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A phosphine-mediated stereocontrolled synthesis of *Z*-enediynes by a vicinal dialkynylation of ethynylphosphonium salts†

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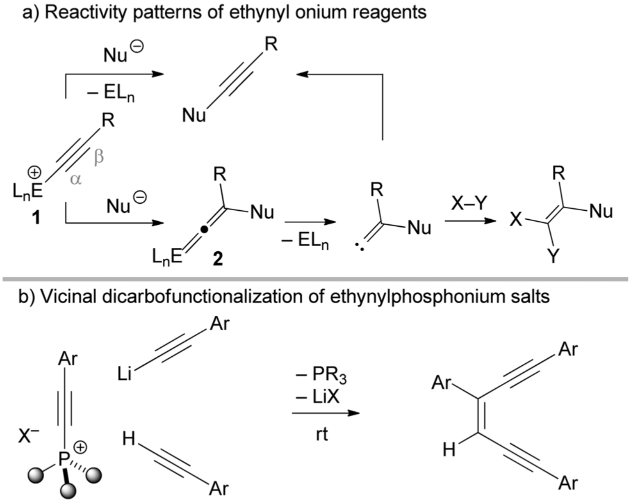
_Z_-Enediynes are prepared by a vicinal dialkynylation of triaryl(arylethynyl)phosphonium cations. The method, which proceeds under mild transition metal-free conditions, can be conducted on multigram scale as a one-pot, phosphine-mediated synthetic cycle giving enediyne products with excellent control of configuration.

Ethynyl onium cations of the p-block elements (**1**, Fig. 1a) are versatile electrophilic reagents in organic synthesis exhibiting multifaceted reactivity. For instance, reactions with nucleophiles leading to bond formation at C_α illustrate the synthetic equivalency of these species with alkynyl cations.[1] Alternatively, addition to the C_β position may generate ylidic intermediates, which have been shown to undergo a range of subsequent chemistries as a function of the nucleofugality of the p-block moiety.[2]

Within this latter framework, reactions leading to vicinal difunctionalization of ethynyl onium compounds by introduction of either one or two heteroatomic substituents are well-known (Fig. 1a),[3] having been featured in several complex target syntheses.[4] By contrast, reactions resulting in vicinal dicarbofunctionalization of the $L_nE^+{-}C_\alpha{\equiv}C_\beta$ moiety are significantly less common.[5] We report here an intermolecular reaction of ethynylphosphonium cations with acetylene derivatives that results in two C–C bond forming events across the C≡C ethynyl onium unit (Fig. 1b). This transformation results in a mild and stereoselective preparation of *Z*-enediynes (*Z*-1,2-diethynylethenes), a valuable class of π-conjugated hydrocarbons with significant biomedical and electronic materials applications,[6] by three-component coupling of acetylene derivatives. In addition to the preparative utility of this reaction, the findings described below suggest a broader role for ethynylphosphonium salts as ditopic electrophilic reagents for conjunctive transformations.


a) Reactivity patterns of ethynyl onium reagents

b) Vicinal dicarbofunctionalization of ethynylphosphonium salts

Fig. 1 (a) Typical reactivity of ethynyl onium reagents. (b) *Z*-Enediynes by dicarbofunctionalization of triaryl(arylethynyl)phosphonium salts.

Triaryl(ethynyl)phosphonium salts are readily prepared under mild conditions by reaction of neutral triarylphosphines with 1-haloalkynes;[7] specifically, treatment of 1-bromo-2-phenylacetylene with tris(*p*-anisyl)phosphine ($P(p\text{-An})_3$) in toluene affords the corresponding ethynylphosphonium salt **3** in good yield. Further reaction of this salt with lithium phenylacetylide in THF produces a small amount of 1,4-diphenylbutadiyne, corresponding to alkynyl transfer at C_α.[8] In addition, a second unsaturated hydrocarbon was also isolated in trace amounts; mass spectral analysis suggested this to be a species containing two addend alkynyl units in addition to the phosphonium-derived ethynyl fragment. X-ray diffraction of a monocrystalline sample showed this species to be a *Z*-enediyne **4a**,‡ corresponding to a functionalization at both C_α and C_β of the ethynylphosphonium cation. With alteration of the reaction conditions, **4a** could be made the major reaction product; deliberate addition of two equivalents of phenylacetylene significantly increased the yield. Highest yields (*ca.* 80%) of *Z*-enediyne **4a** were obtained upon use of

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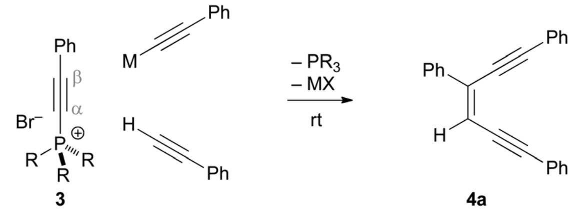
Table 1 *Z*-Enediynes by dicarbofunctionalization of triaryl(arylethynyl)-phosphonium salts

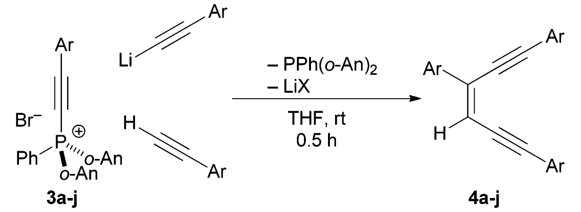


Entry	PR_3	Equiv. MCCPh	Equiv. HCCPh	Yield[a] (%)
1	$P(p\text{-An})_3$	1.0 (M = Li)	0.0	Trace
2	$P(p\text{-An})_3$	0.9 (M = MgBr)	2.0	21
3	$P(p\text{-An})_3$	1.3 (M = MgBr)	1.0	30
4	$P(p\text{-An})_3$	1.3 (M = MgBr)	2.0	49
5	$P(p\text{-An})_3$	1.7 (M = MgBr)	2.0	52
6	$PPh(o\text{-An})_2$	1.5 (M = Li)	2.0	83
7	$PPh(o\text{-An})_2$	1.1 (M = Li)	2.0	80

[a] Yields are for isolated material. *ca.* 7–10% of 1,4-diphenyl-1,3-butadiyne is also isolated. See ESI for details.

lithium phenylacetylide as nucleophilic reagent and bis(*o*-anisyl)-phenylphosphine ($PPh(o\text{-An})_2$) as the phosphine substituent (entries 6 and 7).[9] Under these conditions, we detect minor amounts (7–10%) of the direct C_α alkynylation product, but we do not observe any of the *E* configurational isomer of **4a**. The trivalent phosphorus by-product can be easily recovered and recycled (Table 1).

Table 2 *Z*-Enediynes by dicarbofunctionalization of triaryl(arylethynyl)-phosphonium salts[a]



Entry	Phosphonium	Ar	Product	Yield[b,c] (%)
1	**3a**	C_6H_5–	**4a**	80
2	**3b**	4-MeC_6H_4–	**4b**	71
3	**3c**	2-MeC_6H_4–	**4c**	46[d]
4	**3d**	3-$CF_3C_6H_4$–	**4d**	69
5	**3e**	4-$CF_3C_6H_4$–	**4e**	68
6	**3f**	4-ClC_6H_2–	**4f**	78
7	**3g**	4-BrC_6H_4–	**4g**	79
8	**3h**	β-Naphthyl–	**4h**	64
9	**3i**	4-(Vinyl)C_6H_4–	**4i**	78
10	**3j**	4-(*t*BuC≡C)C_6H_4–	**4j**	56

[a] Conditions: 1.0 equiv. [(*o*-An)$_2$PhP–C≡C–Ar]Br, 1.1 equiv. Li–C≡C–Ar, 2.0 equiv. H–C≡C–Ar, THF, rt, 0.5 h. [b] Yields of isolated *Z*-enediyne following silica gel chromatography. [c] In all cases, mass recovery of $PPh(o\text{-An})_2 > 75\%$. See ESI for full details. [d] 1,4-Di-*o*-tolyl-1,3-butadiyne also isolated in 37%.

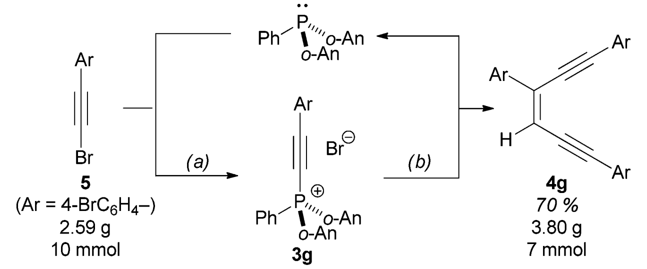


Fig. 2 One-pot, phosphine-mediated synthetic cycle for the multigram preparation of *Z*-enediyne **4g**. (a) PhMe, 45 °C, 72 h; (b) 1.1 equiv. Li–C≡C–Ar, 2.0 equiv. H–C≡C–Ar, PhMe/THF, rt, 1 h.

Treatment of a variety of alkynylphosphonium salts (prepared from the corresponding 1-bromoalkynes)[10] with 1.1 equiv. of lithio(aryl)acetylide and 2.0 equiv. of protio(aryl)acetylene in THF provides the corresponding enediyne in good yield as a single (*Z*) configurational isomer (Table 2). In each of these reactions, free triarylphosphine $PPh(o\text{-An})_2$ can be reisolated with good mass recovery. Both electron-rich (entries 2 and 3) and -deficient (entries 4 and 5) (aryl)acetylenes undergo smooth reaction. Halogen substituents (entries 6 and 7) are well-tolerated, permitting subsequent functionalization by a range of synthetic methods. Steric parameters, however, have a significant impact on the reaction outcome as evidenced in the case of the *o*-tolyl derivative (entry 3), where a significant quantity of 1,4-di-*o*-tolyl-1,3-butadiyne is isolated at the expense of the desired enediyne **4c**. This result is consistent with steric blocking of the β-carbon of the ethynylphosphonium salt that consequently favors direct α-alkynylation. Attempts to prepare differentially aryl-substituted and aliphatic-substituted enediynes have been unsuccessful to date (see ESI† for full details).

The reaction is scalable to multigram batch without significant decrease in yield, and can furthermore be conducted as a one-pot transformation without isolation of the intermediate alkynylphosphonium salt (Fig. 2). Specifically, treatment of 10 mmol of bromoalkyne **5** with bis(*o*-anisyl)phenylphosphine in toluene results in the formation of heterogeneous suspension of the corresponding ethynylphosphonium intermediate **3g**, to which lithium acetylide/protioacetylene can directly be added at ambient temperature to afford 3.80 g of *Z*-enediyne **4g** (70% yield from **5**). Bis(*o*-anisyl)phenylphosphine can also be recovered *via* chromatography, resulting in a closed synthetic cycle with respect to the phosphine promoter.

A mechanistic proposal consistent with the observed *Z*-selective enediyne synthesis is offered in Fig. 3. The sequence is initiated by β-addition of the lithioacetylide reagent[11] to the ethynylphosphonium cation[12] to give a vinylidene phosphorane[13] intermediate **6**, which by virtue of its bent geometry[14] may exist as either *E* or *Z* configurational isomers. In contrast to vinylidene ylides of more electronegative elements, the poor nucleofugality of the triarylphosphine moiety implicates vinylidene phosphorane **6** as a persistent intermediate in solution, assuring equilibration of the geometrical isomers to the less hindered *Z* configuration.[15] Protonation of *Z*-**6** by protioacetylene then fixes the alkene configuration by installation of the vinylic C–H substituent in vinylphosphonium intermediate **7**. This provenance for the vinylic hydrogen is secured by a deuterium isotope labeling experiment in which the use of D–C≡C–Ph (95% *D*) as a component in the dialkynylation reaction results in enediyne **4a**-*d* with 93% deuterium incorporation at the vinylic position (Fig. 4a).

We therefore posit vinylphosphonium **7** as the penultimate intermediate en route to enediyne product. In accord with this notion, subjection of an independently prepared vinylphosphonium

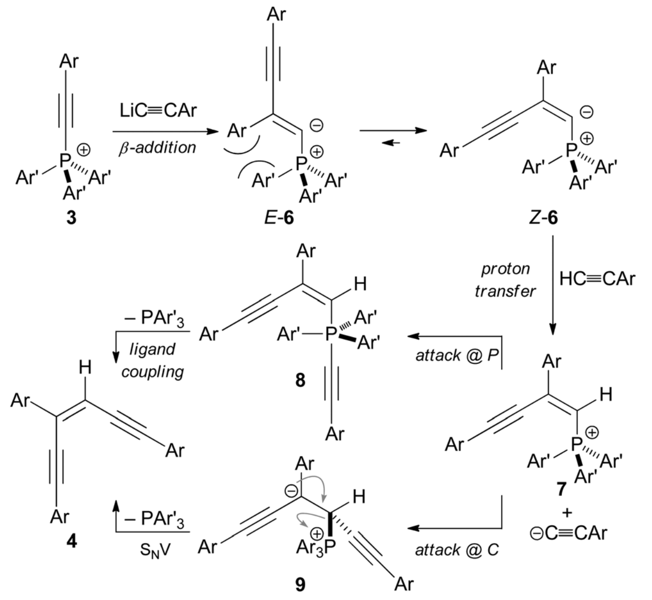
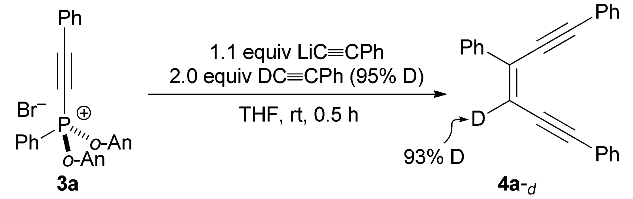


Fig. 3 Mechanistic proposal.

Z-**10** leads stereospecifically and nearly quantitatively to product *Z*-**4a** (Fig. 4b). Two scenarios to describe the mechanistic course for this conversion may be envisioned. In the first, attack of acetylide anion directly at phosphorus could give a phosphorane intermediate (**8**), which may evolve *via* C_{sp}–C_{sp^2} ligand coupling to deliver the observed products (Fig. 3).[16] Alternatively, vinylic substitution by an addition/elimination sequence *via* **9** could account for the observed reactivity.[17] The latter of these two possibilities is suggested by the finding that 48 : 52 *E*/*Z* mixture of **10** is converted into enediyne product *Z*-**4a** (*E*/*Z* ratio 4 : 96), although we cannot rigorously exclude the possibility that an *E* → *Z* isomerization event (for instance, *via* C_α deprotonation/reprotonation or reversible Michael-type β-addition to **10**) precedes a stereospecific C–C ligand coupling.[18] The mechanistic relationship between ligand coupling at phosphorus and vinylic addition/elimination has been previously noted by Trippett.[19] Further efforts to delineate between these mechanistic variants are being pursued.

a) Isotopic labelling study



b) Reactivity of putative vinylphosphonium intermediate

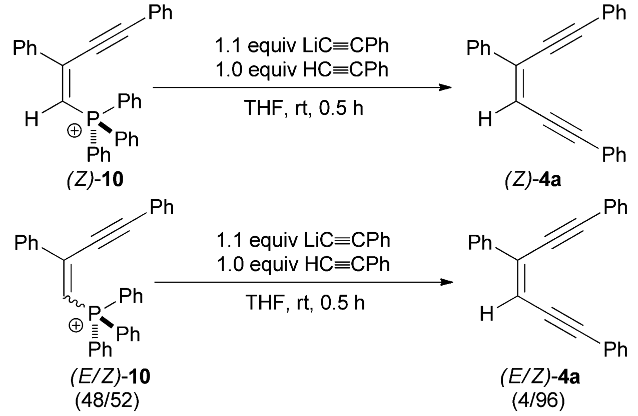


Fig. 4 Supporting mechanistic experiments.

In summary, the described dialkynylation of ethynylphosphonium salts illustrates the capacity of these ditopic electrophilic reagents to behave as vicinal acceptors of carbon-based nucleophiles. The reaction permits the synthesis of *Z*-enediynes with excellent configurational control starting from easily accessible and nonconfigurationally predefined components. In view of the fact that the reaction can be conducted as a closed synthetic cycle with respect to phosphine promoter, the further development of P-catalytic variants of this transition metal-free enediyne synthesis may be envisioned and is the focus of ongoing investigation.

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‡ Crystal structural data have been deposited with the Cambridge Crystallographic Data Centre. See ESI† for details.

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