Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 971–974

TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of chiral β-iodo Baylis–Hillman esters using MgI_2 as promoter via a one-pot three-component reaction

Han-Xun Wei, Dianjun Chen, Xin Xu, Guigen Li and Paul W. Paré*

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA

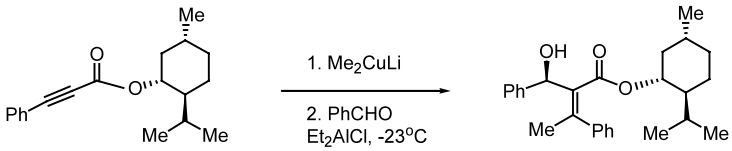
Received 8 January 2003; accepted 17 January 2003

Abstract—An asymmetric synthesis of β-iodo-α-(hydroxyalkyl)acrylates has been developed involving conjugate addition of I^- to menthyl propiolates to give β-iodo allenolate intermediates which undergo 1,2-addition to form β-iodo Baylis–Hillman products. Modest diastereoselectivities (37–58% de) and excellent yields (80–87%) were obtained when (1*R*,2*S*,5*R*)-(−)-menthol was used as a chiral auxiliary. The two diastereoisomers of the product were separated by silica gel chromatography to give diastereomerically pure products.

The stereoselective synthesis of multifunctionalized alkenes is an important goal in organic chemistry.[1–4] Among this class of compounds, Baylis–Hillman adducts are particularly useful as precursors for chemically and biologically important compounds. Although the asymmetric synthesis of terminal non-substituted Baylis–Hillman adducts is well documented, relatively little research has been devoted to the asymmetric synthesis of β-substituted Baylis–Hillman adducts. In 1998, we developed an approach to chiral β-alkyl Baylis–Hillman hydroxy esters via the conjugate addition of R_2CuLi onto β-substituted α,β-acetylenic esters followed by carbonyl coupling with aldehydes.[5] The reaction was promoted by Et_2AlCl (Scheme 1). Since this report, we have achieved the first asymmetric synthesis of β,β-dialkyl Baylis–Hillman amino esters by using chiral *p*-toluenesulfinimines (thiooxime *S*-oxides) as auxiliaries.[6] Subsequently, the first asymmetric catalytic aldol reaction of allenolates with aldehydes for the synthesis of β-iodo Baylis–Hillman hydroxy ketones was reported using *N*-fluoroacetyl oxazaborolidine as the catalyst.[7] Most recently, an asymmetric approach to chiral β-iodo Baylis–Hillman hydroxy esters was developed via a tandem asymmetric I–C/C–C formation reaction, which was carried out by slow addition of diethylaluminium iodide into a mixture of the aldehyde and an α,β-acetylenic menthyl ester in dichloromethane.[8] Moderate to high yields (42–91%) with modest diastereoselectivity were obtained. However, the reaction did not work well with aliphatic aldehydes, generating only low yields of the product (below 60%).

In our continuing development of new Baylis–Hillman-type processes, we were pleased to find that MgI_2 is an excellent Lewis acid for the synthesis of (*Z*)-β-iodo Baylis–Hillman hydroxy ketones and esters.[9] Consequently, we were interested in testing whether this new system would be suitable for the synthesis of chiral β-iodo Baylis–Hillman hydroxy esters and perhaps circumvent some of the limitations of the Et_2AlI-based system. The present communication describes results that have led to a novel and simple method for the asymmetric synthesis of chiral β-iodo Baylis–Hillman hydroxy esters. Indeed the new method presented herein affords higher product chemical yields than the Et_2AlI-based systems (particularly for aliphatic aldehydes).[8] The new procedure is represented in Scheme 2 with results summarized in Table 1.

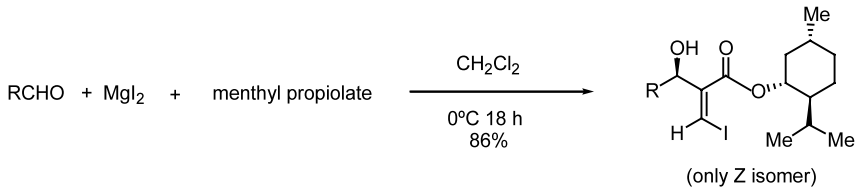
The initial reaction was carried out by stirring menthyl propiolate (1.2 equiv.) with benzaldehyde (1.0 equiv.) in



Scheme 1.

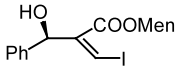
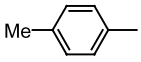
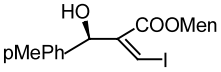
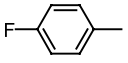
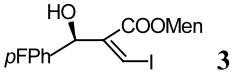
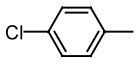
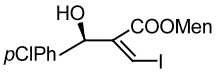
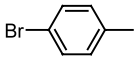
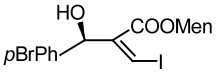
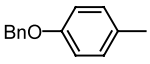
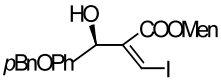
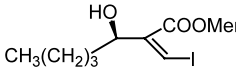
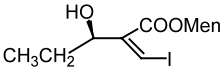
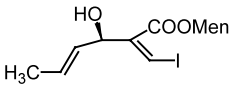
* Corresponding author. Tel.: +1-806-742-3062; fax: +1-806-742-1289; e-mail: paul.pare@ttu.edu

0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00115-0



Scheme 2.

Table 1. Results of chiral β-iodo Baylis–Hillman hydroxy esters[11,12]

Entry	R-	Product[a]	% de[b]	Yield (%)[c]
1		 **1**	44	86
2		 **2**	40	85
3		 **3**	46	87
4		 **4**	44	86
5		 **5**	47	86
6		 **6**	58	80
7	$CH_3(CH_2)_3CHO$	 **7**	40	82
8	CH_3CH_2CHO	 **8**	38	83
9	H_3C  CHO	 **9**	37	85

[a] The absolute structure was determined by the transformations described in reference 5; Men = (1*R*,2*S*,5*R*)-(-)-menthyl
[b] All de values were determined by HPLC using a chiral OD column (eluent: hexane/isopropanol = 100/2.5).
[C] Yields after chromatography.

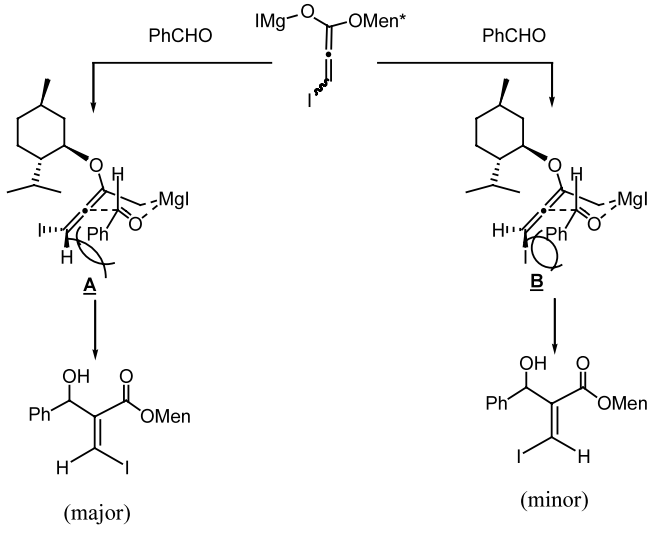
the presence of MgI_2 (1.2 equiv.) dissolved in CH_2Cl_2 at −78°C. Even after an extended reaction time of 24 h, formation of the expected product was not observed. However, the reaction did proceed smoothly when the reaction temperature was raised to 0°C and went to completion within 18 h. The desired chiral β-iodo Baylis–Hillman hydroxy ester product was generated in 86% yield with excellent *Z*/*E* selectivity. Unlike a previously reported MgI_2-based system, in which benzaldehyde and MgI_2 are mixed in CH_2Cl_2 at room temperature for 20 min prior to adding 3-butyn-2-one and methyl propynoate to obtain high yields,[9] or the Et_2AlI-based system, which requires that Et_2AlI be added slowly over 6 h into a mixture of the aldehyde and the α,β-acetylenic menthyl ester in CH_2Cl_2 to obtain reasonable diastereoselectivity;[8] this new synthesis can be conducted conveniently by mixing the three components, MgI_2, aldehyde and menthyl propiolate, together in dichloromethane followed by stirring at 0°C for 18 h to afford the diastereomerically enriched β-iodo Baylis–Hillman hydroxy esters. High yields were obtained for the nine examples tested.

Although the diastereoselectivity was only modest at this stage, we predict that the selectivity can be improved by changing to more effective chiral auxiliaries.

Dichloromethane provided the highest efficiency of 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 lower yields of 40%, 50% and 45% respectively, within a reaction period of 18 h. However, all of the above solvents give high Z/E selectivity (>99%). Attempts to run the reaction in THF resulted in extremely low levels of the desired products.

The reactions afforded the Z configured alkene as the predominant product as revealed by ^{1}H NMR analysis of the crude product. The absolute configuration was confirmed by comparison of the ^{1}H NMR spectrum of **1** with that of a similar adduct derived from the α,β-acetylenic methyl ester for which ^{1}H NMR ROSEY experimental results were generated.[10] The resulting Z geometry indicates that the aldol reaction is kinetically controlled at 0°C under the new condition. Of the two possible chair-like transition states (**A** and **B**), **A** is favoured due to the smaller steric interaction between the hydrogen of the allenoate and the phenyl group of the aldehyde compared with the similar but more marked interaction in transition state **B** (Scheme 3). The chirality of the product was determined by transforming product **1** to methyl (*R*)-α-methoxyphenylacetate, which was derived from (*R*)-menthyl mandelate.[5] The transformation started with the reduction of **1** with $LiALH_4$ in THF and was followed by ruthenium-catalyzed oxidation using periodic acid. The resulting mandelic acid was then subjected to carboxyl group protection. The major isomer was determined to be identical to methyl (*R*)-α-methoxyphenylacetate by HPLC analysis.

The stereoselectivity of the process can be explained using the transition state model shown in Scheme 3.



Scheme 3.

The aldehyde approaches the β-iodo allenoate intermediate from the less hindered side of the C-2 position of the menthyl auxiliary. It is believed that the modest diastereoselectivity is a result of the rotational flexibility of Men*–O–C bonds of the allenoate intermediate.

Both aromatic and aliphatic aldehydes were found to be suitable electrophilic acceptors in the new reaction system and high yields were realized in all of the cases examined. As shown in Table 1, for aromatic aldehydes, the introduction of an electron-withdrawing group (entries 3–5) or an electron-donating group (entries 2 and 4) on the aromatic ring resulted in no obvious effect on the reaction efficiencies (yields and diastereoselectivity). With regard to aliphatic aldehydes (entries 7–9), this MgI_2-promoted reaction resulted in higher yields when aliphatic aldehydes were employed as electrophilic acceptors compared to the previously reported Et_2AlI-based system.[8]

In summary, an efficient and simple route to chiral β-iodo-α-(hydroxyalkyl)acrylates has been developed. The new protocol utilizes MgI_2 both as the iodide source and as a Lewis acid promoter and occurs under relatively mild conditions. High yields and modest diastereoselectivities have been obtained. Subsequent efforts will focus on improving the diastereoselectivity of the reaction.

Acknowledgements

We gratefully acknowledge the Robert A. Welch Foundation (D-478 and D-1361) for the generous support of this research. Funding was also provided by the Texas Excellence Fund.

References

1. Lee, V. J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp. 139–168.
2. (a) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 1988; (b) Trost, B. M.; Pinkerton, A. B. *Angew. Chem., Int. Ed.* **2000**, *39*, 360.
3. Wori, M.; Kuroda, S.; Dekura, F. *J. Am. Chem. Soc.* **1999**, *121*, 5591.
4. Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821.
5. Wei, H.-X.; Willis, S.; Li, G. *Tetrahedron Lett.* **1998**, *39*, 8203.
6. Li, G.; Wei, H.-X.; Whittlesey, B.; Batrice, N. N. *J. Org. Chem.* **1999**, *64*, 1061.
7. Li, G.; Wei, H.-X.; Phelps, B. S.; Purkiss, D. W.; Kim, S. H. *Org. Lett.* **2001**, *3*, 823.
8. Xu, X.; Chen, D.; Wei, H.-X.; Li, G. *Chirality* **2003**, *15*, 139.
9. (a) Wei, H.-X.; Hu, J. L.; Purkiss, D. W.; Paré, P. W. *Tetrahedron Lett.* **2003**, *44*, 949; (b) Wei, H.-X.; Hu, J. L.; Jasoni, R. L.; Paré, P. W. *Synlett* **2003**, submitted.
10. Wei, H.-X.; Gao, J. J.; Li, G.; Paré, P. W. *Tetrahedron Lett.* **2002**, *43*, 5677.

11. **Typical procedure** (Table 1, entry 1): A dry standard glass test tube (150×22 mm) with a magnetic stirring bar was flushed with nitrogen at room temperature. Into the tube, magnesium iodide (341.0 mg, 1.2 mmol), benzaldehyde (0.1 mL, 1.0 mmol), menthyl propiolate (1.3 equiv.) and freshly distilled dichloromethane (8.0 mL) was added. The suspension was stirred at 0°C for 18 h at which time a dark brown homogenous solution was seen to have formed. The reaction was quenched by dropwise addition of 10% aqueous $NaHCO_3$ (3 ml). The aqueous phase was separated and extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Flash chromatography purification (CH_2Cl_2/hexane = 3:1) resulted in pure isomers as colorless oils (86% combined yield).

    Data for (*R*)-**1**: MS (CI, CH_4): *m*/*z* 442.3 (M^+); HRMS calcd for $C_{20}H_{27}IO_3$ 442.3370; Found: 442.3378. ^1H NMR (500 MHz, $CDCl_3$): δ 7.28–7.37 (m, 5H), 7.24 (d, J = 1.5 Hz, 1H), 5.51 (dd, J = 1.5, 7.0 Hz, 1H), 4.73 (dt, J = 4.5, 11 Hz, 1H), 3.04 (d, J = 6.0 Hz, 1H), 1.86–1.91 (m, 1H), 1.58–1.67 (m, 2H), 1.24–1.50 (m, 4H), 0.80–1.02 (m, 2H), 0.86 (d, J = 7.0 Hz, 3H), 0.75 (d, J = 7.0 Hz, 3H), 0.57 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 145.1, 140.2, 128.6, 128.1, 126.4, 86.1, 76.0, 46.8, 40.6, 34.0, 31.4, 25.5, 22.9, 21.9, 20.8, 15.7.

    Data for (*S*)-**1**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.28–7.37 (m, 5H), 7.24 (d, J = 1.5 Hz, 1H), 5.51 (dd, J = 1.5, 7.0 Hz, 1H), 4.73 (dt, J = 4.5, 11 Hz, 1H), 2.75 (d, J = 6.0 Hz, 1H), 1.58–1.67 (m, 2H), 1.24–1.50 (m, 4H), 0.80–1.02 (m, 2H), 0.86 (d, J = 7.0 Hz, 3H), 0.75 (d, J = 7.0 Hz, 3H), 0.57 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 145.5, 140.1, 128.6, 128.3, 126.7, 84.8, 76.5, 76.0, 46.8, 40.6, 34.1, 31.4, 25.6, 23.0, 21.9, 20.8, 15.8.

12. **Spectroscopic data for purified isomers**:

    Data for (*R*)-**3**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.28–7.33 (m, 2H), 7.24–7.26 (m, 1H), 7.00–7.05 (m, 2H), 5.46 (d, J = 6.5 Hz, 1H), 4.75 (dt, J = 4.5, 11 Hz, 1H), 3.19 (d, J = 6.5 Hz, 1H), 1.88–1.95 (m, 1H), 1.59–1.68 (m, 2H), 1.24–1.48 (m, 3H), 0.92–1.02 (m, 2H), 0.88 (d, J = 6.5 Hz, 3H), 0.80–0.90 (m, 1H), 0.75 (d, J = 7.0 Hz, 3H), 0.55 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 163.5, 161.5, 145.0, 136.0, 135.9, 128.2, 128.1, 115.5, 115.3, 86.0, 76.1, 46.8, 40.7, 34.0, 31.4, 25.6, 22.9, 21.9, 20.7, 15.7.

    Data for (*S*)-**3**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.29–7.34 (m, 2H), 7.24–7.26 (m, 1H), 7.00–7.06 (m, 2H), 5.50 (d, J = 5.5 Hz, 1H), 4.74 (dt, J = 4.5, 11 Hz, 1H), 2.70 (d, J = 5.5 Hz, 1H), 1.86–1.92 (m, 1H), 1.60–1.68 (m, 2H), 1.24–1.48 (m, 3H), 0.92–1.02 (m, 2H), 0.88 (d, J = 6.5 Hz, 3H), 0.80–0.90 (m, 1H), 0.76 (d, J = 7.0 Hz, 3H), 0.58 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5, 163.6, 161.7, 145.3, 136.0, 135.9, 128.6, 128.5, 115.6, 115.4, 84.8, 76.1, 75.8, 46.8, 40.6, 34.0, 31.4, 25.7, 22.9, 21.9, 20.7, 15.8.

    Data for (*R*)-**5**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.45–7.49 (m, 2H), 7.26–7.28 (m, 1H), 7.20–7.24 (m, 2H), 5.43 (d, J = 7.0 Hz, 1H), 4.75 (dt, J = 4.5, 11 Hz, 1H), 3.22 (d, J = 7.0 Hz, 1H), 1.88–1.95 (m, 1H), 1.60–1.68 (m, 2H), 1.24–1.48 (m, 3H), 0.92–1.04 (m, 2H), 0.89 (d, J = 6.5 Hz, 3H), 0.80–0.90 (m, 1H), 0.76 (d, J = 7.0 Hz, 3H), 0.54 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 144.6, 139.3, 131.7, 128.0, 122.1, 86.5, 76.4, 76.3, 46.8, 40.7, 34.0, 31.4, 25.6, 22.9, 21.9, 20.7, 15.7.

    Data for (*S*)-**5**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.46–7.50 (m, 2H), 7.26–7.28 (m, 1H), 7.20–7.24 (m, 2H), 5.47 (d, J = 6.0 Hz, 1H), 4.74 (dt, J = 4.5, 11 Hz, 1H), 2.78 (d, J = 6.0 Hz, 1H), 1.86–1.92 (m, 1H), 1.60–1.68 (m, 2H), 1.24–1.46 (m, 3H), 0.92–1.04 (m, 2H), 0.88 (d, J = 6.5 Hz, 3H), 0.80–0.90 (m, 1H), 0.77 (d, J = 7.0 Hz, 3H), 0.58 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5, 145.0, 139.2, 131.7, 128.3, 122.3, 86.4, 76.2, 76.0, 46.8, 40.6, 34.0, 31.4, 25.7, 22.9, 21.9, 20.7, 15.8.

    Data for (*R*)-**7**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.01–7.02 (m, 1H), 4.89 (dt, J = 4.5, 11 Hz, 1H), 4.33 (m, 1H), 2.51 (J = 7.5 Hz, 1H), 2.09–2.15 (m, 1H), 1.95–2.03 (m, 1H), 1.68–1.75 (m, 2H), 1.57–1.64 (m, 2H), 1.46–1.56 (m, 2H), 1.24–1.44 (m, 4H), 1.02–1.18 (m, 2H), 0.86–0.96 (m, 10H), 0.79 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 147.0, 83.5, 76.1, 75.7, 46.9, 40.8, 35.9, 34.1, 31.5, 27.8, 26.0, 23.0, 22.4, 22.0, 20.8, 15.9, 13.9.

    Data for (*S*)-**7**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.00–7.01 (m, 1H), 4.89 (dt, J = 4.0, 11 Hz, 1H), 4.39 (m, 1H), 2.25 (J = 6.0 Hz, 1H), 2.09–2.15 (m, 1H), 1.95–2.03 (m, 1H), 1.68–1.75 (m, 2H), 1.57–1.64 (m, 2H), 1.46–1.56 (m, 2H), 1.24–1.44 (m, 4H), 1.02–1.18 (m, 2H), 0.86–0.96 (m, 10H), 0.78 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 147.4, 82.7, 76.0, 75.1, 46.9, 40.8, 35.8, 34.1, 31.5, 27.5, 26.0, 23.0, 22.4, 22.0, 20.8, 16.0, 13.9.

    Data for (*R*)-**8**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.01–7.02 (m, 1H), 4.88 (dt, J = 4.5, 11 Hz, 1H), 4.27 (m, 1H), 2.51 (J = 7.0 Hz, 1H), 2.09–2.15 (m, 1H), 1.96–2.03 (m, 1H), 1.68–1.74 (m, 2H), 1.60–1.68 (m, 2H), 1.46–1.56 (m, 2H), 1.03–1.18 (m, 2H), 0.88–0.97 (m, 10H), 0.79 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 146.9, 83.5, 76.9, 76.2, 46.9, 40.8, 34.1, 31.5, 29.0, 26.0, 23.0, 22.0, 20.8, 15.9, 9.9.

    Data for (*S*)-**8**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.00–7.01 (m, 1H), 4.88 (dt, J = 4.0, 11 Hz, 1H), 4.33 (m, 1H), 2.27 (J = 6.0 Hz, 1H), 2.09–2.15 (m, 1H), 1.96–2.05 (m, 1H), 1.67–1.74 (m, 2H), 1.58–1.67 (m, 2H), 1.46–1.56 (m, 2H), 1.03–1.18 (m, 2H), 0.86–0.97 (m, 10H), 0.79 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 147.0, 82.8, 76.4, 76.0, 46.9, 40.8, 34.1, 31.4, 29.0, 26.0, 23.1, 22.0, 20.8, 16.0, 9.7.