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Generation of Nucleophilic Chromium Acetylides from *gem*-Trichloroalkanes and Chromium Chloride: Synthesis of Propargyl Alcohols

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Abstract

Nucleophilic mixed chromium(II) and chromium(III) acetylides are generated from the smooth reduction of primary 1,1,1-trichloroalkanes with chromium(II) chloride in the presence of an excess amount of triethylamine at room temperature. These species arise from chromium(III) vinylidene carbenoids. It has been demonstrated that uncommon low-valent Cr^{II} acetylides are formed by C–H insertion of Cr^{II}Cl₂ into terminal alkynes, formed in situ through the Fritsch–Buttenberg–Wiechell (FBW) rearrangement, whereas Cr^{III} acetylides are concomitantly generated by HCl elimination from the chromium(III) vinylidene carbenoid. Both divergent pathways result, overall, in the formation of nucleophilic acetylides. In situ trapping with electrophilic aldehydes afforded propargyl alcohols. Furthermore, deuteration experiments and the use of deuterium labeled 1,1,1-trichloroalkane substrates demonstrated the prevalence of low-valent Cr^{II} acetylides, potentially useful, yet highly elusive synthetic intermediates.

Keywords

Chromium; Carbenoids; Rearrangement; Alkynes; Alcohols

Introduction

Since their discovery in 1957, organochromium reagents have been the focus of constant development and innovations.^[1] Due to their unique combination of chemical features and remarkable compatibility with a wide range of functional groups, these reagents have become indispensable tools for advanced organic synthesis and for natural product synthesis.^[2] The last 10 years, in particular, have witnessed an enormous growth in terms of new reagents and reaction modalities.^[3–11] For instance, our laboratories and others have described several new chromium intermediates including chromium vinylidene carbenoids,^[4] halogenated chromium enolates,^[6] chromium Fischer halocarbenes,^[5,7,11] and

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Dedicated to the memory of Dr. Charles Mioskowski

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Supporting Information (see footnote on the first page of this article): ¹H, ¹³C, and ¹⁹F (for **3i**) NMR spectra of the original compounds.

carbynes.^[9] In continuation of our harvest of novel intermediates with unusual reactivities formed through the chromium-mediated reduction of 1,1,1-trihaloalkanes, we report herein that the reduction of 1,1,1-trichloroalkanes by chromium(II) chloride in the presence of triethylamine (TEA) induces the smooth formation of alkynylchromium reagents in high yields under exceptionally mild reaction conditions. Interception of the alkynylchromium intermediates with electrophilic aldehydes provides convenient access to functionalized propargyl alcohols (Scheme 1).^[12]

Heretofore, the generation of metal acetylides under mild conditions compatible with various functional groups has long been an unresolved synthetic challenge.^[13] Classical methods have mainly exploited the relatively high acidity of terminal acetylenic C–H bonds to form metal alkynylides, either by direct metalation using strong bases, such as *n*-butyllithium or lithium diisopropylamide at low temperature (–100 to –80 °C),^[14] or upon treatment with tertiary amines in the presence of a stoichiometric or catalytic amount of the metal salt of interest (Figure 1, route a).^[15] Lithium and silver acetylides prepared by this approach are also utilized for the preparation of other acetylides by transmetalation with magnesium, zinc, cerium, and other metals (Figure 1, route b).^[16–20] Alternatively, lithium acetylides can also be prepared through the Fritsch–Buttenberg–Wiechell (FBW) rearrangement/metalation of 1,1-dibromoolefins when treated with an excess amount of *n*-butyllithium (Figure 1, route d).^[20,21] An in situ metalation/desilylation strategy has recently been applied successfully to the preparation of highly stable ruthenium acetylides of interest for their electronic properties (Figure 1, route c).^[22]

Chromium(III) acetylides, that are mainly generated by reduction of alkynyl halides with chromium(II) chloride (Figure 1, route e),^[23] or more recently by transmetalation of lithium acetylides (Figure 1, route b),^[24] have received scant attention, in spite of their demonstrated synthetic utility in a great number of natural product total syntheses^[25] and for their interesting electronic properties.^[26]

Results and Discussion

The generation of alkynylchromium(III) reagents by the most widely used reductive route (Figure 1, route e) is, however, plagued by drawbacks, inter alia, dependency upon nickel(II) additives, polar solvents, and/or high reaction temperatures.^[1c] In sharp contrast, we have discovered that alkynylchromiums can be easily synthesized from the reduction of *gem*-1,1,1-trihaloalkanes by using 6 equiv. of CrCl₂ and 10 equiv. of TEA (Figure 1, route f; Scheme 2).

The postulated mechanism for the formation of chromium acetylides likely proceeds through a comparatively stable chromium(III) vinylidene carbenoid **6**, generated through the *syn*-β-elimination of chromium hydride from the unstable 1-chloro-1,1-*bis*-chromium alkane carbenoid **5**, initially formed by the reduction of two C–Cl bonds in 1,1,1-trichloroalkane **4** (Scheme 2).^[4a] Subsequent β-elimination of hydrogen chloride induced by Et₃N abstraction of the vinylic proton of **6** gives rise to chromium(III) acetylide **7** (Scheme 2, path a).

Surprisingly, whereas DBU, pyridine, 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD), and DABCO were completely inactive and even inhibited the reduction of trichloroalkane **4**, TEA was unique amongst the common organic bases and did not interfere with the overall transformations of *gem*-1,1,1-trichloroalkanes. The role of TEA is not known yet, although it is assumed that the dramatic decrease in the p*K*_a of the carbenoid vinylic proton can be ascribed to the concerted metal-assisted ionization phenomenon (MAI),^[27] which triggers the formation of chromium(III) acetylide **7** as shown in postulated binuclear complex **13** (Scheme 3).

Hydrogen abstraction from **13** (Scheme 2, path a) is assumed to be kinetically competitive with the FBW rearrangement that leads to terminal alkyne **9** (Scheme 2, path b).^[28] We postulate that this unprecedented reactivity of chromium vinylidene carbenoids is a result of coordination of the σ -donor lone pair of the basic nitrogen to chromium(III), yielding chromium(III) acetylides **7**. This mechanistic pathway was partially corroborated by the fact that (*Z*)-2-chloroalk-2-en-1-ols **14** were formed in low amounts (4–10%) as byproducts when the reaction was performed under Barbier conditions in the presence of various aldehydes (Scheme 4).

The high yield of propargyl alcohol **3**, combined with the ready availability of 1,1,1-trichloroalkanes **1a–d**, make this methodology very attractive for the preparation of a large panel of propargyl alcohols (Table 1).^[29] Aromatic aldehydes **12a–d** and **12g–i** bearing diverse, sensitive functional groups such as bromo, cyano, acetoxy, methoxy, and fluoro, were well tolerated and afforded expected adducts **3a–d**^[30,31] and **3g–i**^[32] in good to excellent yields (Table 1, Entries 1–4, 7–9). Similarly, an α,β -unsaturated aldehyde like (*E*)-cinnamaldehyde (**12f**) reacted smoothly and delivered cleanly the corresponding propargyl allyl alcohol **3f**^[30] in a good isolated yield of 63% (Table 1, Entry 6). In sharp contrast, the use of an enolizable aliphatic aldehyde like dihydrocinnamaldehyde (**12e**) under the same conditions was problematic, and the yield of addition product **3e**^[33] was drastically decreased to 22% because of competitive cross-aldol as well as elimination. (Table 1, Entry 5).^[34] Primary 1,1,1-trichloroalkanes **1c** reacted moderately and resulted in the formation of **3j**^[35] in reasonable isolated yield (56%) when benzaldehyde (**12j**) was used as the electrophile (Table 1, Entry 10). It is worth mentioning that the use of allylic 1,1,1-trichloroalkane **1d** offered the opportunity to extend the scope of this transformation in generating useful enyn–alcohol **3k**^[36] in excellent yield (Table 1, Entry 11). Attempts to reduce the amount of chromium reagent by using multicomponent redox system for chromium recycling [CrCl₂ (10 mol-%)/Mn⁰/TMSCl]^[37] and TEA (10 equiv.) in THF at room temperature for 12 h were not satisfactory as a result of limited conversion of the starting 1,1,1-trichloroalkanes (<10%). This result suggests, most likely, that the initial generation of key vinylidene carbenoid **6** (Scheme 2) might be the rate-limiting step of the process under these specific conditions.

Mechanistically, to determine whether terminal alkyne **9**, generated by FBW rearrangement from **6**, could eventually be an intermediate in the overall transformation (Scheme 2, path b), we examined the reactivity of terminal alkynes with chromium(III) and chromium(II) chloride in the presence or absence of TEA. Notably, as a control experiment, 1-phenylacetylene (**11**) does not react with chromium(III) chloride in the presence or in the absence of TEA in THF under the same conditions as **1**, thus excluding pathway a in the formation of chromium(III) acetylide **7a** (Scheme 5).

However, we were surprised by the fact that Cr^{II}Cl₂ reacted smoothly with **11** in the presence of TEA (Scheme 5, path b), as evidenced by the formation of a minimum of 60% of adduct **16** when the organometallic species was trapped with benzaldehyde under Barbier conditions. Because the direct insertion of chromium(III) into the C–H bond of terminal alkynes is excluded for the formation of chromium(III) acetylide **7a**, these results suggest strongly that the nucleophilic metalated acetylide is the uncommon low-valent chromium(II) acetylide **15**. This result might be explained by ligand exchange of Cr^{II}, allowing nucleophilic substitution of labile ligands (e.g., Cl) to give nucleophilic chromium(II) acetylide **15**. Indeed, like Zn^{II}, Cu^I, or Au^I acetylides that are generated in situ from terminal alkynes at room temperature upon treatment with an organic base (TEA, *i*Pr₂N*n*Pr, or NH₄OH)^[13,15c,15d,29] by ligand exchange, this substitution reaction occurs for Cr^{II}. This mechanism is supported by kinetic studies reported by Merbach, who showed that this ligand exchange is kinetically very fast and favored for Cr^{II}, whereas Cr^{III} is known to be

extremely resistant to this process.^[38] Indeed, the exchange ligand rates are ca. 15 orders of magnitude higher for Cr^{II} than Cr^{III}.^[39] The synthesis of end-bound acetylide ligands with monovalent and divalent octahedral chromium(II) has been recently reported; however, to the best of our knowledge, there is no report that accounts for their reactivity towards C–C bond-forming reactions.^[26] At this point in our investigation, we provided evidence that the reduction of 1,1,1-trichloroalkanes with chromium(II) chloride in the presence of TEA affords unprecedented mixed chromium(II) and chromium(III) acetylides through two divergent pathways from chromium(III) vinylidene carbenoid **6** (Scheme 2). To further distinguish the prevalence of one pathway with respect to the other, we examined the reduction of deuterated substrate **17** and performed additional deuteration experiments (Scheme 6). Substrate **17** was first treated with 4 equiv. of CrCl₂ under the same experimental conditions as those outlined for compounds **1**. Quenching the reaction with H₂O afforded a 2:3 mixture of protonated terminal alkyne **18** and its deuterated analogue **19** (FBW product) as determined by quantitative GC–MS analysis.

Interestingly, this result was corroborated by the reduction of **1a** with 4 equiv. of CrCl₂,^[4a] in the presence of an excess amount of TEA, and subsequent deuteration with DCl in D₂O, which yielded 30–35% of [D₁]phenylacetylene (**20**), along with 70–65% of **11**. These observations demonstrated unambiguously the propensity of vinylidene carbenoids **6**, prepared in the presence of TEA, to undergo FBW rearrangement predominantly and, therefore, the prevalence of pathway b that leads to Cr^{II} acetylides **10** (Scheme 2). The smooth generation of low-valent chromium(II) acetylides from 1,1,1-trihaloalkanes and CrCl₂ as well as the reactivity of such organometallic species as new alkynylating agents have not been studied earlier. Although their nucleophilic behavior has been shown by trapping with electrophiles such as aldehydes, these reagents could be eventually used either in one-pot, metal (Pd, Ni, Fe) cross-coupling reactions or engaged in situ in [3+2]-Huisgen dipolar cycloaddition with azides.^[40] The optimization as well as the scope and the potential applications of these synthetically useful reagents are underway in our laboratories and will be disclose elsewhere.

Conclusions

In summary, we have found that the reduction of 1,1,1-trichloroalkanes with an excess amount of chromium(II) provides direct access to mixed nucleophilic chromium(II) and chromium(III) acetylides. Both species are formed through divergent pathways, from chromium(III) vinylidene carbenoids, which favor the formation of uncommon low-valent chromium(II) acetylides, generated through the FBW route. We have demonstrated that in situ generated mixed chromium acetylides react smoothly with electrophilic aldehydes, providing access to propargyl alcohols, complementing other known strategies. Further promising developments using this new reductive/oxidation reaction of 1,1,1-trichloroalkanes by CrCl₂ are expected to emerge and will be disseminated shortly.

Experimental Section

General

All reactions were performed under an argon atmosphere. The solvent (THF) was distilled from Na and benzophenone. All commercially available reagents were used without further purification. Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel plates. Visualization of the developed chromatogram was performed by using UV absorbance and staining with a vanillin, phosphomolybdic acid, or cerium sulfate solution. Flash column chromatography was performed with silica gel (40–63 μm) according to a standard technique. Nuclear magnetic resonance spectra (¹H, ¹³C, and ¹⁹F) were recorded with a Bruker 400 MHz spectrometer equipped with a BBI or a DUAL probe. Chemical

shifts for ^1H and ^{13}C NMR spectra are recorded in parts per million by using the residual chloroform as an internal standard (^1H , $\delta = 7.26$ ppm; ^{13}C , $\delta = 77.16$ ppm). Multiplicities are indicated by s (singlet), br. s (broad singlet), d (doublet), t (triplet), and m (multiplet). Mass spectra were recorded with a MS–MS high-resolution Micromass ZABSpecTOF spectrometry. Infrared spectra were recorded with an FTIR spectrometer equipped with KRS-5.

General Procedure for the Generation of Chromium Acetylides and Their Reaction with Aldehydes

All the reactions were performed on 1-mmol scale of trichloroalkanes **1a–d**. To a solution of trichloroalkane **1** (1 equiv.) in THF (15 mL) was added aldehyde **12** (1 equiv.), CrCl_2 (6 equiv.), and TEA (10 equiv.) under an inert atmosphere. The whole mixture was allowed to stir overnight at room temperature (10 h). After completion of the reaction (TLC analysis), the mixture was quenched with 1 N HCl (5 mL) and extracted with EtOAc (2×10 mL). The organic layer was washed with water and brine and dried with Na_2SO_4 . Evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography. Elution with EtOAc/cyclohexane gave desired propargyl alcohol **3** and (*Z*)-2-chloroalk-2-en-1-ol (**14**) as an inseparable mixture. [32]

1-[4-(1-hydroxy-3-phenylprop-2-ynyl)phenyl]ethanone (**3d**)

Yield: 192 mg (72%), colorless sticky solid. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.54$ (d, $J = 8.4$ Hz, 2 H), 7.37–7.39 (m, 2 H), 7.22–7.24 (m, 3 H), 7.03 (d, $J = 8.8$ Hz, 2 H), 5.5 (br. s, 1 H), 2.41 (br. s, 1 H), 2.20 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 169.5$, 169.4, 150.6, 138.2, 131.7, 128.3, 127.9, 122.3, 121.7, 88.5, 86.8, 64.5, 21.1 ppm. IR (film): $\tilde{\nu} = 3414$, 3056, 2183, 1753, 1504, 1195, 1164, 1064, 733 cm^{-1} . HRMS (EI): calcd. for $\text{C}_{17}\text{H}_{14}\text{NaO}_3$ [$\text{M} + \text{Na}$] $^+$ 289.0835; found 289.0845.

1-(4-Methoxyphenyl)-3-(*p*-tolyl)prop-2-yn-1-ol (**3g**)

Yield: 164 mg (65%), light-yellow-colored viscous solid. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.48$ –7.45 (m, 2 H), 7.29 (d, $J = 8.4$ Hz, 2 H), 7.05 (d, $J = 8$ Hz, 2 H), 6.84–6.86 (m, 2 H), 5.56 (d, $J = 5.6$ Hz, 1 H), 3.75 (s, 3 H), 2.27 (s, 3 H), 2.12 (d, $J = 6$ Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 159.7$, 138.7, 131.6, 133.1, 129.2, 129.0, 128.9, 128.1, 128.0, 119.4, 114.0, 88.2, 86.6, 64.8, 55.3, 21.5 ppm. IR (film): $\tilde{\nu} = 3400$, 2921, 2835, 2197, 1608, 1508, 1245, 1170, 1029, 814 cm^{-1} . HRMS (EI): calcd. for $\text{C}_{17}\text{H}_{16}\text{NaO}_2$ [$\text{M} + \text{Na}$] $^+$ 275.1042; found 275.1053.

1-[4-[1-hydroxy-3-(4-methylphenyl)prop-2-ynyl]phenyl]ethanone (**3h**)

Yield: 239 mg (79%), colorless sticky solid. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.53$ –7.51 (m, 2 H), 7.27–7.25 (m, 2 H), 7.03–7.00 (m, 4 H), 5.56 (br. s, 1 H), 2.51 (br. s, 1 H), 2.25 (s, 3 H), 2.20 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 169.5$, 150.5, 138.8, 138.4, 131.6, 129.1, 127.9, 121.7, 119.2, 87.9, 86.9, 64.5, 21.5, 21.3, 21.1 ppm. IR (film): $\tilde{\nu} = 3432$, 3043, 2931, 2195, 1754, 1505, 1194, 1163, 1012, 815, 734 cm^{-1} . HRMS(EI): calcd. for $\text{C}_{18}\text{H}_{16}\text{NaO}_3$ [$\text{M} + \text{Na}$] $^+$ 303.0991; found 303.1000.

1-(4-Fluorophenyl)-3-(*p*-tolyl)prop-2-yn-1-ol (**3i**)

Yield: 195 mg (81%), colorless sticky solid. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.52$ –7.48 (m, 2 H), 7.28–7.26 (m, 2 H), 7.05–6.96 (m, 2 H), 7.04 (d, $J = 8$ Hz, 2 H), 5.57 (d, $J = 5.2$ Hz, 1 H), 2.30 (d, $J = 6$ Hz, 1 H), 2.26 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 163.9$ (d, $^1J = 246$ Hz, C), 161.4, 138.9, 136.6 (d, $^4J = 3$ Hz, C), 131.6, 129.1, 128.6 (d, $^3J = 8$ Hz, C), 128.5, 125.5, 119.1, 115.5 (d, $^2J = 22$ Hz, C), 115.3, 115.2, 87.8, 87.0, 64.4, 21.5, 21.3 ppm. ^{19}F NMR (376.49 MHz, CDCl_3): $\delta = -113.8$ (s, 1 F) ppm. IR (film): $\tilde{\nu} = 3338$, 2921,

2229, 1604, 1506, 1221, 1156, 1013, 836, 814 cm^{-1} . HRMS (EI): calcd. for $\text{C}_{16}\text{H}_{14}\text{FO}$ [$\text{M} + \text{H}$]⁺ 241.1023; found 241.1036.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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32. All the resulting propargyl alcohols were characterized by ^1H NMR, ^{13}C NMR, IR spectroscopy and HRMS. The ^1H and ^{13}C NMR spectra of known compounds were compared with data reported in the literature. See Supporting Information for the ^1H NMR and ^{13}C NMR spectroscopic data for original products 3d, 3g, 3h, and 3i.
33. For the analytical data of 3e see: a) Fang T, Du D-M, Lu S-F, Xu J. *Org. Lett.* 2005; 7:2081–2084. [PubMed: 15901139] b) Gao G, Moore D, Xie RG, Pu L. *Org. Lett.* 2002; 4:1855–1857. [PubMed: 12027631]
34. We have also noticed that ketones reacted sluggishly to furnish propargyl alcohols (<10%), and enolizable ketones afforded cross-aldol and elimination compounds as byproducts.
35. For the analytical data of 3j see: Takita R, Yakura K, Ohshima T, Shibasaki M. *J. Am. Chem. Soc.* 2005; 127:13760–13761. [PubMed: 16201775]
36. For the analytical data of 3e see: Karatholuvhu MS, Fuchs PL. *J. Am. Chem. Soc.* 2004; 126:14314–14315. [PubMed: 15521725]
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39. a) Merbach AE. *Pure Appl. Chem.* 1987; 59:161–172. b) Merbach AE. *Pure Appl. Chem.* 1982; 54:1479–1796.
40. Krasinski A, Fokin VV, Sharpless KB. *Org. Lett.* 2004; 6:1237–1240. [PubMed: 15070306]

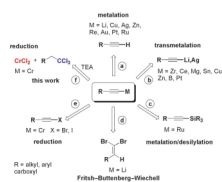
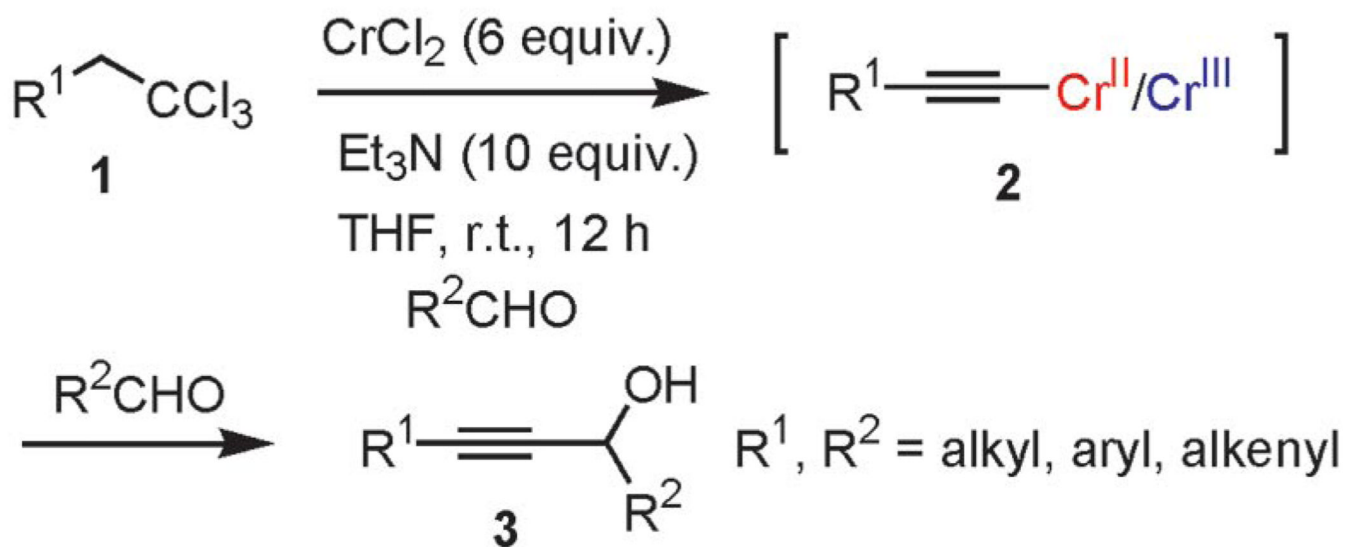
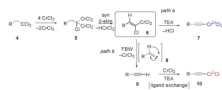


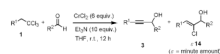
Figure 1.
 General approaches for the generation of metalated acetylides.

**Scheme 1.**

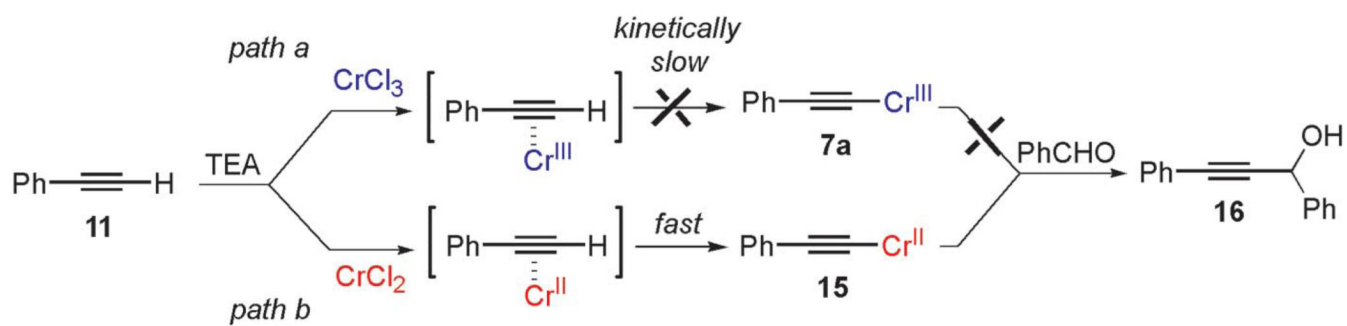
Generation of mixed chromium acetylides from 1,1,1-trichloroalkanes and in situ reaction with aldehydes.

**Scheme 2.**

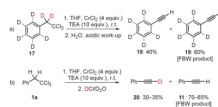
Postulated mechanism for the formation of mixed chromium acetylides.



Scheme 4.
Application to the synthesis of propargyl alcohols.



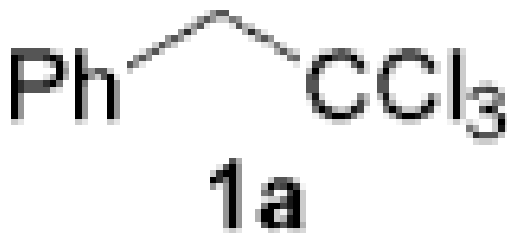
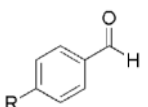
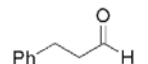
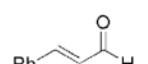
Scheme 5.
Generation of alkynylating chromium agents from phenylacetylene (**11**).



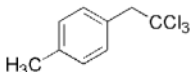
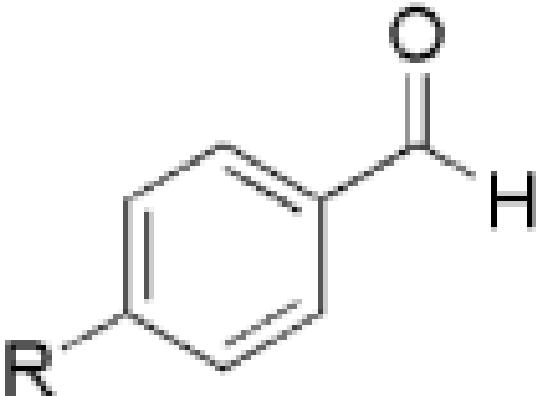


Scheme 6.
Mechanistic deuteration experiments.

Table 1

Synthesis of different propargyl alcohols.

Entry	Trichloroalkane	Aldehyde
	 <p style="text-align: center;">1a</p>	
1	1a	R = CH ₃ 12a
2	1a	R = Br 12b
3	1a	R = CN 12c
4	1a	R = OAc 12d
5	1a	 <p style="text-align: center;">12e</p>
6	1a	 <p style="text-align: center;">12f</p>



Entry	Trichloroalkane	Aldehyde
7	 <p data-bbox="548 338 574 359">1b</p>	
8	1b	R = OAc 12h
9	1b	R = F 12i
10	 <p data-bbox="521 953 594 1010">1c</p>	PhCHO 12j
11	 <p data-bbox="521 1373 594 1430">1d</p>	12j