Pergamon

Tetrahedron 56 (2000) 2397–2401

TETRAHEDRON

# Highly Stereoselective α-Hydroxyalkylation/Chlorination of α,β-Acetylenic Ketones—An Efficient Approach to β-Halogeno Baylis–Hillman Adducts

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Received 5 January 2000; accepted 15 February 2000

**Abstract**—A highly stereoselective method for the synthesis of (*E*)-β-halogeno Baylis–Hillman adducts has been developed. The new method involves a tandem α-hydroxyalkylation/β-chlorination of α,β-acetylenic ketones by using $TiCl_4$ as the chlorine source for α,β-conjugate addition, and concurrently as the Lewis acid promoter for the carbonyl addition. The new system tolerates a broad scope of reactants in which aliphatic and aromatic α-acetylenic ketones can be subjected to the conjugate addition. Both aliphatic and aromatic aldehydes can also be employed as electrophilic acceptors. Good yields (61–88%) and high *E*/*Z* stereoselectivity have been obtained for the nine examples which were examined, only in one case was *E*/*Z* selectivity of 17/1 observed and the two individual isomers are separable via flash column chromatography. 

## Introduction

The development of efficient approaches to multifunctionalized alkenes in stereoselective fashions represents an important goal in organic chemistry and is still being actively explored.[1–4] Among these approaches is the Baylis–Hillman reaction which has recently become an attractive objective in organic synthesis.[5–11] Baylis–Hillman adducts are assembled with multifunctional groups and can serve as chemically and biologically important synthetic precursors. Recently, we and others have developed several methodologies for the synthesis of β-monosubstituted and β,β-disubstituted α-(hydroxyalkyl)-acrylates and α-(aminoalkyl)acrylates which cannot be normally generated under the Baylis–Hillman conditions.[12–14] Very recently, it has been found that these β,β-disubstituted α-(aminoalkyl)acrylates can serve as new lead structures for the design of anti-cancer drugs.[15]

In our continuing development of new Baylis–Hillman-type processes, β-halogeno Baylis–Hillman adducts have captivated our attention because they can conceivably be subjected to many synthetic transformations including C–C coupling and conjugate addition–elimination reactions (for representative references about β-halo vinyl ketones and esters see Refs. 16–19). A literature search reveals that the synthesis of β-iodo Baylis–Hillman ketones was initially carried out by Kishi and Taniguchi[20] in 1986 via the $TiCl_4$-promoted conjugate addition of $(n\text{-Bu})_4NI$ to α,β-acetylenic ketones followed by electrophilic coupling with aldehydes. Afterwards, Lu and coworkers reported a method for synthesizing of β-iodo Baylis–Hillman esters and amides with *Z* geometric isomers as the major products.[21] The later method also employed $(n\text{-Bu})_4NI$ as the halide source for the anionic conjugate addition but used 1.2 equiv. of $ZrCl_4$ as the Lewis acid promoter. Inspired by their previous studies, we reexamined in this methodology and found that α,β-acetylenic ketones can directly participate in the conjugate addition with $TiCl_4$ to give $TiCl_3$-allenolate intermediates which then react with adehydes to generate β-chloro Baylis–Hillman ketones. In this context, we report the details of this new reaction which is represented in Scheme 1 with results summarized in Table 1.

The synthesis is carried out by simply mixing the three components (aldehyde, α,β-acetylenic ketone and $TiCl_4$) in dichloromethane solution in a capped vial of appropriate size with no need to protect it using either argon or nitrogen gases. The reaction goes to completion in a short period (~2 h) at room temperature and can be monitored by TLC or $^1H$ NMR. Good to high yields were realized for all examined cases. The configuration of olefinic products is predominantly *E* for all examples except entry 4 of Table 1 where the *E*/*Z* selectivity of 17/1 was observed. Fortunately, the resulting two isomers in this case can be readily separated by flash column chromatography.

Careful analysis of the data collected in Table 1 shows that this reaction can be conducted using both aromatic and

*Keywords*: halogeno Baylis–Hillman adducts; titanium tetrachloride; α,β-acetylenic ketones.

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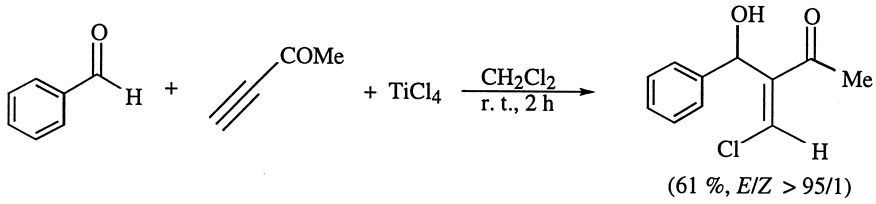
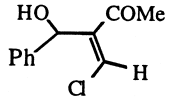
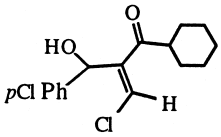
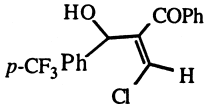
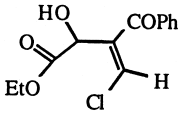
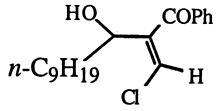
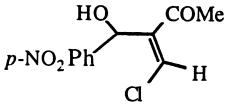
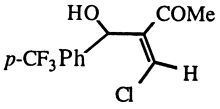
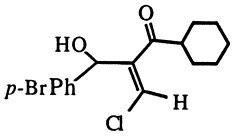
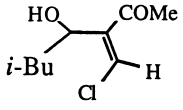
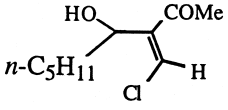
0040–4020/00/$ - see front matter 
PII: S0040-4020(00)00151-4




**Scheme 1.**

**Table 1.** Results of the new tandem *cis* Cl–C/C–C bond formation

| $R^1$ | $R^2$ | Product | | $E/Z$[a] selectivity (%) | Yield[c] (%) |
|---|---|---|---|---|---|
| Ph | Me |  | **1** | >95 | 61 |
| *p*-Cl-Ph |  |  | **2** | >95 | 63 |
| *p*-$CF_3$Ph | Ph |  | **3** | 17:1 | 85 |
|  | Ph |  | **4** | >95 | 71 |
| *n*-$C_9H_{19}$ | Ph |  | **5** | >95 | 65 |
| *p*-$NO_2$Ph | Me |  | **6**[b] | >95 | 84 |
| *p*-$CF_3$Ph | Me |  | **7**[b] | >95 | 88 |
| *p*-Br-Ph |  |  | **8** | >95 | 61 |
| *i*-Bu | Me |  | **9** | >95 | 72 |
| *n*-$C_5H_{11}$ | Me |  | **10** | >95 | 76 |

[a] >95% means only one isomer was observed by crude $^1$H NMR determination.
[b] Mp 114–116°C and 68–70°C for **6** and **7**, respectively.
[c] Isolated yields, and all products are oils except for those of **6** and **7**.

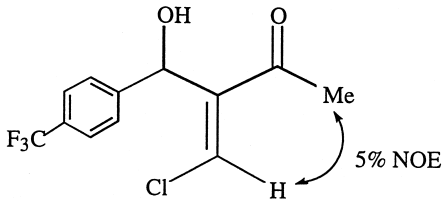



**Figure 1.**

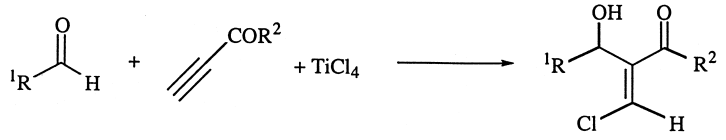
nonaromatic α,β-acetylenic ketones as the conjugate addition acceptors. Also, both aromatic and aliphatic aldehydes can be employed as the electrophilic acceptors to react with titanium intermediates which are derived from conjugate additions. For aromatic aldehydes, substitutions on aromatic rings give no obvious effect on reaction efficiencies (yields and stereoselectivity). As predicted, electron deficient aromatic aldehydes proceed at a faster rate than benzyladehyde, and gives higher yields as well.

An excess of α,β-acetylenic ketone (1.4 equiv.) and $TiCl_4$ (1.2 equiv.) proved to be necessary to achieve good yields since the stoichiometric amount of these reagents resulted in decreased yields (by ~10%). Titanium tetrachloride gave the best results. Various other metal chlorides, such as $ZnCl_2$, $SnCl_4$, $HgCl_2$, $FeCl_3$, etc., were also studied but none of them gave the desired β-chloro Baylis–Hillman ketones even in solvents such as $CH_2Cl_2$, toluene, benzene, MeCN and THF. However, $AlCl_3$ did produce the desired product, but in poor yield (less than 35%). The $CH_2Cl_2$–$TiCl_4$ combination appears to be the best in the present system, whereas $TiCl_4$ combinations with other solvents listed above are not effective. In actuality, no more than a trace amount of desired product was observed in THF. In case 4, *E*/*Z* selectivity of 5:1, 5:3, 1.5:1 were realized in benzene, MeCN and toluene, respectively. Reaction temperature seems to have no effect on the *E*/*Z* selectivity. The reaction can be performed at 0°C but at a much slower rate and failed to give any desired products at temperature below −35°C. This is in contrast to the known $(n\text{-Bu})_4NI/TiCl_4$ and $(n\text{-Bu})_4NI/ZrCl_4$-based systems which can be carried out at −78°C.

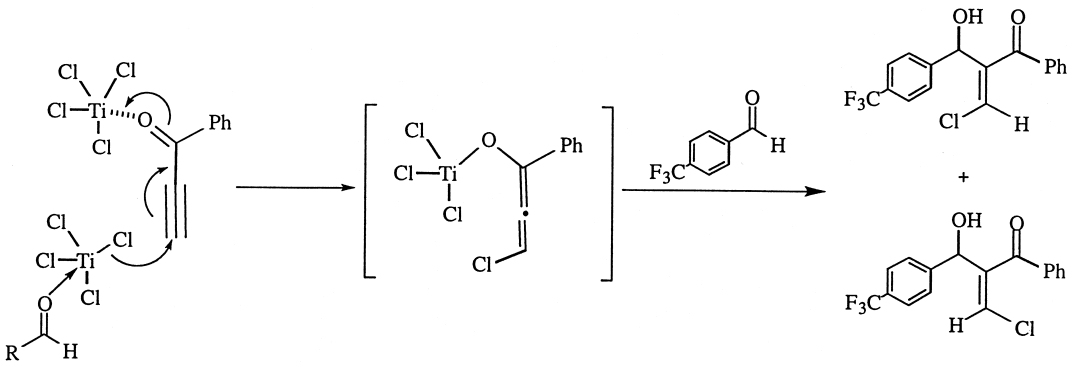
The *E*/*Z* selectivity listed in Table 1 was measured by $^1H$ NMR analyses of the crude products. The geometry of the major isomer was determined by $^1H$ NMR NOE experiments in which 5% of NOE was observed between the signals of vinyl proton and methyl protons (Fig. 1), whereas no such effect was detected between the same vinyl proton and benzylic counterparts (Scheme 2).

To understand the high *Z*/*E*-stereoselectivity of this new system, a cyclic transition state model proposed by Kishi and Taniguchi can be used.[20] In their system, not only the $(n\text{-Bu})_4NI/TiCl_4$ combination but also $Et_2AlI$ and $TiI_4$ were employed for the reaction. The exclusive *Z*-stereoselectivity of β-iodo Baylis–Hillman ketones was achieved at −78°C, while the high *E*-stereoselectivity was observed at 0°C, albeit modest success was realized when $TiI_4$ was used as the promoter. By using a cyclic transition state model, they suggested the *Z*-stereoisomer is the kinetically controlled product, while the *E*-stereoisomer is the thermodynamically controlled counterpart. In our system, the exclusive *E*-stereoselectivity was observed in most cases except for case **4** in which a small amount of minor *Z*-stereoisomer was detected as shown in Table 1. These results suggest that the thermodynamic control played a main role in determining the geometric selectivity. At this point, it is unclear if the vinylic organotitanium intermediates[22] can coexist with titanium alleneoates under the present conditions.

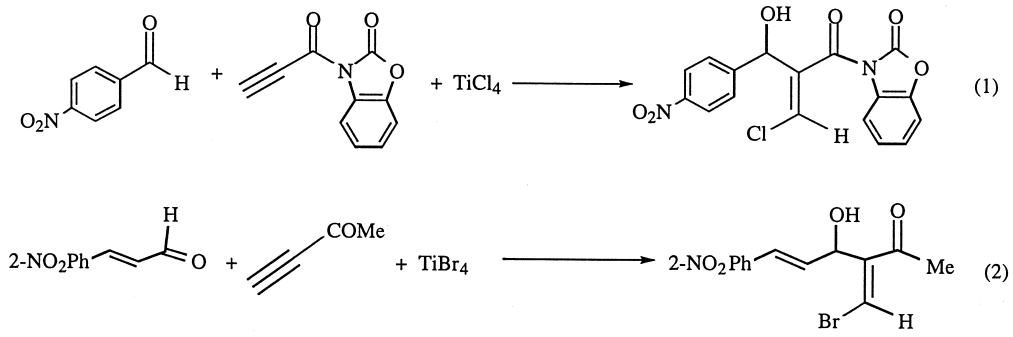
The working hypothesis of this new process is represented in Scheme 3. The initial reaction step involves the addition of $TiCl_4$ to the α,β-acetylenic ketone to generate the $TiCl_3$-allenoate. The formation of this intermediate is accelerated by the coordination of carbonyl oxygen to the Lewis acidic titanium center (C═O–Ti interaction),[23] i.e. the pull–push model plays important roles in further polarizing the α,β-conjugate double bond and freeing the chlorine anion from




**Scheme 2.**




**Scheme 3.**




**Scheme 4.**

$TiCl_4$ prior to the α,β-conjugate addition. The second step proceeds through the nucleophilic attack of the allenoate intermediate to the aldehyde. The later C–C bond-forming step is also activated by the coordination of aldehyde oxygen onto the Lewis acidic species. To obtain more information about the mechanism, we also made several attempts to directly detect the titanium allenoate intermediates by mixing α,β-acetylenic ketone, $TiCl_4$ and aldehydes in $CD_2Cl_2$ in NMR tubes but without success.

From the discussions above, this new reaction system presents opportunities for further modification with regard to expanding its scope through the use of various other α,β-acetylenic substrates and titanium halides. The loading of Lewis acid promoters also needs to be reduced. Our preliminary experiments revealed that α,β-unsaturated *N*-acyl benzoxalinone are promising substrates for this reaction, even though gave low yield (<50%). Titanium tetrabromide is also effective in promoting this process in modest yield and good stereoselectivity (60% and 8:1, respectively) (Scheme 4).

In conclusion, a highly stereoselective and regioselective tandem α-hydroxyalkylation/β-chlorination of α,β-acetylenic ketones has been developed for the synthesis of (*E*)-β-chloro Baylis–Hillman ketones. The new protocol utilizes $TiCl_4$ as the chlorine anion source, and concurrently as the Lewis acid promoter. The reaction can be easily performed at room temperature without the need for inert atmosphere protection. A variety of inexpensive commercial chemicals can be employed as the starting materials.

## Experimental

### General methods

All reactions were conducted at room temperature in a capped vial of appropriate size with magnetic stirring. Dichloromethane was dried and freshly distilled from calcium hydride under the nitrogen atmosphere. Other commercial chemicals were used without further purification and their stoichiometrics were calculated based on the reported purities from the manufacturers. Flash chromatography was performed on E. Merck silica gel 60 (230–400 mesh). $^1$H NMR spectra were recorded on either a Bruker 200 or Varian 500 MHz NMR spectrometer. $^{13}$C NMR spectra were recorded at 125 MHz using $CDCl_3$ as the solvent and the internal reference. High-resolution mass spectral analysis was conducted by the mass spectroscopy laboratory of the Scripps Research Institute.

### Typical procedure

Into a clean dry vial was loaded benzaldehyde (0.1 mL, 1.0 mmol), 3-butyn-2-one (96.0 mg, 1.40 mmol) and freshly distilled dichloromethane (1.5 mL). A solution of $TiCl_4$ in dichloromethane (1.0 M, 1.2 mL, 1.2 mmol) was then added into the resulting solution dropwise via a syringe. The capped vial was immersed in a room temperature bath and was stirred for 2 h at this temperature without the use of an inert gas. TLC or $^1$H NMR determination was used to monitor the reaction which was quenched by the dropwise addition of aqueous $NaHCO_3$ solution (sat. 2 mL). After the $CH_2Cl_2$ was distilled off, the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed sequentially with water and brine, dried over anhydrous magnesium sulfate and concentrated. Purification by flash chromatography (EtOAc/hexane, 1/5, v/v) provided product **1** (128 mg, 61% yield) as colorless oil. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.25–7.45 (m, 5 H), 5.95 (d, $J$=11.3 Hz, 1 H), 4.44 (d, $J$=11.3 Hz, 1 H), 2.30 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 198.2; 143.2, 141.4, 135.6, 128.4, 127.4, 125.1, 70.7, 27.0; IR (THF) 3474, 1666 cm$^{-1}$; HRMS (FAB) *m/z* (M+Na) found 233.0340 calcd for $C_{11}H_{11}ClO_2Na$ 233.0345.

**2:** colorless oil (196 mg, 63% yield); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.26–7.41 (m, 4 H), 5.92 (d, $J$=11.1 Hz, 1 H), 4.58 (d, $J$=10.2 Hz, 1 H), 2.71–2.82 (m, 1 H), 1.07–1.76 (m, 10 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 204.6, 141.1, 140.1, 133.9, 133.1, 128.4, 126.5, 70.6, 46.5, 29.2, 28.7, 25.6, 25.5, 25.3; HRMS (FAB) *m/z* ($M^+$+1) found 313.0330, calcd for 313.0762.

**3:** colorless oil (289 mg, 85% yield); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.40–7.65 (m, 8 H), 7.08 (s, 1 H), 6.15 (d, $J$=10.5 Hz, 1 H), 4.74 (d, $J$=10.6 Hz, 1 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 196.3, 145.4, 141.4, 136.9, 136.2, 133.5, 129.5, 128.7, 125.7, 125.5, 125.4, 71.0; IR (neat) 3455, 1642 cm$^{-1}$; HRMS (FAB) *m/z* (M+Na) found 363.0374, calcd for 363.0376.

**4:** colorless oil (183 mg, 71% yield); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.76–7.44 (m, 4 H), 7.07 (s, 1 H), 5.39 (d,

$J$=7.19 Hz, 1 H), 4.25–4.35 (m, 2 H), 3.69 (d, $J$=7.36 Hz, 1 H), 1.26 (t, $J$=7.07 Hz, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 193.5, 171.8, 140.2, 137.0, 136.7, 133.2, 129.5, 128.6, 67.6, 62.3, 14.0; IR (neat) 3488, 1744, 1655, 1260 cm$^{-1}$; HRMS (FAB) $m/z$ ($M^+$+1) found 269.0578, calcd for 269.0581.

**5:** colorless oil (210 mg, 65% yield); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.43–7.74 (m, 5 H), 6.85, (s, 1 H), 4.82–4.95 (m, 1 H), 3.53 (d, $J$=11.8 Hz, 1 H), 1.69–1.93 (m, 2 H), 1.26–1.50 (m, 14 H), 0.84–0.91 (m, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 196.5, 143.2, 137.5, 134.2, 133.1, 129.6, 128.6, 70.6, 36.3, 31.9, 29.5, 29.3, 29.2, 25.8, 22.7, 14.1; IR (THF) 3490, 1643 cm$^{-1}$; HRMS (FAB) $m/z$ (M+Na) found 345.1594, calcd for 345.1597.

**6:** white solid (215 mg, 84% yield); mp 114–116°C; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 8.20 (d, $J$=8.78 Hz, 2 H), 7.53 (d, $J$=8.00 Hz, 2 H), 6.01 (d, $J$=11.3 Hz, 1 H), 4.43 (d, $J$=11.3 Hz, 1 H), 2.35 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 179.9, 148.3, 147.3, 142.5, 136.9, 126.0, 123.7, 70.2, 26.9; IR (THF) 3490, 1667 cm$^{-1}$.

**7:** white solid (246 g, 88% yield); mp 68–70°C; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.59 (d, $J$=8.44 Hz, 2 H), 7.50 (d, $J$=10.7 Hz, 2 H), 5.98 (d, $J$=11.3 Hz, 1 H), 4.47 (d, $J$=11.3 Hz, 1 H), 2.32 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 198.0, 145.5, 142.8, 136.4, 125.4, 125.5, 125.3, 70.3, 26.9; IR (THF) 3450, 1669 cm$^{-1}$.

**8:** colorless oil (218 mg, 61% yield); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.42–7.46 (m, 2 H), 7.19–7.7.26 (m, 2 H), 5.90 (d, $J$=11.1 Hz, 1 H), 4.56 (d, $J$=11.2 Hz, 1 H), 2.71–2.84 (m, 1 H), 1.15–1.77 (m, 10 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 204.6, 141.3, 140.7, 134.1, 131.4, 126.9, 121.3, 70.6, 46.5, 29.3, 28.7, 25.6, 25.5, 25.3.

**9:** colorless oil (137 mg, 72% yield); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 4.74–4.87 (m, 1 H), 3.54 (d, $J$=11.3 Hz, 1 H), 2.33 (s, 3 H), 1.69–1.86 (m, 2 H), 1.26–1.36 (m, 1 H), 0.94 (d, $J$=6.50 Hz, 6 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 198.3, 144.4, 134.0, 68.5, 45.3, 26.9, 24.6, 23.4, 21.6; IR (neat) 3450, 1669 cm$^{-1}$.

**10:** colorless oil (156 mg, 76% yield); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 4.66–4.79 (m, 1 H), 3.64 (d, $J$=11.3 Hz, 1 H), 2.37 (s, 3 H), 1.74–1.98 (m, 1 H), 1.55–1.63 (m, 2 H), 1.29–1.33 (m, 5 H), 0.85–0.92 (m, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 198.3, 143.9, 134.4, 70.0, 36.3, 31.4, 26.9, 25.3, 22.4, 13.9; IR (neat) 3508, 1666 cm$^{-1}$.

## Acknowledgements

The Robert A. Welch Foundation (grant no. D-1361) is gratefully acknowledged for research support. We thank the National Science Foundation (CHE-9808436) and Texas Tech University for purchasing the 500 MHz NMR.

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