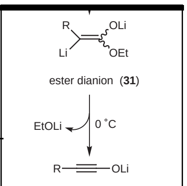
Ynolate anions



CHEMICAL SOCIETY REVIEWS

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Ynolates are carbanions having a triple bond in place of the double bond in enolate anions. For the past 20 years, several methods for the generation of ynolates have been developed. Ynolates are ketene anion equivalents, thus ynolates introduce a ketene unit into substrates and the resulting products possess high reactivity. This allows ynolates to undergo unique reaction sequences. This review provides an overview of the syntheses and the reactions of ynolates including recent progress in the area.

1 Introduction

Carbanions are fundamental reactive species that are widely used for carbon–carbon and carbon–heteroatom bond formation in synthetic organic chemistry. Carbanions stabilized by the conjugation of π-electrons on a double bond, such as enolate anions, imine anions (metaloenamins), hydrazone anions, oxime anions *etc.* are especially well known and their chemistry has been thoroughly studied and established. However, carbanions stabilized by a triple bond have not been well studied. Ynolate anions have a triple bond in place of the double bond in enolate anions. The latter are one of the most important carbanions in synthetic organic chemistry. In contrast to enolate anions, ynolate anions have attracted much less attention and only a few reports are scattered in even comprehensive reviews, this has been due to a lack of general and convenient methods for their synthesis. Their chemistry should be no less interesting than that of enolates, because they are not only carbanions forming a carbon–carbon bond, but also ketene anion equivalents acting as a ketene precursor (Fig. 1). Recently, several groups, including our group, have reported on ynolate chemistry concerning their generation and their reactivity. An indication of the great advances in ynolate chemistry is recognized.

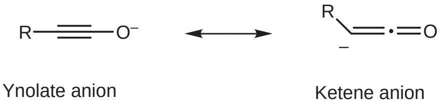

Fig. 1

This recent progress in ynolate chemistry has prompted us to compile a review on this topic. This review will describe methods for the preparation of ynolates, their reactions and their synthetic utility.

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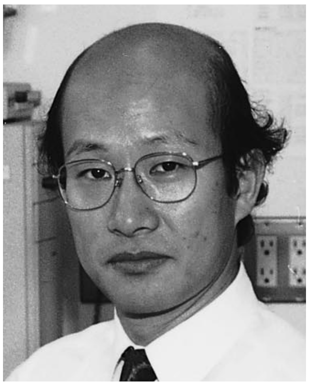
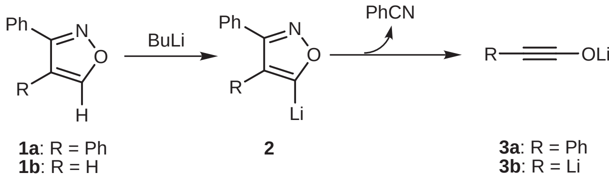


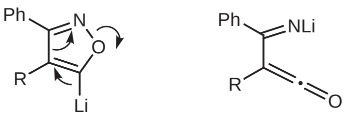
2 Synthesis of ynolates

2.1 Fragmentation of 3,4-diphenyl-5-isoxazolyllithium

In 1975, Schöllkopf and Hoppe reported the first synthesis of ynolates.[1] 3,4-Diphenylisoxazole **1a** was lithiated by BuLi and the resulting 5-lithio-3,4-diphenylisoxazole **2a** spontaneously fragmented into ynolate **3a** and benzonitrile (Scheme 1). They also reported the preparation of an ynolate dianion (dilithio ketene) from 3-phenylisoxazole **1b** by the same protocol.[2] It is not clear whether the fragmentation mechanism is a concerted [2π + 4π] (Fig. 2, **4**) or a stepwise one through α-lithioiminobenzylphenylketene (Fig. 2, **5**). The procedure is simple and the side product would theoretically only be benzonitrile. The yield is up to 79% (as a β-lactone, prepared by the reaction with benzaldehyde, see Section 3.1). However, it is limited to the preparation of aromatic or unsubstituted ynolates.



Scheme 1

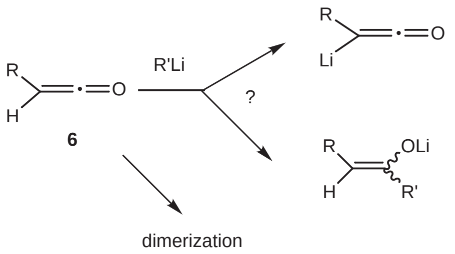


4 **5**

Fig. 2

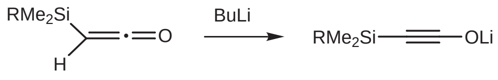
2.2 Lithiation of silylketenes

Ynolates are ketene anion equivalents. Therefore deprotonation of mono-substituted ketenes **6** is expected to afford ketene anions, that is, ynolate anions. However, the synthesis of ynolates by deprotonation of ketene itself or alkylketenes has never been reported to the best of our knowledge. This is probably due to the instability of these ketenes, the low acidity of the vinylic proton, and the strong electrophilicity of the carbonyl carbon (Scheme 2). In contrast to alkylketenes,



Scheme 2

silylketenes are stable and easy to handle, moreover, the acidity of their vinylic proton would be higher than that of alkylketenes. Rathke reported that trimethylsilylketene **7a** when treated with BuLi at −100 °C afforded β-silyl ynolates **8** in good yield (as disilylketenes prepared by the reaction with trialkylsilylchlorides) (Scheme 3).[3] *tert*-Butyldimethylsilylketene **7b** can also be employed.[4] The reaction conditions seem to be critical since when other bases are used, or BuLi is added at −78 °C, the yield of the corresponding disilylketenes decreases to less than 30%.



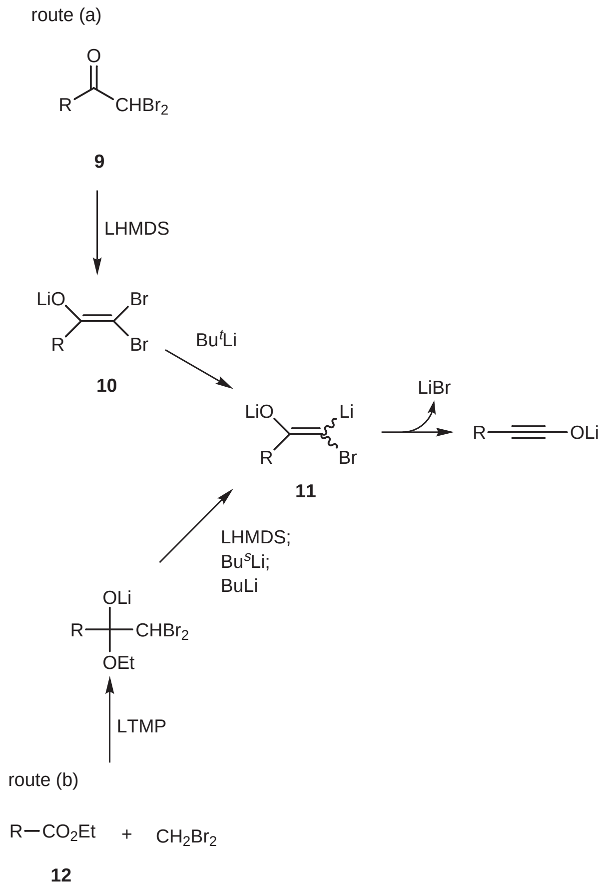
7a: R = Me
7b: R = Bu^t

8

Scheme 3

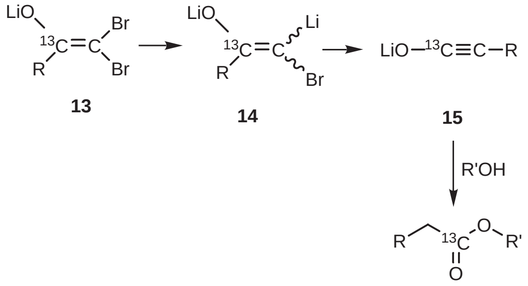
2.3 Rearrangement of α-keto dianions

Kowalski reported synthesis of ynolates *via* rearrangement of α-keto dianions (carbenoids).[5] While simple α-halo enolate monoanions such as **10** are stable, α-keto α-dianions **11**, prepared by lithium–halogen exchange of **10** with Bu^tLi [route (a), Scheme 4] or by addition of dibromomethyllithium to esters **12** [route (b)] followed by base induced elimination (see Section 3.3), rapidly rearrange with loss of lithium bromide to afford ynolates. An experiment using ^{13}C-labeled dibromo ketone enolate **13** indicates that the alkyl group of dianion **14**, not the oxygen, migrates to afford ynolate anion **15** (Scheme 5).



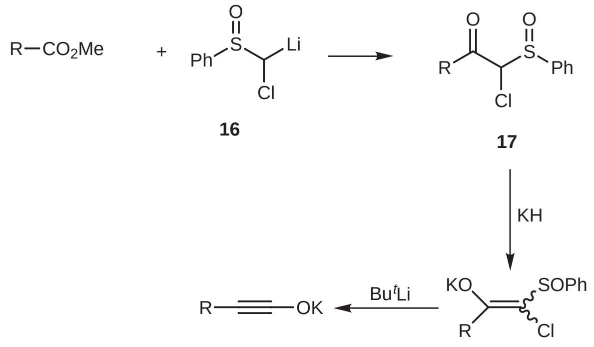
Scheme 4

Therefore, from a mechanistic viewpoint, this rearrangement can be regarded as a carbon analogue of the Hofmann rearrangement. Although the rearrangement is a high-yielding process, an excess amount of strong base is needed to prepare the precursor dianions **11**, especially in route (b). When the ynolate prepared by this rearrangement method is used as a nucleophile, the electrophiles added for the ynolate to react with would have to be inert towards such bases.



Scheme 5

Satoh *et al.* reported that α-chloro-α-sulfinyl ketone **17**, prepared by the reaction of an ester and **16**, can be applied in place of dibromoketone **9** (Scheme 6).[6] Sequential treatment of **17** with KH and Bu^tLi affords ynolates *via* a similar rearrangement.

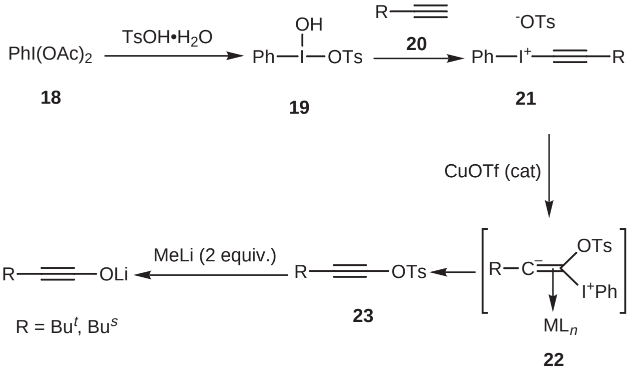


Scheme 6

2.4 From ynol tosylates with MeLi

Enol acetates and silyl enol ethers can be cleaved with MeLi to afford enolates. If this method is applied to the synthesis of ynolates, ynol acetates or silyl ynol ether could be prepared efficiently. Stang[7] and Kowalski[8] independently reported the syntheses of *tert*-butyldimethylsilyl ynol ether and triisopropylsilyl ynol ether (see Section 3.6). Kowalski also reported an efficient generation of lithium ynolates from these silyl ynol ethers with methyllithium. However, as silyl ynol ethers are prepared from ynolates, it remains an unsettled question how to synthesize the desired ynolates. No efficient method for the preparation of silyl ynol ethers or ynol acetates without using ynolates has been reported so far.

Stang found that ynol tosylates can be converted to ynolate anions by methyllithium (Scheme 7).[7] It is worth noting that the ynol tosylates are synthesized by a unique method which does not involve the generation of ynolate anions:[9] commercial

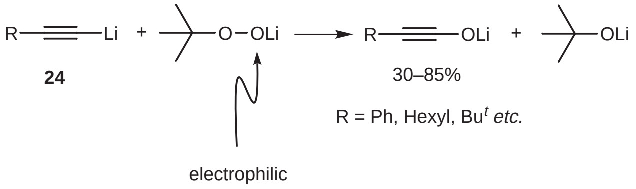


Scheme 7

iodosobenzene diacetate **18** is treated with toluene-*p*-sulfonic acid monohydrate to afford phenylhydroxy(tosyloxy)iodine **19**. This hypervalent organoiodine reacts with terminal alkynes **20** to give iodonium tosylates **21** in 20–60% yields. These tosylates are then treated with 10 mol% CuOTf or AgOTf to afford ynol tosylates **23** in 50–60% yields.[10] A metal assisted nucleophilic acetyleic displacement *via* an addition-elimination process is suggested as the mechanism for this ligand–ligand coupling process. Most of the pure ynol tosylates seem to be stable. As terminal alkynes **20** are the starting molecules, this method can be regarded as overall oxidation of an alkyne.

2.5 Oxidation of acetylides

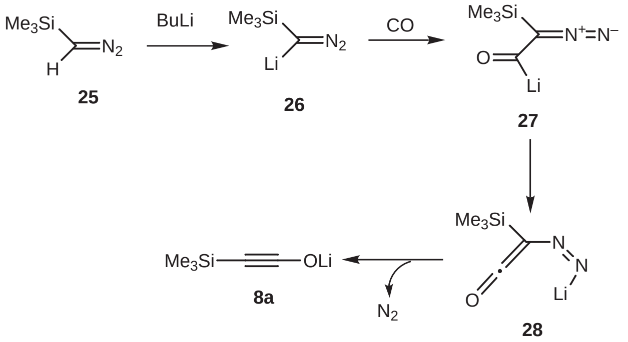
A synthesis of ynolates *via* direct oxidation of a terminal C–H bond on a terminal alkyne has been studied. Since acetylides are easily prepared from terminal alkynes, they are expected to afford ynolate anions *via* reaction with electrophilic oxygen donors. Julia reported that lithium acetylides **24** react with lithium *tert*-butyl peroxide to give the corresponding ynolates in up to 85% yield (isolated as ethyl esters) (Scheme 8).[11] The acetylides do not react with molecular oxygen, as would be expected for a radical process. With trimethylsilyl peroxides, they do not attack oxygen but instead attack silicon. In contrast to these oxygen donors, lithium peroxides having α-heterosubstituted oxyanions *i.e.* oxenoids have electrophilic character, despite the fact that lithium alkoxides are not good leaving groups. This type of oxidation is considered to proceed by an ionic process, not by a radical one.[12]



Scheme 8

2.6 Silyl ynolates from α-diazoacyllithiums

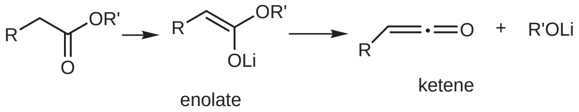
Murai developed the alternative method for the preparation of silyl ynolates in the course of his research on acyllithiums (Scheme 9).[13] A lithiated silyldiazomethane **26**, prepared from commercially available trimethylsilyldiazomethane **25** and BuLi, is exposed to an atmospheric pressure of carbon monoxide at −78 °C to afford trimethylsilyl ynolate in good yield. The mechanism is elucidated by the following scheme: the lithiated silyldiazomethane reacts with carbon monoxides to give a labile acyllithium **27**, which is rapidly converted to a ketene intermediate **28**. This extrudes dinitrogen to provide the desired silyl ynolate. This procedure provides an efficient and operationally simple access to trimethylsilyl ynolates.



Scheme 9

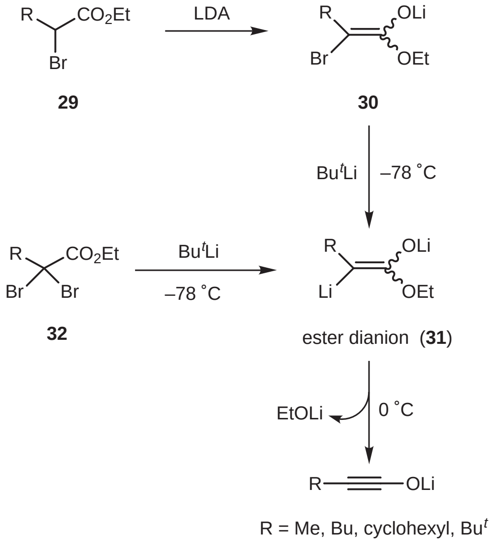
2.7 Cleavage of ester dianions

As described repeatedly, ynolates are equivalent to ketene anions and thus lithium ynolates could be formed *via* lithiation of ketenes at the vinylic position. However, direct lithiation of ketenes is troublesome. Lithiation of the precursors of ketenes, followed by transformation into lithiated ketenes, would be a better route to ynolates. On the basis of this concept, our group has developed the efficient and convenient method for ynolate synthesis.[14] Ester enolates are regarded as a precursor of ketenes because they are known to be converted into ketenes and alkoxides *via* thermally induced cleavage (Scheme 10).[15]



Scheme 10

α-Bromocarboxylic acid esters **29** are converted by LDA into α-bromoenolates **30**, which are treated with *tert*-butyllithium to give the novel ester dianions **31** *via* lithium–halogen exchange at −78 °C. The dianions **31** are thermally cleaved at 0 °C into ynolates in good yields (~90%) (Scheme 11). Based on the same concept, α,α-dibromocarboxylic acid esters **32**, prepared by α-bromocarboxylic acid esters and LDA with dibromotetrafluoroethane, also afford ynolates in a simple fashion.[16] The α,α-dibromocarboxylic acid esters are treated with *tert*-butyllithium at −78 °C, and then the reaction mixture is warmed to 0 °C to give ynolates in good yields. These extremely simple procedures give primary, secondary, and tertiary-alkyl substituted ynolates. It is noteworthy that the latter procedure gives lithium amide (and amine) free ynolates. The starting esters are stable and easily available. From these results, it is clear that this method is one of the most facile methods available and has high generality.

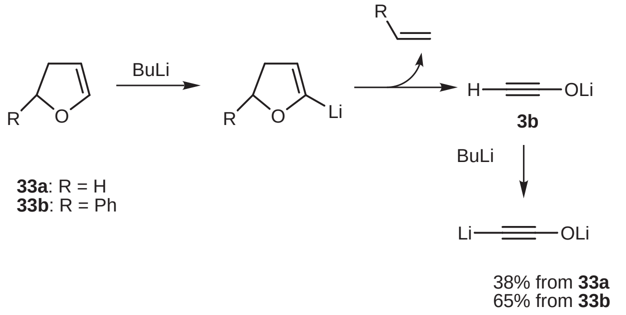


Scheme 11

2.8 Ynolate dianions

Unsubstituted ynolate anions have a terminal alkyne, which is expected to deprotonate to give ynolate dianions. This is a ketene dianion equivalent, therefore it should have great synthetic utility. As described in Section 2.1, an ynolate dianion has been prepared from 3-phenylisoxazole (Schöllkopf's method).

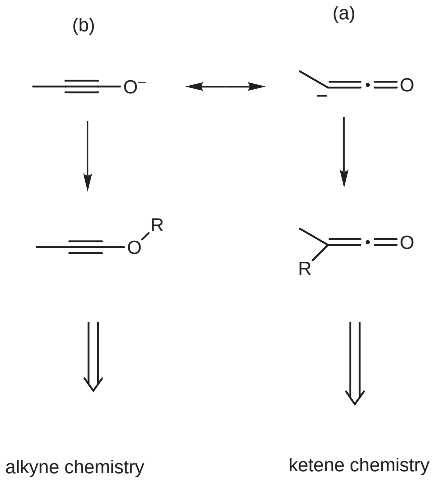
Another approach to an ynolate dianion was reported by Barton.[17] Sequential lithiation of 2,3-dihydrofurans **33** with 2 equiv. of BuLi affords an ynolate dianion in up to 65% yield [isolated as bis(trimethylsilylketene) by quenching with chlorotrimethylsilane] (Scheme 12). In this process, elimination from a dilithiated dihydrofuran cannot be ruled out. Application of ynolate dianions to organic synthesis has never been reported.



Scheme 12

3 Reactions of ynolates

Ynolate anions are regarded as ketene anions, 'ketenylation' reagents, or masked ketenes. Ketenes have been used as important and highly reactive species in organic chemistry. However they are generally not easy to handle due to their instability so that they have usually been synthesized and utilized *in situ.* Ynolate anions give ketenes which are difficult to generate in simpler ways if they react with electrophiles at the β-position (Scheme 13a). Additionally ynolates are also considered as ynol ether (or ester) precursors, when reactions occur at oxygen (Scheme 13b). Ynol ethers are also important reactive species. Thus, ynolates should have great potential in organic chemistry. In this section, a variety of reactions of ynolates studied so far are summarized.

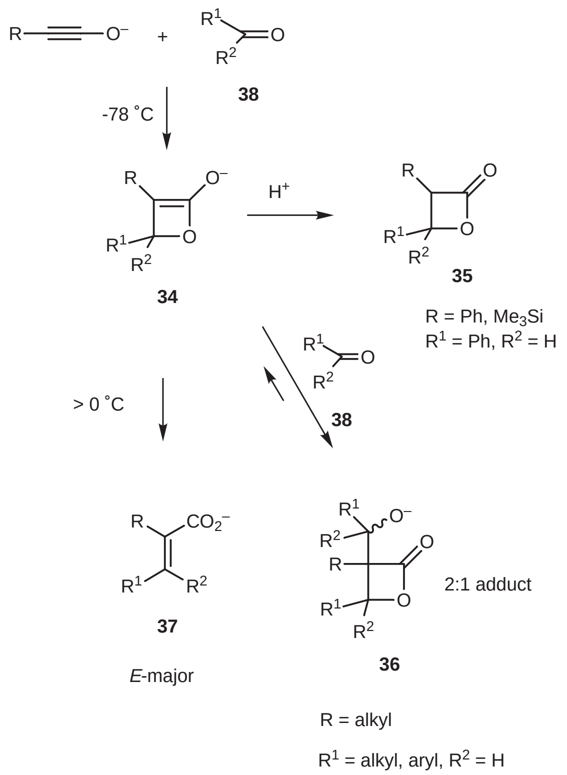


Scheme 13

3.1 Reactions with aldehydes and ketones: synthesis of β-lactone enolates

Ynolates react with aldehydes and ketones **38** to afford β-lactone enolates **34** (Scheme 14). It is not clear whether it is a stepwise mechanism (**A**) or a concerted mechanism (**B**) (Fig. 3). Ynolates bearing a phenyl[1] or silyl substituent[4] give β-lactones after protonation. However, ynolates bearing an alkyl (primary, secondary or tertiary) substituent react with aldehydes to afford 2 : 1 adducts **36** in good to moderate yields[14,16] since the corresponding β-lactone enolates are more reactive than the ynolates themselves.

The β-lactone enolates (**34**: R = Ph, Me_3Si) are stable at low temperature, but above 0 °C they are converted into α,β-unsaturated carboxylates **37** in good to excellent *E*-selectivity. The mechanism is considered to be an electrocyclic thermal ring-opening. The 2 : 1 adduct **36** also gives unsaturated carboxylates at room temperature. These results suggest that the 2 : 1 adducts **36**, which do not seem to be useful by themselves, are converted into β-lactone enolates **34** *via* a retro-aldol reaction. Using our synthetic method for the generation of ynolates (Section 2.7), we have established an efficient method for the highly *E*-selective one-pot synthesis of α,β-unsaturated carboxylic acids **39** starting from α-bromoesters (Scheme 15).[18] This method would be a useful alternative to the classical Horner–Wadsworth–Emmons reaction.



Scheme 14

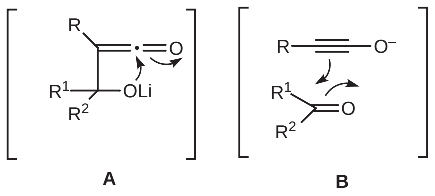
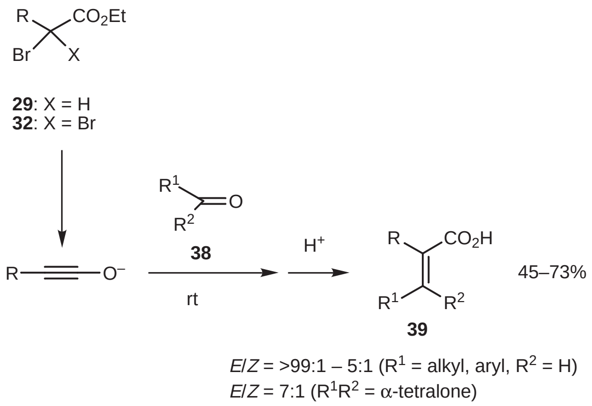


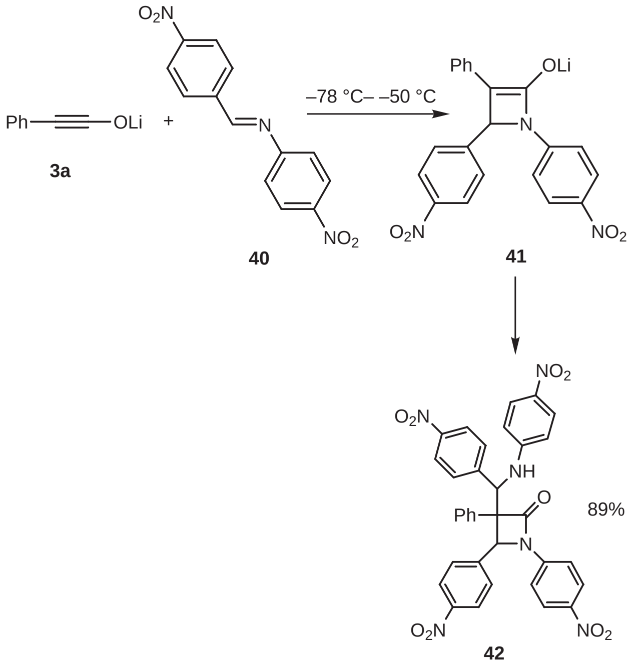
Fig. 3



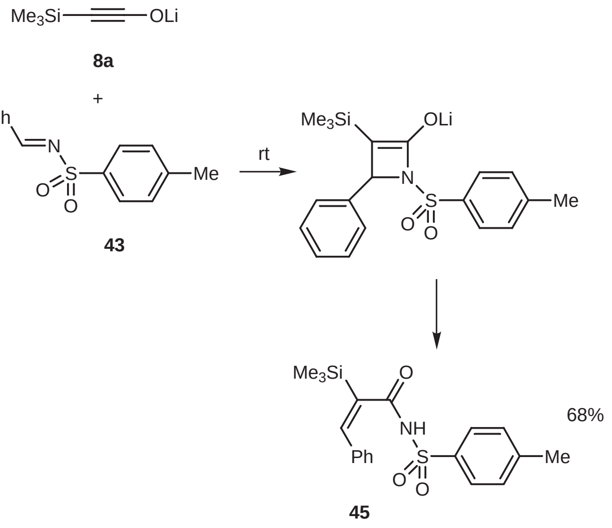
Scheme 15

3.2 Reactions with imines

Ynolate anions are expected to react with imines to give β-lactams. Phenyl ynolate **3a** reacts with imines bearing electron withdrawing groups (*e.g.* **40**) to afford the 2 : 1 adducts **42** in good yields (Scheme 16).[19] The β-lactam enolates **41** are more nucleophilic than the 'stabilized' ynolate. Silyl ynolate **8a** reacts with an imine **43** bearing a toluene-*p*-sulfonyl group at



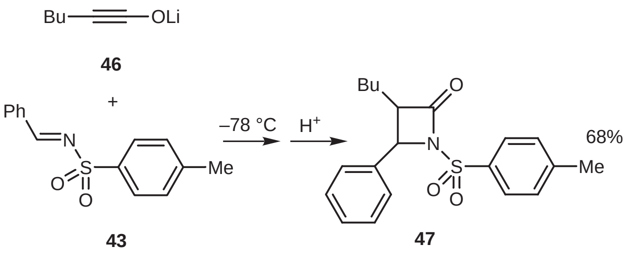
Scheme 16



Scheme 17

room temperature to give (*E*)-α,β-unsaturated amide **45** (Scheme 17). However, these stabilized ynolates do not afford β-lactams efficiently.

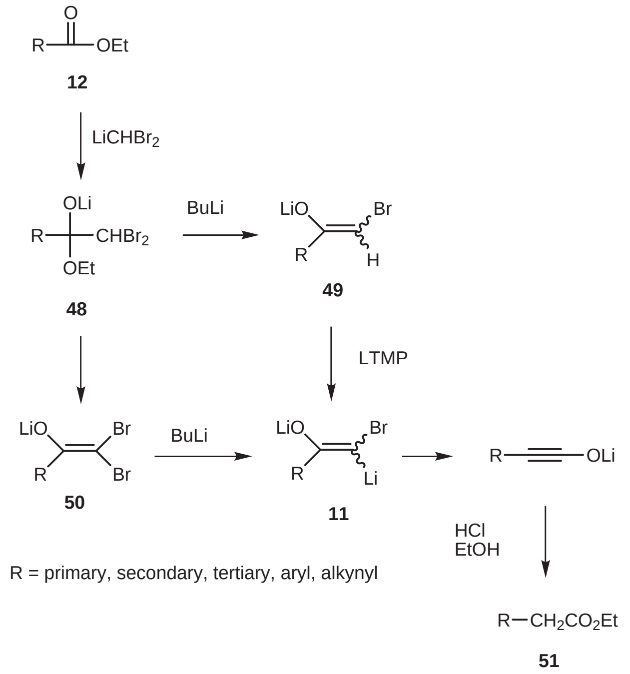
Recently we have found that an alkyl ynolate **46** reacts with a tosyl imine to give a 3,4-disubstituted β-lactam **47** efficiently (Scheme 18).[20] These results indicate that the fine tuning of the nucleophilicity of ynolates and the electrophilicity of imines is critical for the synthesis of β-lactams.



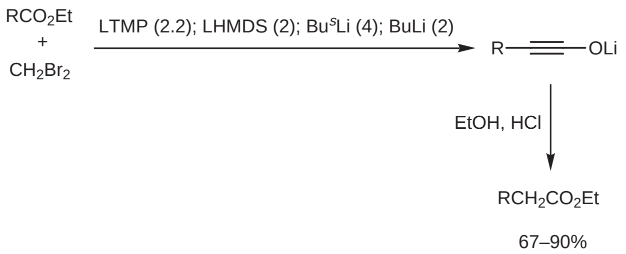
Scheme 18

3.3 Ester homologation

Ynolates are quenched with alcohols to give the corresponding esters. Kowalski extended this reaction to an ester homologation.[21] Esters are treated with dibromomethyllithium, prepared from dibromomethane with LTMP, to give tetrahedral intermediates **48**. These are then converted into α-keto dianions **11** *via* two routes as shown in Scheme 19. As described in Section 2.3, the dianions rearrange to afford ynolates, which are treated with acidic ethanol to give homologated esters **51** in 50–75% yields. By detailed analysis of by-products, the reaction conditions have been optimized as shown in Scheme 20.[22] The yields were improved in 67–90%, although an excess amount of strong bases is still needed in the reaction vessel. This procedure provides an alternative to the Arndt–Eistert reaction.



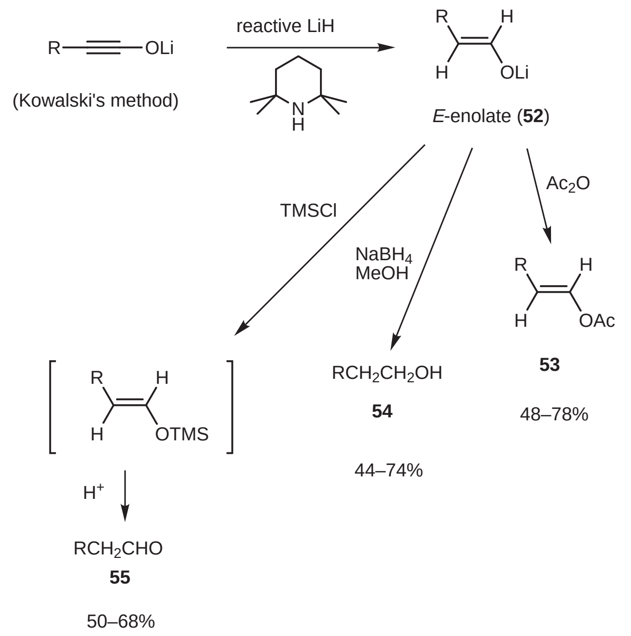
Scheme 19



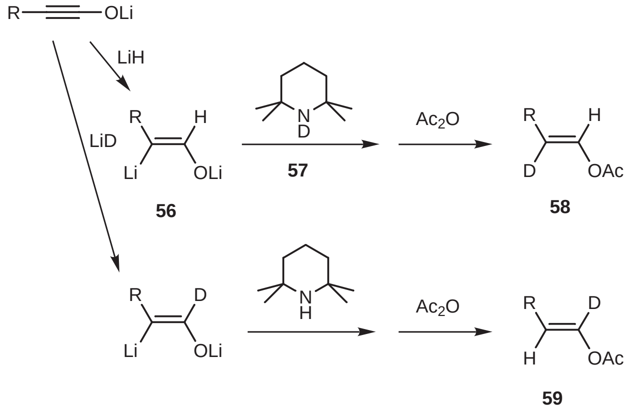
Scheme 20

3.4 Reduction of ynolates

Kowalski found that the triple bond of ynolates is reduced by reactive LiH suspended in THF on refluxing under N_2 to afford the *E*-enolates **52** of aldehydes which should be important carbanions, but can not be otherwise obtained easily (Scheme 21).[23] This LiH is formed *in situ* from cyclohexa-1,3-diene with LTMP or from cyclohexa-1,4-diene with BuLi.[24] On exposure to air, this LiH loses the ability to reduce ynolate anions. Commercial LiH would also be ineffective due to oxidation of the surface. For mechanistic considerations, the following experiments were carried out. In the presence of N-deuterated TMP **57**, the β-position of the product **58** had 50% incorporation of deuterium, and using LiD, α-deuterated product **59** was generated (Scheme 22). These experiments suggest that the hydride adds to the α-position of ynolates to give the dianion **56**,



Scheme 21



Scheme 22

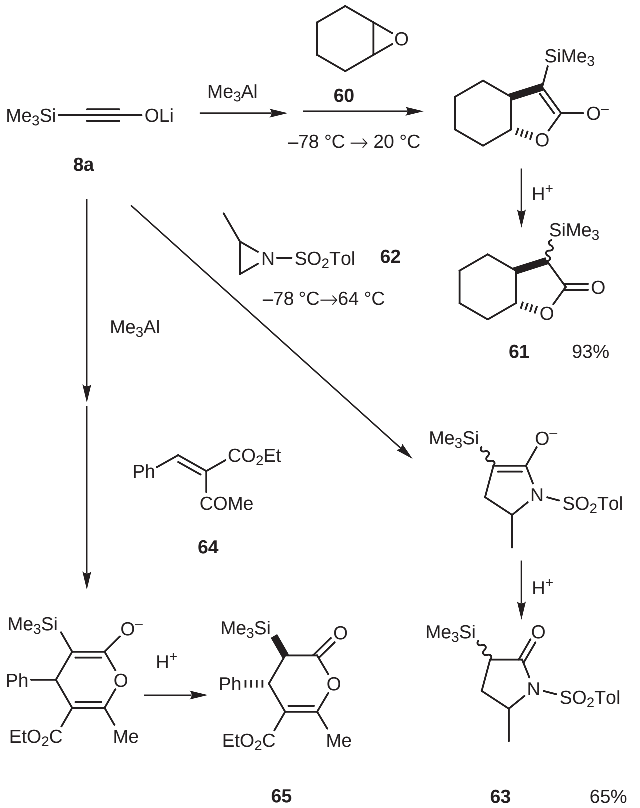
which is C-protonated by TMP in the reaction with retention of configuration. It is noteworthy that, while the reduction of simple triple bonds under this condition was not observed, the electron-rich ynolate anions are reduced completely.

The *E*-enolates are converted to *E*-enol acetates **53** by acetic anhydride in 48–77% yields from the starting esters. It also is applicable to the synthesis of 1,3-dienes which should be important for Diels–Alder chemistry.[25] This reductive homologation process can be applied to the synthesis of alcohols **54** *via* reduction and aldehydes **55** *via* protonation as shown in Scheme 21.

3.5 Miscellaneous reactions

Murai reported the reactions of silyl ynolates with several carbon electrophiles (Scheme 23). Lithium silyl ynolate **8a** reacts with oxirane **60** to afford γ-lactone **61** in the presence of Me$_3$Al, although it did not without the Lewis acid. Me$_3$Al might form an ate complex with lithium ynolate. The reaction of lithium silyl ynolate with aziridine **62** activated by a toluene-*p*-sulfonyl group affords γ-lactam **63** without Me$_3$Al. These reactions involve nucleophilic ring opening and recyclization by the resulting anions and ketenes. Like β-lactam and β-lactone formation, they are kinds of tandem reactions.

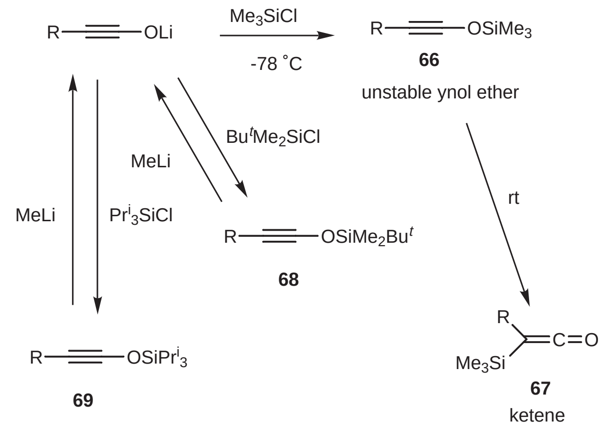
Among α,β-unsaturated carbonyl compounds as electrophiles, acrylates and enones are inactive towards ynolates, but a doubly activated olefin, benzylideneacetoacetate **64**, affords δ-lactone **65** *via* a Michael-type reaction with the ynolate.



Scheme 23

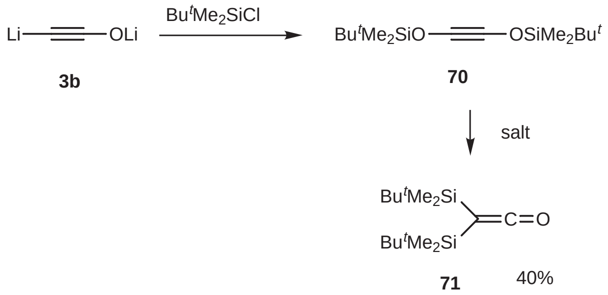
3.6 Silyl ynol ethers

Like enolates, ynolates are expected to form silyl ynol ethers *via* *O*-silylation (Scheme 24). Ynolates are treated with chlorotrimethylsilane at −78 °C to form a mixture of silyl ynol ethers **66** and silyl ketenes **67**.[8] Since this mixture is converted into the silyl ketene **67**, it is suggested that silylation by chlorotrimethylsilane occurs kinetically on oxygen to afford silyl ynol ether **66** and upon warming the mixture, isomerization to the more stable ketene **67** occurs. However, with either chlorotriisopropylsilane and chloro-*tert*-butyldimethylsilane, the silylation occurs on oxygen and the resulting silyl ynol ethers are thermally stable and isolable.[7,8,26] Ynolate dianion **3b**, prepared by Barton's method (Section 2.8), was treated with chloro-*tert*-butyldimethylsilane to afford firstly disilyl ynol ether **70** which was then isomerized into disilyl ketene **71** in the reaction mixture (Scheme 25).[17] Interestingly, under salt free conditions, that is after isolation of the disilyl ynol ether, the ynol ether **70**



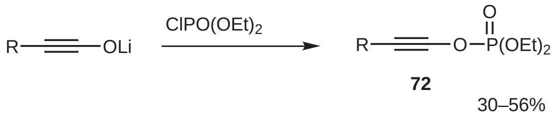
Scheme 24

was not isomerized. This result suggests that the ketene products arise from a salt-promoted isomerization rather than from a purely thermal rearrangement.



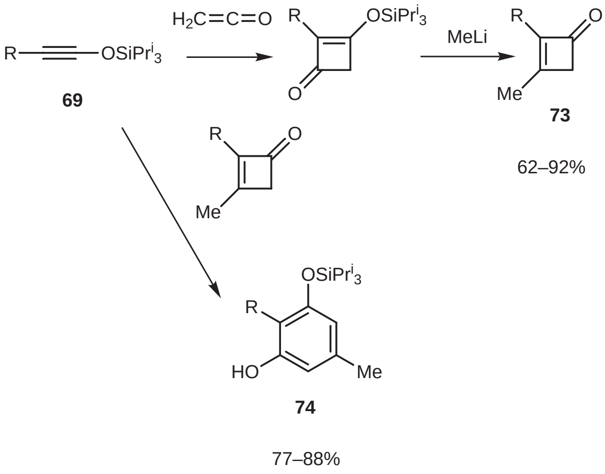
Scheme 25

The reaction of lithium ynolates with diethyl chlorophosphate gives phosphate esters **72** in moderate yields (Scheme 26), whereas the reaction with benzoyl chloride affords both products of O- and C-acylation.[27]



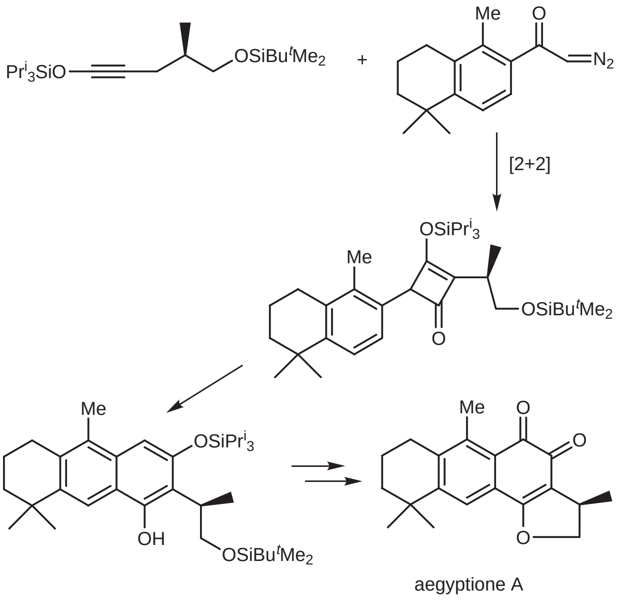
Scheme 26

Silyl ynol ethers are treated with MeLi to give ynolates efficiently (Scheme 24). Silyl ynol ethers are also useful substituents for alkoxy acetylenes in [2 + 2] cycloaddition reactions with ketenes and vinylketenes affording cyclobutenones **73** and resorcinol derivatives **74**, respectively (Scheme 27).[28] These reactions have been applied to the total syntheses of natural products (Scheme 28).[29]

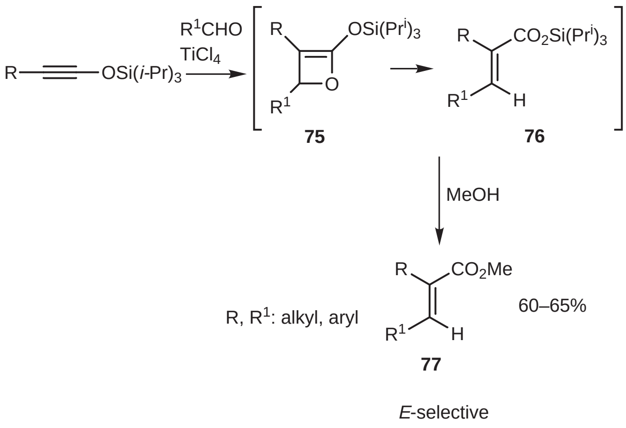


Scheme 27

Silyl ynol ethers prepared by Kowalski's method react with aldehydes, mediated by $TiCl_4$, to give α,β-unsaturated esters in 60–65% yield with high *E/Z*-stereoselectivity after a methanol quench.[30] A proposed mechanism for this reaction is shown in Scheme 29. The intermediate **75**, generated *via* a Mukaiyama-type aldol reaction, is cleaved by conrotatory thermal opening, and then the resulting silyl ester **76** is converted into the methyl ester **77** *via* transesterification.



Scheme 28



Scheme 29

4 Conclusion

Ynolates have great potential in synthetic organic chemistry. Ynolates introduce a ketene unit into substrates, and the resulting products have strong electrophilicity due to their ketene unit and sometimes nucleophilicity, too. This means that a well designed reaction using ynolates should make one-pot multi-step syntheses possible. Ynolate chemistry will contribute not only to ketene chemistry but also to acetylene chemistry. Ynolate chemistry has just begun and much remains to be discovered.

This review will hopefully stimulate further work on the use of ynolates and the development of new reactions.

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