Isomerization of Electron-Poor Alkynes to the Corresponding (*E*,*E*)-1,3-Dienes Using a Bifunctional Polymeric Catalyst Bearing Triphenylphosphine and Phenol Groups

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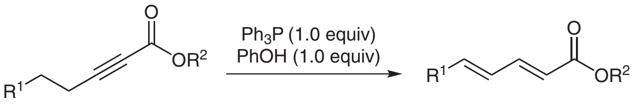
Abstract: The use of a bifunctional non-cross-linked polystyrene bearing both phosphine and phenol groups for the organocatalytic isomerization of alkynes bearing electron-withdrawing ester substituents to afford the corresponding (*E*,*E*)-dienes in excellent yield and stereoselectivity is described. When polystyrene functionalized with only phosphine groups was used as the catalyst, either low or no yield of the desired product was obtained. Thus both of the functional groups of the bifunctional polystyrene catalyst were essential for efficient catalysis to occur. This bifunctional polymeric catalyst was also used to synthesize (*E*,*E*,*E*)-trienes and (*E*,*E*)-diene-substituted 2(*H*)-pyran-2-ones from the corresponding alkynes.

Key words: organocatalysis, polymer-supported catalyst, alkyne isomerization, dienes, triphenylphosphine, phenol

In the early 1990s, the research groups of Trost[1] and Lu[2] reported Ph_3P-catalyzed isomerization of alkynones to the corresponding (*E*,*E*)-dienones. Subsequently, Rychnovsky and Kim reported that the use of PhOH as a co-catalyst allowed less activated alkynoates to be similarly isomerized (Scheme 1),[3] and this advancement has led such isomerization reactions to be used in a variety of organic contexts,[4] especially natural product synthesis.[5] While such reactions are generally high yielding and stereoselective, they suffer from the drawback that even though Ph_3P and PhOH act as catalysts, 0.5–1.0 equivalents of each is generally used for the sake of efficiency. Thus, purification of the desired compound can be tedious and time consuming. Jiang and co-workers have tried to address this issue by using heterogeneous polystyrene-supported Ph_3P as the catalyst in these reactions, but since no PhOH was present, only alkynones were isomerized.[6]



Scheme 1 Alkyne isomerization reactions catalyzed by Ph_3P and PhOH

We have studied polymer supports for organic chemistry,[7] especially those functionalized with phosphine groups,[8] and have recently reported the synthesis and use of a bifunctional non-cross-linked polystyrene bearing both phosphine and phenol groups (**1**, Scheme 2) and its use as a catalyst in a variety of Morita–Baylis–Hillman reactions.[9] Herein we describe the use of **1** to catalyze the isomerization of a wide range of ester-activated alkynes to the corresponding (*E*,*E*)-dienes in reactions where the desired product is obtained after filtration through silica gel and solvent removal.[10]

Catalyst **1** was prepared according to our previously reported procedure (Scheme 2).[9] For the sake of comparison, we also prepared the corresponding monofunctional polymer **2**,[8a] which possesses only phosphine groups, by a similar method. Since both of these polymers are non-cross-linked, they are soluble in many organic solvents, and can thus act as homogeneous catalysts. Their solubility allowed them to be analyzed by ^{31}P NMR in order to confirm the oxidation state of the phosphine groups to be as depicted in Scheme 2. Furthermore, their loading levels were found to be 1.0 and 1.2 mmol $Ph_3P\ g^{-1}$, respectively, by elemental analysis.[10]

As we wanted to extend upon the work of Jiang and see if **1** was capable of catalyzing the isomerization of alkynoates, alkynes **3a**–**d** were treated sequentially with *n*-BuLi and then either ethyl chloroformate or benzyl chloroformate in a one-pot procedure to afford alkynoates **4a**–**h** (Scheme 3).[11]

With the desired substrates in hand, we compared their isomerization using 1.0 equivalent of either **1** or **2** (1 M benzene, 55 °C, 18 h) in parallel reactions. As can be seen from Table 1, in all cases the use of **1** as the catalyst led to excellent yield of the expected corresponding (*E*,*E*)-dienoate **5a**–**h**, and the use of **2** as the catalyst resulted in either low yield or no product formation. These observations confirm that the presence of phenol is a requirement for the efficient phosphine-catalyzed isomerization of alkynoates, and that **1** is a viable alternative to the catalyst combination of Ph_3P and PhOH. For the reactions catalyzed by **2** in which the isomerized product was formed (entries 1, 2, 7, and 8), silica gel chromatography was required to separate the unreacted starting material from the product in order to determine the yield. However, when **1** was used as the catalyst, the desired product was obtained in pure form after filtration through silica gel and solvent removal. Furthermore, in these reactions the identity of the ester group does not seem to influence

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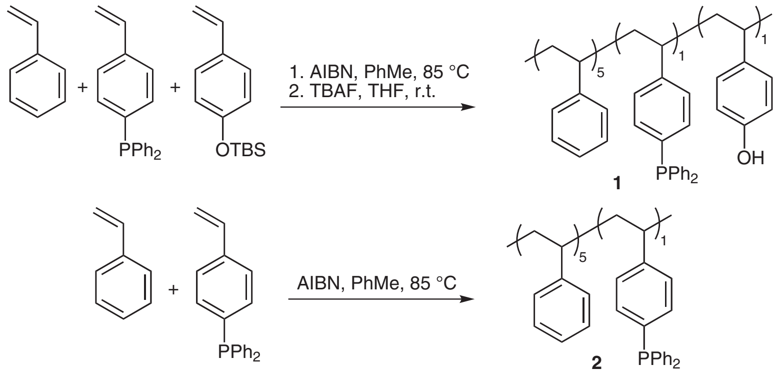
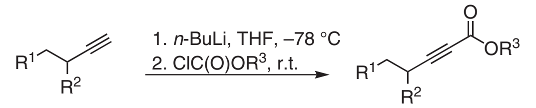


Scheme 2 Synthesis of phosphine functionalized polystyrenes



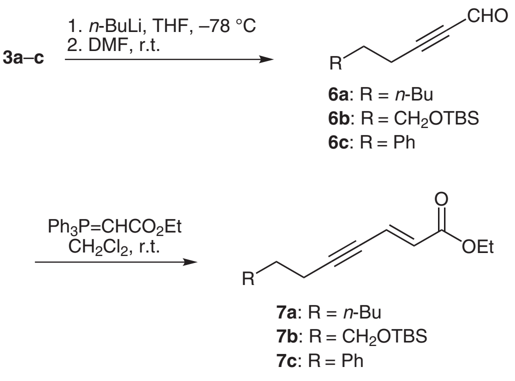
3a: R^1 = *n*-Bu, R^2 = H
3b: R^1 = CH_2OTBS, R^2 = H
3c: R^1 = Ph, R^2 = H
3d: R^1–R^2 = $(CH_2)_4$

4a: R^1 = *n*-Bu, R^2 = H, R^3 = Et
4b: R^1 = *n*-Bu, R^2 = H, R^3 = Bn
4c: R^1 = CH_2OTBS, R^2 = H, R^3 = Et
4d: R^1 = CH_2OTBS, R^2 = H, R^3 = Bn
4e: R^1 = Ph, R^2 = H, R^3 = Et
4f: R^1 = Ph, R^2 = H, R^3 = Bn
4g: R^1–R^2 = $(CH_2)_4$, R^3 = Et
4h: R^1–R^2 = $(CH_2)_4$, R^3 = Bn

Scheme 3 Synthesis of alkynoate isomerization substrates

the efficiency of the reactions (entries 1, 3, 5, and 7 vs. 2, 4, 6, and 8).

Having confirmed that **1** is a good catalyst for the isomerization of alkynoates, we wanted to see if we could also use it to synthesize (*E*,*E*,*E*)-trienoates. Thus, alkynes were used as starting materials again to synthesize the required isomerization substrates, and **3a**–**c** were treated sequentially with *n*-BuLi and DMF to afford the corresponding aldehydes **6a**–**c**. These were purified and then reacted with (carboethoxymethylene)triphenylphosphorane to afford substrates **7a**–**c** (Scheme 4).[11]



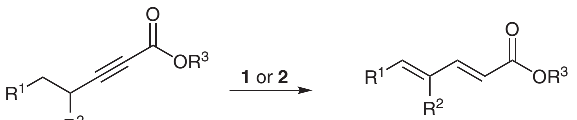
6a: R = *n*-Bu
6b: R = CH_2OTBS
6c: R = Ph

7a: R = *n*-Bu
7b: R = CH_2OTBS
7c: R = Ph

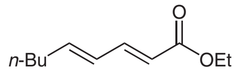
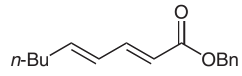
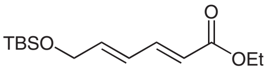
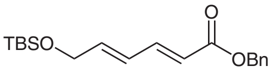
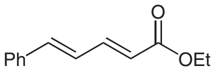
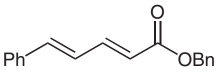
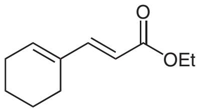
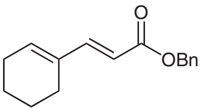
Scheme 4 Synthesis of alkynenoate isomerization substrates

Gratifyingly when **7a**–**c** were subjected to isomerization with catalyst **1** using conditions similar for the isomerization of **4a**–**h** to **5a**–**h**, good yield of the expected corre-

Table 1 Isomerization of **4a**–**h** Using **1** and **2**



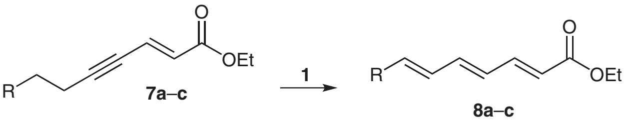
4a–**h** **5a**–**h**

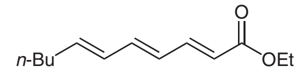
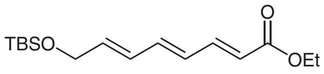
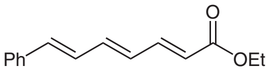
Entry	Substrate	Product	Yield using **1** (%)[a]	Yield using **2** (%)[a]
1	**4a**	 **5a**	84	28
2	**4b**	 **5b**	91	40
3	**4c**	 **5c**	90	0
4	**4d**	 **5d**	89	0
5	**4e**	 **5e**	90	0
6	**4f**	 **5f**	85	0
7	**4g**	 **5g**	84	53
8	**4h**	 **5h**	92	49

[a] Conditions: **4a**–**h** (1.0 mmol), **1** or **2** (1.0 equiv), benzene (1.0 M), 55 °C, 18 h.

sponding (*E*,*E*,*E*)-trienoate **8a–c** was obtained in all cases (Table 2). However, when **2** was used as the catalyst, no desired isomerized product was observed in any of the reactions, even after prolonged reaction times. This seems to indicate that the isomerization of **7a–c** is more dependant upon the presence of phenol groups than are alkynoates **4a–h**.

Table 2 Isomerization of **7a–c** Using **1**



Substrate	Product	Yield (%)[a]
7a	 **8a**	72
7b	 **8b**	76
7c	 **8c**	87

[a] Conditions: **7a–c** (1.0 mmol), **1** (1.0 equiv), benzene (1.0 M), 55 °C, 18 h.

Next, we were inspired by the structure of gymnoconjugatin B[12] (Figure 1) and related natural products to see if alkyne-substituted 2(*H*)-pyran-2-one derivatives could also be isomerized by **1**. For this study substrates **9a–c** (Figure 1) were synthesized according to known procedures,[13–15] and their isomerization was only studied using catalyst **1**.

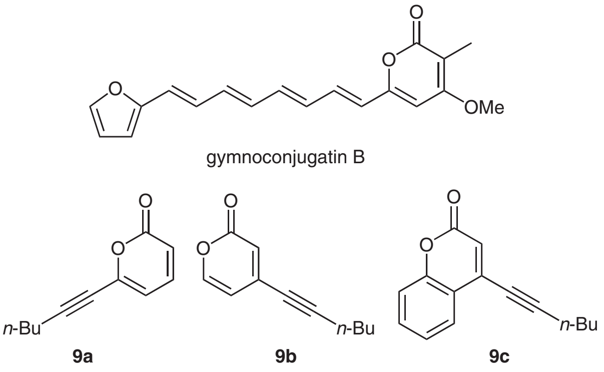
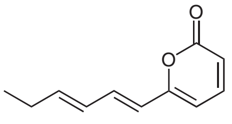
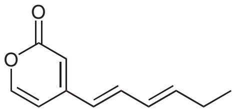
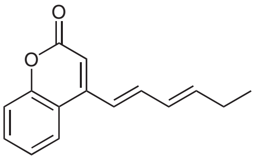


Figure 1 Gymnoconjugatin B and alkyne-substituted 2(*H*)-pyran-2-one isomerization substrates

As can be seen in Table 3, when our standard isomerization conditions using **1** were applied to **9a–c**, high yield of the desired product **10a–c** was obtained in all cases. Thus, the alkyne isomerization reaction might be useful in the synthesis of related biologically interesting natural products, and **1** is a suitable catalyst to study in such applications.

Table 3 Isomerization of **9a–c** Using **1**

$\mathbf{9a–c} \xrightarrow{\mathbf{1}} \mathbf{10a–c}$

Substrate	Product	Yield (%)[a]
9a	 **10a**	100
9b	 **10b**	83
9c	 **10c**	89

[a] Conditions: **9a–c** (1.0 mmol), **1** (1.0 equiv), benzene (1.0 M), 55 °C, 18 h.

In summary, we have found that a bifunctional polystyrene functionalized with both phosphine and phenol groups (**1**) is capable of catalyzing the isomerization of a wide range of ester-activated alkynes to the corresponding (*E*,*E*)-dienes in high yield and stereoselectivity. Because **1** possesses both of the organocatalytic groups necessary for this transformation, isolatation of the desired product of the reactions was greatly simplified compared to when Ph_3P and PhOH are used. When a polymeric catalyst bearing only phosphine groups (**2**) was examined, either low or no yield of the desired product was obtained. Furthermore, we have extended the scope of this isomerization reaction and for the first time report its application to 2(*H*)-pyran-2-one derivatives. It is anticipated that such substrates can be used in the synthesis of natural products, such as gymnoconjugatin B. Such synthetic studies and the development of easily recyclable, heterogeneous versions of **1** are currently under way, and the results of these studies will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) We have previously reported the use of a cross-linked bifunctional analogue of **1** as a catalyst in Morita–Baylis–Hillman reactions, which have some mechanistic similarities to the isomerization reactions reported herein. However, due to its heterogeneous nature and poor swelling properties, it was less efficient than a corresponding cross-linked monofunctional analogue of **2**. See ref. 8d for details.

(11) See Supporting Information for details.

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