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α-Chlorovinylation: Synthesis of 2-Chloropropenyl and Propargyl Alcohols

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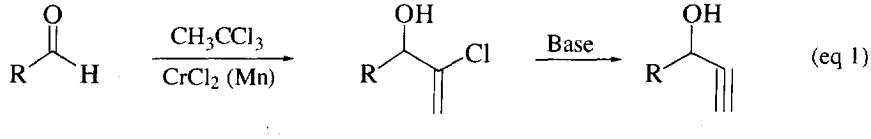
Abstract: Formal α-chlorovinylation of aldehydes using $CH_3CCl_3/CrCl_2$ affords 2-chloropropenyl alcohols from which terminal propargyl alcohols are obtained via base induced elimination.

Keywords: alcohols, alkenyl halides, alkynes, chromium

α-Chlorovinyl and propargyl moieties are critical structural components in a variety of bioactive natural products of current interest, e.g., halomon,[1] spongistatin,[2] and laurediol.[3] Since introduction of the former subunit via nucleophilic addition of an α-anionic intermediate is generally precluded by rearrangement and/or decomposition of the metalated carbenoid,[4] indirect and often low yielding procedures must be used.[5] Lithium and magnesium salts of acetylides, on the other hand, are quite stable, but their generation from gaseous acetylene is inconvenient and potentially hazardous. As part of a continuing commitment to the synthesis of structurally challenging, halogenated natural products and their alkynyl analogs,[6] we report herein an efficient and mild α-chlorovinylation of aldehydes using commercial CH_3CCl_3 and $CrCl_2$ (eq 1). Based induced elimination transforms the resultant 2-chloropropen-3-ol adducts into the corresponding terminal propargyl alcohols.



(eq 1)

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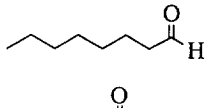
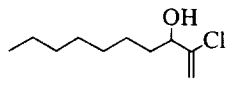
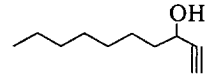
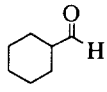
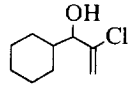
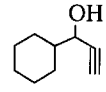
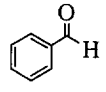
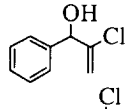
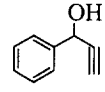
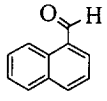
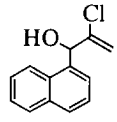
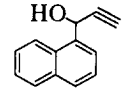
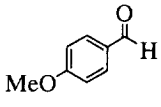
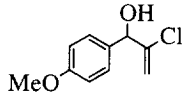
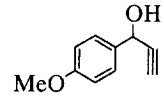
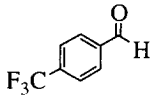
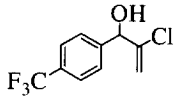
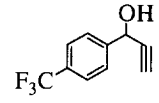
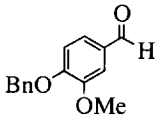
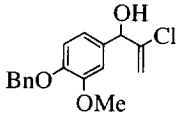
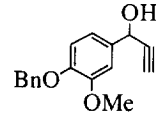
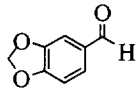
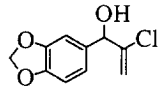
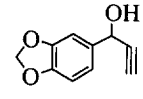
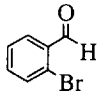
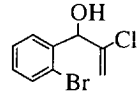
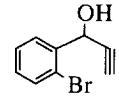
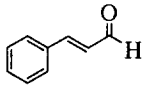
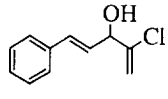
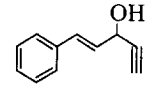
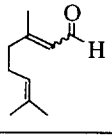
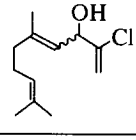
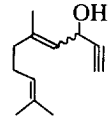
Table 1.

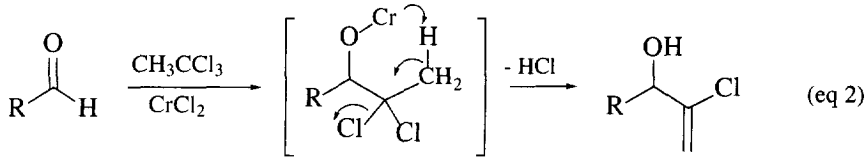
Entry	Aldehyde	Adduct	Yield (%)	Acetylene	Yield (%)
1			85		96
2			73		89
3			83		95
4			72		92
5			70		93
6			83		95
7			75		91
8			81		94
9			76		94
10			65		92
11			71		90

The scope of the α-chlorovinylation procedure was explored using a representative panel of aldehydes[7] (Table 1). With a four-fold excess of $CH_3CCl_3/CrCl_2$ in THF, *n*-alkyl

(Entry 1) and cycloalkyl (Entry 2) aldehydes afforded moderate to good yields of adduct as did the aryl examples benzaldehyde (entry 3) and 1-napthaldehyde (Entry 4). Notably, comparable results were achieved at room temperature utilizing a catalytic system[8] based on Mn powder to recycle the $CrCl_2$.

The reaction was not significantly influenced by electron donating (Entry 5) or withdrawing (Entry 6) aryl substituents and proved compatible with a variety of functional groups including a benzyl ether (Entry 7), methylenedioxy (Entry 8), and bromide (Entry 9). Preparatively useful yields were also obtained with the α,β-unsaturated systems cinnamaldehyde (Entry 10) and citral (Entry 11) without noticable conjugate addition.

In a mechanistic rationale for the observed addition, outlined in equation 2, $CrCl_2$ acts as a reducing agent to generate an anionic intermediate that adds to the carbonyl. Proton abstraction and loss of chloride gives rise to α-chloropropenyl alcohol. In stark contrast to the related Takai reaction,[9] the carbonyl carbon undergoes addition rather than olefination.



(eq 2)

Removal of the elements of HCl from the adducts proceeded smoothly using LDA at low temperature. The uniformly excellent yields of propargyl alcohol (Table 1) make this two-step sequence of α-chlorovinylation and base-induced elimination an attractive alternative to metal acetylides.

General Procedures

α-Chlorovinylation: A solution of aldehyde (1 equiv) and 1,1,1-trichloroethane (3 equiv) in anhydrous THF was added dropwise with stirring to a room temperature suspension of $CrCl_2$ (4 equiv) in THF under argon. After 12 h, the resultant reddish reaction mixture was quenched with water, extracted trice with Et_2O, and the combined ethereal extracts were evaporated *in vacuo*. Chromatographic purification on SiO_2 afforded 2-chloropropen-3-ols in the indicated yields (Table 1).

Mn Supported α-Chlorovinylation: To a stirring, room temperature suspension of $CrCl_2$ (0.7 equiv) and Mn powder (1.7 equiv) in THF was added successively aldehyde (1 equiv), 1,1,1-trichloroethane (2 equiv), and chlorotrimethylsilane (2.4 equiv). After 6 h, the resultant reddish reaction mixture was quenched and the α-chlorovinyl adduct isolated as described above.

LDA Elimination: α-Chlorovinyl adduct (1 equiv) was stirred with a freshly prepared solution of LDA (3 equiv) in anhydrous THF at -78°C. After 1 h, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted trice with EtOAc. The combined extracts were evaporated *in vacuo* and the residue purified by SiO_2 chromatography to give the corresponding propargyl alcohols in the yields indicated in Table 1.

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References and Notes

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5. For example see, Engman, L. *Tetrahedron Lett.* **1987**, *28*, 1463-1466.
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