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Synthetic uses of ynolates

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Keywords: Ynolates; Carbanions; β-Lactones; Olefination; Torquoselectivity; Cycloaddition.

Abbreviations: acac, acetylacetonato; Bn, benzyl; BuLi, butyllithium; *t*-Bu, *tert*-butyl; dba, dibenzylideneacetone; DDQ, 2,3-dichloro-2,3-dicyanobenzoquinone; DiBAH, diisobutylaluminum hydride; Et, ethyl; HMPA, hexamethylphosphoric triamide; cHex, cyclohexyl; LDA, lithium diisopropylamide; LHMDS, lithium hexamethyldisilazane; LTMP, lithium tetramethylpiperidine; Me, methyl; MEM, methoxyethoxymethyl; MOM, methoxymethyl; MeOH, methanol; MPM, *p*-methoxyphenylmethyl; Ms, methanesulfonyl; NBO, natural bond orbital; NBS, *N*-bromosuccinimide; NHMDS, sodium hexamethyldisilazane; Ph, phenyl; PMP, *p*-methoxyphenyl; Pr, propyl; *i*-Pr, isopropyl; TBAF, tetrabutylammonium fluoride; TBHP, *tert*-butylhydroperoxide; TBS, *tert*-butyldimethylsilyl; TES, triethylsilyl; TfOH, trifluoromethanesulfonic acid; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TMS, trimethylsilyl; Tr, trityl; Ts, *p*-toluenesulfonyl.

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1. Introduction

Carbanions are fundamental reactive species that are widely used in synthetic organic chemistry. Some of the carbanions like enolates have been extensively studied and are considered to be an established field. If carbanions demonstrated a higher functionality than the conventional ones, they would most likely play as significant a role in the modern organic chemistry as organometallic reagents do today.

Ynolates **1** have a triple bond in place of the double bond in enolates. Compared with enolates, ynolates have attracted much less attention, with only scattered reports in the literature until recently, partially due to a lack of general and convenient methods for their synthesis. Because ynolates are not only the precursors of alkynyl ethers **2** like silyl ynol ethers, but also ketene anion equivalents **3** acting as ketene precursors, their chemistry should not be less interesting than that of the enolates (Fig. 1). The fact that ynolates can synthesize another reactive species prompted us to focus our attention on this potentially useful and exciting field. As an example, by using the properties of ynolates, a negative–positive switching multireaction process can be realized, as shown in Figure 2. An ynolate, a nucleophile, reacts with an electrophile to give a ketene, an electrophile, which reacts with a nucleophile to afford an enolate, a nucleophile. The enolate can react with an electrophile to furnish a carbonyl compound. Thus, a smart design would enable the one-pot successive reaction sequence.

Since our development of a novel method for the synthesis of ynolates, we have been steadily demonstrating the intriguing multifunctionality of these compounds. This review describes the synthetic uses of ynolates, including silyl ynol ethers.[1]

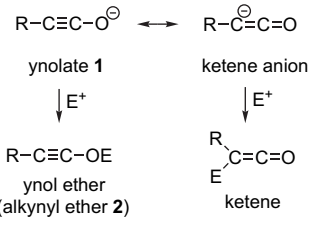


Figure 1. Ynolates as ketene precursors.

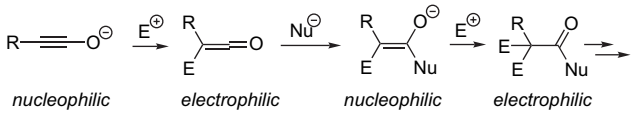


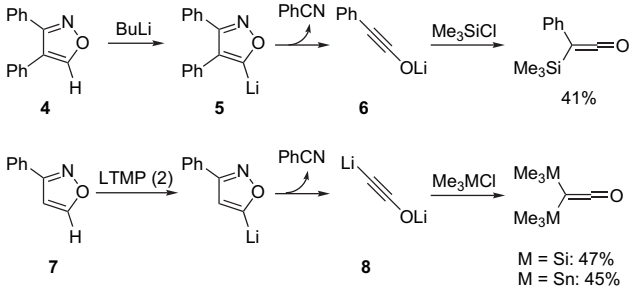
Figure 2. Negative–positive switching process.

2. Preparation of ynolates

Until now, several preparative methods for ynolates have been developed. Since there is no universal method to determine the yield of ynolates, the efficiency of the preparation is estimated from the results of some of the following reactions.

2.1. Fragmentation of isoxazolyllithium

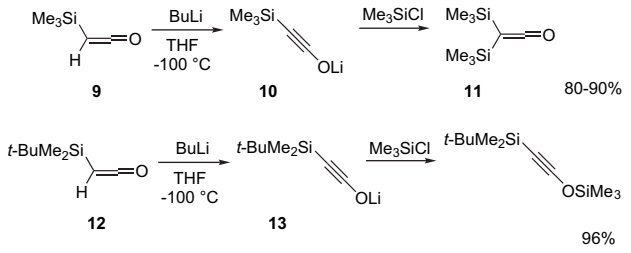
In 1975, Schöllkopf and Hoppe reported the first synthesis of ynolates, which is the seminal work for this class of species. 3,4-Diphenylisoxazole (**4**) was treated with BuLi to give the corresponding isoxazolyllithium **5**, which spontaneously fragmented into the ynolate **6** (Scheme 1).[2] These workers also prepared the ynolate dianion **8** from 3-phenylisoxazole (**7**) by a similar protocol.[3] The maximum yields were around 80%, judged by the yields of the β-lactones (vide infra). This is a convenient method for the preparation of phenyl-substituted ynolates and ynolate dianions.



Scheme 1. Fragmentation of isoxazolyllithium.

2.2. Metalation of trialkylsilylketenes

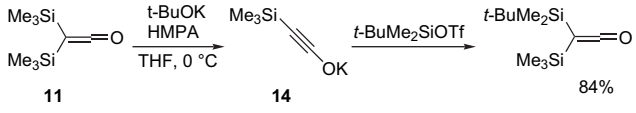
2.2.1. Deprotonation. Since ynolates are ketene anion equivalents, metalation of ketenes is expected to afford ynolates. Direct metalation or deprotonation of monoalkylketenes is fairly difficult, however, due to the high lability of these ketenes (e.g., dimerization) and the strong electrophilicity of the carbonyl carbon.[4] In contrast, silyl ketenes are so stable that Rathke achieved lithiation of trimethylsilylketene (**9**) with BuLi at −100 °C to provide the ynolate



Scheme 2. Deprotonation of trialkylsilylketenes.

10 in good yield (Scheme 2).[5] The TBS-ketene (**12**) was also deprotonated to afford the ynolate **13**.[6]

2.2.2. Transmetalation. Transmetalation of bis(trimethylsilyl)ketene **11** affords the ynolate **14**. Ito examined the reactions with various organometallics and found that *t*-BuOK in the presence of HMPA afforded the best results (Scheme 3).[7] Since it does not give the ynolate without HMPA, the trialkylsilyl group might be activated by the coordination of HMPA.

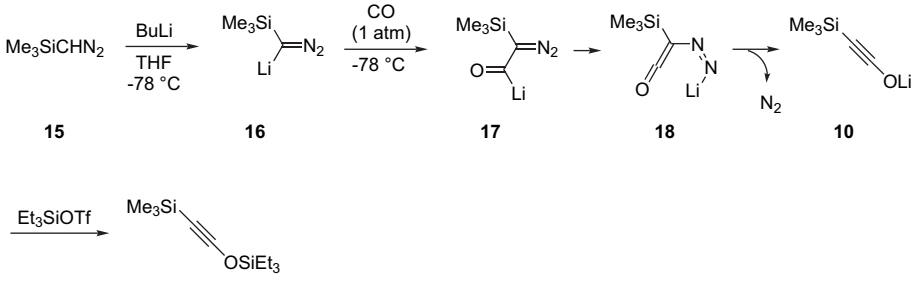


Scheme 3. Transmetalation of bis(trialkylsilyl)ketene.

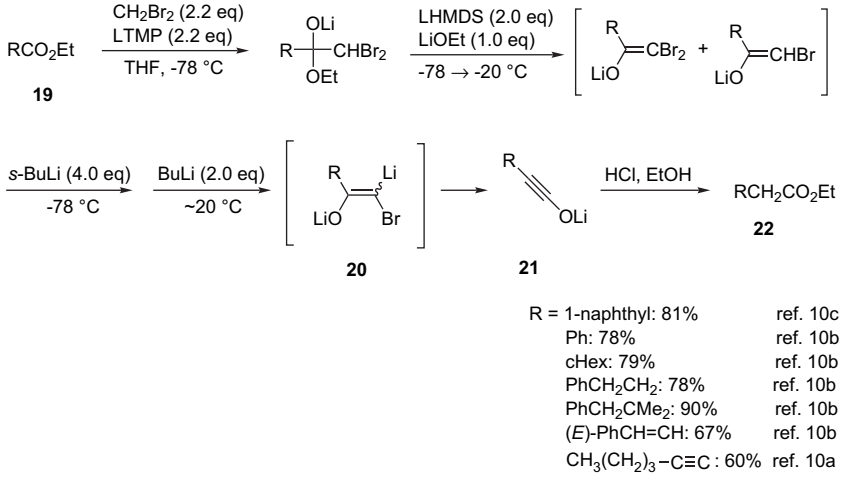
2.2.3. Rearrangement of an α-diazoacyllithium. The preparation of the trimethylsilyl-substituted ynolate **10** via treatment of trimethylsilyldiazomethane (**15**) with BuLi followed by exposure to carbon monoxide was reported by Murai et al. The mechanism is explained by the fact that the lithiated silyldiazomethane **16** adds to the carbon monoxide to give the labile α-diazoacyllithium **17**, which rearranges to the ynolate **10** through the ketene intermediate **18** (Scheme 4).[8]

2.3. Rearrangement of α-keto dianions

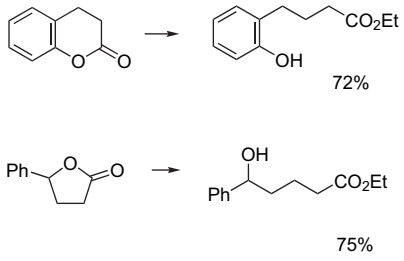
Kowalski, a pioneer in this type of chemistry, reported the synthesis of ynolates via the rearrangement of α-keto dianions **20**,[9] which are prepared by adding dibromomethyllithium to esters **19** followed by base-induced elimination. The dianions **20** rapidly rearrange with loss of LiBr to produce the ynolates **21** (Scheme 5). Experiments using a ^{13}C-labeled substrate suggest that the reaction is a carbon analogue of the Hofmann rearrangement. This process, using an excess amount of strong bases, has been mainly used as a homologation of esters, an alternative to the Arndt–Eistert reaction, giving the one-carbon homologated esters **22** after quenching with acidic alcohol.[10] Lactones are homologated to give hydroxy esters (Scheme 6), although an example of C–O insertion rather than rearrangement was also reported (Scheme 7).[11] α-Amino esters are homologated to the corresponding β-amino acids without the loss of optical purity (Scheme 8).[12]



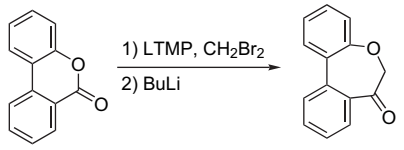
Scheme 4. Rearrangement of α-diazoacyllithium.



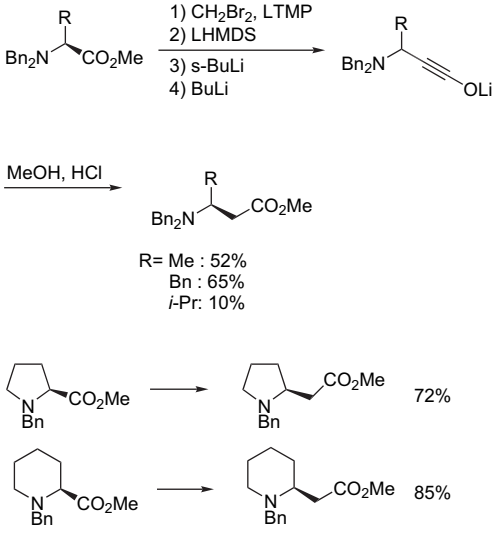
Scheme 5. Homologative formation of ynolates.



Scheme 6. Homologation of lactones.



Scheme 7. C–O insertion into lactone.

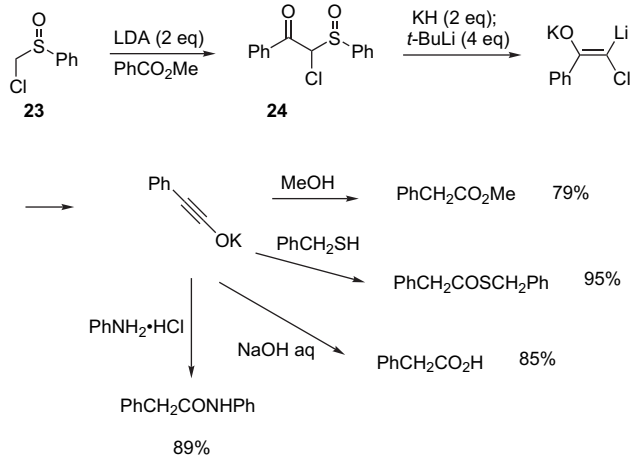


Scheme 8. Homologation of α-amino esters.

Kowalski demonstrated the formal synthesis of oudemansin[10a] using the homologation in fewer steps than that via the classical Arndt–Eistert reaction[13] (Scheme 9).

This homologative formation of ynolates has been used to prepare silyl ynol ethers. The preparation and synthetic uses of these species are described in Section 4.

A similar protocol of ynolate formation via a keto dianion rearrangement starting from the α-chloro-α-sulfinyl ketone **24**, prepared from a benzoate ester and α-lithiated chloromethyl phenyl sulfoxide **23**, was reported by Satoh et al. (Scheme 10).[14] The resulting potassium ynolates are converted into thioesters, carboxylic acids, and amides, as well as esters.



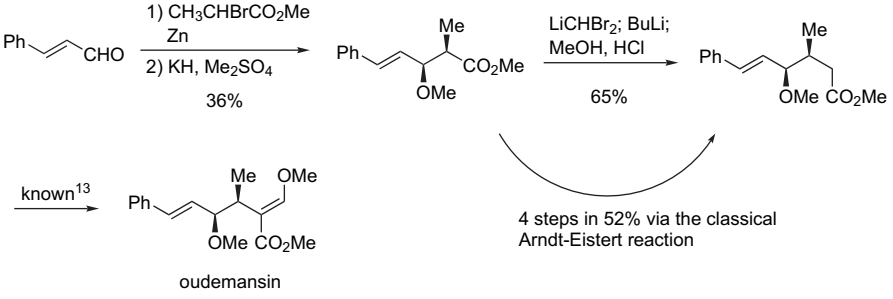
Scheme 10. Ynolates from α-chloro-α-sulfinyl ketones.

2.4. Oxygenation of terminal alkynes

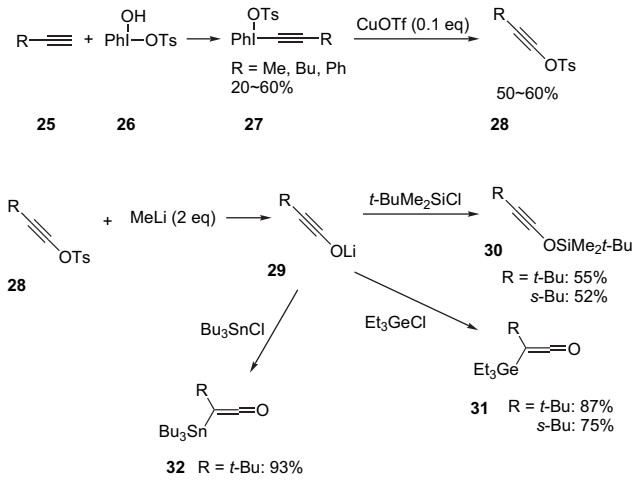
Ynols, which are also known as alkynols, will be generated by oxygenation of terminal alkynes. Based on this concept, several reports on the preparation of ynolates have appeared in the literature.

2.4.1. Stang's method. Stang has synthesized ynol tosylates via a unique sequence (Scheme 11).[15] The hypervalent organoiodine **26**, prepared by treatment of iodosobenzene diacetate with *p*-toluenesulfonic acid monohydrate, reacts with the terminal alkynes **25** to give the iodonium tosylates **27**, which are then treated with 10 mol % of CuOTf or AgOTf to afford the ynol tosylates **28**. Finally, the ynol tosylates **28** are converted into the ynolates **29** by treatment with MeLi.[16] The ynolates are trapped with *tert*-butyldimethylsilyl chloride, triethylgermyl chloride, and tributylstannyl chloride to give the silyl ynol ethers **30**, the germyl ketenes **31** and the stannyl ketene **32**.

2.4.2. Oxygenation of lithium acetylides. Direct oxidation of lithium acetylides to give ynolates was reported by Julia et al. (Scheme 12). Lithium acetylides **33** was reacted with

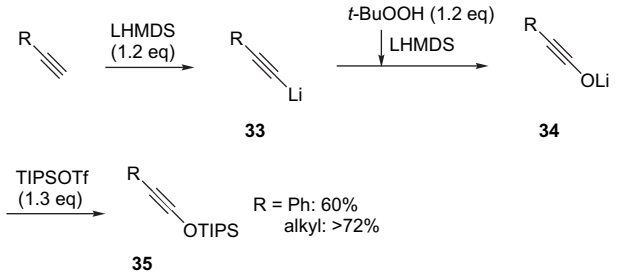


Scheme 9. Formal synthesis of oudemansin.



Scheme 11. Ynol tosylates.

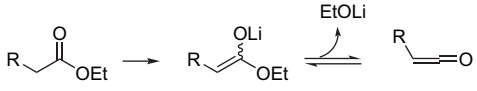
lithium *tert*-butylperoxide, prepared from anhydrous TBHP[17] and LHMDS, to provide the corresponding ynolates **34**.[18] This method has been used as an efficient route for the preparation of the silyl ynol ethers **35**.[19] Dioxygen, *tert*-butyl perborate, and bis(trimethylsilyl)peroxide[20] have been unsuccessful as oxidation reagents.



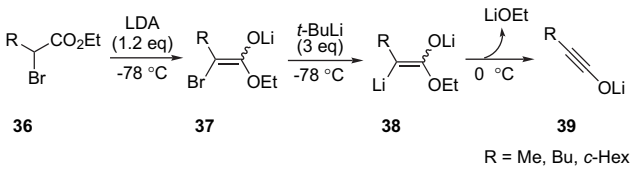
Scheme 12. Oxygenation of lithium acetylides.

2.5. Cleavage of ester dianions

Although ynolates are equivalents of ketene anions, direct metalation of ketenes is often troublesome. Metalation of the precursors of ketenes, followed by transformation into the metalated ketenes, would be a better route to ynolates. Based on this concept, we have developed an efficient method for the synthesis of ynolates, taking advantage of the properties of ester enolates, which are easily converted into ketenes by elimination of alkoxides (Scheme 13).[21] The α-bromo esters **36** are treated with LDA to form the bromo ester enolates **37**, which are subjected to lithium–halogen exchange with *t*-BuLi (3 equiv) at −78 °C. The resulting ester dianions **38** are thermally cleaved at 0 °C into the ynolates **39** in good yields (Scheme 14).[22]

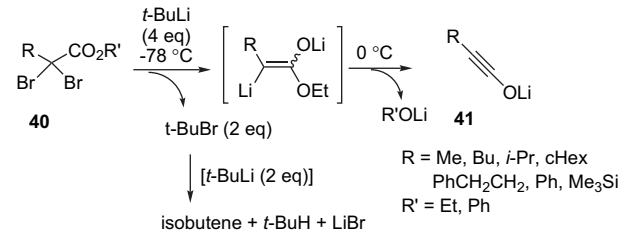


Scheme 13. Lithium ester enolates as precursors of ketenes.



Scheme 14. Ynolates via cleavage of ester dianions (LDA method).

In the reaction vessel, regenerated LDA is present, along with ynolates and alkoxides (Scheme 15). To avoid the effect of the strong base, α,α-dibromo esters **40** are used as the starting materials, which are treated with 4 equiv of *t*-BuLi at −78 °C. The reaction is then warmed to 0 °C to produce the ynolates **41** in excellent yield (Scheme 15).[23] This improved facile method can be carried out simply without the use of lithium amides. In order to avoid the generation of lithium ethoxide, a strong base, in the reaction vessel, dibromo *phenyl* esters can be used as the starting materials, in which the less basic lithium phenoxide is generated. The starting dibromo esters **40** are stable compounds and are easily synthesized via bromination of the α-bromo ester enolates with 1,1,2,2-tetrafluoro- or 1,1,2,2-tetrachloro-1,2-dibromoethane [Scheme 16, (1)][23b,24] or by radical bromination [Scheme 16, (2) and (3)[25]] depending on the substrates.



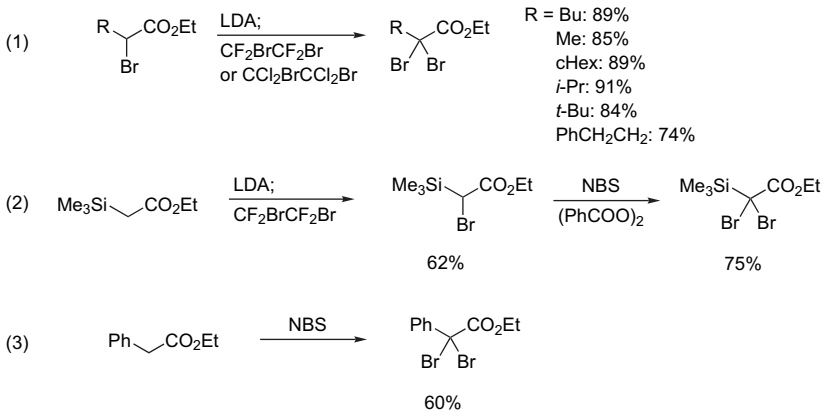
Scheme 15. Ynolates from α,α-dibromo esters.

Although this method is convenient in the laboratory and we have successfully carried out up to a 10-g scale, *t*-BuLi is somewhat expensive and should be handled carefully, especially in a large scale. With this in mind, we have developed a more practical method for the synthesis of ynolates using reductive lithiation. The dibromo esters **42** are treated with lithium naphthalenide to give the ynolates **43** in good yield. Naphthalene-*catalyzed* reductive lithiation[26] of the dibromo esters is also achieved, providing the ynolates more efficiently (Scheme 17).[27] The synthetic methods for ynolates via the cleavage of ester dianions are not only convenient, but also highly general, because alkyl-, aryl-, and silyl-substituted ynolates can be synthesized in good yields.

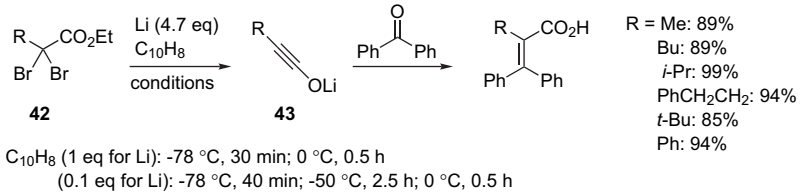
2.6. Ynolate dianions

Since unsubstituted ynolates are also terminal alkynes, their deprotonation should give ynolate dianions. Schöllkopf's method affords an ynolate dianion, starting from 3-phenylisoxazole (Section 2.1).

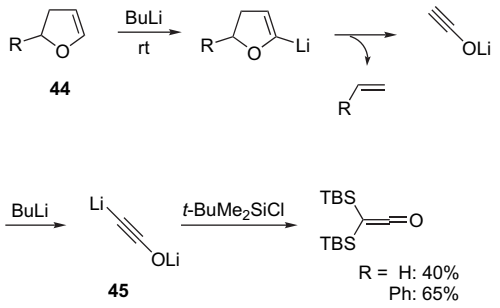
Barton et al. reported the synthesis of the ynolate dianions **45** by lithiation of 2,3-dihydrofurans **44** followed by extrusion of ethylene or styrene (Scheme 18).[28] The synthetic utility has not yet been sufficiently explored.



Scheme 16. Preparation of α,α-dibromo esters.



Scheme 17. Naphthalene-catalyzed reductive lithiation of α,α-dibromo esters.



Scheme 18. Ynolate dianions.

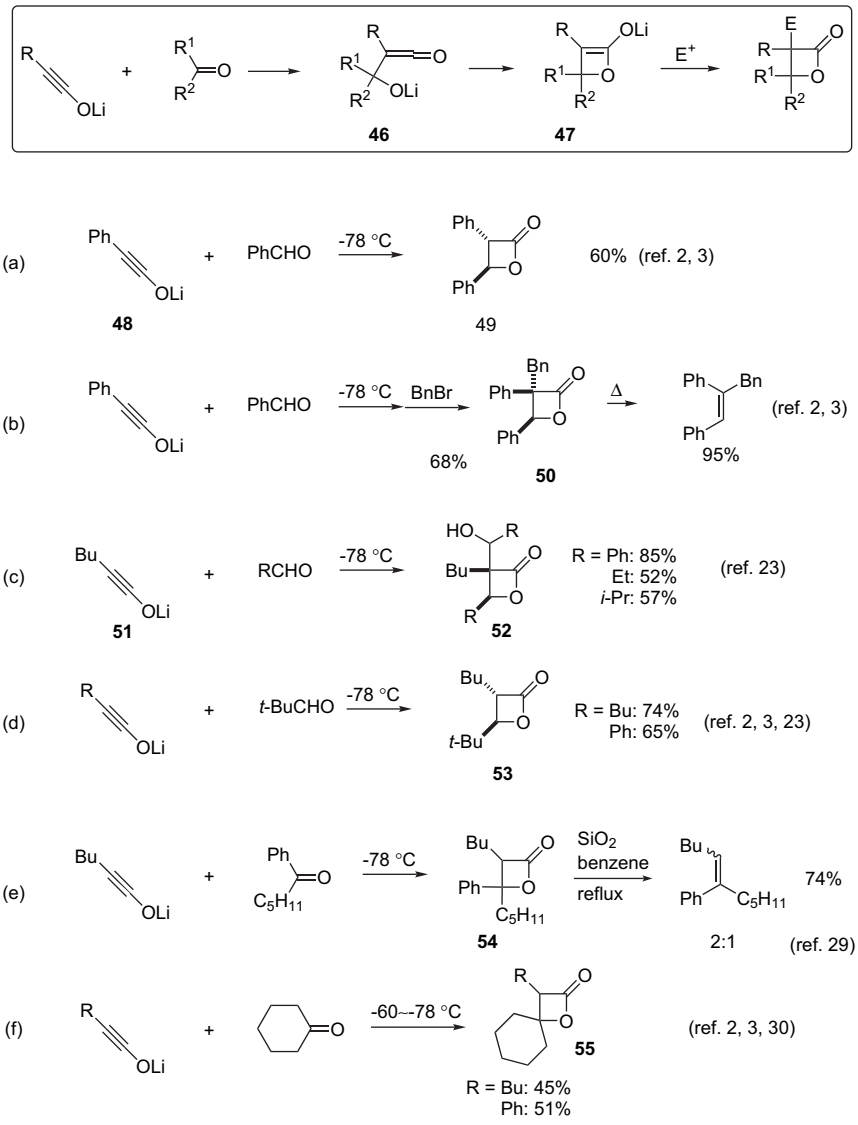
3. Synthetic uses of ynolate anions

3.1. Nucleophilic β-lactone enolates via cycloaddition with aldehydes and ketones

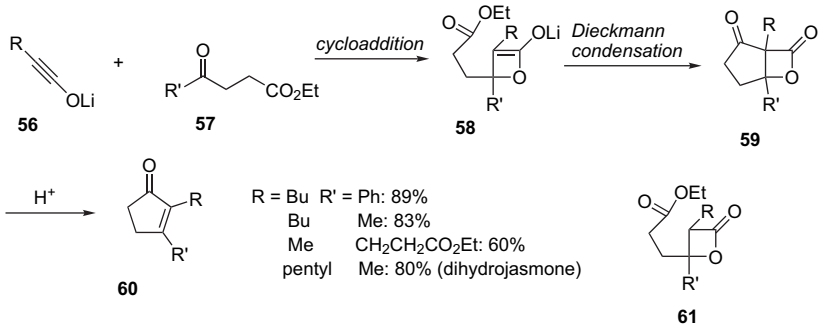
3.1.1. β-Lactones. Ynolates react with aldehydes and ketones at −78 °C to give the β-lactone enolates **47** (Scheme 19). This reaction appears to be a formal [2+2] cycloaddition, although it is unclear whether it occurs via a stepwise or a concerted mechanism. Some experimental results actually suggest the presence of the ketene intermediates **46** (see Sections 3.2.5 and 3.4). The reactions with phenyl-substituted ynolates such as **48**[2,3] afford the β-lactone **49** after protonation or **50** after alkylation [Scheme 19, (a) and (b)]. Alkyl-substituted ynolates (e.g., **51**), however, react with aldehydes to give only the 2:1 adducts **52**, even if less than 1 equiv of aldehydes is used,[22,23] due to the high reactivity of the β-lactone enolates [Scheme 19, (c)]. Ketones and sterically hindered aldehydes (e.g., pivalaldehyde), however, provide the 1:1 adducts (**53**–**55**) because the reactivity is lowered by steric hindrance [Scheme 19, (d)–(f)]. The β-lactones can be decarboxylated efficiently and stereospecifically to give the olefins on heating.

3.1.2. Tandem reactions leading to multisubstituted carbocycles. The β-lactone enolates prepared by the cycloaddition of ynolates with ketones are stable intermediates at −78 °C, but are still nucleophilic. Taking advantage of this reactivity, it would be possible to design a one-pot multistep synthesis (the negative–positive switching process) using ynolates, as described in the introduction. It would be even more efficient if the β-lactone enolates could be prepared by a method not involving enolization of the corresponding β-lactones. Consequently, we have developed novel tandem reactions involving intramolecular cyclization (Scheme 20).[29] The ynolates **56** react with the γ-ketoesters **57** to give the β-lactone enolates **58** as intermediates, which subsequently cyclize via a Dieckmann condensation to afford the bicyclic β-lactones **59**. These are easily decarboxylated on heating in the presence of acids to produce the 2,3-disubstituted cyclopentenones **60** in good overall yield. The direct generation of the β-lactone enolates **58** by treatment of the corresponding β-lactones **61** with LDA was unsuccessful. Therefore, ynolates allow the regioselective formation of the enolates via cycloaddition. This tandem [2+2] cycloaddition–Dieckmann condensation process can be applied to the syntheses of cyclohexenones (e.g., **62**), fused rings (e.g., **63**), and naphthols (e.g., **64**) (Scheme 21).[29,30]

Short-step syntheses of dihydrojasmone (Scheme 20),[29] α-cuparenone (**65**),[29] and cucumin E (**66**)[31] are all achieved via the ynolate-initiated tandem process (Scheme 22).



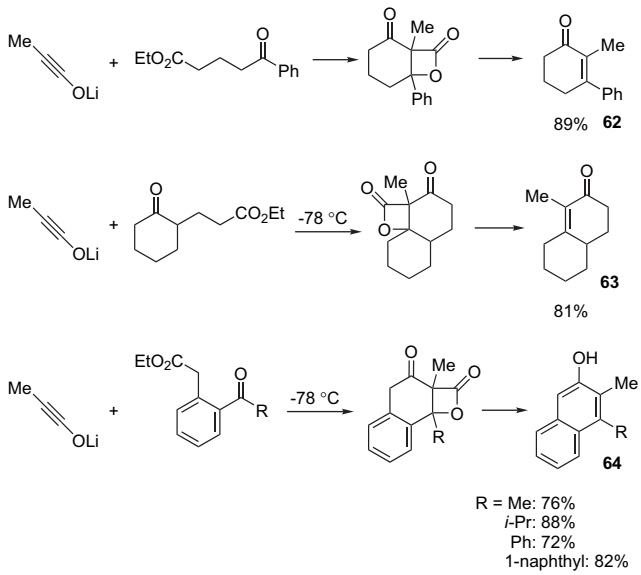
Scheme 19. β-Lactones via cycloaddition of ynolates with carbonyl compounds.



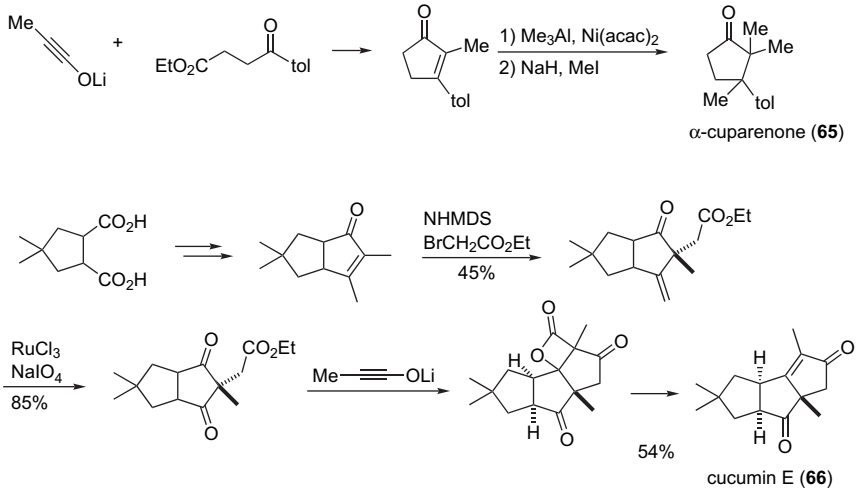
Scheme 20. Tandem [2+2] cycloaddition–Dieckmann condensation.

The Michael reaction can also be applied to the tandem reaction. The ynolate-initiated tandem [2+2] cycloaddition–Michael reaction followed by decarboxylation furnished the polysubstituted five-, six-, and seven-membered cycloalkenes **68** in good overall yield (Scheme 23).[32] The ester enolate intermediates **67** are nucleophilic, and further bond formation would be possible.

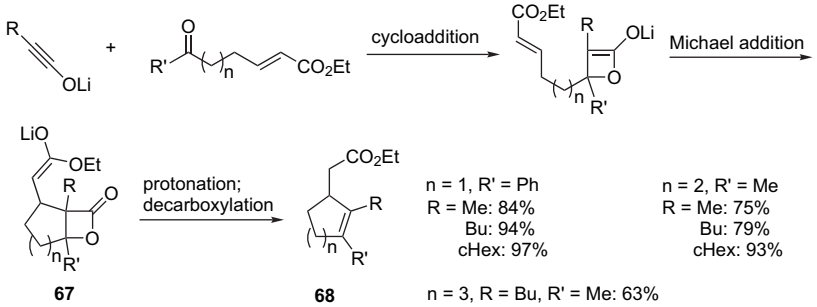
These ynolate-initiated tandem reactions can be regarded as formal [*n*+1] cycloadditions. Since even sterically



Scheme 21. Synthesis of fused rings via tandem reaction.



Scheme 22. Synthesis of natural products via tandem reaction.



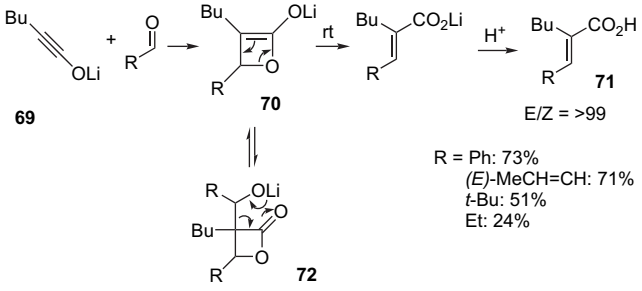
Scheme 23. Tandem [2+2] cycloaddition–Michael reaction.

hindered substrates and ynolates can be used, the tandem processes are efficient for the construction of carbocycles, especially those that are sterically congested ones.

3.2. Torquoselective olefination of carbonyl compounds

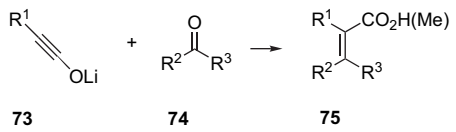
3.2.1. Olefination of unfunctionalized aldehydes and ketones. β-Lactone enolates are stable at −78 °C, but during

warming to room temperature, the small rings are cleaved to give the α,β-unsaturated carboxylates.[33] Kowalski found that ynolates reacted with benzaldehyde at −78 °C to give the β-lactone enolates, which are cleaved to the (*E*)-α,β-unsaturated carboxylic acids at room temperature.[9] We have also reported the reaction of aldehydes with the ynolate **69** *at room temperature* to afford the α,β-unsaturated carboxylic acids **71** in good yield with excellent *E*-selectivity (Scheme 24).[34] This reaction may involve the intermediate **72** that is converted into the enolate **70** via a retro-aldol reaction. This reaction can be considered as an *E*-selective olefination of aldehydes. Actually, the reactions of ynolates with several kinds of aldehydes generally provide the desired olefins with high *E*-selectivity.



Scheme 24. Ring opening of β-lactone enolates.

Stereoselective olefination of ketones giving tetrasubstituted alkenes is challenging in synthetic organic chemistry, because conventional methods like the Wittig reaction exhibit low reactivity toward ketones and afford poor selectivity. The olefination of the unfunctionalized ketones **74** with the ynolates **73** provides the tetrasubstituted olefins **75** in good yield (Scheme 25 and Table 1, entries 1–13).[35] The fact that the Wittig reagents and the Horner–Emmons reagents do not react with *tert*-butyl phenyl ketone indicates that ynolates are much better reagents for the olefination of ketones than those conventional reagents. The geometrical selectivity (3:1 to 8:1) is unprecedentedly good (Table 1, entries 7–13). In most cases, the phenyl group is preferentially trans to the carboxylate group, and the alkyl groups are cis to it. Pinacolone preferentially afforded the *Z*-olefin (entry 13). Even sterically hindered ynolates and ketones afforded the olefins in good yield. Methyl esters can be isolated by adding MeI along with HMPA to the reaction mixture without loss of selectivity or yield.

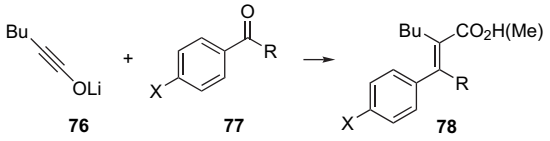


Scheme 25. Olefination of unfunctional ketones with ynolates.

The novel stereoelectronic effect is observed in this olefination.[36] The *E*/*Z*-selectivity of **78** is strongly dependent on the electronic nature of the *para*-substituents (X) in the olefination of *para*-substituted acetophenones **77** (R=Me) with **76** (Scheme 26 and Table 2). The acetophenones with electron-withdrawing groups give lower *E*-selectivity, compared to the unsubstituted compounds. On the other hand, substrates with electron-donating groups afford higher *E*-selectivity (up to >99:1). In the olefination of *para*-substituted benzophenones **77** (R=Ph), in which the steric factor can be negligible, the same trend in the selectivity is observed. This is the first example of stereoselective olefination of benzophenone derivatives. The stereochemistry is controlled by a stereoelectronic, as well as by a steric, effect.

Table 1. Olefination of unfunctional ketones with ynolates[35]

Entry	R^1	R^2	R^3	Yield (%)	*E*:*Z*
1	Me	Ph	Ph	>99	—
2	Bu	Cyclohexanone		68	—
3	Ph	Ph	Ph	94	—
4	*i*-Pr	Ph	Ph	99	—
5	*t*-Bu	Ph	Ph	85	—
6	Me_3Si	Ph	Ph	98	—
7	Me	Ph	Me	>99	80:20
8	cHex	Ph	Me	79	85:15
9	Me	Ph	Pentyl	96	83:17
10	Me	Ph	*t*-Bu	74	85:15
11	Me	Tetralone		96	83:17
12	Me	PhCH=CH	Ph	66	79:21
13	Me	Me	*t*-Bu	67	19:81



Scheme 26. Olefination of *para*-substituted phenyl ketones.

Table 2. Stereoelectronic effect on the olefination of ketones **77**

X	R=Me (acetophenones)		R=Ph (benzophenones)	
	Yield (%)	*E*:*Z*	Yield (%)	*E*:*Z*
NO_2	61	40:60	92	25:75
Cl	68	70:30	92	40:60
F	88	80:20	>99	50:50
H	82	85:15	82	—
Me	89	91:9	90	60:40
MeO	80	95:5	99	67:33
Me_2N	64	>99:1	90	83:17

The mechanism of the ring opening of the β-lactone enolates should be the conrotatory electrocyclic reaction of the oxetene,[37] rather than the 'forbidden β-elimination',[33] and thus Houk's torquoselectivity would be operative in the selectivity.[38] Thermal ring opening of cyclobutenes giving butadienes has been well studied experimentally[39,40] and theoretically.[41] In this reaction, the *E*/*Z* selectivities are determined by the torquoselectivity, and the electron-donating substituents rotate outward and the electron-accepting substituents rotate inward preferentially (Fig. 3). Houk et al. described the orbital interactions between the breaking C–C bond and some bond orbitals on the substituents as an explanation of the torquoselectivity. This concept provides a reasonable explanation for the olefination with ynolates. Theoretical calculations on the transition states suggested the strong interactions between the disconnecting C–O σ

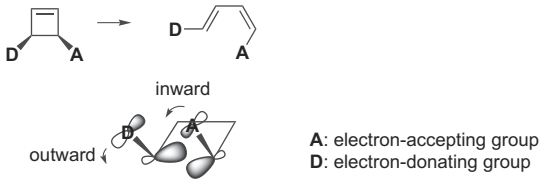


Figure 3. Torquoselectivity for conrotatory electrocyclic ring-opening.

orbital in the oxetene and the π (π*) orbitals of the aromatic ring in the transition states.[42] Usually, since the phenyl group has an electron-rich π-orbital, i.e., a high energy level of the occupied orbital, it can be regarded as an electron-donating group, compared with the alkyl group. The electronic properties, however, depend on the substituents, e.g., in the case of the *p*-nitroacetophenones, the stabilization of the transition state leading to the *Z*-olefins would be due to the overlap of the orbitals of the disconnecting C–O bond with the p-orbitals (π* orbitals), in which the energy level of the antibonding orbital is lowered by the electron-withdrawing substituents, as illustrated in Figure 4. The *p*-nitrophenyl substituent works as an electron acceptor in torquoselectivity.

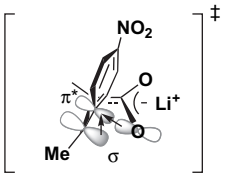


Figure 4. Orbital interactions in the transition state of the ring-opening of the lactone enolate leading to the *Z*-olefin.

The σ* orbitals are also important as acceptors in the torquoselectivity.[43] Since the σ*(C–CH_3) orbital is reported to be more electron accepting than the σ*(C–H),[44] the *tert*-butyl group would rotate inward preferentially (Fig. 5 and Table 1, entry 13).[45]

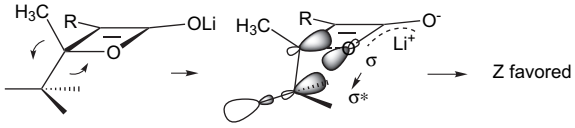
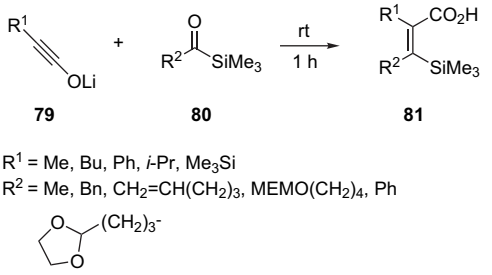


Figure 5. Orbital interactions in the transition state of the ring-opening of the lactone enolate.

3.2.2. Olefination of acylsilanes. Vinylsilanes are powerful tools in synthetic organic chemistry.[46] Although olefination of acylsilanes[47] is expected to become a useful method for the preparation of vinylsilanes, conventional reagents like phosphorous ylides have not yet been used for this purpose, due to their low reactivity and poor selectivity.[48] Extremely, *Z*-selective olefination of the acylsilanes **80** with the ynolates **79** has been achieved, leading to the β-silyl-α,β-unsaturated esters **81** in high yields (Scheme 27).[49] In most cases, the *E* isomers could not be detected by ^{1}H NMR and HPLC. This is the first general method for the stereoselective synthesis of tetrasubstituted olefins.



Scheme 27. *Z*-Selective olefination of acylsilanes with ynolates.

Theoretical calculations and NBO analysis suggest that this remarkable torquoselectivity is due to orbital interactions of n(O)–σ*(Si–C) and the breaking σ(C–O)–σ*(Si–C) in the inward transition state during the ring opening of the β-lactone enolate (Fig. 6).[45] This is in good agreement with the results obtained from the ring opening of silylcyclobutenes reported by Murakami and Houk.[43]

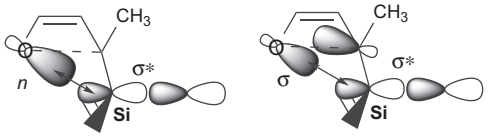
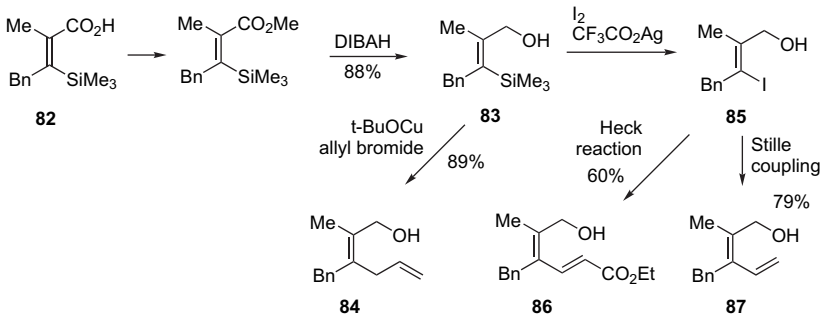


Figure 6. Secondary orbital interactions between NBOs in the transition states.

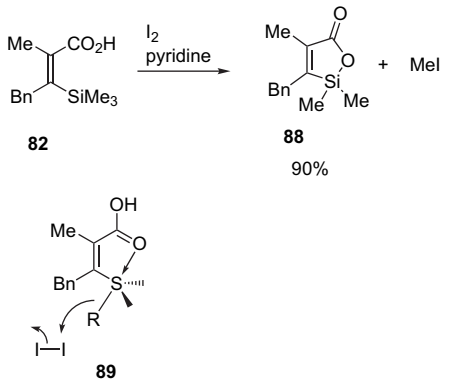
The substituted vinylsilane **82** produced is converted to the silyl allyl alcohol **83**, which is allylated to give the skipped diene **84**,[50] and the iodoalkene **85**, prepared by desilyliodination of **83**,[51] is subjected to metal-catalyzed cross-coupling reactions to afford the dienes **86** and **87** without *E*/*Z* isomerization (Scheme 28).

The (*Z*)-β-trialkylsilylacrylic acids show unusual reactivity. The vinylsilane **82** reacts with iodine to afford the



Scheme 28. Syntheses of tetrasubstituted olefins.

unexpected silalactone **88** along with iodomethane in good yield (Scheme 29).[52] The X-ray crystal structures of (*Z*)-β-trialkylsilylacrylic acids revealed the formation of a pentacoordinate hypervalent silane by intramolecular coordination of the carbonyl group (Fig. 7). Since the silicon–carbon bond is activated by the hypervalency, the C–Si bond was cleaved under mild conditions via a push–pull mechanism (**89**). The palladium-catalyzed cross-coupling of the vinylsilane **82** with aryl iodides (Hiyama coupling) is also activated by the hypervalency to afford the coupling product **90** without the use of fluoride ion, while the inactivated vinylsilane **91** does not react (Scheme 30).[53]



Scheme 29. Electrophilic cleavage of C–Si bond-forming silalactones.

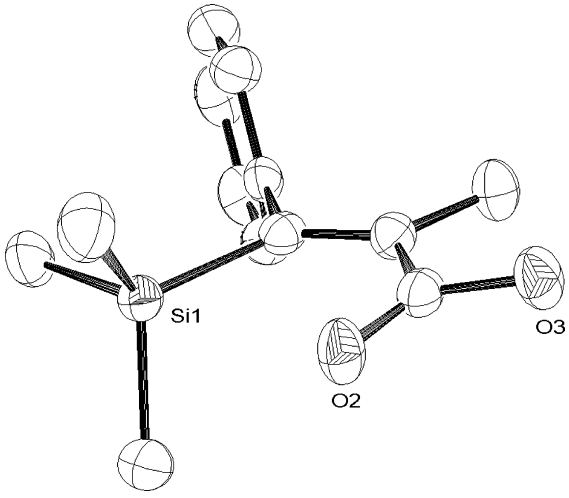
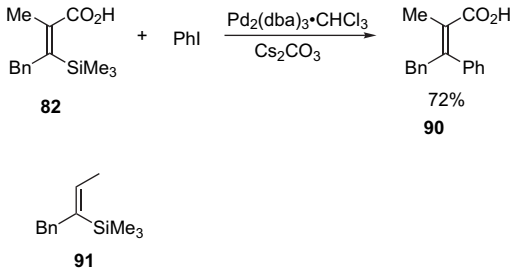


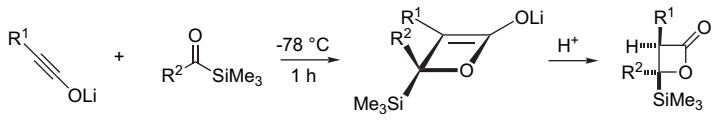
Figure 7. ORTEP drawing of hypervalent vinylsilane **8** (R^1=Me, R^2=Ph).



Scheme 30. Hiyama coupling of β-silyl acrylates.

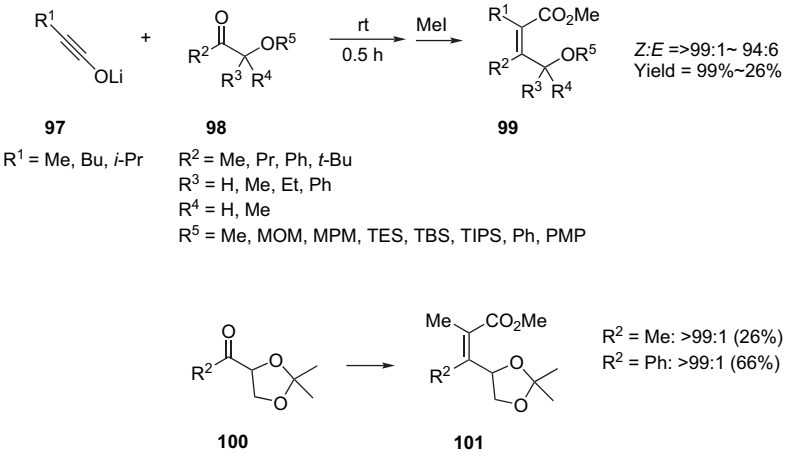
The stereochemical complementary olefination of acylsilanes **93** with ynolates **92** was also reported by us that is not torquoselective olefination. This strategy is based on a stereoselective formation of β-silyl-β-lactones **95**, followed by decarboxylation sequence via *syn*-elimination leading to the vinylsilanes **96**, as shown in Scheme 31.[54] The *E*/*Z*-selectivity is determined in the kinetically controlled protonation of the β-lactone enolates **94**, leading to preferential introduction of the proton *anti* to the trialkylsilyl group. The steric and stereoelectronic effects of the silyl group induce high selectivity.

3.2.3. Olefination of α-oxy and α-amino ketones.[55] The usual ketones RC(=O)R′ have similar substituents R and R′, and thus strong stereocontrolling directing groups for olefination are required in the ketones. The α-alkoxy and α-trialkylsilyloxy acyclic ketones **98** provide the olefins **99** with high *Z*-selectivity by the torquoselective olefination with ynolates **97** (Scheme 32). The ketones **100** bearing the optically pure cyclic acetal at the α-position also gave the (*Z*)-olefins **101** without any loss of optical purity. The α-trialkylsiloxy cyclic ketones **102** afforded the olefins **103** with good to moderate stereoselectivity (Scheme 33), which would depend on the conformation of the siloxy group, because the axially oriented siloxy group induced a high *Z*-selectivity, but the equatorially oriented group did not (Scheme 34). These products **104** are easily converted to the butenolides **105** (Scheme 35).

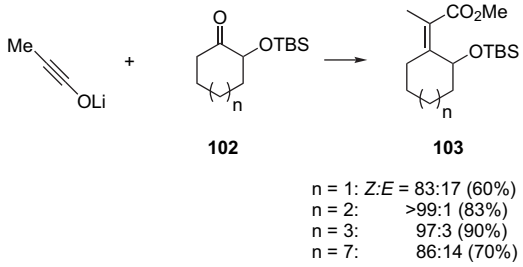


R^1	R^2	*Z*:*E*	Yield (%)
Me	Bn	98:2	72
i-Pr	Bn	94:6	78
Me	Ph	92:8	62
Me	CH_2=CH(CH_2)$_3$	94:6	72

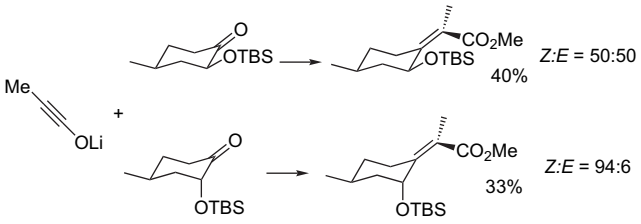
Scheme 31. Stereochemically complementary olefination of acylsilanes with ynolates.



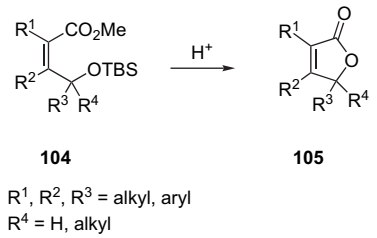
Scheme 32. Olefination of α-alkoxy and α-siloxy linear ketones.



Scheme 33. Olefination of α-siloxy cyclic ketones.



Scheme 34. Olefination of conformationally fixed α-siloxy cyclic ketones.



Scheme 35.

At first, the chelation-control mechanism had been considered, but, from several experimental results, orbital and steric interactions turn out to be reasonable rather than chelation for the following reasons: (1) the sterically hindered siloxy and phenoxy groups are also effective for a high *E*-induction, (2) in the presence of a crown ether, the selectivity still remained high, and (3) an axially oriented siloxy group induced a high *Z*-selectivity. Theoretical calculations indicate that the transition state of inward rotation is stabilized by an orbital interaction between σ(C–O) and σ*(C–OR) (Fig. 8). The torquoselectivity is controlled by the directing group.

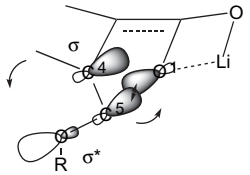
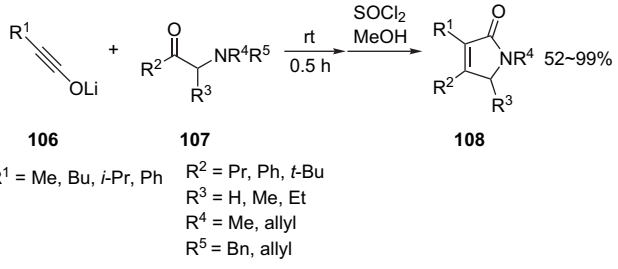


Figure 8. Transition state of inward rotation stabilized by orbital interaction between σ(C–O) and σ*(C–OR).

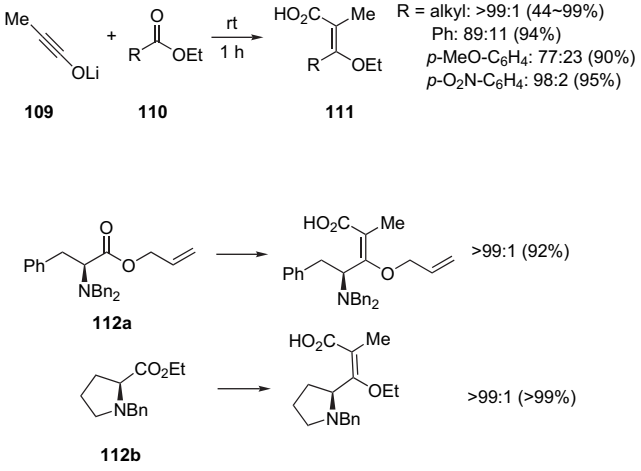
This concept can be applied to the olefination of α-amino ketones. As shown in Scheme 36, the reaction of ynolates **106** with the amino ketones **107** gave the γ-amino unsaturated carboxylates, which were treated with thionyl chloride to provide the unsaturated lactams **108** in good yield without any detection of minor isomers.



Scheme 36. Olefination of α-amino ketones.

3.2.4. Olefination of esters.[56] Olefination of ester carbonyls would appear to be useful for the synthesis of enol ethers, as conventional methods such as the Wittig reaction have generally been unsuccessful in realizing olefination, due to the lower reactivity of the esters. Metal carbenoids, such as Tebbe reagents, accomplish this transformation, but they are limited to the preparation of simple enol ethers. The first

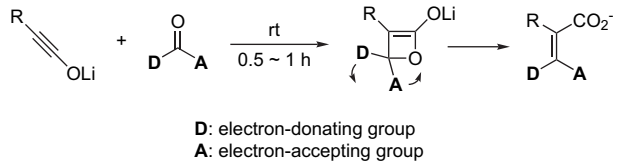
highly stereoselective synthesis of tetrasubstituted, functionalized (*E*)-enol ethers **111** via olefination of esters **110** with ynolates **109** was achieved by our group (Scheme 37). Aliphatic esters afforded excellent *E*-selectivities, and aromatic esters gave good to moderate selectivity, which depended on the electronic properties of the substituents on the aromatic ring. In particular, α-amino esters **112a**,**b** are excellent substrates for this olefination. This torquoselectivity can be elucidated from the fact that the ethoxy group rotates outward preferentially, because of its electron-donating property. The enol ethers produced would be very useful in synthetic organic chemistry.



Scheme 37. Torquoselective olefination of esters.

3.2.5. Homologation of thioesters.[56] In contrast to esters, thiol esters **113** afford the two-carbon homologated β-keto thiol esters **117** in good yield (Scheme 38). Elimination of the thiolates from the ketenes **114** would be followed by the attack of the thiolate on the α-ketoketenes **115** to give the β-keto thiol ester enolates **116**. This homologation can be regarded as the insertion of the ynolate carbon framework into the C–S bond of the thiol esters. The reaction mode, olefination, or homologation, changes depending on the leaving-group ability of the (thiol)alkoxides on the esters.

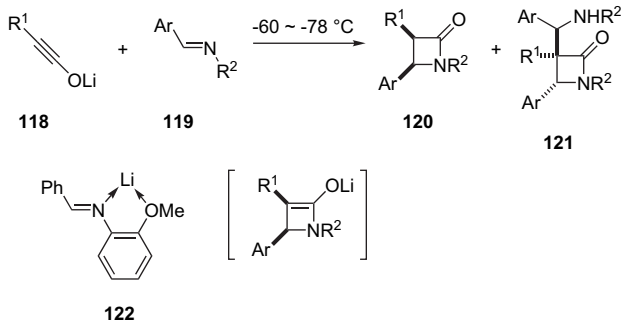
3.2.6. Summary of torquoselective olefination. This is the first general method for the olefination of ketones providing multisubstituted olefins. Torquoselective olefination means the olefination controlled by torquoselectivity. This olefination is mechanistically quite different from other olefinations, and the selectivity would be estimated by the electronic properties of the substituents, namely, electron-donating group at positions trans to carboxylate, and accepting group at cis position (Scheme 39).



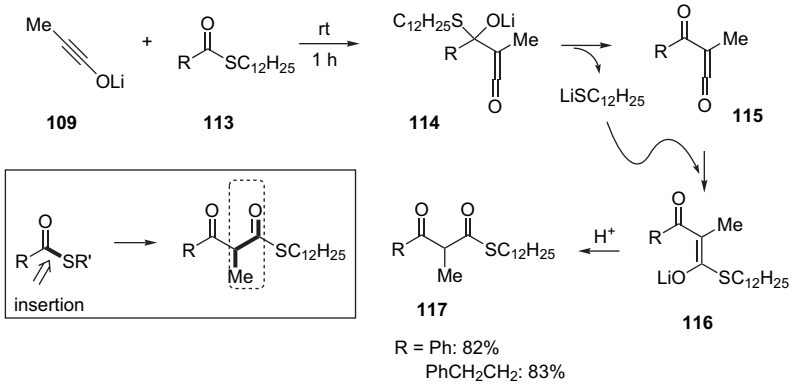
Scheme 39. Torquoselective olefination.

3.3. Reactions with C=N bonds

Imines are versatile and useful electrophilic nitrogen sources and are expected to react with nucleophiles in similar fashion as aldehydes. Since aldimines are, however, less electrophilic than the corresponding aldehydes, they often require activation and/or harsh conditions for the addition of nucleophiles.[57] Barrett et al. reported that the phenyl-substituted ynolate **118** (R^1=Ph) reacts with aldimines **119** having electron-withdrawing groups (*p*-nitrophenyl, etc.) to afford the 2:1 adducts **121** in good yields (Scheme 40 and Table 3, entries 1–4).[58] We found that the unstabilized alkyl-substituted ynolate **118** (R^1=Bu) afforded β-lactams (1:1 adduct) **120** in



Scheme 40. Synthesis of β-lactams.



Scheme 38. Homologation of thiol esters.

Table 3. Synthesis of β-lactams

Entry	R^1	Ar	R^2	Yield (%)		Ref.
				120	**121**	
1	Ph	p-O_2N-C_6H_4	Ph	0	66	58
2	Ph	p-O_2N-C_6H_4	p-O_2N-C_6H_4	0	89	58
3	Ph	p-O_2N-C_6H_4	m-Me-C_6H_4	0	58	58
4	Ph	p-EtO_2C-C_6H_4	p-O_2N-C_6H_4	0	79	58
5	Bu	Ph	Ts	58	11	59
6	Bu	Ph	$PhSO_2$	64	18	59
7	Bu	Ph	$POPh_2$	12	72	59
8	Me	Ph	o-MeO-C_6H_4	0	96	60
9	Me	p-MeO_2C-C_6H_4	o-MeO-C_6H_4	0	97	60
10	Bu	Ph	o-MeO-C_6H_4	0	79	60
11	cHex	Ph	o-MeO-C_6H_4	45	52	60

the reaction with *N*-sulfonyl and *N*-phosphonyl aldimines **119** (R^2=SO_2Ar, and POPh) at −78 °C (Table 3, entries 5–7).[59] *N*-*o*-Methoxyphenyl aldimines react with ynolates at −78 °C to give the 2:1 adducts **121**, although the methoxy group is electron-donating (Table 3, entries 8–11).[60] Since *N*-*p*-methoxyphenyl aldimines are inert to the ynolate, the *N*-*o*-methoxyphenyl aldimines are obviously activated by chelation with lithium (**122**).[61]

β-Lactam enolates are cleaved in a similar fashion to β-lactones. Murai et al. reported that a silyl-substituted ynolate **123** (R=Me_3Si) cycloadds to *N*-sulfonyl aldimines such as **124**, followed by ring opening, to afford the α,β-unsaturated amide **125** at 20 °C (Scheme 41).[8]

The reaction of *N*-*o*-methoxyphenyl aldimines **127** with the ynolates **126** at room temperature produced the α,β-unsaturated amides **129** in good yield with high *E*-selectivity (Scheme 42).[62] Since the 2:1 adduct intermediates **130** can be detected during the reaction, the reaction certainly passes through the retro-Mannich reaction (**130**→**128**). These are also the torquoselective olefinations.

3.4. Reactions with isocyanates

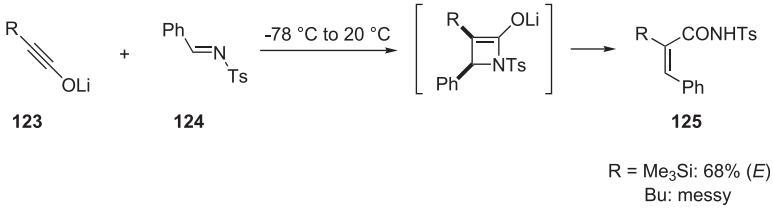
Isocyanates are strong electrophiles having a C=N bond, and are used to synthesize heterocycles such as azetidin-2-ones.[63] Ynolates **131** react with phenyl isocyanate (**132**) to give the azetidin-2,4-diones **133** via [2+2] type cycloaddition in moderate yield (Scheme 43).[64] The sterically hindered 2,6-dimethylphenyl isocyanate (**134**) did not afford the azetidine-2,4-dione, but gave the phenyl ester **136**. This result supports the generation of the ketene intermediates **135** via a stepwise mechanism of the four-membered ring formation using ynolates.

Styryl isocyanate (**138**) reacted with the ynolate **137** to provide the 4-hydroxypyridone **140** in moderate yield via a formal [4+2] cycloaddition. This reaction also indicated the presence of the ketene intermediate **139** (Scheme 44).

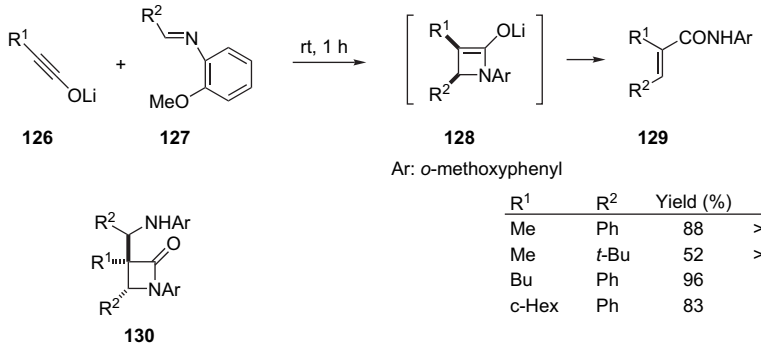
3.5. Reactions with nitrones

The [3+2] cycloaddition of 1,3-dipoles with alkenes is an important method for preparing five-membered heterocycles.[65] Commonly, these cycloadditions of nitrones, representative 1,3-dipoles, involve the reaction of an electron-deficient alkene (LUMO) with a 1,3-dipole (HOMO). In inverse electron-demand 1,3-dipolar cycloadditions, alkenyl ethers or ketene acetals are used as electron-rich dipolarophiles, occasionally requiring activation by Lewis acids. Ynolates are expected to function as electron-rich dipolarophiles in this type of cycloaddition.

The anionic inverse electron-demand 1,3-dipolar cycloaddition of nitrones (**142**) with ynolates **141** (Scheme 45) proceeds at 0 °C to afford the substituted isoxazolidinones.[66] Because the initial products are isoxazolidinone enolates **143**, the relative configuration is determined during the

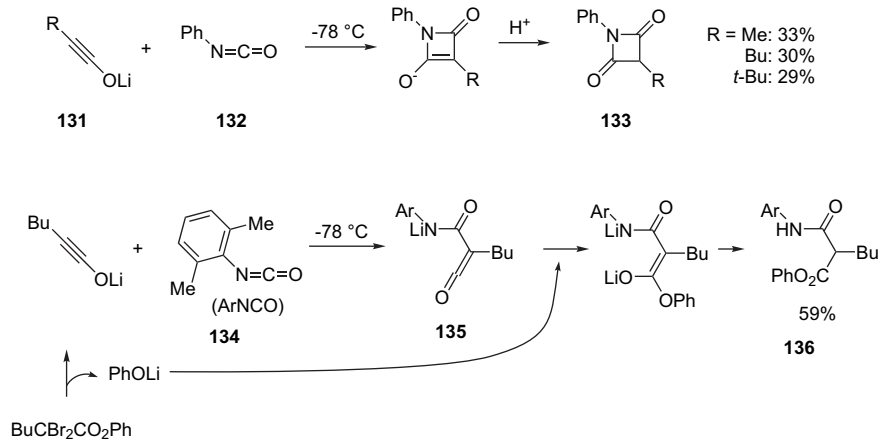


Scheme 41. Olefination of *N*-tosyl aldimines.

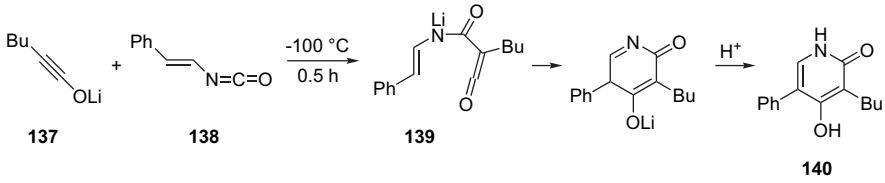


R^1	R^2	Yield (%)	*E*:*Z*
Me	Ph	88	>99:1
Me	*t*-Bu	52	>99:1
Bu	Ph	96	94:6
c-Hex	Ph	83	85:15

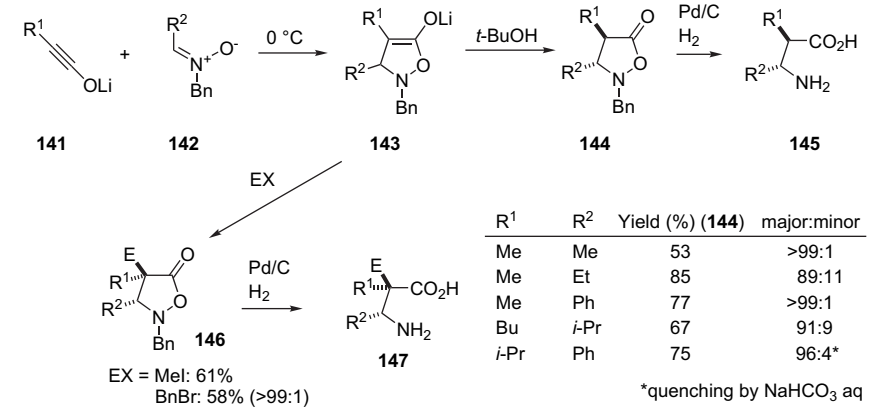
Scheme 42. Olefination of *N*-aryl aldimines.



Scheme 43. Synthesis of azetidin-2,4-diones.



Scheme 44. Synthesis of 4-hydroxypyridone via [4+2] cycloaddition.



Scheme 45. Cycloaddition of nitrones with ynolates.

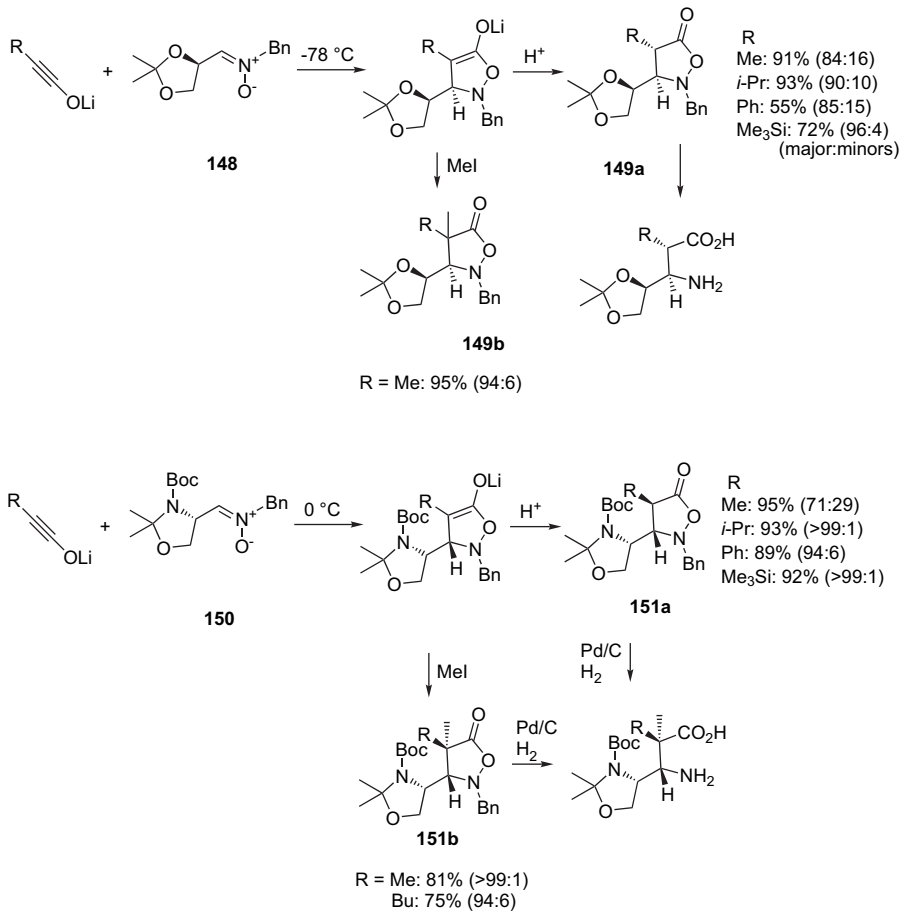
protonation step. With a thermodynamically controlled protonation, the trans products **144** are mainly produced. The in situ alkylation furnishes the trisubstituted isoxazolidinone **146** with high diastereoselectivity. The isoxazolidinones produced are converted into the β-amino acids (**145**, **147**) in good yield.

The asymmetric reactions of the chiral non-racemic nitrones **148** derived from D-mannitol and **150** derived from L-serine afford the desired isoxazolidinones **149a**,**b** and **151a**,**b**, respectively, with high diastereoselectivity. This process can lead to an efficient asymmetric synthesis of β-amino acids (Scheme 46).[67,68] This is the first example of asymmetric reactions with ynolates. It is noteworthy that the ynolates show higher reactivity and stereoselectivity than the corresponding lithium enolates and demonstrate the high potential of ynolates in asymmetric reactions.

3.6. Reactions with oxiranes and aziridines

Oxiranes are less electrophilic than carbonyls and sometimes need activation by Lewis acids. The lithium silyl-substituted ynolate **152** reacts with the oxiranes **153** activated by the addition of Me_3Al to furnish the γ-lactones **154** (Scheme 47).[8] Me_3Al might form an ate complex with the lithium ynolate, according to the NMR spectra.

The reaction of the lithium silyl-substituted ynolate **152** with the aziridine **155** activated by a *p*-toluenesulfonyl group produces the γ-lactam **157** without the use of Lewis acids. The initial product is the enolate **156**, which is trapped by aldehydes to afford the α-alkylidene-γ-lactams **158** via a Peterson-type reaction.[69] These reactions may be considered to be formal [3+2] cycloadditions as well as tandem reactions involving nucleophilic ring opening and cyclization (Scheme 48).



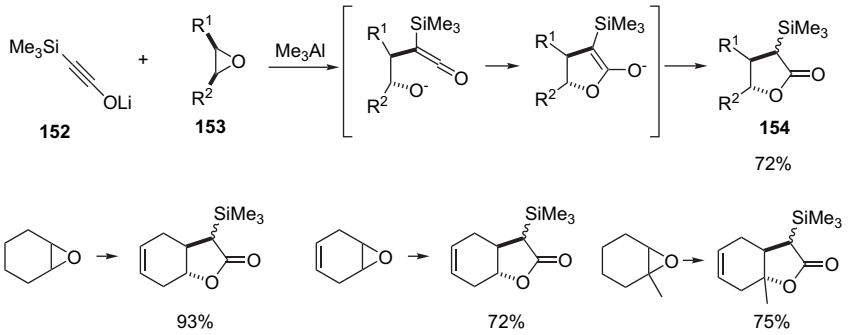
Scheme 46. Asymmetric cycloaddition of ynolates with chiral nitrones.

3.7. Michael-type reactions with α,β-unsaturated carbonyl compounds[8]

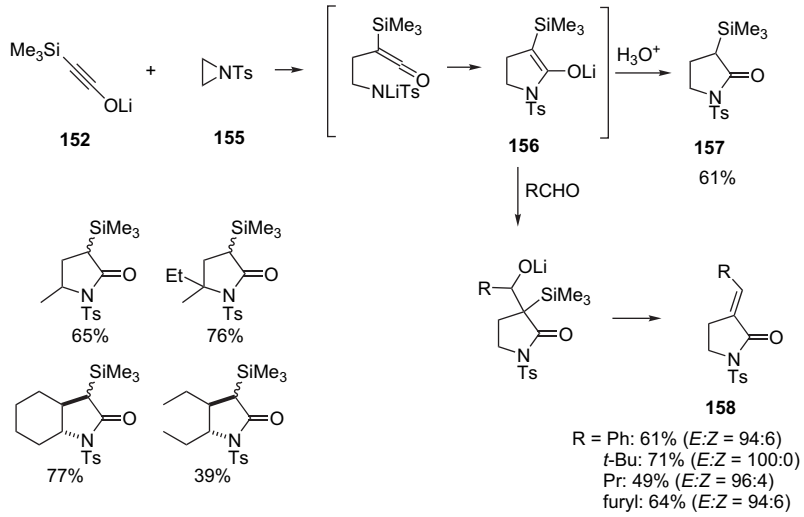
The cycloaddition of the silyl-substituted ynolate **152** with benzylideneacetoacetate **159** gives the γ-lactone **160** via a [4+2] type cycloaddition. Since acrylates are inert to the ynolate, the electrophile should be activated by two electron-withdrawing groups. Benzalmalonate **161** afforded the uncyclized ketene **162** by the reaction of the ynolate. This would also be an evidence for a stepwise mechanism (Scheme 49).

3.8. Benzannulation[70]

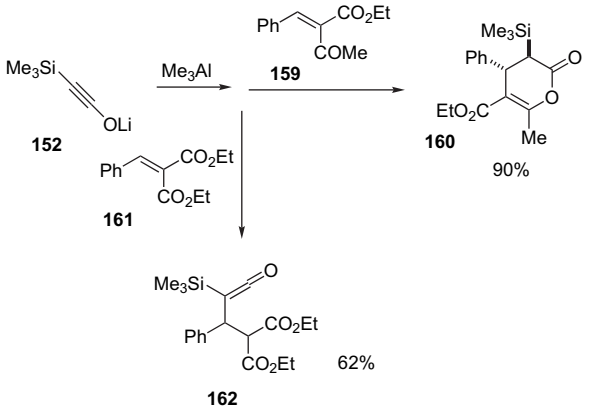
Danheiser et al. reported that lithium ynolates **163** react with stable (trialkylsilyl)vinylketenes **164** to produce the highly substituted phenols **167** in a benzannulation strategy. The ynolates **163** add to the silyl ketenes **164** to provide the



Scheme 47. Reactions of ynolate with oxiranes.



Scheme 48. Reactions of ynolate with aziridines.

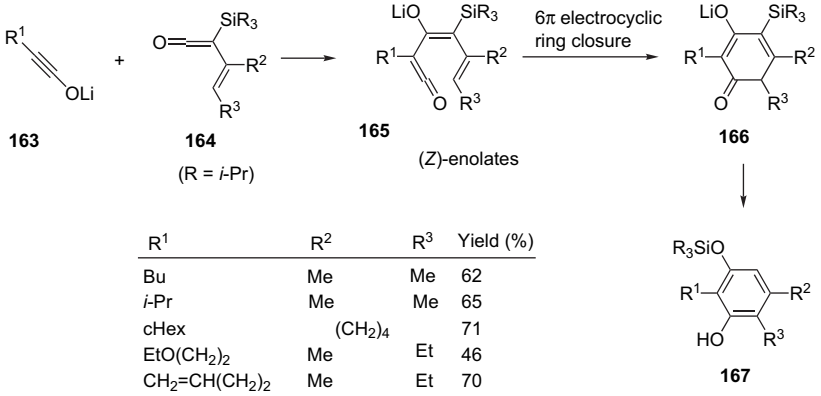


Scheme 49. [4+2] Type cycloaddition.

ketenes **165** bearing (*Z*)-enolates, which undergo 6π electrocyclic ring closure, not β-lactone enolates, to afford the cyclohexadienones **166**. The geometry of the (*Z*)-enolates would be important for the cyclization. The cyclohexadienones **166** isomerize to provide the siloxyphenols **167** via a 1,3-carbon–oxygen silyl shift and aromatization (Scheme 50).

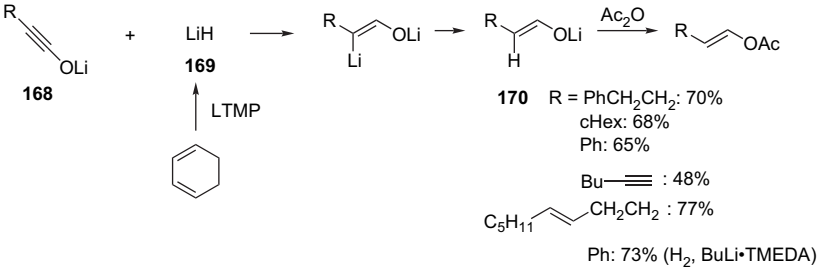
3.9. Reduction of ynolates

The reduction of the triple bond of the ynolates **168** by LiH (**169**) provides the *E*-enolates (**170**) of aldehydes (Scheme 51).[71] Since lithium enolates of aldehydes are not easily prepared by the usual base treatment of the aldehydes, this reaction appears to be useful. The LiH (**169**), which cannot normally reduce simple triple bonds, is prepared in situ from

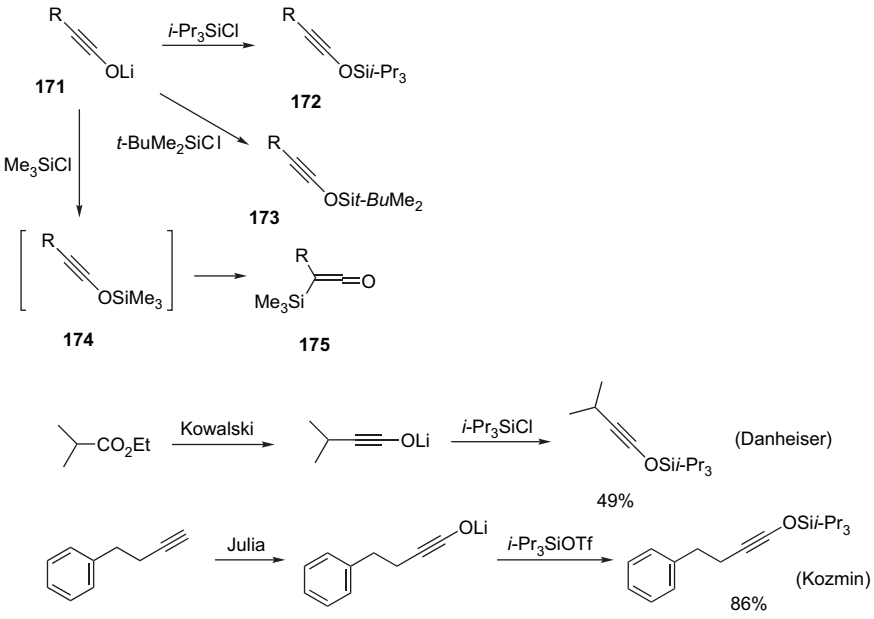


R^1	R^2	R^3	Yield (%)
Bu	Me	Me	62
i-Pr	Me	Me	65
cHex	$(CH_2)_4$		71
$EtO(CH_2)_2$	Me	Et	46
$CH_2{=}CH(CH_2)_2$	Me	Et	70

Scheme 50. Danheiser's benzannulation.



Scheme 51. Reduction of ynolates.



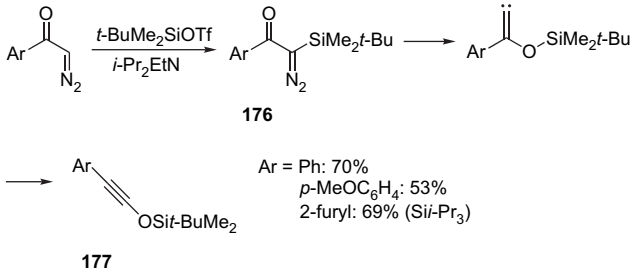
Scheme 52. Silylation of lithium ynolates.

cyclohexa-1,3-diene and LTMP or from cyclohexa-1,4-diene and BuLi. The super-active LiH, prepared from hydrogen with BuLi·TMEDA, can also be used.[72]

4. Synthetic uses of silyl ynol ethers

4.1. Preparation of silyl ynol ethers

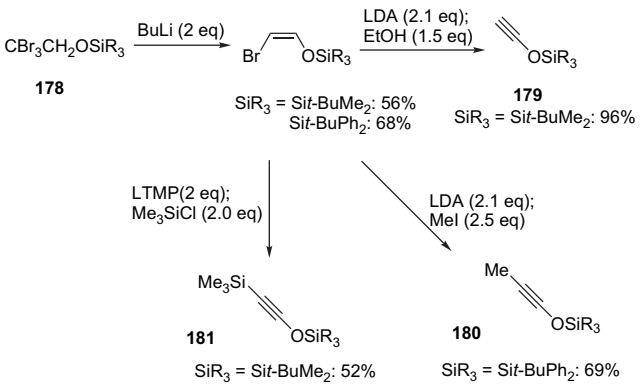
4.1.1. Silylation of lithium ynolates. Lithium ynolates **171** are silylated by TIPSCl and TBSCl to afford the corresponding silyl ynol ethers **172** and **173**, which are thermally stable and isolable, but sensitive toward acids (Scheme 52).[16,73] An experimentally improved procedure for the purification of **172** derived from the Kowalski's method has been described by Danheiser and Helgason.[74] Lithium ynolate derived from Julia's method is also used for the preparation of **172**.[75] TMSCl and TESCl provided silyl ketenes **175**, however, by C-silylation. These small silyl chlorides primarily gave the silyl ynol ethers **174**, but, upon warming the reaction mixture, isomerization to the more stable silyl ketenes occurred. Kita et al. reported that the soft silyl chlorides like Ph_3SiCl afforded silyl ketenes.[6] Disilyl ynol ethers, prepared from ynolate dianions, are rearranged to disilylketenes mediated by salts.[28]



Scheme 53. Wolff rearrangement giving silyl ynol ethers.

4.1.2. Direct formation of silyl ynol ethers. The synthesis of the aryl-substituted silyl ynol ethers **177** via the Wolff rearrangement of the α-silyl-α-diazoketones **176** has been reported by Maas and Brückmann (Scheme 53).[76]

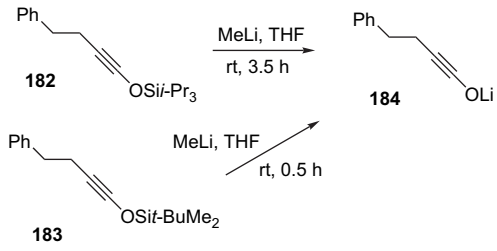
Treatment of tribromoethoxysilanes **178** with base furnishes siloxyacetylene **179** via a double β-elimination (Scheme 54).[77] The acetylides can be alkylated and silylated to give **180** and **181**.



Scheme 54. Double β-elimination of tribromoethoxysilanes.

4.2. Preparation of lithium ynolates free from other lithium species

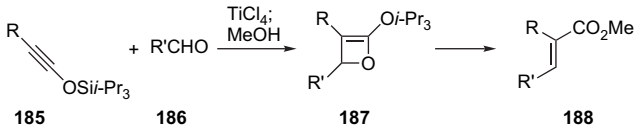
Most of the methods for the preparation of ynolates described above afford lithium ynolates along with other lithium species, which may affect the reactions. Silyl ynol ethers **182** and **183** are precursors of lithium ynolate **184**. Salt-free or amine-free lithium ynolates are obtained by treatment of the ynol ethers with methyllithium at room temperature (Scheme 55).[71]



Scheme 55. Preparation of lithium ynolates from silyl enol ethers.

4.3. Lewis acid-induced olefination

Titanium(IV) chloride-mediated cycloaddition of silyl ynol ethers **185** with aldehydes **186** followed by ring opening of the oxetene intermediates **187** affords the olefins **188** with high *E*-selectivity. Since the stereochemistry is determined in the electrocyclic ring opening, this is also regarded as torquoselective olefination of aldehydes (Scheme 56).[78]



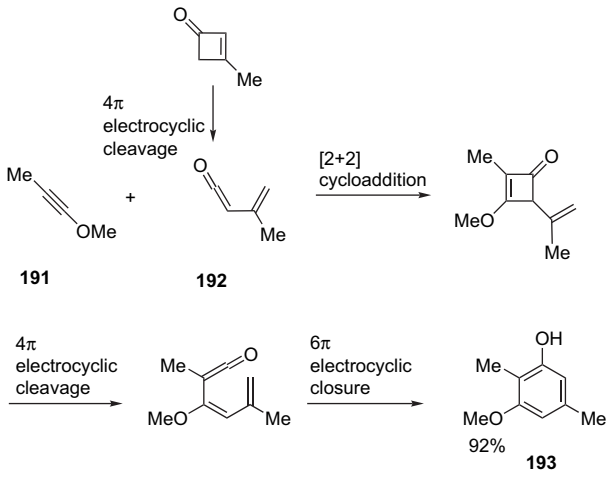
R	R'	*E*:*Z*
pentyl	Ph(CH$_2$)$_2$	100:0
	c-Hex	91:9
	Ph	84:16
Ph	C$_5$H$_{11}$	100:0
	Ph	97:3
c-Hex	Ph	80:20
	c-Hex	95:5

Scheme 56. Torquoselective olefination of aldehydes with silyl ynol ethers.

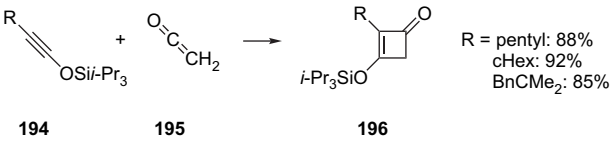
Lanthanide-triflate catalyzed olefination of aldimines **190** with silyl ynol ethers **189** has been reported by our group (Scheme 57).[79]

4.4. Danheiser's benzannulation

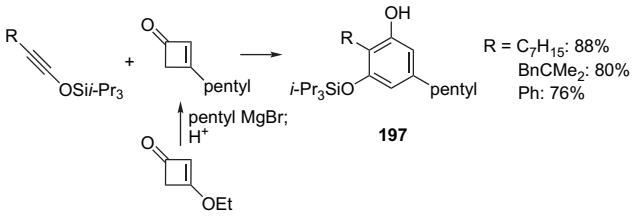
Danheiser's aromatic annulation strategy (Scheme 58),[80] which includes the cycloaddition of vinylketene **192** to alkoxyacetylene **191** giving **193**, can be applied to the reaction of silyl ynol ethers. Kowalski prepared the cyclobutenones **196**, precursors of vinylketenes, via the [2+2] cycloaddition of the silyl ynol ethers **194** with the ketene **195** (Scheme 59).[81] 3-Pentylcyclobutenone, prepared from 3-ethoxycyclobutenone, was subjected to the annulation to produce the resorcinols **197** (Scheme 60).



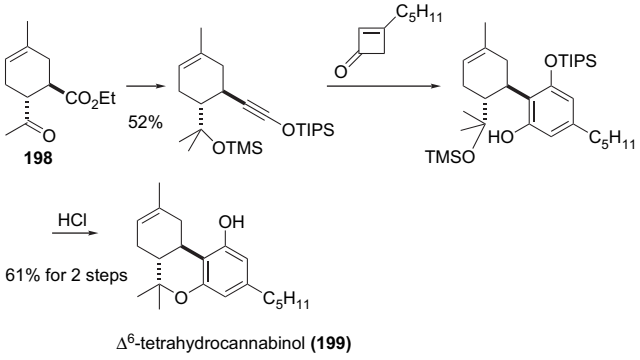
Scheme 58. Danheiser's benzannulation strategy.



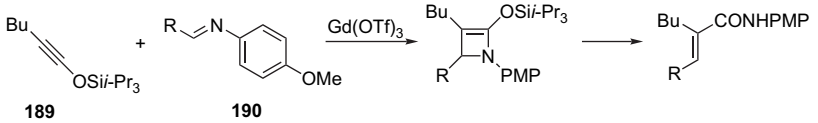
Scheme 59. Preparation of cyclobutenones from silyl enol ethers.



Scheme 60. Synthesis of resorcinols.

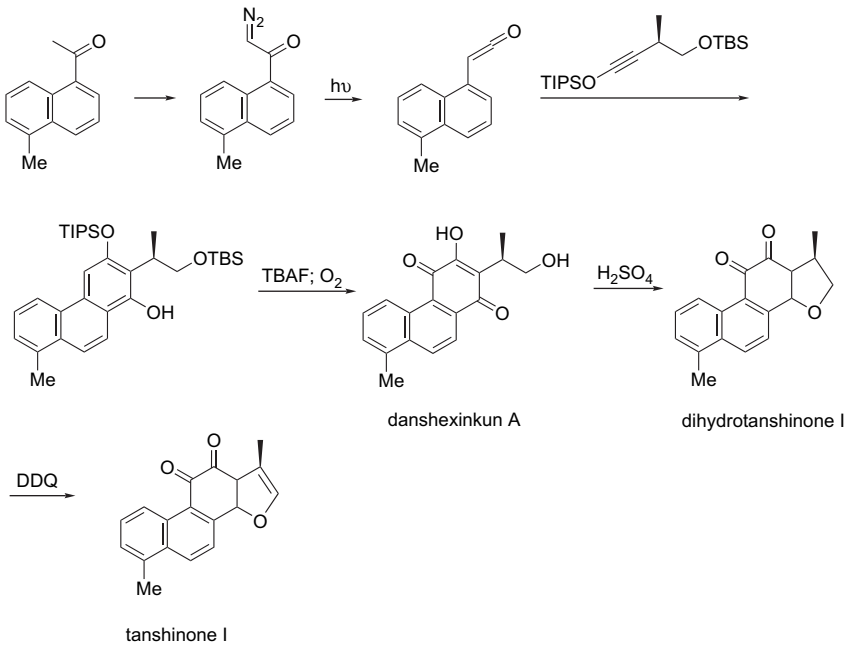


Scheme 61. Synthesis of Δ-6-tetrahydrocannabinol.

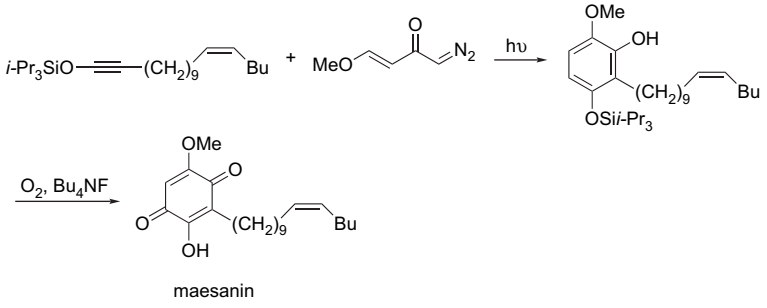


R = Ph: *E*:Z = 100:0 (62%)
(*E*)-PhCH=CH-: 86:14 (56%)
1-naphthyl: 75:25 (62%)

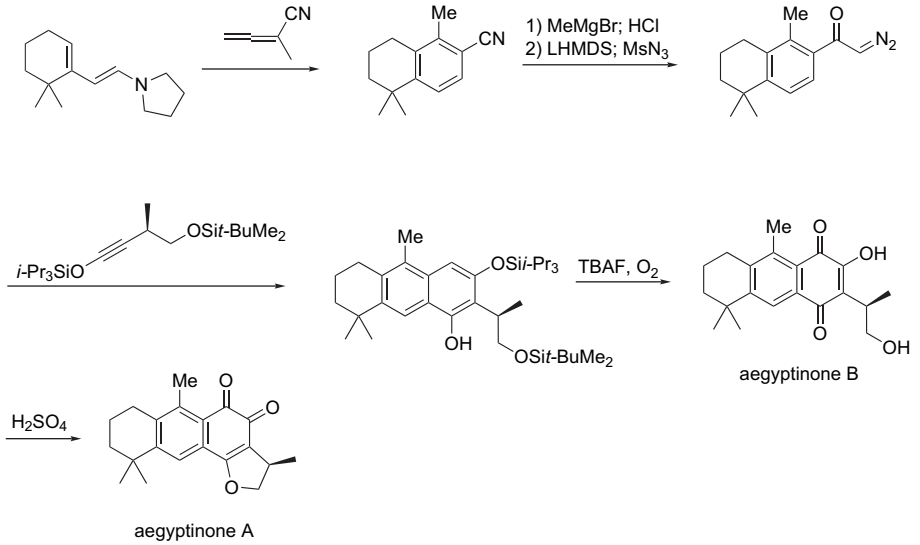
Scheme 57. Olefination of aldimines catalyzed by lanthanide triflates.



Scheme 62. Synthesis of Dan Shen diterpenoids.

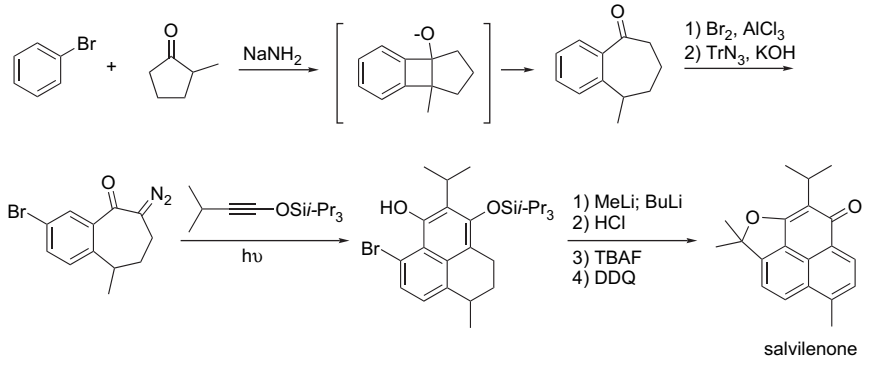


Scheme 63. Synthesis of maesanin.

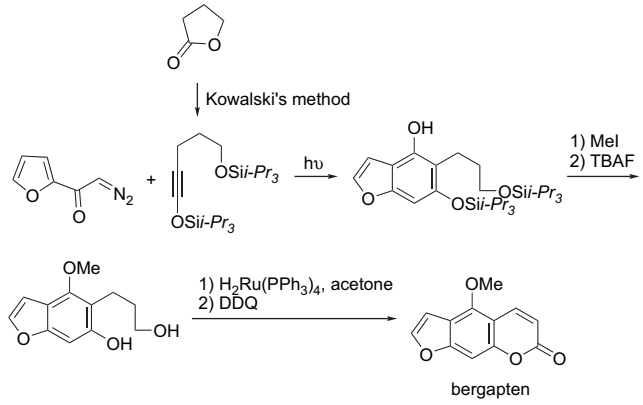


Scheme 64. Synthesis of aegyptinones.

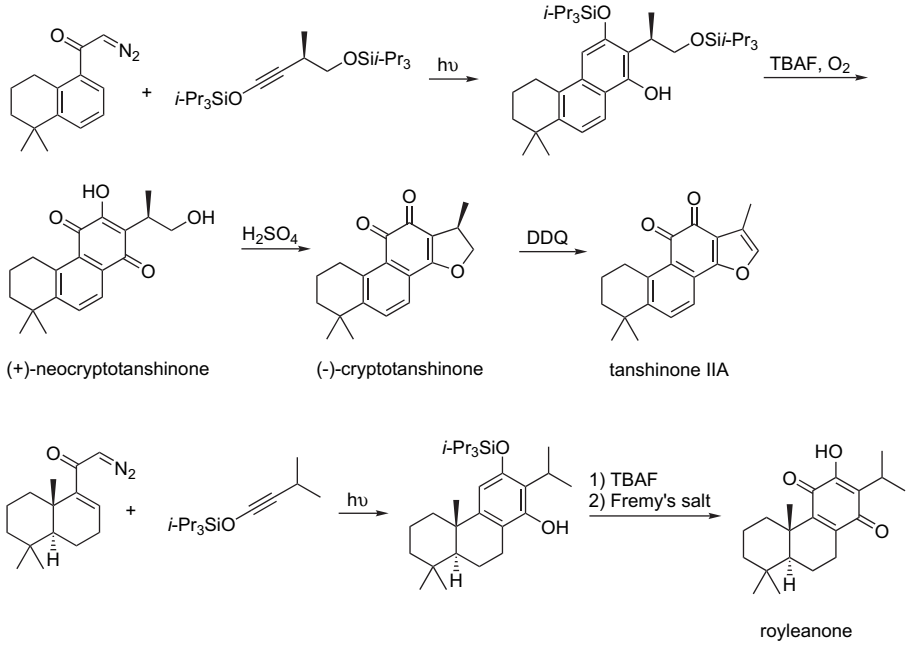
Using this methodology, Kowalski synthesized Δ^6-tetrahydrocannabinol (**199**) in short steps starting from the ester **198** (Scheme 61). Danheiser prepared the unstable vinylketenes via a photochemical Wolff rearrangement in situ, and synthesized Dan Shen diterpenoids (Scheme 62),[82] maesanin (Scheme 63),[83] aegyptinones (Scheme 64),[84] salvilenone (Scheme 65),[74] bergapten (Scheme 66),[85] (+)-neocryptotanshinone, (−)-cryptotanshinone, tanshinone



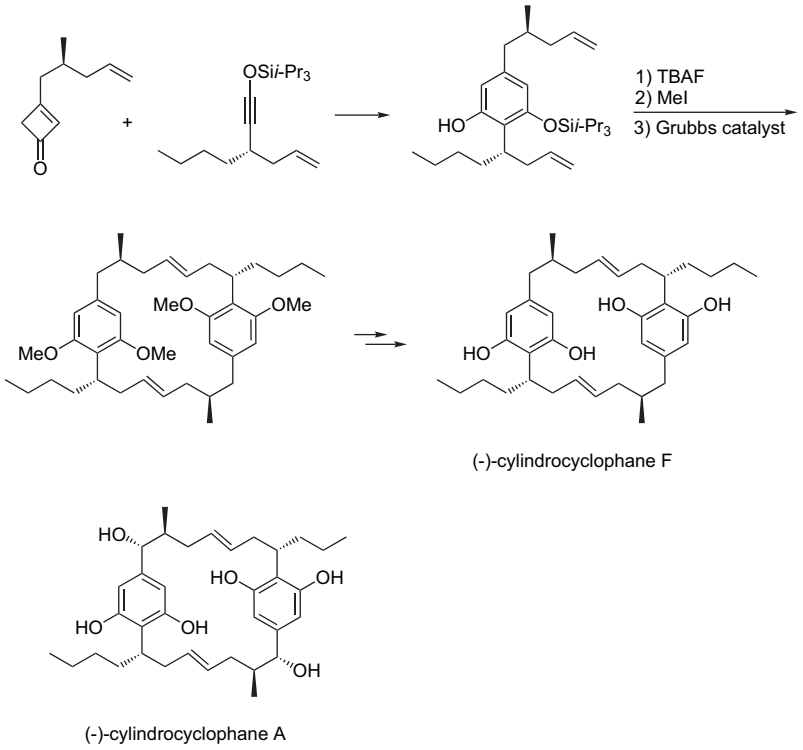
Scheme 65. Synthesis of salvilenone.



Scheme 66. Synthesis of bergapten.



Scheme 67. Synthesis of angularly-fused diterpenoid quinones.



Scheme 68. Synthesis of cylindrocyclophanes.

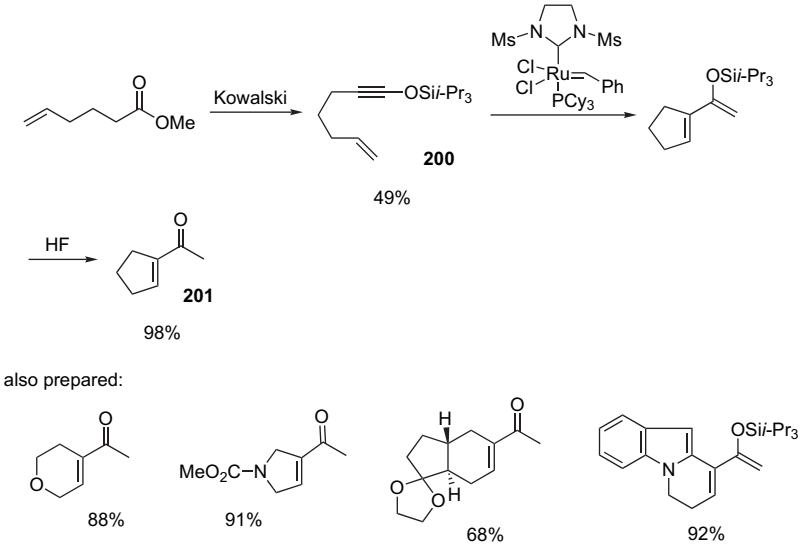
IIA, and royleanone (Scheme 67).[86] Smith synthesized cylindrocyclophanes A and F (Scheme 68).[87]

4.5. Eneyne metathesis

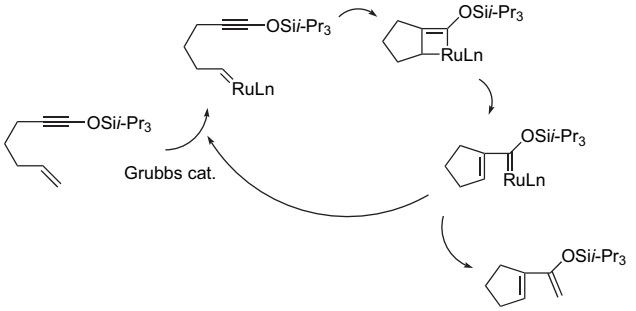
Enyne metathesis is a useful method for the synthesis of 1,3-dienes.[88] Kozmin introduced a siloxy alkyne (silyl ynol ether) as an electron-rich alkyne unit in the substrate **200** and has developed the intramolecular Ru-catalyzed metathesis providing functionalized enones such as **201** (Scheme 69).[89] The mechanism proposed is shown in Scheme 70. The competitive experiments indicated that the terminal alkene is much more reactive than the siloxy alkyne. This methodology was extended to the total synthesis of eremophilanes (Scheme 71).[90]

4.6. Acid-mediated cyclization

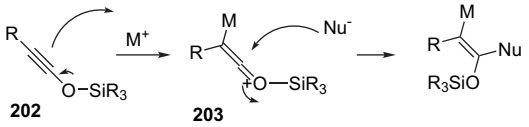
If the silyl ynol ethers **202** are treated with cationic species, such as Lewis acids or Brønsted acids, β-nucleophilic α-electrophilic ketenium ions **203** are expected to be generated (Scheme 72). While ketenes have been widely exploited in organic synthesis, these species have been rarely implicated as reactive intermediates. Kozmin has developed



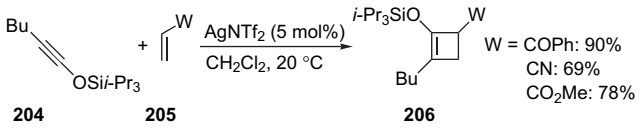
Scheme 69. Enyne metathesis.



Scheme 70. Proposed mechanism of enyne metathesis.



Scheme 72. Ketenium ions from silyl ynol ethers.

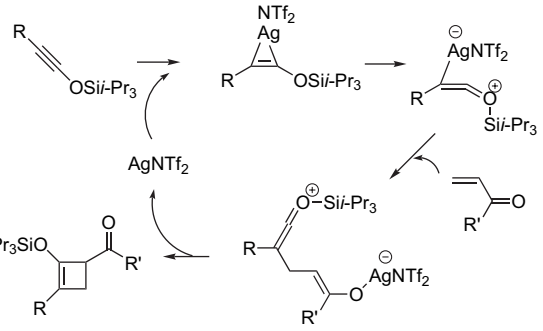


Scheme 73. Silver-catalyzed [2+2] cycloadditions of siloxy alkynes.

several kinds of novel cyclizations with the ketenium ions derived from silyl ynol ethers.

Alkyne [2+2] cycloaddition with alkenes opens up a versatile synthesis of cyclobutenes, and the combination of electron-rich alkynes and electron-deficient alkenes would have a high potential for this purpose. The electron-rich alkynes, such as ynamines,[91] alkynyl sulfides,[92] and alkyneselenolates,[93] have been reported in this type of cycloaddition. Kozmin has developed the $AgNTf_2$-catalyzed [2+2] cycloadditions of silyl ynol ethers **204** with electron-deficient alkenes **205**, such as α,β-unsaturated ketones, esters, and nitriles, providing the siloxycyclobutenes **206** (Scheme 73).[75] Since the various experimental and spectroscopic results suggest a stepwise mechanism, this mechanism has been proposed, as shown in Scheme 74. The catalytic role of the $AgNTf_2$ is most likely to be due to complexation and activation of the siloxy alkyne, and not due to activation of the enone via a lowering of its LUMO energy level.

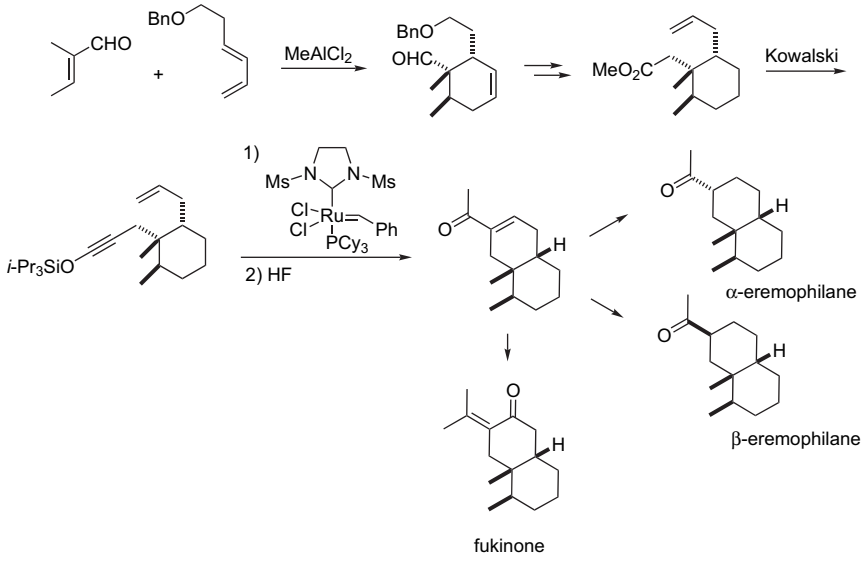
The ketenium cation can be intramolecularly trapped by alkenes. Kozmin has found Brønsted acid-catalyzed cyclization of silyl ynol ethers such as **207** bearing arenes to afford the silyl enol ethers, e.g., **208**, of tetralone derivatives in good yields (Scheme 75).[19] Among the acids, $HNTf_2$ is the



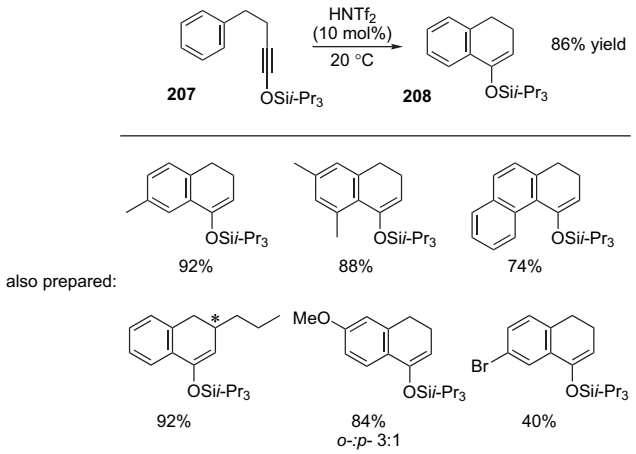
Scheme 74. Proposed mechanism of [2+2] cycloaddition.

most effective catalyst in the cyclization. It is noteworthy that inactivated aromatic substrates can efficiently provide the desired products, while the metal-mediated carbocyclizations of alkynes generally require electron-rich arenes and alkenes.[94]

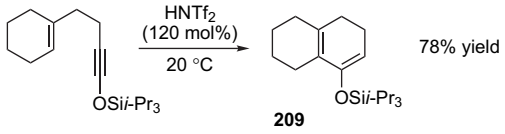
In the enyne cyclization, although a stoichiometric amount of the acid is required, the cyclized product **209** is obtained in good yields, after hydrolysis (Scheme 76).



Scheme 71. Synthesis of eremophilanes.



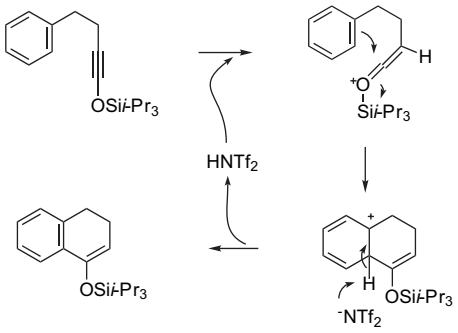
Scheme 75. Brønsted acid-catalyzed cyclization of silyl ynol ethers with arenes.



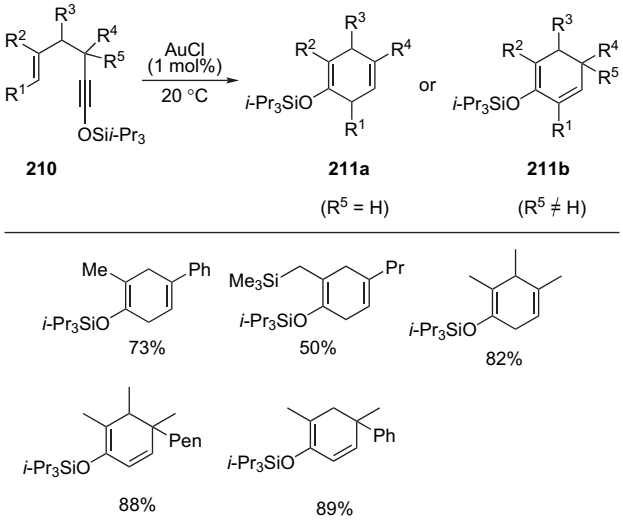
Scheme 76. Brønsted acid-promoted cyclization of enynes.

The reaction mechanism is proposed as depicted in Scheme 77. Since the chiral non-racemic substrate furnished the corresponding product **208** without the loss of optical purity, a mechanism involving a [3,3]-sigmatropic rearrangement, followed by 6π-electrocyclic ring closure, is ruled out.

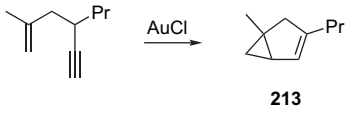
In place of a Brønsted acid, Au(I) induces cycloisomerization of **210** along with skeletal reorganization giving cyclohexadienes **211a** or **b** (Scheme 78).[95] The reaction mechanism is proposed as shown in Scheme 79. Since the standard Au-catalyzed cycloisomerization of enyne compounds provides cyclopropane **213** (Scheme 80),[96] the siloxy alkyne moiety would stabilize the cationic intermediate **212** (Scheme 79).



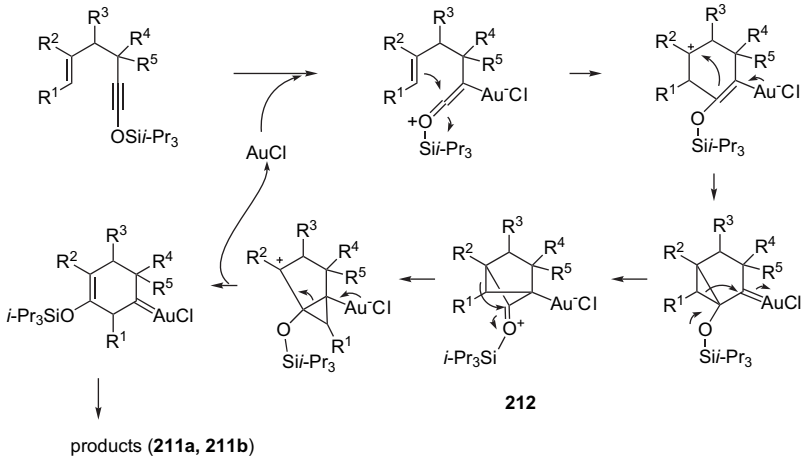
Scheme 77. Proposed mechanism of cyclization.



Scheme 78. Gold-catalyzed cycloisomerization.



Scheme 80. Gold-catalyzed cycloisomerization.



Scheme 79. Proposed mechanism of cycloisomerization.

5. Concluding remarks

Synthetic uses of ynolates have been reviewed. In recent publications, for the direct generation of ynolate anions, Shindo's dibromo ester method has been used, and for the preparation of silyl ynol ethers, Kowalski's homologative method and Julia's oxidative procedure have been used. Numerous advances in ynolate chemistry have improved the synthetic utility of these species. Ynolate anions initiate a negative–positive switching cascade process, torquoselective olefination, and heterocyclization, and silyl ynol ethers act as functional electron-rich triple bond and ketenium precursors. In the near future, ynolates should play an important role in synthetic organic chemistry.

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Biographical sketch

Mitsuru Shindo was born in Tokyo (Japan) in 1963. He received his Ph.D degree on asymmetric synthesis at the University of Tokyo under the supervision of Professors K. Koga and K. Tomioka. From 1990 until 1996, he was an assistant professor in the laboratory of Professor K. Koga. He spent time in Professor R. A. Holton's group (Florida State University, USA) as a postdoctoral fellow from 1992 until 1994. In 1996, he moved to the University of Tokushima as an associate professor working with Professor K. Shishido. In 2005, he joined Kyushu University as an associate professor. He received the PSJ Award for Young Scientists and Eisai Award in Synthetic Organic Chemistry, Japan. His scientific interests focus on the development of new methodologies for synthetic reactions, the total synthesis of biologically important natural products, and the design and synthesis of bioactive organic molecules.