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A novel approach to Morita–Baylis–Hillman (MBH) lactones via the Lewis acid-promoted couplings of α,β-unsaturated lactone with aldehydes

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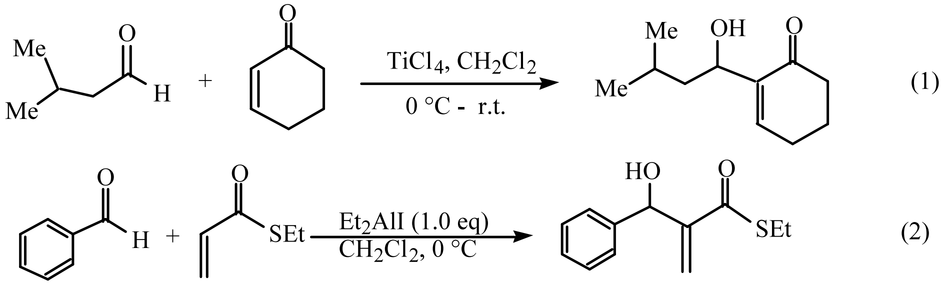
Abstract—The Morita–Baylis–Hillman (MBH)-type reaction of α,β unsaturated δ-lactone with various aldehydes has been achieved without the direct use of a Lewis base. The new MBH process can be conveniently carried out by the slow addition of the diethylaluminum iodide into the solution of lactone and aldehyde in dichloromethane at 0°C. Modest to good yields were obtained (50–65%) for eight examples. © 2003 Elsevier Science Ltd. All rights reserved.

The Morita–Baylis–Hillman (MBH) reaction and related processes have attracted widespread interest in the past few decades.[1] The resulting α-(hydroxyalkyl)acrylates and α-(aminoalkyl)acrylates from the MBH reaction can provide numerous chemically and biologically important precursors having an array of multifunctional groups. We and others have developed several methodologies for the synthesis of β-monosubstituted and β,β-disubstituted α-(hydroxyalkyl)acrylates and α-(aminoalkyl)acrylates which cannot be normally generated under classical MBH conditions.[2–5] Surprisingly, so far the synthesis of MBH lactones has not been well documented. This situation is mainly due to the fact that under normal conditions the MBH reaction does not occur with β-substituted olefinic substrates.[1c]

Recently, we discovered that MBH-type reaction can proceed in the presence of the Lewis acid, $TiCl_4$ without the direct use of any Lewis bases (Scheme 1).[6] The methods provided a concise synthesis of several MBH cyclic ketones. Unfortunately, this method is only limited to the use of aliphatic aldehydes or the aromatic aldehydes with strong electron withdrawing groups (e.g. -NO_2, -CF_3). The limitation also exists for α,β-unsaturated Michael acceptors in which when the reaction substrates were changed to α,β-unsaturated acyclic ketones, the reaction resulted in (*Z*)-2-(halomethyl)vinyl ketones.[7] The later reaction was also studied by using Lewis acid/Lewis base co-promoters under different conditions.[8] The similar method has been established for the synthesis of β-chlorinated MBH adducts using α,β-acetylenic ketones as the substrates.[9]

We have overcome the shortcomings of the narrow aldehyde scope by using diethylaluminum iodide to



Scheme 1.

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replace $TiCl_4$ as Lewis acid promoter and halogen source.[10,11] The MBH-type reaction of α,β-unsaturated cycloketones with a variety of aldehydes can be smoothly performed to give enhanced yields. Meanwhile, the new MBH-type system has also extended the scope to the use of α,β-ethyl thioacrylate as the Michael-type acceptor (Scheme 1). Encouraged by these findings, we revisited the MBH-type reaction of α,β-unsaturated lactones with aldehydes and found the reaction proceeded smoothly under the new conditions. The method provided the novel synthesis of MBH lactones which is represented by Scheme 2 with the results summarized in Table 1.

A multi-step method has been reported for the synthesis of α,β-unsaturated lactones-derived MBH adducts recently.[12] The method involved the use of lithium phenylselenide for tandem Michael addition followed by aldol reaction to give phenylseleno products. The final step of this synthesis is to perform alkylation on selenium center which makes the elemination occur effectively.

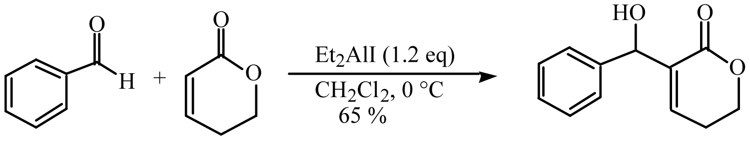
Our present process can be conveniently carried out by the slow addition of the dichloromethane solution of diethylaluminum iodide into a stirred solution of lactone and aldehyde in dichloromethane under the protection of nitrogen gas (Scheme 3). The slow addition was performed over a period of 1 h at 0°C before the reaction was warmed to room temperature. The reaction typically takes 8–24 h for completion. Interestingly, among these substrates, benzaldehyde showed the fastest rate which occurred to completion within 8 h. The reaction can also be finished at 0°C in 8 h to give a similar yield. Entries 1–6 can also be carried out at 0°C in prolonged periods (24 h) to give similar results. However, those aldehydes with electron-donating groups (entries 7 and 8) have to be performed at rt ever 24 h to give similar results as shown in Table 1. Interestingly, carrying out the reaction at low temperature (0°C) was proven to be crucial in our α,β-unsaturated cycloketone-based system where more unknown side products were observed, and the yields were much decreased when the MBH reaction was carried out at room temperature.

Table 1 shows the great substrate scope of aromatic aldehydes which were used for convenient monitoring. Our latest preliminary results revealed that nonaromatic adehydes can also be utilized. However, the yields are not as good as those from their aromatic counterparts. For all cases we studied, THF can also be used as the solvent to give comparable results. Similar to the situation of the α,β-unsaturated cycloketone cases, a catalytic amount of Et_2AlI for the reaction have not been found promising. In fact, a slightly excess amount of Et_2AlI (1.2 equiv) was necessary to achieve the complete conversion.

The mechanism of this reaction is suggested to be similar to that of α,β-unsaturated cycloketone-based system,[11] where intermolecular multiple-component addition serves as the first step. This step is assisted by the coordination of Et_2AlI with aldehyde to further free the halide anion for the Michael-type addition. The intramolecular pathway is ruled out by the rigid characteristic of α,β-unsaturated lactone. In contrast, in α,β-unsaturated thioester-based process an intramolecular pathway at this step could occur due to the flexible structure of the α,β-unsaturated thioester. The later intramolecular pathway is similar to that of the haloaldol reaction promoted by $TiCl_4$–$n$$Et_4NI$ as proposed by Oshima.[13]

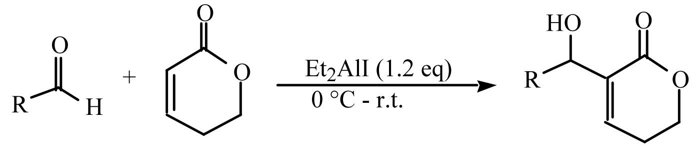
As anticipated, the success of this reaction is attributed to the irreversible deprotonation during the reaction process (step C of Scheme 3). Releasing CH_3CH_3 provides a powerful driving force and makes the reaction irreversible. Since the α,β-unsaturated cycloketone failed to give any product under our previous $TiCl_4$-based conditions. This hypothesis can account for the observation that α,β-unsaturated lactone failed to give any MBH adducts when $TiCl_4$ was employed as the promoter and halide source. This mechanism can also account for the observation that a substoiciometric amount of diethylaluminum iodide failed to promote the reaction to completion. Other two factors that could benefit the reaction include the stability of the resulting cyclic α,β-conjugate Baylis–Hillman structures and the greater reactivity of halogeno-aluminum enolates than their titanium counterparts.

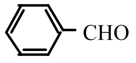
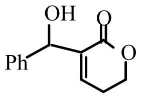
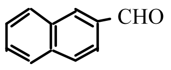
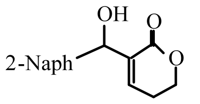
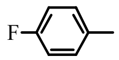
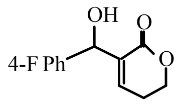
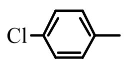
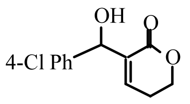
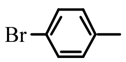
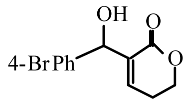
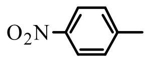
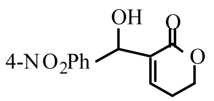
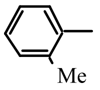
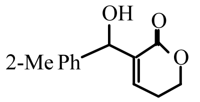
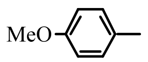
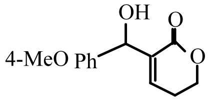
In summary, the MBH reaction of α,β-unsaturated δ-lactone with various aldehydes has been achieved. The reaction has a great scope of aldehydes and provides an effective and concise approach to a variety of MBH lactones. The resulting MBH adducts are very useful for the synthesis of biologically important compounds.

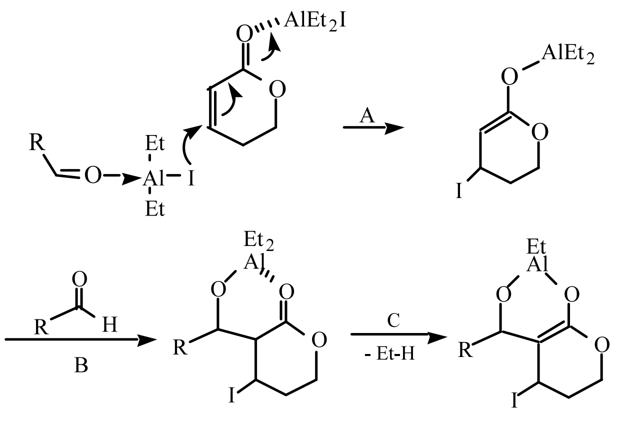


Scheme 2.

Table 1. Results of Et_2AlI-promoted MBH-type reaction[14]



entry	RCHO	product	time (h)	yield (%)
1		 **1**	8	65
2		 **2**	14	66
3		 **3**	14	73
4		 **4**	14	65
5		 **5**	14	72
6		 **6**	24	60
7		 **7**	24	65
8		 **8**	24	50



Scheme 3.

Acknowledgements

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References

1. For reviews regarding the MBH reaction, see: (a) Ciganek, E. *Org. React.* **1997**, *51*, 201; (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. For a review regarding the synthesis of β-branched MBH

adducts, see: (c) Li, G.; Hook, J.; Wei, H.-X. *Recent Res. Develop. Org. Bioorg. Chem.* **2001**, *4*, 49.

2. (a) Trost, B. M.; Oliver, R. T.; Tsui, H. C. *J. Am. Chem. Soc.* **2002**, *122*, 3534; (b) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317; (c) Barrett, A. G. C.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533; (d) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219; (e) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 1539.
3. (a) Li, G.; Wei, H.-X.; Phelps, B. S.; Purkiss, D. W.; Kim, S. H. *Org. Lett.* **2001**, *3*, 823; (b) Li, G.; Wei, H.-X.; Whittlesey, B. R.; Batrice, N. N. *J. Org. Chem.* **1999**, *64*, 1061; (c) Aggarwal, V. K.; Castro, A. M. M.; Mereu, A.; Adams, H. *Tetrahedron Lett.* **2002**, *43*, 1577.
4. (a) Luo, S.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G.; Chen, J.-P. *Tetrahedron Lett.* **2002**, *43*, 7369; (b) Gatri, R.; El Gaied, M. M. *Tetrahedron Lett.* **2002**, *43*, 7835; (c) Shi, M.; Li, C. Q.; Jiang, J. K. *Chem. Commun.* **2001**, 833; (d) Ramachandran, P. V.; Reddy, M. V. R.; Rudd, M. T. *Chem. Commun.* **2001**, 757; (e) Alcaid, B.; Almendros, P.; Aragoncillo, C. *J. Org. Chem.* **2001**, 1612.
5. (a) Kataoka, T.; Iwama, T.; Iwamura, T.; Kinoshita, S.; Tsujiyama, Y.; Iwamura, S.; Watanabe, S. *Synlett* **1999**, *2*, 197; (b) Kataoka, T.; Kinoshita, S.; Kinoshita, H.; Fujita, M.; Iwamura, T.; Watanabe, S. *Chem. Commun.* **2001**, 1958.
6. (a) Li, G.; Wei, H.-X.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1; (b) Basavaiah, D.; Screenivasulu, B.; Rao, J. S. *Tetrahedron Lett.* **2001**, *42*, 1147.
7. Li, G.; Gao, J.; Wei, H.-X.; Enright, M. *Org. Lett.* **2000**, *2*, 617.
8. (a) Uehira, S.; Han, Z.; Shinokubo, H.; Oshima, K. *Org. Lett.* **1999**, *1*, 1383; (b) Shi, M.; Jiang, J. K.; Cui, S. C.; Feng, Y. S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 390.
9. (a) Wei, H. X.; Caputo, T. D.; Purkiss, D. W.; Li, G. *Tetrahedron* **2000**, *56*, 2397; (b) Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T.; Watanabe, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2358; (c) Wei, H.-X.; Gao, J.; Li, G. *Tetrahedron Lett.* **2001**, *42*, 9119; (d) Wei, H.-X.; Gao, J.; Johnson, J.; Li, G. *Synth. Commun.* **2002**, *32*, 1765.
10. (a) Pei, W.; Wei, H.-X.; Li, G. *Chem. Commun.* **2002**, 1856; (b) Pei, W.; Wei, H.-X.; Li, G. *Chem. Commun.* **2002**, 2412.
11. For the pioneering work on the application of Et_2AlI for C(sp^3)–C(sp^2) bond formations, see: (a) Taniguchi, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *27*, 4759; (b) Itoh, A.; Pzawa, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 274. This pioneering system only worked for non-aromatic aldehydes and 2-cyclohexenone substrates. Under modified conditions (see Ref. 10b), aromatic aldehydes were proven to be effective for several α,β-unsaturated cycloketones for this synthesis.
12. (a) Jauch, J. *Synlett* **1999**, 1325; (b) Jauch, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2764; (c) Jauch, J. *J. Org. Chem.* **2001**, *66*, 609.
13. (a) Yagi, K.; Turitani, T.; Shinokubo, H.; Han, Z.; Uehira, S.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 3111; (b) Han, Z.; Uehira, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 7854.

14. Typical procedure represented by entry 1 of Table 1: Into a dry vial was loaded dichloromethane (4.0 ml), benzaldehyde (0.10 ml, 1.0 mmol) and the lactone (0.10 ml, 1.1 mmol). The resulting mixture was protected by nitrogen gas and cooled down to 0°C. A solution of diethylaluminum iodide (25 wt% in toluene, 1.0 ml, 1.20 mmol) was then added via a syringe pump over 1 h. The resulting yellow mixture was then raised to room temperature gradually. The reaction was finished within 8 h as monitored by TLC. The reaction was finally quenched by saturated aqueous $NaHCO_3$ (2.0 ml). The dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane (3×8.0 ml). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. Purification was carried out by column chromatography (ethyl acetate/hexane = 2:3, v/v) to give **1** (0.133 g, 65%) as a colorless oil.

    Compound **1**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.39 (m, 4H), 7.27–7.31 (m, 1H), 6.68 (t, $J=4.5$ MHz, 1H), 5.59 (d, $J=4$ MHz, 1H), 4.36 (m, 2H), 3.47 (d, $J=5$ MHz, 1H), 2.47 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 140.8, 140.6, 134.8, 128.4, 127.8, 126.5, 72.2, 66.2. HRMS (MALDI-FTMS) m/z (MNa^+) found 227.0677, calcd for $C_{12}H_{12}NaO_3$ 227.0679.

    Compound **2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–7.89 (m , 2H), 7.83 (d, $J=8$ MHz, 1H), 7.75 (td, $J=7$ MHz, 1H), 7.51–7.54 (m, 1H), 7.47–7.49 (m, 2H), 6.41 (d, $J=3.5$ MHz, 1H), 6.32–6.34 (m, 1H), 4.36–4.41 (m, 2H), 3.53 (d, $J=4$ MHz, 1H), 2.39 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 142.2, 135.4, 134.5, 133.6, 130.4, 128.8, 128.5, 126.2, 125.6, 125.4, 124.6, 123.6, 68.5, 66.2.

    Compound **3**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.37 (m, 2H), 7.01–7.06 (m, 2H), 6.68–6.70 (m, 1H), 5.56 (d, $J=4.5$ MHz, 1H), 4.32–4.40 (m, 2H), 3.50 (d, $J=5$ MHz, 1H), 2.47–2.50 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 163.2, 161.3, 140.7, 136.48, 136.46, 134.7, 128.3, 128.2, 115.3, 115.1, 71.5, 66.2.

    Compound **4**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 4H), 6.68–6.70 (m, 1H), 5.55 (d, $J=4.5$ MHz, 1H), 4.33–4.41 (m, 2H), 3.49 (d, $J=4.5$ MHz, 1H), 2.47–2.51 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 141.2, 139.4, 134.8, 133.9, 128.8, 128.2, 71.9, 66.5.

    Compound **5**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.48 (m, 2H), 7.24–7.27 (m, 2H), 6.69–6.71 (m, 1H), 5.29 (d, $J=2$ MHz, 1H), 4.31–4.39 (m, 2H), 3.58 (d, $J=5$ MHz, 1H), 2.46–2.50 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 140.9, 139.8, 134.4, 131.4, 128.2, 121.6, 71.5, 66.2.

    Compound **6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21–8.23 (m, 2H), 7.58–7.60 (m, 2H), 6.75–6.76 (m, 1H), 5.66 (d, $J=5.5$ MHz, 1H), 4.38–4.41 (m, 2H), 3.55 (d, $J=6$ MHz, 1H), 2.52–2.55 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 148.0, 147.5, 141.6, 134.0, 127.3, 123.6, 71.7, 66.3.

    Compound **7**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.50 (m, 1H), 7.20–7.26 (m, 2H), 7.14–7.16 (m, 1H), 6.41–6.43 (m, 1H), 5.82 (s, 1H), 4.34–4.41 (m, 2H), 3.36 (d, $J=3.5$ MHz, 1H), 2.42–2.46 (m, 2H), 2.27 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 138.0, 135.2, 134.2, 130.8, 128.7, 127.7, 126.3, 126.2, 68.2, 66.2, 38.6.

    Compound **8**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.29 (m, 2H), 6.88–6.90 (m, 2H), 6.67–6.69 (m, 1H), 5.55 (s, 1H), 4.33–4.41 (m, 2H), 3.80 (s, 3H), 3.31 (s, 1H), 2.46–2.50 (m, 2H).