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
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 corresponding (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.

2 The Reaction

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) [Pd2(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 [RuCl2(PPh3)3] was also an effective catalyst for such transformations,9 while Lu and co-workers reported that dihydridotetrakis(triphenylphosphine)ruthenium(II) [RuH2(PPh3)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, IrH3[P(i-Pr)3]2, was also an efficient catalyst for alkynone to dienone isomerization reactions, especially in the presence of excess phosphine. They then studied the scope of these catalysts for the conversion of compounds 4 into compounds 5 (Scheme 4) and reported the synthesis of both trienones and tetraenones. They even applied these reaction conditions to the isomerization of alkynoates and alkynamides.

### Biographical Sketches

**Cathy Kar-Wing Kwong**

received her B.Sc. degree in chemistry from the University of Hong Kong in 2004. She is currently a Ph.D. student in Professor Toy’s group, and her research is focused on the development of new polymeric reagents and catalysts for organic synthesis.

**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 University of Hong Kong in the group of Professor P. H. Toy. His research centered on the development of new polymer-supported catalysts 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 research 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.
The Alkyne to 1,3-Diene Isomerization Reaction

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]2 (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

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, dienoates 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 allenoate to the corresponding 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, 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](image1)

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). 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-diynone 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-diynoate 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 isomerization reactions, especially for alkynoate substrates.

![Scheme 10](image2)

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). 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](image3)
Recently it was reported that alkyne to 1,3-diene isomerization reactions can be performed in water without the need of an organic solvent. 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, 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 ROMP-gel-supported triphenylphosphine reagent/catalyst \( \text{(Scheme 12)} \). Polymer \( \text{20} \) was prepared by ring-opening metathesis polymerization of a phosphine-functionalized norbornene monomer. The isomerization of alkyne \( \text{21} \) to \( \text{22} \) was performed using 0.4 equivalents of \( \text{20} \), and 0.5 equivalents of acetic acid in toluene at 110 °C over 18 hours to afford \( \text{22} \) in 97% yield and 90% purity.

![Scheme 12](image)

Later Jiang and co-workers reported the use of ‘standard’ commercially available divinylbenzene cross-linked polystyrene-supported triphenylphosphine \( \text{(23)} \) as the catalyst for alkyne to 1,3-diene isomerization reactions of alkynones \( \text{4} \) to products \( \text{5} \) (Scheme 13). These reactions were performed in toluene at 80 °C over 18 hours using 0.2 equivalents of \( \text{23} \). Aromatic, carbocyclic and aliphatic alkynones were used as substrates and the corresponding dienones \( \text{5} \) 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 \( \text{23} \) in these reactions, and found that the catalytic ability decreased slightly with each reuse (4 cycles). It was suggested that the observed decline in the performance of \( \text{23} \) 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 \( \text{4} \) to products \( \text{5} \) and found that the best catalyst was \( \text{Janda/el-supported triphenylphosphine (24, JJPPh3).} \) With the use of 0.1 equivalents of heterogeneous catalyst \( \text{24} \), 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 \( \text{24} \) in these reactions, but, as before, the activity of the catalyst decreased slightly in each subsequent reaction cycle. It was determined by \( ^{31} \text{P NMR analysis of recovered 24} \) that its poor recyclability was due to oxide formation.

![Scheme 13](image)

### 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). Because amides were previously shown by both Trost and Lu to be rather unreactive in these reactions, alkyne substrates \( \text{25} \) and \( \text{26} \) were used as starting materials, with the ester groups being converted, post isomerization, into the required amide groups. In this way,
retrofractamide A, dehydropipernonaline, 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-tetronic 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). Isomerization of 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 biologically important compound was reported by Paterson et al. In this work, a compound corresponding to the C1–C11 subunit of the marine macrolide aplyronine A was prepared from alkynoate 32 (Scheme 17). Isomerization of 32 using Rychnovsky’s conditions (PPh₃ 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 16

### Scheme 17
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 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 milbemycin β3 (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 macrocycle (-)-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 milbemycin β3 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 18

\[
\begin{align*}
\text{MeO} & \quad \text{OTBS} \\
\text{MeO} & \quad \text{OTBS} \\
\text{MeO} & \quad \text{OTBS}
\end{align*}
\]

Scheme 19

\[
\begin{align*}
\text{EtO} & \quad \text{O} \\
\text{EtO} & \quad \text{O} \\
\text{EtO} & \quad \text{O}
\end{align*}
\]

Scheme 20

\[
\begin{align*}
\text{PhCHO, t-BuOK} \\
\text{PhCHO, t-BuOK}
\end{align*}
\]
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 alkynone 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 alkynone 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 (13R,14R,19R)-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.

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.
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 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.

### 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.
Considering the frequent occurrence of the (2E,4E)-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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