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Magnesium mediated carbometallation of propargyl alcohols: direct routes to dihydroxydienes and enediyne alcohols

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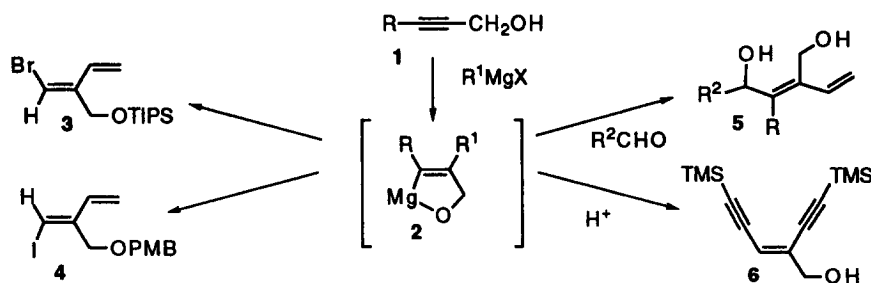
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Abstract

The addition of vinyl and alkynyl Grignard reagents to propargyl alcohols for the direct synthesis of dihydroxydienes and enediyne alcohols from a one pot reaction is described. These products arise from the putative magnesium chelate intermediate **2** upon reaction with the appropriate electrophile. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: diene; diol; magnesium; propargyl; enediyne.

Motivated in part by a combination of our interests in the synthesis of taxoids and the development of tether controlled intramolecular reactions,¹ we have developed routes to stereodefined dienes by both sequential palladium coupling, or more efficiently, by the direct addition of vinyl Grignard reagents to propargyl alcohols **1** (Scheme 1). This reaction is believed to proceed via the intermediate magnesium chelate **2** (or a closely related species). Either of the stereoisomers **3** or **4** may be prepared depending upon the electrophile and synthetic sequence selected.² We wish to report the extension of these investigations to encompass the direct synthesis of diene–diols **5** and enediyne systems **6**.

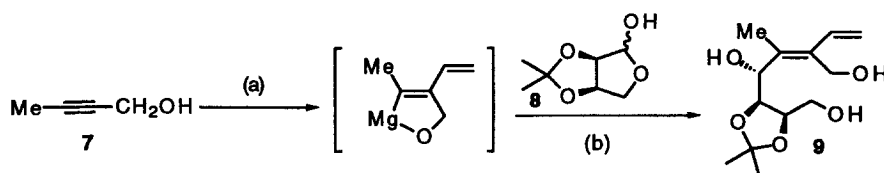


Scheme 1. Magnesium mediated carbometallation of propargyl alcohols

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A variety of other studies related to the addition of magnesium reagents to allylic and acetylenic alcohols have been reported.^{3–6} The initial studies with α -hydroxyolefins³ were extended to propargyl alcohols^{4,5} particularly with allyl magnesium species.⁴ Frequently, other metal salts such as copper or nickel⁵ were added prior to the reaction with a proton source, a carbonyl species or carbon monoxide. These are *anti*-carbometallations relative to the Grignard component and the new hydrogen. This is in contrast to the normal *syn*-addition observed for zirconium, aluminum and copper systems on alkyl alkynes. However, with some homopropargyl alcohols the initial *anti*-product, from the zirconium intermediate, may be thermally isomerized to the *syn*-isomer.⁶ Only a few previous examples of additions of vinyl magnesium reagents to propargyl alcohols are known and generally the yields are low.^{4c}

Direct condensation of the diene unit with carbonyl compounds is attractive, as the independent preparation of the vinyl halide **4** is avoided. In addition, potential complications encountered with lithium–halogen exchange are circumvented.⁷ Scheme 2 illustrates a typical example with a sensitive substrate, in which **2** is condensed with the hemiacetal **8** to afford the triol **9** in 44% yield as a 3:1 mixture of diastereomers. Neither excess *n*-butyllithium nor excess of the lithium salt derived from diene **4** gave any product when reacted with **8**.



Scheme 2. Typical condensation with an aldehyde. (a) 3.2 equiv. CH₂=CHMgCl, C₆H₁₂, 80°C, 19 h; (b) 0°C, 0.5 h, 22°C, 1 h, 3:1, 44%

Table 1 summarizes the results of several addition–condensation reactions with various propargyl alcohols in different solvents. In contrast with earlier reports, metal salts are not required with vinyl Grignards,⁸ and in most cases the yields are improved by conducting the reaction in a refluxing mixture of cyclohexane and the THF derived from the reagent (~60/40). If the quantity of the vinyl Grignard reagent is reduced from 3.2 to 2.1 equivalents, the yield is diminished (entry b), but this eliminates the competition of excess vinyl magnesium chloride for the aldehyde. The presence of a silyl ether group attached to the alkyne appears to affect complex formation and is sufficient to inhibit this reaction (entry d). Entries e and f illustrate that variation in the electron density of the triple bond has a negligible effect on the reactions conducted in the cyclohexane–THF solvent mixture. However, the reaction with **13** (entry f) failed in THF when an electron withdrawing group was attached to the triple bond. This observation is consistent with the mechanistic rationale established earlier from investigations with allylmagnesium halides and α -alkenols, in which the initial reaction step involved an electrophilic attack of the magnesium reagent on the π -system assisted by the proximity of the C–O bond in the alkoxide.^{3e,f} The less polar solvent mixture may also improve the reactivity of the Grignard complex **2**. The reaction with a ketone afforded the expected product in modest yield (entry h).

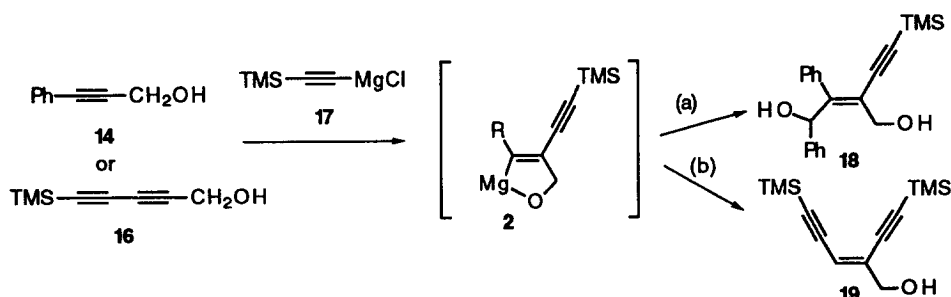
The study and synthesis of enyne and enediyne chromophores is a topic of current interest due to their challenging structures and biological activity as antibiotics and antitumor agents.⁹ An additional application, which illustrates the synthetic utility of this carbometallation method, is the facile preparation of these building blocks. For example, addition of trimethylsilylethynylmagnesium chloride (**17**) to various propargyl alcohols allows direct access to enyne and enediyne synthons.¹⁰ As illustrated in Scheme 3, addition of **17** to **14** provided the type ‘2’ intermediate which, upon condensation with benzaldehyde, gave **18**. In a related fashion addition of **17** to the extended propargyl alcohol **16** provided

Table 1
Preparation of diene-diols of type **5** with vinyl magnesium chloride

Entry	Substrate ^a R—C≡C—CH ₂ OH	Reactant	Yield %	
			C ₆ H ₁₂	THF
a	7 R = Me	PhCHO	80	50
b	7 R = Me ^b	PhCHO	68	44
c	10 R = TMS	PhCHO	78	94
d	11 R = CH ₂ OTBS	PhCHO	0	0
e	12 R = 4-MeOC ₆ H ₄	PhCHO	77	59
f	13 R = 4-CF ₃ C ₆ H ₄	PhCHO	75	0
g	14 R = Ph	PhCHO	86	87
h	15 R = Me	PhCOMe	44	-

^a3.2 eq CH₂=CHMgCl, reflux, 19h; RCHO, 0-22 °C; ^b2.1 eq CH₂=CHMgCl.

the enediyne alcohol **19** (36% yield)¹¹ in a very facile manner. The majority of other routes required palladium mediated coupling.^{9,10}



Scheme 3. A rapid synthesis of enyne systems

Kinetic studies^{3d} were consistent with an intramolecular delivery of the allyl moiety in the case of alkenols, and further research^{3e,f} established the intermediacy of **20** (Fig. 1). As stated above, the net effect of this carbometallation method is a regiocontrolled *anti*-addition of the vinyl group relative to the second carbon-carbon bond. A similar mechanism appears to apply also to the vinyl Grignard reagents with the propargyl alcohols. Thus the stereochemical result suggests that the delivery of the vinyl group may involve an intramolecular process in which the bonding between a-b and c-d occurs in a synchronous manner as illustrated by **21**. A close analogy is provided by the *anti*-hydroalumination of propargyl alcohols with LiAlH₄ or Red-Al,¹² which are considered to involve intermediates of type **22**. Thus, initial addition of the vinyl magnesium chloride to the complexed species related to **21** is followed by collapse to **2**. No evidence was detected in earlier investigations^{3f} for the involvement of a unimolecular one-electron transfer mechanism, although a concerted [$\pi 2_s + \sigma 2_a$] process has also been suggested.¹³

In summary, the magnesium mediated carbometallation protocols described above provide direct access to a number of useful unsaturated systems that may be employed for a variety of synthetic

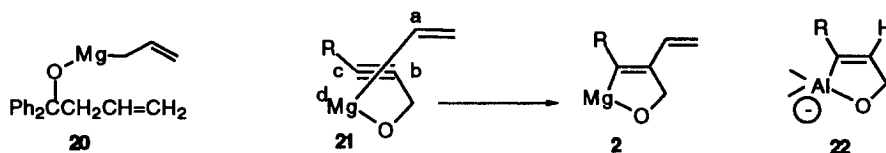


Figure 1. Rational for *trans*-addition of vinyl Grignard

objectives.¹⁴ The potential of this procedure for the synthesis of stereodefined halo-dienes, dihydroxy-dienes and enyne and enediyne alcohols is of interest. In addition, the ease with which these compounds are prepared in one synthetic step renders this sequence attractive for additional applications. The following Communication provides some examples that generate furans and furanones.

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14. General procedure for the carbometallation of propargyl alcohols to dienols: Vinyl magnesium chloride (6.6 mL, 1.3 M in THF, 8.6 mmol) was added to a solution of 2-butyne-1-ol (0.20 mL, 2.6 mmol) in cyclohexane (5 mL) at 22°C. The solution was refluxed for 19 h. The solution was cooled to 0°C and benzaldehyde (0.87 mL, 8.6 mmol) was added. The mixture was stirred for 5 min at 0°C followed by 1 h at 22°C. Saturated aqueous ammonium chloride (5 mL) was added, and after stirring for 20 min, the organic layer was separated and the aqueous phase extracted with ether (3×10 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated. Flash column chromatography on silica gel (3:1 to 1:3 petroleum ether:ether) afforded (1*R**,2*Z*)-3-ethenyl-2-methyl-1-phenyl-2-butene-1,4-diol (80%) as a yellow solid; mp 132–137°C; ¹H NMR δ 1.59 (s, 3H), 3.23 (s, broad, 2H), 4.25 (d, 1H, *J*=11.9), 4.43 (d, 1H, *J*=11.9), 5.07 (dd, 1H, *J*=11.2, 0.7), 5.40 (dd, 1H, *J*=17.5, 1.2), 5.89 (s, 1H), 6.54 (dd, 1H, *J*=17.5, 11.1), 7.05–7.44 (m, 5H); ¹³C NMR δ 13.2, 57.6, 72.1, 114.7, 126.1, 127.1, 128.5, 133.0, 134.6, 141.2, 142.5; IR (NaCl) 3374, 1494, 1450, 1014, 701; MS (*M*⁺–H₂O) calcd 186.1045; obsd 186.1050. Anal. calcd for C₁₃H₁₆O₂: C, 76.44; H, 7.90. Found: C, 76.55; H, 8.13.