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Nucleophilic reactions of propargyl acetates mediated by titanocene dichloride and magnesium

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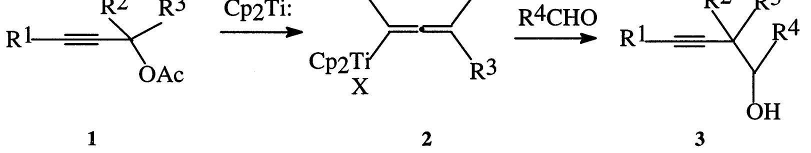
Abstract—Reaction of Cp_2TiCl_2/Mg with propargyl acetates form allenyl titanium intermediates, which undergo nucleophilic addition reactions to aldehydes or ketones to give homopropargyl alcohols in high yields. Subsequent nucleophilic addition to acetonitrile and nucleophilic substitution with allyl bromide are also mentioned. © 2001 Elsevier Science Ltd. All rights reserved.

The preparation of allenyl and propargyl organometallics and their application in organic synthesis have drawn much interest in recent years.[1] Yamamoto and co-workers reported the syntheses of propargyl- and allenyl-titanium intermediates, which were used for the preparation of allenyl and homopropargyl alcohols, respectively.[2] Sato's group reported the synthesis of allenyl and homopropargyl alcohols from propargyl alcohol derivatives with $Ti(O\text{-}Pr^i)_4/2^i PrMgBr$.[3] The preparation and reactions of allenic zirconium species from propargylic ether derivatives has also been reported.[4] Herein we report a new, efficient and practical method to produce allenyltitanium intermediates, which could also be used for the synthesis of allenyl and homopropargyl alcohols.

Recently, in research directed towards a new carbon–carbon bond forming reaction mediated by low-valent titanium, we found that a low-valent titanium compound (presumably 'Cp_2Ti') derived from the reaction of Cp_2TiCl_2 with 2 equiv. of Mg powder could react with propargyl acetate to produce an allenyltitanium intermediate, which could further react with carbonyl compounds to give homopropargyl alcohols in good yields. Cp_2Ti has been considered as the key intermediate by us[5] in intramolecular Pauson–Khand reaction of enynes mediated by Cp_2TiCl_2/Mg. We think that in the presence of propargyl acetate Cp_2Ti could insert into the triple bond of propargyl acetate to form an allenyltitanium intermediate which undergoes nucleophilic addition to carbonyl compounds as shown in Scheme 1.

As a potent nucleophile, the allenyltitanium **2** could also react smoothly with other kinds of electrophiles such as acetonitrile or allyl bromide to give carbon–carbon bond forming products with moderate yield (entries 2 and 3). The results of nucleophilic reactions of various propargyl acetate substrates with electrophiles are shown in Table 1. In contrast to the poor diastereoselectivity in the reaction of benzaldehyde with **2** (entries 9 and 11), the reaction of ring-saturated cyclohexyl carboxaldehyde with **2** shows excellent *anti*-diastereoselectivity (entry 10). We found that the reactions of propargyl acetates and its carbonates gave similar yields (entries 1, 4 and 5, 6), even though propargyl carbonate is usually considered to be more reactive. It is most interesting to find out that the



Scheme 1.

Keywords: titanocene; homopropargyl alcohol; magnesium.

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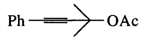
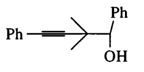
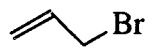
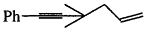
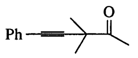
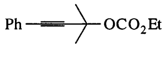
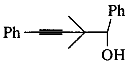
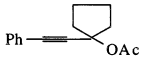
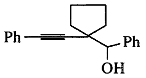
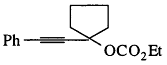
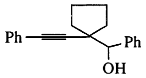
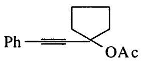
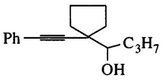
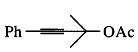
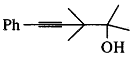
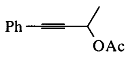
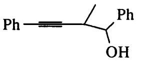
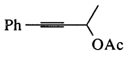
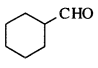
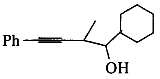
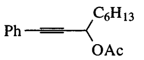
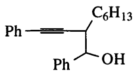
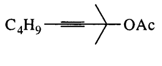
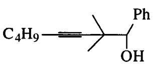
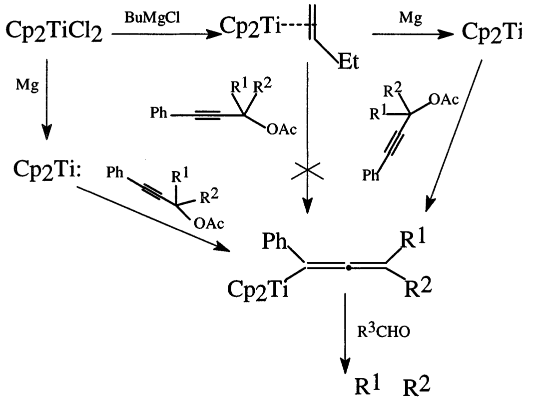
Table 1. The reactions of propargyl acetates with various electrophiles[a]

Entry	Substrate	Electrophile	Product	Yield (%)[b]	*anti*/*syn*[c]
1		PhCHO		72[d]	
2				58[e]	
3		CH_3CN		60.2[f]	
4		PhCHO		74	
5		PhCHO		72.5	
6		PhCHO		75	
7		C_3H_7CHO		52	
8		CH_3COCH_3		75	
9		PhCHO		65	1.3:1
10				56	95:5
11		PhCHO		69	2:1
12		PhCHO		76	

a. Reaction conditions: propargyl ester: Cp_2TiCl_2: Mg powder: nucleophile= 1: 1.1 : 2 : 1.
b. Isolated yield based on propargyl ester. c. Ratios were determined by ^1H NMR (300 MHz).
d. PhCHO was added at 0°C. e. Allyl bromide: propargyl ester= 2:1. f. The reaction proceeded at 25°C for 4 hours and hydrolyzed with 10% HCl at 50°C overnight.

reactive low-valent titanium intermediate Cp_2Ti could not be produced in the reaction system of Cp_2TiCl_2 with BuMgCl, but could be formed only in the presence of Mg powder. We carried out this reaction using the Cp_2TiCl_2/BuMgCl system to replace Cp_2TiCl_2/Mg and found out that most propargyl acetate was unchanged; however, when an additional Mg powder (2 equiv.) was added, the reaction proceeded smoothly again to form the desired homopropargyl alcohol. So we think that the possible mechanism could be as in Scheme 2.



Scheme 2.

Typical experimental procedure: to a solution of titanocene dichloride (275 mg, 1.1 mmol) in THF (10 ml) was added the activated Mg powder (2 mmol) at 0°C under an argon atmosphere. After stirring at 0°C for 1 h, **1** (1 mmol) was added. The resultant mixture was stirred at the same temperature for 6 h. The aldehyde (1 mmol) was added dropwise to the reaction mixture at 0°C and then stirred for 2 h. After being quenched with 10% HCl, the mixture was extracted with ether. The usual work-up and purification by column chromatography on silica gel gave the desired products.[6]

In conclusion, Cp_2TiCl_2/Mg system can be successfully used to transform readily available propargyl acetates into allenyltitanium reagents, which could further react with electrophiles such as aldehydes, ketones and bromides. Thus, we provide a new efficient and practical method to synthesize homopropargyl alcohols.

References

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5. Zhao, Z.; Ding, Y.; Zhao, G. *J. Org. Chem*. **1998**, *63*, 9285–9291.
6. The data of representative products are: 1-phenyl-3,3-dimethyl-5-hexenyne, colorless oil, ν_{max} (neat): 3080, 2971, 2225, 1642, 1599, 1489, 1444, 1363, 1070, 997, 915, 755, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.25 (5H, m, $\underline{Ph}$), 5.93–6.08 (1H, m, $C\underline{H}=CH_2$), 5.13–5.08 (2H, m, $CH=C\underline{H}_2$), 2.25 (2H, d, 7.2 Hz, $C\underline{H}_2$), 1.28 (6H, s, $2C\underline{H}_3$), δ_C (75 MHz, $CDCl_3$) 135.31, 131.60, 128.13, 127.47, 117.37, 77.24, 76.76, 47.74, 31.48, 29.72, 28.89; *m*/*z* (%): 184 (M^+, 2.67), 169 (5.82), 143 (100), 128 (35.66), 115 (11.37) 91 (4.10), 77 (6.04), 51 (2.55), 41 (3.77), HRMS calcd for $C_{14}H_{16}$: 184.12520; found: 184.12595. 1,4-Diphenyl-2,2dimethyl-3-butynol, colorless oil, ν_{max} (neat): 3454, 3063, 3033, 2972, 2927, 2225, 1598, 1492, 1384, 1361, 1181, 1046, 1027, 755, 703, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.48–7.26 (10H, m, $2\underline{Ph}$), 4.59 (1H, d, $J=4.2$ Hz, $PhC\underline{H}OH$), 2.48 (1H, d, $J=4.2$ Hz, $O\underline{H}$), 1.36 (3H, s, $C\underline{H}_3$), 1.20 (3H, s, $C\underline{H}_3$), δ_C (75 MHz, $CDCl_3$) 140.25, 131.63, 128.24, 127.91, 127.85, 127.78, 127.66, 123.42, 94.40, 83.20, 80.58, 38.52, 26.23, 24.88; *m*/*z* (%): 250 (M^+, 0.4), 233 (8.94), 218 (3.93), 191 (0.77), 144 (92.80), 129 (100), 107 (38.96), 91 (5.72), 79 (34.89), 77, (29.80), 51 (9.44), 41 (4.22). 1,1,2,2-Tetramethyl-4-phenyl-3-butynol, colorless oil, ν_{max} (neat): 3468, 2978, 2943, 2235, 1599, 1490, 1376, 1138, 756, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41–7.26 (5H, m, $\underline{Ph}$), 1.92 (1H, br., $O\underline{H}$), 1.34 (6H, s, $2C\underline{H}_3$), 1.33 (6H, s, $2C\underline{H}_3$), δ_C (75 MHz, $CDCl_3$) 131.60, 128.23, 127.81, 123.52, 95.43, 82.41, 74.22, 41.37, 25.02, 24.64; *m*/*z* (%): 203 (M^++1, 0.42), 185 (4.25), 172 (1.31), 157 (1.78), 144 (43.1), 129 (100), 115 (10.75), 91 (6.06), 77 (7.28), 59 (33.81), 43 (12.60), HRMS calcd for $C_{14}H_{18}O$: 202.13576; found: 202.13560.