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A New Stereospecific Synthesis of Unusual (*Z*)-β-Branched Baylis-Hillman Adducts

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Abstract: A new method has been developed for the stereospecific synthesis of unusual (*Z*)-β-branched Baylis-Hillman adducts with high *Z/E* selectivity (>99 %) in modest to good yields. The process involves successful formation of anionic β-substituted [α-(alkoxycarbonyl)vinyl]aluminum intermediates and their coupling with aldehydes and ketones catalyzed by *n*-Bu_2BOTf at -78 °C. © 1998 Elsevier Science Ltd. All rights reserved.

The Baylis-Hillman reaction derived α-(hydroxyalkyl)acrylates and related adducts can provide numerous chemically and biologically important precursors having a multifunctional array of groups.[1-6] Very recently, Greene and coworkers have successfully applied the β-unsubstituted Baylis-Hillman adducts in the design and synthesis of analogs of the anti-tumor drug docetaxol.[7a] Since the original Baylis-Hillman system has serious limitations, the application of β-branched Baylis-Hillman adducts in organic and medicinal chemistry has been limited. For example, the β-substituted acrylate olefins do not undergo the Baylis-Hillman reaction.[3, 8-9] Alternative methods should be developed for synthesizing β-branched Baylis-Hillman adducts.

In 1983, Sato and coworkers reported a three-step synthesis of β-branched Baylis-Hillman adducts by using α-sily *t*-butyl-2-alkenoates as the anion source. In this method, partial success in controlling the *Z/E* selectivity was achieved in the vinyl anion coupling with various aldehydes.[10] Marino and coworkers concurrently reported another method for this stereospecific synthesis by coupling (α-carbethoxyvinyl)cuprate reagents with ketones, but poor *Z/E* selectivity was obtained when aldehydes were used as the electrophilic species.[11] It is well known that the anionic intermediates of β-unsubstituted [α-(alkoxycarbonyl)-vinyl]aluminum can react with aldehydes at room temperature (for *ca* 15 h), which was developed by Tsuda and coworkers 15 years ago.[12] The hydroalumination of β-substituted propiolates was not successful using similar conditions because of the decreased reactivity of β-substituted propiolates. The complex of MeCu-DIBAL-HMPA was then used to replace DIBAL-HMPA for the hydroalumination, but the incomplete conversion was observed.[13] Here, we would like to report the successful formation of anionic β-substituted [α-(alkoxycarbonyl)vinyl]aluminum intermediates and their new couplings with aldehydes and ketones catalyzed by *n*-Bu_2BOTf. The anionic intermediates of β-substituted [α-(alkoxycarbonyl)vinyl]aluminum were formed by reacting DIBAL with β-substituted propiolate in presence of HMPA (3.0 equv) in THF solution at 0 °C for 30 min and then at room temperature for 4 h (Scheme 1). The resulting β-substituted vinylaluminum anionic intermediate reacted with electrophiles very slowly at -78°C. Essentially, only a trace amount of coupling product was observed by TLC and ^1H NMR after several hours at -78°C without the catalyst. However, when the Lewis acid catalyst (10 mol% of *n*-Bu_2BOTf) was added into the reaction mixture, most of the resulting anionic intermediate was consumed at -78 °C in 4 - 6 h.[14]

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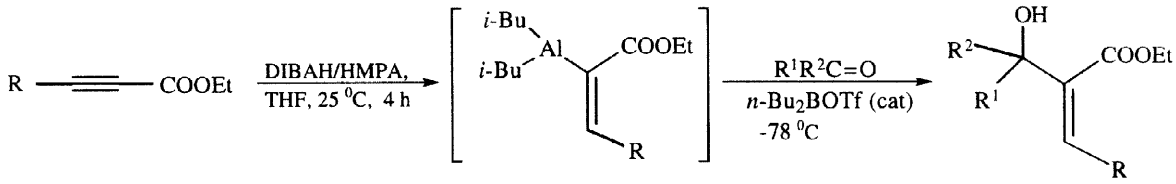
In all of the cases examined, only (*Z*)-isomer of β-substituted α-(hydroxyalkyl)acrylates were observed by ^{1}H NMR analysis of each crude product. Acetophenone showed the poor reactivity in the present catalytic system as expected, and gave low yields (Table 1). In comparison to the orignal procedure, the coupling of anionic intermediates of β-unsubstituted [α-(alkoxycarbonyl)vinyl]aluminum with ketones was carried out at room temperature for 15 h and required the stoichiometric amount of BF_3-Et_2O.[12]

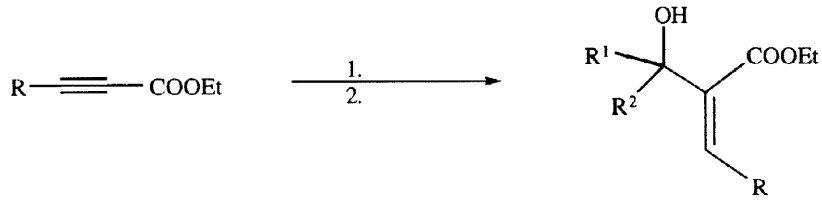


R = Me, Ph; R^1 & R^2 = H, alkyl and aryl groups.

Scheme 1. β-Branched [α-(Alkoxycarbonyl)vinyl]aluminums Forming and Coupling with Aldehydes and Ketones

The representative procedure was illustrated by the coupling reaction of β-phenyl [α-(alkoxycarbonyl)vinyl]aluminum with benzaldehyde. Into a dry, nitrogen flushed flask was added HMPA (1.0 mL, 5.85 mmol) and freshly distilled THF (8 mL). The resulting solution was cooled to 0 °C and a solution of DIBAL in hexane (1M solution in hexane, 1.95 mL, 1.95 mmol) was added. The clear solution was stirred for 30 min at 0 °C before ethyl phenylpropiolate (0.215 mL, 1.30 mmol) was added. The resulting mixture was stirred at 0 °C for an additional 30 min, then the reaction flask was immersed into a room-temperature bath and stirred for 4 h. The colorless solution became yellow as the reaction mixture was stirred. The resulting yellow solution was cooled to -78 °C. Benzaldehyde (0.27 mL, 2.60 mmol, 2.0 equiv) was added into the flask and was immediately followed by the addition of dibutylboron triflate (1M in dichloromethane, 0.13 mL, 0.13 mmol). The resulting mixture was stirred at -78 °C for 4 h, then was allowed to continue at -15 °C for an additional 4 h. The reaction was quenched by dropwise addition of 1N aqueous hydrochloric acid solution. The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were each washed with saturated sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated to dryness. Purification by flash chromatography (EtOAc/hexane, 1/9, v/v) provided coupling product **1** (0.223 g, 61 % yield) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (t, J = 7.1 Hz, 3 H), 3.08 (br, 1H), 4.02 (dd, J = 14.2 Hz, 7.1 Hz, 2 H), 5.60 (s, 1 H), 6.95 (d, J = 1.0 Hz, 1 H), 7.26 - 7.46 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 60.8, 75.8, 76.6, 126.7, 127.9, 128.1, 128.2, 128.5, 135.1, 135.4, 135.8, 141.0, 168.6; MS (EI) *m/z* 282.2 (282.3 calcd for $C_{18}H_{18}O_3$).

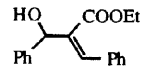
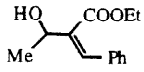
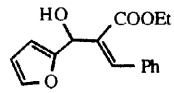
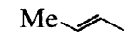
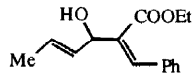
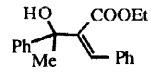
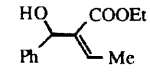
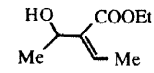
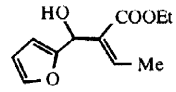
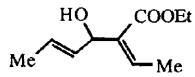
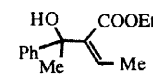
Attempts to couple these anionic β-substituted vinylaluminium intermediates with benzaldehyde *N*-(*tert*-butoxycarbonyl)imine and *N*-(tuluene-*p*-sulfonyl)imine have not been successful. Perhaps stronger imine electrophilic species, such as (pentafluorobenzenesulfonyl)imine or aldehyde *N*-(*p*-nitrobenzenesulfonyl)imine would be more efficient for this coupling process. A similar approach for the synthesis of β,β-disubstituted Baylis-Hillman adducts by using the copper-mediated tandem Michael addition/C-C bond coupling has also been developed[16a] (Scheme 3). This method can provide an alternative approach for the synthesis of (*Z*)-β-branched Baylis-Hillman adducts by using β-unsubstituted propiolates (R = H, in Scheme 3) as the starting materials.



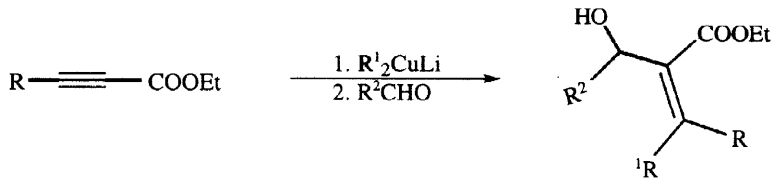
1. DIBAH/HMPA, THF, 25 °C, 4 h;
2. $R^1R^2C=O$, n-Bu_2BOTf (cat), -78 °C

Scheme 2. The One-Pot Synthesis of (Z)-β-Branched Baylis-Hillman Adducts

Table 1. The Results of Synthesis of (Z)-β-Branched Unusual Baylis-Hillman Adducts[15]

R	R^1	R^2	Prodcut		Yield (%)
Ph	H	Ph		**1**	61.0
Ph	H	Me		**2**	57.5
Ph	H			**3**	61.1
Ph	H	Me 		**4**	66.4
Ph	Me	Ph		**5**	42.9[a]
Me	H	Ph		**6**	51.1
Me	H	Me		**7**	55.8
Me	H			**8**	57.0
Me	H	Me 		**9**	57.6[b]
Me	Me	Ph		**10**	<40[a,c]

a. The reaction was carried out at 0 °C for 8 h and room temperature for 7 h; b. The product was difficult to purify, therefore the yield was estimated by ^1H NMR. c. The reaction conditions are being optimized for a and c.



Scheme 3. The Synthesis of β, β-Disubstituted Baylis-Hillman Adducts

We believe that the low-temperature conditions described in this paper will be beneficial to the chiral auxiliary directed processes using chiral aldehyde *N*-(carboxycarbonyl)imines and chiral β-alkyl/aryl propiolate derivatives as the reaction substrates to give optically active β-substituted α-(aminoalkyl)acrylates and β-substituted α-(hydroxylalkyl)acrylates respectively.[16b] Last but not least, this finding has made it possible to develop an asymmetric catalytic version for the present C-C bond formation by using chiral Lewis acids which will be conducted in this laboratory in the near future.

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14. 20 mol% of BF_3-Et_2O and a lesser amount of *n*-Bu_2BOTf (2 mol%, 5 mol%) were able to catalyze the reaction in the similar condition, but gave lower yields.
15. Only (*Z*) isomers were observed by ^1H NMR detemination of the crude products. ^1H NMR data for pure products in Table 1 (200 MHz, $CDCl_3$): **2** δ 1.11 (t, J = 7.1 Hz, 3 H), 1.47 (d, J = 6.5 Hz, 3 H), 2.45 (d, J = 5.9 Hz, 1 H), 4.16 (dd, J = 14.2 Hz, 8.1 Hz, 2 H), 4.65 (m, 1 H), 6.70 (s, 1 H), 7.26 - 7.31 (m, 5 H); **3** δ 1.04 (t, J = 7.2 Hz, 3 H), 3.16 (d, J = 7.2 Hz, 1 H), 4.10 (dd, J = 14.4 Hz, 7.1 Hz, 2 H), 5.60 (dd, J = 7.2 Hz, 1.2 Hz, 1 H), 6.35 (d, J = 1.2 Hz, 2 H), 7.04 (d, J = 1.0 Hz, 1 H), 7.29 - 7.31 (m, 5 H), 7.41 (t, J = 1.2 Hz, 1 H); **4** δ 1.09 (t, J = 7.0 Hz, 3 H), 1.74 (d, J = 6.1 Hz, 3 H), 2.57 (d, J = 6.7 Hz, 1 H), 4.14 (dd, J = 15.0 Hz, 7.1 Hz, 2 H), 4.93 (m, 1 H), 5.59 - 5.92 (m, 2 H), 6.91 (d, J = 0.9 Hz, 1 H), 7.25 - 7.45 (m, 5 H); **5** δ 0.81 (t, J = 7.1 Hz, 3 H), 1.78 (s, 3 H), 3.90 (m, 2 H), 4.15 (s, 1 H), 7.03 (s, 1 H), 7.24 - 7.53 (m, 10 H); **6** δ 1.18 (t, J = 7.1 Hz, 3 H), 2.05 (d, J = 7.5 Hz, 3 H), 3.22 (d, J = 7.2 Hz, 1 H), 4.14 (dd, J = 14.3 Hz, 7.2 Hz, 2 H), 5.42 (d, J = 7.0 Hz, 1 H), 6.31 (dd, J = 14.5 Hz, 7.0 Hz, 2 H), 7.25 - 7.35 (m, 5 H); **7** δ 1.34 (t, J = 6.6 Hz, 3 H), 2.01 (d, J = 7.1 Hz, 3 H), 2.69 (d, J = 6.7 Hz, 1 H), 4.28 (dd, J = 7.1 Hz, 1.6 Hz, 2 H), 4.48 (m, 1 H), 6.29 (dd, J = 7.1 Hz, 0.8 Hz, 1 H); **8** δ 1.26 (t, J = 7.1 Hz, 3 H), 2.08 (d, J = 7.4 Hz, 3 H), 3.29 (d, J = 7.9 Hz, 1 H), 4.22 (dd, J = 14.3 Hz, 7.1 Hz, 2 H), 5.43 (d, J = 7.6 Hz, 1 H), 6.23 - 6.42 (m, 3 H), 7.35 - 7.37 (m, 1 H); **10** δ 1.26 (t, J = 7.1 Hz, 3 H), 1.60 (s, 3 H), 2.32 (d, J = 1.4 Hz, 3 H), 4.10 (s, 1 H), 4.20 (dd, J = 7.1 Hz, 2.5 Hz, 2 H), 6.70 (d, J = 1.2 Hz, 1 H), 7.20 - 7.87 (m, 5 H).
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