#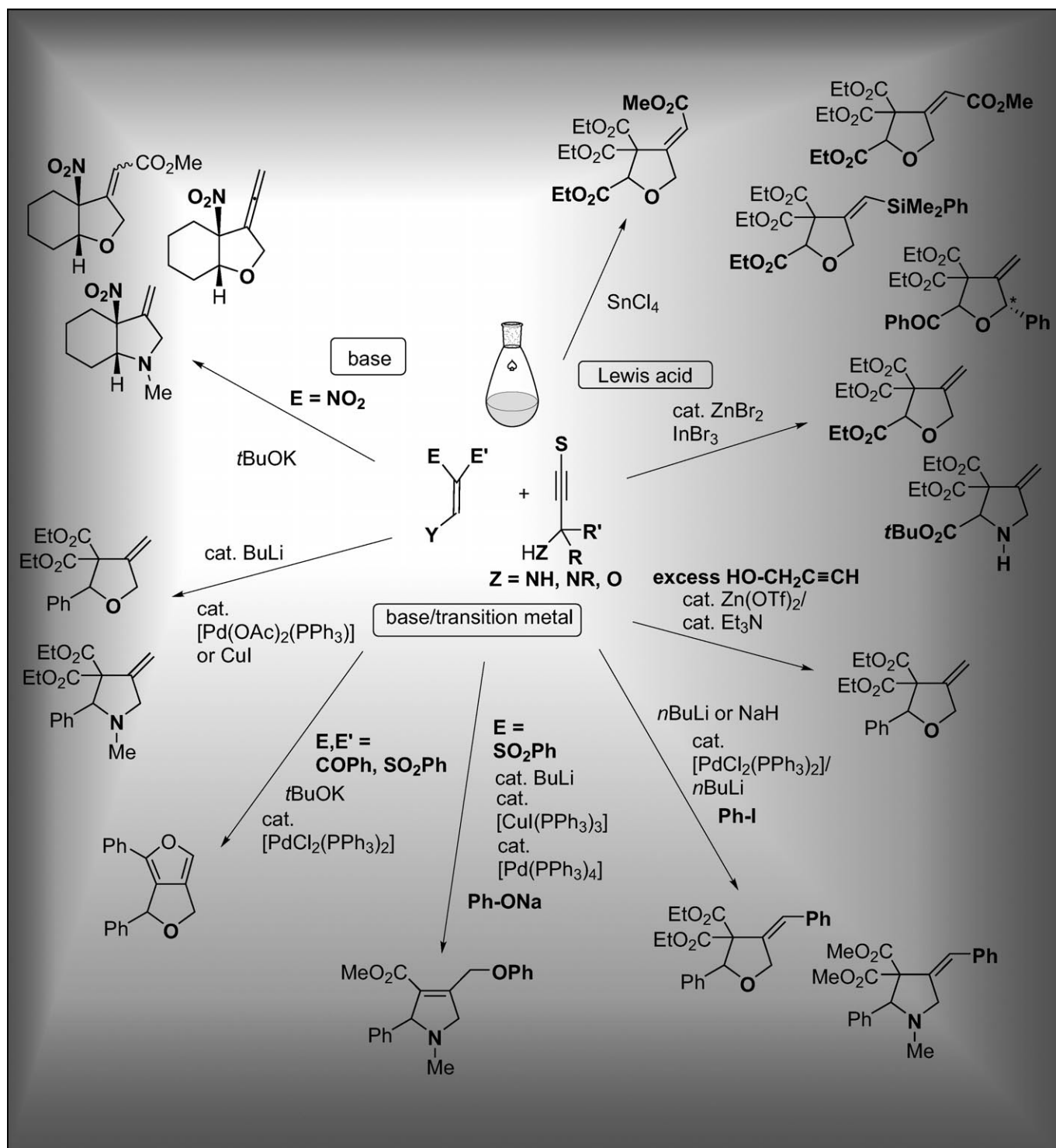 Efficient Synthesis of Methylenetetrahydrofurans and Methylenepyrrolidines by Formal [3+2] Cycloadditions of Propargyl Substrates

Shoko Yamazaki*[a]

Abstract: Recent developments concerning the synthesis of methylenetetrahydrofurans and methylenepyrrolidines by one-pot formal [3+2] cycloadditions involving propargylic (and allylic) alcohols and amines with electrophilic alkenes are described. The synthetic methods provide powerful tools to prepare highly functionalized oxygen- and nitrogen-containing five-membered ring systems. The reactions can be effectively promoted by base, base/transition metals, and Lewis acids, depending on the substrates.

Keywords: alcohols · amines · cycloaddition · one-pot reactions · pyrrolidines · tetrahydrofurans
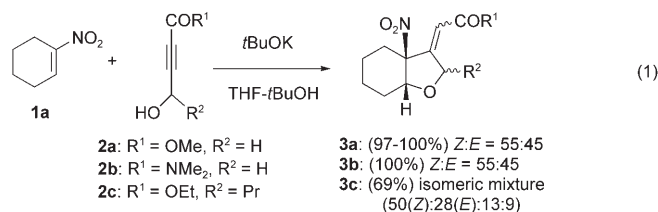
Introduction

Oxygen- and nitrogen-containing five-membered heterocyclic systems are important structures in organic chemistry because of their presence in many biologically active compounds.[1] Methylenetetrahydrofurans and methylenepyrrolidines are potentially useful as their synthetic intermediates[2] and the skeletons also appear in natural products.[3] Various new synthetic methods have been developed and such research is still a very active area.[4] Among the methods developed, propargyl alcohols and amines have been effectively utilized as three-atom components in one-pot formal [3+2] cycloadditions. Both the heteroatom (oxygen or nitrogen) and the alkyne moiety in the substrates can participate in the bond formation. Although both groups can be utilized by sequential steps, the one-pot procedure is effective methodology to construct five-membered rings. In this account we will summarize recent developments in the efficient synthesis of methylenetetrahydrofurans and methylenepyrrolidines by formal [3+2] cycloadditions of propargyl (and related allylic) substrates with electrophilic alkenes.[5] The strategy of these syntheses is based on the dual activation of triple bond and heteroatom or electrophilic alkene.

tBuOK-Promoted Reactions of Nitroalkenes with Propargyl Alcohols or Propargylamines

Tandem reactions involving conjugate (Michael) additions are powerful tools for the construction of ring systems common to many natural products.[6] In the sequence, a nucleophile adds to an activated alkene to produce a stabilized anion, which then adds to a second activated alkene (or

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alkyne) positioned so as to form a cyclic compound. As a route to such compounds, employing an oxygen-nucleophile-initiated, tandem conjugate-addition reaction of alkenes bearing an electron-withdrawing group with hydroxyalkynoates or hydroxyalkenoates was envisioned. The reaction of l-nitrocyclohexene (**1a**) as a Michael acceptor was examined by Ikeda and co-workers.[7] Thus, a tandem conjugate-addition reaction of **1a** with methyl 4-hydroxy-2-butynoate (**2a**) and related compounds in the presence of a base was studied [Eq. (1)].


$$\text{(1)}$$

2a: R^1 = OMe, R^2 = H
2b: R^1 = NMe$_2$, R^2 = H
2c: R^1 = OEt, R^2 = Pr

3a: (97-100%) Z:E = 55:45
3b: (100%) Z:E = 55:45
3c: (69%) isomeric mixture (50(Z):28(E):13:9)

Since **2a** is unstable under basic reaction conditions, two equivalents of **2a** were used. When a solution of **1a** and **2a** in CH$_2$Cl$_2$ was treated with an amine base, such as triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,1,3,3-tetramethylguanidine, only poor yields (less than 27%) of octahydrobenzo[b]furan (**3a**) were obtained. Basic alumina also gave a low yield (8%) of **3a**. On the other hand, alkali-metal bases, such as sodium hydride (NaH) in CH$_2$Cl$_2$, nBuLi in THF, and tBuOK in THF–tBuOH, were found to be effective. Among them, the best result was obtained when either a stoichiometric or catalytic amount of tBuOK was used in THF–tBuOH. The reaction was completed within 10 min at 0°C to give **3a** in 97–100% yields as a mixture of the Z and E isomers in a ratio of 55:45. The Z and E diastereoselectivity was slightly improved to 7:3 and 3:1 by using NaH/CH$_2$Cl$_2$ and nBuLi/THF, but the total yields decreased to 51 and 74%, respectively. The reaction of **1a** with the amide **2b** also proceeded smoothly to give a mixture of (Z)- and (E)-**3b** in quantitative yield in a ratio of 55:45. The reaction of **1a** with secondary alcohol **2c** gave the octahydrobenzo[b]furan **3c** in 69% yield as an inseparable mixture of the four possible isomers in a ratio of 50:28:13:9. The stereochemistry of the two major isomers was assigned as (Z)-ester for the first major isomer and (E)-ester for the second major isomer.

The reaction of acyclic nitroalkene **4a** with **2a** in the presence of tBuOH at 0°C for 10 min, gave a mixture of (Z)- and (E)-3-methyl-3-nitro-2-phenyltetrahydrofurans [(Z)- and (E)-**5**] in 28 and 26% yields, respectively [Eq. (2)].
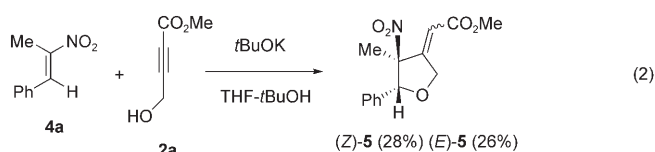

$$\text{(2)}$$

(Z)-**5** (28%) (E)-**5** (26%)

The reactions in Equation (1) may proceed by initial addition of the alkoxy anion to **1a** to give the anion **A1**, which then undergoes a second conjugate addition through a transition state **B1** leading to the anion **C1** (Scheme 1). Subsequent protonation affords (Z) and (E)-**3a**.
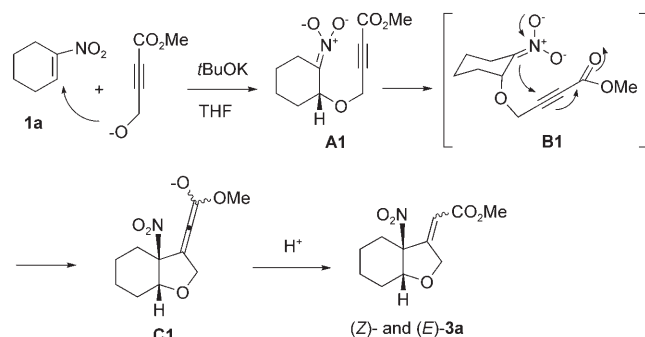
Scheme 1.

Conditions: 0 °C, 10 min, then RT, 15-30 min, 70-78%
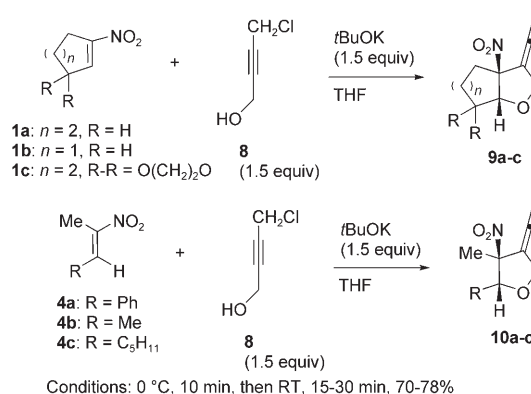
Scheme 2.

Scheme 3.

For both the bicyclic products and monocyclic tetrahydrofurans, diastereoselective formation of the *cis* ring junction and 2,3-substitution were achieved respectively, probably due to stereochemical requirements. For acyclic substrates, allylic 1,3-strain was assumed. On the other hand, for olefinic substitution, mixtures of the E and Z geometrical isomers were obtained.

1-Nitrocyclohexene (**1a**) also reacted with a hydroxyalkenoate. Thus, treatment of **1a** with methyl 4-hydroxy-2-butenoate (**6**) under the same reaction conditions gave an inseparable mixture of the two diastereoisomers of the octahydrobenzo[b]furan **7** in 81% yield and in a ratio of 4:1 [Eq. (3)].
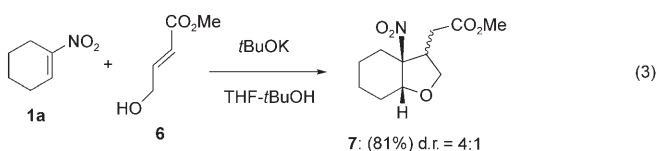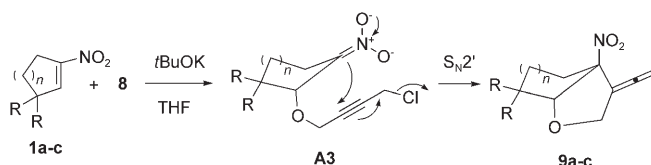

The *t*BuOK-promoted reaction of 4-chlorobut-2-yn-1-ol (**8**) with nitroalkenes **1** and **4** to afford 3-vinylidenetetrahydrofurans **9** and **10** was investigated by Dulcére and Dumez.[8] Nitroalkenes **1** and **4** (Scheme 2) were treated at 0 °C to room temperature in THF with **8**, in the presence of *t*BuOK (1.5 equiv). Vinylidenetetrahydrofurans **9** and **10** were isolated as the sole products (70–78% yield). The oxa-Michael addition first affords nitronate **A3** which then undergoes S_N2' substitution to provide the allenyl moiety (Scheme 3). In these examples, for both the bicyclic products and monocyclic tetrahydrofurans, diastereoselective formation of the *cis* ring junction and 2,3-substitution were also achieved, probably due to stereochemical requirements.

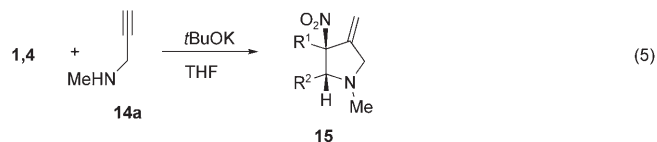The reaction of non-activated propargyl alcohols or propargylamines with nitroalkenes as Michael acceptors in the presence of *t*BuOK was also found to proceed.[9] This is an extension of the two-step synthesis of α-methylene γ-lactams from 1-nitrocyclohexene (**1a**), involving the formation of β-nitroamides, which then undergo a base (Triton B)-promoted carbanion addition to an unactivated terminal alkyne.[10] The *t*BuOK-promoted reaction of propargyl alcohols **11** with nitroalkenes **1** and **4** affords 3-methylenetetrahydrofurans **12** in moderate to good yields regioselectively and diastereoselectively [Eq. (4)]. The diastereoselectivity of 2,3-substitution was also explained by allylic 1,3-strain as above. Minor products, 3,4-dihydropyrans **13** resulting from 6-*endo* cyclization mode were obtained along with the major 5-*exo* adducts **12**, when the reaction was performed with nitroalkenes **1a** and **4c** (ratio 5-*exo*/6-*endo* 1.7–20:1). Tetrahydrofurans **12** and the minor products, 3,4-dihydropyrans **13** by reaction with α-substituted propargyl alcohol **11b** were obtained as a 0.7–0.9/1 mixture of diastereomers.
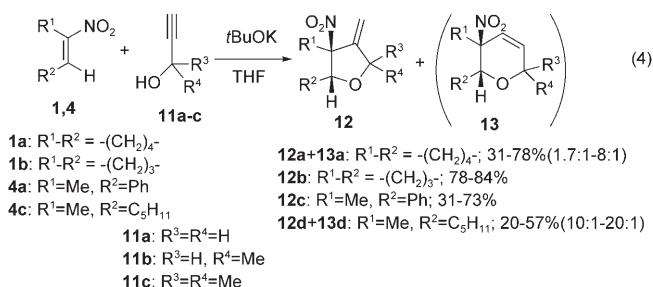
Aza-Michael addition of *N*-methylpropargylamine (**14a**) with nitroalkenes **1** and **4** also proceeded with intramolecular nucleophilic addition to provide, regio- and diastereo-se-

lectively, 3-methylenepyrrolidines **15** [Eq. (5)]. Thus, base promotes intramolecular addition of the generated carbanion to an unactivated terminal alkyne. The substrates for the reported base-promoted reactions were so far limited to α-alkyl nitroalkenes.

(5)

Base/Pd-, Cu-promoted Reactions with Propargyl Alcohol or Propargylamines

Catalytic use of nBuLi/Pd in the reaction of a propargylic alcohol and a Michael acceptor leading to highly functionalized 3-methylenetetrahydrofurans was also investigated by Balme and co-workers.[11] These reaction conditions are an extension of the carbocyclization of alkynyl malonates derivatives promoted by catalytic amounts of an alkoxide and a palladium(0) complex.[12] The strategy towards methylenetetrahydrofurans is based on an oxygen-nucleophile-initiated Michael addition of propargyl alcohols to alkylidene or arylidenemalonates, followed by an in situ palladium-mediated cyclization.

The reaction of propargyl alcohol **11a** (1.5 equiv) with diethyl benzylidenemalonate (**16a**; 1 equiv) in the presence of 10 mol% nBuLi and 5 mol% [Pd(OAc)$_2$(PPh$_3$)] in THF at room temperature gave tetrahydrofuran **17a** (E=E′= CO$_2$Et, R=Ph) in 94% yield [Eq. (6)]. The reaction conditions were applied to the synthesis of various methylenetetrahydrofurans. Reaction of α-substituted propargyl alcohol **11c–d** with **16a** also gave tetrahydrofurans **17** [Eq. (7)]. Compound **17** from 1-phenyl-2-propyn-1-ol (**11d**) was isolated as a separable mixture of diastereomers (cis:trans=1:2).

(6)

(7)
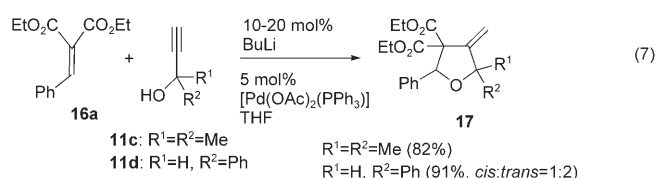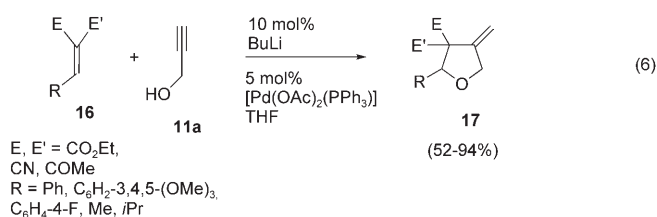
The reaction is also promoted by copper iodide.[13] These reaction conditions were applied to solution-phase combina-

torial synthesis of a large array of 3-methylenetetrahydrofurans. High yields are obtained by reaction between benzylidene- or alkylidenemalonates and propargyl alcohols.

The Li/Pd-mediated process was applied to the synthesis of 3-methylenepyrrolidines from propargylamines **14** and a variety of Michael acceptors. Reaction of N-methylpropargylamine (**14a**) with diethyl benzylidenemalonate (**16a**) under the same reaction conditions as above (10 mol% nBuLi and 5 mol% [Pd(OAc)$_2$(PPh$_3$)] in THF at room temperature) afforded the pyrrolidine **18a** in 79% yield [Eq. (8)].[14] Attempts to accomplish this reaction using propargylamine **14** (R=H) proved to be unsuccessful.

(8)
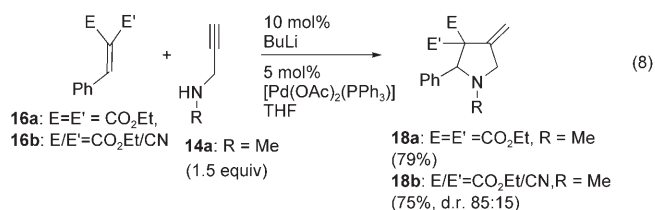
The tandem reaction was also carried out by using a copper catalyst. Thus, the reaction of N-benzylpropargylamine (**14b**) and tosyl amine **14c** with **16a** in the presence of CuI (3%) and nBuLi (10%) in THF at room temperature, afforded the corresponding pyrrolidines **18** in good yield [Eq. (9)]. The procedure with a copper catalyst was compared that with the palladium catalyst. The yields obtained for reactions involving **14a** were improved by substituting [Pd(OAc)$_2$(PPh$_3$)] for CuI. The reaction of a γ-substituted propargylamine **14d** with diester **16a** did not give the desired cyclized products. Reaction of **14d** with malononitrile derivative **16c** gave an (E)-**18c** isomer exclusively [Eq. (10)].

(9)

(10)
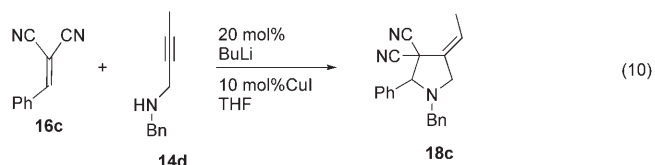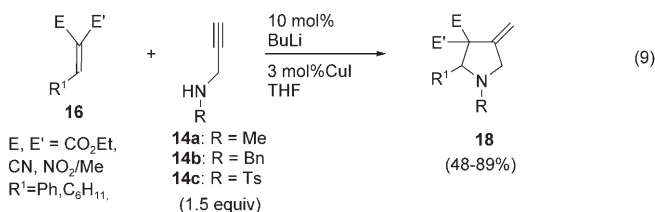
Although the precise role of copper iodide and the differences between copper and palladium are not clear, the mechanism for the formation of the nitrogen heterocycle involving the conjugate addition of the nitrogen anion, fol-

lowed by pyrrolidine cycloisomerization, may be proposed (Scheme 4). Formation of the isomer (E)-**18c** as the only reaction product suggests *anti*-addition of the carbanion to the
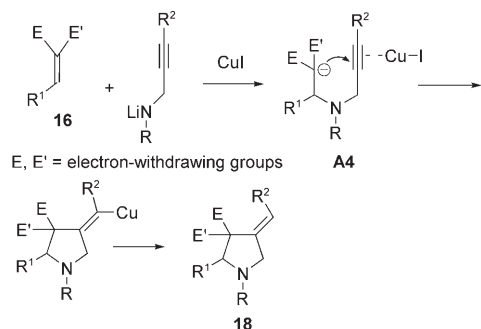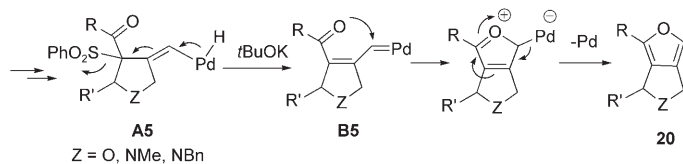

Scheme 4.

acetylenic moiety coordinated to the copper catalyst in **A4**.

The palladium-catalyzed reactions of propargyl alcohols and propargylamines with α-sulfonyl α,β-unsaturated ketones were further developed to a single-step synthesis of furo[3,4-*c*] heterocyclic derivatives utilizing the sulfone group under the palladium-catalyzed conditions.[15] For example, the furofuran **20a** was obtained by treatment of a solution of propargyl alcohol **11a** (1.5 equiv) with *t*BuOK (1.1 equiv) and subsequent addition of α-phenylsulfonyl chalcone **19a** together with a catalytic amount (5 mol%) of [Pd(PPh$_3$)$_2$X$_2$] (X=Cl or OAc) in THF under reflux in 52–57% yield [Eq. (11)]. The methodology was also extended to the synthesis of furopyrroles by using propargylamines.


(11)
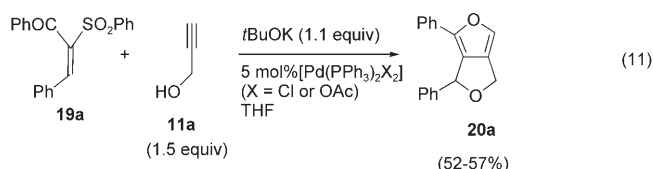
According to mechanistic consideration of the reaction, the arylidene β-ketosulfone **19** acts initially as a Michael acceptor and then as a nucleophilic ionic center. The first cyclization (to give tetrahydrofuran or pyrrolidine rings) is suggested to be promoted by a σ-alkynyl palladium(II) (or IV) hydride species resulting from insertion of the metal into the C–H bond of the terminal acetylene. This would lead to an intermediate species **A5** (Scheme 5). At this

Scheme 5.

stage, the ability of the sulfonyl moiety to act as a leaving group would trigger the generation of a palladium carbene **B5** through sulfinic acid elimination. It is suggested that *t*BuOK intervenes in the elimination step in addition to the first cyclization, possibly by abstracting the hydrogen of the intermediate Pd$^{(II or IV)}$–H species to form the palladium carbene **B5**. The electrophilic palladium carbene **B5** is then attacked by the oxygen of the adjacent ketone, leading to **20** in a 6π-electrocyclization process.

The sulfone and nitro groups in electrophilic olefins are also utilized in sequential one-pot coupling of three components, a propargylamine, a vinyl sulfone (or nitroalkene) and phenols.[16] The one-pot reaction was achieved by the sequential process of a Cu-catalyzed cycloaddition of a propargylamine and a vinyl sulfone and a Pd-catalyzed allylic substitution reaction of sulfone (or nitroalkene) with phenol (Scheme 6). For example, propargylamine **14a** (R=Me)
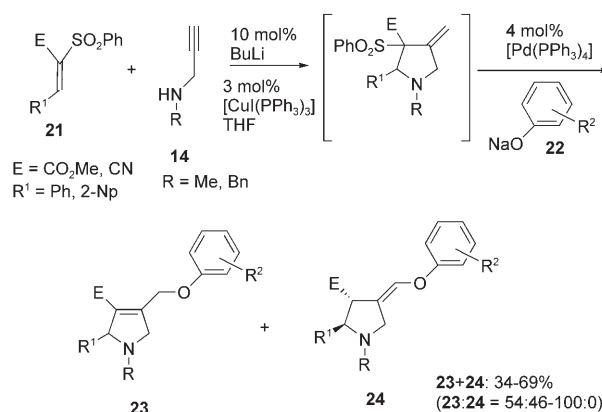

Scheme 6.

(1.1 equiv) and vinyl sulfone **21a** (E=CO$_2$Me, R^1=Ph) (1 equiv) underwent cycloaddition in THF at room temperature in the presence of 3 mol% of [CuI(PPh$_3$)$_3$]. After the reaction had reached completion (ca. 6 h), a solution of sodium phenoxide **22a** (R^2=3,4-OCH$_2$O-) (2 equiv) in THF was added, followed by 4 mol% of [Pd(PPh$_3$)$_4$], and the reaction mixture was stirred overnight at 40°C. This afforded a 56:44 mixture of 4-(phenoxymethyl)-3-pyrroline **23a** and its isomeric 4-(phenoxymethylene) pyrrolidine **24a** in 63% isolated yield.

Next, a one-pot reaction between equimolecular amounts of various propargyl alcohols, Michael acceptors, and unsaturated halide (or triflate) **25** in the presence of a palladium(0) catalyst to provide highly substituted 3-arylidene- (or 3-alkenylidene-) tetrahydrofurans **26** was investigated [Eq. (12)].[17] The methodology is based on a tandem conjugate-addition/carbopalladation involving an unsaturated halide (or triflate). A palladium(0) catalyst generated in situ by reduction of [PdCl$_2$(PPh$_3$)$_2$] with *n*BuLi has been found particularly effective. By using 5 mol% of this catalyst, the reaction took place at room temperature in less than 15 min, leading to the stereoselective formation of **26a** (R^2=Ph) in

89% yield. The three-component one-pot process was applied to synthesis of pyrrolidines. The reaction of *N*-methyl-propargylamine (**14a**; 1.1 equiv) with dimethyl benzylidene-malonate (**16d**; 1.1 equiv) and phenyl iodide (**25a**; 1 equiv) under the given reaction conditions (1.1 equiv NaH, 5 mol% [PdCl$_2$(PPh$_3$)$_2$], THF/DMSO, RT, 3 h) gave **27a** (E = E′ = CO$_2$Me, R^1 = R^2 = Ph) in 65% yield.[18]

$$(12)$$

26: Y = O; 50–90%
27: Y = NMe; 37–81%

E,E′ = CO$_2$R, SO$_2$Ph
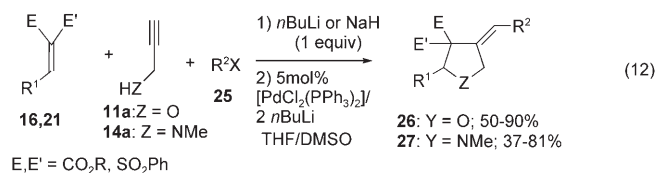
A Pd-catalyzed three-component assembling of highly functionalized 4-benzyl- (and allyl-) pyrrolidines was also achieved by a combination of allylamines **28**, *gem*-diactivated alkenes such as benzylidenemalonates **16** and α-sulfonyl esters **21**, and unsaturated halides (or triflates) in 60–90% yields with diastereomeric ratios of 85:15–75:25 in favor of the *trans* isomer [Eq. (13)].[19]

$$(13)$$

29: 60–90%
(*trans:cis* = 85:15-75:25)

E,E′ = CO$_2$R, SO$_2$Ph
R^1 = Ar
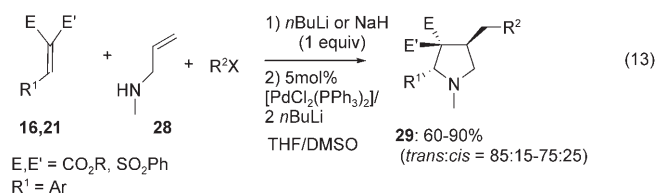
Zn-Promoted Reactions of Alkylidenemalonates with Propargyl Alcohol

A zinc-catalyzed tandem 1,4-addition/cyclization between propargyl alcohol and a Michael acceptor, such as alkylidenemalonate, has been developed by Nakamura and co-workers.[20] In the presence of catalytic amounts of zinc triflate [Zn(OTf)$_2$] and triethylamine (Et$_3$N), various 2-alkylidene-1,3-dicarbonyl compounds reacted with propargyl alcohol to give 3- or 4-methylenetetrahydrofurans in high yields.

A mixture of olefin **16a** and propargyl alcohol **11a** (1:2 mole ratio) was refluxed in THF in the presence of 20 mol% Zn(OTf)$_2$ and 20 mol% Et$_3$N to give the tetrahydrofuran product **17a** in 92% yield [Eq. (14)]. The reaction takes place around room temperature in the absence of solvent, although the use of a large excess of propargyl alcohol **11a** (5 equiv) is required to achieve smooth conversion of the substrate.

A mechanistic rationale for this catalytic coupling reaction is proposed in Scheme 7. First, zinc alkoxide **A7** forms by the reaction of propargyl alcohol with Et$_3$N and Zn-(OTf)$_2$, and the resulting zinc alkoxide adds to the Michael acceptor **16**. The zinc enolate intermediate **B7** is assumed to be reactive enough to undergo cyclization quickly, since the

11a (2 equiv) 70 °C, 15 h, THF 92%
11a (5 equiv) 25 °C, 12 h, neat 93%

$$(14)$$
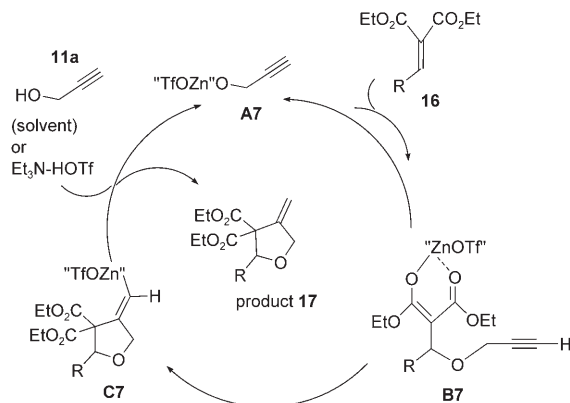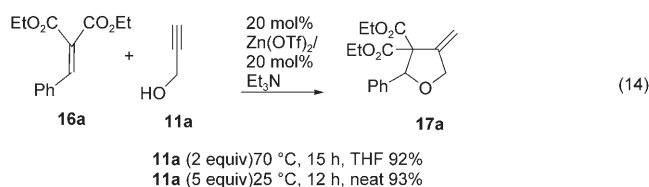
Scheme 7.

initial 1,4-adduct was not observed. On the other hand, the reverse 1,4-addition must be even faster than the cyclization, and overall the equilibrium of the first stage favors the starting material side. The intramolecular carbozincation of **B7** followed by protonation of alkenylzinc intermediate **C7** furnishes the tetrahydrofuran product and regenerates the zinc alkoxide **A7**.
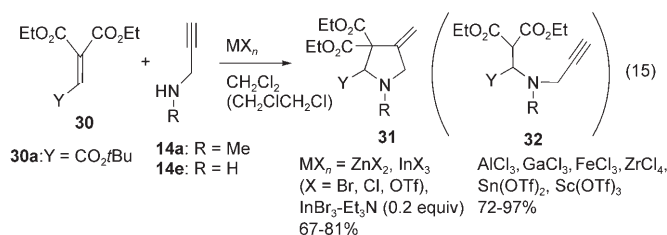
Lewis Acid Promoted Reactions of Ethenetricarboxylates with Propargylamines or Propargyl Alcohols

Zinc- and indium-promoted reactions of ethenetricarboxylates with propargylamines: In our research to date, we have shown that ethenetricarboxylate derivatives are highly electrophilic Michael acceptors in various Lewis acid promoted reactions.[21] For example, they are used in amine additions, [2+1] cycloadditions, and various intramolecular reactions.

Propargyl substrates may react with the metal-coordinated ethenetricarboxylate derivatives and give rise to an intermediate adduct. We proposed that the use of ethenetricarboxylates may be effective in the first conjugate addition step, and soft Lewis acids, such as zinc or indium, may activate the alkyne moieties as well. Facile ring closure may occur from the intermediate to lead to cyclized products. According to this hypothesis, we have investigated the following reactions.

Initially, we examined the reaction of ethenetricarboxylate **30** and propargylamines **14**.[22] The reaction of a 1:1 mixture of these substrates in the absence of Lewis acid gave 1,4-adduct **32** quantitatively. After examining various Lewis acids [Eq. (15)], zinc and indium Lewis acids were found to

be effective for methylenepyrrolidine formation. Treatment of the noncyclic adduct **32 a** (Y=CO$_2$*t*Bu, R=Me) with 1.2 equivalents of ZnBr$_2$ or InBr$_3$ gave **31 a** (Y=CO$_2$*t*Bu, R=Me) in 60% and 66% yields, respectively.

(15)

30 a: Y = CO$_2$*t*Bu
14 a: R = Me
14 e: R = H

MX$_n$ = ZnX$_2$, InX$_3$
(X = Br, Cl, OTf),
InBr$_3$-Et$_3$N (0.2 equiv)
67–81%

AlCl$_3$, GaCl$_3$, FeCl$_3$, ZrCl$_4$,
Sn(OTf)$_2$, Sc(OTf)$_3$
72–97%

Catalytic conditions were examined and using InBr$_3$–Et$_3$N (0.2 equiv) in CH$_2$ClCH$_2$Cl at 80°C for 4 h gave the cyclized product **31 a** in 74% yield. The reaction also proceeds without Et$_3$N in 55% yield. Addition of Et$_3$N may capture the HBr generated in situ and suppress side reactions. The reaction of **30 a** and *N*-propargylamine **14 e** (R=H) in the presence of catalytic InBr$_3$–Et$_3$N (0.2 equiv) at 80°C for 4 h gave a proline derivative **31** (Y=CO$_2$*t*Bu, R=H) in 75% yield. Thus, as we had proposed, zinc and indium can presumably activate alkyne moieties and give cyclized products effectively.

We next decided to examine other highly activated substrates. 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 **30**. In addition to various ester substituted analogs (Y=CO$_2$Et, CO$_2$CH$_2$Ph), amide (Y=CONMeCH$_2$C≡CH) and ketone derivatives (Y=COPh) **30** also gave the novel proline analogs **31** in 45–69% yields. This methodology represents a very rapid and efficient way to construct a variety of potentially useful proline analogues.
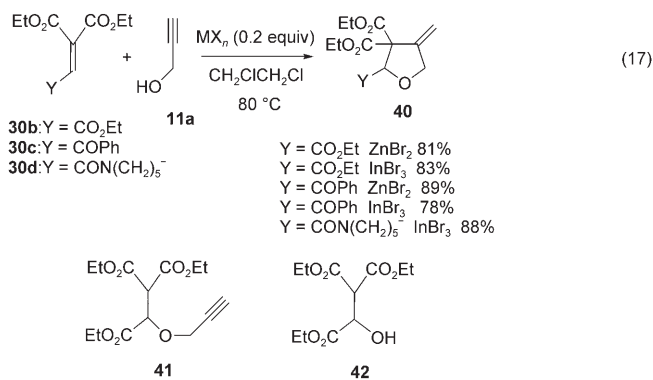
The reactions of other substrates, di-*tert*-butyl methylenemalonate (**33**), diethyl ethylidenemalonate (**16 d**), and diethyl benzylidenemalonate (**16 a**) with propargylamines **14** were investigated in order to examine the effect of 2-substituents [Eq. (16)]. Di-*tert*-butyl methylenemalonate (**33**) gave cyclized product in high yields. Less reactive ethylidenemalonate **16 d** and benzylidenemalonate **16 a** also gave cyclized products in 38–49% yield, along with byproducts **38** (5–12%) and **39** (3% for **16 d**) from the reverse Knoevenagel reaction.

Lewis acid catalyzed reactions of ethenetricarboxylates with propargyl alcohols: The reaction conditions for the zinc and indium catalysis were also found to be suitable for methylenetetrahydrofuran formation. The reactions of ethenetricarboxylate **30 b** with propargyl alcohol **11 a** in the presence of catalytic amount of ZnBr$_2$ gave methylenetetrahydrofuran **40 a** (Y=CO$_2$Et) in 81% yield [Eq. (17)].[22,23] The reaction of *tert*-butyl ester **30 a** and **11 a** in the presence of ZnBr$_2$ or InBr$_3$ did not give the expected methylenetetrahydrofuran, probably because *tert*-butyl cation generated in situ

(16)

33: R^1 = *t*Bu, Y = H
16 d: R^1 = Et, Y = Me
16 a: R^1 = Et, Y = Ph

14 a: R = Me
14 b: R = H

34: R^1 = *t*Bu, Y = H (73–100%)
35: R^1 = Et, Y = Me (38–46%)
36: R^1 = Et, Y = Ph (49%)

38

39
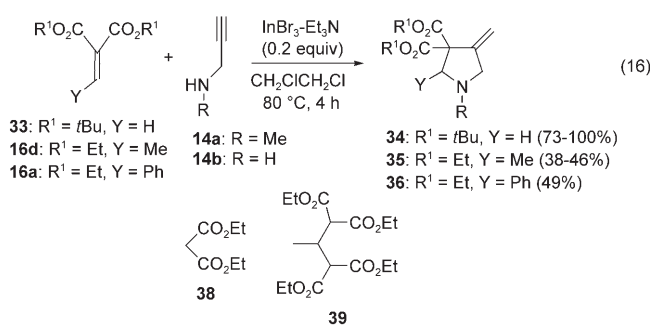
reacts with intermediates.[24] The reaction of **30 b** with **11 a** in the presence of InBr$_3$ gave cyclized product **40 a** in 83% yield. Use of hard Lewis acids such as AlCl$_3$ and SnCl$_4$ gave a small amount of **40 a**, along with the non-cyclized 1,4-addition product and unreacted starting materials.
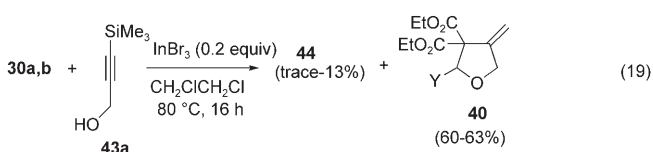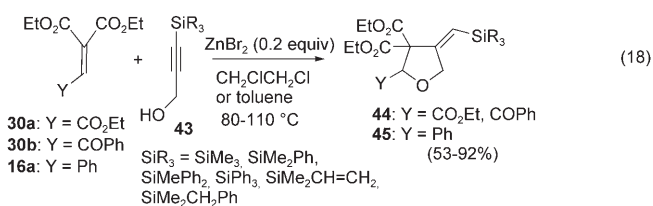

(17)

30 b: Y = CO$_2$Et
30 c: Y = COPh
30 d: Y = CON(CH$_2$)$_5^-$

11 a

40

Y = CO$_2$Et ZnBr$_2$ 81%
Y = CO$_2$Et InBr$_3$ 83%
Y = COPh ZnBr$_2$ 89%
Y = COPh InBr$_3$ 78%
Y = CON(CH$_2$)$_5^-$ InBr$_3$ 88%

41

42

The reaction of **30 b** and **11 a** without ZnBr$_2$ or InBr$_3$ did not proceed. The different reactivity of propargylamines and alcohol arises from the difference of nucleophilicity of nitrogen and oxygen. The use of catalytic amounts of InBr$_3$ (0.2 equiv) at room temperature leads to the formation of 1,4-adduct **41** in 65% yield as a main product, along with the H$_2$O adduct **42** (8%). Formation of **41** is different from the above described reaction of **16 a** with propargyl alcohol in the presence of catalytic Zn(OTf)$_2$–Et$_3$N.[20] Stoichiometric use of propagyl alcohol **11 a** is sufficient to lead to satisfactory yields, in contrast to the reaction of **16 a**. These results arise from the high reactivity of **30** towards propargyl alcohol as described for the reaction with propargyl amines similarly in the first 1,4-addition step, and the reverse 1,4-addition is less favored than in the reaction of **16 a**.

The reaction of ketone derivative **30 c** and piperidine amide **30 d** with **11 a** also gave methylenetetrahydrofurans **40** in 78–89% yield.

Next, a Lewis acid catalyzed cyclization of ethenetricarboxylate derivative with γ-substituted propargyl alcohols to give methylenetetrahydrofurans was investigated. ZnBr$_2$, Zn(OTf)$_2$, and InBr$_3$-catalyzed reaction of triethyl ethenetricarboxylate (**30 b**) and 3-phenyl-2-propyn-1-ol or 2-butyn-1-
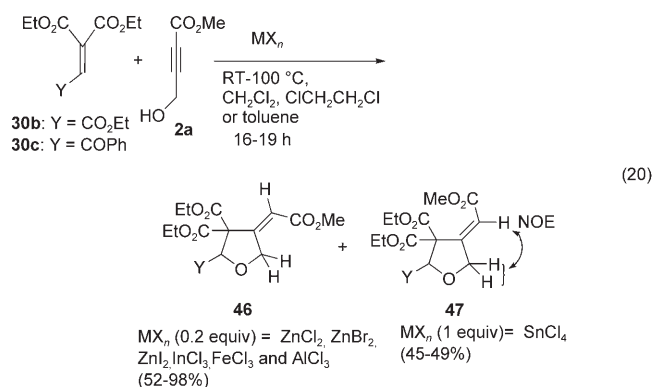
ol gave recovered starting material, a non-cyclized adduct or a complex mixture.

Then, silicon-substituted propargyl alcohols were investigated next. A silicon group may activate the alkyne group towards electrophilic reactions, as indicated by some literature precedent, for example, the reactivity of silyl-substituted propargyl alcohols versus alkyl propargyl alcohols in hydroalumination reactions with Re–Al.[25] The silyl group in the resulting cyclized products with a vinylsilane moiety can be used for further synthetic elaboration.[26] Reaction of **30** and 3-silyl-2-propyn-1-ols **43** 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 **44** stereoselectively [Eq. (18)]. Use of $InBr_3$ as a Lewis acid catalyst in the reaction of **30** and 3-trimethylsilyl-2-propyn-1-ol (**43a**; $SiR_3 = TMS$) gave desilylated cyclized products **40** preferentially [Eq. (19)]. Various silyl groups were examined. Reaction of **30** with TMS-, $PhMe_2Si$-, Ph_2MeSi-, Ph_3Si-, $CH_2=CHMe_2Si$-, and $PhCH_2Me_2Si$-substituted propargyl alcohols gave cyclized products **44** in 53–92 % yield. On the other hand, reaction of **30b** with $tBuMe_2Si$-, $tBuPh_2Si$-, and $(Me_3Si)_3Si$-substituted propargyl alcohols under similar conditions did not give cyclized products effectively. These results probably arise from the combination of electronic and steric effects of substituents on silicon. The reaction of less reactive diethyl benzylidenemalonate **16a** with **43** ($SiR_3 = TMS$, $SiMe_2Ph$) in the presence of $ZnBr_2$ also gave cycloadducts **45** in 63–68 % yields.

(18)

30a: Y = CO$_2$Et
30b: Y = COPh
16a: Y = Ph

SiR_3 = SiMe$_3$, SiMe$_2$Ph, SiMePh$_2$, SiPh$_3$, SiMe$_2$CH=CH$_2$, SiMe$_2$CH$_2$Ph

44: Y = CO$_2$Et, COPh
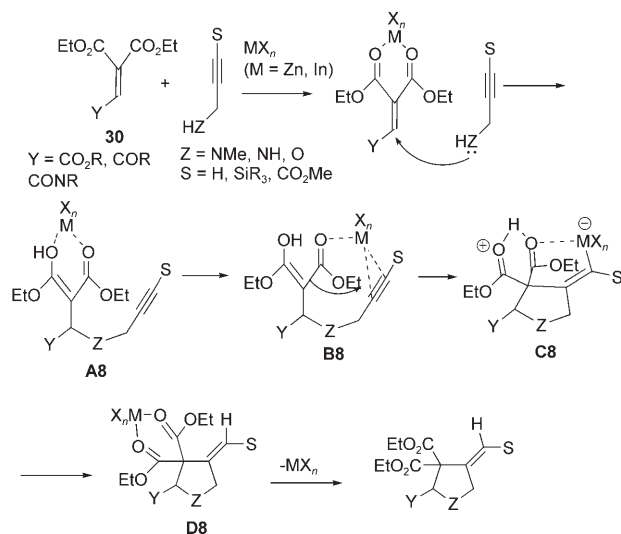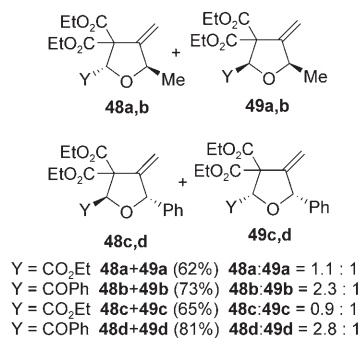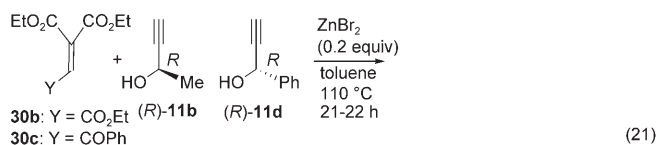**45**: Y = Ph
(53-92%)

(19)

40 (60-63%)

Ester-substituted propargyl alcohols, which are expected to be highly activated in the electrophilic acetylene moiety, were examined. The base-catalyzed reaction of electron-withdrawing-group-substituted propargyl alcohols such as methyl 4-hydroxy-2-butynoate (**2a**) and nitroalkene have been described (vide supra).[7] Lewis acid catalyzed conditions may solve the problems, such as the instability of **2a** under basic conditions and the low stereoselectivity. Reaction of **30b,c** and methyl 4-hydroxy-2-butynoate (**2a**) 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 methylene-tetrahydrofurans **46** stereoselectively in 52–98 % yield

[Eq. (20)]. Use of $InBr_3$, $GaCl_3$, $Sc(OTf)_3$, and $Sn(OTf)_2$ gave complex mixtures. On the other hand, reaction of **30** and **2a** in the presence of $SnCl_4$ at room temperature in CH_2Cl_2 gave the (E)-**47** isomer exclusively in 45–74 % yield. Reproducible yields were obtained when one equivalent of $SnCl_4$ was used at room temperature.[23b] The amount of Lewis acid did not affect the stereochemistry. The Z and E structures were determined by the absence or presence of NOE correlation between the olefinic proton and CH_2 protons. Thus, interesting Lewis acid-dependency on stereoselectivity was found.

(20)

30b: Y = CO$_2$Et
30c: Y = COPh

46
MX_n (0.2 equiv) = $ZnCl_2$, $ZnBr_2$, ZnI_2 $InCl_3$, $FeCl_3$ and $AlCl_3$ (52-98%)

47
MX_n (1 equiv)= $SnCl_4$ (45-49%)

To further examine the stereochemical course of the cyclization with propargyl alcohols, reaction of **30b** with α-substituted propargyl alcohols was investigated. Reaction of triester **30b** and enantiomerically pure (R)-3-butyn-2-ol ((R)-**11b**) in the presence of a catalytic amount of $ZnBr_2$ (0.2 equiv) in toluene at 110 °C for 22 h gave two stereoisomers **48a** and **49a** in 62 % yield in a 1.1:1 ratio and both products demonstrated >95 % enantiomeric excess (ee) [Eq. (21)]. Reaction of ketone derivative **30c** and (R)-**11b** gave stereoisomers **48b** and **49b** in 73 % yield in a 2.3:1 ratio and both products demonstrated >95 % ee. The reaction of **30b,c** with enantiomerically pure (R)-1-phenyl-2-propyn-1-ol ((R)-**11d**) was also examined and gave products in >95 % ee as well. The diastereomer ratios of **48** to **49** increased in the reaction of **30c** relative to that of **30b**, probably because of steric reasons. Thus, the utility of the reaction for synthesis of enantiomerically pure substituted tetrahydrofurans has been shown.

Reaction mechanism: The Zn- or In-promoted reaction mechanism is considered next. The probable mechanism for formation of the five-membered ring is shown in Scheme 8. Conjugate addition of nitrogen or oxygen of propargylic substrates to zinc- (or indium-) coordinated **30** in the diester moiety and proton transfer gives intermediate **A8**. The use of highly electrophilic ethenetricarboxylates **30** may be effective in the first conjugate-addition step. Zinc (or indium) transfer to alkyne leads to intermediate **B8**, and the following cyclization gives **C8**. Protonation of the sp^2 carbon in the intermediate **C8** by the generated proton and zinc (or

D9 transition state (TS) of cyclization step **B9**→**C9**) were carried out (Scheme 9). The optimized structures were successfully obtained, the TS structure reaction coordinate vectors are shown in Figure 1.
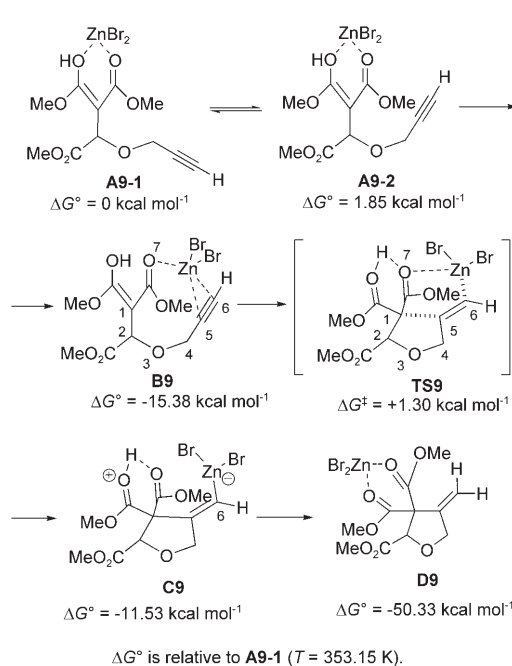
Scheme 8.

Scheme 9.

indium) coordination to the diester moiety gives the more stable intermediate **D8**. The intermediate **D8** furnishes the five-membered rings along with the release of the zinc (or indium) catalyst. The facile cyclization by zinc Lewis acid can be explained by the dual activation ability of the carbonyl and alkyne moieties.[27]

To examine the intermediacy the stereochemical requirements of the proposed intermediates **A8**–**D8** in Scheme 8, B3LYP/6–31G* calculations[28] of models (ZnBr₂–trimethyl-ester propargyl alcohol) for **A8**–**D8** (**A9-1**, **A9-2**, **B9**, **C9**,

For the intermediate **A8** in Scheme 8, two possible conformations **A9-1** and **A9-2** were obtained. These structures have only small differences ($\Delta G° = 1.85$ kcal mol^{-1}) in energy and they are considered to exist as rotamers. The in-
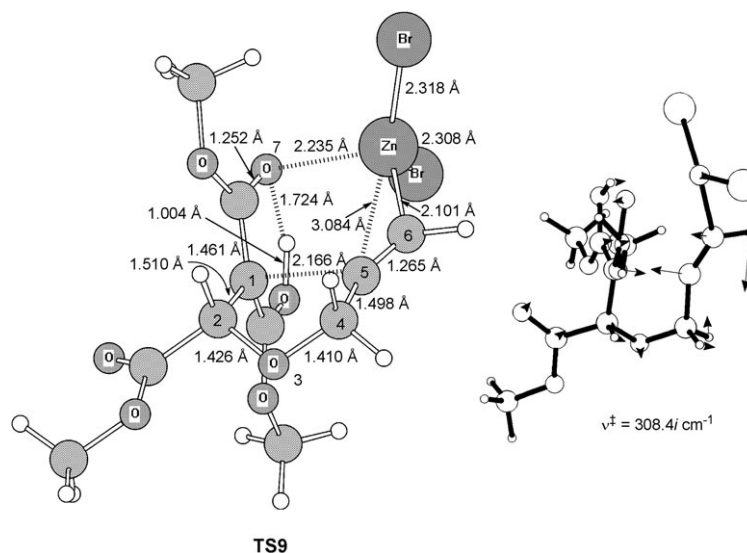

Figure 1. B3LYP/6–31G*-optimized structure of the transition state (**TS9**) of ring closure (**B9**→**C9** in Scheme 9) for model compound (ZnBr₂–trimethyl ethenetricarboxylate) and propargyl alcohol **11a**. Reaction-coordinate vectors corresponding to the sole imaginary frequency are also shown.

termediate **A9-2** may be transformed to the relatively stable zinc–alkyne and carbonyl chelate complex **B9**. In the intermediate **B9**, Zn–C^6 and Zn–C^5 distances (see Scheme 9 for atom numbering) are 2.577 and 2.974 Å, respectively, and the ring forming C^1···C^5 distance is 3.032 Å. Structure of cyclization transition state (**TS9**) shows the effective zinc chelate for C–C bond formation, in which Zn–C^6 and Zn–O^7 are 2.101 and 2.235 Å, respectively. In the TS, the ring forming C^1···C^5 distance becomes 2.166 Å (Figure 1). After the TS, alkenyl–zinc intermediate **C9** was obtained. The structures of the precursor **B9** and alkenyl zinc intermediate **C9** were confirmed by an intrinsic reaction coordinate (IRC) calculation.[29] From **C9**, protonation would occur to the sp^2 carbon C^6 leading to the more stable zinc–diester chelate intermediate **D9**.

The proposed mechanism is in agreement with the observed *Z* selectivity for the zinc Lewis acid promoted reaction of **30** and γ-substituted propargyl alcohols: γ-silicon-substituted propargyl alcohols **43** and 4-hydroxy-2-butynoate (**2a**). Thus, the alkenyl zinc intermediate **C8** in Scheme 8 retains the configuration.

However, regarding the mechanistic interpretations of the zinc catalyzed reactions, there are some problems still unresolved. For example, we propose a neutral zinc-coordinated enol–ester as **A9-1**, because a base is not necessarily required in the Lewis acid conditions. On the other hand, Nakamura suggested zinc alkoxide (in the presence of Et$_3$N) attack leading to an anionic zinc coordinate enolate–ester.[20] The detailed reaction mechanism including neutral alcohol or alkoxide attack is under investigation. How the last mechanistic step occurs (**C9** to **D9**), in which a proton and the zinc change places should be also studied. There is an another issue with the ordering of events in the addition steps. Since the zinc coordination of both alkyne and ester in **B9** is significantly lower in energy than the zinc coordination of both carbonyls of the diester (or enolester) in **A9-1**, a transition state **TS10** in Scheme 10 could be also considered. Further mechanistic studies are required.
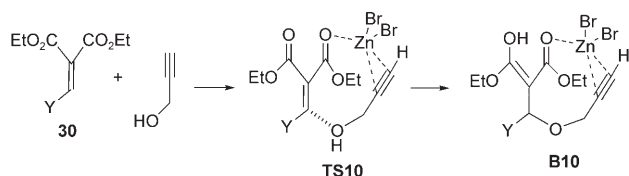
Scheme 10.

The observed *E* selectivity for SnCl$_4$ can be explained as shown in Scheme 11. Initial adduct **A11**, which is the same type as intermediate **A8** in Scheme 8, would transform to intermediate **B11**, not a **B8**-type intermediate in Scheme 8, because the harder Sn^{4+} may prefer carbonyl oxygen to carbon.[30] Ring closure may occur from the intermediate **B11** leading to intermediate **C11**. Intermolecular protonation (or protonation by liberated H$^+$) from outside would
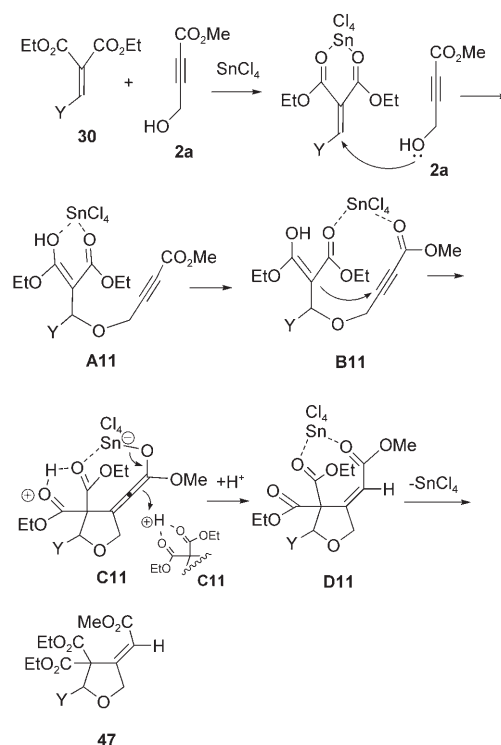
Scheme 11.

lead to Sn–diester chelate intermediate **D11**. Further study of the SnCl$_4$-promoted mechanisms is also required.

Conclusion

In summary, recent developments concerning synthesis of methylenetetrahydrofurans and methylenepyrrolidines by one-pot formal [3+2] cycloadditions involving propargylic (and allylic) alcohols and amines with electrophilic alkenes are described. The synthetic methods provide powerful tools to prepare highly functionalized oxygen- and nitrogen-containing five-membered ring systems. The reactions can be effectively promoted by base, base/transition metal, and Lewis acid, depending on the substrates. These reactions demonstrate the crucial effect of both the substrates and the nature of the catalyst on the reaction process. Further transformation of the highly functionalized products to potentially useful compounds and also extension to other heterocycles are expected future developments.

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