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The Phosphine-Catalyzed Alkyne to 1,3-Diene Isomerization Reaction

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Abstract: The alkyne to 1,3-diene isomerization reaction is a process in which a nucleophilic phosphine catalyst promotes the rearrangement of an electron-withdrawing group activated alkyne to the corresponding conjugated diene. The origin, mechanism, development, and application of this organocatalytic and stereoselective reaction in the synthesis of complex organic molecules are reviewed.

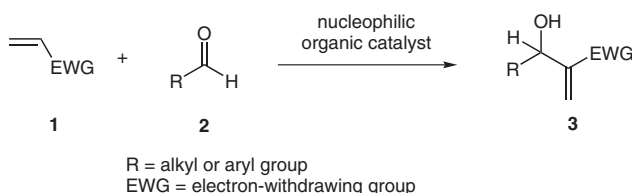
- 1 Introduction
- 2 The Reaction
 - 2.1 Background
 - 2.2 Mechanism
 - 2.3 Development
 - 2.4 Synthetic Applications
- 3 Conclusions

Key words: organocatalysis, isomerization reactions, phosphines, alkynes, 1,3-dienes

1 Introduction

The use of metal-free organic molecules to catalyze organic molecule transformations has enjoyed a renaissance in recent years, and many research groups from around the world have focused their efforts towards discovering new organocatalytic methods for reactions that previously required metal-based catalysts.^{1–3} In this regard, the use of nucleophilic phosphines as catalysts for a range of reactions has garnered great attention.⁴ The catalytic use of phosphines has probably been most widely studied and demonstrated in Morita–Baylis–Hillman reactions in which an electron-withdrawing group activated alkene **1** adds at its α -position to an electrophile, such as an aldehyde **2**, to form the densely functionalized product **3** (Scheme 1).^{5,6}

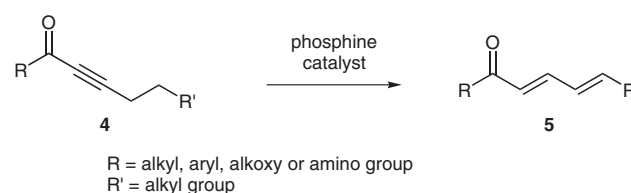
In this review, the literature regarding the use of phosphines as catalysts in the related isomerization of electron-withdrawing group activated alkynes **4** to the correspond-



Scheme 1

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ing (*E,E*)-1,3-dienes **5** is surveyed (Scheme 2). Such dienes are common structural elements in both natural and unnatural products or can be intermediates in the synthesis of such compounds. The work in this field by Professor Xiyan Lu has been summarized in several personal accounts;⁷ however, the aim of this report is to provide a complete review of the literature regarding this reaction from its origins through the end of 2007.



Scheme 2

2 The Reaction

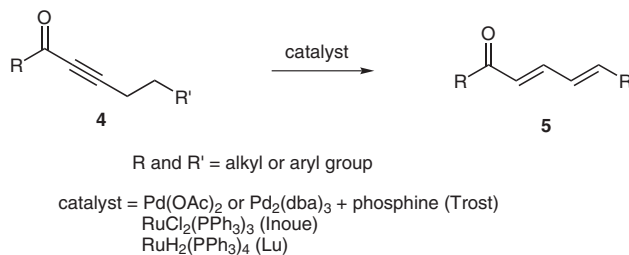
The alkyne to 1,3-diene isomerization reaction has a notable history in that it was discovered independently and virtually simultaneously by both the Barry M. Trost and Xiyan Lu research groups on opposite sides of the Pacific Ocean as they were studying control reactions of isomerization reactions that were originally thought to require a metal-based catalyst. In the late 1980s, numerous research groups were studying the isomerization of electron-withdrawing group activated alkynes to the corresponding 1,3-dienes using organometallic complexes as catalysts,^{8–20} and this work led directly to the reaction reviewed here.

2.1 Background

In 1988, several research groups independently reported the isomerization of various alkynones **4** to the corresponding conjugated dienones **5** using various metal–phosphine complexes as catalysts (Scheme 3). Trost and Schmidt reported that both palladium(II) acetate and tris(dibenzylideneacetone)dipalladium(0) $[\text{Pd}_2(\text{dba})_3]$ were effective catalysts for these isomerization reactions when used together with a phosphine ligand.⁸ Inoue and Imaizumi found that tris(triphenylphosphine)ruthenium(II) dichloride $[\text{RuCl}_2(\text{PPh}_3)_3]$ was also an effective catalyst for such transformations,⁹ while Lu and co-workers reported that dihydridotetrakis(triphenylphosphine)ruthenium(II) $[\text{RuH}_2(\text{PPh}_3)_4]$ was similarly useful.¹⁰ It should be noted that all of these catalysts required similar reaction conditions in terms of temperature and time re-

quired in order to afford high product yield. Interestingly, all three of these research groups postulated the generation of an allenone intermediate prior to final product formation.

Lu and co-workers studied this reaction further and subsequently reported that an iridium complex, $\text{IrH}_5[\text{P}(i\text{-Pr})_3]_2$, was also an efficient catalyst for alkyne to dienone isomerization reactions, especially in the presence of excess phosphine.¹¹ They then studied the scope of these catalysts for the conversion of compounds **4** into compounds **5** (Scheme 4)¹² and reported the synthesis of both trienones¹³ and tetraenones.¹⁴ They even applied these reaction conditions to the isomerization of alkynoates¹⁵ and alkynamides.¹⁶



Scheme 3

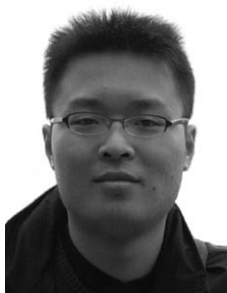
Biographical Sketches



Cathy Kar-Wing Kwong received her B.Sc. degree in chemistry from the University of Hong Kong in 2004.

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Michael Yunyi Fu received his B.Sc. degree in chemistry in 2005 from Xiamen University. He then studied for an M.Phil. degree at the

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and variations of the alkyne to 1,3-diene isomerization reaction and the Mitsunobu reaction.



Cynthia Sze-Lok Lam is currently a final-year student studying for an

M.Chem. degree at Oxford University. She spent the summer of 2006 as a re-

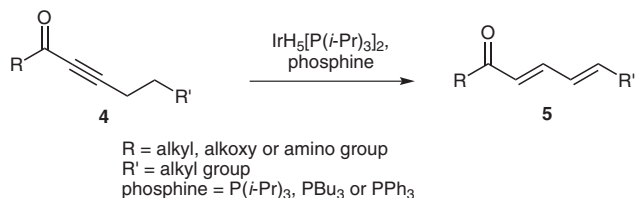
search assistant at the University of Hong Kong in Professor Toy's group.



Patrick H. Toy received his B.S. degree in chemistry from the Ohio State University in 1990. He began his doctoral studies at the University of Minnesota under the direction of the late Professor Paul G. Gassman and Professor Hung-Wen (Ben) Liu, and earned his Ph.D. in 1998 with Professor Martin

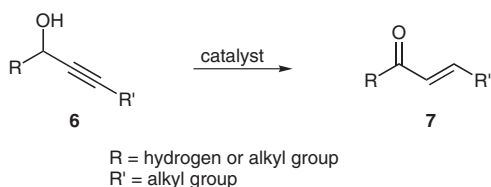
Newcomb at Wayne State University. After two years of post-doctoral research with Professor Kim D. Janda at the Scripps Research Institute, he worked in the combinatorial chemistry department at Wyeth in Pearl River, New York. In October 2001, he took a position as Assistant Professor in the

chemistry department at the University of Hong Kong, where he was recently promoted to the rank of Associate Professor. His research interests include organocatalysis and the use of polymers to facilitate organic synthesis.



Scheme 4

Subsequently, Lu and co-workers reported the isomerization of numerous propargylic alcohols **6** to the corresponding α,β -unsaturated carbonyl compounds **7** promoted by catalytic RuCl₂(PPh₃)₃¹⁷ and IrH₅[P(*i*-Pr)₃]₂¹⁸ (Scheme 5). When a palladium–phosphine catalyst was used to isomerize α,α' -diynols, trienones were isolated in good yields.¹⁹ Finally, perfluoroalkylated dienes could also be prepared from 1-perfluoroalkyl-1-alkynes in a related process using a palladium catalyst system.²⁰

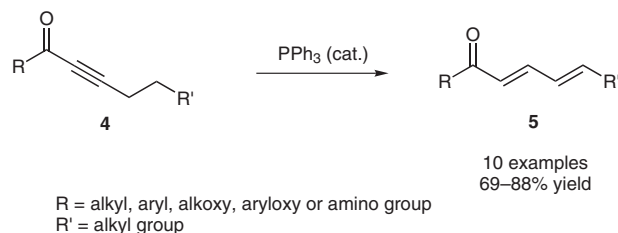


catalyst = RuCl₂(PPh₃)₃ + phosphine or IrH₅[P(*i*-Pr)₃]₂

Scheme 5

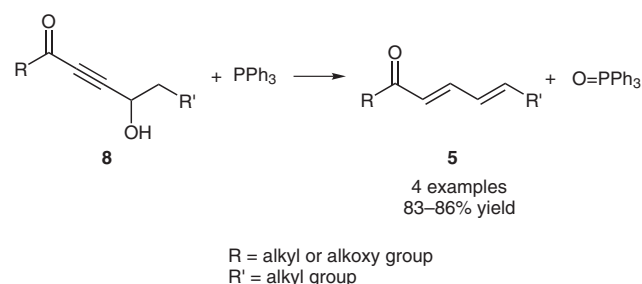
With the use of transition-metal catalysts for the isomerization of electron-withdrawing group functionalized alkynes to the corresponding conjugated diene well established, Trost and Kazmaier reported in 1992 that this isomerization reaction of compounds **4** to products **5** can be catalyzed by phosphines themselves, without the need of a metal center.²¹ In the presence of 0.1 to 0.4 equivalents of triphenylphosphine, electron-poor alkynes, including alkynones, alkynoates and alkynamides, isomerized smoothly in toluene at 80 to 110 °C to afford the corresponding conjugated dienones, dienates and dienamides, respectively, in high yields (Scheme 6). They observed that alkynones, both aromatic and aliphatic, reacted more readily than alkynoates, and that alkynoates reacted faster than alkynamides. Higher reaction temperatures and the addition of 0.5 equivalents of acetic acid were necessary for the isomerization of alkynamides. Thus, the order of reactivity was established to be alkynones > alkynoates > alkynamides. In addition, the isomerization reaction was found to be highly chemoselective, with no isomerization observed for electron-rich alkynes. Furthermore, it was found to be highly stereoselective, with an (*E,E*)-1,3-diene usually being the only product formed. The authors proposed that, as with the transition-metal-complex-catalyzed reactions, an allene intermediate was formed, and they supported this notion by successfully isomerizing an allenolate to the corre-

sponding diene with triphenylphosphine. They also demonstrated that the nucleophilicity of the catalyst – and not its basicity – was responsible for catalysis since no isomerization was observed with tertiary amines, and phosphites were almost unreactive as catalysts.



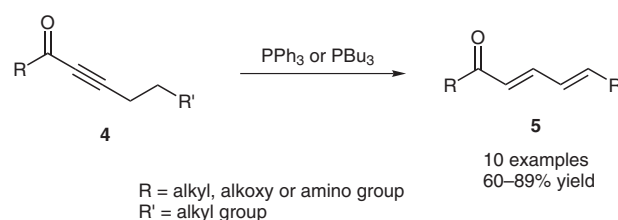
Scheme 6

At virtually the same time, Lu and Guo reported a similar reaction using γ -hydroxy- α,β -ynones and γ -hydroxy- α,β -ynoates as substrates, in which they observed that isomerization of compounds **8** to form diene compounds **5** occurred using a stoichiometric amount of triphenylphosphine in benzene at room temperature (Scheme 7).²² It was proposed that formation of triphenylphosphine oxide led to an allene intermediate and that, as in Trost and Kazmaier's reaction, this intermediate further reacted to form the final conjugated (*E,E*)-1,3-diene product.



Scheme 7

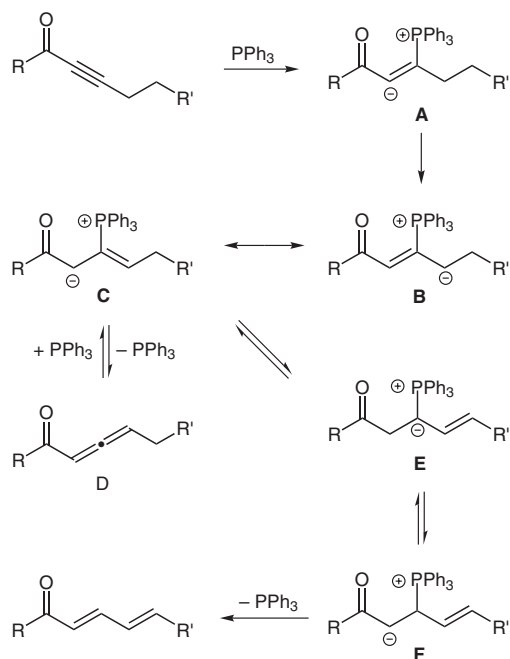
Lu and Guo very soon thereafter followed up with a report of results, analogous to those of Trost and Kazmaier, where a series of alkynones, alkynoates and alkynamides **4** rearranged in the presence of a phosphine catalyst to products **5** (Scheme 8).²³ An important observation made here was that PBu₃ was a good catalyst for the less reactive alkynamide substrates. A tandem propargyl alcohol/ynone isomerization reaction was also described.



Scheme 8

2.2 Mechanism

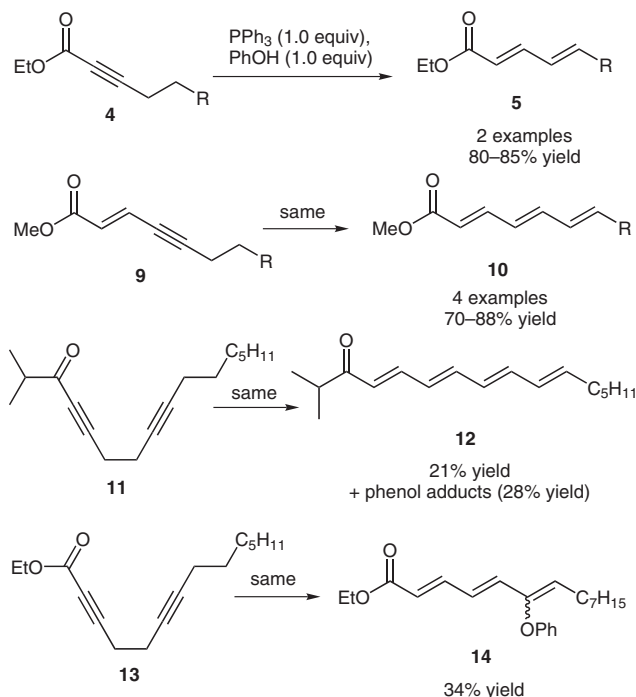
The current generally accepted mechanism for the alkyne to 1,3-diene isomerization reaction, as concisely presented by Kazmaier,²⁴ is depicted in Scheme 9. Initial nucleophilic addition by the phosphine catalyst at the alkyne to form intermediate **A**, followed by a proton shift from the γ -position of **A** to its α -position, leads to resonance structures **B** and **C**, which can reversibly eliminate phosphine to form allene **D**. Intermediate **C** can alternatively undergo additional proton shifts to form **E** and **F** sequentially. Elimination of the catalyst from **F** affords the final product. This mechanism is fully consistent with all reported experimental observations, especially that allene starting materials such as **D** afford the same (*E,E*)-1,3-diene products as do the corresponding alkynes.



Scheme 9

2.3 Development

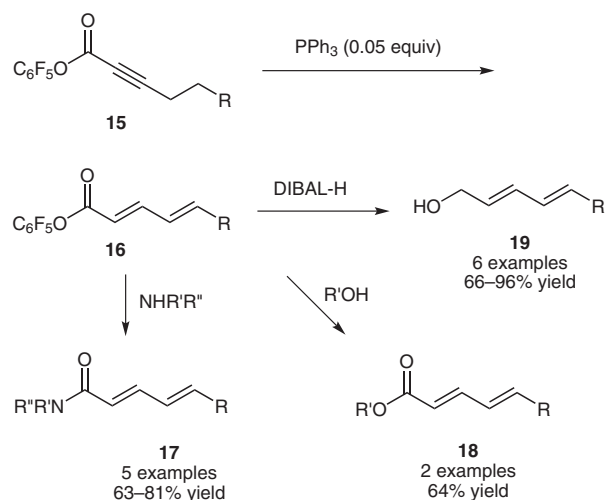
Soon after the initial reports by Trost and Lu, Rychnovsky and Kim described the use of phenol as a co-catalyst in the triphenylphosphine-catalyzed isomerization of compounds **4** to products **5**, and of enynoates **9** to the corresponding (*E,E,E*)-2,4,6-trienoates **10** in high yields (Scheme 10).²⁵ They reported that when acetic acid was used as the co-catalyst, isomerization was sluggish and substrate decomposition was observed, and that the use of phenol resolved such issues. Furthermore, the sequential rearrangement of 2,6-diyne **11** to form conjugated all-*E* tetraenone **12** in modest yield was described using phenol as the co-catalyst. However, various phenol adducts were reported to be the major products. Reaction of analogous 2,6-diyne **13** afforded phenol adduct **14** as the major isolated product. It should be noted that the combination of triphenylphosphine and phenol is now virtually the standard catalyst combination for alkyne to 1,3-diene



Scheme 10

isomerization reactions, especially for alkynoate substrates.

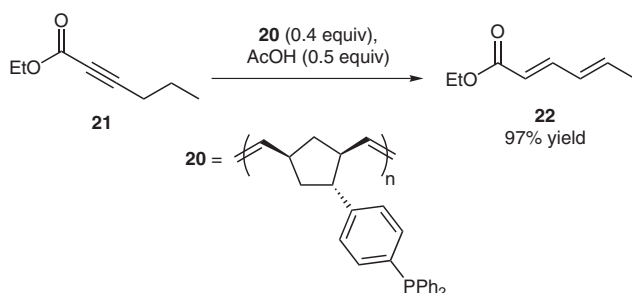
In an attempt to make the isomerization of alkynoates more efficient, Kazmaier applied pentafluorophenyl esters as the activating group. As a result of the strongly electron-withdrawing nature of the pentafluorophenoxy group, isomerization of alkynoates **15** occurred under milder conditions, requiring only 0.05 equivalents of the triphenylphosphine catalyst and no acid co-catalyst to form the desired products **16** (Scheme 11).²⁶ The isomerization product could then react directly, without isolation, with a range of amines and alcohols to afford the corresponding amides **17** and esters **18**, respectively, or reduced with diisobutylaluminum hydride to the corresponding allylic alcohols **19**.²⁴



Scheme 11

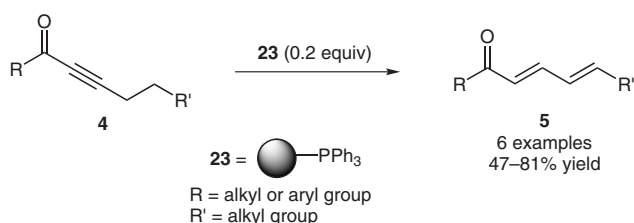
Recently it was reported that alkyne to 1,3-diene isomerization reactions can be performed in water without the need of an organic solvent.²⁷ Xue and co-workers found that alkynones were good substrates in such aqueous reactions catalyzed by triphenylphosphine, with their isomerization being complete in two to four hours in refluxing water (10 examples, 72–89% yield). Unfortunately, ester group activated alkynes were unreactive when subjected to similar reaction conditions. This latter observation highlights the fact that such substrates generally require an acidic co-catalyst in addition to the nucleophilic phosphine catalyst. If an ester group is to be used as the activating group, it needs to be a strongly electron-withdrawing one such as a pentafluorophenol derivative.

Considering the recent rise in the use of polymer-supported reagents in general, and polymer-supported phosphines in particular,^{28–30} it is perhaps not surprising that such materials have been used to catalyze alkyne to 1,3-diene isomerization reactions. The first example of this was reported by Barrett and co-workers when they described the preparation and use of ROMPgel-supported triphenylphosphine reagent/catalyst **20** (Scheme 12).³¹ Polymer **20** was prepared by ring-opening metathesis polymerization of a phosphine-functionalized norbornene monomer. The isomerization of alkynoate **21** to **22** was performed using 0.4 equivalents of **20**, and 0.5 equivalents of acetic acid in toluene at 110 °C over 18 hours to afford **22** in 97% yield and 90% purity.



Scheme 12

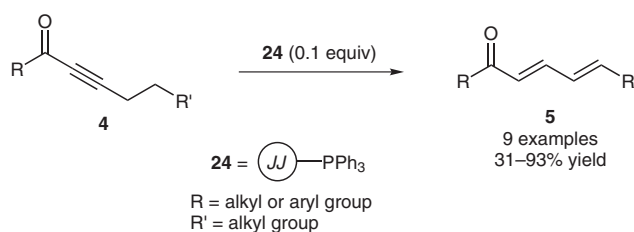
Later Jiang and co-workers reported the use of ‘standard’ commercially available divinylbenzene cross-linked polystyrene-supported triphenylphosphine (**23**) as the catalyst for alkyne to 1,3-diene isomerization reactions of alkynones **4** to products **5** (Scheme 13).³² These reactions were performed in toluene at 80 °C over 18 hours using 0.2 equivalents of **23**. Aromatic, carbocyclic and aliphatic alkynones were used as substrates **4** and the corresponding dienones **5** were obtained in 47–81% yield, with 82–93% conversion. It was noted that both electronic and steric factors strongly affected the reactions. Bulky aliphatic alkynones afforded poorer results in terms of both yield and conversion than did aromatic substrates. They also studied the recyclability of catalyst **23** in these reactions, and found that the catalytic ability decreased slightly with each reuse (4 cycles). It was suggested that the



Scheme 13

observed decline in the performance of **23** was due to its ‘physical destruction’ and the formation of its oxide.

More recently, Jiang et al. screened a series of other polymer-supported phosphine catalysts in the isomerization reaction of alkynones **4** to products **5** and found that the best catalyst was JandaJel-supported triphenylphosphine (**24**, *JJ*-PPh₃).^{33–35} With the use of 0.1 equivalents of heterogeneous catalyst **24**, the reactions were performed solvent-free at 70 °C over 12 hours (Scheme 14). Aromatic, carbocyclic, and aliphatic alkynones and symmetrical bis-alkynones were used as substrates, and the corresponding dienones were obtained in 31–93% yield, with 49–100% conversion. Again, bulky aliphatic substrates afforded poorer results than did aromatic derivatives. They also attempted to recycle **24** in these reactions, but, as before, the activity of the catalyst decreased slightly in each subsequent reaction cycle. It was determined by ³¹P NMR analysis of recovered **24** that its poor recyclability was due to oxide formation.



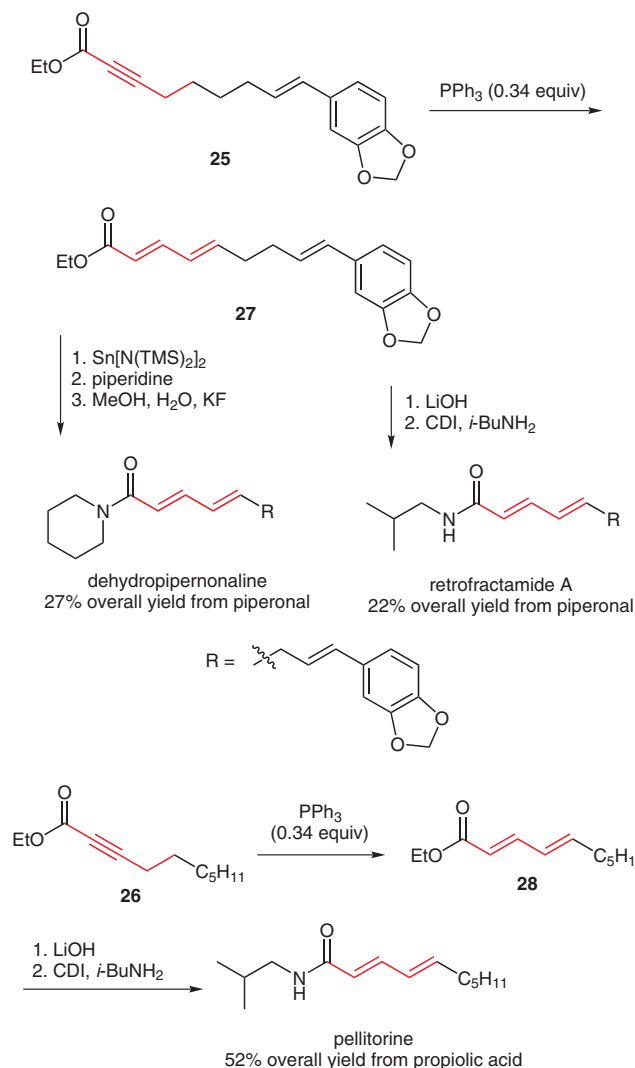
Scheme 14

2.3 Synthetic Applications

The alkyne to 1,3-diene isomerization reaction has been used on numerous occasions in the context of natural product synthesis where the resulting diene is either a synthetic intermediate that is further transformed or an actual structural component of the target molecule, and such applications are summarized in this section. For clarity, the carbon–carbon bonds involved in the reaction are highlighted in red.

Strunz and Finlay reported the earliest synthetic application of the alkyne to 1,3-diene isomerization reaction in their synthesis of a series of unsaturated amide alkaloids (Scheme 15).³⁶ Because amides were previously shown by both Trost and Lu to be rather unreactive in these reaction, alkynoate substrates **25** and **26** were used as starting materials, with the ester groups being converted, post isomerization, into the required amide groups. In this way,

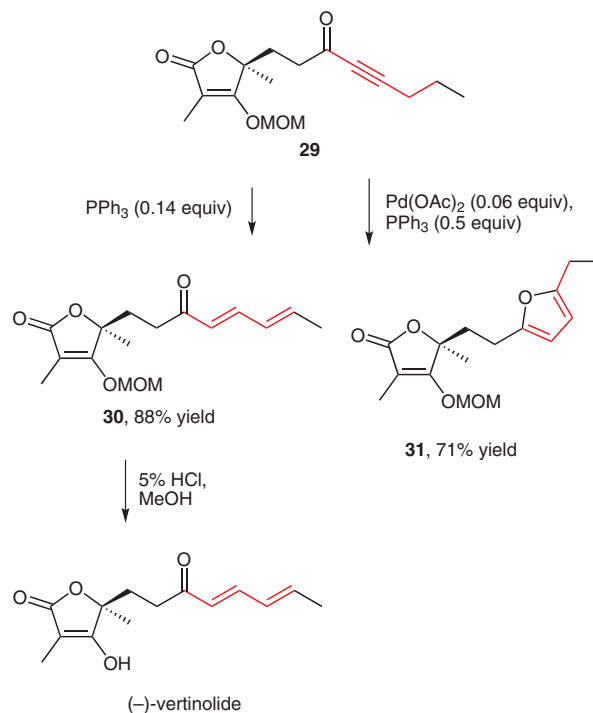
retrofractamide A, dehydropiperonaline, and pellitorine were expediently synthesized from **25** and **26**, via intermediates **27** and **28**, as shown. Numerous other naturally occurring related amides were prepared using analogous reaction sequences.



Scheme 15

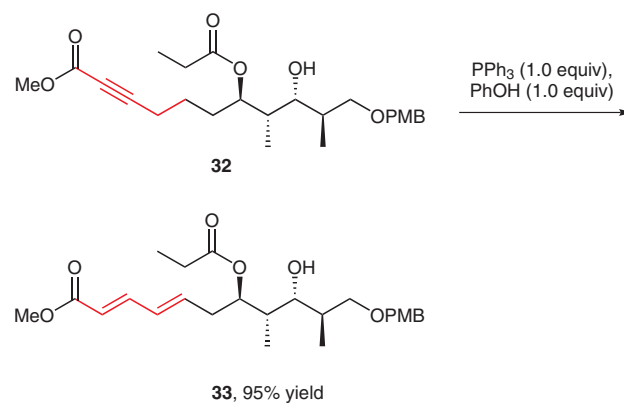
In their synthesis of (–)-vertinolide, a β -tetrone acid derivative from *Verticillium intertextum*, Matsuo and Sakaguchi used an alkyne to 1,3-diene isomerization reaction to install the required dienone functionality of the final product (Scheme 16).³⁷ Isomerization of substrate **29**, prepared from naturally occurring lactic acid, demonstrated how a metal catalyst was not only unnecessary for the desired transformation, but also potentially deleterious. The desired conversion of **29** into **30** occurred with triphenylphosphine catalysis, whereas use of the transition-metal catalyst palladium(II) acetate afforded only furan **31**. Treatment of **30** with acidic methanol completed the synthesis of (–)-vertinolide.

An application of the alkyne to 1,3-diene isomerization reaction in synthetic efforts towards the construction of a



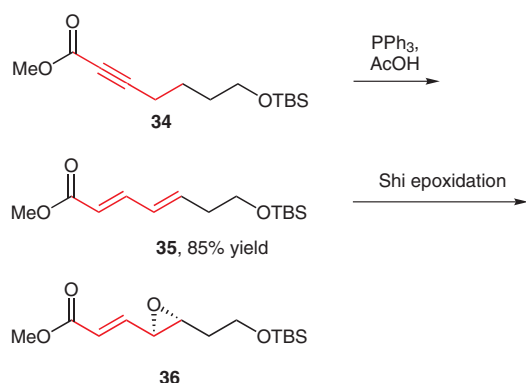
Scheme 16

biologically important compound was reported by Pateron et al.³⁸ In this work, a compound corresponding to the C1–C11 subunit of the marine macrolide aplyronine A was prepared from alkyne **32** (Scheme 17). Isomerization of **32** using Rychnovsky's conditions (PPh_3 and phenol) afforded **33** as a single stereoisomer in excellent yield. Compound **33** was then further elaborated to a protected synthetic intermediate that corresponds to the (*E,E*)-2,4-dienoic acid containing portion of the natural product.



Scheme 17

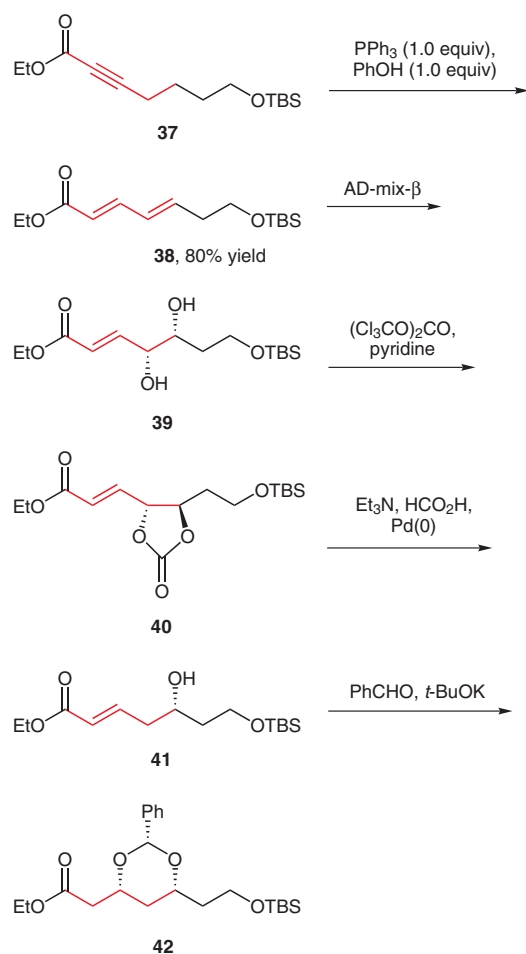
In an example where the alkyne to 1,3-diene isomerization reaction was used to prepare a building block of a complex molecule that does not contain a diene moiety, Campagne and Bluet reported the synthesis of a compound that corresponds to the C1–C7 portion of octalactin A (Scheme 18).³⁹ Alkyne **34** was isomerized using a combination of triphenylphosphine and acetic acid to af-



Scheme 18

ford dienoate **35** in good yield. The δ,γ -double bond of **35** was then asymmetrically epoxidized using a chiral dioxirane to form **36**.

O'Doherty and Hunter reported a similar strategy for selectively oxidizing the δ,γ -double bond of the conjugated dienoate obtained from an isomerization reaction in the context of natural product synthesis. For example, isomerization of **37** with triphenylphosphine and phenol afforded dienoate **38**, which in turn was asymmetrically dihydroxylated at the δ,γ -double bond to yield **39** (Scheme 19).⁴⁰

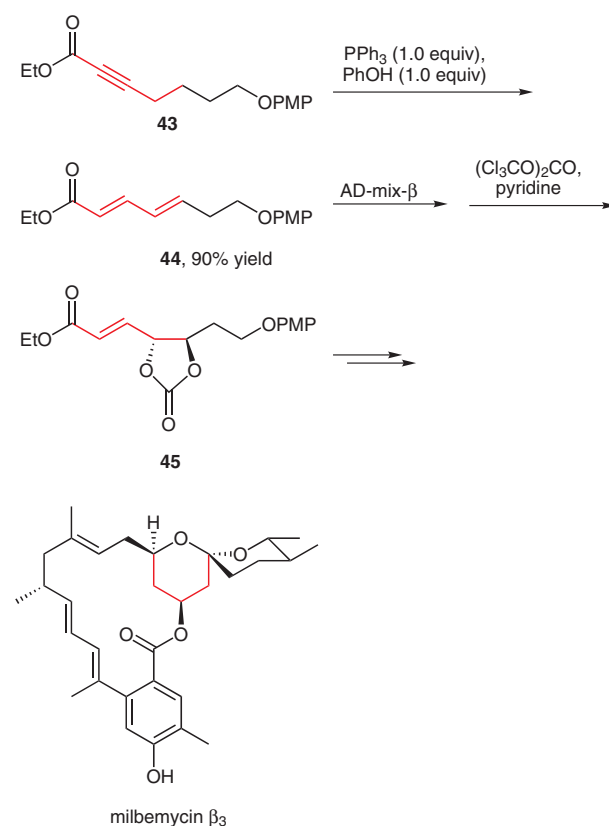


Scheme 19

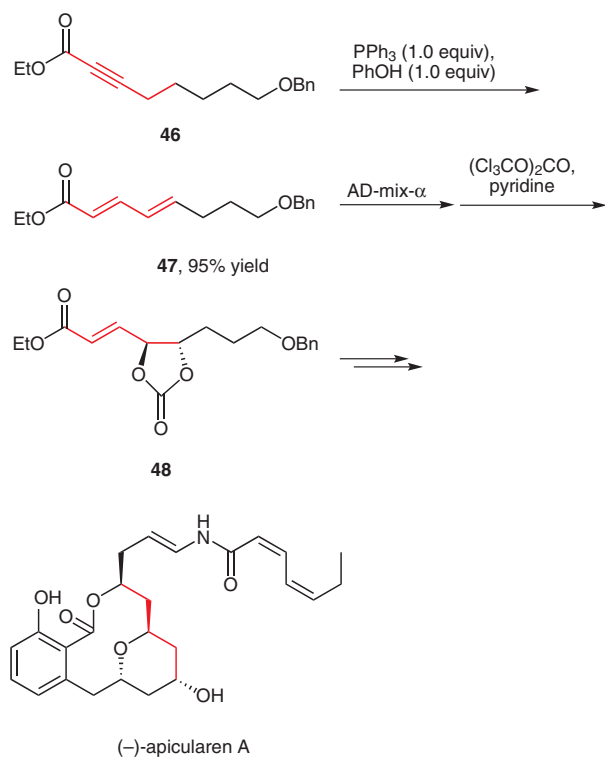
Conversion of **39** into cyclic carbonate **40**, followed by selective reduction, afforded alcohol **41**. Reaction of **41** with benzaldehyde in the presence of base afforded the protected *syn*-1,3-diol **42**, which was envisioned as a versatile chiral building block that corresponds to the C5–C11 portion of leucascandrolide A. Overall, this sequence of reactions provides a convenient method for the synthesis of chiral 3,5-dihydroxy carboxylic acid derivatives from simple alkyne starting materials.

Later, O'Doherty's research group used this methodology in their synthesis of mibemycin β_3 (Scheme 20).⁴¹ Alkynoate **43**, the *p*-methoxyphenyl analogue of **37**, was isomerized to **44**, which was subsequently dihydroxylated and converted into cyclic carbonate **45**, as before. In this synthesis, the initial carboxylate carbon of **43** was transformed into the acetal carbon of the final product. Most recently, O'Doherty and Li reported the synthesis of the macrolide (–)-apicularen A from alkynoate **46**, by way of dienoate **47** and cyclic carbonate **48** (Scheme 21).⁴² Here the carboxylate carbon of starting material **46** became C9 of the target molecule. Given the structural differences between mibemycin β_3 and (–)-apicularen A, it is clear that compounds such as **44** and **45**, and their structural analogues, are indeed versatile building blocks for the synthesis of a broad range of complex molecules that are readily prepared from alkynes using the alkyne to 1,3-diene isomerization reaction.

The macrolactins are a family of 24-membered-ring polyene macrolides produced by a deep sea marine bacterium



Scheme 20

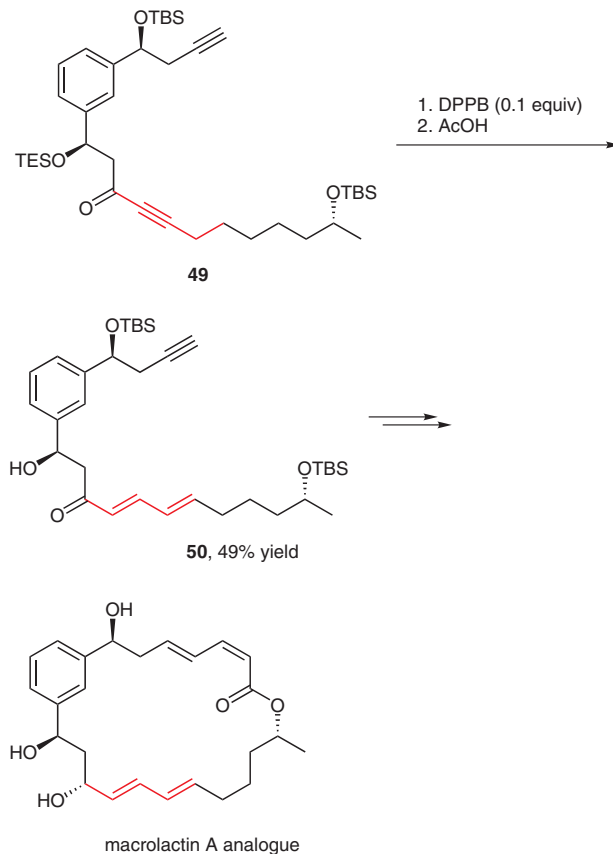


Scheme 21

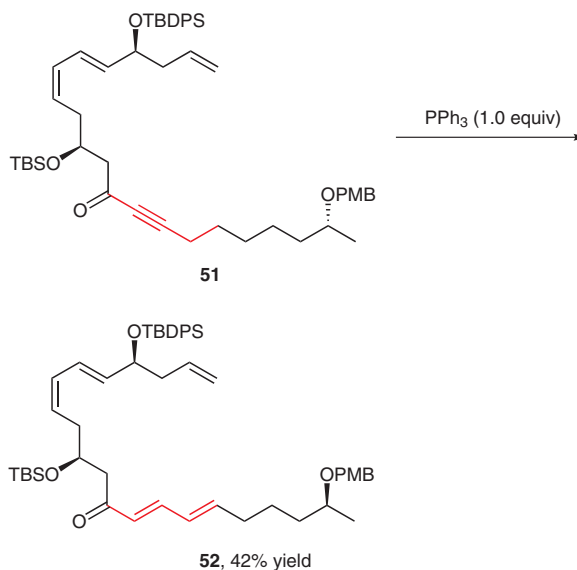
and they possess antiviral and anticancer activity. Thus, many research groups have been interested in the synthesis of such compounds. Takemoto and co-workers have reported the enantioselective synthesis of macrolactin A analogues in which an alkyne to 1,3-diene isomerization was used to prepare a key intermediate (Scheme 22).^{43,44} In this case, the formed (*E,E*)-1,3-diene itself is a structural element of the final product and the activating carbonyl group is reduced to a chiral alcohol. In this work the optimal catalyst for the isomerization of alkyne **49** was found to be bis(diphenylphosphine)butane (DPPB), rather than triphenylphosphine. Dienone **50** was isolated in moderate overall yield after removal of an alcohol protecting group, and was then further elaborated into a series of macrolactin A analogues.

A very similar strategy was used in the synthesis of the C4–C24 fragment of macrolactin A by Campagne and co-workers.⁴⁵ Interestingly, triphenylphosphine (1.0 equiv) was used as the catalyst in refluxing toluene for the conversion of alkyne **51** into **52** (Scheme 23). The obtained yield of 42% was similar to that observed by Takemoto's research group and was reported as being unoptimized.

Most recently, Ma and co-workers reported the asymmetric synthesis of the (13*R*,14*R*,19*R*)-isomer of FR252921, an immunosuppressive agent, via a trienoate prepared by a Rychnovsky-type alkyne to 1,3-diene isomerization reaction (Scheme 24).⁴⁶ Using the catalyst combination of triphenylphosphine and phenol, **53** was converted into conjugated triene **54**, which represents the C1–C9 portion of the target molecule, in excellent yield.

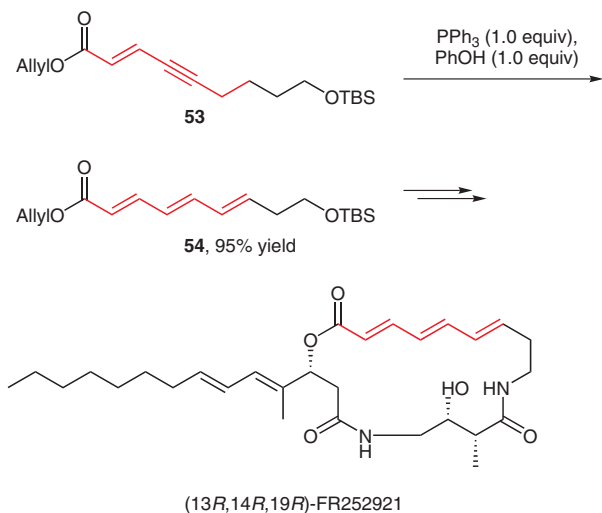


Scheme 22

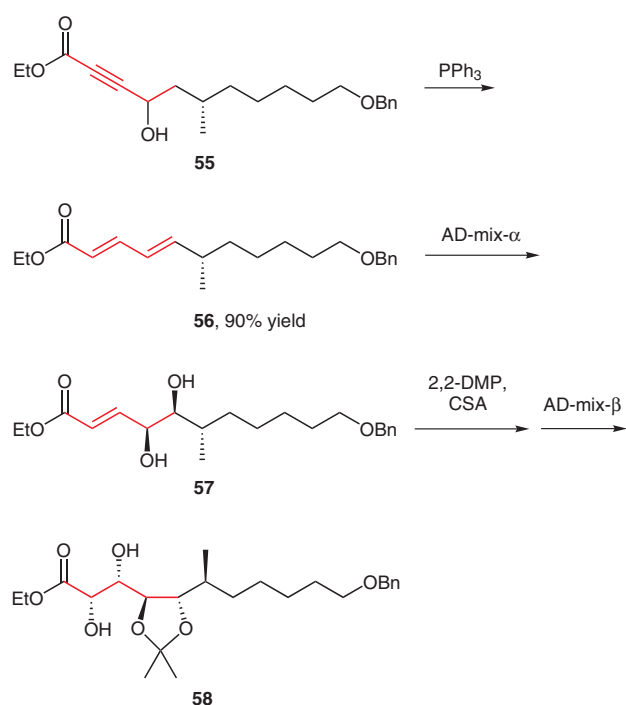


Scheme 23

As discussed at the beginning of this review, the alkyne to 1,3-diene isomerization reaction evolved from a series of similar alkyne isomerization processes, both catalytic and stoichiometric. The final few examples from the literature presented here show how these related reactions of activated alkynes have been used in the context of natural product synthesis.

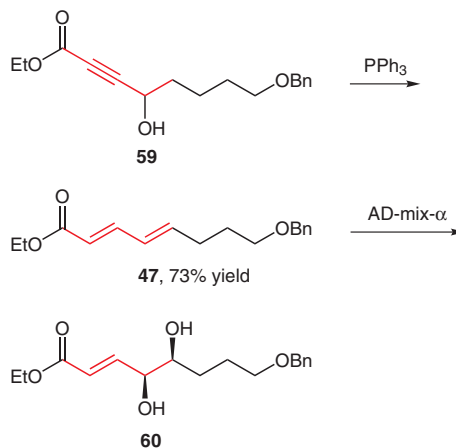


Scheme 24



Scheme 25

In their syntheses of fragments of the microsclerodermins A and B, and palmerolide A, Chandrasekhar et al.^{47,48} used the deoxygenative rearrangement of γ -hydroxy- α,β -ynoates (Scheme 7) originally reported by Guo and Lu to generate dienoates that were regioselectively and enantioselectively dihydroxylated in the manner reported by O'Doherty (Scheme 25). In their synthesis of a compound that corresponds to the C1–C20 portion of microsclerodermins A and B, the resulting carbon–carbon double bonds were oxidized sequentially to form selectively protected polyol **58** from starting material **55**, by way of dienoate **56** and diol **57**. For their synthesis of a C1–C14 palmerolide A fragment (Scheme 26), only the δ,γ -double



Scheme 26

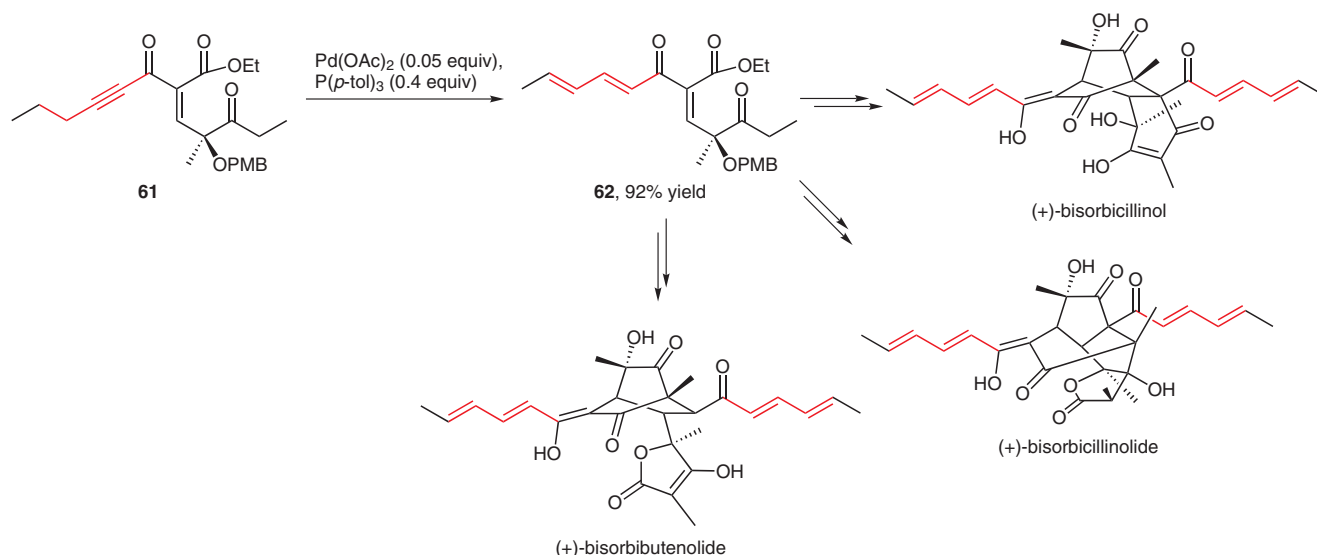
bond of **47** (from **59**) was dihydroxylated to form chiral diol **60**, which O'Doherty had previously converted into carbonate **48**.

Finally, in an example that illustrates the sometimes circuitous nature of chemical research, a report by Deng and co-workers described the isomerization of synthetic intermediate **61** to **62** using palladium(II) acetate and tri(*p*-tolyl)phosphine (Scheme 27).⁴⁹ The authors did not mention whether they attempted this transformation using only phosphine catalysis. Dienone **62** was subsequently cyclized and converted into the structurally related natural products (+)-bisorbicillinol, (+)-bisorbibutenolide, and (+)-bisorbicillinolide.

3 Conclusions

The activated alkyne to (*E,E*)-1,3-diene isomerization reaction is one of a growing set of organic-molecule-catalyzed reactions that is being used in the synthesis of complex organic molecules and natural products. As shown in the examples presented in this review, the conjugated diene that is formed by this reaction can be further transformed into intermediate synthetic building blocks or can be an actual structural element of the synthetic target. Even (*E,E,E*)-1,3,5-trienes can be efficiently synthesized from activated enyne starting materials using such reactions.

Alkynone starting materials are generally reactive enough to require only a phosphine catalyst (usually triphenylphosphine) at elevated temperature in an aromatic solvent. On the other hand, alkynoates typically require the addition of an acid co-catalyst (usually phenol), although pentafluorophenyl esters do not. Such fluorinated esters also have the advantage that they can be reduced, transesterified or transaminated in situ. Furthermore, recent reports have shown that such reactions can be performed using water as the reaction medium, and that easily separable heterogeneous catalysts can also be used, either with or without a solvent.



Scheme 27

Considering the frequent occurrence of the (2*E*,4*E*)-2,4-dienoate structural motif in natural products, the general ease of the synthesis of the required starting materials, and the mild nature and stereoselectivity of the alkyne to 1,3-diene isomerization reaction, it is anticipated this organocatalytic transformation will be increasingly used in organic synthesis in the coming years.

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