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Conjugate addition approach for natural product synthesis inspired by gibberellin and solanoeclepin A targets*

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Abstract: Trimethylzincate is known to react through conjugate addition to α,β-unsaturated ketones, but adds much faster to α,β-unsaturated esters at low temperatures. Since the intermediate zinc enolate behaves differently from that of dimethylcuprate, it offers scope for application in a partial synthesis of gibberellin A_3. A second example involving vinylsulfones having an oxygen atom on the γ-carbon strongly directs incoming nucleophiles in conjugate addition mode. Heteroatom-directed conjugate addition (HADCA) provides very reactive carbanion intermediates leading to cyclobutane ring formation, necessary for synthesis of solanoeclepin A. An alternative reaction for the four-membered carbocyclic ring closure was explored to make a bond formation between the propargylic cation of Nicholas type and allyltrimethylsilane nucleophile of Hosomi–Sakurai type. This method allowed a formation of tricyclo[$5.2.1.0^{1,6}$]decene framework.

Keywords: C–C bond formation; chemical synthesis; cobalt; conjugate addition; gibberellins; organic chemistry; solanoeclepin; stereochemical control; trimethylzincate; vinylsulfone; zinc.

INTRODUCTION

Conjugate addition has been widely used in organic synthesis, owing to the attendant potential for generating multiple C–C bonds. It may be classified in two categories, the first of which usually entails 1,4-addition to various α,β-unsaturated carbonyl system, and the second of which includes addition to the β-carbon of the olefins conjugating to heteroatom groups. In this account we describe some special examples from those two categories, which have been developed as key methods directed toward synthesis of naturally occurring target compounds.

Zincate addition to α,β-unsaturated carbonyl system

In the 1,4-addition of dimethylcuprate to an α,β-unsaturated ketone **1**, the intermediacy of enol intermediates, such as a copper enolate **A**, which soon exchanges to lithium enolate **C** [1], is well recognized. This lithium enolate serves as the good nucleophile, for example, for a second aldol reaction **2**. The product aldol sometimes undergoes retro-aldol reaction, which can be interrupted by addition of $ZnCl_2$, through formation of the stable cyclic zinc complex (Scheme 1).

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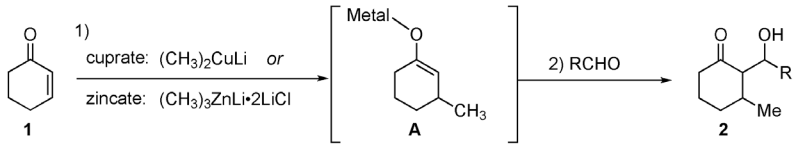


Scheme 1 Typical conjugate addition to unsaturated ketone followed by aldol reaction.

Isobe et al. first reported in 1977 that lithium trialkylzincate $R_3ZnLi{\cdot}2LiX$ reagents (R = Me, *n*-Bu; *sec*-Bu, *t*-Bu, Ph, etc.) undergo conjugate addition to α,β-unsaturated ketones such as cyclohexenones and cyclopentenones [2]. Lithium trimethylzincate(II) can be directly prepared from zinc chloride-tetrahydrofuran (THF) solution (ca. 1 M) or non-hygroscopic, crystalline tetramethylethylenediamine (TMEDA-$ZnCl_2$) complex and 3 equiv of MeLi·LiBr in THF solvent. This procedure was adopted by many organic synthesis groups for enantioselective 1,4-addition with zincate [3–5], or used in total syntheses of natural products [6]. Extensive studies have also been reported on the structure and reactivity of the zinc reagents, including applications in multinuclear catalysis [7]. Mechanisms involving cuprate-conjugate additions are understood to entail a single electron process as **B** and **C**, but zincate invokes ionic mechanisms via **D** and **E** (Scheme 2). The reaction rates of zincate addition vary in response to the counter anions derived from zinc halides, as shown in Table 1.

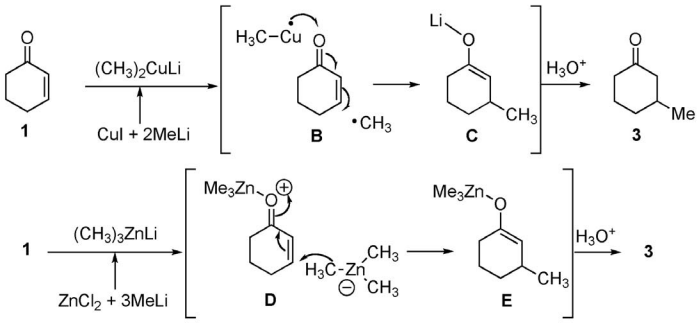


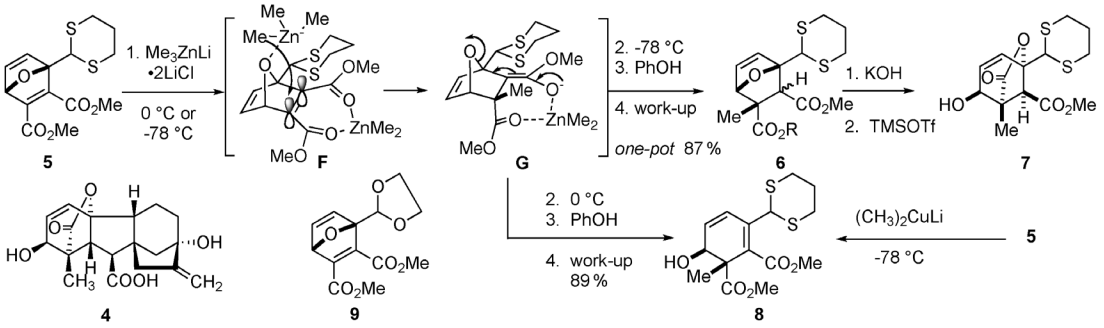
Table 1

$ZnCl_2$ + 3MeLi	92 %
$ZnBr_2$ + 3MeLi	76 %
ZnI_2 + 3MeLi	68 %

in THF at -78 °C, 30 min

Scheme 2 Mechanisms and intermediates of cuprate and zincate conjugate addition.

During the course of our synthetic studies toward gibberellic acid A_3 **4**, we became interested in the possibility of utilizing trimethylzincate $Me_3ZnLi{\cdot}2LiCl$-xLiBr addition to dimethyl oxabicyclo[2.2.1]heptadiene dicarboxylate **5**. In this diester moiety, the zinc reagent can coordinate with two ester groups as well as the bridge oxygen **F**, and the methyl group addition took place on the unsaturated diester from the top face as well as regioselectively away from the noncoordinating dithiane group. The intermediate zinc enolate **G** must accordingly be retained at −78 °C until a proton-source predominant approach either from the α- or β-face to provide the corresponding isomers **6**, whilst the bridge ethereal bonds are retained intact. After group selective ester-hydrolysis of the α-protonated product into a free acid (**6** R = H), it was further lactonized at the allylic position to give the γ-lactone bearing a substructure of gibberellin **7** (Scheme 3) [8].

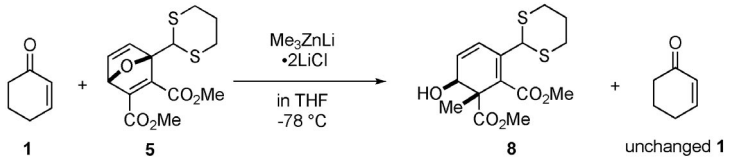


Scheme 3 Trimethylzincate conjugate addition to unsaturated diester through a different nature in the enolate intermediate from cupper/lithium enolate.

In the zinc enolate intermediate **G**, the bridge ether bond was readily cleaved to give the diene-alcohol **8** at 0 °C. This side reaction of **5** could not be suppressed with dimethylcuprate even at −78 °C. The selectivity was lost with the ethylene ketal **9** probably due to disturbance of the zinc cluster by dioxolane oxygen atoms. Recently, similar reactions of oxobicyclic compounds were reported under acidic conditions. Conjugate addition of an aluminum reagent to **10** proceeded largely through ring-opening to provide **11** [9], and reaction of binuclear catalysis Zn- or Al-ate complexes with **12** in the presence of CuTC furnished ring-opening product **13** at −40 °C (Scheme 4) [10].

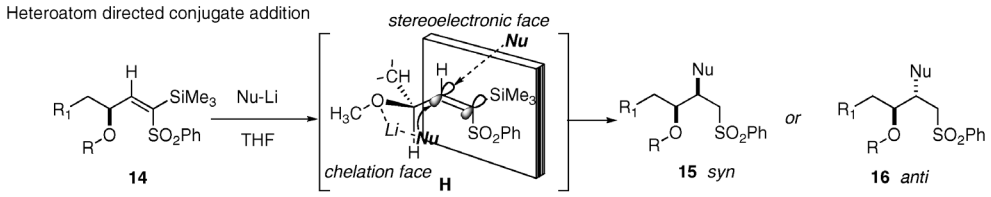
Scheme 4 Similar conjugate addition via acidic conditions [9,10].

A comparison between **1** and **5** disclosed different reactivity; thus, 1 equiv of trimethylzincate was added at −78 °C to a THF solution containing both ketone **1** and diester **5** in just 1 equiv, respectively. After the reaction temperature was gradually raised to 0 °C, the mixture was worked up and analyzed by ^{1}H NMR. An almost quantitative yield of **8** was detected together with unchanged enone **1**. This means that the trimethylzincate reacts >20 times faster to the diester. Incidentally, the dimethylzinc reagent did not give any methyl addition products **3**, **6**, or **8** at all. We found that treatment of **1** with tetramethyl aluminumate resulted in conjugate addition to afford **8** in fair yield (Scheme 5).



Scheme 5 Competitive addition between enone **1** and en-diester **5** with trimethylzincate.

In the above cases, the faster reactivity of the diester carbonyl **5** may be attributed to better metal complex formation than with a simple enone **1**. Recently, many reports disclosed the structure and reactivity of zincates, and more studies are awaited with various examples (Scheme 6) [11].



Scheme 6 HADCA-switchable *syn* to *anti* mode.

CONJUGATE ADDITION OF CARBON NUCLEOPHILES TO VINYL SULFONE SYSTEM

We have designed a highly stereoselective conjugate addition, hetero-conjugate addition [12] (recently renamed as "heteroatom-directed conjugate addition", HADCA), which was originally developed for the vinylsulfone **14**. The methodology was developed for maytansine synthesis [13] as a 100 % *syn*-selective reaction to give only **15** but not **16**. The complete *syn*-selectivity is due to (i) conformational preference due to acyclic allylic strain (AAS) as shown in **H** and (ii) pseudo-intramolecular fast-addition by α-chelation control. During the synthesis of okadaic acid [14], we improved it to a *syn/anti*-switchable method as the second-generation HADCA to provide either *syn* or *anti* product **15** or **16** upon necessity [15].

In our total synthesis of tautomycin [16], we further improved the third-generation HADCA, so that one can synthesize either D or L enantiomer even starting from D-glucopyranoside. The principle of the substrate synthesis includes a first α-axial selective (1*R*)-*C*-glycosidation with a silylacetylene, followed by cobalt-catalyzed acidic epimerization to generate (1*S*)-configuration at the anomeric carbon atom [17]. HADCA was strategically utilized in a total synthesis of ciguatoxin for 58-Me at the C-46 stereogenic center [18]. All of these kinds of selectivity have been based on *substrate control* starting from D-sugar derivatives but not a chiral building block strategy.

DIASTEREO-SWITCHING VIA α-CHELATION AND β-CHELATION CONTROL

Most cases of HADCA react extremely fast (e.g., finishing in 5 min with MeLi·LiBr in THF –78 °C) in the presence of an oxygen atom at the α-position. This condition can be modified to switchable mode by dominant interaction involving either α-chelation or β-chelation effects. Modifications include selecting the counter cation of nucleophile either Li^+ or Mg^{++}, the solvent polarity by addition of *n*-hexane to ether solvent, and the reaction temperatures. For example, as in Scheme 7, an HADCA to **17** (R = H) with MeMgBr in THF at rt followed by KF gave the *anti*-product **19a** in 96 de %. A similar addition to **17** (R = $SiMe_3$) with MeLi·LiBr in a mixture of Et_2O and *n*-hexane at –20 °C afforded *syn*-isomer **18a** in 80 de %. These results implied that the α-ether oxygen atom and magnesium ion might form a different cluster structure not allowing the methyl group to overlap with the π-orbital of the electrophile. On the other hand, a competitive alkoxy oxygen derived from non-protected OH would sustain a stronger and better cluster to capture Me-MgBr and allow bond formation from the β-face to give *anti*-product **19**.

This contrasts with behavior of the acetylide nucleophile. Usually, magnesium acetylide is less reactive. Even lithium acetylide nucleophile in HADCA is much less reactive than MeLi, so the reactions are conducted at temperatures as high as 0 °C. The *syn-anti* selectivity then undergoes a highly distinctive switch from α- to β-chelation in a mixed solvent of hexane-ether, ending up with *syn*-product **18b** or **19b** in almost complete (100 % de) selectivity as shown in Table 2 [19]. It is noteworthy that such a complete switching can be managed only by protection of the β-hydroxyl group or not. This method was originally designed and applied during the course of tautomycin total synthesis.

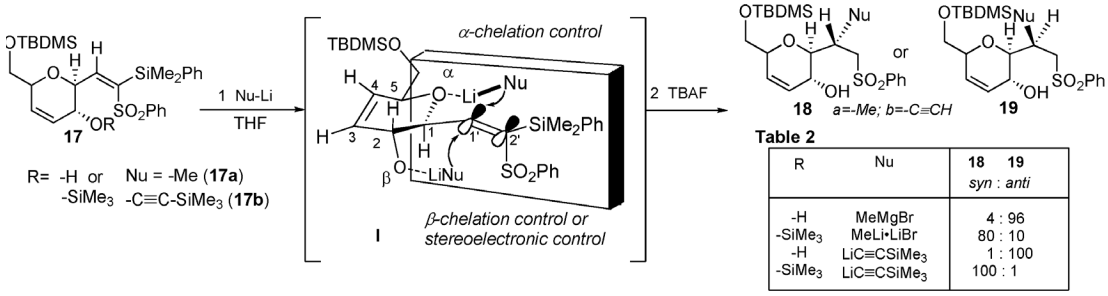


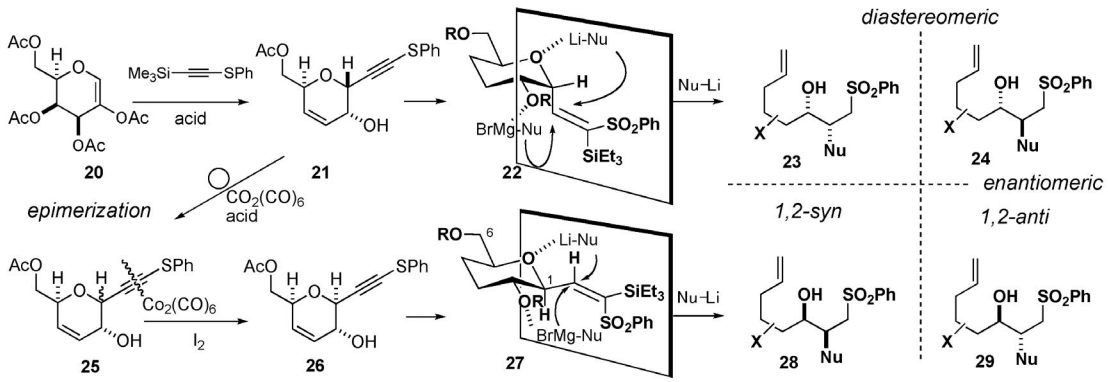
Table 2

R	Nu	18 19 *syn* : *anti*
-H	MeMgBr	4 : 96
-SiMe$_3$	MeLi•LiBr	80 : 10
-H	LiC≡CSiMe$_3$	1 : 100
-SiMe$_3$	LiC≡CSiMe$_3$	100 : 1

Scheme 7 Diastereo-switching HADCA via α- or β-chelation effects.

ENANTIO-SWITCHING AND DIASTEREO-SWITCHING LEADING TO EITHER OF THE FOUR STEREOISOMERS

Practically, the substrates **22** and **27** were prepared from tetra-*O*-acetyl-D-glucal **20** in a few steps. *C*-Glycosidation of the glucal derivative affords **21** via complete α-axial alkynylation, and the alkynyl group was hydrosylilated in the presence of cobalt-catalyst to give regioselective *E*-isomer. Further *m*CPBA oxidation afforded **22** bearing the vinyl-silyl-sulfone in α-axial orientation at the anomeric position (Scheme 8). The alkynyl group in **21** was here epimerized via its dicobalthexacarbonyl complex **25**, in which the anomeric carbenium ion is stabilized by the cobalt atoms in the so-called Nicholas effect. Acidic epimerization followed by oxidative decomplexation gave the isomer **26** bearing the alkynyl group in β-equatorial orientation. The cobalt complex **25** can be directly subjected to hydrosilylation to yield **27** without isolating **26**. Now both of the vinylsulfone substrates **22** and **27** are available from D-glucal. The β-equatorial vinylsulfone **27** accepts the α-chelation nucleophile from the *si* face and the β-chelation from the *re* face, which is reversed in the case of **22**.

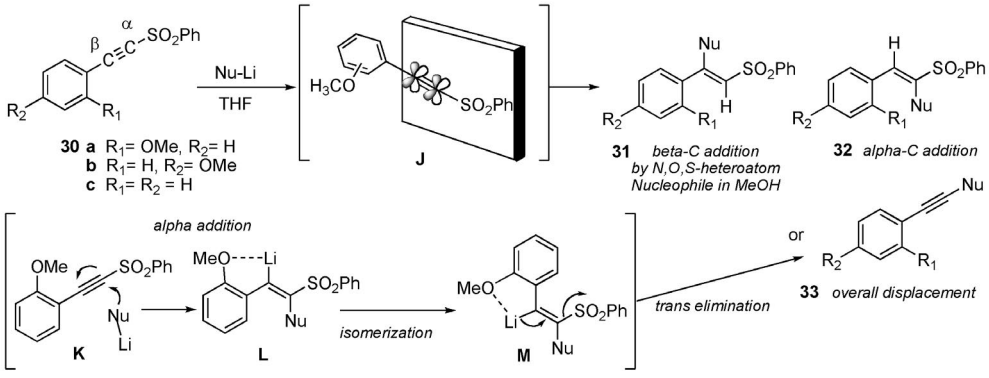


Scheme 8 Enantio-switching HADCA via epimerization of *C*-alkynyl precursor.

The four choices for nucleophile addition provide four diastereoisomers, in which the 6-hydroxyl group (sugar numbering) was iodinated and zinc-reductive elimination afforded the four isomers including two sets of *syn*-enantiomers **23** and **28** and *anti*-enantiomers **24** and **29**. In fact, this method led us to synthesize hybrid-isomers of tautomycin to contribute to disclose the significant type-recognition of the protein phosphatase inhibition mechanism [20].

CONJUGATE ADDITION TO ACETYLENIC SULFONES

In this account, we focus on the intermediate carbanion after the first HADCA process. On the basis of foregoing background, we became interested in the acetylenic sulfone **30** as a principal electrophile. Some results had already been reported by other groups to provide conjugate adducts such as **31**. However, these results were limited to cases of heteroatom nucleophiles such as amine, alcohol, or sulfide in an alcohol solvent [21]. There is little information on carbanion nucleophiles for C–C bond formation in THF solvent, probably due to interference by polymerization among the addition intermediates and electrophile. An alternative zinc-copper bimetallic approach was recently reported at elevated temperatures [22]. To avoid this problem in our research group, a substrate sulfone was slowly added into a dilute solution (<5 mM) containing an excess amount of nucleophile (ca. 5 equiv of MeLi, CH_2=CH–MgBr, N≡C–CH_2Li, or Me_3SiC≡C–Li) (Scheme 9).

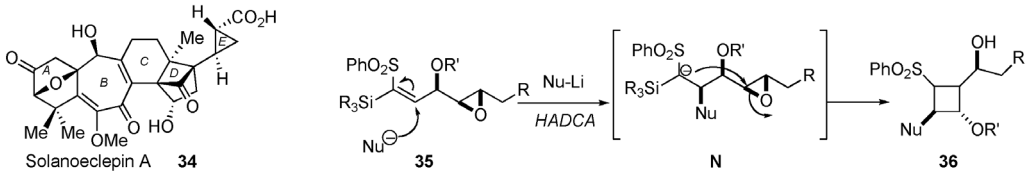


Scheme 9 Unusual α-addition of carbon nucleophile to acetylenic sulfone in THF.

The isolated products demonstrated that reaction took place at the α-carbon **32** rather than the conjugate addition **31** [23]. Chelation control assumable from the vinylsulfone as in Scheme 6 did not affect in the reaction mode of acetylenic sulfone judging from the presence of a OMe group or not. One of the α-sp carbons attaching to the sulfonyl group is electronically so deficient to accept directly the nucleophile **K** and may allow the *trans*-addition intermediate **L**, which is isolable by protonation. Alternatively, this vinyl lithium can await isomerization on the sp^2-carbon to form **M**, which can then eject the sulfonyl group to produce the acetylene **33**. The overall process is a displacement at the α-sp carbon. This displacement, however, seems to be difficult without the *ortho*-methoxy group that supports the *trans*-addition and *isomerization* mechanism facilitated by chelation effect.

FORMATION OF CYCLOBUTANE RING VIA EPOXIDE OPENING AFTER HADCA

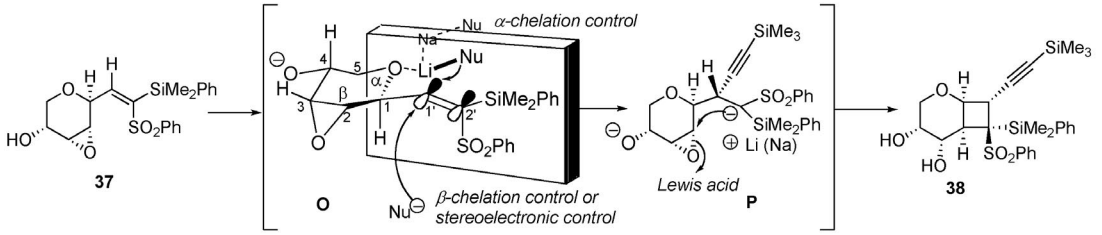
We became interested in the total synthesis of solanoeclepin A **34** as a current target molecule. One of the planned methodologies entailed developing cyclobutane ring cyclization via ionic reactions, and avoiding a photochemically induced 2 + 2 reaction. Stork reported the first example of intramolecular nucleophilic opening of epoxides with a carbanion stabilized by a cyano group to provide cyclobutane but not cyclopentane due to dominant exo-opening [24]. Epoxide opening by a 1,3-dithiane anion is an alternative [25]. These examples of ionic intramolecular cyclobutane ring cyclization still seem to be limited only to small substituents on the ring. We planned that similar epoxide opening in **35** should take place with a carbanion **N** stabilized by a phenylsulfonyl group, which can be generated in situ by HADCA (Scheme 10) to form cyclobutane **36** [26]. The pK_a value of methylphenylsulfone **29** suggests



Scheme 10 Cyclobutane formation via epoxide exo-opening by a carbanion from HADCA.

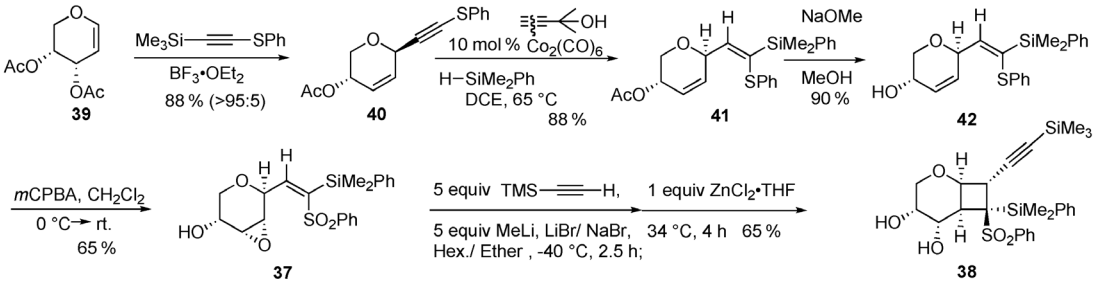
that avoiding α-proton abstraction by means of a strong base causes an alternative abstraction of an epoxidic proton.

As discussed above, vinylsulfones make the neighboring atom/group potentially electrophilic, but the reactivity is expressed drastically differently. It works only in the presence of a neighboring polar atom/group such as oxygenic group in a proper orientation. This is the reason why we renamed the HADCA (vide supra). The oxygen atoms should be located in chelation cluster structures depending upon the substrates, salts, solvents, and temperatures, to direct the rates of the addition reaction. Most of the counter ions are lithium cations, but neither Mg^{++} nor Zn^{++} ions have the covalent character to make the nucleophile orientation too rigid, so that the anion can hardly overlap with the π-orbital of the β-vinyl carbon. This is in strong contrast to those cases of unsaturated carbonyl electrophiles, where Mg or Zn ions immediately coordinate with the oxygen atom to enhance the reactivity for 1,2- or 1,4-additions. On the other hand, Na^+ makes the cluster structures more flexible due to the more ionic nature to enhance reactivity. In the case of **37** bearing the ethereal oxygen atoms connected at the α,β,γ,δ-positions carbon atoms, the selectivity needs to be examined more precisely on those factors with the possible cluster/chelation face selection **O** either in α- or β-chelation control (Scheme 11). This carbanion intermediate **P** could serve as the nucleophile to open epoxide in the ring system, so that the stereochemical outcomes in **38** should be clearer as discussed later with other cases.



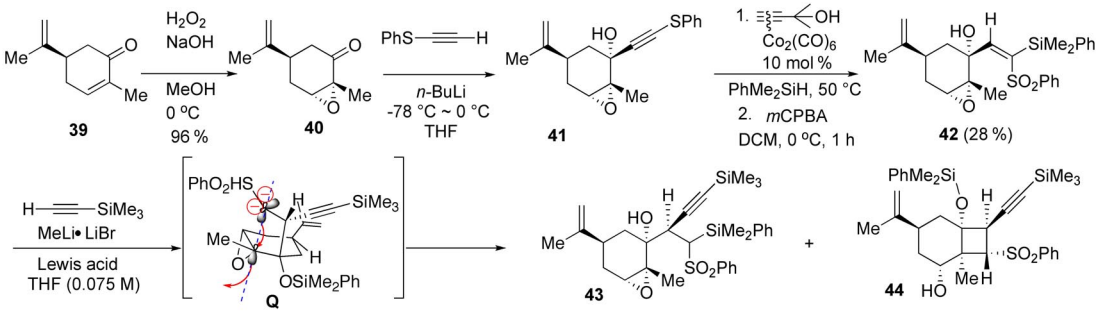
Scheme 11 Sulfone carbanion intermediate can open epoxide ring for cyclobutane ring formation.

The precursor **37** was synthesized from diacetoxy-D-arabinal as in Scheme 12. The *C*-glycosidation of **39** with a silylacetylene provided **40** in complete 1,4-*trans* orientation. A cobalt-catalyzed hydrosilylation of the acetylene followed by oxidation of the sulfide as well as the double bond of allylic alcohol afforded the substrate **37**. It was further treated by lithium acetylide to attack **37** from the α-chelation face affording *syn*-addition product, which can be isolated at this stage to confirm the *syn*-stereochemical purity. In fact, the *syn–anti* ratio was 85:15 under the conditions without NaBr in Scheme 12. So the ratio was improved to almost exclusive (>99:1) by addition of NaBr in the HADCA and an isolated yield of 80 %. When the same reaction was continued without work-up, by addition of zinc chloride-THF and raising of the temperatures up to 34 °C, it provided the cyclobutane compound **38** [27]. Its enantiomer **ent-38** was also synthesized from D-xylal. The stereochemistry of the cyclobutane ring was determined by X-ray crystallographic analysis. We have some more examples of the cyclobutane formation via HADCA method, and will discuss the carbanion stereochemistry later [28].



Scheme 12 Chiral cyclobutane synthesis to both of the enantiomers.

Another chiral model electrophile **42** was prepared from a monoterpene *R*-carvone **39** in 4 steps (Scheme 13). After addition of lithium trimethysilylacetylide to **42** at −78 °C, the reaction temperature was raised to 0 °C. Then addition of $ZnCl_2$-THF and further stirring at 60 °C afforded **43** in 86 % yield. The cyclobutane derivative **44** was obtained only in 15–20 % with various additives. This may be due to a 1,3-diaxial interaction between the sulfonylmethyl group and isopropenyl group at the transition state **Q**, although the dianion intermediate **Q** should be very reactive.



Scheme 13 HADCA of lithium acetylide to the vinylsulfone derived from carvone.

Lithium acetylide forms a lithium cluster around the epoxide oxygen atom, which allows the acetylide to attack from the *re*-face. This addition leaves the corresponding carbanion with the *S*-configuration, which isomerizes to *R*-configuration. When this anionic carbon undergoes rotation it suffers from a 1,3-diaxial-like interaction with the isopropenyl group. This interaction diminishes the reactivity of epoxide opening by enforcing a twist-boat conformation in the transition state. During this time, Brook rearrangement takes place to form an O–Si bond leaving the α,α-dianion formation, which is less bulky and more reactive to open the epoxide ring to form the cyclobutane, although in low yield.

An alternative example of cyclobutane ring formation is demonstrated in a simpler cyclohexene epoxide bearing the similar vinyl(silyl)sulfonyl group as **48**. This compound was prepared from cyclohexanone **1** as shown in Scheme 14. 1,2-Addition of the acetylide was followed by hydrosilylation and oxidation to afford **46**. Direct epoxidation of the ring-double bond was not possible with *m*-chloro peroxybenzoic acid (*m*CPBA), perhaps due to an unusual deactivation effect by the vinylsulfone group. It was then converted via bromohydrin **47** to the epoxide **48**. In this substrate, there are two ethereal oxygen atoms, one a OMe group located at the junction and coplanar with the sp^2-plane, and the other epoxide-oxygen. As was suggested previously, β,γ-chelation of the nucleophile is less effective than α-chelation for HADCA, so the ratio of **49**:**50** was suspected from the final result of **51**:**52** to be 71:14 (entry 2 of Table 2). After lithium acetylide anion was added at –40 °C to **48**, the mixture of salts NaBr-

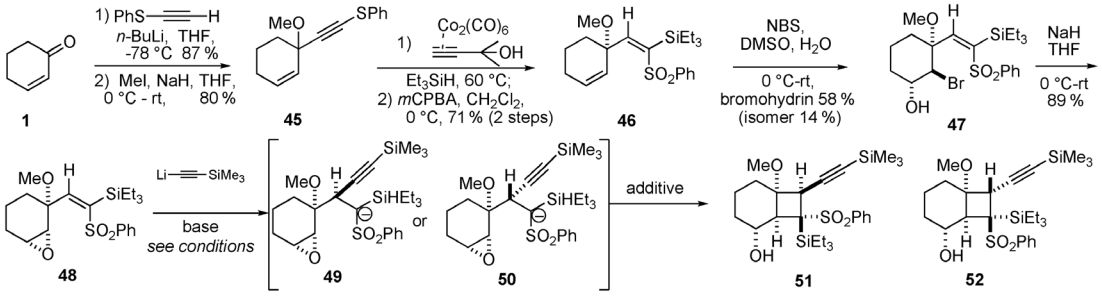


Table 3 conditions and products

entry	Acetylene equiv.	base	additive	temp.	hr	product	(%)
1	1.5	MeLi •LiBr 1.35 eq	-	-78 °C 0 °C +30 °C	1 2 3	**51**	54
2	10	MeLi •LiBr 9.5 eq	BF_3•OEt_2 at (-40 °C)	-78 °C -40 °C +30 °C	2 2 3	**51** **52**	71 14
3	5.5	MeLi 5.0 eq	NaBr:LiBr (5:1)	-40 °C -20 °C +22 °C	2 2 3	**51**	75

Scheme 14 Preparation of a epoxyvinylsulfone **48** and HADCA to cyclize **51** with cation effects.

LiBr (5:1) in THF solution was further added at −20 °C, and then the mixture was allowed to react at +22 °C to yield **51** as a single isolated product in 75 % [29].

HADCA of lithium acetylide to **48** was improved to a level of complete selectivity by addition of NaBr, which not only enhanced the selectivity of the first addition, but also enhanced the reactivity for cyclobutane ring formation to afford only **51**. When the same reaction was conducted without NaBr, the minor product **52** was obtained in 17 % yield, besides **51** in 71 % yield. Both of these structures were confirmed by X-ray crystallographic analysis as **51a** and **52a** (Fig. 1), which also disclosed the *cis*-orientation of the alkynyl and silyl groups to each other. The common stereochemical course implies that nucleophilic conjugate addition to the vinyl group should take place from the cluster face in *trans* manner to the corresponding carbanion in *S*-configuration; and the anionic lobe quickly reverts back to the *R*-configuration so that anion assemble with metal cations in cluster (overall seems to be *cis*-addition); and then rotates the orientation with retaining this configuration to attack the epoxide to form the cyclobutane rings **51** and **52** (Scheme 15).

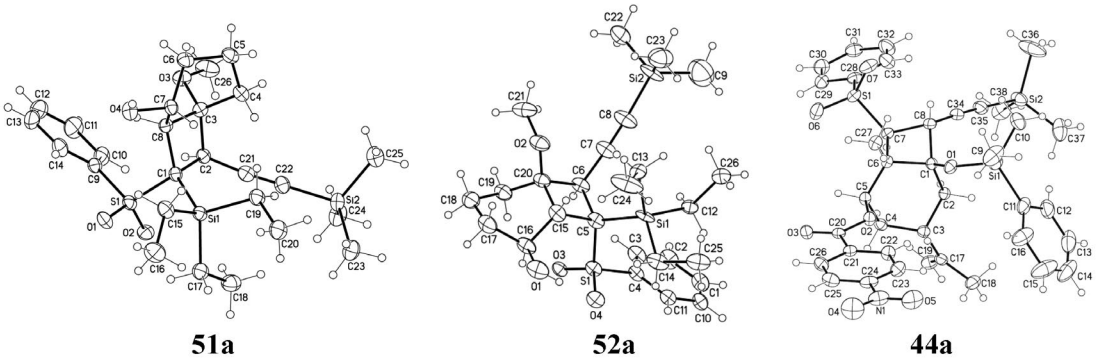
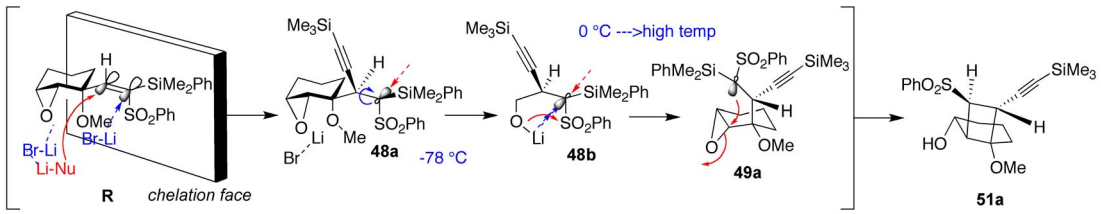


Fig. 1 ORTEP drawing of crystal structures of *syn/anti* HCADA to form cyclobutane rings.



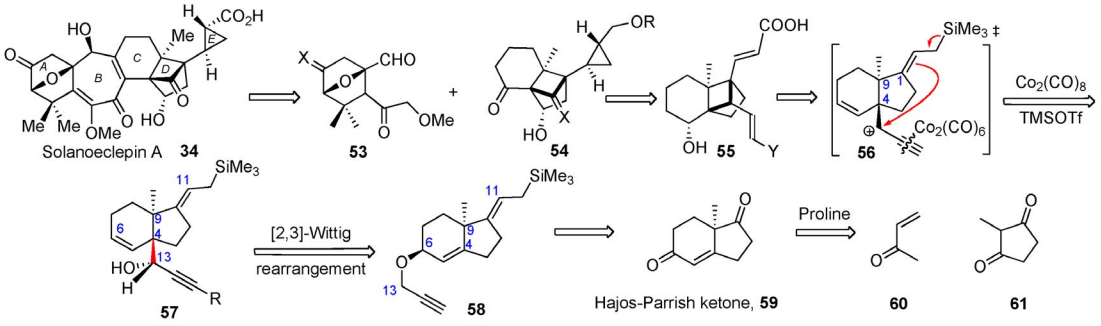
Scheme 15 Stereochemical course of HADCA includes *trans*-addition from the chelation face, and the a-sulfonyl carbanion reverts back to the chelation face.

CONCLUSION 1

HADCA mechanisms involve a common process for the formation of cyclobutane rings. When it is extended to the acetylenic sulfone, the first addition products are isolable, and confirm *trans*-addition without isomerization. In this case, the *ortho*-OMe group promotes isomerization on the sp^2-carbon ending up with the elimination of the phenylsulfonyl group, to yield the overall displacement product at the sp-carbon atom. We have surveyed the significant effects in the C–C bond-forming process with stereochemical control. Such effects have been considered as salt effects, and this article focused on those metal cation effects through cluster structures. More highly efficient HADCA reactions are now in progress in this laboratory to implement multiple C–C bond formation with high stereochemical control.

Synthesis of the tricyclic ring framework for solanoeclepin A under acidic conditions

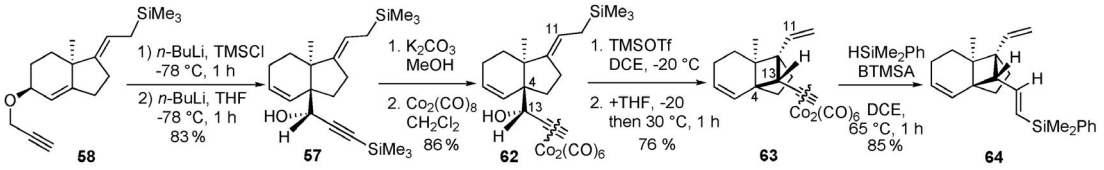
The above conjugate addition chemistry includes carbanion nucleophiles with moving the multiple-bond electrons. The following is an alternative retro-synthesis of solanoclelepin A **34**, which needs to have carbenium electrophilic center **56** for the formation of the cyclobutane ring **55** by an attack with allyl trimethylsilane under the condition. The precursor **57** needs to have *trans*-oriented Me- and propargyl-groups at the ring junctions. To achieve this *trans*-orientation, a Wittig rearrangement from the β-propargylether **58** was planned, and this would come from the diketone **59** available in optically active form via Robinson-type annulation with a chiral catalyst as D-proline (Scheme 16).



Scheme 16 Retrosynthesis of solanoeclepin A right segment tricyclo[5.2.1.$0^{1,6}$]decene framework under acidic condition.

In fact, the [2,3]Wittig rearrangement was implemented in one-pot process after temporarily protecting the terminal acetylenic proton by trimethylsilyl group under the deprotonation conditions of the propargylic proton. This rearrangement of **58** is highly stereoselective to give a single isomer **57**. Once

the acetylene was converted to dicobalthexacarbonyl complex **62**, this was subjected to acidic condition to form the propargylic cation **56**, which was stabilized by the Nicholas effect. This electrophile was further allowed to react with the allyltrimethylsilane as a Hosomi–Sakurai-type nucleophile to afford the cyclobutyl compound **63**. Hydrosilative decomplexation of this acetylenedicobalthexacarbonyl moiety gave the tricyclo[5.2.1.$0^{1,6}$]decene **64** (Scheme 17).



Scheme 17 Synthesis of solanoeclepin A right segment tricyclo[5.2.1.$0^{1,6}$]decene framework.

CONCLUSION 2

Chemistry of acetylene dicobalthexacarbonyl complex has been well studied during our total synthesis of ciguatoxin, in which carbenium ion electrophiles were attacked by oxygen nucleophile to form medium ether rings of seven-, eight-, and nine-membered sizes [30]. Generation of the carbenium cation is best done under nonpolar solvent, while the nucleophile hardly approaches this cationic center due to the presence of counter anion. Some additional polar solvent such as THF to the cationic reactants did solve this problem to form the ether rings. The cation **56** for solanoeclepin synthesis located at the propargylic carbon, which is spatially protected by the CO ligands and no deprotonation process occurred to make the cation for a longer lifetime, while intramolecular nucleophile allyltrimethylsilane can make the cyclopropyl bond. The final decomplexation to the vinylsilane allowed the detailed NMR analysis.

Conjugate addition of carbanion nucleophile to α,β-unsaturated systems includes the electron movements in the conjugate system. Similarly, the carbenium ionic reactions in the above example includes two conjugate systems in the electrophile and nucleophile. These reactions should be called a conjugate addition under acidic conditions. Conjugate additions are quite useful methods for multiple bond formations in the target-oriented synthesis of natural products.

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