Very Important Publication

Phosphine-Mediated Dimerization of Conjugated Ene-Yne Ketones: Stereoselective Construction of Dihydrobenzofurans

Cheng-Zhi Zhu,[a] Yao-Liang Sun,[a] Yin Wei,[c] and Min Shi[a,b,c,*]

[a] Key Laboratory for Advanced Materials and Institute of Fine Chemicals, School of Chemistry & Molecular Engineering, East China University of Science and Technology, 130 Mei Long Road, Shanghai 200237, People's Republic of China
[b] State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China
[c] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China
Fax: (+86)-21-6416-6128; e-mail: mshi@mail.sioc.ac.cn

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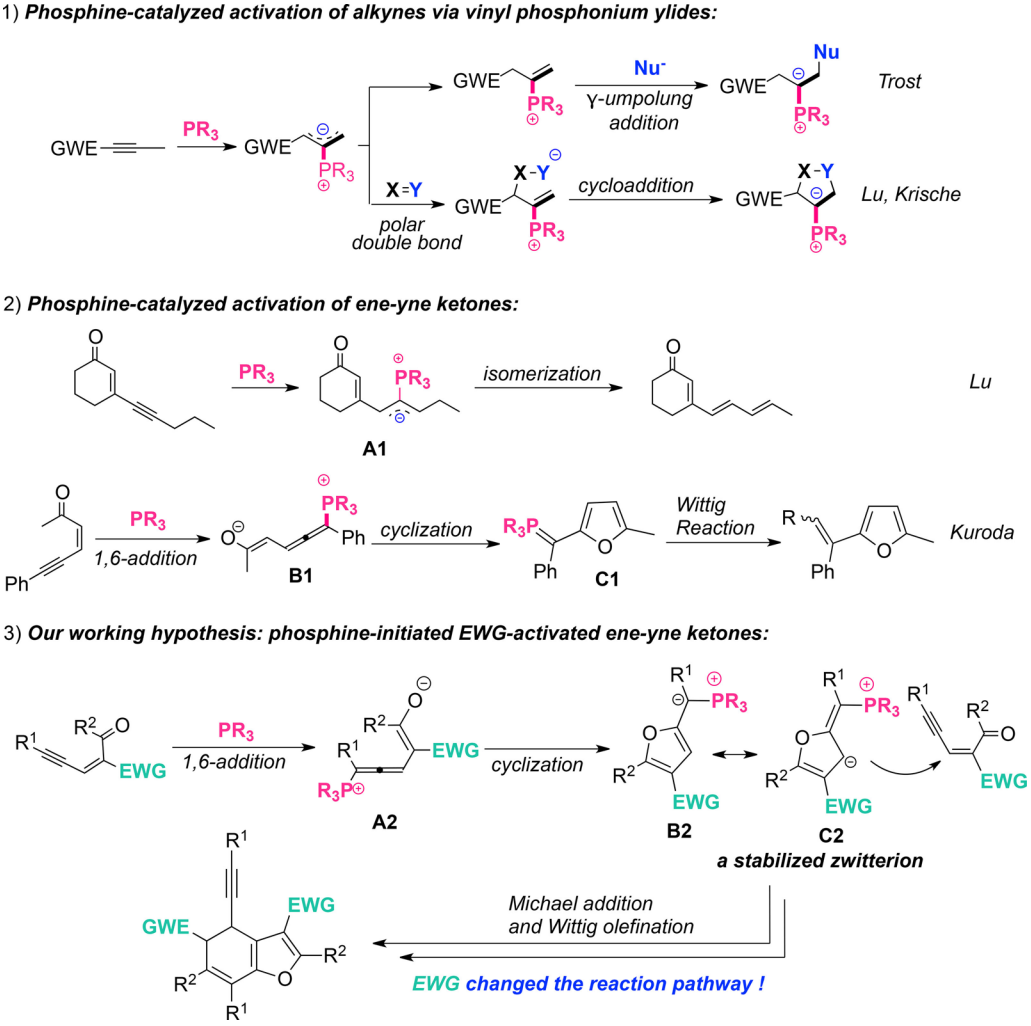
Abstract: A new strategy for the phosphine-mediated dimerization of conjugated ene-yne ketones to produce functionalized dihydrobenzofurans has been developed, affording diversified 4,5-dihydrobenzofurans in moderate to excellent yields with high diastereoselectivities under mild conditions. This new synthetic method can tolerate a variety of functional groups and can be performed on a gram scale and in an asymmetric variant using the chiral phosphine Xyl-BINAP to give the desired products with up to 94% *ee*.

Keywords: dimerization; ene-yne ketones; functionalized furans; phosphines; Wittig olefination

In the past two decades, nucleophilic phosphine organocatalysis has been developed to a powerful synthetic tool for the construction of a wide variety of novel molecules.[1] Among these synthetic protocols, phosphine-mediated/catalyzed annulations of activated ene-ynes, allenes or Morita–Baylis–Hillman (MBH) carbonates have played pivotal roles for the synthesis of functionalized carbo- and heterocyclic skeletons.[2] A phosphonium dienolate as a reactive species can be easily generated from activated alkynes upon phosphine catalysis to conduct γ-umpolung addition or cycloaddition reactions as explored by Trost, Lu and Krische (Scheme 1, 1).[3] In the phosphine-catalyzed activation of ene-yne ketones, the isomerization of carbon-carbon multiple bonds to the conjugated trienes has been reported by Lu also *via* the *in situ* generated phosphonium dienolate **A1** (Scheme 1, 2).[4] Moreover, Kuroda and co-workers reported another example of the phosphine-initiated reaction of ene-yne ketones *via* the phosphonium enolate **B1**. In this reaction, the cyclization of **B1** gave phosphonium ylide **C1**, affording a vinylfuran *via* a Wittig-type olefination (Scheme 1, 2).[5] It could be realized that, in all the cases, the *in situ* generated active species, a vinylphosphonium ylide, sets the stage for the elimination of the phosphine along with one or more proton transferring processes to accomplish the isomerization or cyclization reactions.

Thus far, successful examples for the construction of functionalized furans by isomerization of carbonyl group-containing ene-ynes have been extensively explored.[6] On the basis of these outstanding precursory examples, we envisaged that EWG-activated ene-yne ketones would go through a similar process as Kuroda's one to generate a phosphonium ylide **B2** and a resonance zwitterionic intermediate **C2** *via* intermediate **A2**. Since the existing additional EWG can stabilize the anionic intermediate, the resonance structure may more lean to the zwitterionic intermediate **C2**, which could be more easily captured by another ene-yne ketone molecule, thus affording a different reaction outcome (Scheme 1, 3). To our delight, we found that the dimerization of ene-yne ketones indeed took place *via* zwitterionic intermediate **C2** through a Michael addition and a subsequent Wittig olefination to produce dihydrobenzofurans.

Furan derivatives are of considerable interest in both synthetic and medicinal chemistry due to the numerous natural products and pharmaceuticals incorporating this key heterocyclic framework.[7] However, synthetic methods for preparing dihydrobenzofurans from alkenes or alkynes have been less explored until now. To the best of our knowledge, only one example has been reported, affording 3,6-dimethyl-4,5-dihydrobenzofuran as a minor product.[8] Our phosphine-mediated dimerization reaction of conjugated ene-yne

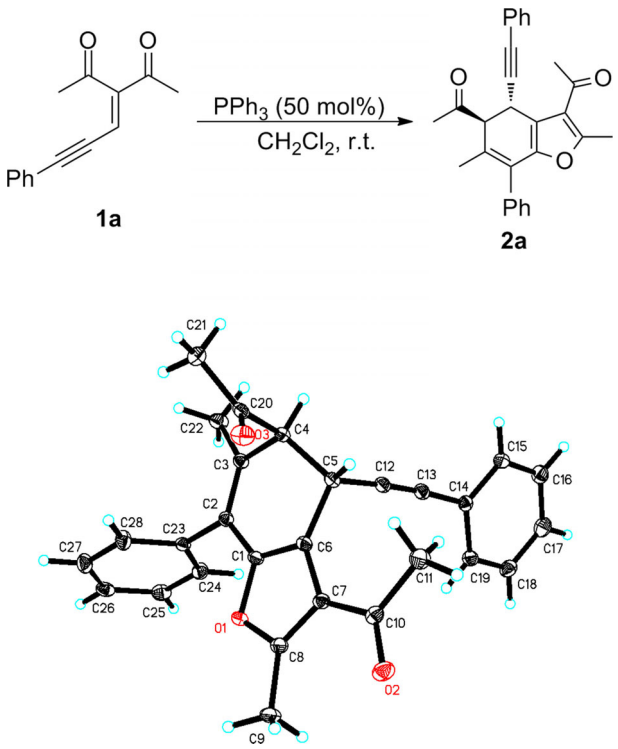


Scheme 1. Previous work and our working hypothesis.

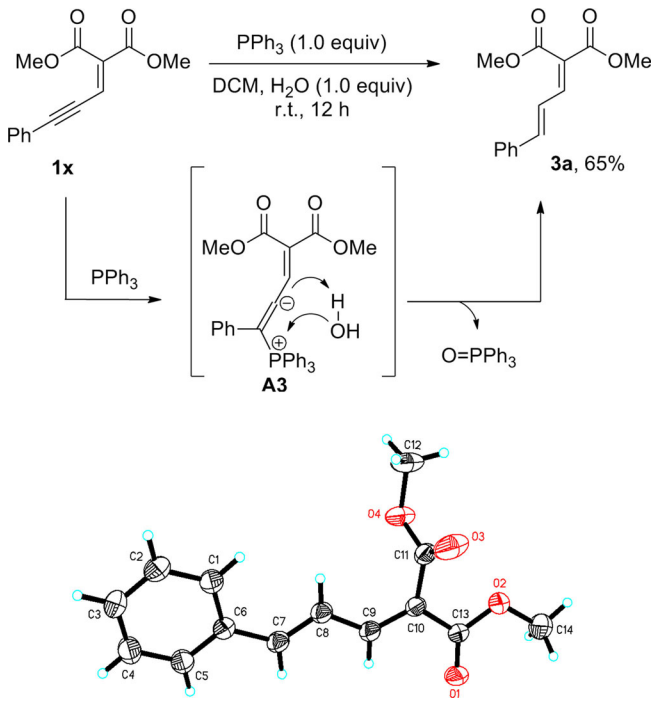
ketones described above can efficiently deliver functionalized 4,5-dihydrobenzofurans under mild conditions from readily available starting materials. This interesting finding encouraged us to further explore this novel synthetic method under phosphine mediation.

Initial studies using ene-yne ketone **1a** as the substrate were aimed at determining the reaction outcome and subsequently optimizing the reaction conditions. The results are summarized in Table S1 in the Supporting Information and we finally identified that the optimal conditions comprise carrying out the reaction in CH_2Cl_2 at room temperature and using a half molar equivalent of PPh_3 as the promoter to give **2a** in 98% yield (Scheme 2). When a larger amount of PPh_3 was used, the yield of **2a** could not be improved further. The structure of **2a** has been unambiguously assigned by X-ray diffraction and the CIF data are shown in the Supporting Information.[9]

Having established the optimal reaction conditions, we next investigated the substrate scope with respect to a wide range of substituents (R^1) on the alkyne moiety of the conjugated ene-yne ketones **1** (Table 1). As illustrated, when R^1 was a substituted phenyl group with different electronic properties (e.g., electron-neutral, electron-rich, or electron-deficient) such as methyl, methoxy, halogen-substituted phenyl group, the reactions proceeded very well, affording the corresponding products **2a**–**2g** in high yields. A heterocyclic aromatic ring was also tolerated to give the respective product **2h** in 90% yield. An interesting consequence was that when R^1 was an *ortho*-substituted aromatic group, the products **2i**–**2k** were produced as two diastereometric mixtures, probably due to the fact that steric hindrance blocked the free rotation, giving two diastereomeric rotamers. Unfortunately, a sterically encumbered substrate, the 1-naphthyl group-substituted ene-yne ketone **1l**, did not give the corresponding product **2l** under the standard conditions. When R^1 was an aliphatic group, the reaction also worked smoothly after increasing the concentration of the employed substrates **1m–1o**, giving the desired products **2m–2o** in reasonable yields ranging



Scheme 2. The optimal conditions for the PPh_3-mediated dimerization of **1a**.



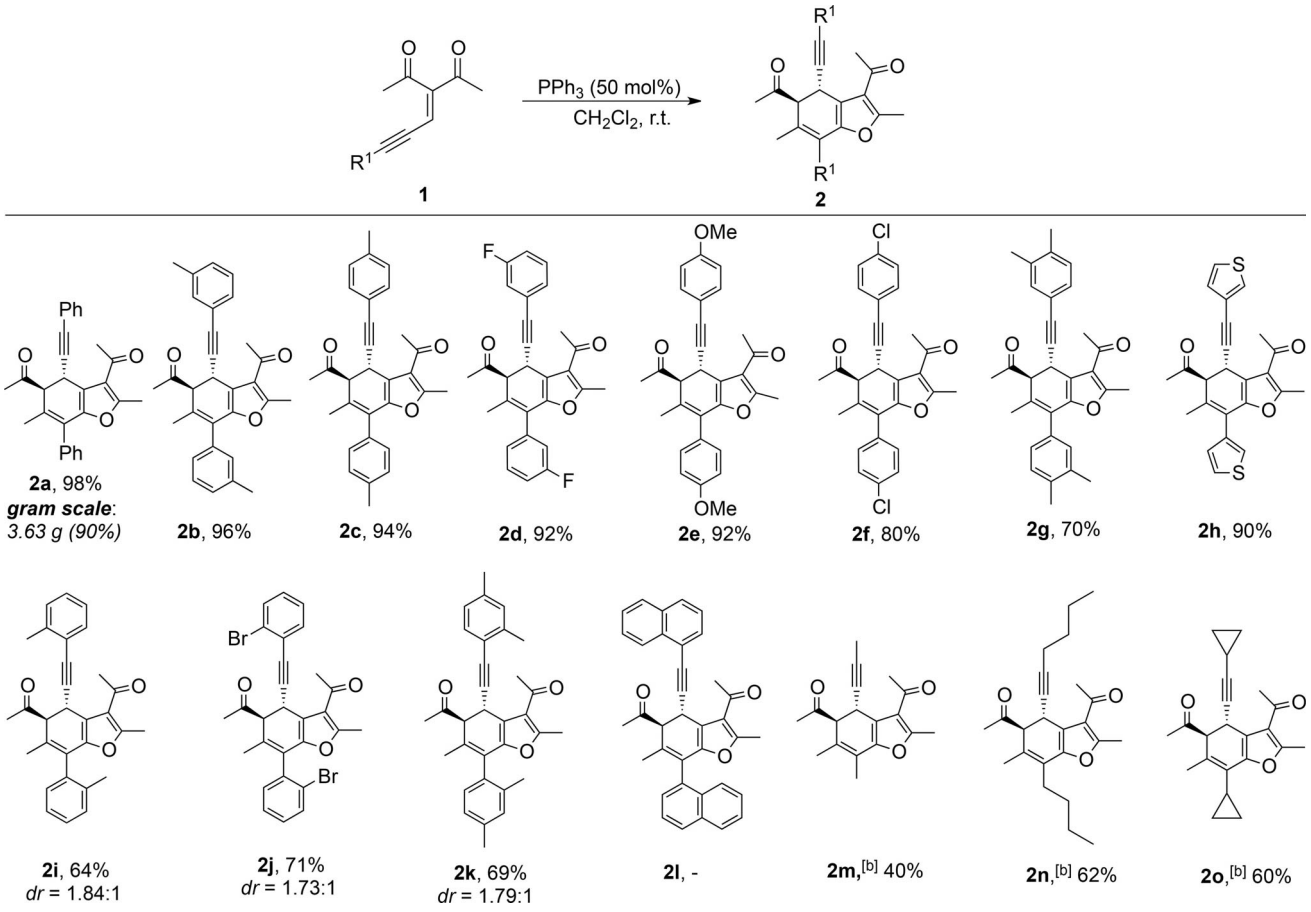
Scheme 3. The phosphine-mediated reaction of **1x**.

from 40% to 62%. The reason why these products were formed in lower yields could be that the corresponding vinylphosphonium ylide bearing an aliphatic group produced upon phosphine attack was not as stable as those of the aromatic ones (see intermediate **G4** in Scheme 5). This straightforward protocol allows for the gram-scale synthesis, as shown for **2a** (Table 1). In all the cases, the corresponding products were formed exclusively in the *trans*-configuration.

Subsequently, we evaluated the substrate scope with respect to various electron-withdrawing groups substituted carbonyl moiety and the results are shown in Table 2. When the acetyl group was replaced by propionyl, the reaction proceeded smoothly to afford the corresponding product **2p** in 63% yield. As for substrate **1q** bearing a sterically hindered isopropyl group, no reaction occurred, presumably due to the steric effect. Furthermore, benzoyl group-containing substrates **1ra**–**1rf** could also give the corresponding products **2ra**–**2rf** in 60–85% yields. As summarized in Table 2, when R^1 group was a *para*-methoxyphenyl, *meta*-methylphenyl, *para*-chlorophenyl, 3,4-dimethylphenyl and 3-thienyl group, all of the reactions proceeded smoothly, indicating that the electronic properties of the aromatic group did not have a significant impact on the reaction outcome. When the EWG was an ester group, substrate **1s** could undergo the reaction very well to give the desired product **2s** in 60% yield. However, it should be noted that one carbonyl group was essential because dimethyl malonate as substrate **1x** did not go through the same reaction under the standard conditions, but afforded 1,3-diene **3a** in 65% yield upon increasing the amount of PPh_3 to 1.0 equiv. and using water (1.0 equiv.) as an extra additive (Scheme 3). It was believed that **3a** was the consequence of H_2O addition to the vinylphosphonium intermediate **A3** generated by phosphine addition,[10] which could be evidence for a 1,6-addition of phosphine to the alkynyl moiety rather than the alkenyl moiety. The structure of **3a** has been identified by X-ray diffraction and the related information has been presented in the Supporting Information.[9] When the EWG was a benzenesulfonyl group, the corresponding benzofurans **2ta** and **2tb** were obtained in 44% and 45% yields, respectively, suggesting that a subsequent α-elimination of the benzenesulfonyl group took place to give the aromatization product.[11] The structure of **2ta** has been also determined by X-ray diffraction and the CIF data are given in the Supporting Information.[9] The NO_2-containing substrate **1u** produced the corresponding product **2u** in 50% yield. The geometric configurations of these substrates did not affect the reaction outcome. However, for substrates **1v** and **1w** in which the EWG is CN or CF_3, the reactions only gave complex product mixtures.

To further clarify the pathway of this phosphine-mediated dimerization of conjugated ene-yne ketone reaction, ^{31}P-NMR spectroscopic tracing experiments have been conducted. As indicated in Scheme 4,

Table 1. Substrate scope of substituents (R^1) on the alkynyl moieties.[a]



[a] Unless otherwise stated, all reactions were carried out with **1** (1.0 mmol), PPh_3 (0.5 mmol) in CH_2Cl_2 (3.0 mL) at room temperature.

[b] Reactions were carried out with **1** (3.0 mmol), PPh_3 (1.5 mmol) in CH_2Cl_2 (3.0 mL).

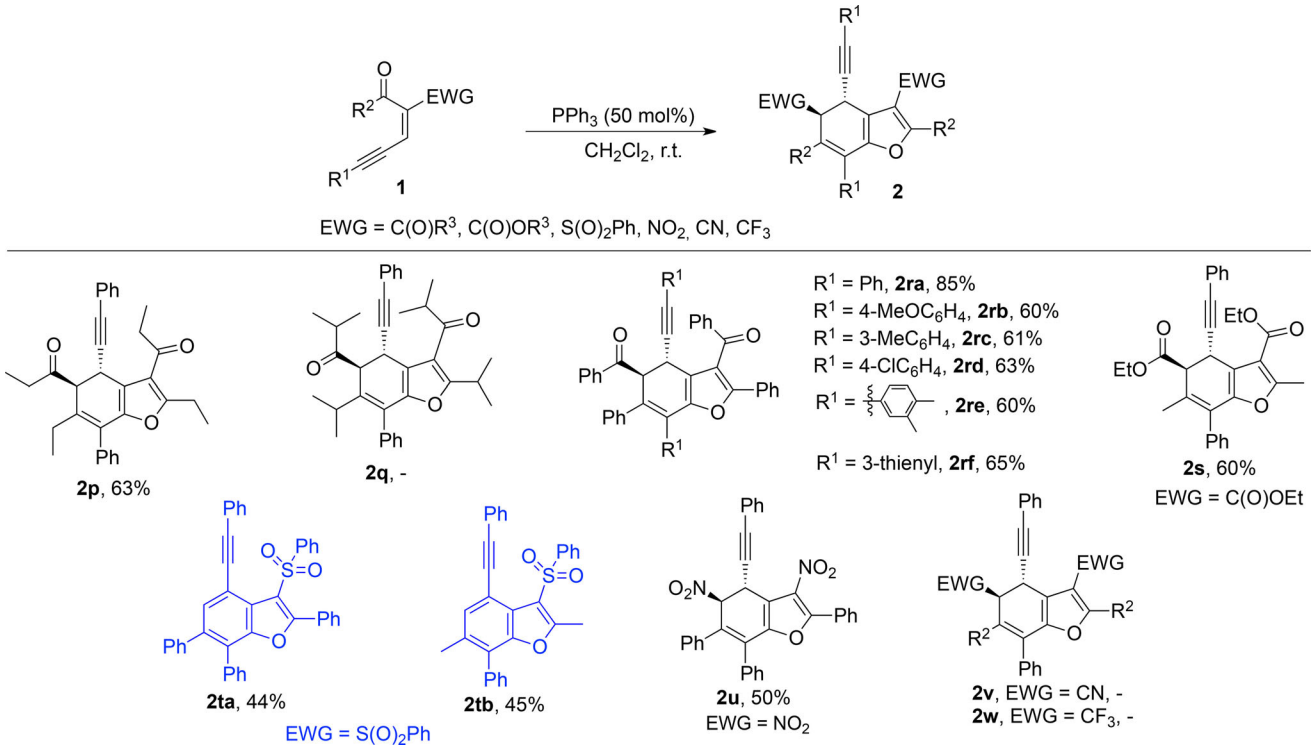
under the standard conditions, the reaction of **1a** was carried out in a NMR tube. After a reaction time of 3 min, the peak **B** of O=PPh_3 appeared (peak **A** is PPh_3) and a peak **C**, corresponding to a reaction intermediate, were clearly present. As the reaction proceeded, the signal of PPh_3 decreased and the signal of O=PPh_3 increased. After 60 min, PPh_3 was transformed to O=PPh_3 completely (Scheme 4).

According to the above experimental results and further NMR spectroscopic tracings, a plausible reaction mechanism for the phosphine-mediated dimerization of conjugated ene-yne ketones to afford dihydrobenzofurans has been proposed as shown in Scheme 5 by using **1a** as a model substrate. The reaction is initiated by a 1,6-addition of phosphine to **1a**, followed by cyclization to yield the key zwitterionic intermediate **D4**, stabilized by EWG (acyl group) *via* intermediates **A4**, **B4** and **C4**, which undergoes Michael addition with another molecule of **1a** to give intermediate **E4**. After an isomerization and a subsequent 1,5-proton shift, ylide **G4** is generated which undergoes an intramolecular Wittig reaction to afford dihydrobenzofuran **2a** and O=PPh_3.[12]

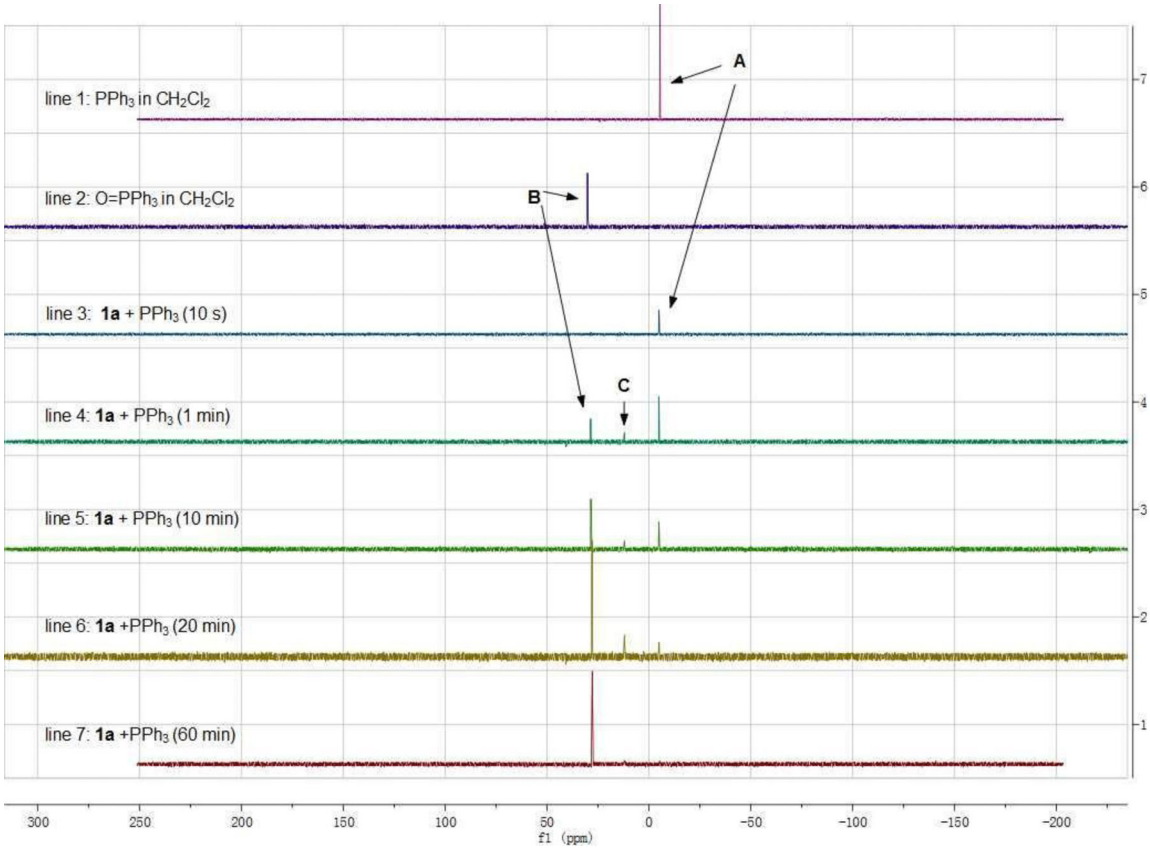
In a preliminary attempt, the asymmetric variant of **1a** for the production of enantiomerically enriched **2a** was evaluated with several chiral phosphine (see Table S2 in the Supporting Information for the details). We found that chiral xyl-BINAP worked very well, enabling the isolation of product **2a** in 50% yield along with 90% *ee* (Table 3). As a consequence, substrates **1b**, **1c**, **1e**, **1g** and **1h** were utilized in this newly established asymmetric dimerization, affording the desired products **2a**–**2f** in moderate yields with 75–90% *ee* values (Table 3). This is the first example of the asymmetric synthesis of dihydrobenzofuran derivatives under phosphine mediation.

In conclusion, we have developed a novel phosphine-mediated dimerization reaction of ene-yne ketones to stereoselectively produce functionalized dihydrobenzofurans in good yields. A mechanistic investigation involving the NMR spectroscopic tracing experiments revealed that this transformation pro-

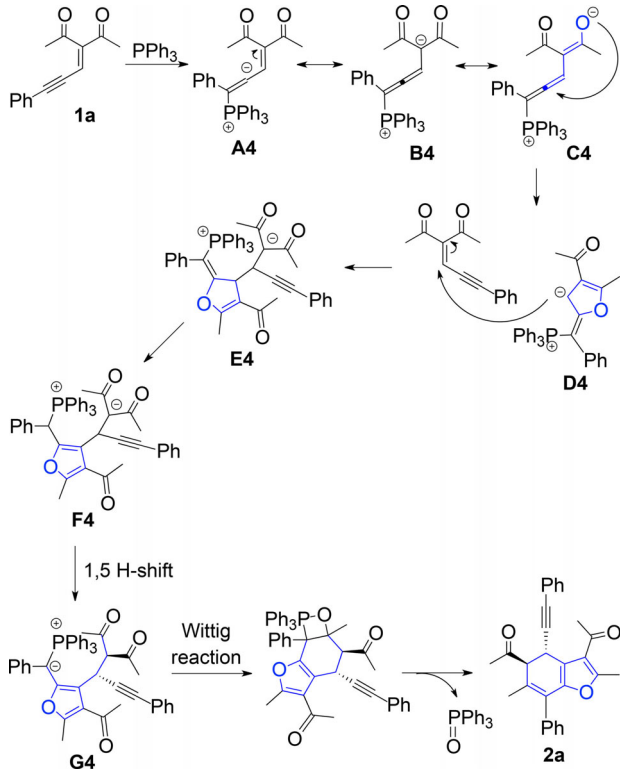
Table 2. Substrate scope for the formation of dihydrobenzofurans or benzofurans by the EWG activated ene-yne ketones.[a]



[a] Unless otherwise stated, all reactions were carried out with **1** (1.0 mmol), PPh_3 (0.5 mmol) in CH_2Cl_2 (3.0 mL) at room temperature.



Scheme 4. ^{31}P NMR spectroscopic tracing experiments.



Scheme 5. A plausible mechanism for the formation of **2a**.

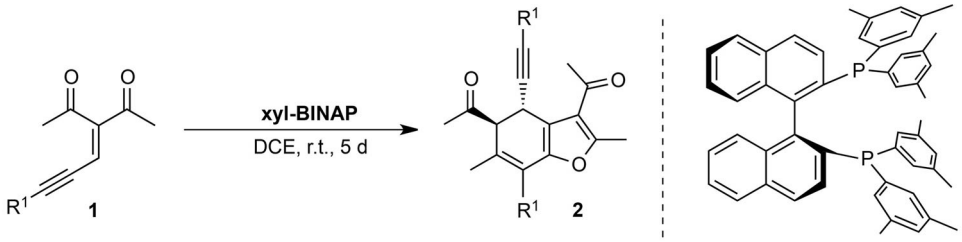
ceeds through an isomerization/Michael addition/Wittig reaction cascade. A variety of functional groups can be tolerated and a gram-scale synthesis is possible. Furthermore, the asymmetric variant can be achieved, giving the desired dihydrobenzofurans in good *ee* values. This is a new reaction mode in phosphine-catalyzed/mediated chemical transformations. Efforts are underway to discern the reaction mechanism and apply this new reaction to the synthesis of biologically active substances.

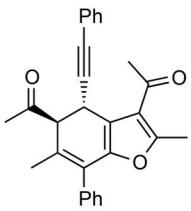
Experimental Section

General Procedure for Synthesis of Benzofurans 2

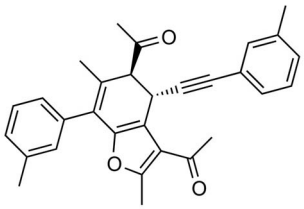
Under an argon atmosphere, PPh_3 (0.5 mmol, 0.5 equiv.) was added to a solution of conjugated ene-yne ketone **1** (1.0 mmol, 1.0 equiv.) and dry dichloromethane (3.0 mL) in a Schlenk tube. The reaction mixture was stirred for 12 h at room temperature until **1** was completely consumed by TLC monitoring. Then the solvent was removed under reduced pressure and the residue was purified by a silica gel flash column chromatography (eluent: petroleum ether/EtOAc, 10/1) to give the product **2**.

Table 3. Xyl-BINAP-mediated asymmetric dimerization.[a,b]

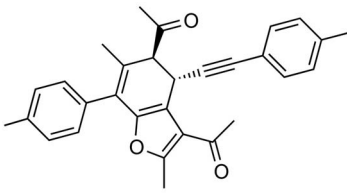




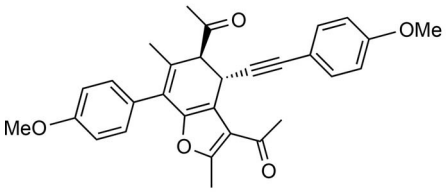
2a, 50% yield, 90% *ee*[c]



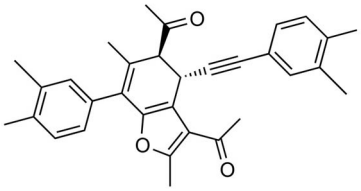
2b, 50% yield, 87% *ee*[c]



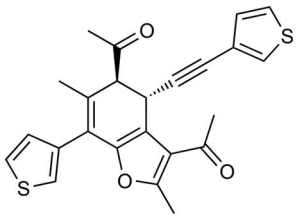
2c, 45% yield, 86% *ee*[c]



2e, 40% yield, 94% *ee*[c]



2g, 56% yield, 89% *ee*[c]



2h, 53% yield, 75% *ee*[c]

[a] All reactions were carried out on a 0.2 mmol scale in 3.0 mL of solvent.
[b] Isolated yields.
[c] Determined by chiral HPLC.

Supporting Information

Detailed descriptions of experimental procedures and their spectroscopic data as well as the crystal structures are presented in the Supporting Information. CCDC 1520712 (**1v**), CCDC 1061650 (**2a**), CCDC 1418261 (**3a**), and CCDC 1493781 (**2ta**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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[9] CCDC 1520712 (**1v**, *E* configuration), CCDC 1061650 (**2a**), CCDC 1418261 (**3a**), and CCDC 1493781 (**2ta**) the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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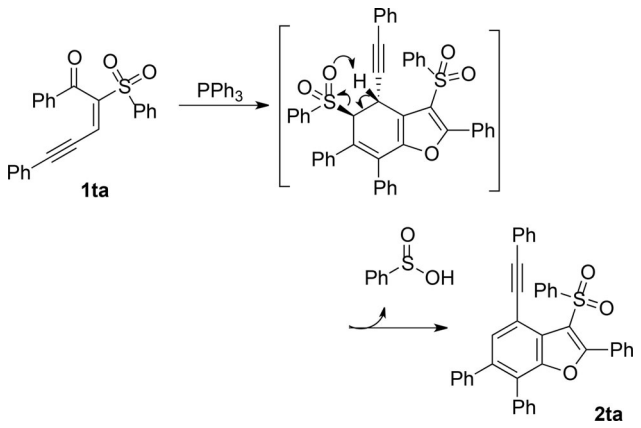
[11] The reaction of **1ta** (*E*-configuration) under phosphine mediation is shown below.



[12] For utilization of conjugated ene-yne ketones as a Michael addition acceptor, see: Y. Yu, Y. Chen, W. Wu, H. Jiang, *Chem. Commun.* **2017**, *53*, 640.

Phosphine-Mediated Dimerization of Conjugated Ene-Yne Ketones: Stereoselective Construction of Dihydrobenzofurans

Adv. Synth. Catal. **2017**, *359*, 1 – 9

Cheng-Zhi Zhu, Yao-Liang Sun, Yin Wei, Min Shi*