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Zn(OTf)₂ catalyzed addition–cyclization reaction of allenylphosphine oxides with propargyl alcohol-unexpected formation of 2,5-dimethylenetetrahydrofurans and 2-substituted furans

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Allenes are excellent precursors for compounds that have wide applications in pharmaceutical and materials sciences.¹ Allenvlphosphonates/allenvlphosphine oxides (cf. compounds 1-9. Chart 1) are also useful substrates for the preparation of synthetically important molecules.^{2,3} Due to the versatile reactivity of allenes, they can easily undergo cycloaddition/cyclization reactions affording a plethora of carbocycles as well as heterocycles.⁴ Recently, we reported a simple base catalyzed nucleophilic addition-cyclization reaction of allenes with salicylaldehydes or 3-chloro-2-formylindole leading to chromenes or pyrroloindoles, respectively.⁵ In this context, we thought that it should be possible to use the -OH and C=C functionalities of a propargyl alcohol in its reaction with allenes to synthesize substituted furans. However, to our knowledge, only two examples of reactions of allenes with propargyl alcohol as a nucleophile have been reported (Scheme 1);⁶ in both the cases, no cyclized product was obtained. We surmised that employing a Lewis acid may lead to the furan system (cf. I-II) via cyclization as shown in Scheme 2. Such tetrahydrofuran derivatives are present in many drugs and hence considerable effort has been devoted toward developing viable synthetic methods for them.⁷ In this Letter, we disclose a rather different and unexpected type of cyclization leading to alkylidenefuran systems. Allenylphosphine oxides with a terminal =CH₂ group lead to a different furan system; the same reaction affords a β.ω-diketophosphonate when an allenylphosphonate is used. These results are also highlighted herein.

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ABSTRACT

A novel synthesis of 2,5-dimethylenetetrahydrofurans, 2-substituted furans and a β , ω -diketophosphonate in good to excellent yields has been achieved by the reaction of allenylphosphine oxides/allenylphosphonate with propargyl alcohol using zinc triflate/triethylamine combination.

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Our initial experiment started by treating the less substituted allene Ph₂P(O)CH=C=CH₂ (1) with propargyl alcohol [HC=CCH₂OH] by using catalytic amount (10 mol%) of Zn(OTf)₂ and DABCO (20 mol %). There was no reaction under these conditions due to the conversion of allene **1** to the corresponding alkyne $Ph_2P(O)C \equiv$ CMe (10).^{4b,8} We then reacted the allene $Ph_2P(0)CH=C=CMe_2$ (2) with propargyl alcohol in the presence of Zn(OTf)₂/DABCO and were delighted to get the β , γ -addition-cyclization product **11** (Scheme 3). Although the product **11** is also a hydrofuran system, *it is not* formed by cyclization as expected according to Scheme 2. The reaction did not proceed in the presence of other Zn^{II} salts like ZnBr₂, ZnCl₂ or Zn(OAc)₂ even at 110 °C. Other metal triflates like Sc(OTf)₃, Cu(OTf)₂ and Gd(OTf)₃ were also not effective for this transformation (³¹P NMR). There was no reaction in the absence of base (Table 1; entry 1) in toluene at 100 °C. The use of DABCO (20 mol %) at 25 °C/24 h also did not give the product (entry 2), but the product readily



Chart 1. Allenes used in the present study.



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Scheme 1. Reactions of allenes with propargyl alcohol leading to non-cyclized products.



Scheme 2. Expected formation of furans **I-II** via Lewis-acid catalyzed addition-cyclization reaction of an allene with propargyl alcohol.



Scheme 3. Reaction of allene **2** with propargyl alcohol leading to 2,5-dimethylenetetrahydrofuran **11**.

formed (80%) when the mixture was heated at 100 °C for 10 h (entry 3). Use of other bases like DBU (20 mol %) and K₂CO₃ (20 mol %) (entries 4–5) also afforded the product **11**, but the reaction needed longer time for completion (9–14 h). Yield of the product was increased (98%) when Et₃N (20 mol %) was used as the base (entry 6).⁹ When the amount of Et₃N was reduced from 20 mol % to 10 mol %, the reaction needed more time for completion (8 h) and

Table 1

Details on the conditions of the reaction shown in Scheme 3^a

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	Entry	Base (mol %)	T (°C)	<i>t</i> (h)	Yield ^b (%)
	1	_	100	24	n.r.
	2	DABCO (20)	25	24	n.r.
	3	DABCO (20)	100	10	80
	4	DBU (20)	100	9	82
	5	$K_2CO_3(20)$	100	14	64
	6	Et ₃ N (20)	100	6	98
	7	Et ₃ N (10)	100	8	88

^a Other parameters: Allene **2** (1.0 mmol), propargyl alcohol (3.0 mmol), Zn(OTf)₂ (0.1 mmol) in toluene (1.0 mL).

^b Based on ³¹P NMR analysis.

Table 2

ffect of solvent on the reaction shown in Scheme 3 using	Zn(OTf) ₂ /Et ₃ N ⁴
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Entry	Solvent	T (°C)	<i>t</i> (h)	Yield ^b (%)
1	1,4-Dioxane	100	14	64
2	THF	60	10	84
3	CH₃CN	70	8	75
4	DCE	80	12	82
5	DMF	90	8	56
6	Toluene	100	6	98

^a Other parameters in this reaction: Allene **2** (1.0 mmol), propargyl alcohol (3.0 mmol), Zn(OTf)₂ (0.1 mmol), triethylamine (0.2 mmol).

^b Based on ³¹P NMR analysis.

Table 3Scope of the reaction shown in Scheme 3^a



^a These are yields of isolated products.

the yield of the product **11** was less (88%, entry 7). We checked the role of the solvent in this reaction and found toluene was the best solvent (Table 2) compared to other solvents like 1,4-dioxane, THF, CH_3CN , and DMF (entries 1–5, respectively). Hence, we performed the remaining cyclization reactions using triethylamine as the base and toluene as the solvent.

After ascertaining that the above Zn-catalyzed reaction works, we explored the reactivity of other γ -disubstituted allenylphosphine oxides **3–6** with HC=CCH₂OH under the optimized conditions. In these reactions also we were able to isolate the similar dihydrofurans **12–15** in good to excellent yields (Table 3, entries 1–4). Structure of the compound **12** was also confirmed by X-ray



Figure 1. ORTEP diagram of compound **12**. Selected bond lengths [Å] with esd's in parentheses: P1–O1 1.474(3), P1–C1 1.807(4), P1–C7 1.809(4), P1–C13 1.773(4), O2–C14 1.363(4), C13–C14 1.316(5), C15–C23 1.528(5), C24–C25 1.308(5).



Scheme 4. Reaction of 2 with HC=C-CH(Me)OH leading to the product 18.



Scheme 5. Reaction of all enylphosphonate 9 with propargyl alcohol leading to the $\beta{,}\omega{-}diketophosphonate$ 19.



Figure 2. ORTEP diagram of compound **19**. Selected bond lengths [Å] with esd's in parentheses: P1–O1 1.567(2), P1–O2 1.572(2), P1–O3 1.459(2), P1–C6 1.818(3), O4–C13 1.202(3), O5–C16 1.220(4), C6–C13 1.534(4).

analysis (Fig. 1).¹⁰ These 2,5-dimethylenetetrahydrofuran products are clearly different from those expected (cf. Scheme 2). In contrast to these, the reaction using α -aryl substituted allenylphosphine oxides **7–8** afforded the (β , γ)-addition-cyclization products **16–17** (Table 3, entry 5). In these products, the five membered ring was aromatized to lead to the furan ring.

Next, we turned our attention to the reaction of allenes with methyl substituted propargyl alcohol $HC \equiv CC(Me)(H)(OH)$. The allene $Ph_2P(O)CH = C = CMe_2$ (2) when treated with $HC \equiv CC(Me)$ (H)(OH) afforded the cyclized product 18 in good yield (Scheme 4). This product is formed in a manner similar to 11, but a proton migration from the five-membered ring to the exocyclic double bond has occurred. The newly formed CH_2CH_3 group is clearly observed in the ¹H NMR spectrum.

In contrast to the above, the reaction of allenylphosphonate **9** with propargyl alcohol [HC=CCH₂OH] surprisingly afforded a non-cyclized β , ω -diketophosphonate **19** (Scheme 5). This compound was also characterized by X-ray crystallography (Fig. 2).¹⁰ It can be noted that this product is a result of the addition of a molecule of water after the propargylic group adds to the allene. Since this type of product was not of interest to us, we did not study this aspect further.

We have utilized one of the compounds (**14**) further in hydrogenation reaction. This compound was partially hydrogenated at the less substituted alkene side forming the methylenetetrahydrofuran **20** (Scheme 6).

We propose a mechanistic rationale for the catalytic coupling reaction of allene **2** with propargyl alcohol in Scheme 7.^{7b} First, zinc alkoxide **III** is formed by the exchange of propargyl alcohol with a triflate group of Zn(OTf)₂. Then the zinc species **III** adds on to the allene **2** forming species **IV** wherein the phosphinyl oxygen coordinates to zinc. Isomerization of the species **IV** to allene **V**



Scheme 6. Reduction of compound 14 leading to 20.



Scheme 7. Plausible mechanism for the formation of 2,5-dimethylenetetrahydrofuran 11 from the allene 2.

followed by intramolecular cyclization by the attack of oxygen connected to β -carbon on the central carbon of **V** leads to species **VI**. This is followed by protonation of intermediate **VI** furnishing the product **11** and regenerating the zinc alkoxide **III**.

In summary, we have discovered a novel Zn-catalyzed additioncyclization reaction of allenylphosphine oxides and propargyl alcohol leading to hydrofuran derivatives in very good yields. In reactions using =CH₂ terminal allenes, 2-substituted furans are also obtained. Further work in order to make the system more efficient and to broaden the scope of this catalytic system is in progress.

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Supplementary data

Supplementary data (experimental data and crystal data (CIF file) for compounds **12** and **19**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.020.

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- Representative procedure for the synthesis of hydrofurans: A mixture of $Ph_2P(O)C(H) = C = CMe_2$ (2) (0.27 g, 1.0 mmol), $HC = CCH_2OH$ (0.80 mL, 3.0 mmol), Zn(OTf)₂ (0.036 g, 0.1 mmol) and triethylamine (0.01 g, 0.2 mmol) in toluene (2 mL) was heated at 100 °C for 6-8 h. Progress of the reaction was monitored by TLC and ³¹P or ¹H NMR. When there was no starting material present, the reaction mixture was cooled to 25 °C, quenched with distilled water (5 mL) and extracted with ethyl acetate (2×10 mL). The organic layer was dried (Na₂SO₄), solvent removed under reduced pressure and the compound 11 was purified by column chromatography (silica gel; hexaneethyl acetate, 2:3). Yield: 0.29 g (90%); gummy liquid; IR (neat, cm⁻¹) 3056, 2967, 2930, 2876, 1634, 1437, 1186, 1030; ¹H NMR (400 MHz, CDCl₃) δ 1.29 (s, 6H, 2 CH₃), 2.40 (s, 2H, CH₂), 4.07 (s, 1H, C=CH_ACH_B), 4.31 (s, 1H, C=CH_ACH_B), 20 (4.7 (d, 20 /(P–H) = 9.6 Hz, 1H, PCH), 7.44–7.50 (m, 6H, Ar-H), 7.75–7.80 (m, 4H, Ar-H); 13 C NMR (100 MHz, CDCl₃) δ 27.0, 41.2, 42.7 (d, 3 /(P–C) = 8.8 Hz, PC=CC), 85.6 (d, ¹J(P-C) = 108.3 Hz, PCH), 86.6, 128.1, 128.3, 130.0, 131.2, 131.4, 131.8, 134.4 (d, 1 /(P-C) = 106.4 Hz), 157.9, 178.6 (d, 2 /(P-C) = 3.3 Hz, PC=C); 31 P NMR (162 MHz, CDCl₃) δ 22.0; LC-MS m/z 324 [M+1]⁺; Anal. Calcd for C₂₀H₂₁O₂P: C, 74.06; H, 6.53. Found: C, 74.15; H, 6.48.
- 10. X-ray data were collected on a Bruker AXS SMART diffractometer using Mo- K_{α} ($\lambda = 0.71073$ Å) radiation. The structures were solved and refined by standard methods. Crystal data for **12**: $C_{25}H_{23}O_2P$, M = 386.40, Monoclinic, Space group P2(1)/c, a = 19.112(8), b = 6.357(3), c = 17.348(7) Å, $\beta = 103.677(7)^\circ$, V = 2047.9(15) Å³, Z = 4, $\mu = 0.152$ mm⁻¹, data/restraints/parameters: 3607/0/254, R indices ($I > 2 \sigma$ (I)): R1 = 0.0795, wR2 (all data) = 0.1720. CCDC no. 830608. Crystal data for **19**: $C_{17}H_{23}O_5P$, M = 338.32, Monoclinic, Space group P2(1)/c, a = 9.975(5), b = 16.638(5), c = 11.202(5) Å, $\beta = 108.52(6)^\circ$, V = 1762.8(13) Å³, Z = 4, $\mu = 0.178$ mm⁻¹, data/restraints/parameters: 3099/0/211, R indices ($I > 2 \sigma$ (I)): R1 = 0.0469, wR2 (all data) = 0.1103. CCDC no. 830609.