Synthesis of Substituted α-(Hydroxymethyl)-β-iodoacrylates *via* MgI_2-Promoted Stereoselective Aldol Coupling

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The efficient and highly stereoselective syntheses of a variety of (*Z*)-configured, substituted α-(hydroxymethyl)-β-iodo-acrylates from prop-2-ynoate and various aldehydes was achieved. The synthetic protocol involves a simple one-pot coupling reaction under mild conditions, promoted by MgI_2, which serves both as a *Lewis* acid and iodine source for a *Baylis–Hillman*-type reaction. All adducts were generated in good-to-excellent yields, the (*Z*)-isomers being formed in high selectivity (> 98%). The conversion of methyl prop-2-ynoate into an active 'β-iodo allenolate' intermediate, which then nucleophilically attacks an aldehyde, is proposed as a plausible reaction mechanism.

Introduction. – *Baylis–Hillman* (*BH*)-type couplings belong to the most-important C,C-bond-forming processes in organic synthesis [1–3]. Highly functionalized *BH* adducts can be subjected to transformations for the synthesis of natural products and synthetic derivatives [4].

Recently, we have developed several methodologies [5] for the synthesis of substituted 'α-(hydroxymethyl)-β-iodoacrylates' (=(*Z*)-2-(hydroxymethyl)-3-iodoprop-2-enoates; **A**) and substituted 'α-(hydroxymethyl)-β-iodovinyl ketones' (=2-(hydroxymethyl)-3-iodoprop-2-enyl alkyl ketones; **B**), as shown in *Scheme 1*. These methods allowed us to react β-substituted acrylate olefins, which, in the original *BH* reaction, could not be used as substrates [1a][6][7]. Moreover, Et_2AlI (*Scheme 1,a*) is a moisture-sensitive reagent difficult to handle, and the route *via* the intermediary cumulene **C** (*Scheme 1,b*) suffers from long reaction times, in contrast to the synthesis of ketones of type **B**, which proceeds both rapidly and efficiently.

Because esters of type **A** are more-useful than the corresponding ketones **B**, we focused our efforts on extending the scope of our modified *BH* reaction by means of MgI_2 catalysis.

Results and Discussion. – In our initial synthetic protocol, Et_2AlI had been used as the promoter [5d]. When methyl prop-2-ynoate (1.3 mmol) and benzaldehyde (1.0 mmol) were dissolved at 0° in CH_2Cl_2 in the presence of MgI_2 (1.2 mmol), only low rates of conversion were observed (after 1 h and 24 h, 50 and 60% consumption, respectively, of the aldehyde). At ambient temperature (25°), the reaction did not proceed faster (55% consumption after 24 h), which called for further modifications. Screening different solvents to improve the yield of the reaction also met with limited

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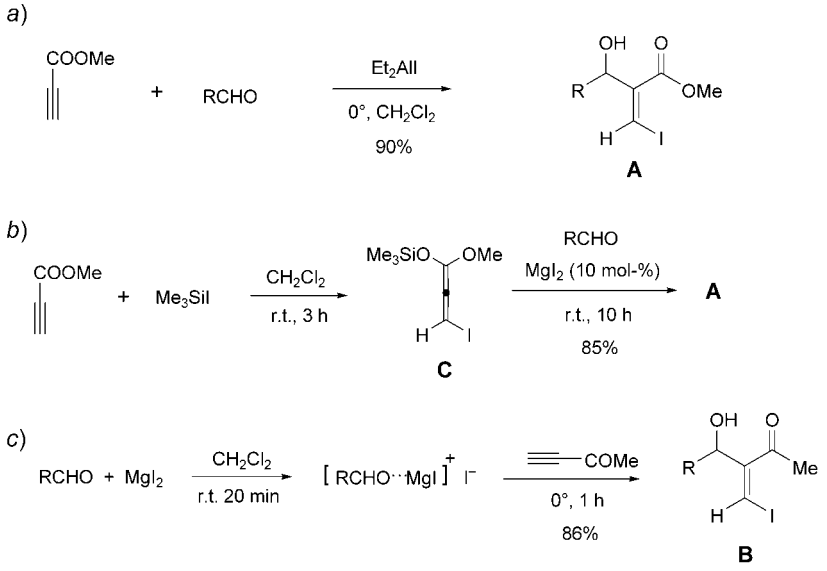
Scheme 1



success. However, after several experiments, we determined that the order in which the starting materials had to be introduced was a critical parameter. We found that the aldehyde and MgI_2 had to be mixed in CH_2Cl_2 at room temperature for 20 min before addition of the propargylic ester. Under these conditions, the reaction between, *e.g.*, benzaldehyde and methyl prop-2-ynoate was complete within 1 h, and the desired product **1** was obtained in 90% yield with a (*Z*)/(*E*) ratio of *ca.* 98 : 2 (*Table*).

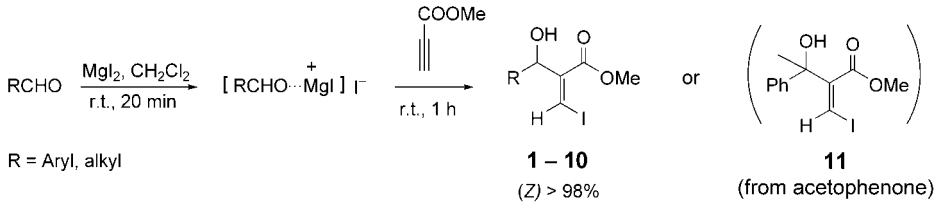
In general, good-to-excellent yields (82 – 91%) were achieved for compounds **1** – **10**, derived from a variety of aldehydes, and the (*Z*)/(*E*) ratio was, in all cases, at least 98 : 2. A somewhat lower yield (60% after 1 h, but 78% after 24 h; *Entry 11* in the *Table*) was observed in the case of the less-reactive acetophenone.

CH_2Cl_2 provided the best results in terms of both yield (90%) and (*Z*)/(*E*) ratio (> 98 : 2), when benzaldehyde was used as the electrophile. Et_2O, benzene, and toluene gave considerably poorer results in this respect (40, 50, and 45% yield, resp.) after a 1-h reaction time. However, all these solvents gave rise to (*Z*)/(*E*) selectivities above 98 : 2. Interestingly, attempts to run the reaction in THF completely failed.

Both aromatic *and* aliphatic aldehydes were found to be suitable electrophiles for this new catalytic system, and high yields were realized in all experiments conducted (*Table*). For aromatic aldehydes, substitution by electron-withdrawing (*Entries 2 – 4*) or an electron-donating groups (*Entries 5* and *6*) on the aromatic ring had no obvious effect on the reaction in terms of yield and selectivity. In contrast, with the Et_2AlI-based system [5d], the reaction with, *e.g.*, 4-methoxybenzaldehyde, required much longer to go to completion under standard conditions.

With regard to aliphatic aldehydes (*Entries 7 – 10*), our new reaction protocol was also more effective at generating the desired product than that of the Et_2AlI-based system. For example, the reaction between valeraldehyde (*Entry 9*) and methylprop-2-

Table. *MgI_2-Mediated Synthesis of the* Baylis–Hillman *β-Iodo Adducts* **1**–**11**



R = Aryl, alkyl

1 – 10
(*Z*) > 98%

11
(from acetophenone)

Entry	R	Product	(*Z*)-Isomer [%] [a]	Yield [%] [b]
1	Ph	**1**	> 98	90
2	4-F-C_6H_4	**2**	> 98	91
3	4-Cl-C_6H_4	**3**	> 98	91
4	Naphthalen-2-yl	**4**	> 98	87
5	4-MeO-C_6H_4	**5**	> 98	88
6	4-Me-C_6H_4	**6**	> 98	90
7	$PhCH_2$	**7**	> 98	86
8	Prop-1-en-1-yl	**8**	> 98	84
9	Bu	**9**	> 98	85
10	*t*-Bu	**10**	> 98	82
11	[c])	**11**	> 98	60[d])

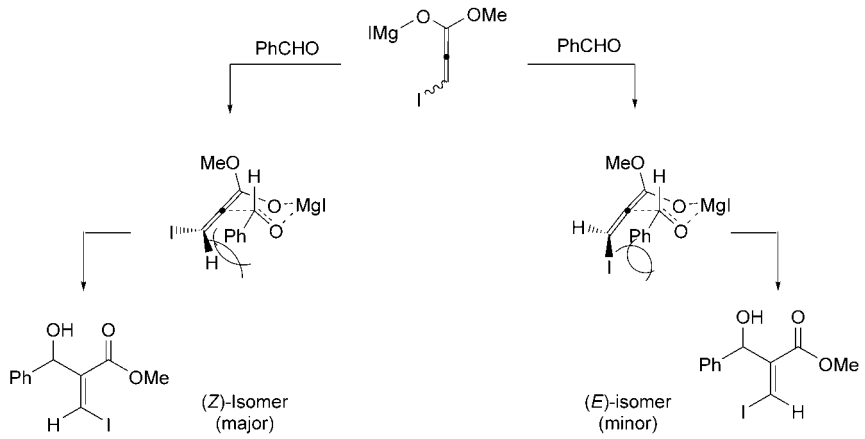
[a]) Determined by ^{1}H-NMR analysis of the crude mixture. [b]) After column-chromatographic purification of the 1-h reaction mixture. [c]) Acetophenone (PhC(O)Me) was used as the substrate instead of an aldehyde, giving rise to a tertiary OH group in **11** (*C*-methylated analog of **1**). [d]) After 24 h, 78% of **11** were isolated.

ynoate afforded 85% *vs.* 58% of **9**, with (*Z*)/(*E*) selectivities of > 98% *vs.* 60%, respectively, for the MgI_2- *vs.* Et_2AlI-catalyzed systems. These results may be due, in part, to MgI_2 being a weaker *Lewis* acid than Et_2AlI, which reduces side reactions. The lower reactivity of MgI_2 also rationalizes the observation that this new system is somewhat less-efficient when ketones, *e.g.*, acetophenone (*Entry 11*), rather than aldehydes are used as electrophiles.

(*Z*)/(*E*) Ratios were determined by ^{1}H-NMR spectroscopic analyses of the crude product mixtures. In all cases, the α-H-atom signals for the (*Z*)- and (*E*)-isomers were clearly distinguishable, the former being shifted upfield relative to the (*E*)-isomer. The isomers could be readily separated by flash chromatography, and the geometries were confirmed by ROESY-NMR experiments in the case of (*E*)- and (*Z*)-**1**. Thereby, for (*Z*)-**1**, irradiation of the vinyl H-atom resulted in an enhancement of the HO–CH_2 resonance, whereas the (*E*)-isomer gave rise to an enhancement of the MeO signal.

The mechanism of this new process, as represented in *Scheme 2*, can be formulated as discussed in [5c]. By means of a cyclic transition-state model, *Kishi* and co-workers [8] suggested that the (*Z*)- and (*E*)-stereoisomers correspond to the kinetically and thermodynamically controlled products, respectively. However, in the system reported here, the (*Z*)-isomer was strongly favored at *different* temperatures, suggesting that kinetic control plays a significant role in determining the geometric selectivity even at ambient temperature. Our results, thus, are contrary to those previously reported for $TiCl_4$-mediated reactions carried out at room temperature, in which the thermodynamically controlled (*E*)-isomers had been obtained predominantly [9].

Scheme 2



In summary, we have developed a simple and efficient synthesis of substituted α-(hydroxymethyl)-β-iodoacrylates. Our new protocol functions under mild conditions and uses, instead of the moisture-sensitive Et_2AlI, MgI_2 both as an I^- source and a *Lewis* acid catalyst. All examples presented here gave better yields and higher stereoselectivities than obtained with our previously reported method [5c][5d].

Experimental Part

General. CH_2Cl_2 was freshly distilled from CaH under N_2 atmosphere. All chemicals used were commercially available and used without further purification; the stoichiometrics were calculated based on the purities reported by the manufacturers. All reactions were conducted under N_2 gas in dry glassware equipped with a magnetic stirring bar. Flash chromatography (FC) was performed on *Silica Gel 60* (230–400 mesh; *Merck*). Infrared (IR) spectra were recorded on a *Shimadzu FT-IR-8400* spectrophotometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra were recorded on a *Varian* spectrometer (at 500 and 125 MHz, resp.) in $CDCl_3$; chemical shifts δ in ppm rel. to Me_4Si (= 0 ppm), coupling constants J in Hz. Mass spectra were recorded on a *JEOL JMS-D300* mass spectrometer; in *m*/*z*. High-resolution (HR) mass spectra were recorded at the Mass Spectroscopy Laboratory at the *Crompton Corporation*.

Typical Procedure (see the *Table*, *Entry 1*). A moisture-free standard-glass test tube (150 × 22 mm), equipped with a magnetic stirring bar, was flushed with N_2 at r.t., and loaded with MgI_2 (340 mg, 1.2 mmol), benzaldehyde (0.1 ml, 1.0 mmol), and anh. CH_2Cl_2 (8.0 ml). The mixture was stirred at r.t. for 20 min. Then, methyl prop-2-ynoate (0.12 ml, 1.3 mmol) was added dropwise *via* syringe, and the mixture was stirred at r.t. for 1 h. Then, the reaction was quenched by dropwise addition of 2N aq. HCl soln. The two phases were separated, and the aq. layer was extracted with AcOEt (3 × 15 ml). The combined org. phases were washed with brine, dried ($MgSO_4$), and concentrated. The remaining residue was purified by FC (hexane/AcOEt 5:1) to give the pure condensation product (**1**).

*Methyl (*Z*)-2-[Hydroxy(phenyl)methyl]-3-iodoprop-2-enoate* (**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; 128.3; 218.6; 140.0; 145.1; 166.3. CI-MS (CH_4): 318.1 (M^+). HR-MS: 317.9756 (M^+, $C_{11}H_{11}IO_3^+$; calc. 317.9753).

*Methyl (*Z*)-2-[(4-Fluorophenyl)(hydroxy)methyl]-3-iodoprop-2-enoate* (**2**). Colorless oil. 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. HR-MS: 335.9655 (M^+, $C_{11}H_{10}FIO_3^+$; calc. 335.9659).

*Methyl (*Z*)-2-[(4-Chlorophenyl)(hydroxy)methyl]-3-iodoprop-2-enoate* (**3**). Colorless oil. 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*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 51.9; 75.4; 87.7; 127.8; 128.8; 134.1; 138.5; 144.6; 166.1. HR-MS: 351.9368 (M^+, $C_{11}H_{10}ClO_3^+$; calc. 351.9363).

*Methyl (*Z*)-2-[Hydroxy(naphthalen-2-yl)methyl]-3-iodoprop-2-enoate* (**4**). Colorless oil. 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; 127.6; 128.1; 128.5; 133.1; 137.3; 145.0; 166.3. HR-MS: 367.9903 (M^+, $C_{15}H_{13}IO_3^+$; calc. 367.9909).

*Methyl (*Z*)-2-[Hydroxy(4-methoxyphenyl)methyl]-3-iodoprop-2-enoate* (**5**). Colorless oil. 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; 127.9; 132.1; 145.4; 159.5; 166.4. HR-MS: 347.9862 (M^+, $C_{12}H_{13}IO_4^+$; calc. 347.9859).

*Methyl (*Z*)-2-[Hydroxy(4-methylphenyl)methyl]-3-iodoprop-2-enoate* (**6**). Colorless oil. 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; 129.3; 137.0; 138.1; 145.2; 166.3. HR-MS: 331.9912 (M^+, $C_{12}H_{13}IO_3^+$; calc. 331.9909).

*Methyl (*Z*)-3-Hydroxy-2-(iodomethylidene)-4-phenylbutanoate* (**7**). Colorless oil. IR (neat): 3477, 3102, 2899, 1716. ^{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; 129.4; 129.4; 136.8; 166.4. HR-MS: 331.9905 (M^+, $C_{12}H_{13}IO_3^+$; calc. 331.9909).

*Methyl (2*Z*,4*E*)-3-Hydroxy-2-(iodomethylidene)hex-4-enoate* (**8**). Colorless oil. ^{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). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.7; 51.9; 74.7; 85.6; 129.5; 129.7; 145.4; 166.5. HR-MS: 281.9758 (M^+, $C_8H_{11}IO_3^+$; calc. 281.9753).

*Methyl (*Z*)-3-Hydroxy-2-(iodomethylidene)heptanoate* (**9**). Colorless oil. ^{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. HR-MS: 298.0069 (M^+, $C_9H_{15}IO_3^+$; calc. 298.0066).

*Methyl (*Z*)-3-Hydroxy-2-(iodomethylidene)-4,4-dimethylpentanoate* (**10**). Colorless oil. IR (neat): 3401, 3009, 1716, 1614. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.89 (*s*, 9 H); 2.68 (*d*, *J* = 6.1, 1 H); 3.82 (*s*, 3 H); 4.25 (*dd*, *J* = 6.1, 1.4, 1 H); 7.07 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 25.5; 36.0; 52.0; 82.5; 85.6; 145.5; 167.9. HR-MS: 298.0061(M^+, $C_9H_{15}IO_3^+$; calc. 298.0066).

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