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Titanocene-catalyzed metallation of propargylic acetates in homopropargyl alcohol synthesis

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ABSTRACT

The titanium-catalyzed metallation and subsequent carbonyl addition of propargylic acetates enable the direct formation of homopropargylic alcohols in good yields. The corresponding products were obtained as single regioisomers without the corresponding allene adducts observed.

Despite the growing number of uses for homopropargyl alcohols in π-Lewis acid mediated rearrangements,[1] the addition of propargylic or allenic organometallics to carbonyls has received less attention than the closely related allylation.[2] The use of main group organometallics[3] often yields regioisomeric mixtures of homopropargylic and allenic alcohols, and the metallation conditions are typically incompatible with sensitive functionality.[4] In contrast, the *in situ* formation of propargyl zinc,[3d,5] chromium,[6] zirconium,[7] and titanium[8] complexes can avoid issues of chemoselectivity, while regioselectivity is highly dependent on the substitution pattern of the propargylic substrate.[8f,9] Herein, we have developed a complementary protocol that allows for the mild generation of a propargyl organometallic, that proceeds with a high degree of regioselectivity in the carbonyl addition event (Fig. 1a). Our protocol utilizes a combination of catalytic titanocene and stoichiometric zinc dust to facilitate the metallation of readily prepared propargylic acetates.[2a,h,10]

We were encouraged by reports from Ding[11] and Cuerva[12] illustrating the stoichiometric titanation of propargylic acetates and titanocene-catalyzed carbonyl addition of propargyl halides, respectively, to explore the titanocene-catalyzed metallation-carbonyl addition sequence involving propargylic acetates and aldehydes. We speculated that catalytic Cp_2TiCl_2 and zinc dust would facilitate the direct metallation of propargylic acetates **1** in the presence of aldehyde **2** to regioselectivity generate the desired alcohol adduct **3** (Fig. 1b).[13]

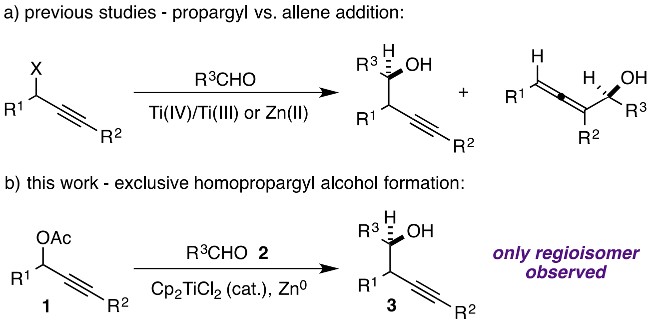

Figure 1. Propargyl metal addition to aldehydes.

Inspired by our previous work on titanocene-catalyzed catalyzed metallations and multicomponent couplings,[2a,h,13,14] we sought to establish the use of propargylic acetate **1a** as a viable organometallic precursor in the synthesis of alcohol **3a** (Table 1). In general, we discovered that Zn dust (2 equiv) was superior to both Mg turnings and Mn powder as the terminal reductant, and that the amount of titanocene proved crucial to achieving a good yield of **3a**. For example, while 5 mol % Cp_2TiCl_2 and Zn dust in CH_2Cl_2 gave homopropargylic alcohol **3a** in 12% yield, increasing the catalyst loading to 10 mol % showed a dramatic increase in yield to 57% (entries 1 and 2). Ultimately, 20 mol % of Cp_2TiCl_2 led to 69% yield of **3a** (entry 4). While too much catalyst proved detrimental, titanocene was necessary to achieve any product formation as the absence of the catalyst led to complete recovery of starting material even after prolonged reaction times (>48 h, entry

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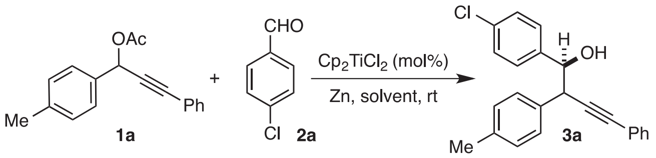
Table 1
Optimization of reaction conditions[a]



Entry	Cp_2TiCl_2 (mol %)	Solvent	Yield[b] (%)
1	5	CH_2Cl_2	12[c]
2	10	CH_2Cl_2	57
3	20	CH_2Cl_2	69
4	25	CH_2Cl_2	52[c]
5	0	CH_2Cl_2	—
6	20	DCE	21
7	20	THF	—

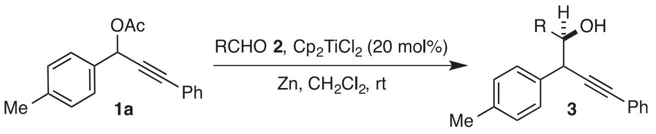
[a] Reaction conditions: **1a** (0.19 mmol), **2a** (0.38 mmol), Cp_2TiCl_2, and Zn (0.38 mmol), rt, 48 h.
[b] Isolated yields with an *anti*/*syn* = 1:1 determined by either 500 MHz ^1H NMR or HPLC, see Supporting information for details.
[c] Yields determined by 500 MHz ^1H NMR.

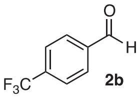
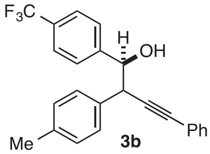
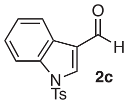
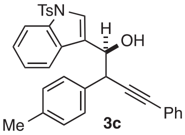
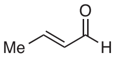
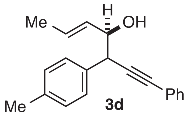
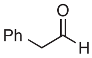
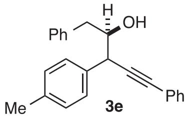
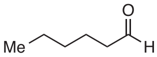
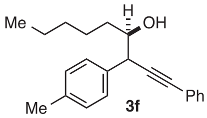
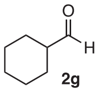
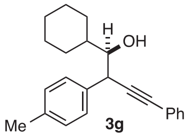
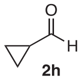
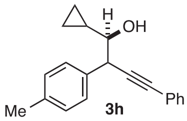
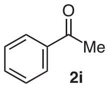
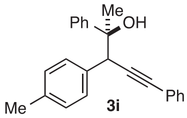
6). In each experiment depicted in Table 1, alcohol **3a** was obtained as a 1:1 mixture of *anti*/*syn* diastereomers across a broad spectrum of reaction temperatures (0 °C–80 °C).

With optimized conditions in hand, we turned our attention toward evaluating the structural variability of aldehyde **2** in the formation of alcohol **3**. In general, good yields of the corresponding homopropargyl alcohols were obtained upon treatment of propargyl acetate **1a** and a variety of aldehydes **2** with Cp_2TiCl_2 (20 mol %) and Zn dust (Table 1). Aryl aldehydes **2b** and **2c** gave decent yields of alcohols **3b** and **3c** (entries 1 and 2). It should be noted that electron rich aryl aldehydes proceeded in lower yields than the more electron deficient counterparts (e.g., *p*-$MeOC_6H_4CHO$–25%). α,β-Unsaturated aldehyde **2d** underwent exclusive 1,2-addition to provide the corresponding allylic alcohol **3d** in 55% yield (entry 3). Aliphatic aldehydes also proved viable in providing the corresponding alcohols in decent yields along with improved diastereoselectivities. Phenyl acetaldehyde (**2e**) and hexanal (**2f**) gave alcohols **3e** and **3f** in good yields and 1.6:1 and 2:1 dr, respectively, (entries 4 and 5). In contrast, carbocycle-substituted aldehydes, **2g** and **2h** underwent propargylation to give homopropargylic alcohols **3g** and **3h** in good yields and further improved diastereoselectivities (entries 6 and 7). Diastereomeric ratios are not enhanced when performed at lower temperatures, and inferior yields were observed. While ketones proved viable, the corresponding alcohols were formed in diminished yields. For example, acetophenone (**2i**) yielded alcohol **3i** in 30% yield and with a dr = 1.2:1 (entry 8).

We next turned our attention toward evaluating the functional group flexibility on propargyl acetate **1** in the coupling to aldehyde **2a** (Table 3). In contrast to the stoichiometric Cp_2Ti^{II}-mediated propargylation,[11c] aliphatic substrates were unreactive under this catalytic protocol. Neutral acetate **1b** and acetates **1c** and **1d** bearing electron rich aryl groups at R^2 gave alcohols **4a**, **4b**, and **4c** in comparable yields (entries 2 and 3). However, acetates with strong electron-withdrawing aryl groups at R^2 (e.g., *p*-O_2N-C_6H_4, *p*-Cl-C_6H_4, *p*-MeO_2C-C_6H_4) gave only trace quantities (<5%) of the expected product. Allyl acetate **1e** was sufficiently activated to facilitate metallation to give alcohol **4d** in 35% yield (entry 4). Electron rich aryl substitution on the alkyne in acetate **1f** gave alcohol **4e** in modest yield, while the corresponding electron poor aryl derivatives failed to undergo metallation (entry 5). Alkyl substitution on the alkyne proved beneficial, providing alcohols **4f** in 49% yield and **4g** in 60% yield (entry 6 and 7). In general, the metallation event proved highly dependent on the propargylic C–O bond strength given the mild reductants Cp_2TiCl_2 (cat.) and Zn dust employed.

Table 2
Carbonyl electrophile structural variability[a]



Entry	2	3	Yield[b,c] (%)
1	 2b	 3b	74 dr = 1:1
2	 2c	 3c	40 dr = 1:1
3	 2d	 3d	55 dr = 1.2:1
4	 2e	 3e	48 dr = 1.6:1
5	 2f	 3f	60 dr = 2:1
6	 2g	 3g	53 dr = 8:1
7	 2h	 3h	68 dr = 2.4:1
8	 2i	 3i	30 dr = 1.2:1

[a] Reaction conditions: **1** (0.19 mmol), **2** (0.38 mmol), Cp_2TiCl_2 (20 mol %), and Zn (0.38 mmol) in CH_2Cl_2 (0.25 M), rt, 48 h.
[b] Isolated yields.
[c] Ratios determined by either 500 MHz ^1H NMR or HPLC, see Supporting information for details.

In previous studies we reported that the addition of substoichiometric titanocene facilitated the formation of organozinc reagents directly from the corresponding halides.[2a,13] While allylic acetates proved unreactive, our subsequent work on a titanocene-catalyzed multicomponent coupling for the construction of tertiary all-carbon centers yielded evidence to suggest the intermediacy of a propargylic metal species.[14] To gain a better understanding we examined in more detail the conversions of **1a** and **2a** to alcohol **3a**. The absence of Cp_2TiCl_2 or Zn dust resulted in near quantitative recovery of the starting acetate **1a**. Using a stoichiometric amount of Cp_2TiCl or Cp_2TiCl_2 without Zn dust also gave ≤5% of the homopropargyl alcohol **3a**. These results suggest that neither titanocene nor Zn^0 are capable of independently facilitating both the metallation and carbonyl addition steps. Additionally, replacing Cp_2TiCl_2 with BF_3.OEt2 failed to provide