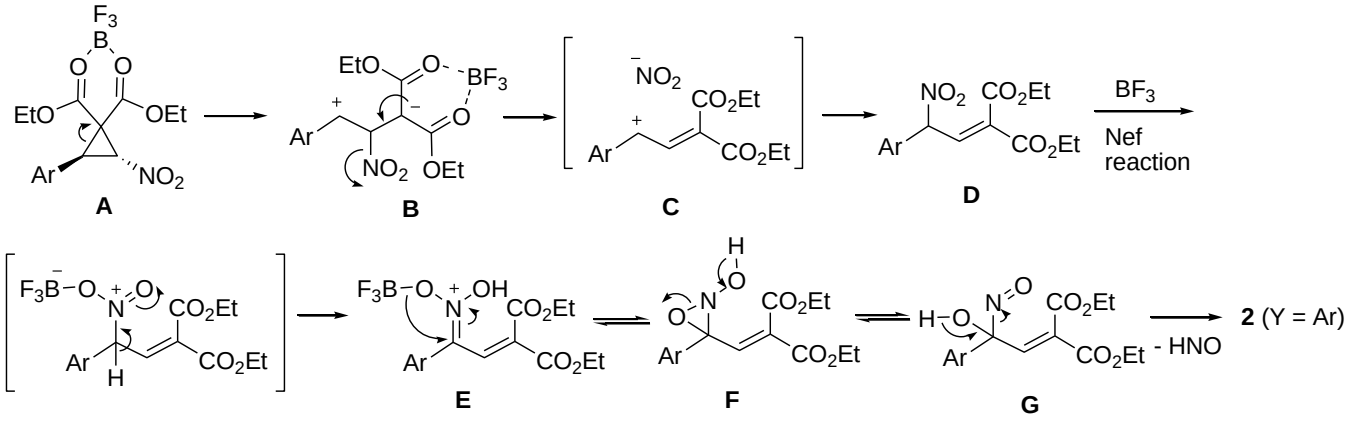
Other 2-carbonyl group substituted derivatives such as acetylmethylidene and benzoylmethylidene-malonates are also prepared by Wittig reactions.[3e,f,7] The following method to prepare various aroylmethylidenemalonates **2** (Y = Ar) from easily accessible *trans*-2-aryl-3-nitro-cyclopropane-1,1-dicarboxylates **4** was reported by Selvi and Srinivasan.[8]

Treatment of *trans*-2-aryl-3-nitro-cyclopropane-1,1-dicarboxylates **4** with $BF_3{\cdot}OEt_2$ afforded aroylmethylidenemalonates **2** (Y = Ar) (Scheme 3).



Scheme 3

The mechanism shown in Scheme 4 for the formation of aroylmethylidenemalonates **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 $BF_3{\cdot}OEt_2$ furnishes the product **2** (Y = Ar). It was presumed that the Nef reaction took place via nitronic acid−BF_3 complex **E**, oxaziridine **F**, and hydroxynitroso intermediate **G**.



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

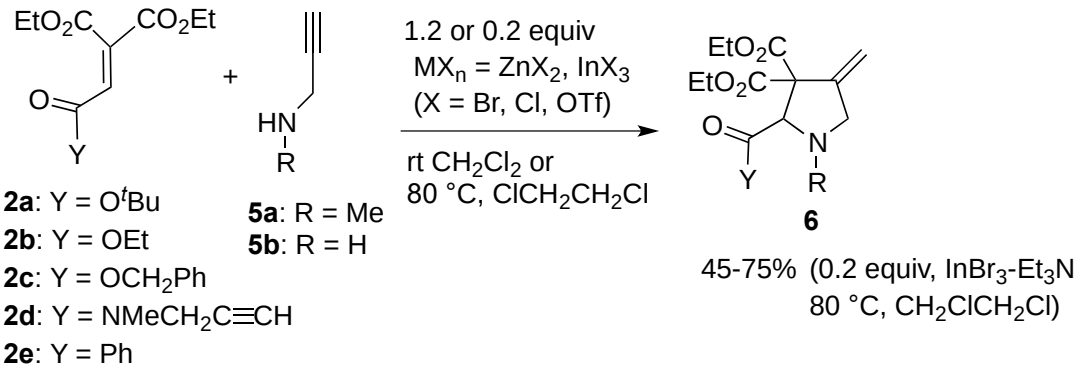
3. CYCLOADDITION REACTIONS

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.[9] Propargyl alcohols and amines have been effectively utilized in one-pot formal [3+2] cycloadditions to lead to methylenetetrahydrofurans and methylenepyrrolidines.[10,1c]

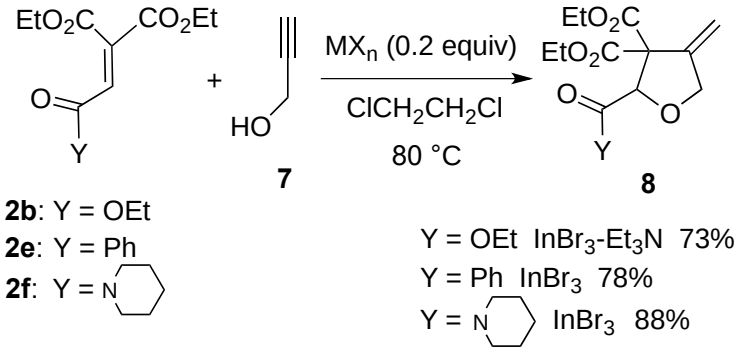
We have reported zinc- and indium-promoted conjugate addition-cyclization reaction to afford methylenepyrrolidines and methylenetetrahydrofurans. Triester **2a** (Y = O^{t}Bu) and *N*-methylpropargylamine (**5a**) reacted in the presence of $ZnBr_2$ (1.2 equiv) in CH_2Cl_2 at room temperature overnight to afford five-membered proline derivative **6a** (Y = O^{t}Bu, R = Me) in 81% yield (Scheme 5).[11] Catalytic conditions using $InBr_3$–Et_3N (0.2 equiv) in CH_2ClCH_2Cl 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 $InBr_3$–Et_3N (0.2 equiv) at 80 °C for 4 h gave a proline derivative **6b** (Y = O^{t}Bu, R=H) in 75% yield.



Scheme 5

The reaction conditions for the indium bromide catalysis (0.2 equiv $InBr_3$–Et_3N, in CH_2ClCH_2Cl, 80 °C, 4 h) were also shown to be applicable to various ethenetricarboxylates **2**. In addition to various esters **2b**,**c** (Y = OEt, OCH_2Ph), amide **2d** (Y = $NMeCH_2C{\equiv}CH$) 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 methylenetetrahydrofuran formation. The reactions of ethenetricarboxylate **2** with propargyl alcohol **7** in the presence of catalytic amount of $InBr_3$–Et_3N 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).

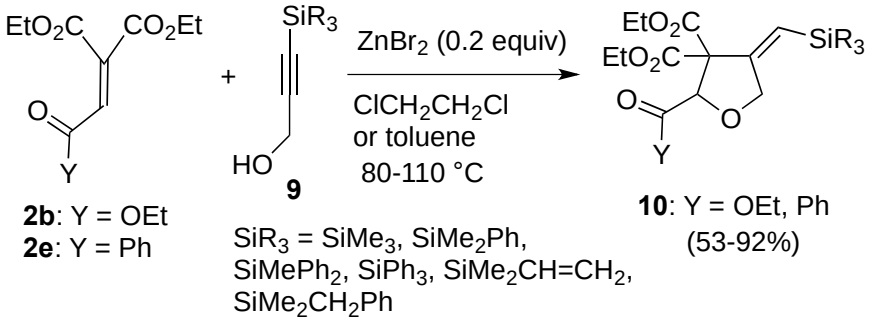


Scheme 6

Stoichiometric use of propagyl 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).[10a,1c] 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.

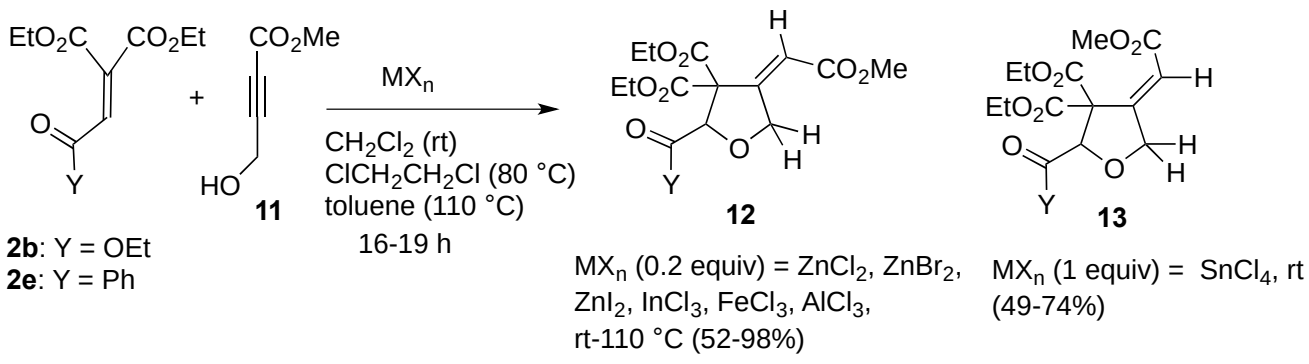
Reaction of **2b** and **2e** in the presence of $ZnBr_2$ (0.2 equiv) gave **8** in good yields (Y = OEt, 81%; Y = Ph, 89%). Use of $AlCl_3$ and $SnCl_4$ gave a small amount of **8**, accompanied by the noncyclized adduct and starting material **2**.

A Lewis acid catalyzed cyclization of ethenetricarboxylate derivatives was applied to that with γ-substituted propargyl alcohols.[12] Reaction of **2** and 3-silyl-2-propyn-1-ols **9** in the presence of a catalytic amount of $ZnBr_2$ (0.2 equiv) in $ClCH_2CH_2Cl$ 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-, $PhMe_2Si$-, Ph_2MeSi-, Ph_3Si-, $CH_2=CHMe_2Si$-, and $PhCH_2Me_2Si$-substituted propargyl alcohols gave cyclized products **10** in 53–92% yield. The reaction of less reactive diethyl benzylidenemalonate **1a** with **9** (SiR_3 = TMS, $SiMe_2Ph$) in the presence of $ZnBr_2$ also gave cycloadducts in 63–68% yields.



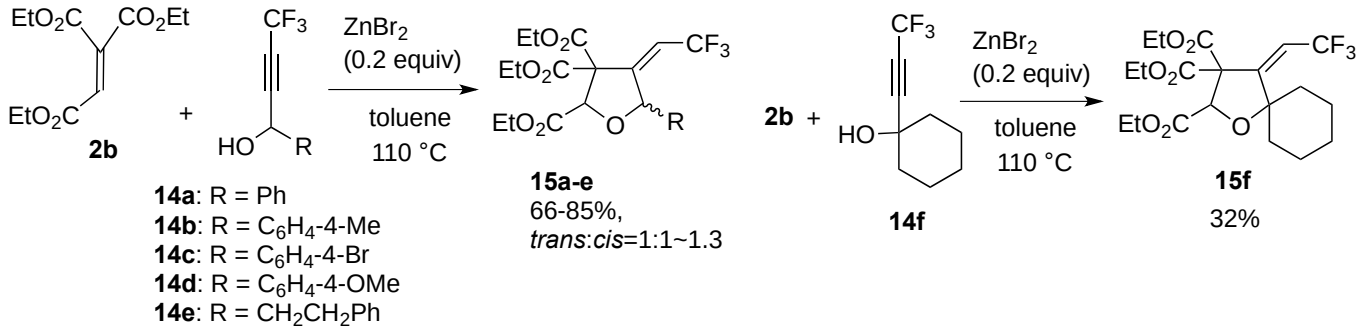
Scheme 7

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 ZnX_2, $InCl_3$, $FeCl_3$ and $AlCl_3$ (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 $SnCl_4$ at room temperature in CH_2Cl_2 gave the *E*-isomer **13** exclusively in 49–74% yield.



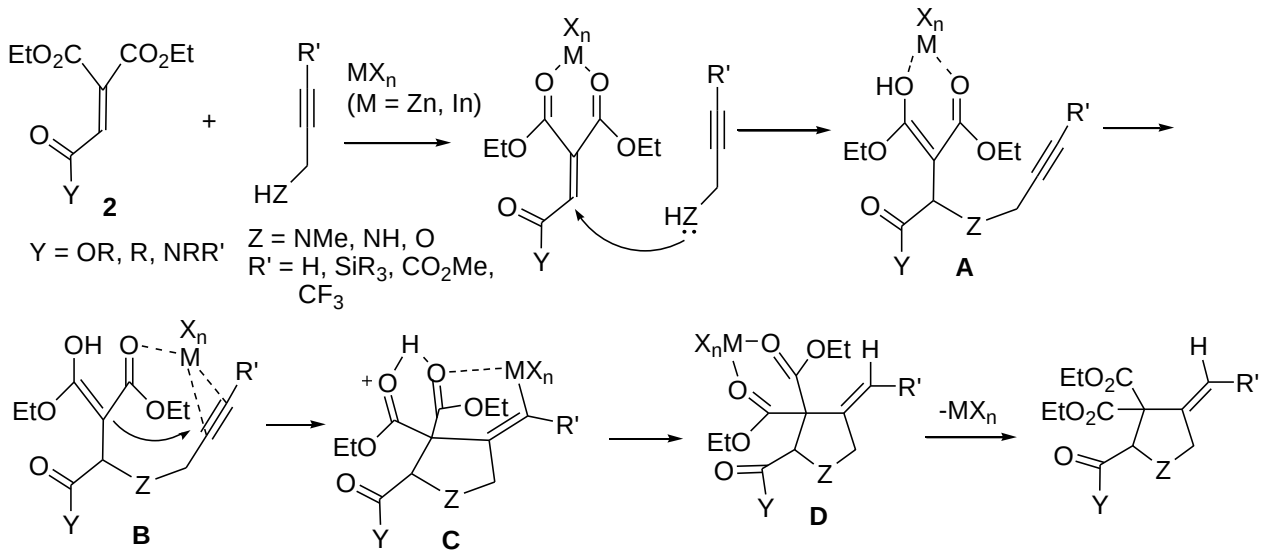
Scheme 8

The reaction of triethyl ethenetricarboxylate **2b** and γ-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**

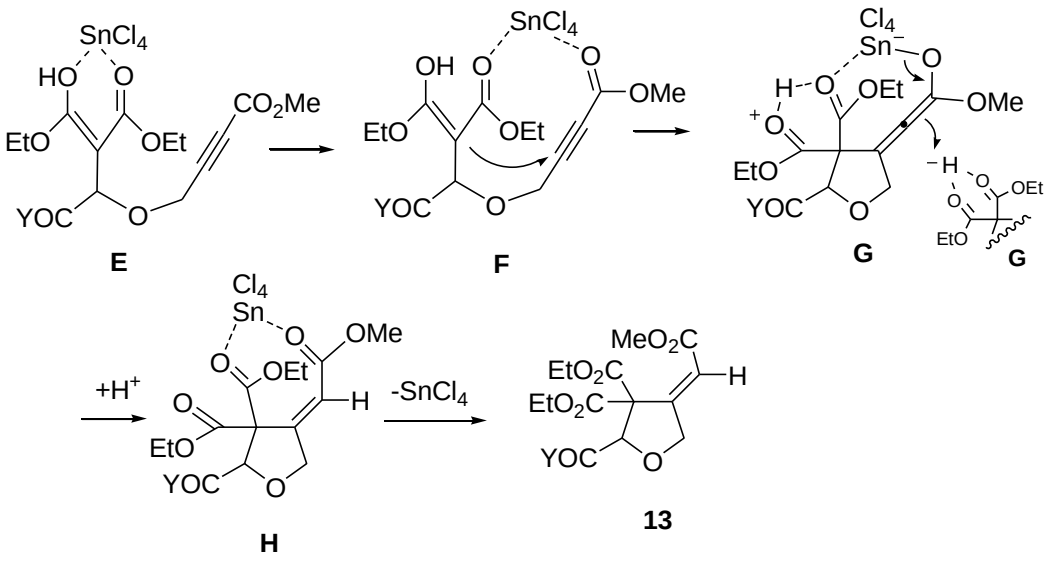


Scheme 10. Proposed mechanism for the reaction of **2** and propargyl amines and alcohols with MX_n (M = Zn, In)

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.[14,1c] DFT calculations support the proposed mechanism involving the effective zinc chelate for C-C bond formation.[10a]

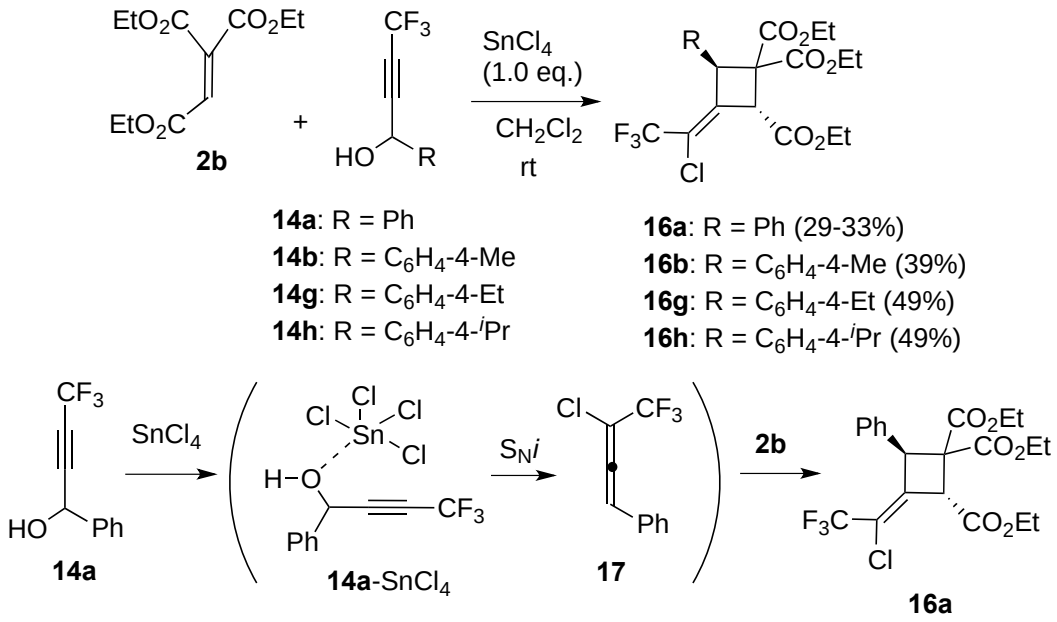
The proposed mechanism is in agreement with the observed *Z* selectivity for the zinc Lewis acid promoted reaction of **2** and γ-substituted propargyl alcohols: γ-silicon substituted propargyl alcohols **9**, 4-hydroxy-2-butynoate (**11**), and γ-CF_3-substituted propargyl alcohols **14**. Thus, the alkenyl zinc intermediate **C** in Scheme 10 retains the configuration.

The observed *E* selectivity for $SnCl_4$ 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 Sn^{4+} 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**.



Scheme 11. Proposed mechanism for the reaction of **2** and 4-hydroxy-2-butynoate (**11**) with $SnCl_4$

On the other hand, reaction of γ-trifluoromethyl-α-aryl propargyl alcohols **14** with **2b** in the presence of 1 equiv of $SnCl_4$ gave cyclobutane derivatives **16** in 29–49% yield (Scheme 12).[13] 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 $SnCl_4$.

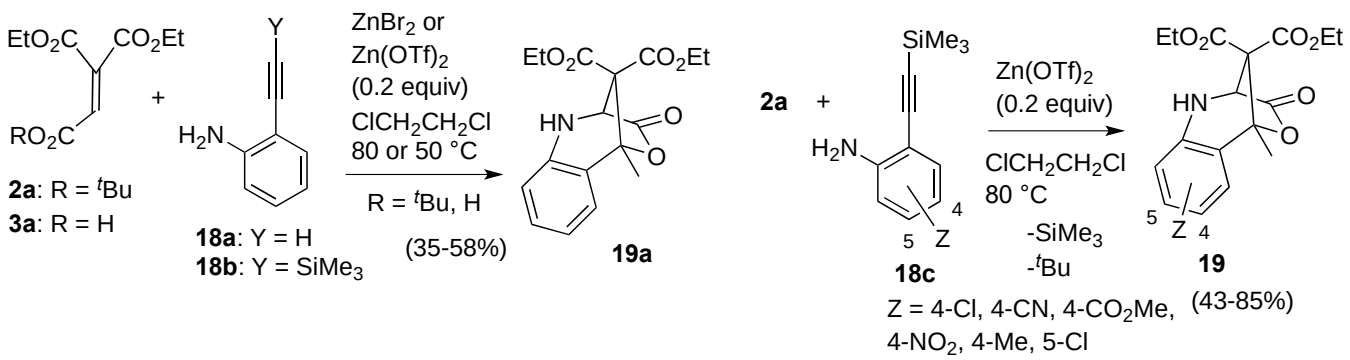


Scheme 12

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.[15] 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.[16]

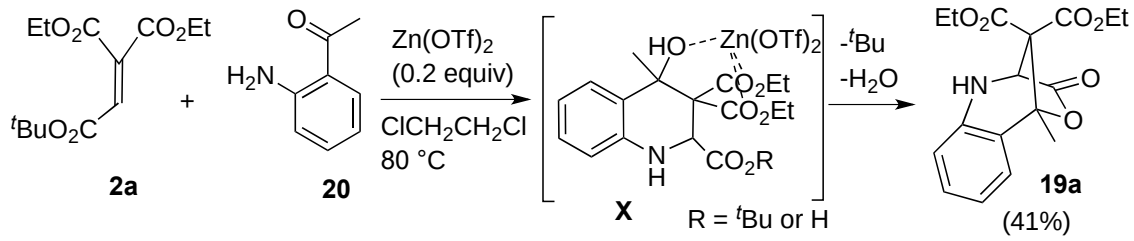
We have examined the reaction of ethenetricarboxylates **2** or **3a** and 2-ethynylanilines **18** as the one-carbon homologues for propargylamines **5** in the presence of zinc Lewis acids.[17] The $ZnBr_2$ and $Zn(OTf)_2$ catalyzed reaction of *tert*-butyl ester **2a** and **18a** in $ClCH_2CH_2Cl$ at 80 °C gave an unexpected compound **19a** as a major isolable product in 35 and 50% yields, respectively (Scheme 13). Interestingly, the $ZnBr_2$ and $Zn(OTf)_2$ catalyzed reaction of **2a** and **18b** also gave **19a** in 38 and 58% yields, respectively. Apparently, ^{t}Bu and TMS groups were lost under the reaction conditions.



Scheme 13

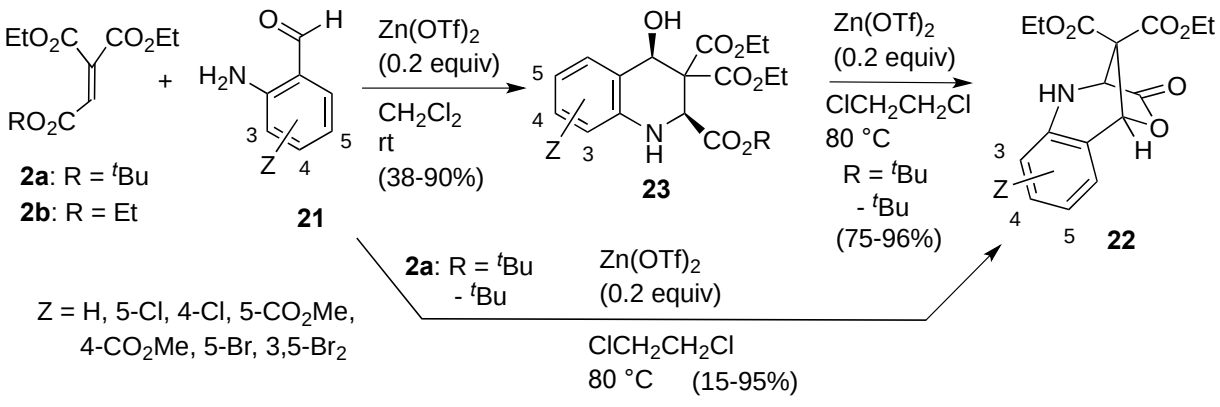
Furthermore, reactions between a substrate bearing a free CO_2H **3a** and 2-ethynylaniline **18a** gave **19a** in 43–58% yield. The reaction of various 2-ethynylaniline derivatives **18c** was also examined and they gave the bridged quinolone products **19**. 4-CN-Derivative **18c** (Z = 4-CN) gave 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**.



Scheme 14

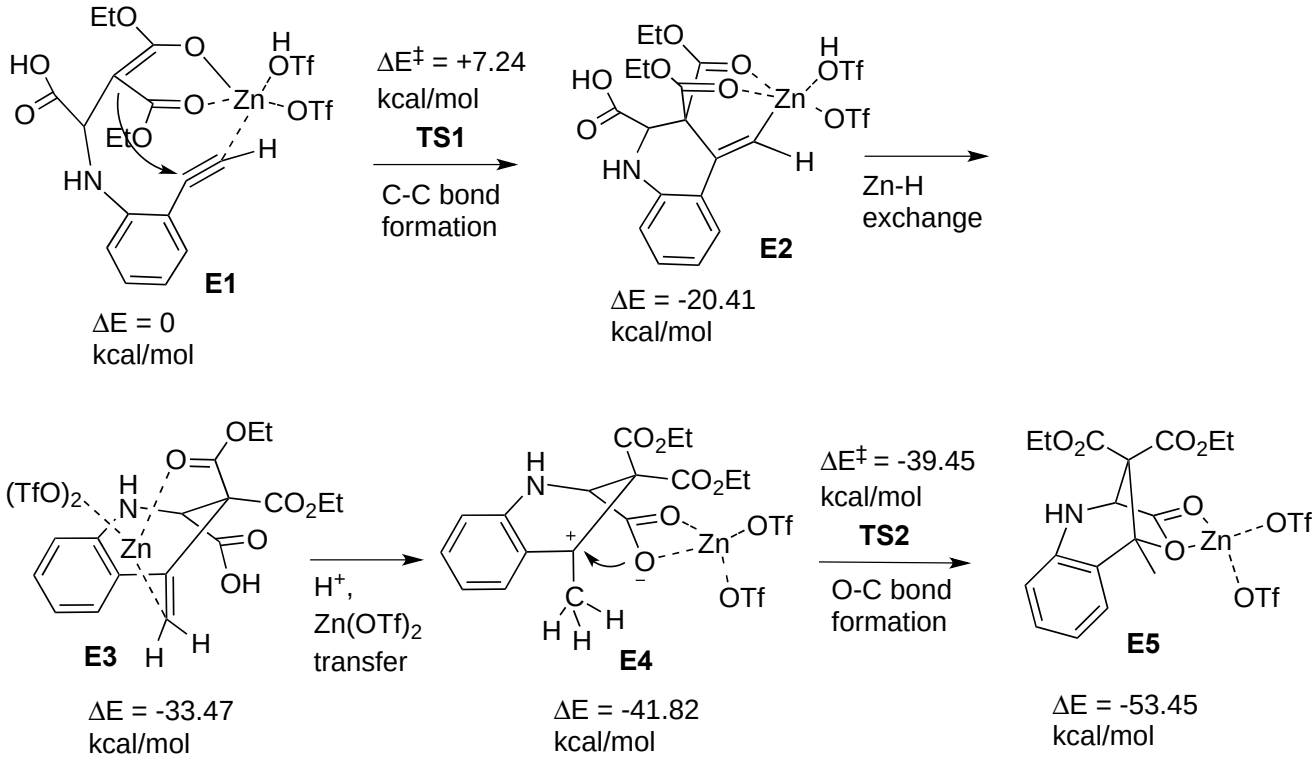
2-Aminobenzaldehydes **21** are expected to be more reactive than 2'-aminoacetophenone **20**. Zinc triflate-catalyzed reaction of **2a** with 2-aminobenzaldehydes **21** at 80 °C in $ClCH_2CH_2Cl$ gave bridged quinoline derivatives **22** in 15–95% yield (Scheme 15), similar to the reaction of **2a** 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_2Cl_2 gave hydroxyquinoline derivatives **23** in 38–90% yield.[18] The major isolated diastereoisomers obtained for the hydroxyqunoline derivatives **23** have 1,3-*cis* stereochemistry, probably due to the stable diequatrial (OH and CO_2R) 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**.



Scheme 15

Heating **23** (R = ^{t}Bu) with zinc triflate (0.2 equiv) at 80 °C in $ClCH_2CH_2Cl$ 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.

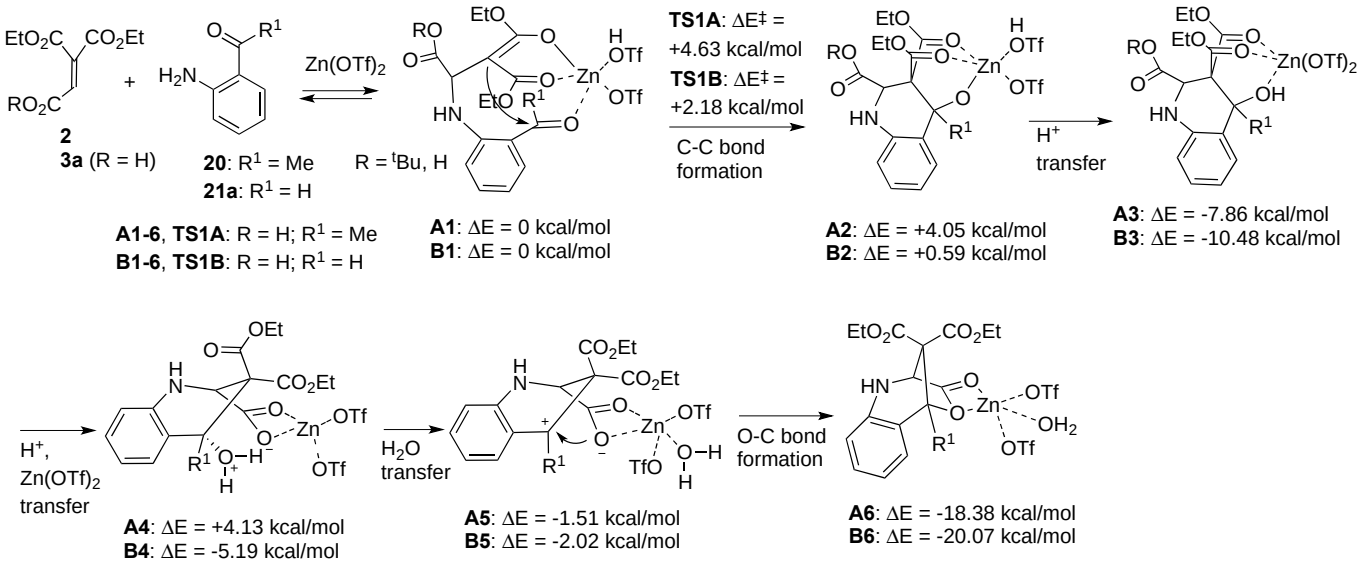


Scheme 16. Proposed mechanism for the reaction of **3a** and 2-ethynylaniline **18a** with $Zn(OTf)_2$ and B3LYP/6-31G* calculated energies. ΔE = sum of electronic and zero-point energies (kcal/mol).

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**.

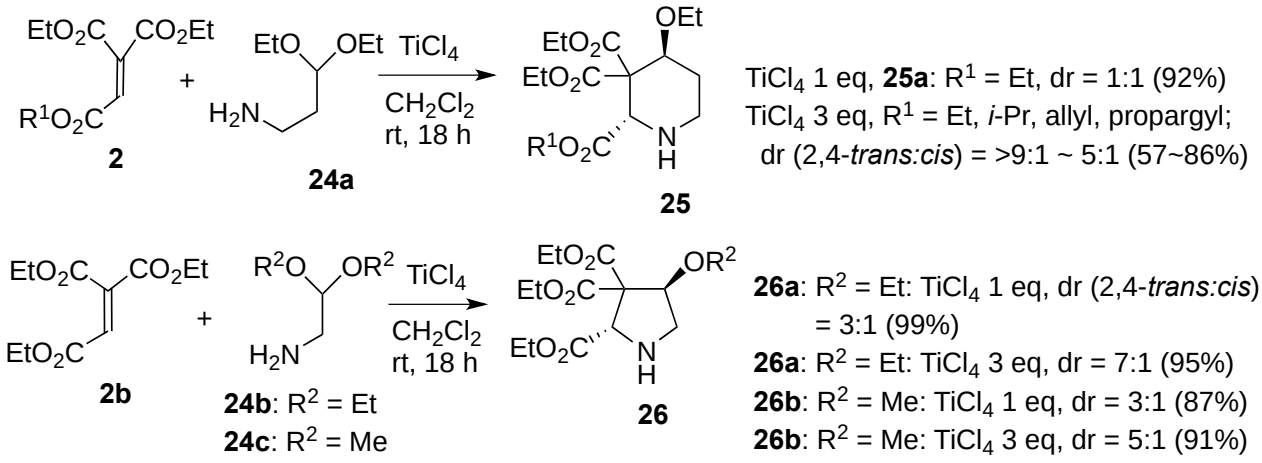
The reaction mechanism for 2-aminobenzaldehyde **21a** is also proposed in Scheme 17. DFT calculations suggest the facile first ring closure (**TS1B** < **TS1A**) and the stability of the formed hydroxyquinoline intermediates **B2** and **B3** compared with those of the corresponding 2'-aminoacetophenone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

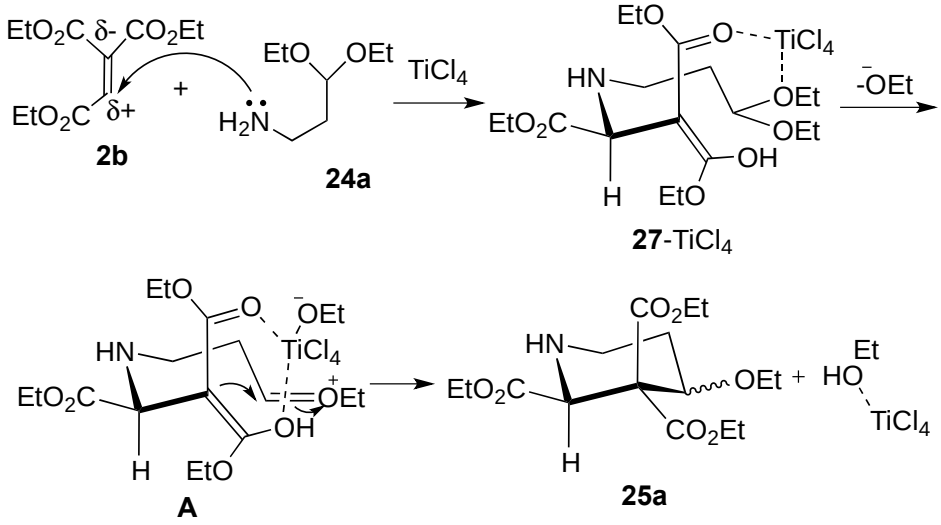
3-1-3. Lewis Acid-Promoted Cyclization Reactions with Aminoacetals Leading to Nitrogen-Containing Heterocycles

We have reported that Lewis acid-catalyzed cyclization of aminoacetals (**24**) and triethyl ethenetricarboxylate (**2b**).[3d] The reaction of 3-aminopropionaldehyde diethyl acetal (**24a**) and **2b** in the presence of 1 equivalent of $TiCl_4$ at room temperature gave 4-ethoxypiperidine-2,3,3-tricarboxylate **25a** (R^1 = Et) in 92% yield with 2,4-diastereomer ratio 1:1 (Scheme 18). The reaction in the presence of 3 equivalents of $TiCl_4$ gave 2,4-*trans*-piperidine derivative **25a** (R^1 = Et) in 86% yield predominantly. The reaction of aminoacetaldehyde diethyl/dimethyl acetals **24b**,**c** and **2b** with 3 equivalents of $TiCl_4$ gave 2,4-*trans*-4-pyrrolidine-2,3,3-tricarboxylates (**26a**,**b**) predominantly.



Scheme 18

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**.

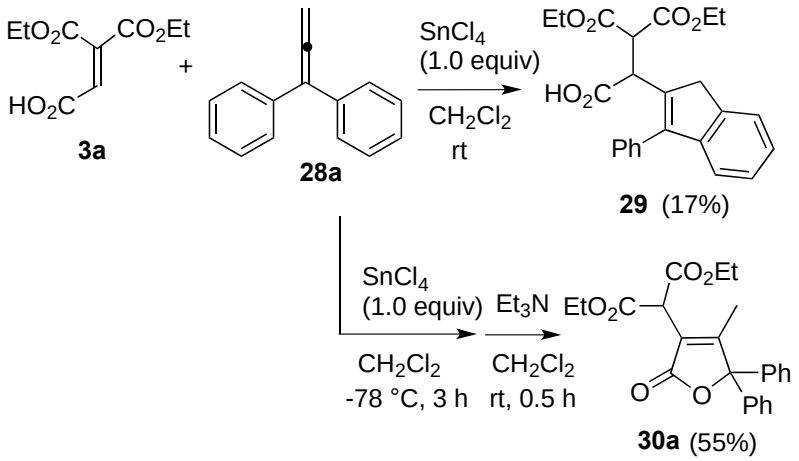


Scheme 19

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.

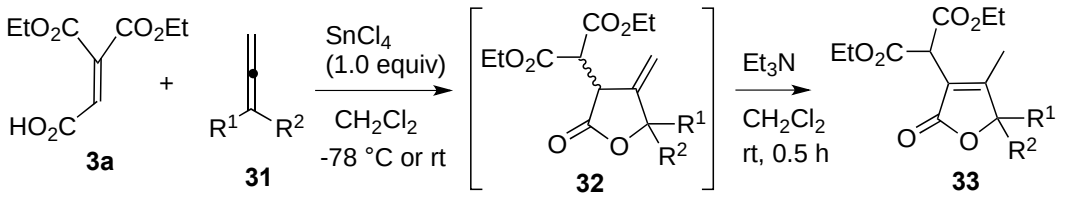
3-1-4. Lewis Acid-Promoted Reactions with Allenes: Synthesis of γ-Lactones via Conjugate Addition/Cyclization Reaction

We have reported that the reaction of arylallenes and ethenetricarboxylate triesters **2** with $SnCl_4$ gave indene derivatives efficiently, via a conjugate addition/Friedel-Crafts cyclization reaction.[19] The reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate (**3a**) and allene **28a** in the presence of $SnCl_4$ (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 Et_3N gave γ-lactone **30a** in 55% yield (Scheme 20).



Scheme 20

The reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate (**3a**) and various aryl and alkyl allenes **31** in the presence of $SnCl_4$ 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 Et_3N gave γ-lactones **33**.

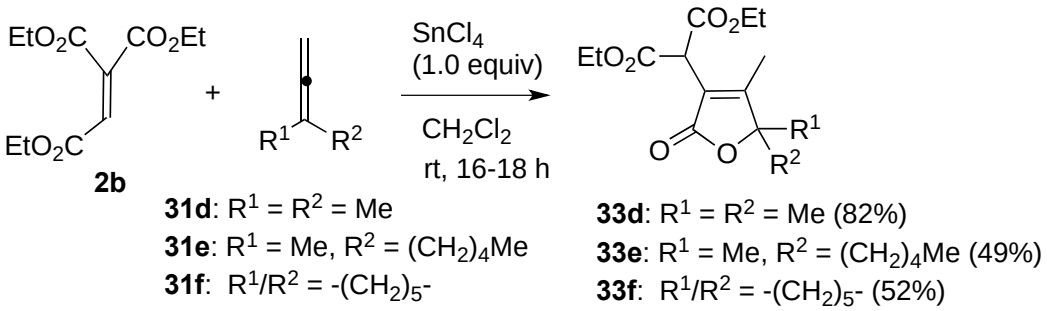


31a: R^1 = Me, R^2 = Ph
31b: R^1 = Me, R^2 = 4-Cl-C_6H_4
31c: R^1 = H, R^2 = Ph
31d: R^1 = R^2 = Me
31e: R^1 = Me, R^2 = $(CH_2)_4$Me
31f: R^1/R^2 = -$(CH_2)_5$-

33a: R^1 = Me, R^2 = Ph (49%)
33b: R^1 = Me, R^2 = 4-Cl-C_6H_4 (45%)
33c: R^1 = H, R^2 = Ph (63%)
33d: R^1 = R^2 = Me (49%)
33e: R^1 = Me, R^2 = $(CH_2)_4$Me (17%)
33f: R^1/R^2 = -$(CH_2)_5$- (31%)

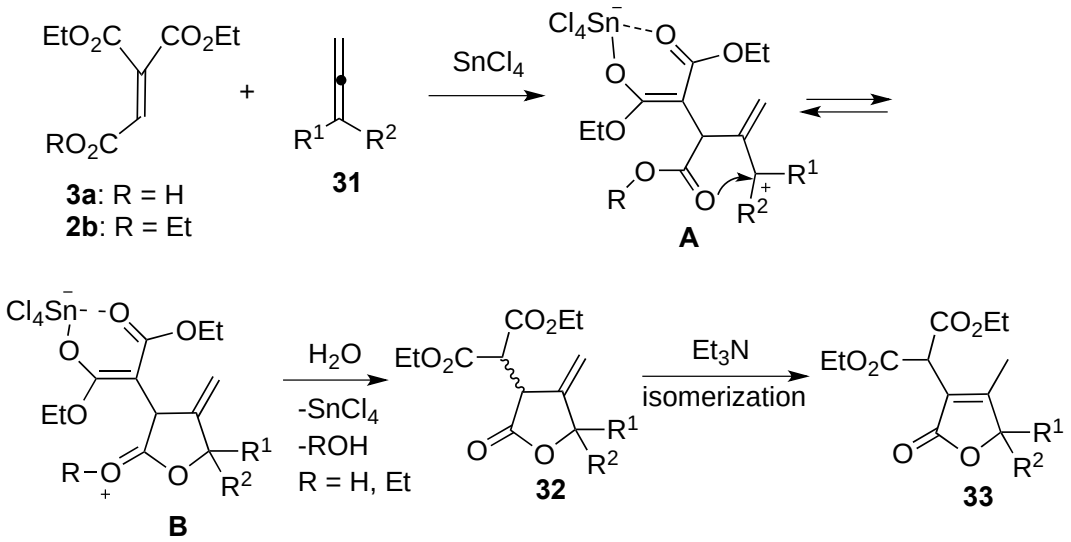
Scheme 21

Next, the reactions of triethyl ethenetricarboxylate (**2b**) and alkylallenes **31d**,**e**,**f** in the presence of $SnCl_4$ 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

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.

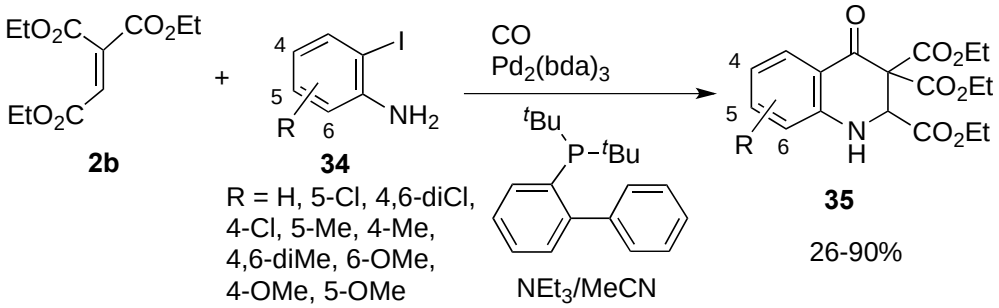


Scheme 23

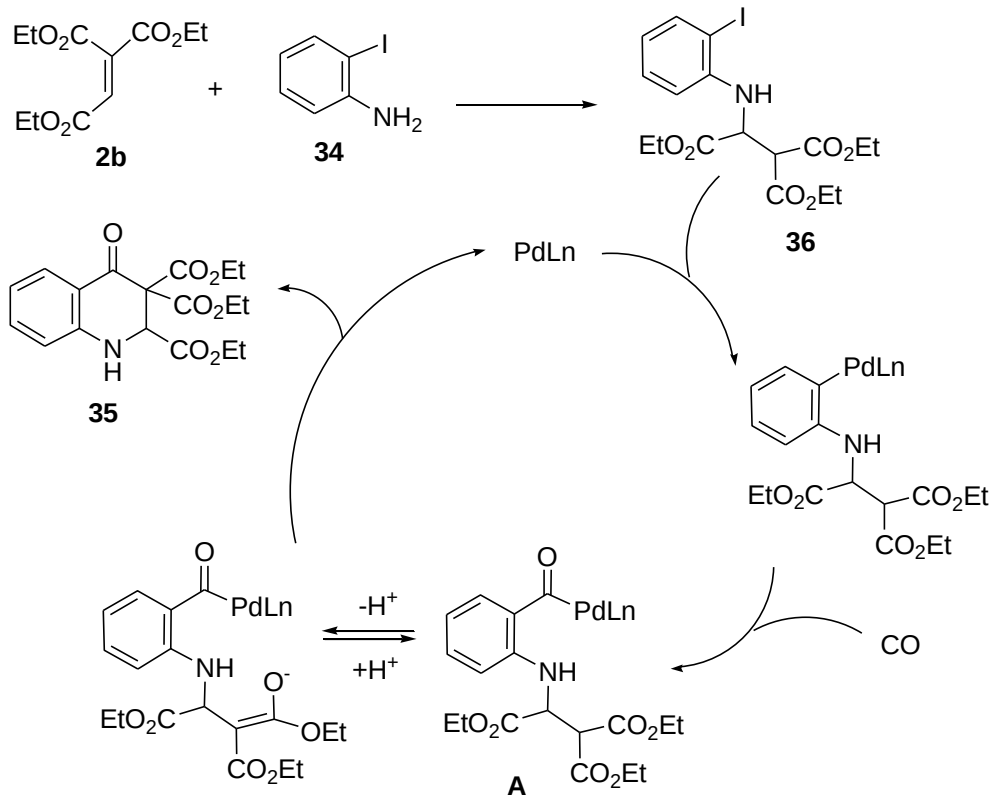
3-2. Palladium-Catalyzed Cyclocarbonylation

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(1*H*)-quinolinone derivatives **35** in 26–90% yields (Scheme 24).[20] They initially tried several reactions of 2-iodoaniline **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(1*H*)-quinolinones **35** and regenerates the Pd(0) species.



Scheme 24

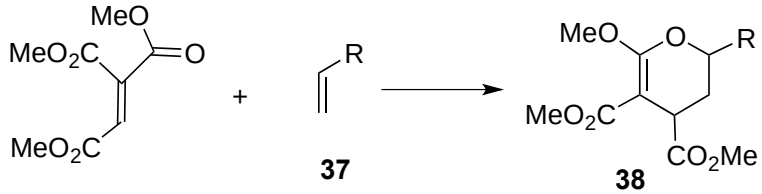


Scheme 25. Possible reaction mechanism for formation of **35**

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-2*H*-pyrans (Scheme 26).[21] For the reaction of **2g** and phenyl vinyl sulfide **37c**, [2+2] cycloadduct is formed in the presence of Lewis acids ($ZnCl_2$ or ethereal $LiClO_4$).[21b,c]



2g

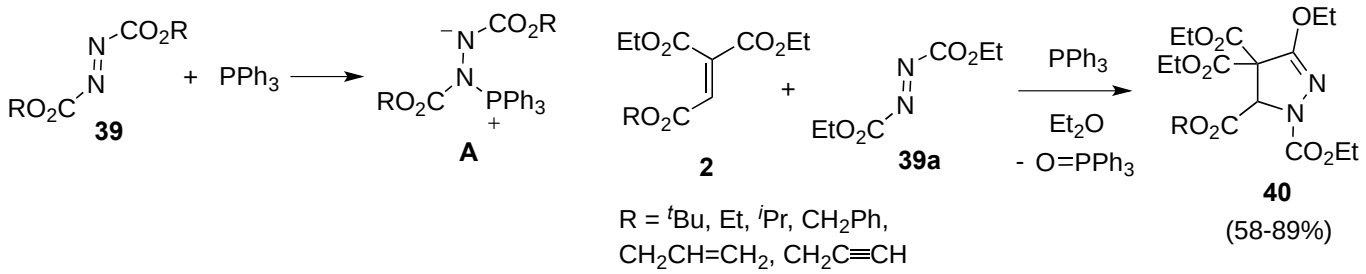
37a: R = C_6H_4-4-OMe — 70 °C/no solvent **38a**: (30%)
37b: R = SMe — 25 °C/no solvent **38b**: (47%)
37c: R = SPh — 25 °C/acetonitrile **38c**: (100%)
37d: R = OCH_2CHMe_2 — 25 °C/$CDCl_3$ **38d**: (70%)

Scheme 26

3-3-2. Reaction with Huisgen Zwitterions

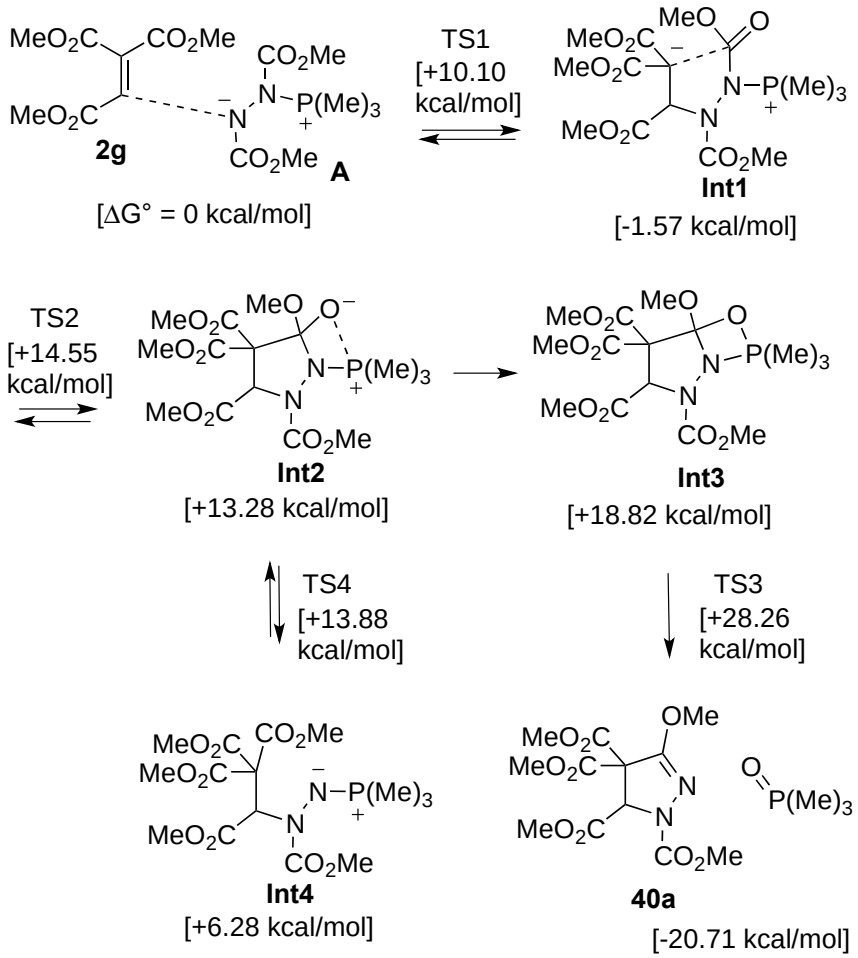
We have studied that reaction of the Huisgen zwitterions, derived from triphenylphosphine and azodicarboxylates with ethenetricarboxylates **2**. The reaction of dialkyl azodicarboxylates **39** and triphenylphosphine leads to the formation of Huisgen zwitterions **A** (Scheme 27),[22] which plays an important role in the Mitsunobu reaction.[23] Brunn and Huisgen reported that the cycloaddition reaction of the zwitterion **A** with dimethyl acelylenecarboxylate afforded pyrazoles.[24] The reactions of the zwitterion and allenes, phenyl isocyanate, phenylisothiocyanate or ketone derivatives leading to various nitrogen-containing heterocycles have been reported.[24a,25,26] Few cycloaddition reactions of the zwitterion and alkenes leading to pyrazolines have been reported.[27]

The reaction of ethenetricarboxylate **2a** (R = O^{t}Bu) and diethyl azodicarboxylate **39a** with 1 equivalent of PPh_3 in ether at room temperature for 18 h gave pyrazoline **40a** (R = O^{t}Bu) in 85% yield and quantitative triphenylphosphine oxide. Reaction of various ethenetricarboxylates **2** and diethyl azodicarboxylate **39a** with PPh_3 gave pyrazolines **40** efficiently (Scheme 27). The reaction of less reactive diethyl ethylidenemalonate (**1b**) and **39a** with PPh_3 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 PPh_3 gave an inseparable mixture possibly containing cycloadduct with the starting alkene **1a** at room temperature and higher temperatures.



Scheme 27

The formation of the pyrazoline ring may undergo similar to the reaction of zwitterions **A** and dimethyl acetylenedicarboxylate or allenic esters.[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.

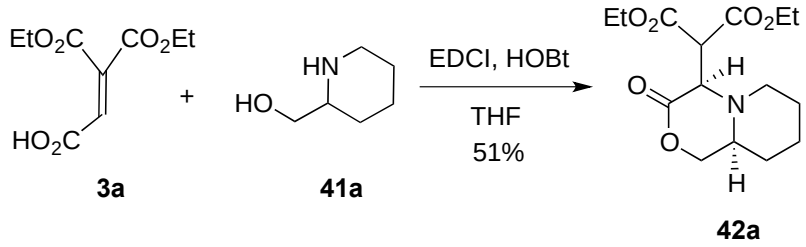


Scheme 28. Proposed mechanism for the reaction of model compounds **2g**, **39** (R = Me) and trimethylphosphine and B3LYP/6-31G* calculated Gibbs free energies (T = 298.15 K and P = 1 atm).

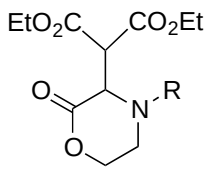
Conjugate addition of nitrogen of the zwitterion **A** (generated from **39** (R = Me) and trimethylphosphine) to ethenetricaboxylate **2g** gives the stable intermediate **Int1** (ΔG° = -1.57 kcal/mol). The use of highly electrophilic ethenetricarboxylates **2** may facilitate this addition step. The 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

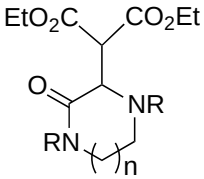
We have examined reactions of **3a** and reagents with oxygen and nitrogen nucleophilic moieties. The reaction of **3a** with 2-aminoalcohols **41** in the presence of EDCI and HOBt in one pot gave *N*,*O*-containing heterocyclic compounds **42**, regioselectively.[6] In addition to various 2-aminoalcohols, 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).



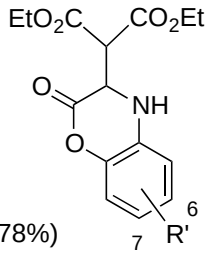
3a **41a** **42a**



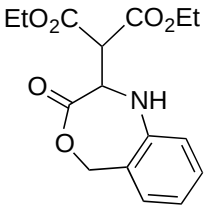
42b: R = Me (68%, regioisomer 13%)
42c: R = CH_2Ph (52%)
42d: R = Cyclohexyl (40%)



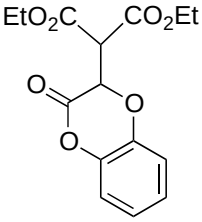
43a: R = CH_2Ph, n = 1 (78%)
43b: R = Et, n = 2 (68%)



44a: R' = H (74%)
44b: R' = 6-Me (65%)
44c: R' = 7-Me (72%)
44d: R' = 6-Cl (72%)



45 (44%)



46 (46%)

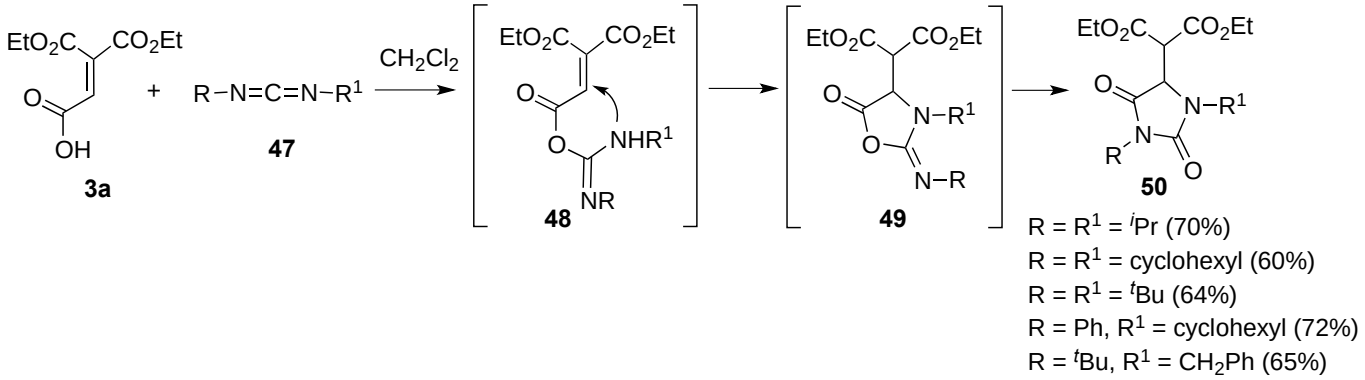
Scheme 29

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 CH_2Cl_2 at room temperature. Even sterically hindered *tert*-butylcarbodiimide **47** (R = R^1 = ^{t}Bu) gave **50** in 64% yield.[28]

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

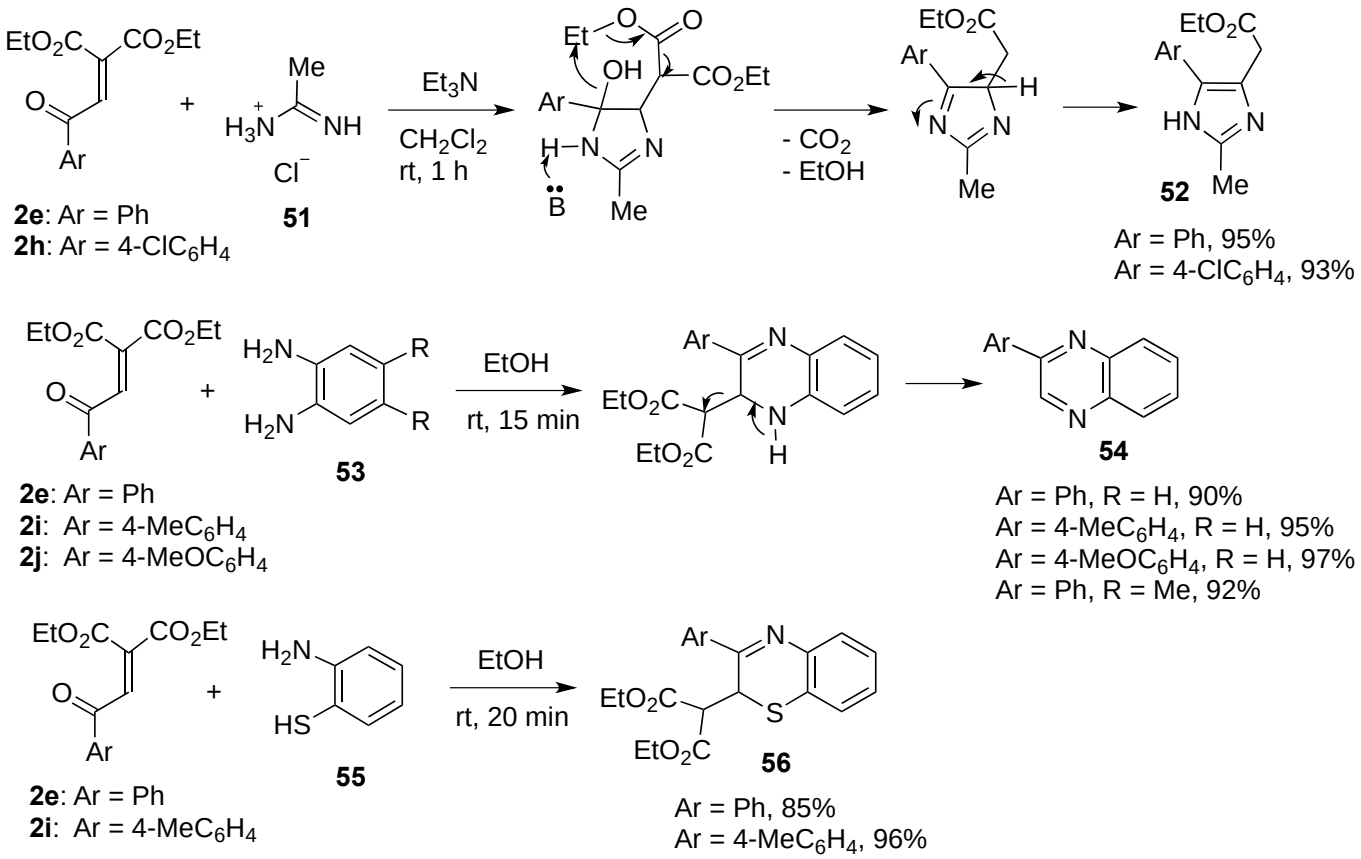


Scheme 30

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 Aroylmethylidenemalonates with Diamines

Selvi and Srinivasan reported that the cyclocondensation of aroylmethylidenemalonates **2e**,**h** with acetamidine hydrochloride **51** in the presence of triethylamine in CH_2Cl_2 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**.



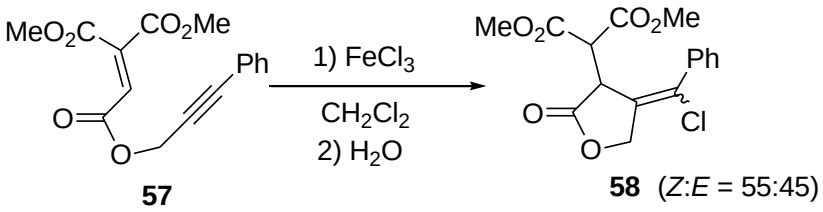
Scheme 31

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 $FeCl_3$ to give chlorinated γ-lactones (Scheme 32).[3b]

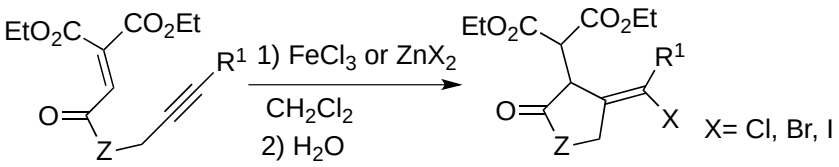


Scheme 32

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 $ZnBr_2$ (1.2 equiv)-THF (1.0 equiv) or $FeCl_3$ (1.2 equiv) at -40 °C in CH_2Cl_2 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.

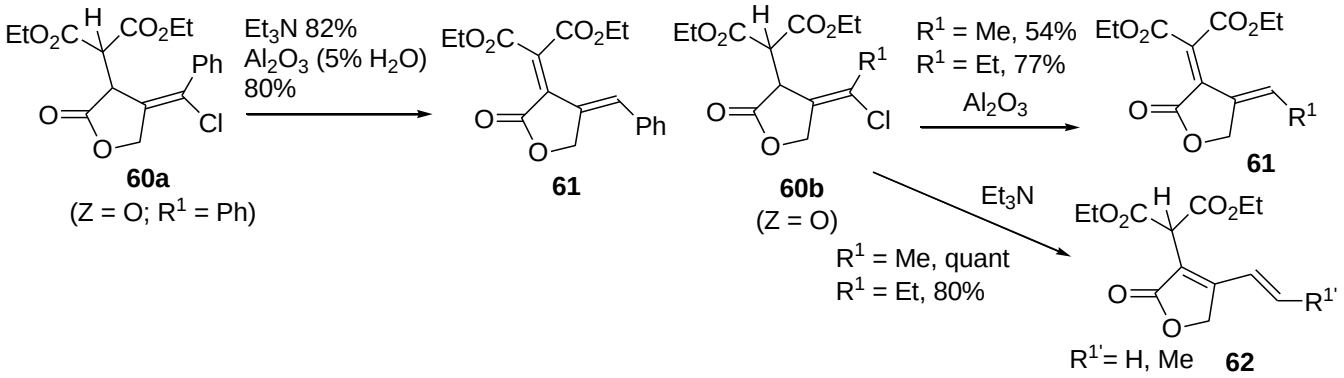


59a: (Z = O; R^1 = aryl)
59b: (Z = O; R^1 = alkyl)
59c: (Z = NMe; R^1 = alkyl, aryl)

60a: (Z = O; R^1 = aryl) (52-98%)
60b: (Z = O; R^1 = alkyl) (31-76%)
60c: (Z = NMe; R^1 = alkyl, aryl) (42-84%)

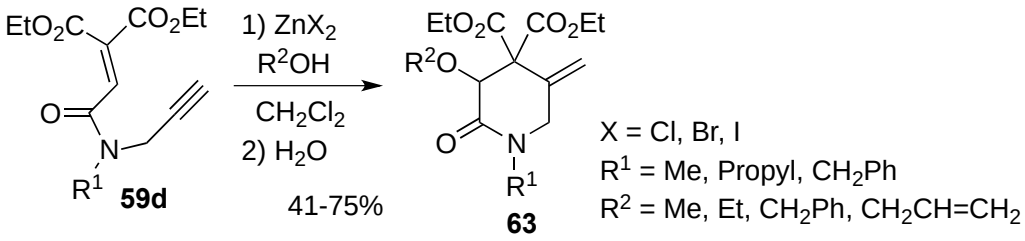
Scheme 33

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.[29]



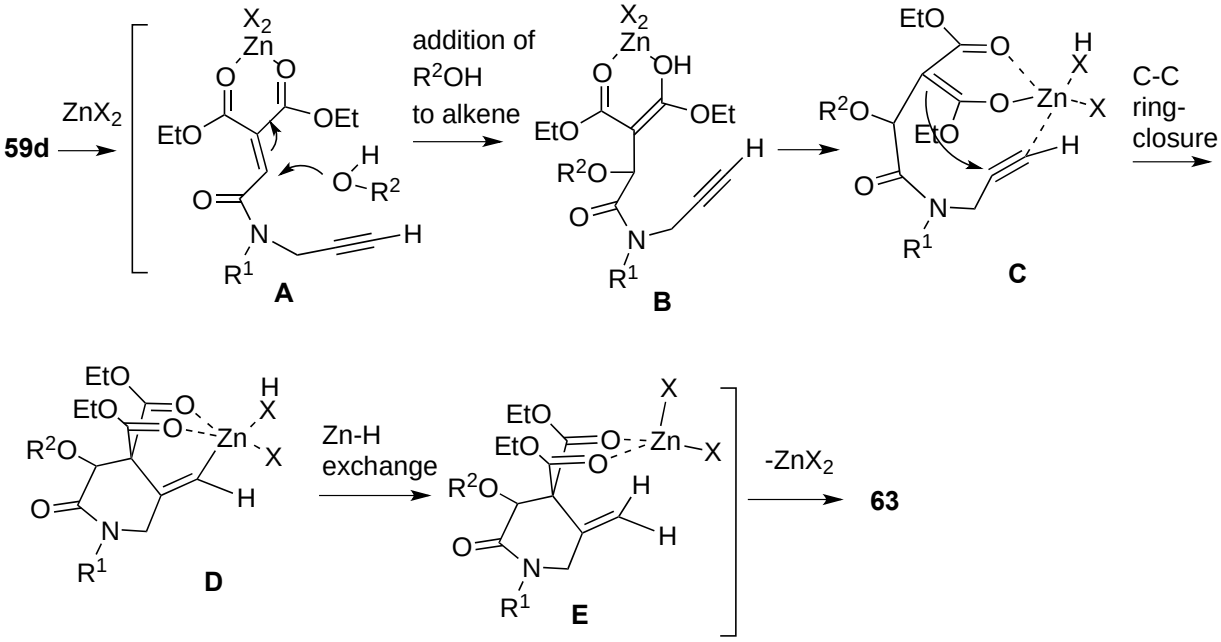
Scheme 34

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.



Scheme 35

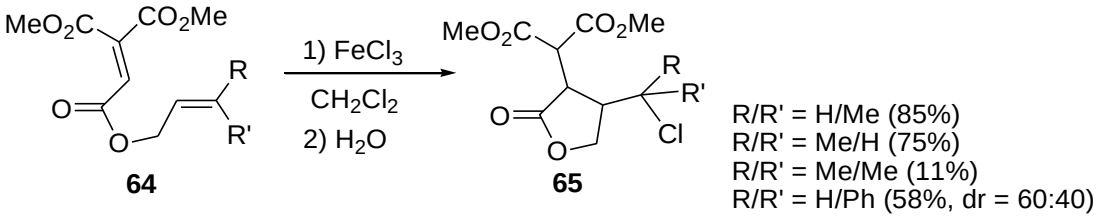
The probable mechanism for formation of these six-membered rings **63** can be shown in Scheme 36, similar to the intermolecular reaction in Section 3-1-1. Conjugate addition of oxygen of alcohol to zinc-coordinated **A** in the diester moiety and proton transfer gives intermediate **B**. Zinc coordination 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.



Scheme 36

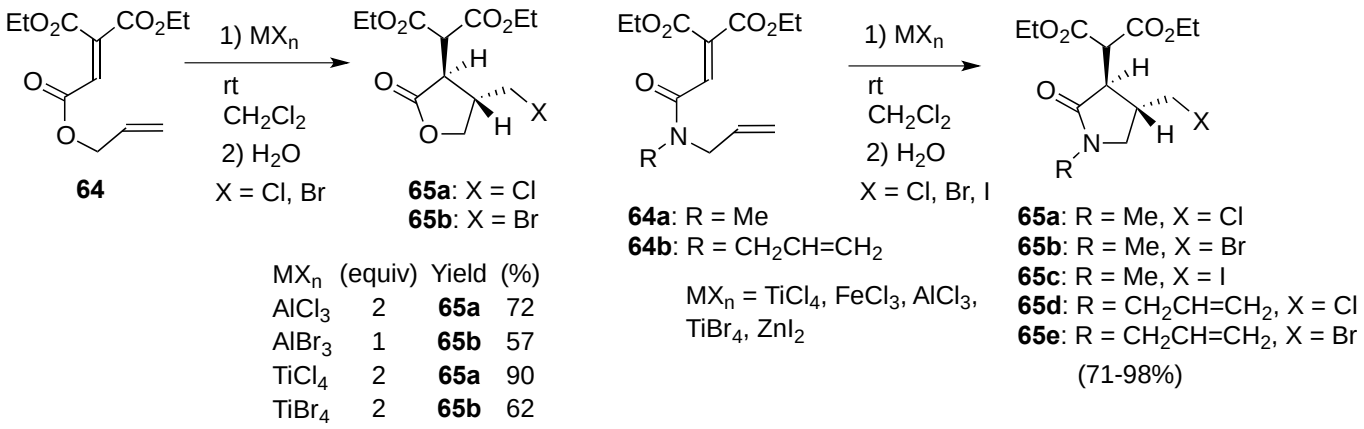
4-1-2. Lewis Acid-Promoted Intramolecular Cyclization Reactions of Alkenyl and Allenyl Esters and Amides

Snider and Roush reported that Lewis acid-promoted intramolecular reactions of alkenyl ethenetricarboxylates **64** gave chlorinated γ-lactones **65** (Scheme 37).[3b]



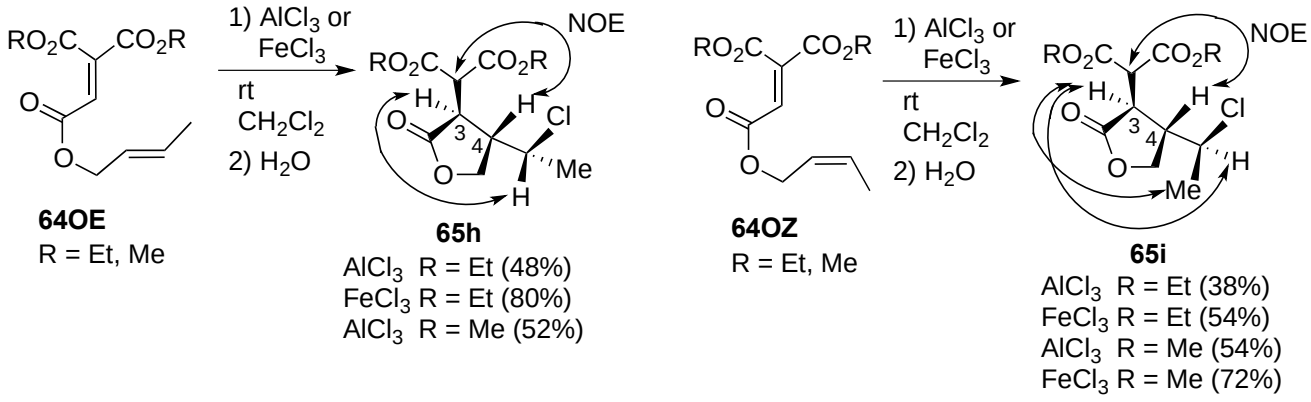
Scheme 37

We have studied Lewis acid-promoted intramolecular reactions of alkenyl ethenetricarboxylates and the corresponding amides in detail. Reaction of allyl ethenetricarboxylates and the amides **64** with Lewis acids (1-2 equiv) such as $TiCl_4$, $TiBr_4$, $AlCl_3$ and $AlBr_3$ gave 3,4-*trans* halogenomethyl γ-lactone and γ-lactam derivatives **65** stereoselectively in high yields (Scheme 38).[4] The 3,4-stereochemistry of **65** was determined by NOE experiments.



Scheme 38

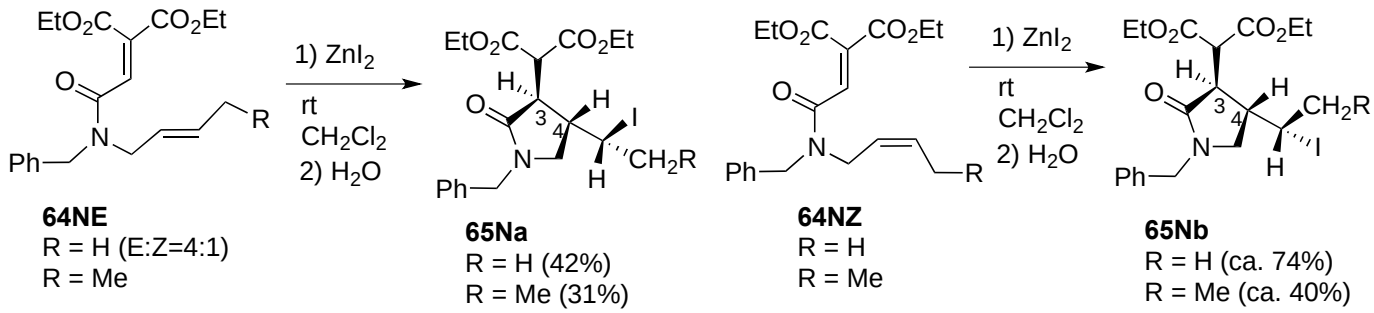
We have also examined the reaction of (*E*)/(Z)-2-butenyl esters **64OE/Z** with Lewis acid. The (*E*)/(Z)-2-butenyl dimethyl esters **64OE/Z** (R = Me) are the substrate which Snider and Roush reported.[3b]



Scheme 39

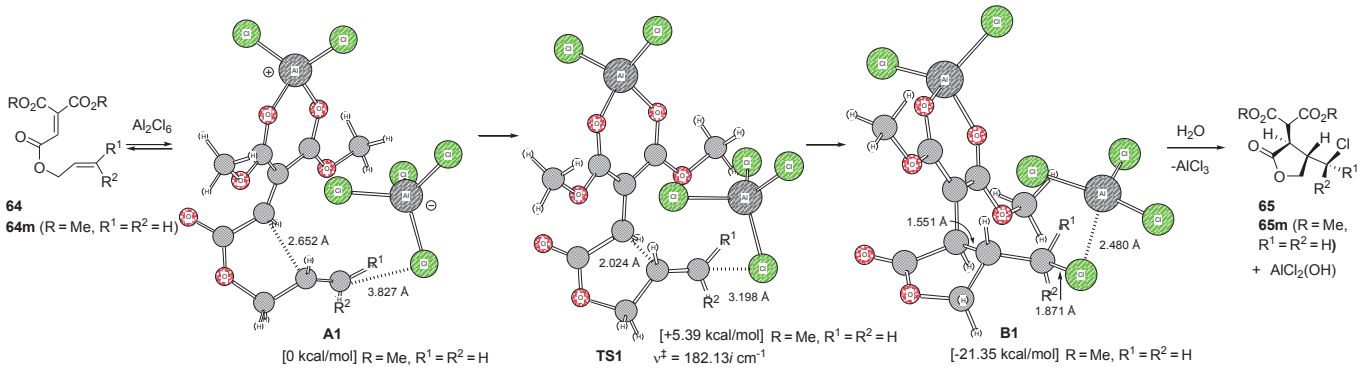
The reaction with 1 equivalent of $AlCl_3$ or $FeCl_3$ at room temperature overnight gave chloro-substituted γ-lactones **65h**,**i** as major products. The 3,4-*cis* stereochemistry was suggested for **65h**,**i** (R = Me) by Snider and Roush based on coupling constants[3b] and we have assigned the stereochemistry as 3,4-*trans* based on NOE.[4] The relative configurations of *C*HClMe 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 ZnI_2 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 *C*HI(CH_2R) 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.



Scheme 40

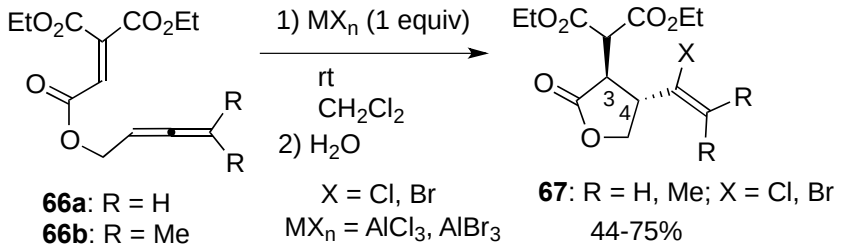
The proposed reaction mechanism to give the halogenated five-membered heterocycles **65** is shown in Scheme 41.



Scheme 41. Proposed reaction mechanism for cyclization of allylic esters **64** and B3LYP/6-31G*-optimized structures and Gibbs free energies (T = 298.15 K and P = 1 atm) for intermediates and TSs (transition states) of the model compounds (**64m** (R = Me, $R^1 = R^2$ = H) + Al_2Cl_6).

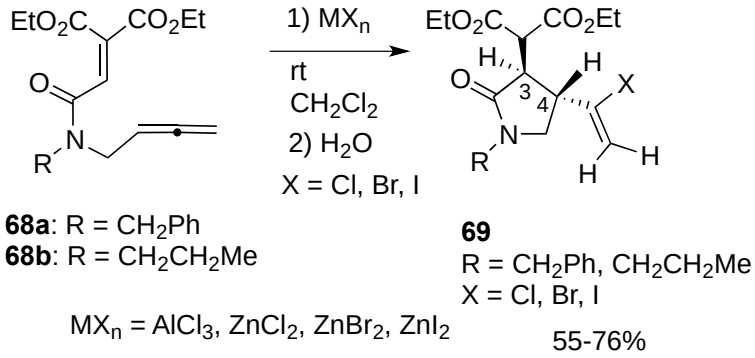
The structures of the intermediates and transition states of model compounds (the corresponding methyl ester **64m** and Al_2Cl_6) were calculated using B3LYP/6-31G*. The reaction may proceed stereospecifically via the concerted Cl-C bond formation by intermolecular Cl^- anti attack and C-C bond formation. Protonation and removal of $AlCl_2OH$ yield the product **65**. The relative configuration of *C*HClMe 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**.[4a]

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 $AlCl_3$ and $AlBr_3$ in CH_2Cl_2 at room temperature gave 3,4-*trans* haloalkenyl γ-lactone derivatives **67** stereoselectively (Scheme 42).[31]



Scheme 42

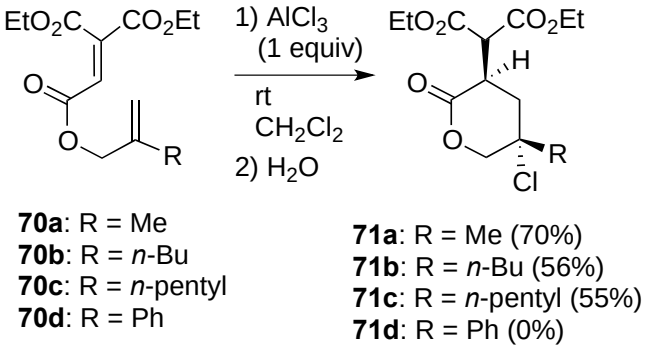
Reaction of allenyl amides (**68b**) with $AlCl_3$, $ZnCl_2$, $ZnBr_2$, and ZnI_2 at room temperature gave 3,4-*trans* γ-lactams **69** in 55–76% yield (Scheme 43). The 3,4-*trans* stereochemistry was determined by NOEs.



Scheme 43

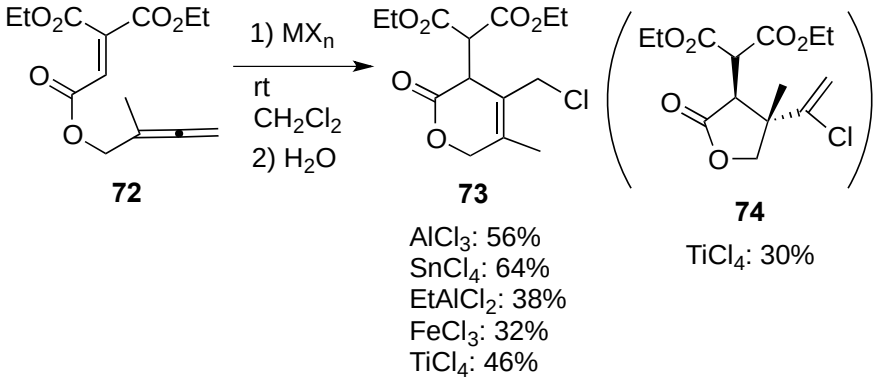
Furthermore, we have examined Lewis acid-promoted reactions of 2-substituted 2-alkenyl esters of ethenetricarboxylate **70**.[32] Interestingly the six-membered ring formation from **70** was found. Thus, the reaction of the substrates **70a**,**b**,**c**, with $AlCl_3$ (1 equiv) gave chlorinated 2-oxotetrahydro-2*H*-pyrans

71a,**b**,**c** in 55–70 yield as the major products (Scheme 44). However, the reaction of **70d** with $AlCl_3$ or $FeCl_3$ gave a complex mixture.



Scheme 44

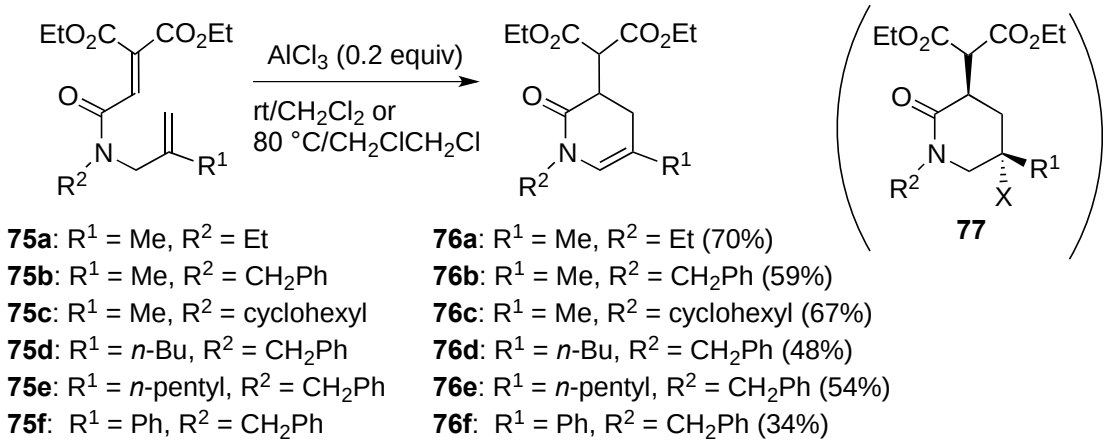
The reaction of allenyl ester was examined as the extension for six-membered ring formation of the ester analog.[32] The reaction of 2-methylbuta-2,3-dienyl ethenetricarboxylate **72** with 1 equivalent of various Lewis acids such as $AlCl_3$, $SnCl_4$, $EtAlCl_2$, $TiCl_4$, and $FeCl_3$ in CH_2Cl_2 at room temperature gave δ-lactone **73** as a major product along with a small amount of γ-lactone **74** (Scheme 45). Use of $TiCl_4$ gave δ-lactone **73** (46%) and γ-lactone **74** (30%).



Scheme 45

The reaction of ethenetricarboxylate 2-methyl-2-propenyl amide **75a** with $AlCl_3$ (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 $AlCl_3$ (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 $EtAlCl_2$ or $FeCl_3$ (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.



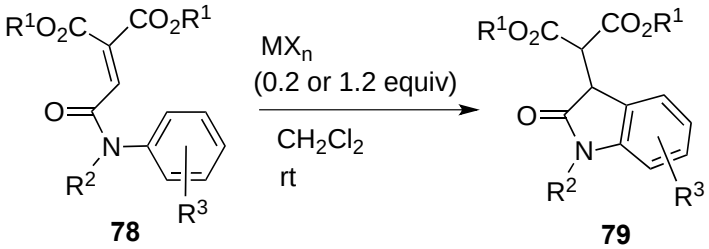
75a: R^1 = Me, R^2 = Et
75b: R^1 = Me, R^2 = CH_2Ph
75c: R^1 = Me, R^2 = cyclohexyl
75d: R^1 = *n*-Bu, R^2 = CH_2Ph
75e: R^1 = *n*-pentyl, R^2 = CH_2Ph
75f: R^1 = Ph, R^2 = CH_2Ph

76a: R^1 = Me, R^2 = Et (70%)
76b: R^1 = Me, R^2 = CH_2Ph (59%)
76c: R^1 = Me, R^2 = cyclohexyl (67%)
76d: R^1 = *n*-Bu, R^2 = CH_2Ph (48%)
76e: R^1 = *n*-pentyl, R^2 = CH_2Ph (54%)
76f: R^1 = Ph, R^2 = CH_2Ph (34%)

Scheme 46

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.[5] For example, the reaction of diethyl 2-[(*N*-methyl-*N*-phenylcarbamoyl)methylene]malonate (**78a**, $R^1 = R^2 = R^3 = H$) in the presence of $ZnCl_2$ at room temperature gave diethyl 2-(1-methyl-2-oxoindolin-3-yl)malonate (**79a**) in 98% yield (Scheme 47). The reactions also proceeded with a catalytic amount of a Lewis acid such as $AlCl_3$, $ZnCl_2$, $ZnBr_2$, $Sc(OTf)_3$, or $InBr_3$. Reaction of substrates with various alkyl groups on nitrogen proceeded to give oxindole derivatives. Interesting regioselectivity was observed for *meta* halogen substrates.[33] Dimethoxyisoquinoline analogs were also obtained by this reaction using a catalytic Lewis acid.

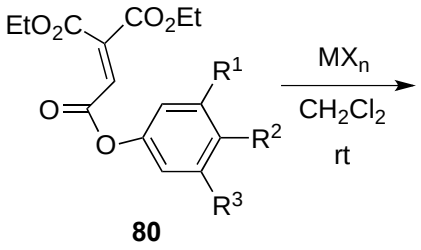


78 **79**

R^1 = Et, R^2 = Me, R^3 = H
MX_n = $ZnCl_2$, $ZnBr_2$, $AlCl_3$, $GaCl_3$, $InBr_3$, $SnCl_4$, $Zn(OTf)_2$, $Sc(OTf)_3$
(72-98%)

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 $ZnBr_2$ in CH_2Cl_2 at room temperature did not proceed, however, reaction with the stronger Lewis acid $FeCl_3$ (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 ZnX_2 but reacted with $FeCl_3$. On the other hand, the reaction of *m*-methoxyphenyl esters **80b**–**d** with $ZnCl_2$ or $Sc(OTf)_3$ gave 2-oxobenzofuran derivatives **81** in high yields and regioselectivity.



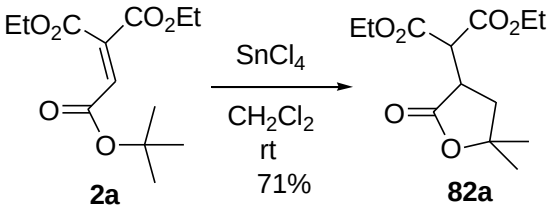
80 **81**

80	R^1	R^2	R^3	MX_n	equiv	**81** (Yield)
80a	H	H	H	$FeCl_3$	1.2	65
80b	H	H	OMe	$ZnBr_2$	1.2	67
80b	H	H	OMe	$ZnCl_2$	1.2	84
80b	H	H	OMe	$ZnCl_2$	0.2	84
80c	OMe	H	OMe	$ZnCl_2$	1.2	88
80c	OMe	H	OMe	$ZnCl_2$	0.2	64
80c	OMe	H	OMe	$Sc(OTf)_3$	0.2	94
80d	H	OMe	OMe	$ZnCl_2$	1.2	61

Scheme 48

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

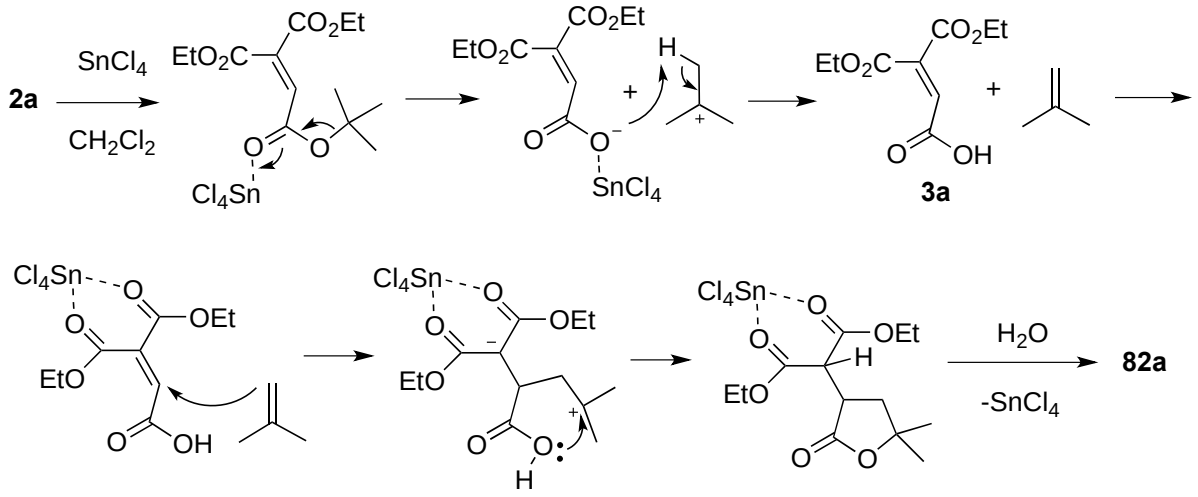
We have reported that a novel cyclization of 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate (**2a**) in the presence of a Lewis acid afforded a 5,5-dimethyl-γ-lactone derivative **82a** (Scheme 49).[3c]



2a **82a**

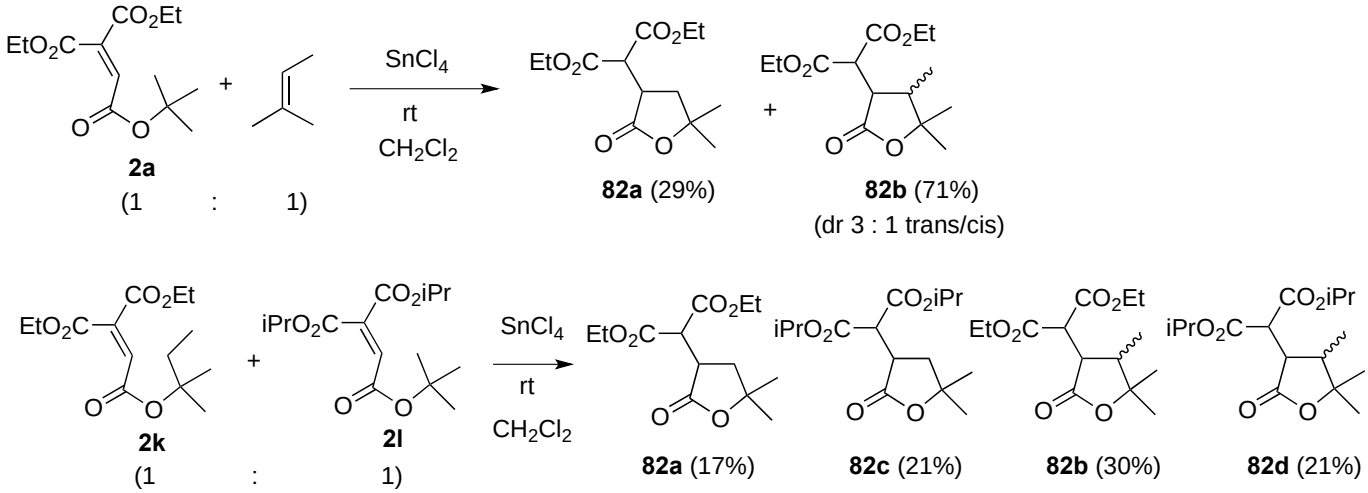
Scheme 49

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).



Scheme 50

To obtain information on the mechanism, the reaction of **1a** with 2-methyl-2-butene (1.0 equiv for **2a**) with $SnCl_4$ (1.2 equiv for **2a**) in CH_2Cl_2 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 $SnCl_4$ 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.



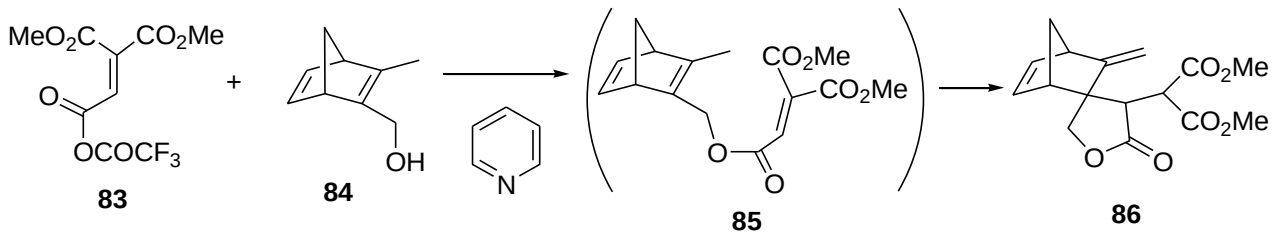
Scheme 51

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.[3c]

4-2. Thermal Cyclizations Including Sequential Reactions

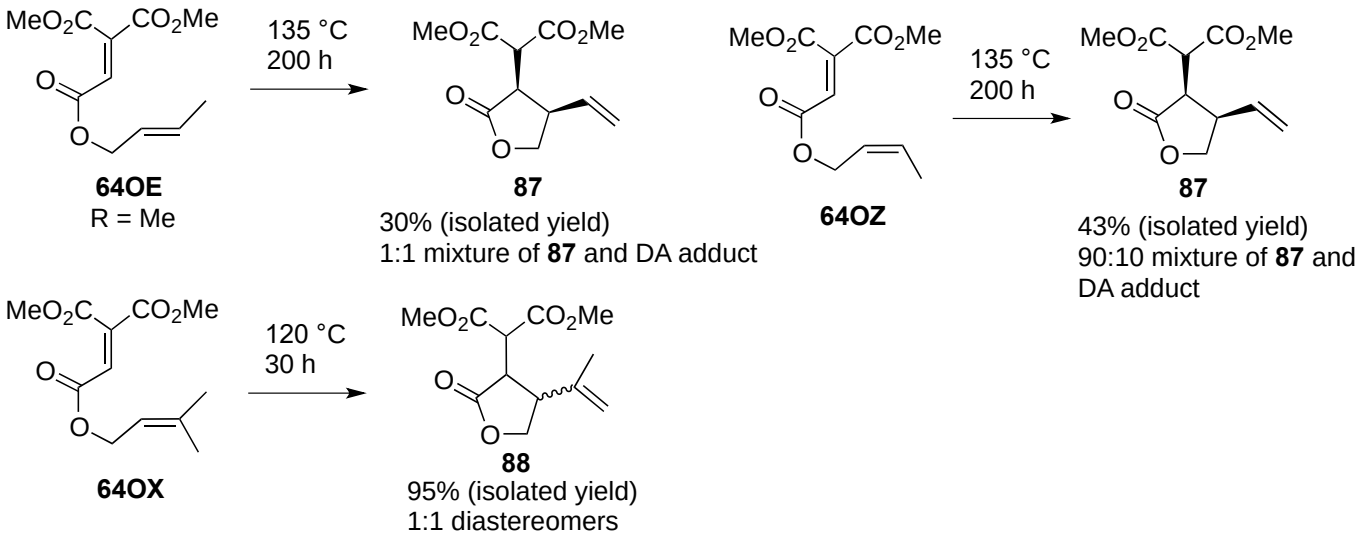
4-2-1. Ene Reactions

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).[2a] Steric (strain relief) and electronic effects (tetra-substituted electron-rich double bond) may make this example a facile ene reaction.[2c]



Scheme 52

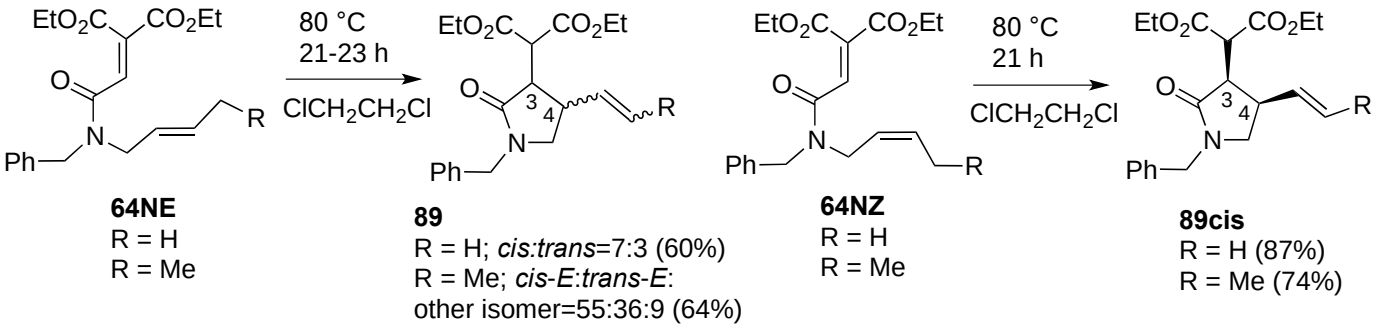
Snider et al. reported that treatment of **64OE**/**Z** (R = Me) at 135 °C for 200 h gave ene products **87** along with the hetero Diels-Alder adduct as described in the next section 4-2-2.[2c] The 3-methyl-2-butenyl ester **64OX** is slightly more reactive than **64OE**/**Z** (R = Me), giving a 70:30 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).



Scheme 53

We have reported that the ene cyclization of *Z*-alkenyl amides **64NZ** proceeds stereoselectively (Scheme 54).[4b] At room temperature or 80 °C, (*Z*)-amides **64NZ** were transformed to 3,4-*cis* ene adducts **89**. The

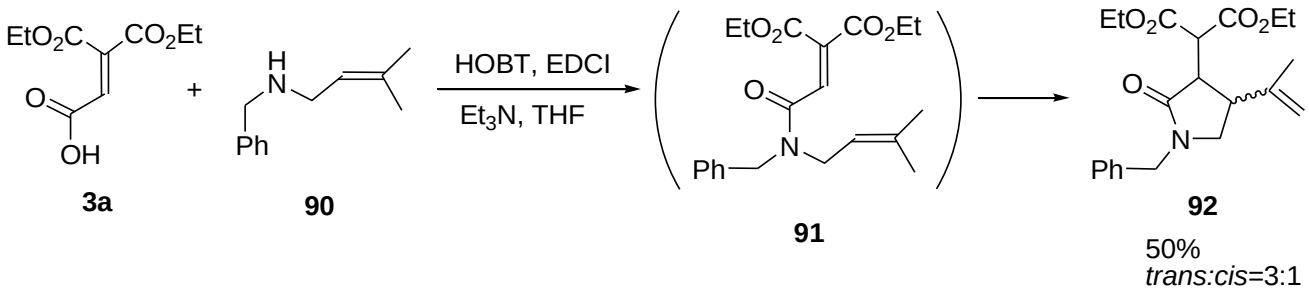
$t_{1/2}$ of **64NZ** (R = H) is approximately 90 h in $CDCl_3$ at 24 °C. (*E*)-amides **64NE** were transformed to 3,4-*cis* and *trans* ene adduct mixtures **89** at room temperature or 80 °C.



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]

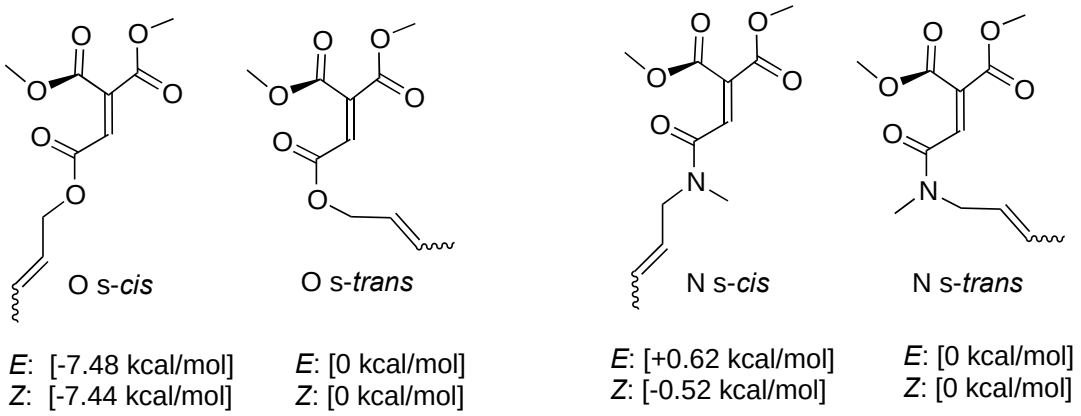
Attempted preparation of amide precursor *N*-benzyl-*N*-(3-methyl-2-butenyl)amide **91** led directly to ene-cyclized product **92** with 3:1 *trans*/*cis* diastereomeric ratio in 50% yield (Scheme 55).



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

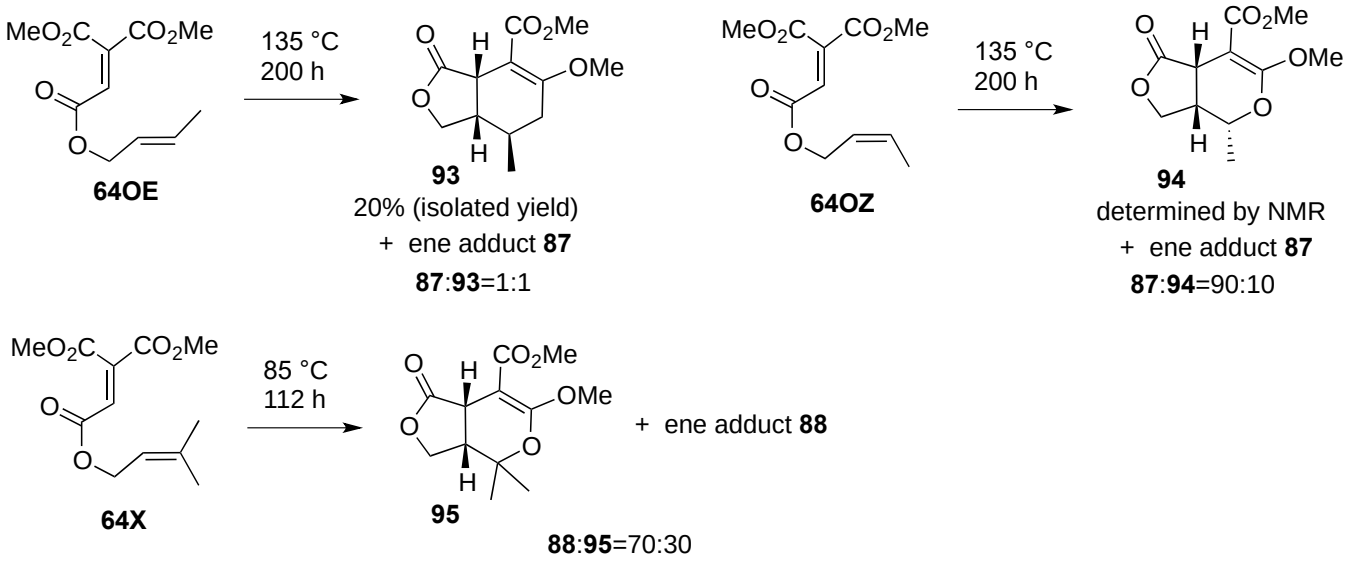
must have s-*trans* conformations. The rate enhancement observed with the ene reaction of amides probably originates from higher ratio of the reactive conformer.[35,4b]



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 K and P = 1 atm) for s-*cis* *E/Z* conformational isomers are obtained by B3LYP/6-311+G(d,p) SCRF = (PCM, solvent = CH_2Cl_2) // B3LYP/6-31G* and they are relative to O s-*trans* and N s-*trans* models, respectively.

4-2-2. Diels-Alder Reactions

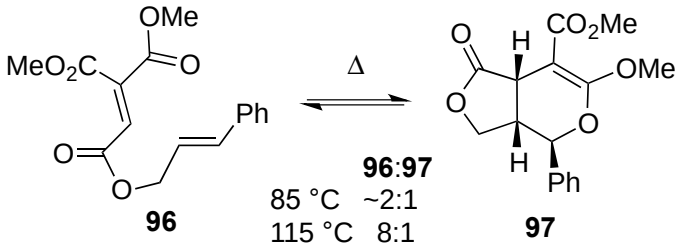
Snider et al. described reversible formation of hetero Diels-Alder adducts as biproducts of ene adducts as described in the previous section, on treatment of allylic ethenetricarboxylates **64** (Scheme 57).[2c]



Scheme 57

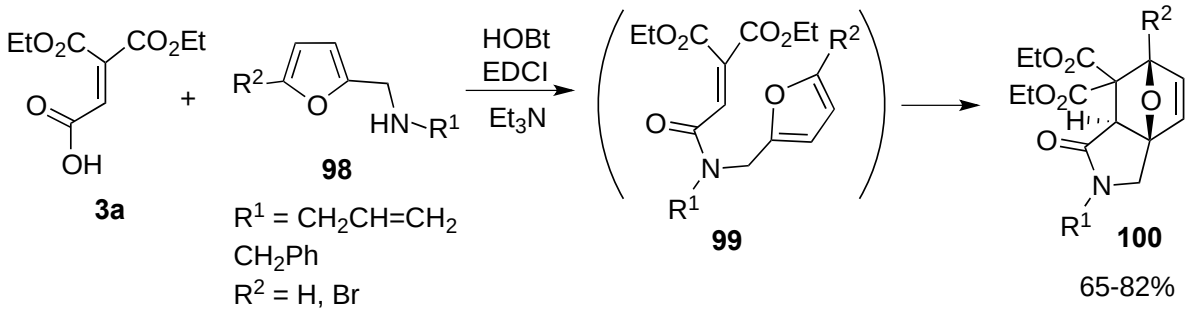
Snider et al. also reported that heating cinnamyl triester **96** in benzene-d_6 at 85 °C led to a ~2:1 mixture of **96** and hetero Diels-Alder adduct **97**. On raising the temperature to 115 °C the equilibrium shifts, giving a

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

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/Et_3N at room temperature led directly to an intramolecular Diels-Alder adducts **100** in 65–82% yield stereoselectively (Scheme 59).[36] 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.$0^{1,5}$]dec-8-ene **100** was determined by X-ray analysis.



Scheme 59

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

1. (a) M. Christl, R. Huisgen, and R, Sustmann, *Chem. Ber.*, 1973, **106**, 3275; (b) S. A. Ali, P. A.

Senaratne, C. R. Illig, H. Meckler, and J. J. Tufariello, *Tetrahedron Lett.*, 1979, **20**, 4167; (c) M. Nakamura, C. Liang, and E. Nakamura, *Org. Lett.*, 2004, **6**, 2015; (d) Z.-Z. Huang, Y.-B. Kang, J. Zhou, M.-C. Ye, and Y. Tang, *Org. Lett.*, 2004, **6**, 1677; (e) S. J. Pastine, K. M. McQuaid, and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 12180; (f) A. Salomone, V. Capriati, S. Florio, and R. Luisi, *Org. Lett.*, 2008, **10**, 1947; (g) S. Duan, R. Jana, and J. A. Tunge, *J. Org. Chem.*, 2009, **74**, 4612; (h) S. Murarka, C. Zhang, M. D. Konieczynska, and D. Seidel, *Org. Lett.*, 2009, **11**, 129; (i) J. D. White, Y. Li, and D. C. Ihle, *J. Org. Chem.*, 2010, **75**, 3569; (j) K. Mori, T. Kawasaki, S. Sueoka, and T. Akiyama, *Org. Lett.*, 2010, **12**, 1732; (k) S. Nakano, K. Kakugawa, T. Nemoto, and Y. Hamada, *Adv. Synth. Catal.*, 2014, **356**, 2088.

2. (a) T. R. Kelly, *Tetrahedron Lett.*, 1973, 437; (b) H. K. Hall, Jr. and R. C. Daly, *Macromolecules*, 1975, **8**, 22; (c) B. B. Snider, D. M. Roush, and T. A. Killinger, *J. Am. Chem. Soc.*, 1979, **101**, 6023; (d) S. B. Evans, M. Abdelkader, A. B. Padias, and H. K. Hall, Jr., *J. Org. Chem.*, 1989, **54**, 2848.
3. (a) M. S. Ouali, M. Vaultier, and R. Carrié, *Synthesis*, 1977, 626; (b) B. B. Snider and D. M. Roush, *J. Org. Chem.*, 1979, **44**, 4229; (c) S. Yamazaki, K. Ohmitsu, K. Ohi, T. Otsubo, and K. Moriyama, *Org. Lett.*, 2005, **7**, 759; (d) S. Yamazaki and M. Takebayashi, *J. Org. Chem.*, 2011, **76**, 6432; (e) S. Yamazaki, H. Kumagai, T. Takada, S. Yamabe, and K. Yamamoto, *J. Org. Chem.*, 1997, **62**, 2968; (f) S. Yamazaki, K. Yamada, S. Yamabe, and K. Yamamoto, *J. Org. Chem.*, 2002, **67**, 2889.
4. (a) S. Yamazaki, K. Fujinami, Y. Maitoko, K. Ueda, and K. Kakiuchi, *J. Org. Chem.*, 2013, **78**, 8405; (b) S. Yamazaki, J. Wada, and K. Kakiuchi, *Can. J. Chem.*, 2015, **93**, 1122.
5. S. Yamazaki, S. Morikawa, Y. Iwata, M. Yamamoto, and K. Kuramoto, *Org. Biomol. Chem.*, 2004, **2**, 3134.
6. S. Yamazaki, Y. Iwata, and Y. Fukushima, *Org. Biomol. Chem.*, 2009, **7**, 655.
7. (a) A. Ma and D. Ma, *Org. Lett.*, 2010, **12**, 3634; (b) S. Lang and R. J. K. Taylor, *Tetrahedron Lett.*, 2006, **47**, 5489.
8. T. Selvi and K. Srinivasan, *J. Org. Chem.*, 2014, **79**, 3653.
9. (a) B. M. Trost and M. T. Rudd, *J. Am. Chem. Soc.*, 2005, **127**, 4763; (b) L. Ferrie, D. Bouyssi, and G. Balme, *Org. Lett.*, 2005, **7**, 3143; (c) S. Garcon, S. Vassiliou, M. Cavicchioli, B. Hartmann, N. Monteiro, and G. Balme, *J. Org. Chem.*, 2001, **66**, 4069; (d) E. J. Corey and X.-M. Cheng, The Logic of Chemical Synthesis, Wiley, 1989; (e) D. R. Williams and K. G. Meyer, *J. Am. Chem. Soc.*, 2001, **123**, 765.
10. (a) S. Yamazaki, *Chem. Eur. J.*, 2008, **14**, 6026; (b) X. Marat, N. Monteiro, and G. Balme, *Synlett*, 1997, 845; (c) M. Cavicchioli, X. Marat, N. Monteiro, B. Hartmann, and G. Balme, *Tetrahedron Lett.*, 2002, **43**, 2609; (d) T. Yakura, S. Yamada, M. Shiima, M. Iwamoto, and M. Ikeda, *Chem. Pharm. Bull.*, 1998, **46**, 744.

11. S. Morikawa, S. Yamazaki, Y. Furusaki, N. Amano, K. Zenke, and K. Kakiuchi, *J. Org. Chem.*, 2006, **71**, 3540.
12. S. Morikawa, S. Yamazaki, M. Tsukada, S. Izuhara, T. Morimoto, and K. Kakiuchi, *J. Org. Chem.*, 2007, **72**, 6459.
13. S. Yamazaki, Y. Yamamoto, and Y. Mikata, *Tetrahedron*, 2009, **65**, 1988.
14. R. Takita, Y. Fukuta, R. Tsuji, T. Ohshima, and M. Shibasaki, *Org. Lett.*, 2005, **7**, 1363.
15. (a) M. Balasubramanian and J. G. Keay, In *Comprehensive Heterocyclic Chemistry II*, ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Pergamon, Oxford, 1996, Vol. 5, p 245; (b) J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 166; (c) J. P. Michael, *Nat. Prod. Rep.*, 2007, **24**, 223; (d) J. P. Michael, *Nat. Prod. Rep.*, 2005, **22**, 627; (e) J. P. Michael, *Nat. Prod. Rep.*, 2004, **21**, 650.
16. For recent examples of synthesis of quinolines, (a) S. Madapa, Z. Tusi, and S. Batra, *Curr. Org. Chem.*, 2008, **12**, 1116; (b) V. V. Kouznetsov, L. Y. V. Mendez, and C. M. M. Gomez, *Curr. Org. Chem.*, 2005, **9**, 141; (c) Y. Laras, V. Hugues, Y. Chandrasekaran, M. Blanchard-Desce, F. C. Acher, and N. Pietrancosta, *J. Org. Chem.*, 2012, **77**, 8294; (d) H. Venkatesan, F. M. Hocutt, T. K. Jones, and M. H. Rabinowitz, *J. Org. Chem.*, 2010, **75**, 3488; (e) R. G. Schmidt, E. K. Bayburt, S. P. Latshaw, J. R. Koenig, J. F. Daanen, H. A. McDonald, B. R. Bianchi, C. Zhong, S. Joshi, P. Honore, K. C. Marsh, C.-H. Lee, C. R. Faltynek, and A. Gomtsyan, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 1338; (f) A. B. Richard and N. Baskar, *J. Heterocycl. Chem.*, 2011, **48**, 613; (g) F. Pisaneschi, J. J. P. Sejberg, C. Blain, W. H. Ng, E. O. Aboagye, and A. Spivey, *Synlett*, 2011, 241; (h) J. B. Bharate, R. A. Vishwakarma, and S. B. Bharate, *RSC Adv.*, 2015, **5**, 42020.
17. S. Yamazaki, S. Morikawa, K. Miyazaki, M. Takebayashi, Y. Yamamoto, T. Morimoto, K. Kakiuchi, and Y. Mikata, *Org. Lett.*, 2009, **11**, 2796.
18. S. Yamazaki, M. Takebayashi, and K. Miyazaki, *J. Org. Chem.*, 2010, **75**, 1188.
19. S. Yamazaki, Y. Yamamoto, Y. Fukushima, M. Takebayashi, T. Ukai, and Y. Mikata, *J. Org. Chem.*, 2010, **75**, 5216.
20. K. Okuro and H. Alper, *J. Org. Chem.*, 2012, **77**, 4420.
21. (a) H. K. Hall, Jr., H. A. A. Rasoul, M. Gillard, M. Abdelkader, P. Nogues, and R. C. Sentman, *Tetrahedron Lett.*, 1982, **23**, 603; (b) W. Srisiri, A. B. Padias, and H. K. Hall, Jr., *J. Org. Chem.*, 1993, **58**, 4185; (c) W. Srisiri, A. B. Padias, and H. K. Hall, Jr., *J. Org. Chem.*, 1994, **59**, 5424.
22. (a) R. Huisgen, In *The Adventure Playground of Mechanisms and Novel Reactions: Profiles, Pathways and Dreams*, ed. by J. I. Seeman, American Chemical Society, Washington, DC, 1994, p 62; (b) R. Huisgen, H. Blaschke, and E. Brunn, *Tetrahedron Lett.*, 1966, **7**, 405.
23. (a) O. Mitsunobu, *Synthesis*, 1981, 1; (b) D. L. Hughes, *Org. React.*, 1992, **42**, 335; (c) D. L. Hughes, *Org. Prep. Proced. Int.*, 1996, **28**, 127.

24. (a) E. Brunn and R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 513; (b) C. Cookson and J. M. Locke, *J. Chem. Soc*., 1963, 6062.
25. (a) V. Nair, A. T. Biju, K. Mohanan, and E. Suresh, *Org. Lett.*, 2006, **8**, 2213; (b) M. Chakravarty, N. N. B. Kumar, K. V. Sajna, and K. C. K. Swamy, *Eur. J. Org. Chem*., 2008, 4500.
26. (a) R. D. Otte, T. Sakata, I. A. Guzei, and D. Lee, *Org. Lett*., 2005, **7**, 495; (b) S.-L. Cui, J. Wang, and Y.-G. Wang, *Org. Lett*., 2008, **10**, 13.
27. V. Nair, S. C. Mathew, A. T. Biju, and E. Suresh, *Angew. Chem. Int. Ed*., 2007, **46**, 2070.
28. (a) A. Volonterio, C. Ramirez de Arellano, and M. Zanda, *J. Org. Chem.*, 2005, **70**, 2161; (b) A. Volonterio and M. Zanda, *Tetrahedron Lett.*, 2003, **44**, 8549.
29. S. Yamazaki, K. Yamada, T. Otsubo, M. Haruna, E. Kutsuwa, and H. Tamura, *Chem. Commun.*, 2001, 69.
30. S. Yamazaki, S. Inaoka, and K. Yamada, *Tetrahedron Lett*., 2003, **44**, 1429.
31. Y. Fukushima, S. Yamazaki, and A. Ogawa, *Org. Biomol. Chem*., 2014, **12**, 3964.
32. S. Yamazaki, K. Ueda, Y. Fukushima, A. Ogawa, and K. Kakiuchi, *Eur. J. Org. Chem.*, 2014, 7023.
33. S. Yamazaki, M. Yamamoto, and S. Morikawa, *Heterocycles*, 2006, **67**, 269.
34. (a) W. Oppolzer and V. Snieckus, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 476; (b) W. Oppolzer, *Pure Appl. Chem.*, 1981, **53**, 1181.
35. (a) D. D. Sternbach, D. M. Rossana, and K. D. Onan, *Tetrahedron Lett.*, 1985, **26**, 591; (b) R. K. Boeckman, Jr. and S. S. Ko, *J. Am. Chem. Soc.*, 1982, **104**, 1033; (c) W. Oppolzer and W. Fröstl, *Helv. Chim. Acta*, 1975, **58**, 590; (d) W. Oppolzer, W. Fröstl, and H. P. Weber, *Helv. Chim. Acta*, 1975, **58**, 593; (e) J. D. White, F. W. J. Demnitz, H. Oda, C. Hassler, and J. P. Snyder, *Org. Lett.*, 2000, **2**, 3313. (f) D. J. Tantillo, K. N. Houk, and M. E. Jung, *J. Org. Chem.*, 2001, **66**, 1938; (g) M. D. Weingarten, M. Prein, A. T. Price, J. P. Snyder, and A. Padwa, *J. Org. Chem.*, 1997, **62**, 2001; (h) M. E. Jung and J. Gervay, *J. Am. Chem. Soc.*, 1991, **113**, 224; (i) C. Giessner-Prettre, S. Hükel, J. Maddaluno, and M. E. Jung, *J. Org. Chem.*, 1997, **62**, 1439.
36. S. Yamazaki, H. Sugiura, M. Niina, Y. Mikata, and A. Ogawa, *Heterocycles*, 2016, **92**, 485.

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