Ring-Conformer Effects of the Cyclopropyl Group: First Use of *trans*-(2*R*,3*R*)-Cyclopropanecarbaldehydes as Electrophiles in Diastereoselective Baylis–Hillman Reaction

Palakodety Radha Krishna,* S. Kishore, P. Srinivas Reddy

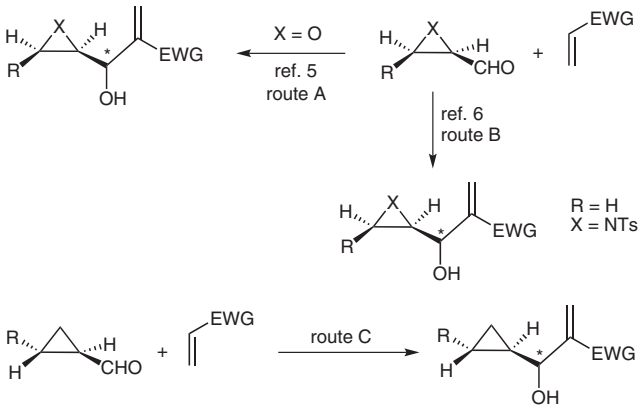
D-211, Discovery Laboratory, Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad 500 607, India
Fax +91(40)27160387; E-mail: prkgenius@iict.res.in

Received 22 July 2009

Abstract: *trans*-(2*R*,3*R*)-Cyclopropanecarbaldehydes are used as novel electrophiles in the Baylis–Hillman reaction to afford adducts in good yields (75–85%) and diastereoselectivities (60–90%).

Key words: *trans*-(2*R*,3*R*)-cyclopropanecarbaldehydes, Baylis–Hillman reaction, electrophiles, diastereoselectivity

Highly strained cyclopropane ring present in a wide variety of naturally occurring compounds[1] had prompted the development of the chemistry of cyclopropanes. Additionally, many quinolone antibiotics[2] such as ciprofloxacin, agrochemicals like chrysanthemic acid[3] and anticancer compounds[4] contain a cylcopropane ring, and the activity of these products is often attributed to it. Interestingly, either incorporation or deletion of cyclopropane rings in a bioactive chemical entity increases or decreases the activity of the molecule under consideration mostly due to the unsaturated character that it adds up or otherwise. Earlier,[5] we reported the first use of *cis*-2,3-epoxy aldehydes in diastereoselective Baylis–Hillman reaction (Scheme 1, route A) to result in adducts with considerable selectivities, while the aziridines-2-(*S*)-carboxaldehydes[6] reportedly gave the corresponding adducts in low diastereoselectivity (Scheme 1, route B). It is well documented in the literature[7] that heteroatom-containing three-membered rings like epoxides, aziridines, and episulfides attain different ring conformations than their cyclopropane congeners and quite understandably possess different properties owing to the presence of heteroatom. Analogously, cyclopropanecarbaldehydes assume differential spatial arrangement in their transition states,[8] and their importance in synthetic organic chemistry as valuable starting materials gave us impetus to consider them in Baylis–Hillman reaction. In addition to the above-cited unique properties of cyclopropanecarbaldehydes and our own interest in asymmetric Baylis–Hillman reaction,[9] herein substituted *trans*-(2*R*,3*R*)-cyclopropanecarbaldehydes are explored as novel electrophiles for the first time in Baylis–Hillman reaction. The reason for their choice is twofold: firstly, to check if there are any diastereodifferentiating effects and, secondly, any steric effects due to the restricted ring system that tend to dictate the overall outcome.



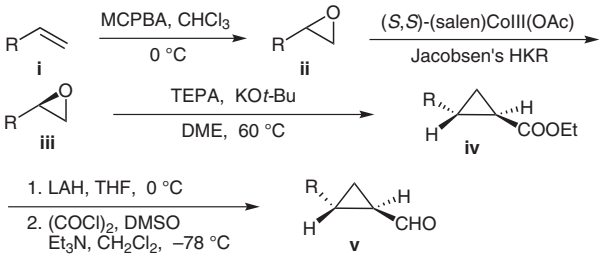
Scheme 1 Different three-membered ring carboxaldehydes in Baylis–Hillman reaction

To the best of our knowledge, so far, chiral cyclopropanecarboxaldehydes and more so the *trans*-(2*R*,3*R*)-cyclopropanecarbaldehydes were never utilized as electrophiles in Baylis–Hillman reaction. The results emanating from the study are presented herein (Scheme 1, route C).

Though several methods have been reported for accessing *trans*-(2*R*,3*R*)-cyclopropanecarbaldehydes,[10] we chose the practical method of their preparation from epoxides via the Horner–Wadsworth–Emmons (HWE)-type reaction.[11]

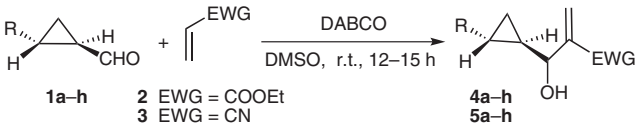
The strategy stems from the fact that chiral terminal epoxides could be accessed through the Jacobsen's HKR which in turn could be converted into chiral cyclopropyl esters and thence into aldehydes in optically pure form with predictable stereochemistry. Thus, while the configuration is inverted at C2 carbon of epoxide, the newly created carbonyl-bearing carbon assumes a relative *trans*-geometry. A converse *trans*-cyclopropyl ester is obtained from the enantiomeric epoxide starting material. Thus, 1-alkene **i** on epoxidation–Jacobsen's hydrolytic kinetic resolution,[12] HWE reaction gave the chiral cyclopropyl ester **iv**. Later, the thus generated cyclopropyl ester on further transformations gave the corresponding aldehyde **v** (Scheme 2). The absolute stereochemistry of the cyclopropyl esters and the aldehydes thereof were deduced based on the literature evidence.[11]

SYNLETT 2009, No. 16, pp 2605–2608
Advanced online publication: 10.09.2009
DOI: 10.1055/s-0029-1218019; Art ID: G18109ST



Scheme 2 General synthetic scheme for the preparation of cyclopropyl aldehydes

After having identified a synthetic protocol for accessing cyclopropanecarbaldehydes, a test Baylis–Hillman reaction of *trans*-(2*R*,3*R*)-cyclopropanecarbaldehyde **1a** with ethyl acrylate (**2**) or acrylonitrile (**3**) was tried under several solvents like THF, 1,4-dioxane–H_2O, DMF, and DMSO catalyzed by DABCO. Out of all the trials, the reaction in DMSO resulted in adducts **4a** and **5a**, respectively, in high diastereoselectivity and good yields (Scheme 3, Table 1).

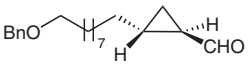
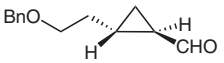
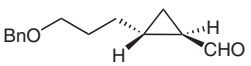
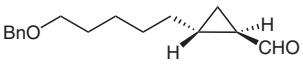
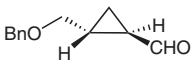
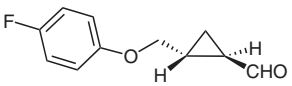
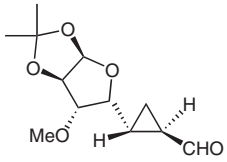
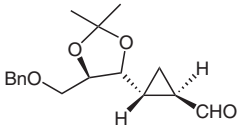


Scheme 3

Inspired by the result, several aldehydes decorated with varied functional groups, such as possessing 3-alkoxy substituents or otherwise, were selected for the Baylis–Hillman reaction in order to define the role of the substituents for any possible secondary interactions or steric factors that might influence the stereochemical outcome. Thus, firstly aldehydes **1a–d** bearing 3-*n*-alkyl groups with varied chain length were subjected to Baylis–Hillman reaction under the optimized conditions to afford **4a–d** and **5a–d** as adducts in uniformly good yields and de (entries 1–4, Table 1). Later, the other set of aldehydes **1e–h**, those decorated with 3-alkoxy substitutions were subjected to Baylis–Hillman reaction under similar reaction conditions, with olefins **2** and **3**, to afford the corresponding adducts **4e–h** and **5e–h** (entries 5–8, Table 1) in comparable yields albeit in lesser de.[13,14] The factors responsible for such dramatic difference will be discussed later.

The diastereomeric ratio in **4a** was evaluated based on the relative integration of the differential protons. For instance, ^{1}H NMR of **4a** displays the diagnostic olefinic protons at δ = 6.21 ppm as a singlet for the major isomer (0.95 H), at δ = 6.15 ppm as a singlet for the minor isomer (0.05 H), at δ = 5.83 ppm as a singlet for the major isomer (0.95 H), and at δ = 5.80 ppm as a singlet for the minor isomer (0.05 H). The allylic proton resonated at δ = 4.37 ppm as a doublet of doublet (*J* = 4.0, 8.0 Hz) integrating for one proton. Similarly, the ^{1}H NMR of **4g** displayed the olefinic protons at δ = 6.23 ppm as a singlet for minor isomer (0.15 H), δ = 6.18 ppm for the major isomer (0.85 H), δ = 5.82 ppm as a singlet for minor isomer (0.15 H), and δ = 5.78 ppm as a singlet for major isomer (0.85 H) while the anomeric proton resonated at δ = 6.09 ppm as a doublet (*J* = 2.9 Hz) for the minor isomer (0.15 H), δ = 5.90 ppm as a doublet (*J* = 3.9 Hz) for the major isomer (0.85 H). The allylic proton resonated at δ = 5.00 ppm as a triplet (*J* = 6.2 Hz) for the minor isomer (0.15 H) and δ = 4.8 ppm as a triplet (*J* = 6.6 Hz) for the major isomer (0.85 H). The de were also evaluated by HPLC and found consistent with NMR calculations.

Table 1 Baylis–Hillman Reaction of *trans*-(2*R*,3*R*)-Cyclopropanecarbaldehydes with Olefins[a]

Entry	Aldehyde	Product[b]	Yield (%)[c]	de *anti*/*syn* (%)[d]
1		**4a**	82	95:5
		5a	88	95:5
2		**4b**	80	85:15
		5b	85	87:13
3		**4c**	80	90:10
		5c	82	90:10
4		**4d**	82	92:8
		5d	85	92:8
5		**4e**	80	80:20
		5e	85	80:20
6		**4f**	85	85:15
		5f	85	87:13
7		**4g**	75	85:15
		5g	80	85:15
8		**4h**	80	80:20
		5h	85	80:20

[a] Aldehyde (1.0 mmol) in DMSO (1.0 mL) was added DABCO (0.5 mmol) and the olefin (1.5 mmol) and the mixture stirred at r.t. for 12–15 h.
[b] All the products are characterized by their spectral data.
[c] Combined yield.
[d] As determined by ^{1}H NMR.

The absolute stereochemistry of the newly created center in **4a** was initially determined based on the transition models (Figure 1) as well as on the literature evidence.[8] It is well known that cyclopropanecarbaldehydes exist in bisected conformations, namely *s-cis* and *s-trans* conformers wherein cyclopropane ring exists predominantly in *s-trans* form (Figure 1). Consequently, nucleophilic attack occurs via these bisected conformations, that is, from the less hindered *si*-face facilitated by the strong interactions between the cyclopropane electrons (strong π-donor) and

the antibonding orbital of the incipient bond of the nucleophile and the carbonyl carbon to result in the formation of major *anti* product. Thus, the major isomer was assigned as *S*-isomer (*anti*-isomer) and the minor as *R*. However, for the alkoxy-substituted aldehydes, weak interactions[15] between the enolate and alkoxy group(s) of the cyclopropanecarbaldehyde(s) stabilizes the *s-cis* transition state to result in *syn* products alongside.

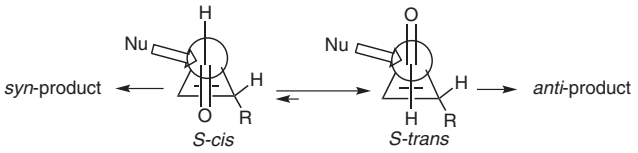
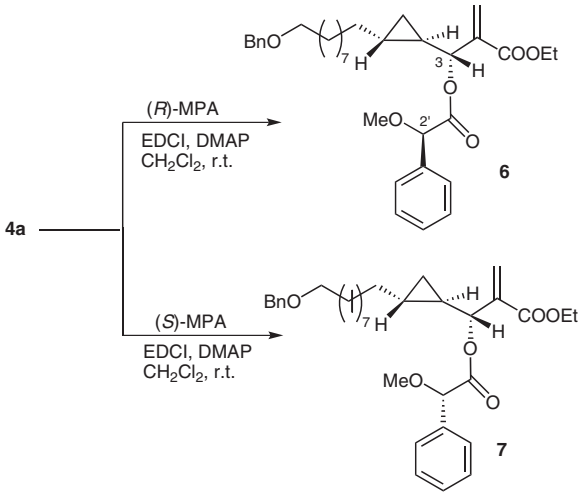


Figure 1 Transition-state models

Further, to assign the absolute stereochemistry unambiguously, Mosher esters of **4a** were prepared (Scheme 4) and their NMR studied. For instance, in the ^{1}H NMR spectrum of **6**, the ester attached proton (H3) appeared at δ = 5.85 ppm as a doublet for the major isomer while the same proton appeared at δ = 4.85 ppm in ester **7** (major isomer). Since the H3 of (3*S*,2′*R*)-ester **6** was found to be the most deshielded, it can be deduced and unequivocally established that the absolute stereochemistry of the newly created carbon atom in adduct **4a** to be 'S' for the major isomer in accordance with the conformational models of MPA-esters.[16] Analogously, the absolute stereochemistry of the newly created stereogenic center in all other adducts (major isomer) was assigned as 'S'.



Scheme 4 MPA esters of **4a**

Interestingly, extending the analogy, the *cis*-2,3-cyclopropanecarbaldehydes presumably afford similar selectivities as the alkoxy bearing substrates **1e**–**h** screened in the present study due to the related transition-state conformational preferences.

In conclusion, *trans*-(2*R*,3*R*)-cyclopropanecarbaldehydes were used for the first time as electrophiles in a diastereoselective Baylis–Hillman reaction to afford the corresponding adducts in good yields and selectivities. It was found that the ring conformation and substituents play decisive role in the stereoselection of the product largely in favor of *anti* isomer. While the 3-alkyl-substituted aldehydes **1a**–**d** possessing nonparticipating group gave *anti* product in greater ratios, the 3-alkoxy-substituted *trans*-(2*R*,3*R*)-cyclopropanecarbaldehydes **1e**–**h** furnished adducts in comparatively lower selectivities due to decreased facial selectivity. An investigation into the utility of the adduct in the total synthesis of solandelactone E[17] is in progress.

Acknowledgment

Authors (S.K.) and (P.S.R.) thank the CSIR, New Delhi, for financial support in the form of fellowships. We are thankful to the Department of Science and Technology, New Delhi, for the financial assistance of the Grants-in-Aid project under SERC (No. SR/S1/OC-59/2006).

References and Notes

(1) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589.
(2) *Quinolones*; Andriole, V. T., Ed.; Academic Press: London, **2000**.
(3) (a) *Recent Advances in the Chemistry of Insect Control*; James, N. F., Ed.; RCS: London, **1985**, 26. (b) *Recent Advances in the Chemistry of Insect Control*; James, N. F., Ed.; RCS: London, **1985**, 73. (c) *Recent Advances in the Chemistry of Insect Control*; James, N. F., Ed.; RCS: London, **1985**, 33. (d) Suckling, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 537.
(4) *Anticancer Agents from Natural Products*; Cragg, G. M.; Kingston, D. G. I.; Newman, D. J., Eds.; CRC Press: Boca Raton, **2005**, 402.
(5) RadhaKrishna, P.; Krishnarao, L.; Kannan, V. *Tetrahedron Lett.* **2004**, *45*, 7847.
(6) Navak, S. K.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1999**, *40*, 981.
(7) (a) Greenberg, A.; Liebman, J. F. In *Strained Organic Molecules*; Academic Press: New York, **1978**. (b) Wieberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312.
(8) (a) Bartell, L. S.; Carrol, B. L.; Guillory, J. P. *Tetrahedron Lett.* **1964**, 705. (b) Ono, S.; Shuto, S.; Matsuda, A. *Tetrahedron Lett.* **1996**, *37*, 221.
(9) (a) Radha Krishna, P.; Sharma, G. V. M. *Mini-Rev. Org. Chem.* **2006**, *3*, 137. (b) Radha Krishna, P.; Rachna Sachwani Srinivas Reddy, P. *Synlett* **2008**, 2897.
(10) Label, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.
(11) (a) Singh, A. K.; Rao, M. N.; Simpson, J. H.; Li, W.-S.; Thornton, J. E.; Kuehner, D. E.; Kacsur, D. J. *Org. Process Res. Dev.* **2002**, *6*, 618. (b) Delhaye, L.; Merschaert, A.; Delbeke, P.; Briône, W. *Org. Process Res. Dev.* **2007**, *11*, 689.
(12) (a) Tokunaga, M.; Larrow, J. F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
(13) **General Experimental Procedure**
To a cold solution (0 °C) of cyclopropanecarbaldehyde (1.0 mmol) in DMSO were added DABCO (0.5 mmol) and the activated alkene (1.5 mmol) and the reaction mixture stirred for 12–15 h at r.t. After completion of reaction (by TLC), the reaction mixture was partitioned between Et_2O (2 × 50 mL)

and H_2O (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 to afford products **4a**–**h** and **5a**–**h** in good yields (75–85%).

(14) **Spectral Data of Selected Compounds**
Compound **4a**: thick yellow syrup; $[\alpha]_D^{25}$ +1.07 (*c* 1.55, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 5 H), 6.21 (s, 0.95 H), 6.15 (s, 0.05 H), 5.83 (s, 0.95 H), 5.80 (s, 0.05 H), 4.46 (s, 2 H), 4.37 (dd, 1 H, *J* = 4.0, 8.0 Hz), 4.21 (q, 2 H, *J* = 7.3 Hz), 3.42 (t, 2 H, *J* = 6.5 Hz), 2.55 (t, 1 H, *J* = 6.5 Hz), 2.39 (t, 1 H, *J* = 7.3 Hz), 2.06–1.71 (m, 1 H), 1.56 (q, 2 H, *J* = 6.5 Hz), 1.36–1.21 (m, 15 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.1, 142.3, 138.6, 128.2, 127.5, 127.3, 124.8, 72.7, 70.6, 70.4, 60.7, 42.8, 38.8, 31.8, 29.2, 29.1, 26.0, 24.4, 23.8, 14.0. HPLC column: Waters HRC18, 300 × 309 mm, 6 μm, 50% MeCN in H_2O, flow rate: 1 mL/min, t_R(major) = 2.783 min, t_R(minor) = 3.639 min. IR (neat): 3440, 2928, 2855, 1716 cm^{-1}. ESI-MS: *m/z* = 400 $[M - H]^+$, 441 $[M + 39]^+$. Anal. Calcd (%) for $C_{25}H_{34}O_4$: C, 74.59; H, 9.51. Found: C, 74.61, H, 9.50.
Compound **4g**: colorless syrup; $[\alpha]_D^{25}$ –109.1 (*c* 0.85, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 6.23 (s, 0.15 H), 6.18 (s, 0.85 H), 6.09 (d, 0.15 H, *J* = 2.9 Hz), 5.96 (d, 0.85 H, *J* = 3.9 Hz), 5.82 (s, 0.15 H), 5.78 (s, 0.85 H), 5.0 (t, 0.15 H, *J* = 6.2 Hz), 4.86 (t, 0.85 H, *J* = 6.6 Hz), 4.21 (q, 2 H, *J* = 7.0 Hz), 3.99 (q, 2 H, *J* = 3.1 Hz), 3.51 (s, 0.85 Hz), 3.34 (s, 0.15 H), 2.15–1.87 (m, 2 H), 1.50–1.45 (m, 2 H), 1.40–1.25 (m, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 131.5, 127.2, 105.8, 105.5, 105.3, 86.1, 86.0, 85.8, 85.2, 81.4, 71.9, 58.1, 57.2, 36.4, 35.3, 26.8, 26.3, 26.1. HPLC column: Waters HRC18, 300 × 309 mm, 6 μm, 50% MeCN in H_2O, flow rate: 1 mL/min, t_R(major) = 4.496 min, t_R(minor) = 8.199 min. IR (neat): 3447, 2924, 2854, 1718, cm^{-1}; ESI-MS: *m/z* = 341 $[M - H]^+$, 381 $[M + 39]^+$. Anal. Calcd (%) for $C_{17}H_{26}O_7$: C, 59.64; H, 7.65. Found: C, 59.70; H, 7.58.

(15) (a) Kazuta, Y.; Yamamoto, T.; Matsuda, A.; Shuto, S. *Tetrahedron* **2004**, *60*, 6689. (b) Reetz, M. T.; Kessler, K.; Schidtberger, S.; Westermann, J.; Steinback, R. *Angew. Chem.* **1983**, *22*, 989.

(16) Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17.

(17) Seo, Y.; Cho, K. W.; Rho, J.-R.; Shin, J.; Kwon, B.-M.; Bok, S.-H.; Song, J.-I. *Tetrahedron* **1996**, *52*, 10583.