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Diastereoselective Baylis–Hillman reaction: first use of chiral 2,3-epoxy aldehydes as novel electrophiles☆

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Abstract—Chiral 2,3-epoxy aldehydes have been effectively utilized for the first time as novel electrophiles in Baylis–Hillman reactions with activated alkenes to result in densely functionalized adducts in good yields (61–80%) and in moderate to good diastereoselectivities (40–72% de).

The Baylis–Hillman reaction is an important C–C bond forming reaction, which gives multifunctional products with complete atom economy.[1] The introduction of novel electrophiles is important for the extension of the scope of the Baylis–Hillman reaction. Zwanenburg and co-workers[2] have reported the Baylis–Hillman coupling of *N*-trityl aziridine-2-(*S*)-carboxaldehydes with activated alkenes to result in adducts, albeit with poor diastereoselectivity. Chiral 2,3-epoxy alcohols are versatile intermediates used in the enantio- and stereoselective total syntheses of natural products with polyfunctional groups.[3] However, to the best of our knowledge, epoxy aldehydes have not been utilized as electrophiles in Baylis–Hillman reactions. Since chiral epoxides are important synthetic intermediates that can be easily generated with predictable stereochemistry from allyl alcohols by Sharpless asymmetric epoxidation[4] and based on our interest in asymmetric Baylis–Hillman reactions,[5] herein we introduce chiral 2,3-epoxy aldehydes (Eq. 1) for the first time as electrophiles in Baylis–Hillman reactions with alkenes to give densely functionalized adducts in good yields (61–80%) and in moderate to good diastereoselectivities (40–72% de).

(1)

The epoxy aldehydes used in the present study were prepared by adopting a general synthetic strategy (Scheme 1).[6] Subsequently, the first Baylis–Hillman coupling of an epoxy aldehyde **1** was tried with ethyl acrylate (**a**) in THF, dioxane–H_2O[7] (1:1) and DMF catalyzed by DABCO (0.5 equiv) at room temperature. Amongst all the solvents tried, DMF proved to be the appropriate solvent with a faster reaction rate.

Thus the *trans* epoxy aldehydes (**1**–**4**, Scheme 2) on Baylis–Hillman reaction with alkenes **a** and **b** under the standardized reaction conditions (DABCO, DMF, rt) afforded the *anti*-isomers as major products (**1a**, **2b**, **3a**,**b** and **4a**,**b**) while *cis* epoxy aldehydes (**5**–**7**, Scheme 2) afforded the *syn*-isomers as major products (**5a**,**b**, **6a**,**b** and **7a,b**). The observed selectivity could be explained by the Cornforth model[8] wherein nucleophilic attack occurs from the least hindered side (Fig. 1). For instance, in the case of *cis* epoxy aldehydes, the *Re* face is more available for nucleophilic attack leading to *syn*-adducts as major isomers, while for *trans* epoxy aldehydes the *Si* face is more open for nucleophilic attack ensuring *anti*-adducts as major products. Incidentally, the de of adducts originating from *cis* epoxy aldehydes was more than that of the adducts from *trans* epoxy aldehydes primarily due to the steric crowding of substituents on either side of the epoxide ring.

The *syn*:*anti* ratio of the adducts was determined by ^{1}H NMR and HPLC (Chiral OD column) analysis. The ^{1}H NMR spectra of similar products revealed the allylic protons for the *syn*-isomers resonating upfield compared with their *anti* counterparts.[9] For instance, the major isomer in **4a** was assigned as *anti* because of the

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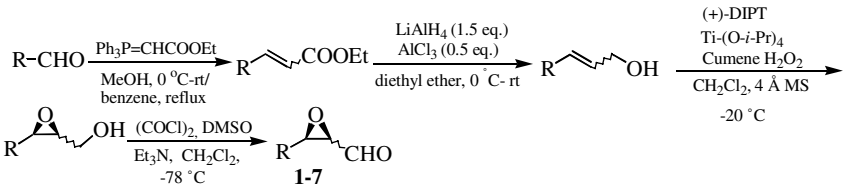
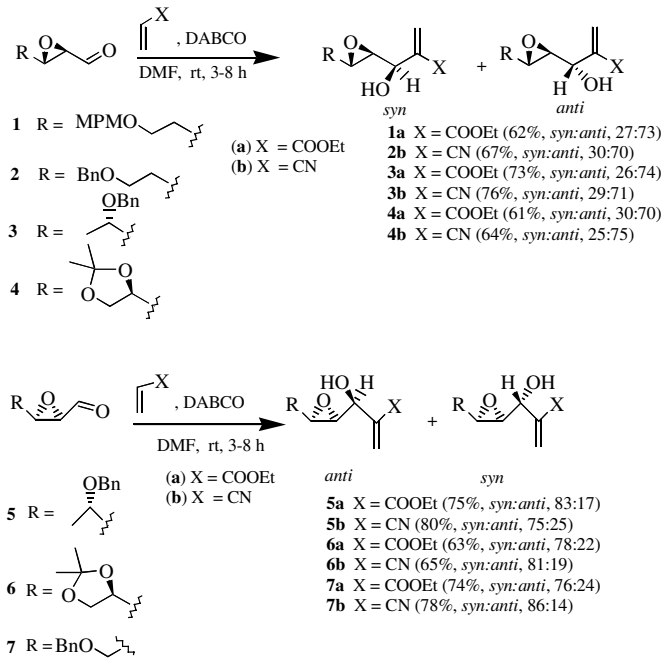


Scheme 1.



Scheme 2. Baylis–Hillman reaction of *trans* epoxy aldehydes **1**–**4** and *cis* epoxy aldehydes **5**–**7**.

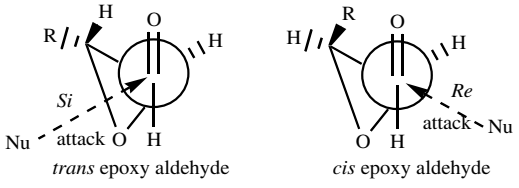
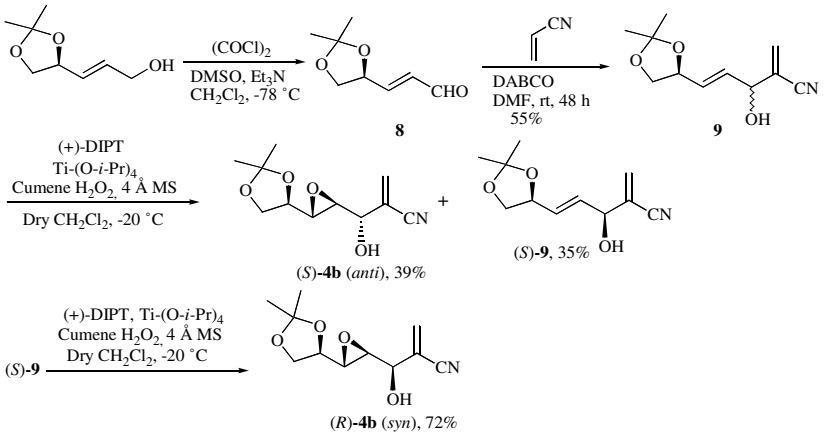


Figure 1. Cornforth Model.

downfield resonance of the allylic proton at δ 4.58 while the same proton resonated at δ 4.39 for the minor isomer. Also, **4a** had the olefinic protons resonating at δ 6.36 and 6.01 for the major isomer, while the same protons resonated at δ 6.32 and 5.94 for the minor isomer with a 7:3 integral ratio. Likewise, the ^{1}H NMR spectrum of **4b** demonstrated one of the olefinic protons resonating at δ 6.24 for the major isomer and at δ 6.09 for the minor isomer with an integral ratio of 7.5:2.5. The allylic proton resonated at δ 4.50–4.43 as a multiplet for the major isomer, integrating for 0.75H, while the signal of the corresponding proton merged with the $-OCH_2$ signal for the minor isomer.[10] Similarly, in the ^{1}H NMR spectrum of **5a** the olefinic protons resonated at δ 6.30 and δ 5.91 for the minor isomer, while the comparable protons appeared at δ 6.27 and δ 5.81 for the major isomer. Also, the allylic proton for the major isomer resonated at δ 4.01 while the signals for the comparable proton of the minor isomer merged with the ester $-CH_2$ protons.

Additionally, a chemical correlation was undertaken (Scheme 3) to determine the stereochemistry of the newly created centre of the adducts. Accordingly, allyl aldehyde **8** on Baylis–Hillman reaction (DABCO/DMF/rt) with acrylonitrile (**b**) afforded adduct **9** (55%), which on Sharpless asymmetric epoxidation with (+)-DIPT resulted in enantiopure (*S*)-**4b** *anti* (39%) and (*S*)-**9** (35%). Further, (*S*)-**9** on Sharpless asymmetric epoxidation with (+)-DIPT gave enantiopure (*R*)-**4b** *syn* (72%). Both these products were used as standard samples for comparison with **4b** obtained earlier as an *anti*:*syn* mixture (cf. Scheme 2). The ^{1}H NMR spectrum of *S*-**4b** showed the allylic proton resonance at δ 4.46, a doublet with $J = 16.6$ Hz (*anti*-isomer) while the same proton for *R*-**4b** resonated at δ 4.13 as a doublet with $J = 4.5$ Hz (*syn*-isomer). Likewise, the HPLC of the enantiopure (*S*)-**4b** *anti*- and (*R*)-**4b** *syn*-adducts independently, upon correlation with the earlier sample (**4b**, Scheme 2) proved unequivocally that the major isomeric adduct was *anti*. Similarly, HPLC of enantiopure *syn*-**4b** (Scheme 3) matched with the minor isomer of **4b** (Scheme 2).



Scheme 3.

The increased reactivity of the 2,3-epoxy aldehydes in the Baylis–Hillman coupling, compared to that of allylic aldehyde **8**, can be explained by the presence of a more electronegative oxygen atom in the epoxide ring making the adjacent carbonyl carbon more electrophilic. The diastereoselectivity in the formation of Baylis–Hillman adduct **7b** was increased from 72% to 84% when the reaction was conducted at −20 °C in DMF, though the rate of the reaction was slower.

In conclusion, we have demonstrated for the first time the use of chiral 2,3-epoxy aldehydes in Baylis–Hillman reactions to generate chiral epoxy alcohols with an α-methylene group, in good yields and selectivity.[11,12] The Cornforth model clearly suggests that the *cis* epoxides give *syn*-adducts as major compounds while the *trans* epoxides resulted in *anti*-adducts as major products under standard base-catalyzed conditions. Interestingly, this protocol can also be extrapolated to the other isomeric epoxy aldehydes. Thus, chemically more sensitive substrates can be useful as electrophiles in the Baylis–Hillman reaction. Further work on the use of these adducts is in progress.

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10. In general it was observed that the ^{1}H NMR spectra of the adducts resulting from the *trans* 2,3-epoxy aldehydes showed the allylic proton (both for *syn*- and *anti*-isomers) resonating downfield when compared to the adducts obtained from *cis*-2,3-epoxy aldehydes.
11. General experimental procedure: To a cold solution (0 °C) of epoxy aldehyde (1 mmol) in DMF were added DABCO (0.5 mmol) and the activated alkene (1.5 mmol) and the mixture stirred for 3–8 h at room temperature. After completion of reaction (by TLC), the reaction mixture was partitioned between diethyl ether (2 × 50 mL) and water (1 × 60 mL). The organic phase was washed with brine (2 × 50 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 8.5:1.5–8:2, *n*-hexane–EtOAc) to afford products **1a**, **2b**, **3a**,**b**, **4a**,**b**, **5a**,**b**, **6a**,**b**, and **7a**,**b** in good yields (61–80%).
12. Spectral data for selected compounds: Compound **4a**: Pale yellow syrup; $[\alpha]_D^{25}$ +42.6 (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.36 (s, 0.7H, olefinic), 6.32 (s, 0.3H, olefinic), 6.01 (s, 0.7H, olefinic), 5.94 (s, 0.3H, olefinic), 4.58 (br s, 0.7H, allylic), 4.39 (br s, 0.3H, allylic), 4.24–4.20 (m, 2H, CH_2), 4.05–3.98 (m, 2H, –O–CH_2–), 3.80–3.70 (m, 1H, –O–CH–), 3.30–2.98 (m, 2H, epoxide), 2.66 (d, 0.3H, *J* = 4.5 Hz, OH), 2.43 (d, 0.7H, *J* = 6.04 Hz, OH), 1.38–1.25 (m, 9H, 3 × CH_3); HPLC (column: chiral OD, 10% isopropanol in *n*-hexane, flow rate: 1 mL/min,

t_r(major) = 8.59 min, t_r(minor) = 8.29 min; IR (neat): 3465, 2987, 1716 cm^{-1}; FABMS *m/z* 273 (M^++1); Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40; found: C, 57.18; H, 7.42. Compound **4b**: Pale yellow syrup; $[\alpha]_D^{25}$ +7.25 (*c* 0.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.24 (s, 0.75H, olefinic), 6.12 (s, 1H, olefinic), 6.09 (s, 0.25H, olefinic), 4.50–4.43 (m, 0.75H, allylic), 4.13–4.06 (m, 2.25H, allylic, –O–CH_2–), 3.96–3.88 (m, 1H, –O–CH–), 3.66 (br s, 1H, OH), 3.23–3.11 (m, 2H, epoxide), 1.39–1.25 (m, 6H, $2 \times CH_3$); HPLC (column: chiral OD, 10% isopropanol in *n*-hexane, flow rate: 1 mL/min, t_r(major) = 12.76 min, t_r(minor) = 13.93 min; IR (neat): 3473, 2994, 2362 cm^{-1}; FABMS *m/z* 226 (M^++1); Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; found: C, 58.74; H, 6.69. Compound **5a**: Pale yellow syrup; $[\alpha]_D^{25}$ −52.3 (*c* 0.75, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.32–7.18 (m, 5H, Ar–H), 6.30 (s, 0.17H, olefinic), 6.27 (s, 0.83H, olefinic), 5.91 (s, 0.17H, olefinic), 5.81 (s, 0.83H, olefinic), 4.78–4.69 (m, 1H, benzylic), 4.59–4.51 (m, 1H, benzylic), 4.32–4.15 (m, 2.17H, CH_2, allylic), 4.01 (d, 0.83H, *J* = 5.2 Hz, allylic), 3.57–3.42 (m, 1H, –CH–), 3.13–3.00 (m, 2H, epoxide), 1.29 (d, 0.51H, *J* = 6.6 Hz, CH_3), 1.17 (d, 2.49H, *J* = 6.6 Hz, CH_3), 1.25–1.19 (m, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.53, 138.79, 128.32, 127.77, 127.34, 126.99, 73.36, 71.12, 70.12, 61.32, 55.00, 17.65, 14.10; HPLC (column: chiral OD, 10% isopropanol in *n*-hexane, flow rate: 1 mL/min, t_r(major) = 10.21 min, t_r(minor) = 15.06 min; IR (neat): 3472, 2981, 1713 cm^{-1}; FABMS *m/z* 307(M^++1); Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; found: C, 66.51; H, 7.25. Compound **5b**: Pale yellow syrup; $[\alpha]_D^{25}$ −33.3 (*c* 0.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.46–7.19 (m, 5H, Ar–H), 6.09 (d, 0.5H, *J* = 10.6 Hz, olefinic), 6.05 (d, 1.5H, *J* = 7.1 Hz, olefinic), 4.73–4.56 (m, 2H, benzylic), 4.18 (d, 0.25H, *J* = 7.1 Hz, allylic), 4.06 (d, 0.75H, *J* = 5.4 Hz, allylic), 3.70–3.54 (m, 1H, –CH–), 3.20–3.03 (m, 2H, epoxide), 2.67 (br s, 1H, -OH), 1.39–1.22 (m, 3H, CH_3); HPLC (column: chiral OD, 10% isopropanol in *n*-hexane, flow rate: 1 mL/min, t_r(major) = 12.45 min, t_r(minor) = 11.29 min; IR (neat): 3429, 2981, 2367 cm^{-1}; FABMS *m/z* 260 (M^++1); Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48, H, 6.61; found: C, 69.36, H, 6.59.