The Aldol Reaction of Allenolates with Aldehydes in the Presence of Magnesium Diiodide (MgI_2) as Catalyst

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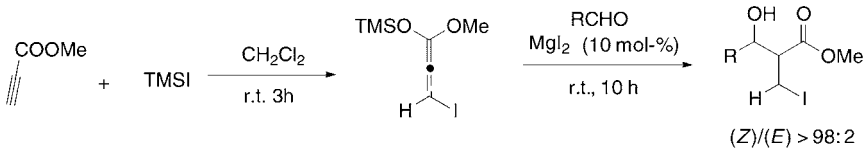
Stereoselective synthesis of (*Z*)-*α*-(hydroxyalkyl)-*β*-iodoacrylates (=(2*Z*)-2-(hydroxyalkyl)-3-iodoprop-2-enoates) was achieved in a one-pot coupling reaction from methyl prop-2-ynoate, Me_3SiI, and an alkanal under mild conditions with MgI_2 as catalyst (→ **1**–**9**; see *Table* and *Scheme 1*). *Baylis-Hillman β*-iodo adducts were generated in excellent yields with high (*Z*)-selectivity. The conversion of methyl prop-2-ynoate to an active methyl 3-iodo-1-[(trimethylsilyl)oxy]allenolate intermediate *in situ* followed by carbonyl addition is proposed as the reaction sequence (*Schemes 1* and *2*).

Introduction. – Reactions that provide for the functionalization of C=C and C≡C bonds in a stereoselective fashion are important tools for the synthesis of natural products and synthetic derivatives [1][2]. Among these procedures, the *Baylis-Hillman* reaction, which couples *α*,*β*-unsubstituted acrylate C=C bonds with aldehydes *via* an aldol-type addition, is widely utilized for functional transformations [3]. In cases where the acrylate C=C bond is substituted at the *β*-position, conditions for catalysis are limited [4]. An alternative method for synthesizing *Baylis-Hillman β*-iodo ketones was initially carried out by *Kishi* and co-workers [5]. Addition of Bu_4NI to *α*,*β*-acetylenic ketones was catalyzed by $TiCl_4$-promoted conjugation followed by electrophilic coupling to a series of aldehyde substrates. *Baylis-Hillman*-type (*E*)-*β*-iodo ketones have also been obtained with Et_2AlI as the promoter and the halogen source [6]. Subsequently, *Zhang* and *Lu* reported a method for the synthesis of *Baylis-Hillman β*-iodo esters and amides with the (*Z*)-isomer as the major product [7]. The latter method also employed Bu_4NI as the halide source for the anionic conjugative addition, but used 1.2 equiv. of $ZrCl_4$ as the *Lewis* acid promoter.

Inspired by these previous studies, we and other groups have developed several methodologies for the synthesis of *β*-monosubstituted and *β*,*β*-disubstituted *α*-(hydroxyalkyl)acrylates, *α*-(aminoalkyl)acrylates and *Baylis-Hillman β*-halo ketones [8–10]. Very recently, we reported an efficient synthetic method for (*Z*)-*α*-(hydroxyalkyl)-*β*-iodo-acrylates based on diethylaluminium iodide (Et_2AlI) as the I-source, and concurrently as a *Lewis*-acid promoter under relatively mild conditions [11]. In our continuing development of new *Baylis-Hillman*-type processes, we now found that (*Z*)-*α*-(hydroxyalkyl)-*β*-iodo-acrylates can also be obtained when MgI_2 is employed as the catalyst. This new method gives better (*Z*)/(*E*) selectivity for the products (particularly in the case of aliphatic aldehydes) as compared to the Et_2AlI-

based system [11]. Thus, in this communication, we report a *Michael*-type addition of Me_3SiI with methyl prop-2-ynoate to form an active 3-iodo-1-[(trimethylsilyl)oxy]-allenolate intermediate, which, in turn, attacks various aldeydes in the presence of MgI_2 as catalyst to afford *Baylis-Hillman* β-iodo adducts in excellent yields with high (Z)-selectivity (see *Scheme 1* and *Table*).

Scheme 1



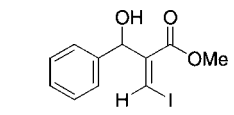
Results and Discussion. – Initially, the reaction was carried out at room temperature by treating methyl prop-2-ynoate (1.3 equiv.) with Me_3SiI (1.2 equiv.) in CH_2Cl_2 for 3 h to form the 3-iodo-2-[(trimethylsilyl)oxy]-allenolate intermediate, which then reacted with benzaldehyde to produce the *Baylis-Hillman* β-iodo adducts; unfortunately, only 70% yield of the adducts with a (Z/E) selectivity of 80:20 was obtained, even after a reaction time prolonged to 24 h, with less than 90% consumption of benzaldehyde. Finally, we found that, on adding 10% of MgI_2 as catalyst, the above reaction was much faster and went to completion within 10 h to give the desired α-(hydroxyalkyl)-β-iodoacrylates in 85% yield with a (Z)/(E) selectivity of 98:2, as determined by ^{1}H-NMR analysis of the crude product (*Table*, *Entry 1*). All reactions went to completion within 10 h as indicated by TLC or ^{1}H-NMR analysis ($\rightarrow$ **1**–**9**; *Entries 2–9*), except for the reaction with acetophenone as the electrophilic acceptor, which gave only 50% yield of product **10** even when the reaction was run at room temperature for 24 h with 90% of consumption of acetophenone (*Table*, *Entry 10*).

Screening of different solvents to improve the yield met with very limited success. Among the solvents tested, CH_2Cl_2 provided the highest efficiency in terms of yield and (Z)/(E) selectivity when using benzaldehyde as the electrophilic acceptor. Et_2O,

Table. *MgI_2-Catalyzed Reaction for the Synthesis of* Baylis-Hillman *β-Iodo Adducts*

Entry	Substrate	Product	(Z)/(E) Selectivity[a]) [%]	Yield[b]) [%]
1	Benzaldehyde	**1**	> 98	85
2	4-Fluorobenzaldehyde	**2**	> 98	87
3	4-Chlorobenzaldehyde	**3**	> 98	87
4	2-Naphthaldehyde	**4**	> 98	81
5	4-Methoxybenzaldehyde	**5**	> 98	80
6	4-Methylbenzaldehyde	**6**	> 98	82
7	Phenylacetaldehyde	**7**	> 98	78
8	(2E)-But-2-enal	**8**	> 98	76
9	Pentanal	**9**	> 98	75
10	Acetophenone	**10**	> 98	50[c])

[a]) > 98% Means that another isomer (< 2%) was observed by ^{1}H-NMR of the crude product. [b]) Yields after purification by column chromatography. [c]) Reaction for 24 h.



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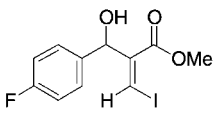

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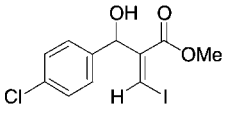

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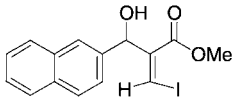

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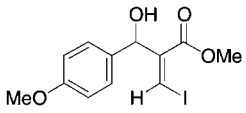

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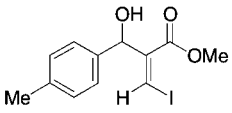

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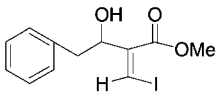

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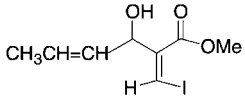

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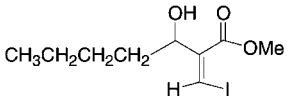

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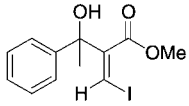

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benzene, and toluene gave rise to a lower yield of 60%, 70%, and 75% respectively, within a 10 h reaction period. However, all these solvents also gave high (*Z*)/(*E*) selectivity (> 98%). It is noteworthy that almost no desired product was detected when THF was employed as the solvent.

Both aromatic and aliphatic aldehydes were suitable electrophilic acceptors in the new reaction system, and good yields were realized for most examples that we examined. In the case of aromatic aldehydes, substitution by an electron-withdrawing group (*Table*, *Entries 2–4*) or an electron-donating group (*Entries 5* and *6*) at the aromatic ring resulted in no obvious effect on the reaction efficiencies (yields and stereoselectivity), in contrast to the Et_2AlI-based system [11] in which the reaction with 4-methoxybenzaldehyde needed a much longer time to proceed to completion under standard conditions. With regard to aliphatic aldehydes (*Entries 7–9*), our new system worked a little better than the Et_2AlI-based system. For example, under identical conditions (10 h at room temperature), the reaction with pentanal gave a 75% yield of **9** with > 98% (*Z*)/(*E*) selectivity in the presence of MgI_2 as compared to a 65% yield of product with a (*Z*)/(*E*) selectivity ratio of 60 : 40 in the presence of Et_2AlI. This result may be due to the fact that MgI_2 is a relatively weaker *Lewis* acid and is less reactive, thus producing little side reaction. It is noteworthy that the new system did not work well for ketones such as acetophenone (see above, *Entry 10*), but still gave a very good (*Z*)/(*E*) selectivity (> 98%).

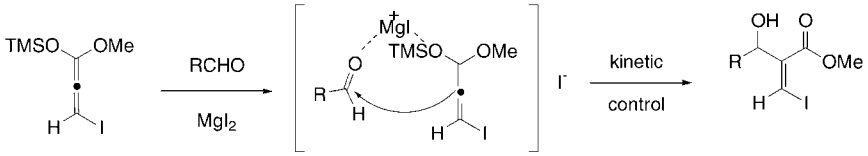
The (*Z*)/(*E*) selectivities listed in the *Table* were measured by ^{1}H-NMR-spectroscopic analyses of the crude product mixture. In all cases, the C*H*(OH)-proton signals for the (*Z*)- and (*E*)-isomers were clearly distinguishable, with the proton of the (*Z*)-isomer upfield relative to that of the (*E*)-isomer. Isomers could be readily separated by flash chromatography, and the geometries for the two isomers of the

benzaldehyde reaction were confirmed by ROESY NMR experiments. For the (*Z*)-isomer, olefinic-proton irradiation resulted in enhancement of the C*H*(OH) signal, whereas, for the (*E*)-isomer, olefinic-proton irradiation resulted in enhancement of the MeO signal.

To explain the high (*Z*)/(*E*) stereoselectivity produced by this new system, a cyclic-transition-state model proposed by *Kishi* and co-workers can be invoked [5]. In their system, not only the $Bu_4NI/TiCl_4$ combination but also Et_2AlI and TiI_4 were employed for the reaction. Exclusive (*Z*)-stereoselectivity of *Baylis-Hillman* β-iodo ketones was obtained at $-78°$, while high (*E*)-stereoselectivity was observed at $0°$. Invoking a cyclic transition state, they suggested that (*Z*)-stereoisomer was the kinetically controlled product, while the (*E*)-stereoisomer was the thermodynamically controlled product. In the system we report here, the (*Z*)-isomer was favored under all reaction conditions tested. These results suggest that the kinetic control plays a significant role in determining the geometric selectivity at room temperature. This is in contrast to a previously reported $TiCl_4$-mediated reaction carried out at room temperature in which (*E*)-isomers were predominantly obtained [10] by a process believed to be under thermodynamic control.

The working hypothesis of this new process is represented in *Scheme 2*. The reaction proceeds *via* the nucleophilic attack of the allenolate intermediate on the aldehyde. This (C–C)-bond-forming step is activated by the coordination of the aldehyde O-atom with the *Lewis* acid species.

Scheme 2



In summary, an efficient synthetic method for α-(hydroxyalkyl)-β-iodo acrylates was developed. The new protocol utilized MgI_2 as catalyst under relatively mild conditions. This reaction system provided extensive functionalization of acrylate C=C bonds with high chemical yields and geometric selectivity.

Experimental Part

General. CH_2Cl_2 was dried and freshly distilled from P_2O_5 under N_2. Other commercial chemicals were used without further purification, and their stoichiometrics were calculated based on the reported purities from the manufacturers. Flash chromatography (FC): *Merck* silica gel *60* (230–400 mesh). NMR Spectra: *Varian-500-MHz-NMR* spectrometer; at 500 (^{1}H) or 125 MHz (^{13}C); $CDCl_3$ as solvent and internal reference for ^{13}C; chemical shifts δ in ppm from Me_4Si, *J* in Hz. MS: *Jeol-JMS-D300* spectrometer, direct-inlet electron-impact ionization (70 eV); in *m*/*z*.

Typical Procedure (*Table*, *Entry 1*). Methyl prop-2-ynoate (0.12 ml, 1.3 mmol), freshly distilled CH_2Cl_2 (5.0 ml), and Me_3Si (0.18 ml, 1.2 mmol) were stirred (magnetic bar) at r.t. for 3 h in a dry standard glass test tube (150×22 mm; previously flushed with N_2 at r.t.). Then benzaldehyde (0.1 ml, 1.0 mmol) and MgI_2 (28.0 mg, 0.1 mmol) were added. The mixture was stirred at r.t. for 10 h. The reaction was quenched by dropwise addition of 2N aq. HCl. The aq. phase was extracted with AcOEt (3×15 ml), the combined org. phase washed with brine, dried ($MgSO_4$), and evaporated, and the residue purified by FC (hexane/AcOEt 5:1): products

(270.4 mg, 85%) as colorless oil. The residue was separated by FC (hexane/AcOEt 10:1): **1** (αZ)-isomer (264 mg, 83%) and corresponding (αE)-isomer (6.4 mg, 2.0%).

Methyl (αZ)-β-Hydroxy-α-(iodomethylene)benzenepropanoate (**1**): Colorless oil. IR (neat): 3443, 3063, 2950, 1714. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.91 (*d*, *J* = 5.5, 1 H); 3.72 (*s*, 3 H); 5.54 (*dd*, *J* = 5.5, 1.5, 1 H); 7.27 (*d*, *J* = 1.5, 1 H); 7.30–7.36 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 51.9; 76.0; 87.1; 126.5 (×2), 128.3; 218.6 (×2); 140.0; 145.1; 166.3. CI-MS (CH_4): 318.1 (M^+). HR-MS: 318.1105 (M^+; calc. 318.1110).

(αE)-Isomer of **1**: Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.72 (*s*, 3 H); 4.20 (*d*, *J* = 11.4, 1 H); 5.83 (*d*, *J* = 11.4, 1 H); 7.26–7.44 (*m*, 5 H); 8.14 (*s*, 1 H).

Methyl (αZ)-4-Fluoro-β-hydroxy-α-(iodomethylene)benzenepropanoate (**2**): Colorless oil (293 mg, 87%; >98% (αZ) in the crude). IR (neat): 3499, 3071, 2952, 1731. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.93 (*d*, *J* = 6.0, 1 H); 3.72 (*s*, 3 H); 5.52 (*dd*, *J* = 6.0, 1.5, 1 H); 7.00–7.06 (*m*, 2 H); 7.28–7.32 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 51.9; 73.9; 87.1; 115.4; 115.7; 128.4; 135.8; 144.9; 160.8; 164.1; 166.2.

Methyl (αZ)-4-Chloro-β-hydroxy-α-(iodomethylene)benzenepropanoate (**3**): Colorless oil (309 mg, 87%; >98% (αZ) in the crude). IR (neat): 3453, 3068, 2958, 2359, 1720. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.23 (*d*, *J* = 6.0, 1 H); 3.72 (*s*, 3 H); 5.48 (*dd*, *J* = 6.0, 1.4, 1 H); 7.22–7.32 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 51.9; 75.4; 87.7; 127.8 (×2); 128.8 (×2); 134.1; 138.5; 144.6; 166.1. CI-MS (CH_4): 352.5. HR-MS: 352.5551 (M^+; calc. 352.5558).

Methyl (αZ)-β-Hydroxy-α-(iodomethylene)naphthalenepropanoate (**4**): Colorless oil (298 mg, 81%; >98% (αZ) in the crude. IR (neat): 3447, 3055, 2949, 1715. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.04 (*d*, *J* = 6.0, 1 H); 3.70 (*s*, 3 H); 5.69 (*dd*, *J* = 6.0, 1.5, 1 H); 7.29 (*s*, 1 H); 7.47–7.50 (*m*, 3 H); 7.80–7.84 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 51.9; 76.1; 87.5; 124.2; 125.6; 126.3 (×2); 127.6; 128.1; 128.5; 133.1 (×2); 137.3; 145.0; 166.3.

Methyl (αZ)-β-Hydroxy-α-(iodomethylene)-4-methoxybenzenepropanoate (**5**): Colorless oil (278 mg, 80%; >98% (αZ) in the crude). IR (neat): 3448, 3001, 2950, 2835, 1718. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.06 (*d*, *J* = 6.0, 1 H); 3.69 (*s*, 3 H); 3.77 (*s*, 3 H); 5.45 (*dd*, *J* = 6.0, 1.5, 1 H); 6.83–6.86 (*d*, *J* = 6.0, 2 H); 7.19–7.22 (*m*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 51.9; 55.2; 75.6; 86.4; 114.0 (×2); 127.9 (×2); 132.1; 145.4; 159.5; 166.4.

Methyl (αZ)-β-Hydroxy-α-(iodomethylene)-4-methoxybenzenepropanoate (**6**): Colorless oil (272 mg, 82%; >98% (αZ) in the crude). IR (neat): 3450, 3024, 2949, 1713. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.32 (*s*, 3 H); 3.07 (*d*, *J* = 6.0, 1 H); 3.68 (*s*, 3 H); 5.46 (*dd*, *J* = 6.0, 1.5, 1 H); 7.11–7.20 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.1; 51.8; 75.8; 86.7; 126.4 (×2); 129.3 (×2); 137.0; 138.1; 145.2; 166.3.

Methyl (αZ)-β-Hydroxy-α-(iodomethylene)benzenebutanoate (**7**): Colorless oil (259 mg, 78%; >98% (αZ) in the crude). ^{1}H-NMR (500 MHz, $CDCl_3$): 2.42 (*d*, *J* = 5.5, 1 H); 2.79 (*dd*, *J* = 13.5, 8.0, 1 H); 3.01 (*dd*, *J* = 13.5, 4.5, 1 H); 3.84 (*s*, 3 H); 4.63 (*m*, 1 H); 7.10 (*d*, *J* = 1.0, 1 H); 7.19–7.32 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 42.9; 51.9; 75.3; 85.7; 126.8; 128.5 (×2); 129.4 (×2); 129.4; 136.8; 166.4.

Methyl (2Z,4E)-3-Hydroxy-2-(iodomethylene)hex-4-enoate (**8**): Colorless oil (214 mg, 76%; >98% (2*Z*) in the crude). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.71 (*m*, 3 H); 2.65 (*d*, *J* = 5.5, 1 H); 3.83 (*s*, 3 H); 4.89 (*m*, 1 H); 5.51 (*m*, 1 H); 5.77 (*m*, 1 H); 7.20 (*d*, *J* = 1.0, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.7; 51.9; 74.7; 85.6; 129.5; 129.7; 145.4; 166.5.

Methyl (2Z)-3-Hydroxy-2-(iodomethylene)heptanoate (**9**): Colorless oil (223 mg, 75%; >98% (2*Z*) in the crude). ^{1}H-NMR (500 MHz, $CDCl_3$): 0.90 (*t*, *J* = 7.0, 3 H); 1.26–1.40 (*m*, 4 H); 1.60 (*m*, 2 H); 2.62 (*d*, *J* = 6.0, 1 H); 3.84 (*s*, 3 H); 4.39 (*m*, 1 H); 7.12 (*d*, *J* = 1.0, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 13.8; 22.3; 27.5; 35.7; 51.9; 74.8; 84.4; 146.9; 166.9.

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