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Highly Selective Reaction of α-Halo-α,β-unsaturated Esters with Ketones or Aldehydes Promoted by SmI_2: An Efficient Alternative Access to Baylis−Hillman Adducts

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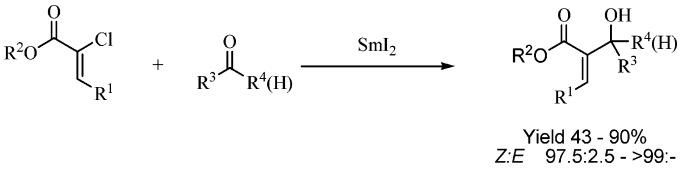

A samarium diiodide promoted addition of aromatic or aliphatic β-substituted-α-halo-α,β-unsaturated esters **1** or **3** to both ketones (in THF) and aldehydes (in acetonitrile) led to (*Z*)-2-(1-hydroxyalkyl)-2,3-alkenoates **2** and **4** in good yields and very high stereoselectivity. This method constitutes an efficient and valuable alternative to the synthesis of Baylis−Hillman adducts. A mechanism is proposed to explain this transformation.

Introduction

Since its introduction into organic synthesis,[1] the Baylis−Hillman reaction (also named the Morita−Baylis−Hillman reaction) has become one of the most useful methodologies to generate the C−C bond and to obtain multifunctionalized molecules.[2] However, the Baylis−Hillman reaction with β-substituted-α,β-unsaturated esters required high pressure.[3] In addition, the synthesis of Baylis−Hillman adducts by using organometallic compounds derived from β-substituted-α,β-unsaturated esters afforded a mixture of regioisomers.[4] For this, alternative methodologies to obtain the Baylis−Hillman β-substituted adducts with high selectivity would be necessaries.[5] Moreover, simple ketones need high pressure to undergo the Baylis−Hillman reaction,[6] and for this, a methodology to use ketones as electrophiles under mild conditions could be an important achievement.

Introduced by Kagan in 1977,[7] samarium diiodide has been used to perform various organic reactions, including carbon−carbon bond formation.[8] However, only two papers describing the generation and synthetic applications of vinylsamarium reagents, derived from acrylamides[99] and α,β-unsaturated ketones,[10] have been published. The authors of the preparation of vinylsamarium reagents from acrylamides attempted to obtain Baylis−Hillman adducts from α-halo-α,β-unsaturated esters promoted by SmI_2 and were unsuccessful.[9]

In our previous paper,[10] we described the addition of vinylsamarium reagents, derived from (*Z*)-α-chloro-α,β-unsaturated phenones, to aldehydes or ketones to obtain (*Z*)-alkylidene hydroxyketones. These transformations were highly stereoselective, and a total or very high

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(1) (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815−2821. (b) Baylis, A. B.; Hillman, M. E. D. German patent 2155113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q.

(2) To see reviews of the Baylis−Hillman reaction: (a) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653−4670. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001−8062.

(3) Hill, J. S.; Isaacs, N. S. *J. Chem. Res.* (*S*) **1988**, *10*, 330−331.

(4) Takai, K.; Tezuka, M.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 5980−5982.

(5) (a) Li, G.; Wei, H.-X.; Wills, S. *Tetrahedron Lett.* **1998**, *39*, 4607−4610. (b) Ramachandran, P. V.; Reddy, M. V. R.; Rudd, M. T. *Tetrahedron Lett.* **1999**, 627−630. (c) Ramachandran, P. V.; Reddy, M. V. R.; Rudd, M. T. *Chem. Commun.* **1999**, 1979−1980.

(6) Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett.* **1986**, *27*, 5007−5010.

(7) Namy, J.-L.; Girard, P.; Kagan, H. B. *New J. Chem.* **1977**, *1*, 5−7.

(8) Reviews of synthetic applications of SmI_2: (a) Soderquist, J. A. *Aldrichim. Acta* **1991**, *24*, 15−23. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29−68. (c) Molander, G. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 1, pp 251−282. (d) Molander, G. A. In *Organic Reactions*; Paquette, L. A., Ed.: John Wiley: New York, 1994; Vol. 46, pp 211−367. (e) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338. (f) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321−3354. (g) Krief, A.; Laval, A. M. *Chem. Rev.* **1999**, *99*, 745−777. (h) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727−2751. (i) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351−10372. (j) Concellón, J. M.; Rodríguez-Solla, H. *Chem. Soc. Rev.* **2004**, *33*, 599−609.

(9) Youn, S. W.; Park, H. S.; Kim, Y. H. *Chem. Commun.* **2000**, 2005−2006.

(10) Concellón, J. M.; Huerta, M.; García-Granda, S.; Díaz, M. R. *Chem. Eur. J.* **2003**, *9*, 5343−5347.

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SCHEME 1. Addition Reaction of Methyl α-Bromocinnamate to Aldehydes and Ketones

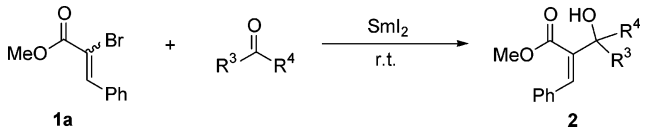


TABLE 1. Addition of Methyl α-Bromocinnamate 1a to Aldehydes and Ketones (R^1 = Ph)

entry	product	R^3	R^4	yield[a]	*Z*:*E*[b]
1	**2a**	Et	Me	79	>99:–
2	**2b**	cyclohexyl	Ph	22	>99:–
3	**2c**[c]	cyclohexyl	H	30	97.5:2.5

[a] Isolated yield (%) after column chromatography based on the starting α-bromo-α,β-unsaturated ester **1a**. [b] See text. [c] Reaction carried out in CH_3CN as solvent.

inversion of the stereochemistry of the C=C double bond took place, furnishing the *Z* stereoisomer.[11]

Here, we describe an efficient stereoconvergent coupling reaction of vinylsamarium reagents, derived from β-substituted-α-chloro-α,β-unsaturated esters **1**, with aldehydes and ketones, stereospecifically obtaining (*Z*)-alkylidene hydroxyesters **2**.[12] A mechanism is proposed to explain this transformation.

Results and Discussion

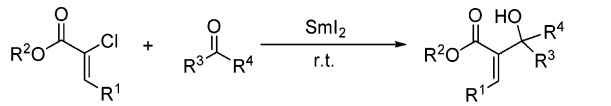
Preparation of Baylis–Hillman Adducts by Using Aromatic α-Halo-α,β-unsaturated Esters. Our studies were performed with 1:1 mixtures of methyl (*Z*/*E*)-2-bromocinnamate and ketones. Thus, the treatment of a solution of methyl (*Z*)- and (*E*)-2-bromocinnamate **1a** and a ketone in THF, with SmI_2, at room temperature afforded the corresponding (*Z*)-alkylidene hydroxyesters **2** in low or moderate yield and with very high or total *Z*-stereoselectivity (Scheme 1 and Table 1). It is noteworthy that, although a mixture of stereoisomers of 2-bromocinnamate **1a** is used as the starting compound in the described reactions, the corresponding (*Z*)-alkylidene hydroxyesters **2** were obtained with very high or total stereoselectivity, which was determined by ^{1}H NMR and GC-MS analysis on the crude products.

Ethyl (*Z*)-2-chlorocinnamate **1b** was used as an alternative starting compound to enhance the yield, taking into account the previous results obtained from α-haloenones, which showed that the SmI_2-promoted Baylis–Hillman reaction from chloroenones took place in higher yield than that from bromoenones (Scheme 2).

In this case, higher yields of the Baylis–Hillman adducts were obtained and with similar stereoselectivity (Table 2, entries 1, 3, and 4).

When the reaction was carried out with aldehydes under the same reaction conditions, complex mixtures of products resulted. To overcome this difficulty the reaction was performed in acetonitrile and consequently

SCHEME 2. Addition Reaction of Ethyl and Phenyl α-Chloro-α,β-unsaturated Esters to Aldehydes and Ketones



1b (R^1 = Ph, R^2 = Et)
3a (R^1 = *n*Bu, R^2 = Ph)
3b (R^1 = cyclohexyl, R^2 = Ph)

2 (R^1 = Ph, R^2 = Et)
4 (R^1 = *n*Bu, cyclohexyl; R^2 = Ph)

TABLE 2. Addition of Ethyl and Phenyl α-Chloro-α,β-unsaturated Esters 1b and 3 to Aldehydes and Ketones

entry	product	R^1	R^2	R^3	R^4	yield[a,b]
1	**2d**	Ph	Et	Et	Me	90
2	**2e**	Ph	Et	$-(CH_2)_4-$		65
3	**2f**	Ph	Et	cyclohexyl	Ph	73
4	**2g**[c]	Ph	Et	cyclohexyl	H	54
5	**2h**[c]	Ph	Et	$CH_3(CH_2)_6$	H	63
6	**4a**	*n*-Bu	Ph	$-(CH_2)_5-$		68
7	**4b**	*n*-Bu	Ph	$CH_3(CH_2)_5$	Me	57
8	**4c**	cyclohexyl	Ph	Et	Me	43
9	**4d**	cyclohexyl	Ph	$PhCH_2$	Me	50

[a] Isolated yield (%) after column chromatography based on the starting α-chloroester **1b** or **3**. [b] In all cases, the ^{1}H NMR and GC-MS analysis on the crude product showed the existence of the single *Z*-stereoisomer (*Z*:*E* = >99:–). [c] Reaction carried out in CH_3CN as solvent.

the SmI_2 was generated in this solvent from a mixture of 1,2-diiodoethane and samarium powder, using our previously published method.[10] Thus, the reaction of ethyl (*Z*)-2-chlorocinnamate **1b** with cyclic or linear aliphatic aldehydes in acetonitrile afforded compounds **2** (Table 2, entries 4 and 5). Similar to ketones, the yields of the reaction of bromocinnamate with aldehydes were lower than those obtained from chlorocinnamate (Table 1, entry 3 and Table 2, entry 4). The same reaction conditions with benzaldehyde provided the corresponding pinacol rather than the Baylis–Hillman adduct. Attempts to carry out the reaction with aromatic aldehydes in the presence of tetraethylene glycol dimethyl ether,[13] which can retard the pinacol coupling,[14] were also unsuccessful.

The stereisomeric purity of **2** was determined by ^{1}H NMR (300 MHz) and by GC-MS chromatography of the crude reaction mixtures. In all cases, except compound **2c** (de = 95%), other isomers were not detected in the crude reaction mixtures.

The *Z* stereochemistry of compounds **2** was established by NOESY experiments of compounds **2a**, **2d**, and **2g**. NOE effects were observed between the olefinic proton and the protons of methyl and ethyl groups of **2a** and **2d** (R^3= Et, R^4= Me), and between the olefinic hydrogen and the C*H*OH of **2g**. The relative configuration of the C=C of the other compounds **2** was assigned by analogy.

Preparation of Baylis–Hillman Adducts Starting from Aliphatic α,β-Unsaturated Esters. Important differences were observed when the above-described

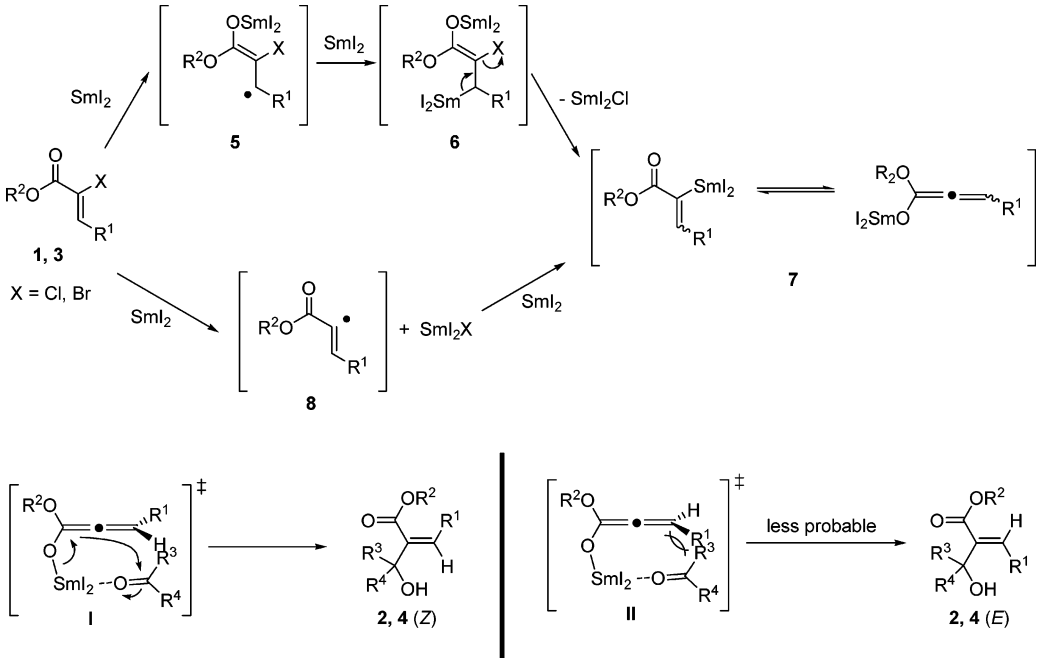
(11) Although a true inversion of configuration of the C=C double bond takes place, the nomenclature to designate the relative configuration of the starting unsaturated ketone and the Baylis–Hillman product is *Z* in both cases.

(12) This (*Z*)-adducts are complementary of those obtained by organocopper 1,4-adition-aldol reactions of propargylic esters, which can produce (*E*)-adducts: Kozlowski, J. A. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 5, pp 169–198.

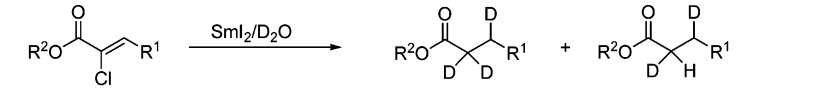
(13) Imamoto, T.; Hatajima, T.; Takiyama, N.; Takeyama, T.; Kamiya, Y.; Yoshizawa, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3127–3135.

(14) SmI_2 is strongly oxophilic and readily forms complexes with polyethers, and SmI_2–polyether complexes would display strong one-electron-transfer ability but with a reduced ability to coordinate with carbonyl oxygen, thus pinacol coupling would be reduced.

SCHEME 3. Proposed Mechanism



SCHEME 4. Reduction of α-Chloro-α,β-unsaturated Esters with SmI_2/D_2O



1b (R^1 = Ph, R^2 = Et)
3a (R^1 = *n*Bu, R^2 = Ph)

9 **10**

Yield (9a + 10a) 85%; **9a:10a** = 1:1 (R^1 = Ph, R^2 = Et)
Yield (9b + 10b) 92%; **9b:10b** = 1:1.3 (R^1 = *n*Bu, R^2 = Ph)

reaction conditions (in THF or acetonitrile) were applied to aliphatic β-substituted-α,β-unsaturated esters (R^1 and $R^2 \neq$ Ph). In these cases, mixtures of unreacted starting materials and dechlorinated starting esters were obtained. The use of NiI_2[15] or HMPA[16] to enhance the redox potential of SmI_2 was unsuccessful. None of the desired products were identified in the mixtures that were obtained. To overcome this limitation, phenyl esters **3** were prepared by treatment of phenyl 2,2-dichloro-3-hydroxyesters with samarium diiodide, following our previously described methodology.[17] When the phenyl β-substituted-α,β-unsaturated esters **3** were allowed to react with various ketones in THF, under the reaction conditions described above, the corresponding Baylis–Hillman adducts **4** were obtained in good to moderate yields and with total stereoselectivity. The reaction can also be performed with linear or cyclic aliphatic ketones (Scheme 2 and Table 2, entries 6–9).

The reaction of esters **3** with aldehydes under the same reaction conditions was unsuccessful. None of the desired products were identified in the mixtures that were obtained.

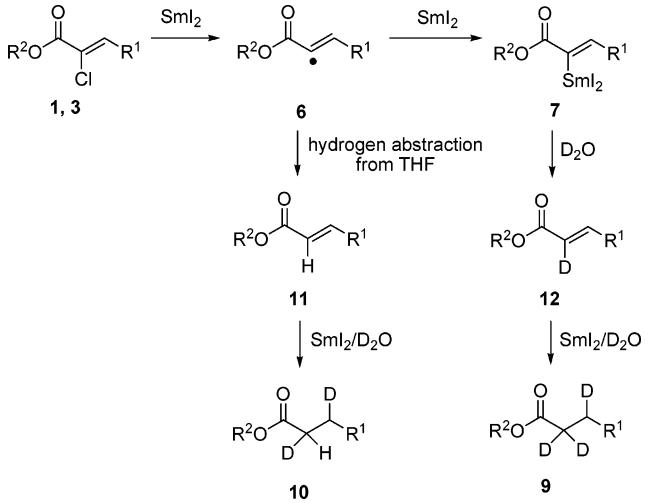
As with the reactions of aromatic unsaturated esters, the stereisomeric excess of the double bond of **4** (>98%) was determined by ^{1}H NMR and GC-MS of the crude reaction products. The *Z* stereochemistry of compounds **4** was also established by NOESY experiments of compound **4c**.

Mechanism. This reaction may be rationalized by assuming that the initial one-electron reduction of **1** or **3** with SmI_2 generates radical enolate **5** (Scheme 3), which can undergo a second electron transfer from another equivalent of SmI_2 affording a dianion **6**. An elimination of SmI_2Cl in **6** produces the vinylsamarium reagent **7**. Alternatively, the reduction of the C–Cl bond of **1** or **3** with SmI_2 can generate the radical **8** and its subsequent reduction affords the same vinylsamarium reagent **7**. Two transition states **I** and **II** are possible to justify the nucleophilic addition of **7** to the corresponding aldehyde or ketone. Transition state **I** is preferred, due to the steric repulsions between R^1 and R^3 or R^4 in **II**, and, consequently, the final product **2** or **4** is obtained with a *Z*-double bond.

Support for this proposed mechanism is provided by the synthesis of the corresponding 2,3-dideuterio- and 2,2,3-trideuterioesters from treatment of α-chloro-α,β-unsaturated esters **1b** and **3a** with samarium diiodide in the presence of D_2O (Scheme 4). The synthesis of the trideuterated ester **9** is a consequence of the successive deuteriolysis of the vinylsamarium reagent **7** followed by the reduction of the α-deuterio-α,β-unsaturated ester **12** with SmI_2 in the presence of D_2O (Scheme 5).[18] The formation of dideuterioester **10** can be explained as a consequence of an abstraction of hydrogen from THF and

(15) (a) Machrouhi, F.; Hamann, B.; Namy, J.-L.; Kagan, H. B. *Synlett* **1996**, 633–634. (b) Molander, C. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 7418–7429.
(16) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2005**, 3393–3403.
(17) Concellón, J. M.; Huerta, M.; Llavona, R. *Tetrahedron Lett.* **2004**, *45*, 4665–4667.

SCHEME 5. Proposed Mechanism for the Attainment of Di- and Trideuterated Esters 9 and 10



further reduction of the α,β-unsaturated ester **11** (Scheme 5). The same reaction of **1b** and **3a** with SmI_2 was carried out in the presence of H_2O instead of D_2O. Comparison of the ^1H and ^{13}C NMR data of the obtained nondeuterated esters with **9** and **10** allowed us to establish unambiguously the structure of **9** and **10**.

The powerful influence of the phenyl group of the aliphatic esters in the reaction can be explained by taking into account that the α-carbon of the starting aliphatic esters bearing the phenyl group is more electron deficient than the equivalent bearing alkyl groups. Thus, the vinyl radical can undergo further reduction by a reaction with a second equivalent of samarium diiodide to obtain a vinylsamarium reagent. This fact was in accordance with the Baylis–Hillman reaction of vinylsamarium reagent derived from acrylamides,[9] which only could be performed by using acrylamides derived from aromatic amines.

In conclusion, we have described the third example of the nucleophilic addition of vinylsamarium reagents, derived from α-chloro-β-substituted-α,β-unsaturated esters, to ketones or aldehydes. (*Z*)-α-Alkylidene-β-hydroxyesters **2** or **4** were isolated in good yield and with high or total selectivity. The reaction between aromatic α-halo-α,β-unsaturated esters and aldehydes was carried out in acetonitrile. This described reaction constitutes an efficient alternative to obtain the Baylis–Hillman adducts derived from β-substituted alkenoates and ketones under mild reaction conditions. A mechanism has been proposed to explain the reaction.

Experimental Section

Preparation of a Geometrical Isomer Mixture of Methyl α-Bromocinnamate. Bromine (0.72 mL) was added to a solution of commercially available methyl cinnamate (2 g) in dichloromethane (20 mL) at 0 °C. The reaction was stirred for 3 h and then triethylamine (10 mL) was added at room temperature. The resulting mixture was stirred for a further 4 h, quenched with NH_4Cl, and extracted with dichloromethane (3 × 20 mL), then the organic layers were combined and washed with aqueous HCl (1 M, 2 × 20 mL). The sample was concentrated in vacuo to obtain the pure ester **1a** in 87% yield as a 1:1 mixture of *Z*/*E* stereoisomers.

Methyl (*Z*/*E*)-2-bromo-3-phenylpropenoate (1a): ^1H NMR (300 MHz, $CDCl_3$) δ 8.22–7.30 (m, 12 H), 3.86 (s, 3 H), 3.72 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4 (C), 163.3 (C), 140.7 (CH), 139.6 (CH), 134.3 (C), 133.2 (C), 129.9 (3 × CH), 128.6 (CH), 128.1 (4 × CH), 127.8 (2 × CH), 112.1 (C), 110.6 (C), 53.2 (CH_3), 52.6 (CH_3); IR (neat) $\tilde{\nu}$ 3063, 3030, 2996, 2952, 1734, 1610, 1447, 1240, 1031 cm^{-1}.

Synthesis of Ethyl (*Z*)-α-Chlorocinnamate 1b.[19] A solution of $NaClO_2$ (8 g) in water (70 mL) was added dropwise over 2 h to a stirred mixture of α-chlorocinnamaldehyde (6.6 g) in acetonitrile (50 mL), NaH_2PO_4 (1.6 g) in water (20 mL), and 5.0 mL of 35% H_2O_2, maintaining a temperature of 10 °C by water cooling. Oxygen evolved from the solution was monitored until the end of the reaction (about 1 h) with a bubbler connected to the apparatus. A small amount (0.5 g) of Na_2SO_3 was added to destroy the unreacted HOCl and H_2O_2. Acidification with 10% aqueous HCl afforded α-chlorocinnamic acid as a crystalline solid.

The esterification of the resulting carboxylic acid was carried out with EtOH (50 mL) and chlorotrimethylsilane (2.8 mL) at reflux overnight. The reaction was quenched with water, the solid removed by filtration, and the liquid-phase extracted with dichloromethane and concentrated in vacuo to obtain the ethyl α-chlorocinnamate in 85% yield.

(*Z*)-2-Chloro-3-phenylpropenoic acid: ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.93–7.90 (m, 2 H), 7.50–7.28 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (C), 139.2 (CH), 132.5 (C), 130.9 (CH), 130.7 (CH), 128.6 (CH), 120.9 (C).

Ethyl (*Z*)-2-chloro-3-phenylpropenoate (1b): ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1 H), 7.87–7.81 (m, 2 H), 7.45–7.39 (m, 3 H), 4.35 (q, J = 6.9 Hz, 2 H), 1.38 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1 (C), 136.6 (CH), 132.7 (C), 130.4 (CH), 129.9 (CH), 128.3 (CH), 121.9 (C), 62.3 (CH_2), 14.0 (CH_3).

Attainment of the Baylis–Hillman Adducts by Reaction of α-Haloacrylates with Ketones. To a solution of SmI_2 (1.2 mmol) in dry THF (15 mL) was added in one step a solution of the corresponding α-halo-α,β-unsaturated ester (0.4 mmol) and the ketone (0.8 mmol) in THF (2 mL). The reaction mixture was stirred for 12 h at room temperature and then quenched with aqueous HCl (0.1 M), extracted with dichloromethane, and concentrated in vacuo. The purification of the resulting product by flash column chromatography over silica gel (hexane/AcOEt 20:1) gave the pure Baylis–Hillman adduct.

Methyl (*Z*)-2-[(1-hydroxy-1-methyl)propyl]-3-phenylpropenoate (2a): R_f 0.22 (hexane/AcOEt 5:1); HRMS ^1H NMR (200 MHz, $CDCl_3$) δ 7.29–7.26 (m, 5 H), 6.82 (s, 1 H), 3.64 (s, 3 H), 2.55 (br s, 1 H), 1.80 (dq, J = 7.4, J = 3.3 Hz, 2 H), 1.49 (s, 3 H), 0.96 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (C), 140.5 (C), 135.6 (C), 129.5 (CH), 128.2 (CH), 127.8 (CH), 127.7 (CH), 74.5 (C), 51.7 (CH_3), 34.0 (CH_2), 26.9 (CH_3), 8.1 (CH_3); MS (70 eV, EI) *m*/*z* (%) 234 [M^+] (<1), 205 (51), 173 (100), 159 (8), 145 (7), 131 (98), 115 (20), 103 (44), 91 (16), 77 (31); IR (neat) $\tilde{\nu}$ 3459, 3083, 3024, 2977, 2945, 2881, 1713, 1637, 1494, 1447, 1372, 1203 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1248. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.84; H, 7.87.

Methyl (*Z*)-2-[(cyclohexylhydroxyphenyl)methyl]-3-phenylpropenoate (2b): R_f 0.37 (hexane/AcOEt 5:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.51–7.05 (m, 11 H), 3.42 (s, 3 H), 2.41–1.15 (m, 11 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.3 (C), 143.0 (C), 138.8 (C), 135.7 (C), 130.6 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 126.8 (CH), 125.9 (CH), 80.1 (C), 51.6 (CH_3), 44.5 (CH), 27.1 (CH_2), 26.5 (CH_2), 26.4 (CH_2); MS (70 eV, EI) *m*/*z* (%) 350 [M^+] (<1), 267 (27), 235 (61), 207 (6), 179 (9), 167 (9), 105 (100), 91 (9), 83 (16), 77 (32); IR (neat) $\tilde{\nu}$ 3527, 3058,

(18) To see reduction of α,β-unsaturated esters promoted by SmI_2 in the presence of H_2O or D_2O: Concellón, J. M.; Rodríguez-Solla, H. *Chem. Eur. J.* **2001**, *7*, 4266–4271.

(19) Dalcanale, E. *J. Org. Chem.* **1986**, *51*, 567–569.

3026, 2933, 2852, 1755, 1493, 1446, 1265, 1217, 1069 cm^{-1}; HRMS calcd for $C_{23}H_{26}O_3$ 350.1882, found 350.1901.

Ethyl (*Z*)-2-[(1-hydroxy-1-methyl)propyl]-3-phenylpropenoate (2d): R_f 0.30 (hexane/AcOEt 3:1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.30−7.27 (m, 5 H), 6.84 (s, 1 H), 4.13 (q, J = 7.2 Hz, 2 H), 2.63 (br s, 1 H), 1.85−1.74 (m, 2 H), 1.49 (s, 3 H), 1.08 (t, J = 7.2 Hz, 3 H), 0.97 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.9 (C), 140.8 (C), 135.7 (C), 129.4 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 74.5 (C), 60.8 (CH_2), 34.0 (CH_2), 26.7 (CH_3), 13.5 (CH_3), 8.1 (CH_3); MS (70 eV, EI) *m/z* (%) 248 [M^+] (7), 219 (37), 173 (100), 159 (7), 131 (92), 115 (11), 103 (28), 91 (10), 77 (20); IR (neat) $\tilde{\nu}$ 3490, 3059, 3026, 1976, 2880, 1720, 1462, 1372, 1206, 1034 cm^{-1}; HRMS calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1415.

Ethyl (*Z*)-2-(1-hydroxycyclopentyl)-3-phenylpropenoate (2e): R_f 0.32 (hexane/AcOEt 3:1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.29−7.27 (m, 5 H), 6.91 (s, 1 H), 4.14 (q, J = 10.8 Hz, 2 H), 2.63 (br s, 1 H), 1.94−1.76 (m, 8 H), 1.09 (t, J = 10.8 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.1 (C), 139.6 (C), 135.6 (C), 129.4 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 82.6 (C), 60.9 (CH_2), 38.9 (CH_2), 23.2 (CH_2), 13.6 (CH_3); MS (70 eV, EI) *m/z* (%) 260 [M^+] (<1), 242 (10), 213 (11), 197 (6), 185 (15), 169 (100), 153 (12), 141 (57), 128 (16), 115 (19), 102 (13), 91 (21), 77 (14); IR (neat) $\tilde{\nu}$ 3446, 3060, 2960, 2872, 1721, 1638, 1446, 1372, 1206, 1108, 1019 cm^{-1}; HRMS calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1427.

Ethyl (*Z*)-2-[(cyclohexylhydroxyphenyl)methyl]-3-phenylpropenoate (2f): R_f 0.33 (hexane/AcOEt 7:1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.52−7.26 (m, 10 H), 7.07 (s, 1 H), 3.90 (q, J = 7.1 Hz, 2 H), 3.34 (br s, 1 H), 1.94−1.49 (m, 11 H), 0.86 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.8 (C), 143.0 (C), 138.9 (C), 135.8 (C), 130.5 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 126.7 (CH), 126.1 (CH), 80.1 (C), 60.6 (CH_2), 44.3 (CH), 27.5 (CH_2), 27.0 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 13.3 (CH_3); MS (70 eV, EI) *m/z* (%) 346 [$M^+ - H_2O$] (3), 281 (38), 235 (84), 188 (14), 131 (26), 105 (100), 77 (45), 55 (35); IR (neat) $\tilde{\nu}$ 3523, 3083, 3025, 2923, 2851, 1712, 1493, 1446, 1372, 1211, 1068, 1017 cm^{-1}; HRMS calcd for $C_{24}H_{28}O_3$ 364.2038, found 364.2031. Anal. Calcd for $C_{24}H_{28}O3$: C, 79.09; H, 7.74. Found: C, 79.45; H, 7.69.

Phenyl (*Z*)-2-(1-hydroxycyclohexyl)hept-2-enoate (4a): R_f 0.28 (hexano/AcOEt 5:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.16 (m, 5 H), 6.12 (t, J = 7.5 Hz, 1 H), 2.40 (apparent q, J = 6.8 Hz, 2 H), 1.98−1.27 (m, 14 H), 0.96 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0 (C), 150.2 (C), 139.6 (C), 135.1 (CH), 129.4 (CH), 125.9 (CH), 121.5 (CH), 72.6 (C), 38.9 (CH_2), 31.2 (CH_2), 29.5 (CH_2), 25.3 (CH_2), 22.2 (CH_2), 21.8 (CH_2), 13.8 (CH_3); MS (70 eV, EI) *m/z* (%) 302 [M^+] (<1), 284 (6), 208 (97), 191 (90), 165 (40), 135 (50), 106 (48), 93 (100), 79 (83), 65 (80); IR (neat) $\tilde{\nu}$ 3446, 2933, 2859, 1737, 1605, 1455, 1368, 1265, 1185, 1127, 973 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.83; H, 8.76.

Phenyl (*Z*)-2-[(1-hydroxy-1-methyl)heptyl]hept-2-enoate (4b): R_f 0.22 (hexane/AcOEt 5:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.11 (m, 5 H), 6.08 (t, J = 7.7 Hz, 1 H), 2.59 (br s, 1 H), 2.40 (apparent q, J = 6.7 Hz, 2 H), 1.85−0.89 (m, 23 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6 (C), 150.3 (C), 138.4 (C), 136.1 (CH), 129.5 (CH), 126.0 (CH), 121.5 (CH), 74.4 (C), 41.6 (CH_2), 31.8 (CH_2), 31.4 (CH_2), 29.5 (CH_2), 27.4 (CH_3), 24.1 (CH_2), 22.5 (CH_2), 22.3 (CH_2), 13.9 (CH_3), 13.8 (CH_3); MS (70 eV, EI) *m/z* (%) 239 [M^+ − OPh] (91), 221 (47), 193 (36), 181 (22), 153 (53), 137 (47), 123 (35), 109 (43), 94 (100); IR (neat) $\tilde{\nu}$ 3455, 2956, 2929, 2858, 1745, 1606, 1492, 1466, 1377, 1186, 1124 cm^{-1}; HRMS calcd for $C_{21}H_{32}O_3$ 332.2351, found 332.2324.

Phenyl (*Z*)-3-cyclohexyl-2-[(1-hydroxy-1-methyl)propyl]propenoate (4c): R_f 0.23 (hexane/AcOEt 5/1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.47−7.12 (m, 5 H), 5.86 (d, J = 10.0 Hz, 1 H), 3.8 (br s, 1 H), 1.83−1.74 (m, 8 H), 1.47 (s, 3 H), 1.36−1.09 (m, 5 H), 0.94 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2 (C), 150.3 (C), 140.6 (CH), 136.4 (C), 129.5 (CH), 125.9 (CH), 121.5 (CH), 74.4 (C), 39.1 (CH), 34.2 (CH_2), 32.8 (CH_2), 26.9 (CH_3), 25.7 (CH_2), 25.6 (CH_2), 8.4 (CH_3); MS (70 eV, EI) *m/z* (%) 302 [M^+] (<1), 284 (4), 273 (12), 209 (95), 191 (92), 179 (42), 173 (27), 163 (48), 108 (52), 93 (100), 80 (52), 66 (55); IR (neat) $\tilde{\nu}$ 3458, 2975, 2926, 2850, 1765, 1593, 1504, 1450, 1377, 1189 cm^{-1}; HRMS calcd for $C_{19}H_{26}O_3$ 302.1882, found 302.1864.

Phenyl (*Z*)-3-cyclohexyl-2-[(1-hydroxy-1-methyl-2-phenyl)ethyl]propenoate (4d): R_f 0.20 (hexano/AcOEt 5:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.79−7.19 (m, 10 H), 5.57 (d, J = 10.0 Hz, 1 H), 3.14 (AB system, J = 13.3 Hz, 2 H), 1.94−1.6 (m, 5 H), 1.50 (s, 3 H), 1.28−0.99 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5 (C), 150.4 (C), 141.6 (CH), 136.6 (C), 135.2 (C), 130.8 (CH), 129.5 (CH), 127.9 (CH), 126.0 (CH), 121.6 (CH), 74.0 (C), 47.6 (CH_2), 39.0 (CH), 32.5 (CH_2), 32.4 (CH_2), 27.3 (CH_3), 25.9 (CH_2), 25.7 (CH_2), 25.6 (CH_2); MS (70 eV, EI) *m/z* (%) 272 [M^+ − OPh + 1] (52), 271 [M^+ − OPh] (52), 253 (48), 179 (100), 143 (40), 91 (53); IR (neat) $\tilde{\nu}$ =3477, 3062, 3029, 2926, 2851, 1754, 1592, 1493, 1450, 1381, 1265, 1186 cm^{-1}. Anal. Calcd for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74. Found: C, 79.26; H, 7.97.

Preparation of the Product from the Coupling of α-Halo-α,*β*-unsaturated Esters and Aldehydes. To a solution of SmI_2 (0.9 mmol) in CH_3CN (12 mL) was added in one step a solution of α-halo-α,*β*-unsaturated ester (0.4 mmol) and the corresponding aldehyde (0.8 mmol) in dry CH_3CN (2 mL). The resulting reaction mixture was stirred at room temperature for 24 h, and quenched with aqueous HCl (0.1 N). Usual workup and purification by flash column chromatography over SiO_2 (hexane/AcOEt 20:1) yielded the correponding adduct.

Methyl (*Z*)-2-(cyclohexylhydroxymethyl)-3-phenylpropenoate (2c): R_f 0.17 (hexane/AcOEt 5:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.21 (m, 5 H), 6.80 (s, 1 H), 4.08 (d, J = 7.4 Hz, 1 H), 3.67 (s, 3 H), 2.09−0.89 (m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5 (C), 135.2 (C), 135.0 (C), 134.4 (CH), 128.1 (4 × CH), 128.0 (CH), 79.6 (CH), 51.7 (CH_3), 42.3 (CH), 29.6 (CH_2), 28.5 (CH_2), 26.2 (CH_2), 25.9 (CH_2), 25.8 (CH_2); MS (70 eV, EI) *m/z* (%) 274 [M^+] (<1), 191 (62), 159 (100), 131 (38), 103 (45), 77 (28), 55 (58); IR (neat) $\tilde{\nu}$ 3333, 3057, 3025, 1940, 2860, 1708, 1459, 1217, 1082 cm^{-1}; HRMS calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1558. Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.60; H, 8.06.

Ethyl (*Z*)-2-(cyclohexylhydroxymethyl)-3-phenylpropenoate (2g): R_f 0.22 (hexane/AcOEt 3:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29−7.27 (m, 5 H), 6.80 (s, 1 H), 4.21−4.09 (m, 3 H), 2.71 (br s, 1 H), 1.74−1.58 (m, 11 H), 1.07 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 (C), 135.4 (C), 134.3 (CH), 128.2 (CH), 128.0 (CH), 79.8 (CH), 60.8 (CH_2), 42.4 (CH), 29.6 (CH_2), 28.6 (CH_2), 26.3 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 13.6 (CH_3); MS (70 eV, EI) *m/z* (%) 288 [*M*$^+$] (5), 243 (11), 225 (12), 205 (96), 177 (22), 158 (100), 131 (82), 115 (35), 102 (92), 91 (33), 83 (35), 76 (46); IR (neat) $\tilde{\nu}$ 3470, 3084, 3026, 2926, 2852, 1751, 1450, 1393, 1224, 1021 cm^{-1}; HRMS calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1772. Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.82; H, 8.06.

Ethyl (*Z*)-2-(1-hydroxyoctyl)-3-phenylpropenoate (2h): R_f 0.25 (hexane/AcOEt 5:1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.36−7.20 (m, 5 H), 6.9 (s, 1 H), 4.42−4.36 (m, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 2.06−1.20 (m, 12 H), 1.1 (t, J = 7.1 Hz, 3 H), 0.88 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (C), 136.7 (C), 135.4 (C), 133.1 (CH), 128.2 (CH), 128.0 (CH), 74.5 (CH), 60.8 (CH_2), 36.1 (CH_2), 31.7 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 25.6 (CH_2), 22.5 (CH_2), 14.0 (CH_3), 13.6 (CH_3); MS (70 eV, EI) *m/z* (%) 304 [M^+] (2), 286 (9), 231 (13), 205 (100), 177 (41), 159 (100), 141 (17), 131 (42), 115 (30), 103 (36), 91 (32), 77 (31); IR (neat) $\tilde{\nu}$ 3445, 3082, 3059, 3026, 2952, 2855, 1720, 1466, 1377, 1223, 1093, 1029 cm^{-1}; HRMS calcd for $C_{19}H_{28}O_3$ 304.2038, found 304.2026.

Reduction of Esters 1b and 3a with Use of SmI_2/H_2O or SmI_2/D_2O. A solution of the corresponding α-chloro-α,*β*-unsaturated ester (0.4 mmol) in THF (2 mL) was added to a solution of SmI_2 (2.4 mmol) in THF (30 mL) and deoxygenated water (2 mL; deoxygenation was achieved by bubbling nitrogen through the water for 5 min). The reaction was stirred at room

temperature for 12 h. The remaining samarium diiodide was oxydized by bubbling air through the reaction mixture, and the reaction was quenched with HCl (0.1 N). The usual workup yielded the corresponding saturated ester.

When D_2O was used instead of H_2O, it was necessary to stir the reaction mixture for a longer time (2 days).

Ethyl 3-phenylpropanoate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94−7.22 (m, 5 H), 4.16 (q, J = 7.2 Hz, 2 H), 2.98 (t, J = 7.4 Hz, 2 H), 2.65 (t, J = 7.4 Hz, 2 H), 1.26 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9 (C), 140.4 (C), 128.4 (CH), 128.2 (CH), 126.2 (CH), 60.3 (CH_2), 35.5 (CH_2), 30.5 (CH_2), 14.1 (CH_3); MS (70 eV, EI) *m/z* (%) 178 [M^+] (36), 133 (13), 107 (42), 105 (44), 104 (100), 91 (54), 77 (11).

Ethyl 2,2,3-trideuterio-3-phenylpropanoate and ethyl 2,3-dideuterio-3-phenylpropanoate (9a and 10a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94−7.22 (m, 10 H), 4.16 (q, J = 7.2 Hz, 4 H), 2.98 (br s, 2 H; 2 × CHDPh), 2.65 (br s, 1 H; $CHDCO_2$), 1.26 (t, J = 7.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9 (C), 140.4 (C), 128.4 (CH), 128.2 (CH), 126.15 (CH), 60.3 (CH_2), 35.5 (CHD, t, J(C,D) = 19.7 Hz), 30.5 (CHD + CD_2, apparent dt, J(C,D) = 19.7 Hz, J(C,D) = 4.6 Hz), 14.1 (CH_3); MS (70 eV, EI) *m/z* (%) 181 (32), 180 (34), 136 (13), 135 (14), 108 (100), 107 (98), 106 (91), 92 (98), 81 (14), 80 (23), 79 (21), 78 (25).

Phenyl heptanoate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.10 (m, 5 H), 2.6 (t, J = 7.5 Hz, 2 H), 1.95−1.30 (m, 8 H), 0.96 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (C), 150.7 (C), 129.2 (CH), 125.6 (CH), 121.4 (CH), 34.3 (CH_2), 32.2 (CH_2), 28.6 (CH_2), 24.8 (CH_2), 22.4 (CH_2), 13.9 (CH_3).

Phenyl 2,2,3-trideuterioheptanoate and phenyl 2,3-dideuterioheptanoate (9b and 10b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.10 (m, 10 H), 2.6 (br s, 1 H; O_2CCHD), 1.95−1.30 (m, 14 H; 6 × CH_2 + 2 × CHD), 0.96 (t, J = 6.6 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (C), 150.7 (C), 129.2 (CH), 125.6 (CH), 121.4 (CH), 34.3 (CH_2), 32.2 (CHD + CD_2, apparent dt J(C,D) = 20.1 Hz, J(C,D) = 4.5 Hz; C_α), 28.6 (CH_2), 24.8 (CHD, t, J(C,D) = 19.9 Hz; C_β), 22.4 (CH_2), 13.9 (CH_3); MS (70 eV, EI) *m/z* (%) 209 (17), 208 (17), 116 (56), 115 (78), 95 (100), 94 (71), 87 (25), 86 (38), 77 (23), 65 (33).

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Supporting Information Available: ^{13}C NMR spectra of compounds **2** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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