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Stereoselective Synthesis of Baylis–Hillman-Type Adducts via Allenolates Generated by Acyl Migration

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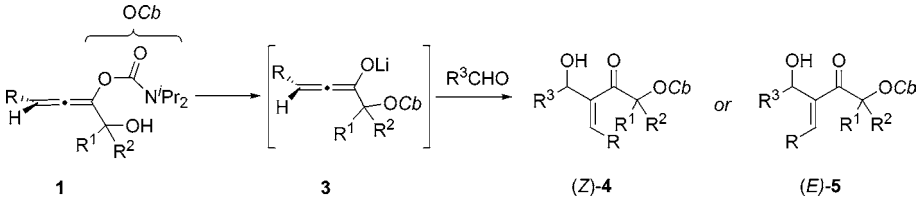
ABSTRACT



1 **3** (*Z*)-**4** (*E*)-**5**

The rearrangement of the carbamoyl group in allenyl carbamate 1 in the presence of *n*-BuLi in situ generates the allenolate 3, which is subsequently intercepted with aromatic aldehydes furnishing (*Z*)- or (*E*)-configured Baylis–Hillman-type adducts 4 or 5. The double bond isomers can be interconverted by a *retro* aldol-type reaction.

Allenes are important building blocks for the synthesis of various complex compounds.[1] As a consequence, there is a growing demand in exploring their application. Among them are Baylis−Hillman-type adducts that have found application for a wide variety of chemical and biological purposes[2] and thus have attracted interest in the recent past. Although some of these compounds can be synthesized by the Baylis−Hillman reaction,[2] there exist alternative methods via the intermediacy of allenolates, which are subsequently trapped with aldehydes and ketones to result in Baylis−Hillman-type adducts. There are in principle three general methods to arrive at allenolates: (a) 1,4-addition to unsaturated conjugated propargyl systems,[3] (b) Brook[4] and *retro* Brook[5] rearrangement, and (c) desilylation of α-silyl enones.[6]

Our research group has been involved in the synthesis of allenes and their applications in organic synthesis for some time.[7] Recently, we have reported a concise approach for the synthesis of enantioenriched cyclopentenones from enantioenriched allenes by a modified Nazarov cyclization reaction via allenolates.[7f] Herein we report a novel approach for the synthesis of Baylis−Hillman-type adducts by an in situ generation of allenolates from allenes. The working hypothesis for our approach is as follows: If the allenyl carbamate **1** is treated with a base, it forms the alkoxide **2**, which upon warming undergoes an intramolecular nucleo-

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(1) (a) Hoffmann-Röder, A.; Krause. N. (a) *Angew. Chem.* **2004**, *116*, 1216; *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 1196. (b) Zimmer, R. *Synthesis* **1993**, 165. (c) Patai, S. *The Chemistry of Ketenes, Allenes, and Related Compounds*; John Wiley & Sons: Chichester, 1980. (d) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; John Wiley & Sons: New York, 1984. (e) Landor, S. R. *The Chemistry of the Allenes*; Academic Press: New York, 1982.

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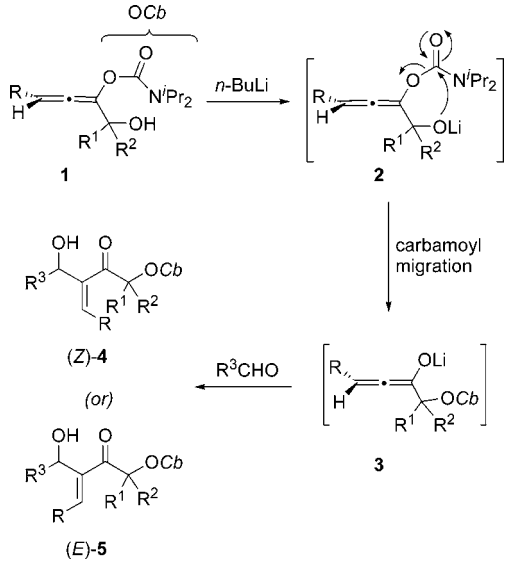
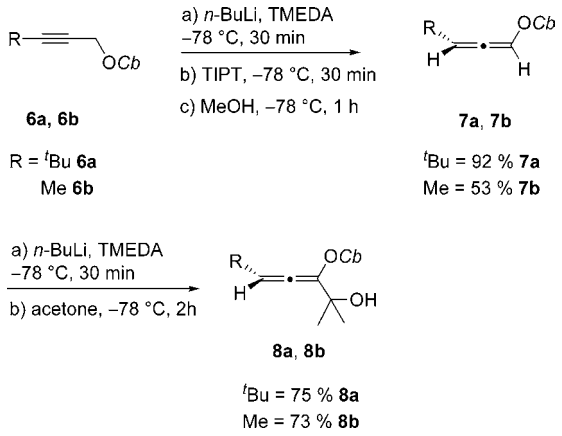
philic attack at the carbamoyl group[7i] resulting in the allenolate **3**, which is trapped with aldehydes, achieving Baylis−Hillman-type adducts (*Z*)-**4** or (*E*)-**5** (Scheme 1).

Scheme 1. In Situ Generation of Allenolate



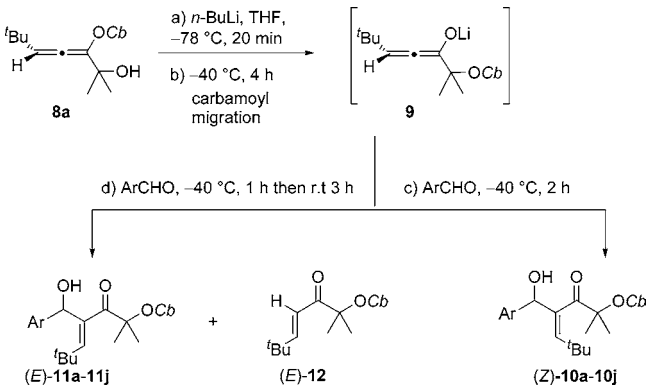
The starting points for our investigation are the allenyl carbamates **8a** and **8b**, which are prepared in a two-step sequence from the corresponding 2-alkynyl carbamates **6a** and **6b** in overall yields of 86% and 61% (Scheme 2).[7b]

Scheme 2. Synthesis of Allenyl Carbamates **8a** and **8b**



After several optimization experiments, it was found that the ideal base and solvent to effect the complete migration of the carbamoyl group in the allenyl carbamate **8a** are *n*-BuLi and THF. Upon treatment with 1.1 equiv of *n*-BuLi at −78 °C followed by rapid warming of the reaction mixture to −40 °C, the allenyl carbamate **8a** generated the allenolate **9**, which underwent addition to different aromatic aldehydes, resulting in the Baylis−Hillman-type adducts **10a**−**10j** with exclusively (*Z*) double bond geometry. After the reaction mixture had been warmed to room temperature following the addition of the aldehyde, Baylis−Hillman-type adducts **11a**−**11j** with (*E*) double bond geometry along with a minor amount (<3%) of ketone (*E*)-**12** were isolated (Scheme 3).[8]

Scheme 3. Synthesis of Baylis−Hillman-Type Adducts



The results with various aromatic aldehydes are shown in Table 1. Thus, the geometry of the double bond can be controlled by the temperature at which the reaction is performed.

Table 1. Stereoselective Synthesis of (*Z*) and (*E*) Baylis−Hillman-Type Adducts **10a**−**j** and **11a**−**j**

entry	Ar	yield (%) (−40 °C)	yield (%) (rt)
1	Ph	79 (*Z*)-**10a**	72 (*E*)-**11a**
2	*p*-Br-Ph	69 (*Z*)-**10b**	63 (*E*)-**11b**
3	*p*-NO_2-Ph	83 (*Z*)-**10c**	60 (*E*)-**11c**
4	*p*-MeO-Ph	91 (*Z*)-**10d**	60 (*E*)-**11d**
5	*o*-Me-Ph	67 (*Z*)-**10e**	63 (*E*)-**11e**
6	2-Naphthyl	82 (*Z*)-**10f**	76 (*E*)-**11f**
7	*p*-Cl-Ph	82 (*Z*)-**10g**	50 (*E*)-**11g**
8	furyl[11]	54 (*Z*)-**10h**	62 (*Z*)-**11h**
9	2,4,6-MeO-Ph	79 (*Z*)-**10i**	68 (*E*)-**11i**
10	(*E*)-Me-C═CH-Ph	78 (*Z*)-**10j**	71 (*E*)-**11j**

The assignment of the configuration of the double bond was performed on the basis of extensive NOE experiments.[9]

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(8) In some examples, enone (*E*)-**12** and (*Z*)-adducts (<2%) were isolated after aqueous workup.

(9) In the (*E*)-configured adducts a NOE between the olefinic proton and the methyl groups adjacent to the carbamate group is present, whereas in the (*Z*)-configured adducts a NOE between the olefinic proton and the benzyl proton is observed.

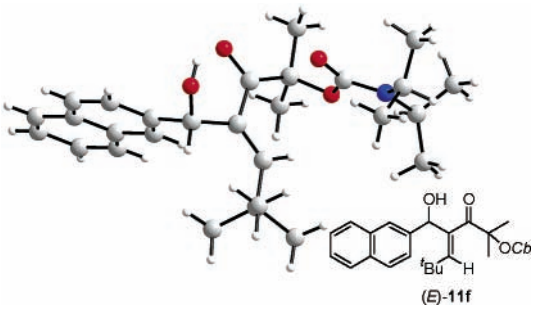


Figure 1. Crystal structure analysis of *rac*-(*E*)-**11f**.[10b]

Further solid evidence for the configuration of the double bond in the Baylis−Hillman-type adducts is drawn from the X-ray crystal structure analysis[10] of the products (*E*)-**11f** and (*Z*)-**10d** (Figures 1 and 2).

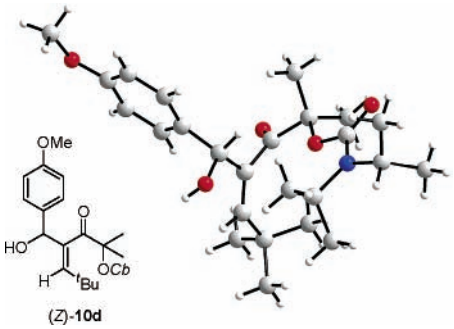
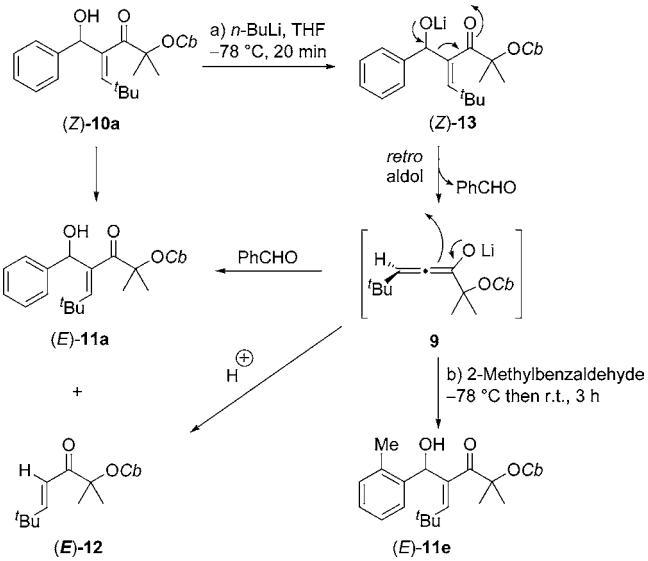


Figure 2. Crystal structure analysis of *rac*-(*Z*)-**10d**.[10c]

During these investigations an interesting observation was made. Treatment of (*Z*)-**10a** with *n*-BuLi at −78 °C for 20 min, followed by warming the reaction mixture to room temperature, led to the formation of the double bond isomer (*E*)-**11a** (46%) along with the enone (*E*)-**12** (30%), which arises from the protonation of the allenolate **9** (Scheme 4).

Scheme 4. *retro* Aldol Mechanism



Likewise, (*Z*)-**10a** was treated with *n*-BuLi at −78 °C, and after 20 min, 3.0 equiv of 2-methylbenzaldehyde was added. The reaction mixture was rapidly warmed to room temperature, furnishing Baylis−Hillman-type adducts (*E*)-**11a** (30%), (*E*)-**11e** (38%, which results from the addition of 2-methylbenzaldehyde), and enone (*E*)-**12** (10%), respectively (Scheme 4). The above results shed an insight on the course of the reaction, which can be interpreted as follows: Upon treatment with *n*-BuLi at −78 °C, the hydroxy proton of (*Z*)-**10a** is abstracted to form the alcoholate (*Z*)-**13**, which undergoes a *retro* aldol-type reaction[12] to generate the allenolate **9** and benzaldehyde.

Upon warming of the reaction mixture to room temperature, the allenolate **9** positions itself in such a manner that the bulky *tert*-butyl group and the ketone side chain are displaced to remote positions from each other. Under these circumstances, the allenolate **9** has equal opportunity to undergo addition to benzaldehyde or 2-methylbenzaldehyde. Hence, it adds to both aldehydes to furnish (*E*)-**11a** and (*E*)-**11e** in 30% and 38% yields, respectively.

Moreover unreacted allenolate **9** is protonated to result in the ketone (*E*)-**12** in 10% yield. It can be said that there exists a dynamic equilibrium between the allenolate **9** and aldehyde on one side and the Baylis−Hillman-type adducts on the other side. This led us to consider the (*Z*) Baylis−Hillman-type adducts as kinetically controlled products and the (*E*)

(10) (a) Crystals suitable for X-ray diffraction analysis were grown by slow evaporation of an ethereal solution. (b) X-ray crystal structure analysis of *rac*-(*E*)-**11f**: formula $C_{28}H_{39}NO_4$, $M = 453.60$, colorless crystal 0.40 × 0.30 × 0.20 mm^3; $a = 8.660(1)$, $b = 13.115(1)$, $c = 23.230(1)$ Å, $V = 2638.4(4)$ Å^3; $\rho_{calc} = 1.142$ g cm^{-3}, $\mu = 5.96$ cm^{-1}, empirical absorption correction ($0.796 \le T \le 0.890$), $Z = 4$, orthorhombic, space group $P2_12_12_1$ (No. 19), $\lambda = 1.54178$ Å, $T = 223(2)$ K, ω and φ scans, 10241 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sin θ)/λ] = 0.59 Å^{-1}, 4027 independent ($R_{int} = 0.026$) and 3280 observed reflections [$I \ge 2\sigma(I)$], 309 refined parameters, $R = 0.056$, $wR^2 = 0.141$, Flack parameter 0.0(4), max residual electron density 0.40 (−0.26) e Å^{-3}, hydrogens calculated and refined as riding atoms. (c) X-ray crystal structure analysis of *rac*-(*Z*)-**10d**: formula $C_{25}H_{39}NO_5$, $M = 433.57$, colourless crystal 0.40 × 0.20 × 0.15 mm^3, $a = 8.395(1)$, $b = 16.627(1)$, $c = 17.977(1)$ Å, $\beta = 92.14(1)°$, $V = 2507.5(4)$ Å^3; $\rho_{calc} = 1.148$ g cm^{-3}, $\mu = 6.33$ cm^{-1}, empirical absorption correction ($0.786 \le T \le 0.911$), $Z = 4$, monoclinic, space group $P2_1/c$ (No. 14), $\lambda = 1.54178$ Å, $T = 223(2)$ K, ω and φ scans, 16787 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sin θ)/λ] = 0.59 Å^{-1}, 4179 independent ($R_{int} = 0.037$) and 3286 observed reflections [$I \ge 2\sigma(I)$], 291 refined parameters, $R = 0.042$, $wR^2 = 0.131$, max residual electron density 0.33 (−0.17) e Å^{-3}, hydrogens calculated and refined as riding atoms. Data sets were collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction Denzo-SMN (Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307), absorption correction SORTAV (Blessing, R. H. *Acta Crystallogr.* **1995**, *A51*, 33. Blessing, R. H. *J. Appl. Crystallogr.* **1997**, *30*, 421), structure solution SHELXS-97 (Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467), structure refinement SHELXL-97 (Sheldrick, G. M. Universität Göttingen, 1997), graphics Diamond (Brandenburg, K. Universität Bonn, 1997).

(11) In the case of furfural (entry 8), the (*Z*) adduct is formed irrespective of the condition at which the reaction is performed.

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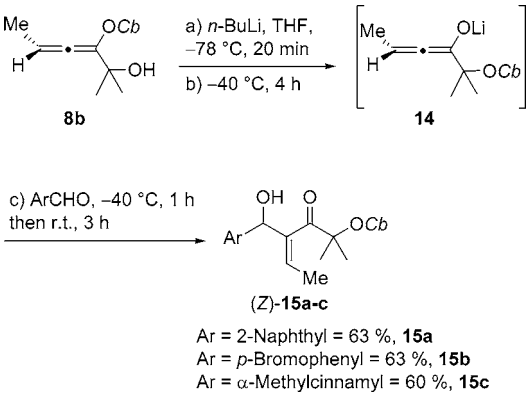
Baylis−Hillman-type adducts as the thermodynamically controlled products.

To demonstrate the versatility of this method, methyl-substituted allenyl carbamate **8b** was treated with 1.1 equiv of *n*-BuLi at −78 °C in THF and warmed to −40 °C for 4 h, to generate the allenolate **14**. Various aromatic aldehydes were added, and stirring was continued for 1 h at −40 °C followed by rapid warming to room temperature. To our surprise, the (*Z*) Baylis−Hillman-type adducts (*Z*)-**15a**−**15c** were formed (Scheme 5).

Scheme 5. Methyl-Substituted Baylis−Hillman-Type Adducts



The configuration of the double bond is proven by NOE experiments and X-ray crystal structure analysis (Figure 3).[13] It is amazing to note that under similar reaction conditions, the *tert*-butyl-substituted allenyl carbamate **8a** formed the (*E*) Baylis−Hillman-type adducts, whereas the methyl analogue **8b** formed the (*Z*) isomers. At present, it is not clear whether the reason for the difference is of thermodynamic or kinetic origin.

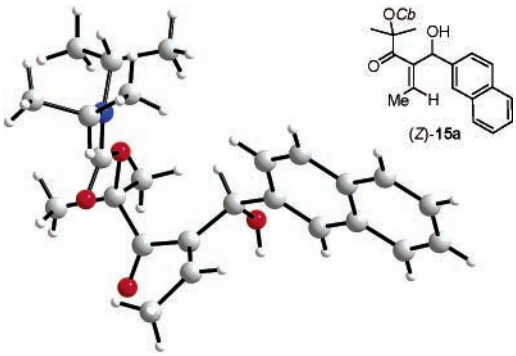


Figure 3. Crystal structure analysis of *rac*-(*Z*)-**15a**.[13]

In summary, a novel and simple method for the stereoselective synthesis of (*Z*)- and (*E*)-configured β-substituted Baylis−Hillman-type adducts via in situ generated allenolates has been demonstrated. Moreover, it has been shown that a *retro* aldol-type reaction makes the interconversion of the (*Z*) isomer to the (*E*) isomer possible. This method provides a unique opportunity to prepare Baylis−Hillman-type adducts that bear a large substituent at the distal end of the alkene moiety, which are otherwise not achievable by the conventional Baylis−Hillman reaction.

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Supporting Information Available: Experimental procedures, spectroscopic data for all compounds, and X-ray crystal data of *rac*-(*Z*)-**10d**, *rac*-(*E*)-**11f**, and *rac*-(*Z*)-**15a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) X-ray crystal structure analysis of *rac*-(*Z*)-**15a**: formula $C_{25}H_{33}NO_4$, M = 411.52, colourless crystal 0.30 × 0.20 × 0.10 mm^3, a = 8.880(1), b = 18.897(1), c = 14.191(1) Å, β = 100.24 (1)°, V = 2343.4(3) Å^3; ρ_{calc} = 1.166 g cm^{-3}, μ = 6.24 cm^{-1}, empirical absorption correction (0.835 ≤ T ≤ 0.940), Z = 4, monoclinic, space group $P2_1/n$ (No. 14), λ = 1.54178 Å, T = 223(2) K, ω and φ scans, 12808 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.59 Å^{-1}, 3808 independent (R_{int} = 0.040) and 2776 observed reflections [$I \geq 2\sigma(I)$], 279 refined parameters, R = 0.054, wR^2 = 0.143, max residual electron density 0.49 (−0.25) e Å^{-3}, hydrogens calculated and refined as riding atoms.