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Stereoselective aldol coupling of α,β-acetylenic ketones promoted by MgI_2

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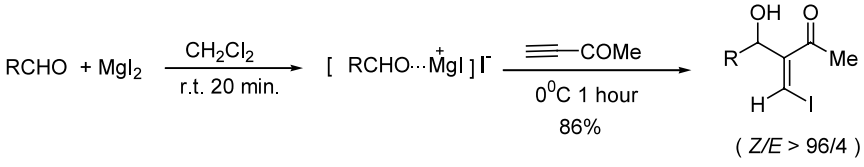
Abstract—A highly stereoselective synthesis of (*Z*)-β-iodovinyl ketone has been achieved with the tandem formation of C–C and C–I bonds in a three-component reaction. This new catalysis utilizes MgI_2 as a Lewis acid as well as an iodine source for a Michael-type addition. α,β-Acetylenic ketone is initially converted to an active β-iodo allenolate intermediate and then can be attacked by a variety of aldehydes to afford *Z*-selective Baylis–Hillman adducts in excellent yields.

The synthesis of multifunctionalized alkenes in a stereoselective fashion continues to be an important goal in organic chemistry.[1–4] Among these procedures, the Baylis–Hillman reaction that couples α,β-unsubstituted acrylate olefins with aldehydes by way of an aldol type addition is widely utilized for functional transformations. The synthesis of β-iodovinyl ketones was initially carried out by Kishi et al.[5] via a $TiCl_4$-promoted conjugative addition of tetrabutyl-ammonium iodide ($(n\text{-Bu})_4NI$) to α,β-acetylenic ketones followed by electrophilic coupling with a variety of aldehydes. The *Z*/*E* selectivity of the products in this system was dependent on the reaction temperature, namely, at −78°C, the *Z* isomer was the major product while at 0°C the *E* isomer was the exclusive product obtained.

Recently several methods have been developed for the synthesis of β-alkyl and β,β-dialkyl α-(hydroxyalkyl)acrylates and α-(aminoalkyl)acrylates since these products cannot be normally generated under the Baylis–Hillman conditions.[6–8] Most recently, we have developed methods for the synthesis of β-halo Baylis–Hillman adducts,[9] based on $TiCl_4$, $TiBr_4$, $TiCl_4/(n\text{-Bu})_4I$, Et_2AlI, and TMSI as halogen sources and promotors. Among the above reagents used at 0°C, $TiCl_4$, $TiBr_4$, $TiCl_4/(n\text{-Bu})_4I$ generate the *E* isomer as major product, and Et_2AlI and TMSI generated the *Z* isomer as the major product. In our continuing development of new Baylis–Hillman-type processes, we are pleased to find that α-substituted-β-iodovinyl ketones (referred to as *Z*-β-iodo Baylis–Hillman adducts) were obtained by mixing a variety of aldehydes, with α,β-acetylenic ketone and magnesium iodide in CH_2Cl_2 at 0°C. In this communication, we report on this new procedure that is represented in Scheme 1 with results summarized in Table 1.

The initial reaction was carried out by reacting 3-butyn-2-one (1.3 equiv.) with benzaldehyde (1.0 equiv.) in the presence of MgI_2 (1.2 equiv.) in CH_2Cl_2 at 0°C based on a previously described metal-catalyzed reaction system.[10] Initially a 60% yield of the expected product was obtained and even by extending the reaction time to 24 h less than 85% of the benzaldehyde was consumed.



Scheme 1.

Keywords: Baylis–Hillman adducts; magnesium iodide; α,β-acetylenic ketones; (*Z*)-β-iodovinyl ketone.
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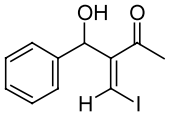
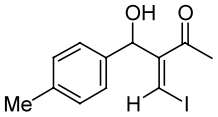
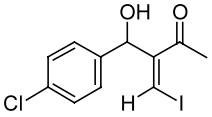
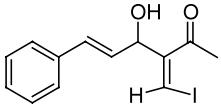
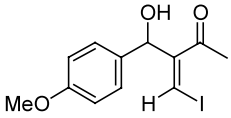
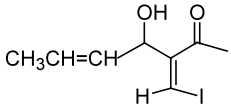
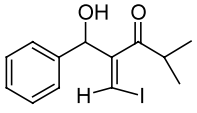
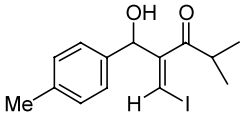
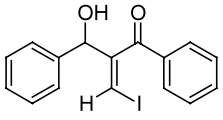
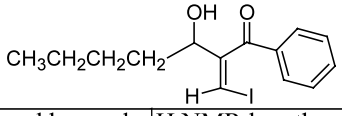
Table 1. Results of the MgI_2-mediated reaction for synthesis of β-iodo Baylis–Hillman adducts[11,12]

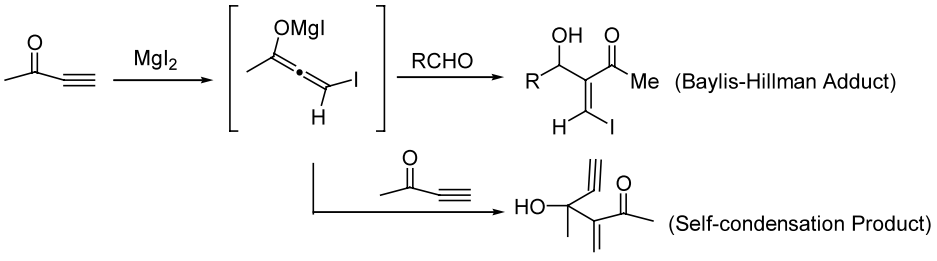
Entry	Substrate	Product	*Z/E* selectivity %[a]	Yield (%)[b]
1	benzaldehyde		>96	86
2	4-*p*-tolualdehyde		>96	85
3	4-chlorobenzaldehyde		>96	90
4	*trans*-cinnamaldehyde		>96	82
5	p-anisaldehyde		>96	85
6	crotonaldehyde		>96	81
7	benzaldehyde		>96	82
8	4-*p*-tolualdehyde		>96	81[c]
9	benzaldehyde		>96	88
10	*n*-valeraldehyde		>96	86

[a] >96% means that another isomer was observed by crude ^1H NMR less than 4%.

[b] Yields after purification by column chromatography.

[c] All products were obtained as oils except for entry 8 which had a mp = 103 – 105 C.

Raising the reaction temperature to 25°C resulted in little improvement, with ca. 65% product yield with a 24 h reaction time. In addition to the expected product, 10–15% of a self-condensation product was observed by using this one-pot reaction (Scheme 2). The screening of different solvents also did little to improve product



Scheme 2.

yield. After several exploratory experiments, we found that changing the order of loading starting materials was critical for the success of the reaction. Namely, mixing benzaldehyde and MgI_2 in CH_2Cl_2 (8.0 mL) at room temperature for 20 min before adding the 3-butyn-2-one resulted in the β-iodo Baylis–Hillman product in 86% yield with Z/E selectivity ratio of 97:3. The reaction was run at 0°C and required to stir for 1 h after the ketone was added for the reaction to go to completion. In the meantime, the self-condensation product was reduced to less than 2% (Scheme 2). Reaction yields were calculated based on TLC and/or ^{1}H NMR peak integrations.

Dichloromethane provided the highest efficiency among the solvents tested in terms of yield and Z/E selectivity when using benzaldehyde as the electrophilic acceptor. Diethyl ether, benzene and toluene gave rise to a lower yield of 65, 60 and 55% respectively, within a 1 h reaction period. However, all the above solvents also gave high Z/E selectivity (>96%). Attempts to run the reaction in THF resulted in very low yield of the desired product.

Both aromatic and aliphatic acetylenic ketones were successfully employed as Michael-type acceptors to generate MgI–allenolates. In addition, aromatic and aliphatic aldehydes were suitable electrophilic acceptors in the new reaction system and high yields were realized for all examples that we examined. As shown in Table 1, for aromatic aldehydes, substitution of an electron-withdrawing group (entry 3) or an electron-donating group (entries 2, 5 and 8) on the aromatic ring resulted in no obvious effect on the reaction efficiencies (yields as well as stereoselectivity). With regard to aliphatic aldehydes (entries 4, 6 and 10), the products were predominantly produced as Z configuration for all cases in our new system as revealed by ^{1}H NMR analyses of the crude products. This result was contrary to Et_2AlI-based system[5] in which only E configuration products were produced when aliphatic aldehydes were employed as electrophilic acceptors at 0°C.

The Z/E selectivity listed in Table 1 were measured by ^{1}H NMR analysis of crude products. In all cases, the terminal olefin proton signals for Z and E isomers were clearly distinguishable with the proton for the Z isomer upfield relative to the proton for the E isomer. Isomers could be readily separated by flash chromatography, and the geometry was determined by NOE experiments of ^{1}H NMR spectroscopy in which a 5% NOE was observed between the signals of vinyl proton and methyl protons of the E isomer of the product which is listed in Table 1, entry 1.

To explain the high Z/E stereoselectivity of this new system, a cyclic transition state model proposed by Kishi can be invoked.[5] 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 obtained at −78°C, while the high E-stereoselectivity was observed at 0°C. By using a cyclic transition state model, they suggested the 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 0°C. This is in contrast to a previously reported Et_2AlI-mediated reaction carried out at 0°C in which E isomers were predominantly obtained.[5]

The working hypothesis of this new process is represented in Scheme 3. The initial reaction step involves the formation of a coordination complex $[RCH{=}O\cdots MgI]^+I^-$, the I^- anion then goes to attack the 3-butyn-2-one to form an active MgI–allenolate. The formation of this intermediate is accelerated by the coordination of carbonyl oxygen to the Lewis acid magnesium center (C=O···Mg interaction). The second step proceeds through the nucleophilic attack of the allenolate intermediate to the aldehyde. The later C–C bond-forming step is also activated by the coordination of aldehyde oxygen onto the Lewis acid species.

In summary, an efficient synthetic method for (Z)-β-iodo Baylis–Hillman ketones has been developed. The new protocol utilizes MgI_2 as the iodine anion sources, and concurrently as a Lewis acid promoter under relatively mild conditions. This new reaction system provides extensive functionalization of vinyl ketones with high chemical yields and geometric selectivity. Further scope extension to other conjugate addition acceptors and electrophilic acceptors will be published in due course.

Acknowledgements

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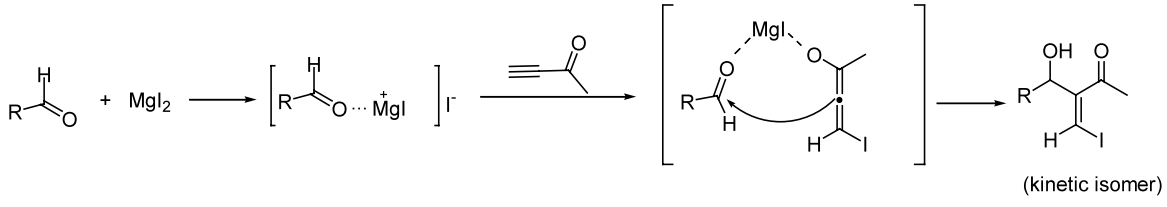

Scheme 3.

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11. Typical procedure: (Table 1). A dry standard glass test tube (150×22 mm) with a magnetic stirring bar was flushed with nitrogen at rt. Into the tube, magnesium iodide (340 mg, 1.2 mmol), benzaldehyde (0.1 mL, 1.0 mmol and freshly distilled dichloromethane (8.0 mL) was added. The mixture were stirred at rt for 20 min; the temperature was then lowered to 0°C before 3-butyn-2-one (0.12 mL, 1.3 mmol) were added drop-wise via a syringe. The mixture was stirred at 0°C for 1 h and the reaction was quenched by drop-wise addition of 10% aqueous $NaHCO_3$ (3 mL). The separated aqueous phase was extracted with ethyl acetate (3×15 mL) and the combined organic layers were then washed with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (hexane:EtOAc, 5/1, v/v) to provide the products. Table 1, entry 1, the *Z*-isomer (252.2 mg) and *E*-isomer (7.8 mg) were colorless oils (86% combined yield). **1*Z***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.71 (d, $J=1.6$ Hz, 1H), 5.45 (dd, $J=5.5$, 1.6 Hz, 1H), 6.69 (d, $J=1.6$ Hz, 1H), 7.26–7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.1, 77.2, 79.2, 126.5×2, 128.5, 128.8×2, 139.6, 154.5, 204.3. MS (CI, CH_4): m/z (%) 302 $[M]^+$; HRMS calcd for 302.1116; found: 302.1110. **1*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 3H), 4.35 (d, $J=11.0$ Hz, 1H), 5.79 (dd, $J=11.0$, 1.5 Hz, 1H), 7.32–7.39 (m, 5H), 8.11 (d, $J=1.5$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.4, 77.5, 103.1, 125.1×2, 127.4, 128.4×2, 141.2, 151.1, 196.9.
12. The physical date of new compounds: **3*Z***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.29 (s, 3H), 3.24 (d, $J=5.0$ Hz, 1H), 5.42 (d, $J=5.0$ Hz, 1H), 6.72 (d, $J=1.5$ Hz, 1H), 7.25–7.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30, 76, 80, 128×2, 129×2, 134, 138, 154, 204. **6*Z***: ^{1}H NMR (500 MHz, $CDCl_3$): δ1.72 (dd, $J_1=0.5$ Hz, $J_2=7.0$ Hz, 3H), 2.46 (s, 3H), 2.66 (d, $J=4.0$ Hz, 1H), 4.82 (s, 1H), 5.49 (m, 1H), 5.78 (m, 1H), 6.70 (d, $J=1.5$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18, 30, 75, 78, 130, 130.0, 154, 204. **8*Z***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (d, $J=7.0$ Hz, 3H), 1.00 (d, $J=7.0$ Hz, 3H), 2.33 (s, 3H), 2.78 (d, $J=5.0$ Hz, 1H), 3.14 (m, 1H), 5.43 (d, $J=5.0$ Hz, 1H), 6.64 (d, $J=1.5$ Hz, 1H), 7.15–7.22 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176, 18, 21, 39, 77, 80, 127×2, 129×2, 137, 138, 155, 210. **10*Z***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (t, $J=7.0$ Hz, 3H), 1.24–1.68 (m, 6H), 2.56 (d, $J=6.0$ Hz, 1H), 4.44 (m, 1H), 6.80 (d, $J=1.0$ Hz, 1H), 7.50 (m, 2H), 7.62 (m, 1H), 7.98 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14, 22, 28, 36, 76, 78, 129×2, 130×2, 134, 134, 154, 198.