

Reactions of Electron-Deficient Alkynes and Allenes under Phosphine Catalysis

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ABSTRACT

The development of some new synthetic reactions derived from nucleophilic addition of phosphines to electron-deficient carbon-carbon triple bonds is described. These reactions show that the phosphine plays the role of a nucleophile as well as an excellent leaving group. The central problem is to generate a 1,3-dipole from alkynoates or allenates (2,3-butadienoates) by interaction with various phosphines. This study illuminates the unusual phenomena and shows how this understanding allows control of the reaction.

Introduction

Organophosphorus compounds have been widely used in organic synthesis, for example, phosphonium ylides in the Wittig reaction and transition metal-catalyzed reactions in which the phosphines act as ligands. There are only sporadic reports on reactions in which phosphines act as a catalyst.^{1–7} Recently, our group and B. M. Trost's group independently developed a series of reactions of electron-deficient alkynes catalyzed by a tertiary phosphine. In these reactions, a nucleophilic tertiary phosphine adds to the triple bond of an electron-deficient alkyne first and finally eliminates from the reaction product after a series of transformations. The tertiary phosphine plays the role of a catalyst. In this Account, we present some new synthetic reactions discovered in our laboratory and some related reactions from other laboratories.

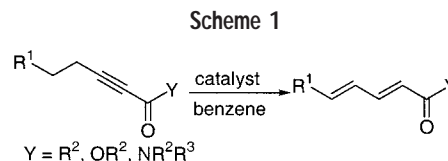
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Zhenrong Xu was born in Jiangsu, China, in 1965. He received his Ph.D. degree in 1998 from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, under the supervision of Professor Xiyang Lu. After postdoctoral work with Professor James M. Takacs at the University of Nebraska—Lincoln, he is currently a postdoctoral fellow with Professor Marisa C. Kozlowski at the University of Pennsylvania.

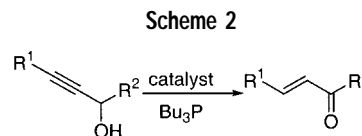
The Discovery of the Catalytic Conversion of Electron-Deficient Alkynes to Dienes by Tertiary Phosphines

We have reported that α,β -ynones stereoselectively isomerize to (*E,E*)- $\alpha,\beta,\gamma,\delta$ -dienones when $\text{RuH}_2(\text{PPh}_3)_4$ is used as the catalyst (Scheme 1).⁸ Trost et al. and Inoue et al. reported similar reactions in the same year.⁹ Further study showed that the reaction could occur under much milder conditions in high yield if $\text{IrH}_5(i\text{-Pr}_3\text{P})_2$ or $\text{RuH}_2(\text{Ph}_3\text{P})_4$ was used as the catalyst and excess phosphine was added as the ligand. Aliphatic phosphines were more reactive than aromatic phosphines.¹⁰

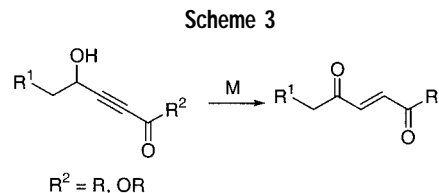


Similarly, 2-ynoic esters and amides stereoselectively isomerize to the corresponding (*2E,4E*)-dienoic esters and amides in high yields, respectively.¹¹ These reactions provided a convenient synthesis of (*E,E*)-diene carbonyl compounds from the corresponding acetylenic derivatives with phosphine-complexed transition metal species as the catalyst.¹²

In addition, we studied the isomerization of propargylic alcohols in which the triple bond is not electron-deficient but is adjacent to a hydroxyl group. The corresponding α,β -unsaturated aldehydes and ketones were also obtained using $\text{IrH}_5(i\text{-Pr}_3\text{P})_2$ or $\text{Pd}_2(\text{dba})_3\text{-CHCl}_3/i\text{-Pr}_3\text{P}$ as the catalyst (Scheme 2).¹³



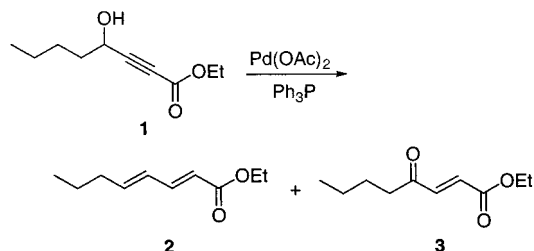
We wished to use our methodology to synthesize enediacarbonyls via transition metal complex-catalyzed isomerization of acetylenic derivatives (Scheme 3).¹⁴



The isomerization of ethyl 4-hydroxyoct-2-ynoate (**1**) using $\text{Pd}(\text{OAc})_2$ (2.5 mol %)- Ph_3P (35 mol %) as the catalyst surprisingly gave ethyl octa-2,4-dienoate (**2**) as the major product and ethyl 4-oxo-oct-2-enoate (**3**) as the minor one (Scheme 4). How was the dienoate **2** produced? Further study revealed that the yield of **2** depended on the amount of triphenylphosphine added as “the ligand”. When 1 equiv of triphenylphosphine was used, **2** was obtained in 86% isolated yield as the sole product, and

triphenylphosphine oxide was also isolated in nearly quantitative yield, indicating that triphenylphosphine initially added as the ligand did participate in the reaction with the alkyne. Furthermore, a control experiment showed that **2** could also be obtained in good yield by using only triphenylphosphine at room temperature without the addition of a palladium complex.

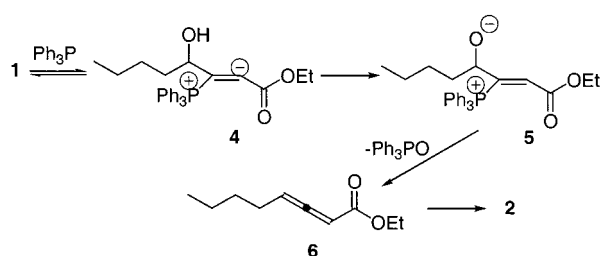
Scheme 4



Pd(OAc) ₂ (mol%)	Ph ₃ P (mol%)	2 (%)	3 (%)
2.5	35	33	10
2.5	55	52	11
2.5	100	88	0
0	100	88	0

Thus, we proposed the reaction mechanism outlined in Scheme 5 on the basis of the nucleophilicity and deoxygenation of the phosphine.¹⁵ The IR spectra of the reaction mixture halfway to completion of the deoxygenation–isomerization reaction of **1** showed an absorption at 1965 cm⁻¹, confirming the existence of the allene intermediate **6** in this reaction.

Scheme 5

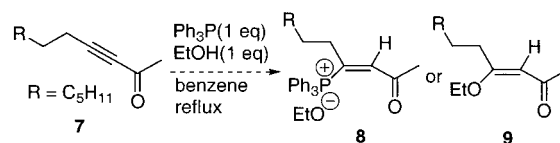


Similar conditions were applied to the deoxygenation–isomerization reaction of γ -hydroxy- α,β -ynones, and the corresponding (*E,E*)- α,β - γ,δ -dienones were also obtained in good yields.

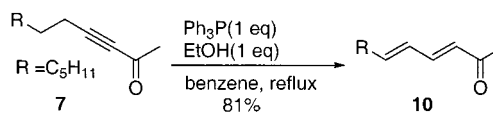
On the basis of the analysis of the possible mechanism of the deoxygenation–isomerization reaction of γ -hydroxy- α,β -ynoates and ynones, we anticipated that if the hydroxy group and the electron-deficient carbon–carbon triple bond were reacted intermolecularly, the deoxygenation reaction (intermediate **5** in Scheme 5) could be inhibited, and the vinylphosphonium salt **8** or the product (**9**) of the triphenylphosphine-catalyzed Michael addition of alcohol to ynone would be obtained (Scheme 6). However, unexpectedly, neither the phosphonium salt **8** nor the adduct **9** was obtained, but the isomerization product **10** was formed directly (Scheme 7). The result prompted us to undertake a reinvestigation of the catalytic

isomerization of triple bonds to see whether the transition metal is necessary.

Scheme 6



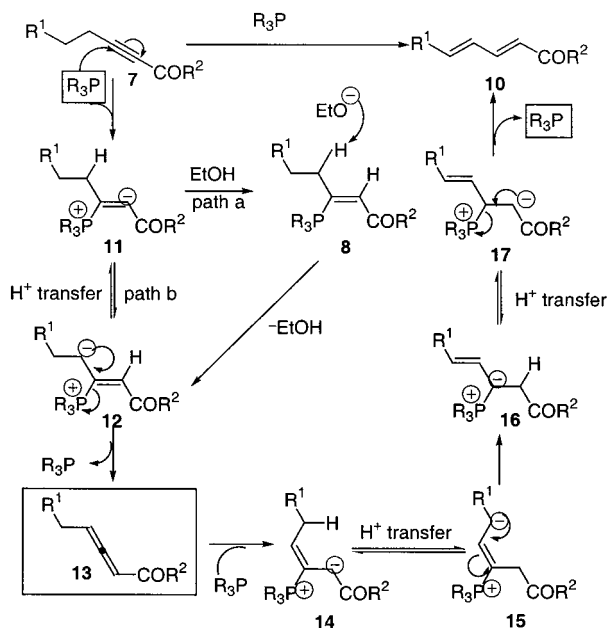
Scheme 7



In further experiments, we found that the isomerization reaction could also occur smoothly in the presence of only catalytic amounts of triphenylphosphine and alcohol. Moreover, ynones could also isomerize to dienones without the addition of the alcohol only in the presence of a catalytic amount of triphenylphosphine.¹⁶

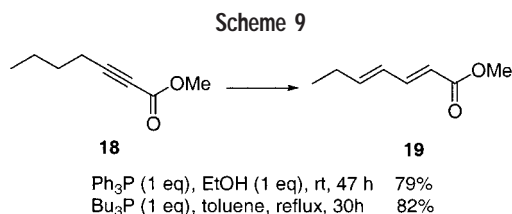
During our study, Trost published the same reaction and reported that a proposed allenic intermediate was subjected to the reaction conditions and demonstrated to react faster than the alkyne. Trost suggested that it is an internal redox reaction that proceeds through a series of prototropic shifts via an allenic intermediate.¹⁷ On the basis of his proposition and our own results, the mechanism was suggested to be that shown in Scheme 8.

Scheme 8



Similarly, ynoates could also isomerize to the corresponding dienates in the presence of a phosphine (Scheme 9). The alcohol was essential as a cocatalyst when triphenylphosphine was used as the catalyst. When the more nucleophilic tributylphosphine was used as the catalyst, the reaction occurred easily without the addition of the alcohol.¹⁶ Trost also reported that the reaction of

an ester is best done in the presence of a weak acid such as acetic acid.¹⁷

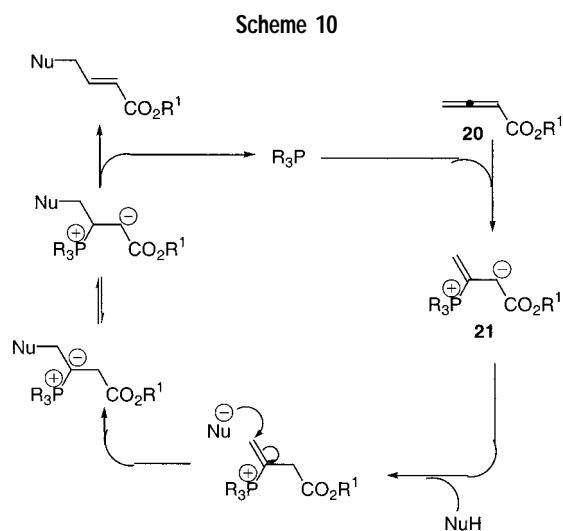


However, no isomerization occurred for ynols in the presence of a phosphine, implying that only the carbon–carbon triple bond of electron-deficient alkyne might accept the nucleophilic attack of a phosphine. Therefore, the isomerization of acetylenic derivatives was differentiated into two types—phosphine-catalyzed and transition metal-catalyzed—on the basis of this work.¹⁶

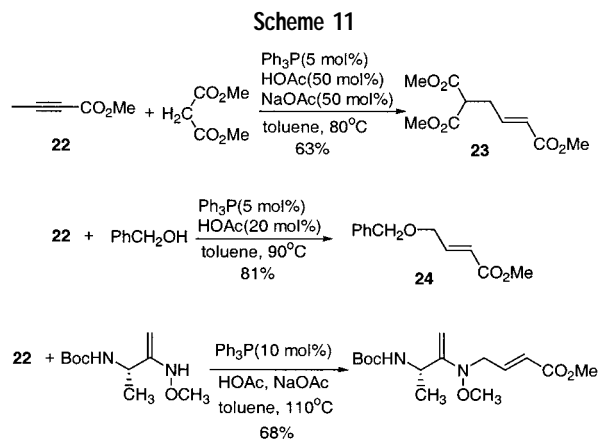
This simple and highly stereoselective isomerization reaction catalyzed by a phosphine provides a practical method for the synthesis of useful polyenyl carbonyl compounds.¹⁸

Umpolung Addition

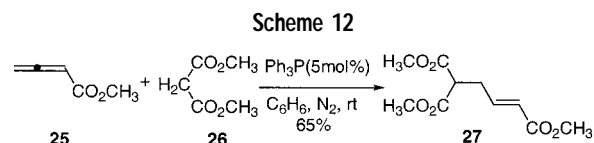
In the proposed mechanism shown in Scheme 8, the reactivities of the α - and γ -carbons of the carbonyl group in intermediate **14** are different: the α -carbon is nucleophilic, while the γ -carbon is electrophilic. Therefore, we assumed that if terminal allenates **20** were used as substrates, the isomerization reaction would be inhibited, and the vinylphosphonium salt intermediate **21** might be trapped by a nucleophile (Scheme 10). Cristau et al. reported the addition of nucleophiles to the γ -atom of electron-deficient allenes by multistep transformations.¹⁹ In their reaction, a stoichiometric amount of triphenylphosphine and multiple operations were required.



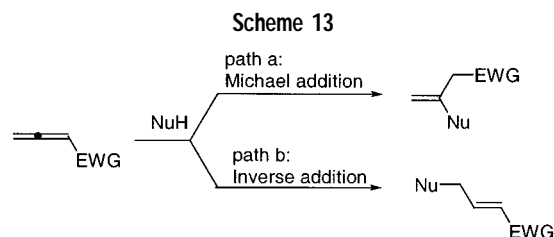
Trost first reported the phosphine-catalyzed γ -addition of nucleophiles to 2-alkynoates (Scheme 11).²⁰ On the basis of his work, we studied the similar addition of oxygen and carbon nucleophiles to the allenates.²¹



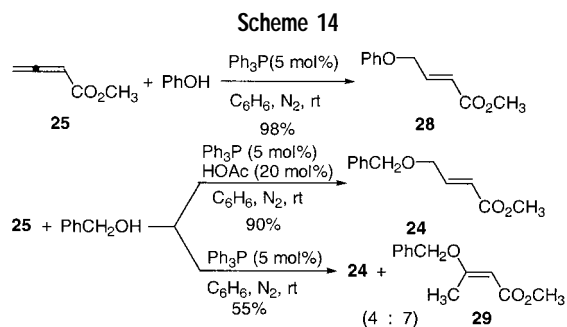
Treatment of methyl 2,3-butadienoate (**25**) with dimethyl malonate (**26**) in the presence of 5 mol % triphenylphosphine in benzene at room temperature gave the adduct **27** in 65% isolated yield (Scheme 12).²¹



Normally, addition of nucleophiles to electron-deficient allenes occurs at the electrophilic α,β -carbon–carbon double bond to give Michael-type adducts (path a in Scheme 13). However, in the presence of triphenylphosphine, the addition takes place at the relatively electron-rich nucleophilic β,γ -carbon–carbon double bond, which in fact is an inverse addition of nucleophiles to electron-deficient allenes (Scheme 13, path b).

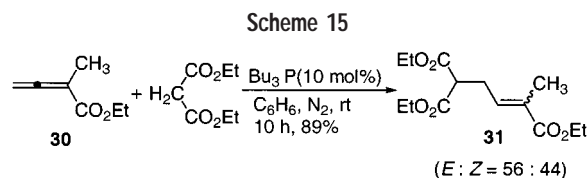


Similar results were obtained in high yields for other carbon and oxygen nucleophiles (Scheme 14). When



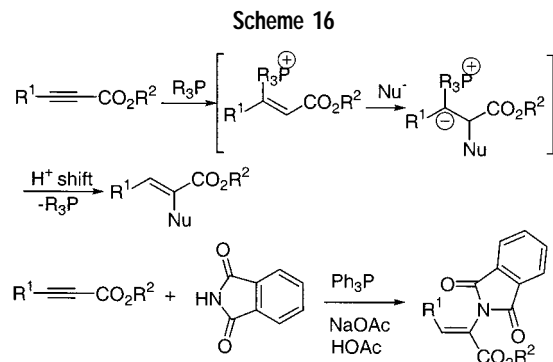
alcohols, e.g. benzyl alcohol, were used as the nucleophile, a catalytic amount of an acid as a cocatalyst was essential for prohibiting the formation of Michael adduct **29**.²¹ A more nucleophilic tributylphosphine was required for

the reaction of allenates with a substituent at the α -position such as ethyl 2-methyl-2,3-butadienoate (**30**) (Scheme 15).²¹



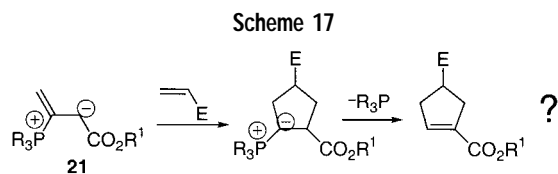
Carboxylates can also be used as pronucleophiles in the phosphine-catalyzed γ -addition reaction to alkynes bearing electron-withdrawing groups, giving rise to the functionalized allylic carboxylates.²²

Recently, Trost's group reported a phosphine-catalyzed α -addition of nucleophiles to 2-alkynoates in the presence of sodium acetate–acetic acid buffer (Scheme 16).²³ The ability to redirect the regioselectivity of the addition of a nucleophile from the classical β -addition mode to an α -addition mode by simply changing the base is quite remarkable.



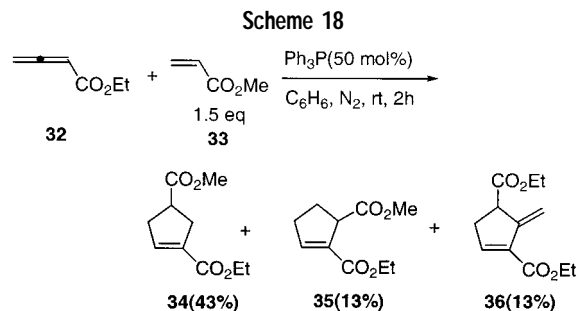
[3 + 2] Cycloaddition

The interesting reactivity of intermediate **21** mentioned in Scheme 10 inspired us to investigate its reactions further. We wondered if such a reactive allylic anion species **21** could function as the three-carbon synthon and undergo the [3 + 2] cycloaddition reaction with alkenes (Scheme 17).²⁴

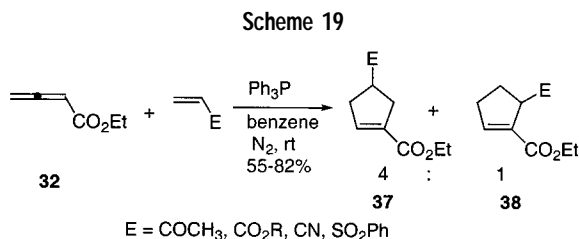


Our initial attempt explored the reaction of ethyl 2,3-butadienoate (**32**, 1.0 mmol) with methyl acrylate (**33**, 1.5 mmol) in the presence of triphenylphosphine (0.5 mmol) in dry benzene (5 mL) at room temperature, and three products (**34**, **35**, and **36**) were isolated after 2 h (Scheme 18). The ¹H NMR spectra show that **34** and **35** are the cycloaddition products of **32** and **33**, while **36** is the self-cycloaddition product of **32**. Finally, 10 equiv of the acrylate and 10 mol % of triphenylphosphine in dry

benzene at room temperature were chosen as our standard conditions.

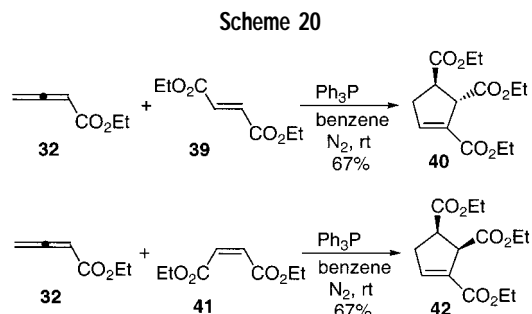


The structure of the olefin is crucial to the reaction. Electron-deficient olefins including esters, ketones, and a nitrile reacted with **32** to give the cycloadducts in moderate to good yields (Scheme 19).²⁴ For the reaction of **32** with 1-hexene, methyl (*E* or *Z*)-crotonate, or methyl methacrylate, none of the expected product was isolated, except for a self-cycloaddition product, **36**, of **32**. This implies that **32** is more active as a trapping olefin here.



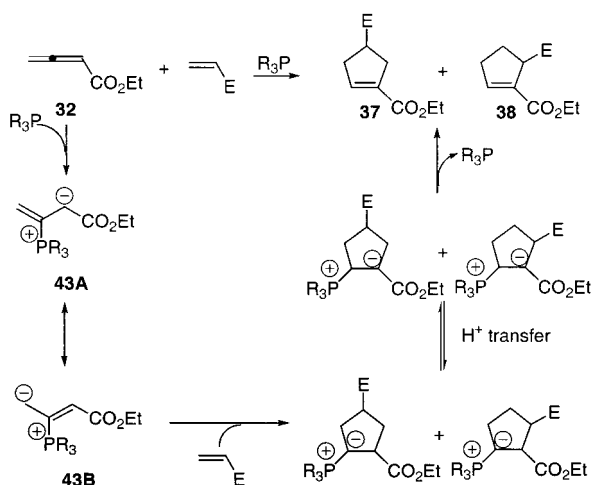
When the more nucleophilic tributylphosphine was used, the reaction took place more rapidly but gave the corresponding cycloadducts **37** and **38** in slightly lower yields, along with a small amount of the dimerization product of **33**.² No reaction occurred when triethylamine was used instead of the phosphine. When the allenone, 3,4-pentadien-2-one, was used as the three-carbon synthon, the cycloaddition occurred as well.

trans-Diethyl fumarate (**39**) and *cis*-diethyl maleate (**41**) were employed as the dipolarophile to react with **32** to afford the single product *trans*-**40** and *cis*-**42**, respectively, indicating that the stereochemistry remained unchanged in the cycloaddition reaction (Scheme 20). The proposed mechanism of the reaction is outlined in Scheme 21.



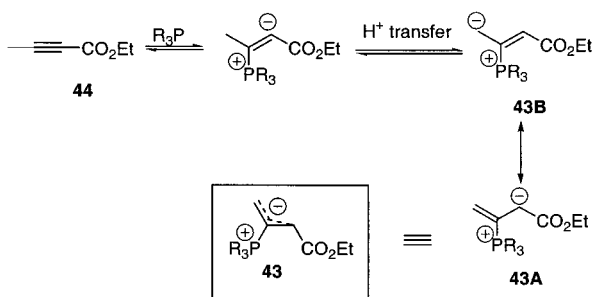
Since the phosphine-catalyzed isomerization of ynoates to 2,4-dienoates was hypothesized to go through the intermediary of a 2,3-dienoate,^{16,17} we wondered if it would

Scheme 21



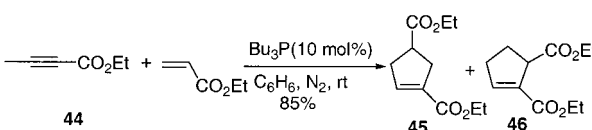
be possible to generate the intermediate **43** in situ from ethyl 2-butynoate (**44**) (Scheme 22). Should it be possible, the cycloaddition reaction could also occur with 2-butynoates used as the starting material.

Scheme 22



Treatment of **44** (1.0 mmol) with ethyl acrylate (2.0 mmol) in the presence of 10 mol % of tributylphosphine in dry benzene at room temperature under nitrogen gave the same cycloadducts **45** and **46** in higher yield and regioselectivity (Scheme 23).

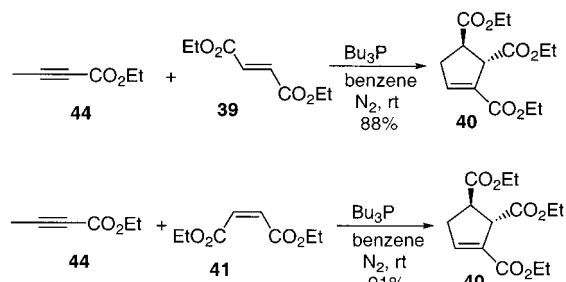
Scheme 23



In contrast to the triphenylphosphine-catalyzed reaction of 2,3-butadienoates, the tributylphosphine-catalyzed reaction of 2-butynoates with both diethyl fumarate (**39**) and diethyl maleate (**41**) gave *trans*-**40** as the sole product, possibly due to the rapid isomerization of **41** to **39** in the presence of tributylphosphine (Scheme 24).

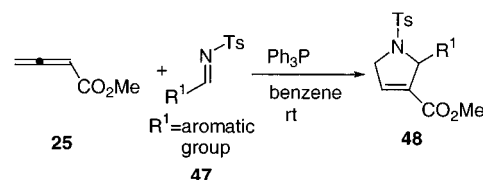
The discovery of the new three-carbon synthon, generated in situ from the reaction of 2,3-butadienoates or 2-butynoates with an appropriate phosphine as the catalyst, aroused us to explore its reactivity toward other dipolarophiles. *N*-Tosylimines with the highly reactive carbon–nitrogen double bond have been successfully applied in cycloaddition reactions. We tried the reaction of methyl 2,3-butadienoate (**25**) with *N*-tosylimines (**47**),

Scheme 24



and the corresponding [3 + 2] cycloaddition product **48** was formed in excellent yield and high chemoselectivity (Scheme 25).²⁵

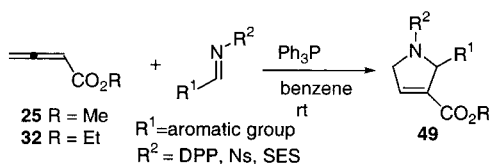
Scheme 25



Unlike the reactions of 2,3-butadienoates with electron-deficient olefins,²⁴ the reactions of **25** with *N*-tosylimines in the presence of a catalytic amount of triphenylphosphine all gave single cycloaddition products, except for *N*-tosyl 2-furaldimine, which afforded two isomers.²⁵ For aliphatic *N*-tosylimines, merely trace amounts of cycloadducts were detected due to the low reactivity of imines and to self-cycloaddition of **25**.

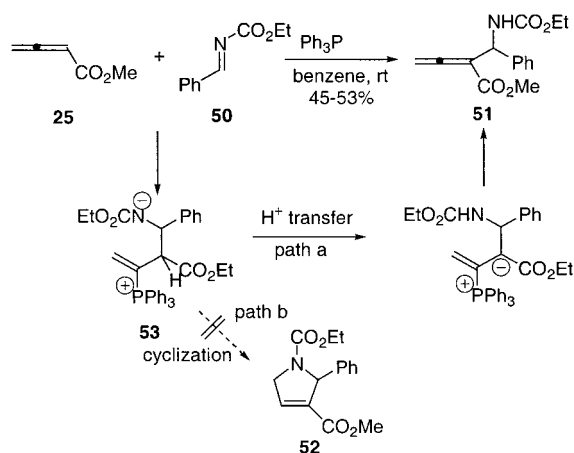
To further examine the synthetic scope of this three-carbon synthon, imines bearing other electron-withdrawing groups on the nitrogen atom, such as diphenylphosphinyl (DPP), *p*-nitrobenzenesulfonyl (Ns), and β -trimethylsilylethanesulfonyl (SES), that similarly activate the imine but are easier to remove after reaction were tried (Scheme 26). Again, the cycloaddition reaction occurred. In particular, the SES imines gave the cycloadducts in high yields. The success of the reaction of these imines further expands the synthetic flexibility of the cycloaddition products.

Scheme 26

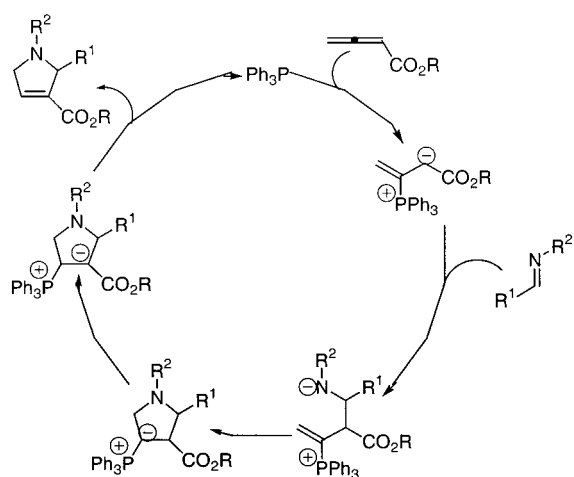


However, under the same conditions, *N*-(ethoxycarbonyl)benzaldimine (**50**) reacted with **25** to afford a noncyclized adduct **51** in 45–53% yield. None of the expected [3 + 2] cycloaddition product **52** was isolated, implying that the proton transfer (path a) is faster than the intramolecular cyclization (path b) in the ethoxycarbonylnitrogen anion **53** (Scheme 27).²⁶ From the isolation of the noncyclized adduct **51**, a stepwise mechanism for the [3 + 2] cycloaddition reaction of the electron-deficient imines was proposed as outlined in Scheme 28.

Scheme 27

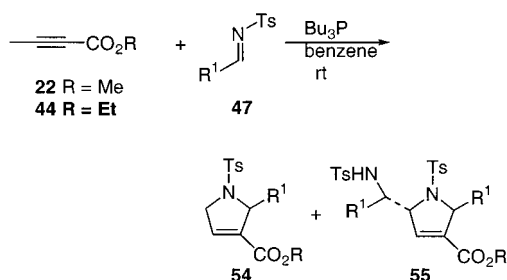


Scheme 28



The success of the cycloaddition of 2,3-butadienoates with *N*-sulfonylimines encourages us to further explore the reaction of 2-butynoates. Interestingly, treatment of 2-butynoates with *N*-tosylimines in dry benzene in the presence of a catalytic amount of tributylphosphine at room temperature gave the corresponding [3 + 2] cycloadduct **55** as the major product and a small amount of the three-component adduct **54** in high overall yields, which is also different from the reaction of 2-butynoates with electron-deficient olefins (Scheme 29).²⁶

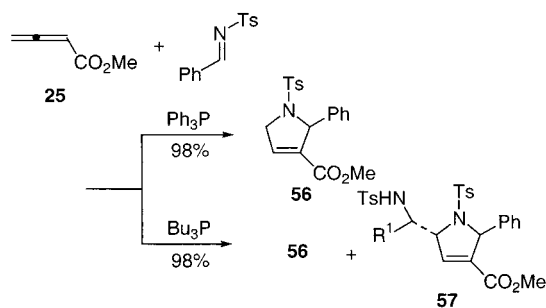
Scheme 29



Furthermore, the reaction of **25** with *N*-tosyl benzaldimine using tributylphosphine instead of triphenylphosphine as the catalyst afforded the same result as the reaction of 2-butynoates (Scheme 30). Thus, the electro-

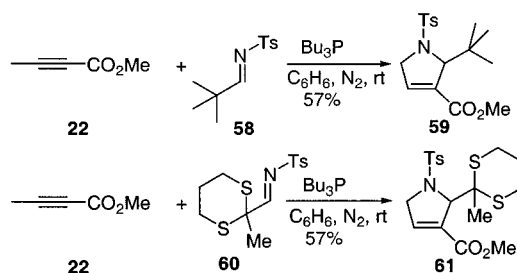
philicity of the vinylphosphonium salt intermediate may also play a role in this reaction.²⁶

Scheme 30



For the reaction of **25** with aliphatic *N*-tosylimine, *N*-tosyl pivalaldimine (**58**), the corresponding cycloaddition product **59** was isolated in 57% yield. Similarly, **61** was obtained in 47% yield (Scheme 31). Here, the success of the reaction of the aliphatic imines **58** and **60** further expanded the synthetic utility of this cycloaddition reaction. For the aliphatic *N*-tosylimines, the tributylphosphine-catalyzed reaction of 2-butynoates gave better results.²⁶

Scheme 31



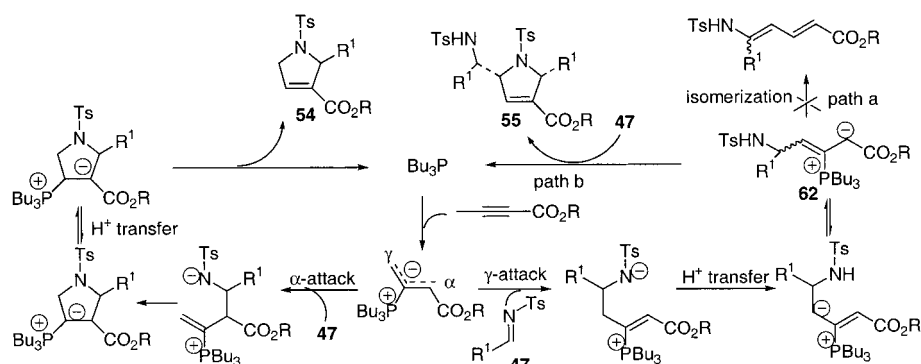
[3 + 2] Cycloaddition of Substituted 2-Alkynoates

Because substituted 2-alkynoates can isomerize to 2,4-dienoates under catalysis by a phosphine,^{16,17} no work on the [3 + 2] cycloaddition reaction of substituted 2-alkynoates was reported.^{24–26} In Schemes 29 and 30, the three-component adducts **55** and **57** were composed of one molecule of alkyne and two molecules of the imine. A reaction mechanism was proposed as outlined in Scheme 32.

Surprisingly, under our reaction conditions, the presumed intermediate **62**, having a substituted group on the γ -carbon atom, did not isomerize to dienoates (path a) but further reacted with another molecule of the imine **47** to afford the three-component adduct **55** (path b). It occurred to us that substituted 2-alkynoates might also react with *N*-tosylimines to afford the normal [3 + 2] cycloaddition products.²⁷

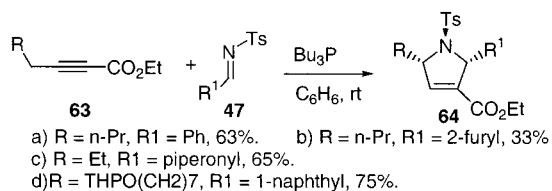
Treatment of ethyl 2-heptynoate (**63a**) with *N*-tosyl benzaldimine in the presence of a catalytic amount of tributylphosphine in dry benzene at room temperature gave the corresponding [3 + 2] cycloaddition product **64a** in 63% isolated yield. Similar conditions were applied to

Scheme 32



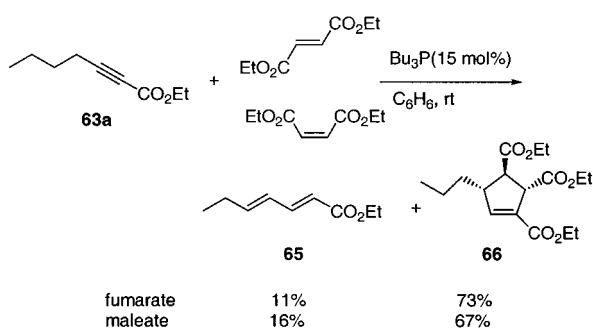
other 2-alkynoates and *N*-tosylimines, and the expected [3 + 2] cycloadducts were also obtained in moderate to good yields (Scheme 33).²⁷ The success of these reactions not only expands the synthetic scope of the cycloaddition reaction but also further confirms the mechanism of the formation of the three-component adduct **55**.

Scheme 33



The reaction of ethyl 2-heptynoate (**63a**) and diethyl fumarate or dimethyl maleate in dry benzene in the presence of 15 mol % of tributylphosphine at room temperature gave **66** as the major product along with a small amount of ethyl 2,4-heptadienoate (**65a**), a phosphine-catalyzed isomerization product of **63a** (Scheme 34).²⁷

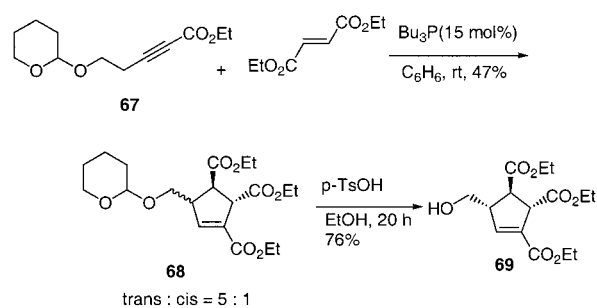
Scheme 34



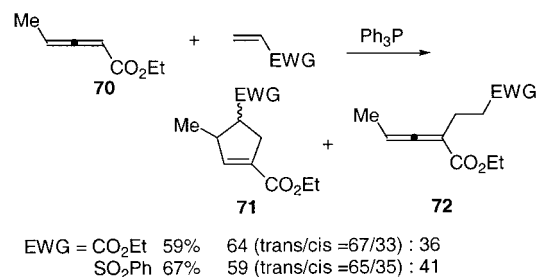
For the 2-alkynoate **67** with a functional group on the δ -carbon atom, the cycloaddition reaction also occurs (Scheme 35). Thus, multifunctionalized cyclopentene derivatives could be obtained.

Similarly, the reaction of ethyl 2,3-pentadienoate (**70**) and ethyl acrylate or vinyl phenyl sulfone in dry benzene with 10 mol % of triphenylphosphine at room temperature gave the cycloadduct **71**, together with noncyclic adduct **72** (Scheme 36).²⁷

Scheme 35

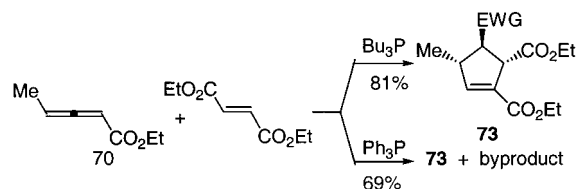


Scheme 36



For the triphenylphosphine-catalyzed reaction of **70** with diethyl fumarate, a small amount of uncharacterized byproduct was produced in addition to the cycloadduct **73**. However, when tributylphosphine was used, the sole cycloadduct **73** was produced in higher yield, again showing that phosphine has a notable impact on this reaction (Scheme 37).²⁷

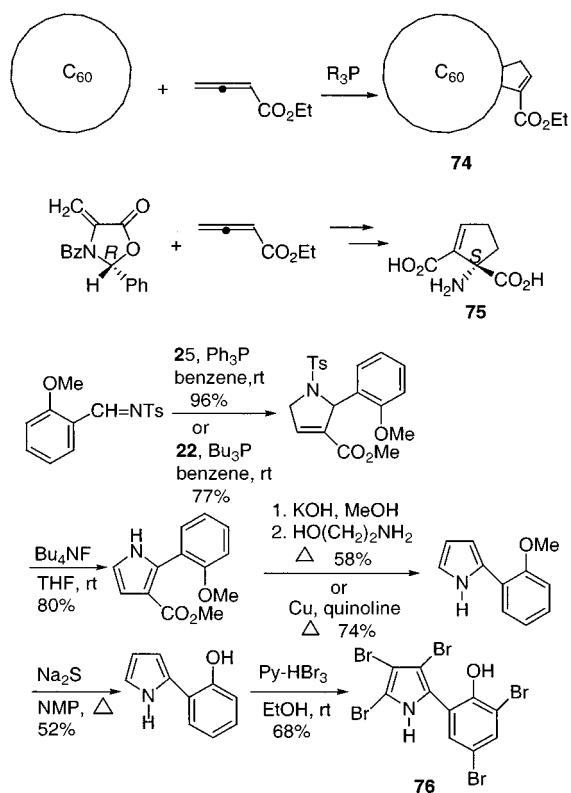
Scheme 37



The new [3 + 2] reaction exhibits a wide range of applications in organic synthesis, e.g., the synthesis of [60]-fullerene cycloadducts,²⁸ L-glutamate analogues (**75**),²⁹ and pentabromopseudilin (**76**) (Scheme 38).²⁶

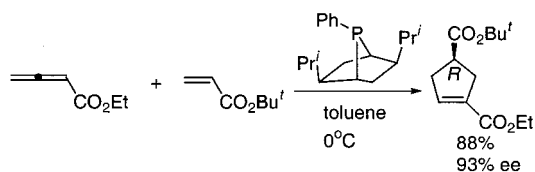
In particular, Zhang et al. recently reported asymmetric [3 + 2] cycloaddition of 2,3-butadienoates with electron-deficient olefins catalyzed by novel chiral phosphines

Scheme 38



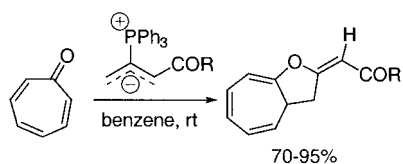
(Scheme 39).³⁰ This asymmetric [3 + 2] reaction further extended the synthetic utilization of the reaction toward homochiral cyclopentanoids.

Scheme 39



Recently, an unusual [8 + 2] annulation from allenic ester/ketone-derived 1,3-dipoles with tropone was reported (Scheme 40).³¹

Scheme 40

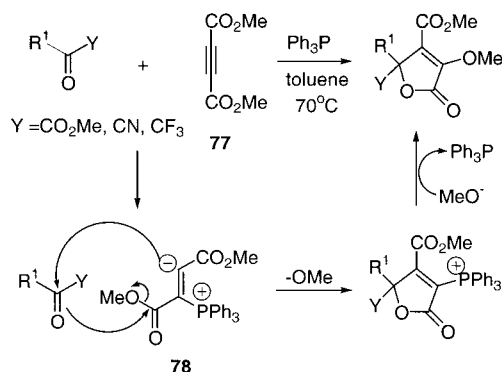


Miscellaneous Reactions

A number of organic transformations of zwitterionic intermediate **78**, generated from the reaction of triphenylphosphine with dimethyl acetylenedicarboxylate (**77**), were reported in the literature, but use of this reaction in a catalytic cycle has as yet been limited.^{32–34} Recently, Nozaki et al. reported a triphenylphosphine-catalyzed cyclization of α -ketoesters, α -ketonitriles, or α, α, α -trifluoroacetophenone with dimethyl acetylenedicarboxylate

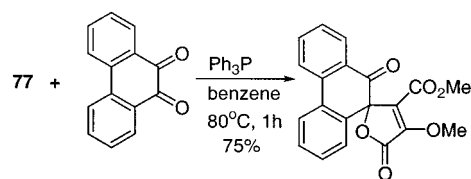
to produce highly functionalized α, β -unsaturated γ -butyrolactones in moderate yields (Scheme 41).³⁵

Scheme 41



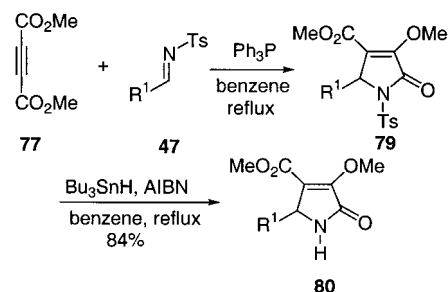
Similarly, the reaction of **77** with *o*-quinones under the catalysis of triphenylphosphine was reported to give highly functionalized γ -spirolactones (Scheme 42).³⁶

Scheme 42



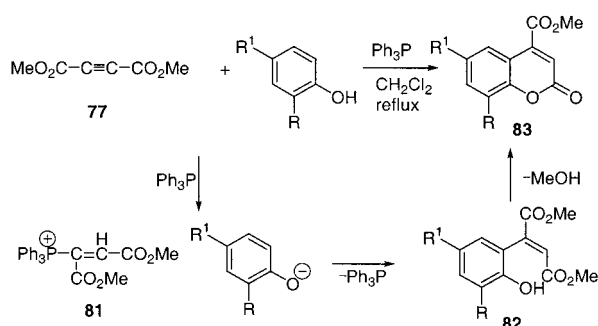
In these reactions, an electron-withdrawing group attached to the carbonyl group is essential. We anticipated that *N*-sulfonylimines could also undergo the cyclization reaction in place of the electron-deficient carbonyl compounds as trapping reagents. Treatment of dimethyl acetylenedicarboxylate with *N*-tosylimines in the presence of 20 mol % of triphenylphosphine in dry benzene under reflux gave pyrrolin-2-ones in high yields (Scheme 43).²⁶

Scheme 43



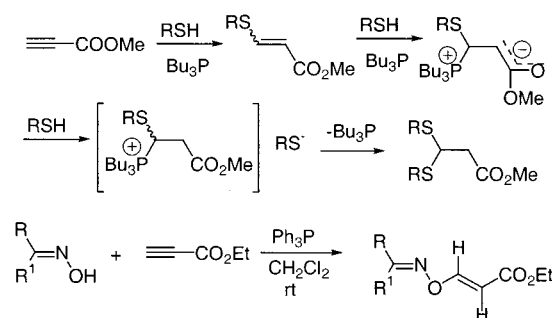
Recently, Yavari et al. reported a new and efficient approach to 4-carboxymethylcoumarins via triphenylphosphine-mediated reaction of phenols with dimethyl acetylenedicarboxylate.³⁷ The mechanism of this reaction was envisaged as proceeding via the vinyltriphenylphosphonium salt **81**,³⁴ generated from protonation of the zwitterionic intermediate **78** by phenols. The vinyltriphenylphosphonium cation then underwent aromatic electrophilic substitution reaction with the phenolate conjugate base, followed by intramolecular lactonization of the intermediate **82** to produce coumarins (Scheme 44).

Scheme 44



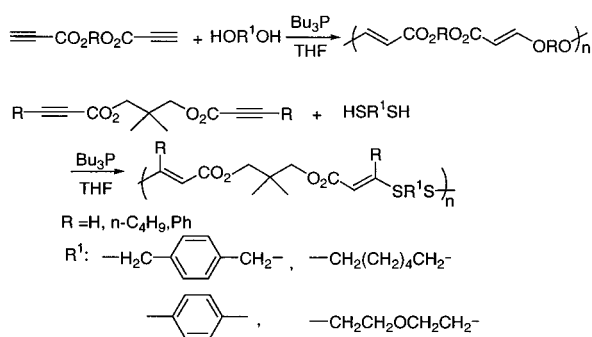
Propynoates gave a special kind of reactivity. There are many reports of the substitution of alcohols,⁶ thiols,³⁸ and other nucleophiles³⁹ to the propynoates (Scheme 45).

Scheme 45



A similar reaction could also be used in the synthesis of polymers (Scheme 46).⁴⁰

Scheme 46



Concluding Remarks

In summary, we present some new synthetic reactions derived from nucleophilic addition of phosphines to electron-deficient carbon-carbon triple bonds. These reactions show that the phosphine plays the role of a good nucleophile as well as an excellent leaving group. In fact, both roles are critical for the catalytic action of a phosphine. With the understanding of the properties of the phosphine, this may open up broad possibilities for its utilization in organic synthesis. It should be emphasized that these reactions were serendipitously discovered in our laboratory and then gradually developed on the basis of the deep and careful analyses of the reaction mechanism, with inspiration from other laboratories. The central problem is to generate a 1,3-dipole from 2,3-butadienoates

or alkynoates by interaction with various phosphines. This study shows how an understanding of the unusual phenomena gave us the ability to carry forward the research work.

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