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Wittig Olefination between Phosphine, Aldehyde, and Allylic Carbonate: A General Method for Stereoselective Synthesis of Trisubstituted 1,3-Dienes with Highly Variable Substituents

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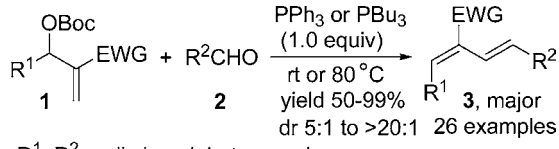
ABSTRACT



R^1, R^2 = alkyl, aryl, hetero-aryl;
EWG = CO_2Et, COMe;
Boc = *tert*-butoxycarbonyl.

A clean and salt-free Wittig olefination between phosphines, aldehydes, and allylic carbonates is described. It represents a general method for convenient and efficient synthesis of 1,2,4-trisubstituted 1,3-dienes from readily available starting materials. This method exhibits high synthetic efficiency, high stereoselectivity, and high variability of substituent.

Conjugated dienes represent one class of widely occurring and important organic compounds. Their importance stems largely from their versatility in organic transformations like the Diels−Alder reaction[1] and the widespread occurrence of the 1,3-diene motif in a vast array of natural products of biological and medicinal interest.[2] The development of methods for the efficient, stereoselective, and practical construction of conjugated dienes has attracted extensive efforts from chemists over several decades. Many powerful synthetic methods for accessing dienes have been established, mostly based upon conventional P-, S-, and Si-based carbonyl olefinations[3] and newer transition-metal-catalyzed diene formations.[4] Despite the effectiveness of the existing methods, there remains significant room for the development of additional complementary processes, especially aiming at the challenging synthesis of polysubstituted conjugated dienes. Recently, remarkable efforts have been devoted to this area.[5]

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(2) (a) Negishi, E.-I.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474, and references cited therein. (b) Glasby, J. S. *Encyclopaedia of the Terpenoids*; Wiley: Chichester, UK, 1982. (c) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*; Academic: New York, NY, 1972; Vol. II.

(3) For leading reviews, see: (a) Vedejs, E.; Peterson, M. J. *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; Jai Press Inc.: Greenwich, CT, 1996; Vol. 2. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (c) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563. (d) Ager, D. J. *Org. React.* **1990**, *38*, 1–223.

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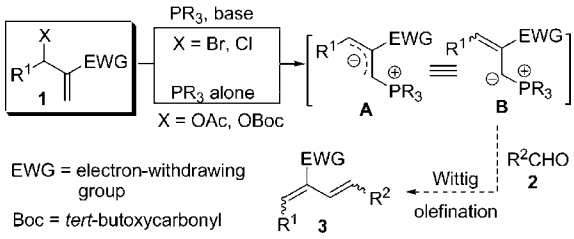
The Wittig reaction occupies a long-standing position of importance in organic synthesis as the highly effective means to generate carbon−carbon double bonds with generally high levels of stereocontrol.[3b,6] In spite of an enormous number of theoretical and experimental studies over its half-century history, the Wittig reaction still attracts much interest in improving its synthetic efficiency, stereoselectivity, and reaction conditions.[7] To avoid the basic conditions and the interference from alkali metal salts (a byproduct concomitantly generated in the formation of a phosphorane) which are often encountered in the conventional Wittig reaction, much effort has been directed toward developing neutral and salt-free processes.[7d−j]

Recently, a class of modified allylic derivatives **1** (Scheme 1) have been explored by Lu, Krische, and others as versatile

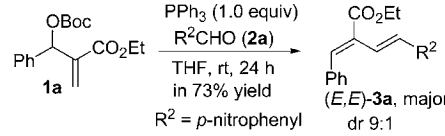
Scheme 1. Strategy to Construct 1,2,4-Trisubstituted 1,3-Dienes via Wittig Olefination of in Situ Generated Allylic Phosphorus Ylide



C_3 synthons in many phosphine-catalyzed, synthetically important reactions such as [3 + 2] annulations and allylations.[8] In those reactions, an allylic phosphorus ylide, which could be expressed as the delocalized form **A** or the localized **B** (Scheme 1), is supposedly generated by a S_N2 or addition−elimination process as the common active intermediate.[8a] Intrigued by those elegant studies and a pioneering phosphine-mediated synthesis of dienes from the Baylis−Hillman adduct,[5i] we envisaged that a nearly neutral and salt-free Wittig olefination could be realized between tertiary phosphine, allylic carbonate **1** (X = OBoc), and aldehyde **2**, providing a convenient and clean synthesis of trisubstituted 1,3-dienes **3** (Scheme 1). Herein, we wish to report preliminary results from such investigations.

Initially, our studies started with phenyl-substituted allylic carbonate **1a** (Scheme 2). Under very mild conditions, the

Scheme 2. PPh_3-Mediated Olefination between **1a** and **2a**

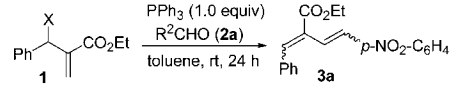


reaction between **1a**, *p*-nitrobenzaldehyde (**2a**), and PPh_3 was run in THF. To our delight, the anticipated olefination readily proceeded, giving the corresponding trisubstituted 1,3-diene **3a** in 73% isolated yield (based on **1a**) and 9:1 diastereomeric ratio with the isomer (*E*,*E*)-**3a** being the major (Scheme 2).

With this encouraging result, the reaction conditions were further optimized using the olefination of **1a** with **2a** as a model (for details, see Supporting Information). Screening of the solvent revealed that toluene was the best with respect to the yield and diastereoselectivity in the PPh_3-mediated olefination (yield of **3a** 88%, dr 17:1). Polar solvents like DMSO were detrimental to the reaction, giving the diene in a low yield (27%). The protic solvent ethanol resulted in a lowered stereoselectivity (dr 2.4:1), although the yield was high (93%). Choosing toluene as solvent, a series of tertiary phosphines including Ph_2PMe, $PhPMe_2$, PBu_3, and tris(*p*-substituted phenyl)phosphines (*p*-Cl, CF_3, CH_3, CH_3O) were screened. In principle, phenylphosphines gave comparable yields (65−91%) and high levels of stereoselectivity (dr 9:1−16:1). In contrast, use of PBu_3 led to much lower yield (20%) and modest stereoselectivity (dr 5.6:1). Considering its ready availability, cost-effectiveness, and efficiency, PPh_3 was chosen as the preferable phosphine.

Other allylic derivatives than allylic carbonate **1a** were also explored (Scheme 3). Methoxy-substituted allylic de-

Scheme 3. PPh_3-Mediated Olefination of Methylated or Acetylated Derivatives of the Baylis−Hillman Adduct



X	yield of **3a**
MeO (**1aa**)	0%
AcO (**1ab**)	82% (dr 3:1)

rivative **1aa** (X = MeO) failed to bring about the olefination product under similar conditions;[9] allylic acetate **1ab** (X = AcO) did give the diene **3a** in 82% isolated yield but with only modest 3:1 diastereoselectivity [(*E*,*E*)-**3a** versus the sum of other isomers].

With the optimized conditions in hand, the scope of this olefination was further examined (Table 1). Employing allylic

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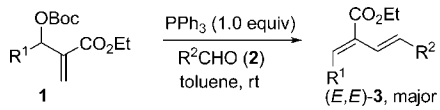
Table 1. Synthesis of 1,2,4-Trisubstituted 1,3-Dienes **3** from Allylic Carbonates **1** and Aldehydes **2**[a]



entry	R^1 in **1**	R^2 in **2**	time (h)	yield (%)[b]	dr[c]
1	C_6H_5	4-$NO_2C_6H_4$	24	**3a**, 88	17:1
2	C_6H_5	2-$NO_2C_6H_4$	29	**3b**, 84	>20:1
3	C_6H_5	3-$NO_2C_6H_4$	30	**3c**, 97	>20:1
4	C_6H_5	4-$CF_3C_6H_4$	24	**3d**, 99	10:1
5[d]	C_6H_5	4-FC_6H_4	11	**3e**, 94	7:1
6[d]	C_6H_5	4-ClC_6H_4	9	**3f**, 89	10:1
7[d,e]	C_6H_5	2,4-$Cl_2C_6H_3$	6	**3g**, 99	9:1
8[e,f]	C_6H_5	C_6H_5	23	**3h**, 81	>20:1
9	C_6H_5	2-HO-5-$CH_3C_6H_3$	25	**3i**, 95	16:1
10	C_6H_5	2-HO-5-$CH_3OC_6H_3$	24	**3j**, 96	10:1
11	C_6H_5	2-furyl	25	**3k**, 84	>20:1
12	C_6H_5	2-thiofuryl	24	**3l**, 84	>20:1
13	C_6H_5	3-pyridyl	29	**3m**, 97	13:1
14[g]	C_6H_5	C_2H_5	2	**3n**, 79	6:1
15[g]	C_6H_5	n-C_3H_7	3	**3o**, 90	5:1
16	4-ClC_6H_4	4-$NO_2C_6H_4$	30	**3p**, 92	>20:1
17	4-ClC_6H_4	4-$CH_3OC_6H_4$	11	**3q**, 50	>20:1
18	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	8	**3r**, 89	13:1
19	4-$NO_2C_6H_4$	4-$CH_3OC_6H_4$	30	**3s**, 63	>20:1
20	4-$CH_3OC_6H_4$	4-$NO_2C_6H_4$	29	**3t**, 96	20:1
21	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	24	**3u**, 81	>20:1
22	2-furyl	4-$NO_2C_6H_4$	22	**3v**, 80	20:1
23[e,f]	2-furyl	4-$CH_3OC_6H_4$	12	**3w**, 81	20:1
24[e]	n-C_3H_7	4-$NO_2C_6H_4$	29	**3x**, 85	16:1
25[e]	n-C_3H_7	4-$CH_3OC_6H_4$	24	**3y**, 74	9:1

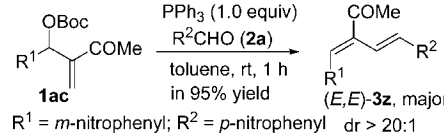
[a] For experimental details, see Supporting Information. [b] Isolated yield. [c] Referring to the major (*E*,*E*)-**3** versus the sum of others and determined by ^{1}H NMR assay on the crude product (entries 4, 8, 10, 12, 13, 16, 18, 20, 21), otherwise on the isolated. [d] Reaction temperature: 80 °C. [e] **1** (0.6 mmol) and **2** (0.5 mmol) employed. [f] THF was used instead of toluene. [g] PBu_3 was used instead of PPh_3.

carbonate **1a** as one reactant, a variety of aldehydes **2** were explored. Aromatic aldehydes bearing either electron-withdrawing or -donating groups worked well in the PPh_3-mediated olefination, giving good to excellent yields and high stereoselectivity (entries 1−10). Heteroaromatic aldehydes were also effective, readily affording their corresponding dienes in high yields and diastereoselectivity (entries 11−13). For aliphatic aldehydes propionaldehyde and butyraldehyde, however, their olefinations were best mediated by PBu_3, giving the corresponding dienes in satisfactory yields and stereoselectivity (entries 14 and 15). However, under similar conditions, ketones like acetophenone and acetone failed in giving the expected olefination products with the allylic carbonate **1a**.

Choosing *p*-nitrobenzaldehyde and *p*-methoxybenzaldehyde as two representative reactants, a series of differently substituted allylic carbonates **1** were tested. Under the mediation of PPh_3, all selected carbonates **1** including aryl-, heteroaryl-, and alkyl-substituted **1** (R^1 = 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 2-furyl, *n*-propyl) readily reacted with the two representative aldehydes, affording their corresponding dienes **3** in moderate to excellent yields with high stereoselectivity (Table 1, entries 16−25).

A single case of the olefination was studied, in which an allylic carbonate **1ac** bearing an electron-withdrawing group (EWG) acetyl was used (Scheme 4). The expected diene **3z** was easily obtained in 95% yield and >20:1 diastereoselectivity.

Scheme 4. PPh_3-Mediated Olefination of Acetyl-Activated Allylic Carbonate **1ac**



The above results from the scope investigation clearly demonstrated that the Wittig olefination between allylic carbonates **1**, aldehydes **2**, and tertiary phosphines has a broad substrate scope. The modified allylic carbonates **1** can be conveniently prepared from the adducts of Morita−Baylis−Hillman reaction by a simple one-step operation.[8d] Therefore, this olefination constitutes a general method for highly efficient and stereoselective synthesis of trisubstituted 1,3-dienes **3** with a flexible selection of the substituents at the 1,4-positions from readily available starting materials. As shown in Table 1, a variety of aryl-substituted 1,3-dienes **3** could be easily accessed by this three-component Wittig olefination. Aryl-substituted conjugated dienes often possess special photochemical and photophysical properties and are widely used as advanced materials in nonlinear optics and liquid crystals.[10]

In all cases of the olefination, the isomer (*E*,*E*)-**3** was obtained as the major product with high stereoselectivity. The structures of **3** were identified by a combination of ^{1}H and ^{13}C NMR including NOESY analysis and X-ray crystallographic determination [for (*E*,*E*)-**3c** and (*E*,*E*)-

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3j, CCDC 755471 and 755472, respectively; also see Supporting Information]. Generally, an allylic phosphorus ylide is defined as the semistabilized ylide which often lacks stereoselectivity in its Wittig reaction. In this study, the high *E*-selectivity observed in the olefination could be attributable to the presence of the electron-withdrawing group (EWG = CO_2Et, COMe), which presumably increases the stability of the modified allylic phosphorus ylide as well as the steric effect of the allylic group in the oxaphosphetane transition state (Figure 1).[11]

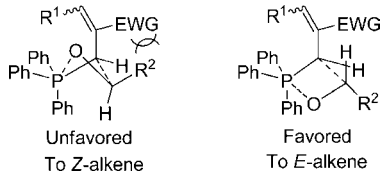
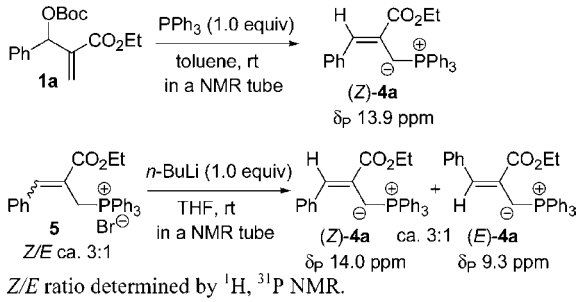


Figure 1. Rationale for the *E*-selectivity of disubstituted alkene.

Although allylic phosphorus ylides (form **A** or **B**) are usually proposed to be the active intermediates in the phosphine-catalyzed transformations involving modified allylic derivatives **1** (Scheme 1),[8] the following experiments provided more insight into their structures. In a ^{31}P NMR tracking experiment (160 MHz and a sealed capillary containing C_6D_6 was used for field locking and shimming), a signal at δ 13.9 ppm was observed when equivalent **1a** and PPh_3 were mixed in toluene in an NMR tube, which disappeared upon addition of *p*-nitrobenzaldehyde **2a** into the sample (for details, see Supporting Information). This result indicated that the signal most likely corresponded to the in situ formed allylic phosphorus ylide **4a** (Scheme 5).

Scheme 5. ^{31}P NMR Investigation on in Situ Generated Allylic Phosphorus Ylides



For the purpose of comparison, an isomeric mixture (*Z*/*E* ca. 3:1) of modified allylphosphonium salt **5** was treated with equivalent *n*-BuLi in THF in an NMR tube. Two signals at δ 14.0 and 9.3 ppm with an intensity ratio of ca. 3:1 were observed, which both disappeared upon addition of **2a** (Scheme 5). On the basis of the above results, the allylic phosphorus ylide with δ_p 13.9 ppm (in toluene) from allylic carbonate **1a** and that with δ_p 14.0 ppm (in THF) from allylphosphonium salt **5** could be both assigned with confidence as the allylic phosphorus ylide having *Z*-alkene (*Z*)-**4a** (Scheme 5). Regarding the mechanism of the olefination between allylic carbonates **1**, aldehydes **2**, and phosphines, the following pathway could be rationalized: under the mediation of phosphine, the allylic carbonate **1** predominantly, if not exclusively,[12] generates an allylic phosphorus ylide with *Z*-alkene like (*Z*)-**4a** via the generally accepted addition−elimination process;[8a] subsequently, the (*Z*)-allylic ylide is intercepted by aldehyde **2** via a salt-free, *E*-selective Wittig reaction to afford (*E*,*E*)-diene **3** as the major product.

In summary, a nearly neutral and salt-free Wittig olefination between allylic carbonates, aldehydes, and phosphines has been successfully developed, which provides a general method for convenient and efficient synthesis of 1,2,4-trisubstituted 1,3-dienes from readily available starting materials. On the basis of the well-documented theory on the stereoselectivity and mechanism of the Wittig reaction, as well as ^{31}P NMR investigation on the in situ generated allylic phosphorus ylides in this study, the high *E*-selectivity and mechanism of this three-component Wittig olefination has been well rationalized. Since this method possesses such advances as simplicity, high efficiency, high stereoselectivity, and broad substrate scope, we anticipate it could find wide application in organic synthesis.

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Supporting Information Available: Experimental details, characterization data, and ^1H and ^{13}C NMR spectra for dienes **3**, as well as the X-ray crystallographical data (CIF files) for dienes (*E*,*E*)-**3c** and (*E*,*E*)-**3j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) In ref 5i, a PBu_3-mediated synthesis of trisubstituted 1,3-dienes with modest diastereoselectivity from an analogue of **1aa** and aldehyde was reported.

(10) (a) For applications in nonlinear optics, see the special issue: *Chem. Phys.* **1999**, *245*, issues 1−3. (b) Brettle, R.; Dunmur, D. A.; Hindley, N. J.; Marson, C. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 775. (c) Davis, R.; Mallia, V. A.; Das, S. *Chem. Mater.* **2003**, *15*, 1057.

(11) A computational study by Aggarwal et al. provides unequivocal support for the generally accepted oxaphosphetane mechanism in the salt-free Wittig reaction. See ref 7a.

(12) In a few cases such as **3c** and **3h**, small amounts of dienes having the trisubstituted *Z*-alkene unit were observed.