

3,3,3-Trichloropropyl-1-triphenylphosphorane: A Reagent for the Synthesis of (Z)-1,3-Enynes, (Z,Z)-1-Chloro-1,3-dienes, and 1,3-Diynes[†]

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Conjugated π -systems, including (Z)-1,3-enynes, (Z,Z)-1,3-dienes, and 1,3-diynes, such as those found in histrionicotoxin **2**,¹ leustrodiscin H **3**,² and the dialula diyne **4**,³ are features which may be advantageously employed as connective segments in synthesis (Figure 1).

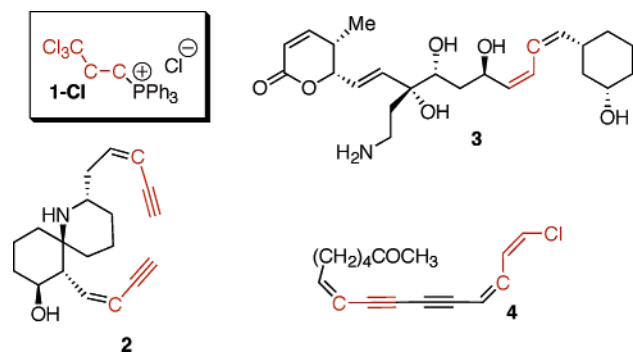
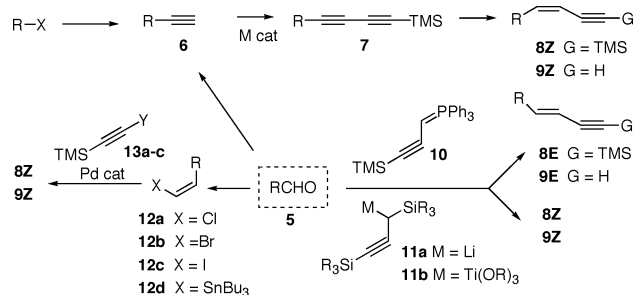


Figure 1. 3,3,3-Trichloropropyl-1-triphenylphosphorane and natural product targets.

Natural products containing the 1,3-diyne moiety are fairly common and have been synthesized by S_N2 reactions with acetylene followed by organocopper or palladium-mediated coupling (Scheme 1). An alternative introduction of the initial alkyne involves conversion of an aldehyde **5** to acetylene **6** using a variety of one-carbon reagents.⁴ Typically, the second acetylene is used in excess, and TMS-acetylene offers the advantage that the product can often be selectively semihydrogenated at the less-hindered alkyne⁵ to generate a protected (Z)-1,3-enyne (**8Z**), suitable for subsequent coupling operations after silyl deprotection to **9Z** (Scheme 1). In cases where several acetylenic functions reside in the target molecule, the semihydrogenation approach may not be a realistic option.

Scheme 1

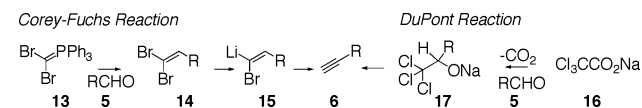


In such cases, an alternative approach to the (Z)-1,3-enyne, **8Z**, is required. While Wittig reagents, such as **10**, provide excellent

yields of the (E)-1,3-enyne, **8E**, Peterson reactions with bis-silylated propynylic anions, **11a,b**, represent the current state-of-the-art generation of **8Z** with a three-carbon reagent. Alternatively, a stepwise approach is often employed for construction of olefins **12a-d** and followed by palladium-catalyzed coupling with **13** to generate (Z)-1,3-enyne, **8Z** (Scheme 1).

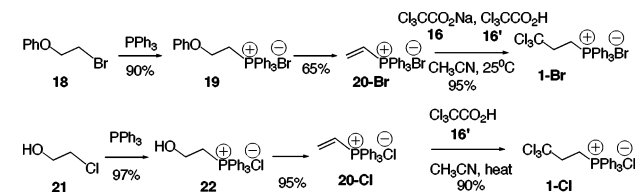
We reasoned that a reagent where the acetylene moiety was present in latent form at the time of the Wittig reaction should favor formation of the (Z)-olefin. Acetylene **6** is available from 1,1-dibromoolefin **14**, prepared from aldehyde **5** and ylide **13**.⁶ Moreover, a group at DuPont has developed a beautiful and economical one-carbon protocol, adding a trichloromethyl anion to aldehyde **5** followed by transmetalation of adduct **17** to acetylene **6** (Scheme 2).⁷

Scheme 2



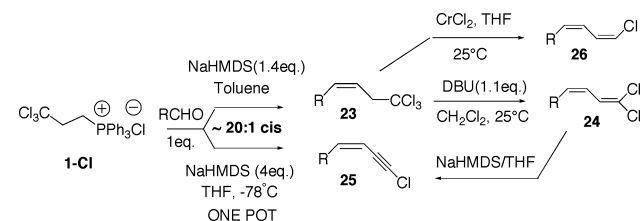
Our current study melded both of the above reactions. Stirring a mixture of 1.5 equiv of **16** and **16'** at 25 °C with the Schweizer vinylphosphonium salt (**20-Br**)⁸ in acetonitrile delivers a 95% yield of pure **1-Br**. A more economical synthesis of vinylphosphonium chloride (**20-Cl**) involves the heating of 2-chloroethanol (**21**) with a slight excess of triphenylphosphine neat for 48 h at 100 °C to afford β -hydroxyethyl phosphonium chloride (**22**).⁹

Scheme 3



Dehydration of **22** was best accomplished by heating the mixture with oxalyl chloride until gas evolution had ceased.¹⁰ Purification delivered **20-Cl** in 95% overall yield. Conversion of **20-Cl** to **1-Cl** was equivalent to the formation of the more expensive **1-Br** (Scheme 3), without requiring purification for any of the intermediate steps.

Scheme 4



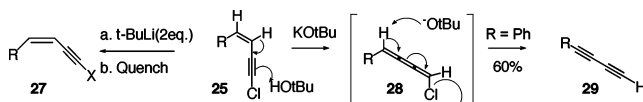
[†] Conjunctive reagents for the Chiral Carbon Catalog 2 (for 1, see: Li, X.; Lantrip, D.; Fuchs, P. L. *J. Am. Chem. Soc.* **2003**, *125*, 14262–14263).

Table 1. Reactions of Reagent 1-Cl

| RCHO 5 | R-CH=CH-CCl ₃ 23 | | R-CH=CH-Cl 24 | | R-CH=CH-C≡C-Cl 25 ONE POT | | 26 27 29 | |
|-----------|--|-----------------|------------------|----------|---------------------------------|-------------------|-----------------|---|
| | R= | Yield(%) | Z/E ^a | Yield(%) | Z/E ^a | Yield(%) | Yield(%) | |
| 5a | Ph- | 80 | 95/5 | >95 | 95/5 | 90 | 93/7 | 26a 80, 29a 60 27a ₁ X=Me 65 27a ₂ X=PhCHOH 78 27a ₃ X=SiMe ₃ 60 27b X=H 63 |
| 5b | 4-Cl-Ph- | 85 | 92/8 | 94 | 92/8 | 95 | 92/8 | |
| 5c | 2-Br-Ph- | 83 | 55/45 | 98 | 55/45 | 79 | 50/50 | |
| 5d | o-Phthaldehyde | 85 | 93/7 | 98 | 93/7 | 79 | 90/10 | |
| 5e | 3-MeO-Ph- | 77 | 97/3 | 96 | 97/3 | 75 | 96/4 | |
| 5f | 4-MeO-3-AcO-Ph- | (94 borsm) | 90/10 | 99 | 90/10 | (92 borsm) | 75 ^c | 90/10 |
| 5g | Ph-CH ₂ -CH ₂ - | 66 | Z only | 95 | Z only | 83 | Z only | |
| 5h | | 64 | Z only | 95 | Z only | 79 | Z only | |
| 5i | | 69 | Z only | 95 | Z only | 79 | Z only | |
| 5j | PhCH ₂ O(CH ₂) ₃ CH ₂ | 46 ^b | 95/5 | 95 | 95/5 | 43 ^b | Z only | |
| 5k | TBS-C≡C- | (76 borsm) | Z only | 99 | Z only | (73 borsm) | Z only | |
| 5l | | 50 | Z only | 96 | 92/8 | 28 | Z only | |
| 5m | | (75 borsm) | Z only | 97 | Z only | (78 borsm) | Z only | |
| | | 72 ^f | 92/8 | 96 | 92/8 | 35 ^{b,c} | 92/8 | |
| | | | | | | (42 borsm) | | |
| | | 63 | Z only | 97 | Z only | 78 ^d | Z only | 26l 89 |
| | | 72 | Z only | 97 | Z only | 62 | Z only | 26m 82 ^g |

^a Z/E ratio for trichloroethylenes and chloroenynes are from ¹H NMR; however, for dichlorodienes, the Z/E ratio is reported based on the Z/E ratio of trichloroethylenes. Most dichloro compounds show poor separation of isomers in NMR solvents, such as CDCl₃, C₆D₆, and CD₃OD. ^b LHMDs was used instead of NaHMDS. ^c Yield corresponds to the transformation from **24k**; see the Supporting Information. ^d Single enantiomer from chiral HPLC. ^e Acetate hydrolyzed to methoxyphenol. ^f Yield is for the two steps starting from the corresponding propargyl alcohol. ^g See the Supporting Information.

Scheme 5



Metalation of **1-Cl** in toluene ($-78\text{ }^{\circ}\text{C}$) followed by the addition of aldehyde gives Wittig adduct **23** or chloro (*Z*)-1,3-enyne **25** when the reaction is conducted in THF using excess sodium hexamethyldisilazane (NaHMDS). Application of the Cr[II] vinylidene carbenoid method of Falck and Mioskowski¹¹ to (*Z*)-olefin **23** gives the (*Z,Z*)-chlorodiene **26** in 80% yield. Alternatively, treatment of **23** with DBU in dichloromethane gives (*Z*)-dichlorodiene **24** (Scheme 4).

Transmetalation of **25** to lithioacetylide **27** ($X = \text{Li}$), followed by conversion to functionalized (*Z*)-1,3-enynes (**27**), was effected by trapping with a variety of electrophiles (Table 1, last column). Potassium *tert*-butoxide presumably effects bis-elimination of **25** to 1,3-diyne **29** via the cumulene intermediate **28**¹² (Scheme 5).

Acknowledgment. Thanks are due to Dr. Douglas Lantrip for assistance in manuscript preparation.

Supporting Information Available: Additional experiments, discussion, experimental procedures, and ¹H and ¹³C spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA045112V