

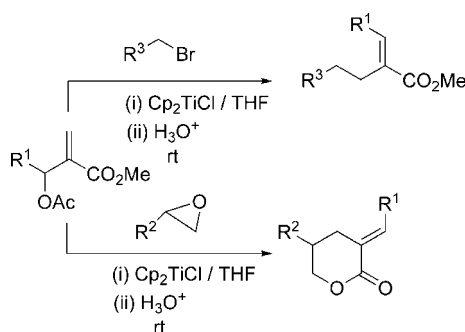
Titanocene(III) Chloride Mediated Radical-Induced Addition to Baylis–Hillman Adducts: Synthesis of (*E*)- and (*Z*)-Trisubstituted Alkenes and α -Methylene/Arylidene δ -Lactones

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Baylis–Hillman adduct underwent smooth radical-induced condensation with activated bromo compounds and epoxides using titanocene(III) chloride (Cp_2TiCl_2) as the radical generator. The reactions of activated bromo compounds with 3-acetoxy-2-methylene alkanooates provided (*E*)-alkenes exclusively, whereas similar reactions with 3-acetoxy-2-methylenealkanenitriles led to (*Z*)-alkenes as the major product. The reactions of epoxides with Baylis–Hillman adduct furnished α -methylene/arylidene- δ -lactones in good yield via addition followed by in situ lactonization.

Acetates of Baylis–Hillman adduct have been established for stereoselective synthesis of different multifunctional molecules.¹ Moreover, the substituted alkene moiety is a part of varieties of naturally occurring bioactive molecules along with several important pheromones and antibiotics and also the key intermediate in the stereospecific synthesis of important compounds.² Various α -substituted acrylate esters have been extensively used in the synthesis of pseudopeptides, including inhibitors of metalloproteases and ATP-dependent ligases based on the 1,4-addition reaction.³ Several methods are reported in the literature for the synthesis of substituted alkenes from

Baylis–Hillman adducts such as Pd-catalyzed cross-coupling reaction,⁴ reaction with Grignard reagent,⁵ Friedel–Crafts reaction,⁶ and more recently reaction of trialkylindium reagent.⁷ Earlier, Das et al. have a considerable amount of contribution in the synthesis of alkenes from Baylis–Hillman adducts.⁸ They have also developed a very elegant and high-yielding similar transformation using Zn in aqueous medium where both

(1) (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, 24, 94. (b) Basavaiah, D.; Bakthadoss, M.; Pandiaraju, S. *Chem. Commun.* **1998**, 1639. (c) Silveira, G. P. de C.; Coelho, F. *Tetrahedron Lett.* **2005**, 46, 6477.

(2) (a) Bradshaw, J. W. S.; Baker, R.; Howse, P. E. *Nature* **1975**, 258, 230. (b) Rossi, R.; Carpita, A.; Messari, T. *Synth. Commun.* **1992**, 22, 603. (c) Marfort, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, 44, 3888.

(3) (a) Jackson, P. F.; Cole, D. C.; Slusher, B. S.; Stetz, S. L.; Ross, L. E.; Donzanti, B. A.; Trainor, D. A. *J. Med. Chem.* **1996**, 39, 619. (b) Vassiliou, S.; Mucha, A.; Cuniassse, P.; Georgiadis, D.; Lucet-Levannier, K.; Beau, F.; Kannan, R.; Murphy, G.; Knäuper, V.; Rio, M. C.; Basset, P.; Yiotakis, A.; Dive, V. *J. Med. Chem.* **1999**, 42, 2610. (c) Valiaeva, N.; Bartley, D.; Konno, T.; Coward, J. K. *J. Org. Chem.* **2001**, 66, 5146. (d) Hin, B.; Majer, P.; Tsukamoto, T. *J. Org. Chem.* **2002**, 67, 7365.

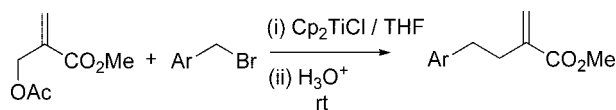
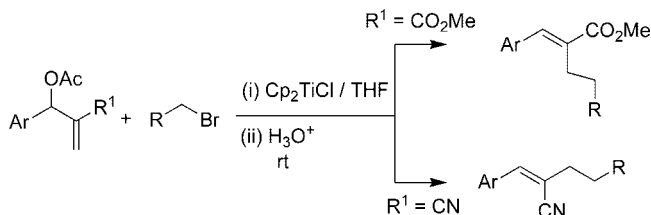
(4) (a) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Org. Lett.* **2003**, 5, 3803. (b) Kabalka, G. W.; Dong, G.; Venkataiah, B.; Chen, C. *J. Org. Chem.* **2005**, 70, 9207.

(5) Basavaiah, D.; Sarma, P. K. S.; Bhavani, A. K. D. *J. Chem. Soc., Chem. Commun.* **1994**, 1091.

(6) (a) Basavaiah, D.; Pandiaraju, S.; Padmaja, K. *Synlett* **1996**, 393. (b) Basavaiah, D.; Krishnamacharyulu, M.; Hyma, R. S.; Pandiaraju, S. *Tetrahedron Lett.* **1997**, 38, 2141.

(7) Ranu, B. C.; Chattopadhyay, K.; Jana, R. *Tetrahedron Lett.* **2007**, 48, 3847.

(8) (a) Das, B.; Banerjee, J.; Chowdhury, N.; Majhi, A.; Holla, H. *Synlett* **2006**, 1879. (b) Das, B.; Venkateswarlu, K.; Krishnah, M.; Holla, H.; Majhi, A. *Helv. Chim. Acta* **2006**, 89, 1417. (c) Das, B.; Chowdhury, N.; Banerjee, J.; Majhi, A.; Mahender, G. *Chem. Lett.* **2006**, 35, 358. (d) Das, B.; Chowdhury, N.; Damodar, K.; Banerjee, J. *Chem. Pharm. Bull.* **2007**, 55, 1274. (e) Das, B.; Holla, H.; Srinivas, Y.; Chowdhury, N.; Bandgar, B. P. *Tetrahedron Lett.* **2007**, 48, 3201.

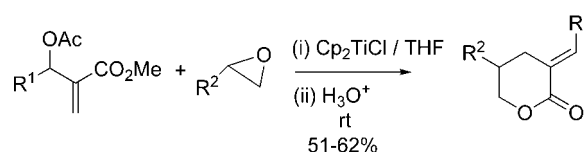
SCHEME 1. Ti(III)-Mediated Addition of Activated Bromo Compounds to Baylis–Hillman Adduct

SCHEME 2. Ti(III)-Mediated Addition of Activated Bromo Compounds to Alkenoates and Alkenenitriles


activated and nonactivated bromo compounds could be utilized.⁹ But to the best of our knowledge, there is no report to prepare substituted alkenes regioselectively from Baylis–Hillman adducts by radical-induced method specially using a Ti(III) species.

Carbon–carbon bond formation through radical reactions became one of the important powerful tools in organic synthesis.¹⁰ It is very effective for the synthesis of variety of complex natural products due to its mildness and wide range of functional group tolerance.¹¹

The Baylis–Hillman reaction has already been proved to be an important tool for providing molecules possessing hydroxy, alkene or electron withdrawing group in close proximity in a number of stereoselective processes.¹² This prompted us to explore the radical addition reactions to the Baylis–Hillman adducts for the synthesis of valuable intermediates using titanocene(III) chloride (Cp₂TiCl) as the radical generator.¹³ We report herein the radical-induced addition of the activated bromo compounds¹⁴ and epoxides to Baylis–Hillman adducts using Cp₂TiCl to yield selectively (*E*)- and (*Z*)-trisubstituted alkenes (Scheme 1) and α -methylene/arylidene δ -lactones (Scheme 3) respectively in satisfactory yields.

Thus, the treatment of 3-acetoxy-2-methylenealkanoates with activated bromo or iodo compounds using Ti(III) species as the radical initiator provided *E*-2-substituted 2-alkenoates exclusively, whereas 3-acetoxy-2-methylenealkenenitriles furnished

SCHEME 3. Ti(III)-Mediated Addition of Epoxides to Baylis–Hillman Adduct


an *E/Z* mixture with *Z*-2-substituted 2-alkenenitrile as the major product (Scheme 2).

A series of Baylis–Hillman adducts were subjected to titanocene(III) chloride mediated reaction with various activated bromo compounds, and the results are summarized in Table 1. Activated iodo compounds also underwent similar reactions to furnish *E*-2-substituted 2-alkenoates (entries 12, 13, 15, 17, and 18, Table 1). But, nonactivated iodo compound (entry 20, Table 1) or an electron-withdrawing group (NO₂) in the aromatic moiety (entry 19, Table 1) did not respond at all under the reaction conditions.

The reaction initially underwent 1,4-addition of the radical species followed by β -acetoxy elimination.¹⁵ During the course of the reaction, it was observed that benzyl bromides provided the desired products in good yields, whereas allyl bromides gave moderate yields of the products (entries 7 and 11, Table 1). Elimination of the OM_s group is also as efficient as the OAc group leading to the desired alkene (entry 1, Table 1). The stereochemistry of the product is governed by the electron-withdrawing groups present in the adducts. The *E*- and *Z*-selectivity can be rationalized from the difference in stability of the chelated (**A**) and nonchelated (**B**) transition states (Figure 1) as reported by Basavaiah⁵ and Das⁹ in similar transformations. The *E/Z* ratio was determined from the ¹H NMR spectra of the crude products. The stereochemistry of the products was established by comparing the NMR value of the olefinic proton with the reported values.^{4–6}

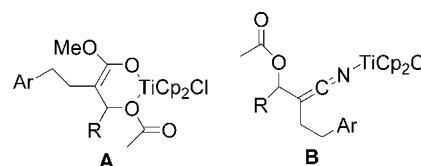


FIGURE 1. Chelated and nonchelated transition states of the alkenoate and alkenenitrile.

α -Methylene/arylidene δ -lactone is found to be an important structural fragment in a wide range of natural occurring biologically active compounds.¹⁶ In addition, these lactones are used as valuable synthetic intermediates toward natural products.¹⁷ Over the past decades, considerable efforts have been devoted to the synthesis of α -methylene/arylidene δ -lactones by numerous approaches, more significantly toward α -methylene δ -lactones.¹⁸ Basavaiah et al. have reported an excellent method

(9) Das, B.; Banerjee, J.; Mahender, G.; Majhi, A. *Org. Lett.* **2004**, *6*, 3349.
(10) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, U. K., 1992. (b) Leonard, J.; Diez-Barra, F.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051.

(11) (a) Giese, B. *Radicals In Organic Synthesis, Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (c) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic: London, 1991. (d) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals In Organic Chemistry*; Wiley: New York, 1995. (e) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (f) Srikrishna, A. *Curr. Sci.* **1987**, *56*, 392.

(12) (a) Drewes, S. E.; Ross, G. H. P. *Tetrahedron* **1988**, *44*, 4653. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(13) (a) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986, and references cited therein. (b) Cuerva, J. M.; Justicia, J.; Oller-López, J. L.; Oltra, J. E. *Top. Curr. Chem.* **2006**, *264*, 63. (c) Barrero, A. F.; Quílez del Moral, J. F.; Sánchez, E. M.; Arteaga, J. F. *Eur. J. Org. Chem.* **2006**, 1627. (d) Gansäuer, A. *Synlett* **1998**, 801. (e) Gansäuer, A.; Bluhm, H. *Chem. Commun.* **1998**, 2143. (f) Gansäuer, A.; Lauterbach, T.; Bluhm, H.; Noltemeyer, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2909. (g) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5556. (h) Journet, M.; Malacria, M. *J. Org. Chem.* **1994**, *59*, 718. (i) Devin, P.; Festerbank, L.; Malacria, M. *J. Org. Chem.* **1998**, *63*, 6764.

(14) (a) Jana, S.; Guin, C.; Roy, S. C. *Tetrahedron Lett.* **2004**, *45*, 6575. (b) Mandal, S. K.; Jana, S.; Roy, S. C. *Tetrahedron Lett.* **2005**, *46*, 6115. (c) Paira, M.; Banerjee, B.; Jana, S.; Mandal, S. K.; Roy, S. C. *Tetrahedron Lett.* **2007**, *48*, 3205. (d) Mandal, S. K.; Roy, S. C. *Tetrahedron Lett.* **2007**, *48*, 4131.

(15) Justicia, J.; Oller-López, J. L.; Compana, A. G.; Oltra, J. E.; Cuerva, J. M.; Buñuel, E.; Cardenas, D. *J. Am. Chem. Soc.* **2005**, *127*, 14911.

(16) (a) Kupchan, S. M.; Hemingway, R. J.; Werner, D.; Karim, A.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1968**, *90*, 3596. (b) Kupchan, S. M.; Eakin, M. A.; Thomas, M. A. *J. Med. Chem.* **1971**, *14*, 1147. (c) Weinheimer, A. J.; Matson, J. A.; Hossain, M. B.; van der Helm, D. *Tetrahedron Lett.* **1977**, 2923. (d) Cane, D. E.; Rossi, T. *Tetrahedron Lett.* **1979**, 2973. (e) Imai, H.; Suzuki, K.; Morioka, M.; Numasaki, Y.; Kadota, S.; Nagai, K.; Sato, T.; Iwanami, M.; Saito, T. *J. Antibiot.* **1987**, *40*, 1475. (f) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942. (g) Nangia, A.; Prasuna, G.; Rao, P. B. *Tetrahedron* **1997**, *53*, 14507. (h) Liao, X.-B.; Han, J.-Y.; Li, Y. *Tetrahedron Lett.* **2001**, *42*, 2843.

(17) Liu, Z.-Y.; Zhao, L.-Y. *Tetrahedron Lett.* **1999**, *40*, 5593.

TABLE 1. Ti(III)-Mediated Synthesis of Alkenes from Baylis–Hillman Adduct

Entry	Substrate	Halides	Product ^a	Yield (%) ^b	Entry	Substrate	Halides	Product ^a	Yield (%) ^b
1				For 1a (61) For 1a' (58)	11				43
2				65	12				58
3				66	13				53
4				75	14				63
5				57	15				52
6				63	16				64
7				45	17				51
8				59	18				62
9				63	19			No reaction	
10				64	20			No reaction	

^a Products were characterized by IR, NMR and HRMS studies. ^b Yields refer to pure isolated products. ^c Isomeric ratio was determined from ¹H NMR data.

for the synthesis of bis-lactones from the Baylis–Hillman adducts.¹⁹ In this paper, we disclose a brilliant synthetic methodology leading to α -methylene/arylidene δ -lactones in one pot using titanocene(III)-mediated radical-induced addition of epoxides to Baylis–Hillman adducts.

Thus, as a representative example, epoxide **1c** on treatment with Cp₂TiCl in THF underwent Michael addition with 3-acetoxy-2-methylenepropanoate **1a** followed by in situ lactonization afforded finally the lactone **1d** in 62% yield (Table 2, entry 1). Lactone **1d** displayed the IR absorption at 1724 cm⁻¹ and ¹H NMR signals for two olefinic protons at δ 5.47 and 6.36 as

two separate doublets. We extended this methodology using different types of epoxides and 3-aryl-substituted 3-acetoxy-2-methylenepropanoates to furnish δ -lactones in moderate yields and the results are summarized in Table 2. The ¹H NMR signal for the β -substituted proton around δ 7.80–8.00 suggests the *E*-selectivity (96 to 100%). It is presumed that the presence of the carbomethoxy group directs the –OAc elimination as observed in the case of addition of activated bromo compounds to Baylis–Hillman adducts. On the other hand, the reaction of the epoxide **2c** with 3-acetoxy-2-methylenenitrile **6a** furnished the nitrile **17** as an inseparable mixture of *E*- and *Z*-isomers in

TABLE 2. Ti(III)-Mediated Synthesis of δ -Lactones from Baylis–Hillman Adduct

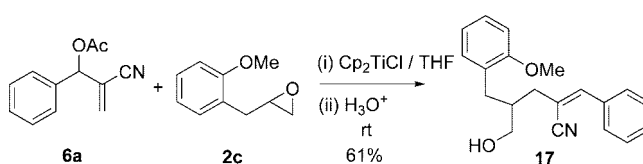
Entry	B-H adduct	Epoxide	Product ^a	Yield(%) ^b	Entry	B-H adduct	Epoxide	Product ^a	Yield(%) ^b
1				62	9				60
2				60	10				58
3				53	11				62
4				51	12				57
5				53	13				56
6				59	14				72 ^c (1:1.5)
7				55	15				67 ^c (1:1.1)
8				61	16				48

^a All products were characterized from NMR, IR, and HRMS data. ^b Yields refers to pure isolated product. ^c Cis/trans mixture at the ring junction.

a ratio of 84:16 in 61% yield (Scheme 4). The ratio isomers in **17** was determined from the only distinguishable signal at δ 3.82 (s, OMe for the minor isomer) and 3.85 (s, OMe for the major isomer) in the ¹H NMR spectrum. Since the two isomers could not be separated by usual chromatographic methods, it is not possible to determine in this stage which isomer is which.

(18) (a) Jones, E. R. H.; Shen, T. Y.; Whiting, M. C. *J. Chem. Soc.* **1950**, 230. (b) Baldwin, S. W.; Crimmins, M. T.; Cheek, V. I. *Synthesis* **1978**, 210. (c) Ghera, E.; Yechezkel, T.; Hassner, A. *J. Org. Chem.* **1990**, 55, 5977. (d) Liang, K.-W.; Li, W.-T.; Peng, S.-M.; Wang, S.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **1997**, 119, 4404. (e) Chandrasekharam, M.; Chang, S.-T.; Liang, K.-W.; Li, W.-T.; Liu, R.-S. *Tetrahedron Lett.* **1998**, 39, 643. (f) Leroy, B. *Tetrahedron Lett.* **2005**, 46, 7563. (g) Kim, E. J.; Ko, S. Y. *Bioorg. Med. Chem.* **2005**, 13, 4103. (h) Matsuda, I. *J. Organomet. Chem.* **1987**, 321, 307. (i) Grieco, P. A. *Synthesis* **1975**, 67. (j) Demuth, M.; Schaffner, K. *Angew. Chem., Int. Ed. Engl.* **1982**, 21, 820. (k) Tomioka, K.; Masumi, F.; Yamashita, T.; Koga, K. *Tetrahedron Lett.* **1984**, 25, 333. (l) Righby, J. H.; Wilson, J. Z. *J. Am. Chem. Soc.* **1984**, 106, 8217. (m) Kallmerten, J.; Gould, T. J. *J. Chem. Soc.* **1985**, 50, 1128. (n) Falsone, G.; Wingen, U. *Tetrahedron Lett.* **1989**, 30, 675. (o) Krawczyk, H.; Sliwinski, M.; Wolf, W. M.; Bodalski, R. *Synlett* **2004**, 1995. (p) Raju, R.; Allen, L. J.; Le, T.; Taylor, C. D.; Howell, A. R. *Org. Lett.* **2007**, 9, 1699. (q) Gupta, A.; Vankar, Y. D. *Tetrahedron* **2000**, 56, 8525. (19) Basavaiah, D.; Satyanarayana, T. *Org. Lett.* **2001**, 3, 3619.

SCHEME 4. Ti(III)-Mediated Addition of Epoxide to Alkenenitrile



Disubstituted epoxides such as cyclohexane epoxide **7c** also reacted in a similar fashion with Baylis–Hillman ester **5a** to obtain the lactone **14d** as a mixture of two isomers (1:1.5) with respect to the ring junction (entry 14, Table 2). The major trans isomer in **14d** was separated by fractional crystallization, and the NMR data was compared with the reported values.^{18d} The minor cis isomer could not be obtained in pure form; it was always contaminated with the major isomer. Similarly, reaction of **2a** with **7c** in the presence of Ti(III) species gave **15d** as a mixture of two isomers in a ratio of 1:1.1 (entry 15, Table 2). The major trans isomer was separated by fractional crystallization, but the minor cis isomer could not be obtained in pure form. The

epoxide **8c** with an electron-withdrawing group also gave the desired addition product **16d** when reacted with **4a** (entry 16, Table 1).

In summary, we have developed a novel protocol for the radical-induced synthesis of substituted alkenes stereoselectively by the reaction of activated bromo compounds with Baylis–Hillman adducts using titanocene(III) chloride as the radical initiator. This methodology provided stereoselective products depending on the functionality present in the adducts. We have also extended this titanium mediated radical technology toward efficient synthesis of α -methylene/arylidene δ -lactones by addition of the epoxides to Baylis–Hillman adducts.

Experimental Section

Typical Procedure for the Synthesis of (*E*)- and (*Z*)-Trisubstituted Alkenes. To a stirred solution of Cp_2TiCl_2 (523 mg, 2.1 mmol) in deoxygenated THF (26 mL) with activated Zn dust (262 mg, 4 mmol) (activated zinc dust was prepared by washing 20 g of commercially available zinc dust with 60 mL of 4 N HCl followed by thorough washing with water until the washings became neutral and finally washing with dry acetone and then drying in vacuo) was added, and the stirring was continued for another 1 h to get a green solution. This green solution was transferred to a dropping funnel via cannula and was added dropwise over 10 h to a solution of benzyl bromide (171 mg, 1 mmol) and 2-acetoxymethylacrylic acid methyl ester (**1a**) (158 mg, 1 mmol) in deoxygenated THF (12 mL) under argon. After 2 h (monitored by TLC), the reaction was quenched slowly with 10% H_2SO_4 . Most of THF was removed under reduced pressure, and the resulting residue was extracted with diethyl ether (3 $\times$ 25 mL). The organic layer was washed successively with water (2 $\times$ 10 mL) and brine (2 $\times$ 10 mL) and finally dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude material obtained was purified by column chromatography over silica gel (3% ethyl acetate in light petroleum) to furnish methyl 2-methylidene-4-phenylbutanoate (**2b**) (123 mg, 65%) as a colorless oil: IR (neat) 1720, 1631, 1496 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.54 (t, J = 8.4 Hz, 2H), 2.72 (t, J = 8.4 Hz, 2H), 3.69 (s, 3H), 5.43 (s, 1H), 6.01 (s, 1H), 7.10–7.13 (m, 3H), 7.18–7.23 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 34.0, 35.0, 52.0, 125.5, 126.1, 128.5 (2C), 128.6 (2C), 140.0, 141.5, 167.7; HRMS calcd for $\text{C}_{12}\text{H}_{14}\text{O}_2\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 213.0892, found 213.0887.

Methyl (2*E*)-2-(4-chlorobenzylidene)-4-phenylbutanoate (6b**):** colorless oil; IR (neat) 1712, 1490 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.79–2.83 (m, 4H), 3.84 (s, 3H), 7.16–7.22 (m, 5H), 7.26–7.33 (m, 4H), 7.65 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 29.7, 35.2, 52.2, 126.2 (2C), 128.6 (3C), 128.8 (2C), 130.4 (2C), 133.2, 134.1, 134.4, 138.6, 141.3, 168.6; HRMS calcd for $\text{C}_{18}\text{H}_{17}\text{ClO}_2\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 323.0815, found 323.0821.

4-(4-Chlorophenyl)-2-(4-methylbenzylidene)butanenitrile (9b**):** crystalline solid; mp 76–78 $^\circ\text{C}$; IR (neat) 2206, 1490 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.28 (s, 3H), 2.56 (t, J = 7.7 Hz, 2H), 2.84 (t, J = 7.7 Hz, 2H), 6.68 (s, 1H), 7.02–7.18 (m, 6H), 7.48 (d, J = 8.0 Hz, 2H) [in addition, only one distinguishable signal at δ 2.65 (t, J = 8.2 Hz) appeared with low intensity for the *E*-isomer]; ^{13}C NMR (75 MHz, CDCl_3) δ 20.4, 32.9, 37.0, 107.6, 117.8, 127.5 (2C), 127.6 (2C), 128.5 (2C), 128.9 (2C), 129.7, 131.1, 137.3, 139.5, 143.4 [in addition, four distinguishable signals at δ 20.3, 30.0, 32.4,

144.2 appeared with low intensity for the *E*-isomer]; HRMS calcd for $\text{C}_{18}\text{H}_{16}\text{ClNNa}$ [$\text{M} + \text{Na}$] $^+$ 304.0869, found 304.0866.

Typical Procedure for the Synthesis of α -Methylene/Arylidene δ -Lactones. To a well-stirred solution of epoxide **1c** (198 mg, 1 mmol) and Baylis–Hillman adduct **1a** (158 mg, 1 mmol) in dry deoxygenated THF was added dropwise a green solution of Cp_2TiCl_2 (2.1 mmol) (prepared in the same way as described above) in dry deoxygenated THF over 10 h under argon. After 2 h (monitored by TLC), the reaction mixture was quenched slowly with 20% H_2SO_4 . Most of THF was removed under reduced pressure, and resulting residue was extracted with diethyl ether (3 $\times$ 25 mL). The organic layer was washed successively with water (2 $\times$ 10 mL) and brine (2 $\times$ 10 mL) and finally dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude material obtained was purified by column chromatography over silica gel (7% ethyl acetate in light petroleum) to furnish 5-(5-chloro-2-methoxybenzyl)-3-methylidenetetrahydro-2*H*-pyran-2-one (**1d**): colorless crystalline solid; mp 116–118 $^\circ\text{C}$; IR (KBr) 1724, 1627, 1490, 1247 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.25–2.35 (m, 2H), 2.46–2.63 (m, 3H), 3.73 (s, 3H), 4.00 (dd, J = 9.1, 10.3 Hz, 1H), 4.24 (br d, J = 10.3 Hz, 1H), 5.47 (d, J = 1.2 Hz, 1H), 6.36 (d, J = 0.9 Hz, 1H), 6.72 (d, J = 8.7 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 7.11 (dd, J = 2.4, 8.7 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 31.7, 33.5, 34.1, 55.6, 73.2, 111.6, 125.2, 127.7, 128.5, 129.0, 130.4, 133.1, 156.1, 165.4; HRMS calcd for $\text{C}_{14}\text{H}_{15}\text{ClO}_3\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 289.0607, found 289.0604.

(3*E*,4*R*,8*S*)-3-(4-Chlorobenzylidene)octahydro-2*H*-chromen-2-one (15d**):** colorless crystalline solid; mp 182–184 $^\circ\text{C}$; IR (KBr) 1697, 1608, 1245, 1191 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.06–1.74 (m, 6H), 1.85–1.92 (m, 2H), 2.17 (brd, J = 10.8 Hz, 1H), 2.31–2.42 (m, 1H), 2.87 (dd, J = 3.2, 16.5 Hz, 1H), 3.99 (ddd, J = 4.2, 10.4, 12.7 Hz, 1H), 7.37 (brs, 4H), 7.83 (brs, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 24.0, 25.0, 31.2, 32.2, 33.3, 38.5, 81.9, 126.5, 128.9(2C), 131.5(2C), 133.6, 135.2, 139.9, 167.0; HRMS calcd for $\text{C}_{16}\text{H}_{17}\text{ClO}_2\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 299.0815, found 299.0818.

(2*Z*)-2-Benzylidene-5-hydroxy-4-(2-methoxybenzyl)pentanenitrile (17**):** colorless oil; IR (KBr) 3452, 2210, 1494, 1244 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.18–2.29 (m, 1H), 2.47 (dd, J = 6.7, 13.9 Hz, 1H), 2.61–2.81 (m, 3H), 3.43–3.53 (m, 2H), [3.82 (s, OMe for the minor isomer) and 3.85 (s, OMe for the major isomer), total 3H], 6.87–6.95 (m, 2H), 7.01 (s, 1H), 7.16–7.24 (m, 2H), 7.36–7.43 (m, 3H), 7.74 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 30.6, 38.5, 40.6, 55.6, 60.6, 109.9, 110.6, 118.9, 121.1, 127.8, 127.9, 128.7(2C), 128.9(2C), 130.0, 131.2, 133.8, 145.0, 157.4; HRMS calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_2$ [$\text{M} + \text{H}$] $^+$ 308.1651, found 308.1643.

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Supporting Information Available: General experimental procedures and spectroscopic data. Copies of ^1H NMR spectra of **1b–15b**, **1d–16d**, and **17** and ^{13}C NMR spectra of **1b–15b**, **1d–16d**, and **17**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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