The First Enantioselective Halo Aldol Reaction of Ethyl Propiolate and Aldehydes

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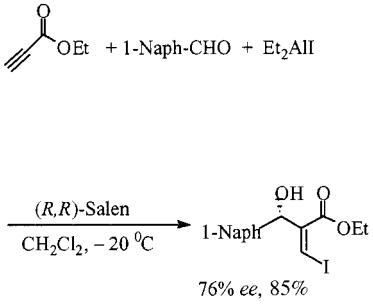
The first enantioselective halo aldol reaction of ethyl propiolate with aldehydes has been established by using Jacobsen's chiral cyclohexylsalen ligand. The reaction was conducted at –20 °C in dichloromethane with Et_2AlI as the source of halogen and Lewis acid promoter. Excellent geometric selectivity (only the *Z* isomer) has been achieved for all 14 examples examined. The reaction works well with aromatic aldehydes; it also works with aliphatic aldehydes and α,β-unsaturated aldehydes, albeit with diminished yields and *ee*. This method provides the first enantioselective synthesis of β-iodo Morita–Baylis–Hillman (MBH) esters.

Introduction

The asymmetric aldol reaction is among the most important carbon−carbon bond formation reaction in organic chemistry.[1−3] However, the halo aldol reaction and its asymmetric versions have not been well explored thus far. Recently, we and others reported several halo aldol reactions and the corresponding asymmetric versions.[4,5] These reactions led to versatile building blocks that can be functionalized with an array of functional groups, and therefore, can serve as important precursors to a variety of chemically and biologically important compounds. One of our previous asymmetric halo aldol processes deals with the reaction of α,β-unsaturated ketones with aldehydes in the presence of *N*-C_3F_7CO oxazaborolidine catalyst[2,4a] in which the fluorinated protecting group was found to play a crucial role in controlling enantiomeric and geometric selectivities. This asymmetric reaction provided the first enantioselective approach to β-halo Morita−Baylis−Hillman (MBH) [6,7] ketones.

In our next study we tried to establish an asymmetric approach to β-halo Morita−Baylis−Hillman (MBH) esters which are more useful than their ketone counterparts in organic synthesis. Our initial attempts at using allenoates to replace allenolates for the asymmetric reaction under similar catalytic conditions[4a] resulted in very limited success. Essentially, the *N*-C_3F_7CO oxazaborolidine catalyst did not result in any enantioselectivity. Later, a chiral auxiliary-controlled asymmetric strategy with (1*R*,2*S*,5*R*)-menthol was utilized for the synthesis of chiral β-iodo Morita−Baylis−Hillman esters.[8] However, this method suffered as a result of the extra steps for the chiral auxiliary coupling/cleavage. In this paper, we would like to report that β-halo Morita−Baylis−Hillman (MBH) esters can be enantiomerically synthesized by reacting allenoate with aldehydes in the presence of Jacobsen's chiral salen ligand.[9] This method indeed presents the first enantioselective synthesis of β-iodo MBH esters as represented by Scheme 1.



Scheme 1

Results and Discussion

Benzaldehyde was used as the electrophile to react with β-iodoallenoate for the model reaction study. Since MgI_2 has been successfully utilized in the racemic and chiral auxiliary-directed halo aldol reaction of allenoates with aldehydes and since it is also very easy to handle,[10] it was first tested as both a halogen source and a Lewis acid activator for the present system. Unfortunately, when two common chiral ligands (**A** and **B**, Figure 1) were coordinated to MgI_2, the desired product was not observed.

Et_2AlI was then used for the formation of chiral complexes with a variety of enantiomerically pure protic li-

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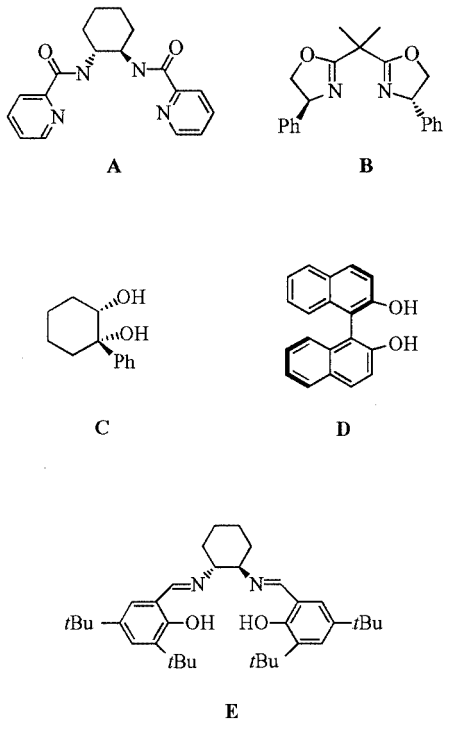
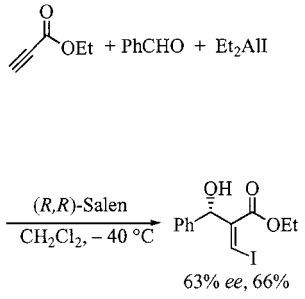


Figure 1. Chiral ligands for halo aldol reaction

gands, such as vicinal diols, binaphthol and Jacobsen's salen ligand (Figure 1). It was found the ligands **C** and **D** did give the desired MBH esters; however, enantiomeric excesses were poor (less than 13% *ee*). To our satisfaction, when Jacobsen's chiral cyclohexylsalen ligand **E** was utilized, an enantiomerically enriched product was generated to give *ee* of 63% and a chemical yield of 71% (Scheme 2).



Scheme 2

The reaction conditions were optimized by varying the solvents, temperatures and reactant loading sequences. The reaction did not proceed in THF, Et_2O, or CH_3CN (Entry 1−3, Table 1); only CH_2Cl_2 and toluene proved to be effective for this reaction, and CH_2Cl_2 was superior in most cases. In the case of benzaldehyde, the two solvents gave similar yields and enantioselectivities (Entry 4−7, Table 1). However, for other substrates, such as 4-benzoxybenzaldehyde and 1-naphthaldehyde, the reaction gave lower yields and enantiomeric excesses in toluene (Entries 9−12, Table 1) than in CH_2Cl_2. This is probably due to the low solubility of the reaction species in toluene at low temperature since some solids were observed during the reaction process. As indicated in Table 1, the optimal reaction temperature is −20 °C; lowering the temperature to −40 °C did not lead to better enantioselectivity. Furthermore, there were no products detected at −78 °C in either CH_2Cl_2 or toluene.

Table 1. Solvent and temperature effects on aromatic aldehyde-based reactions

Entry	R	Solvent	Temperature (°C)	Yield (%)[a]	*ee* %[b]
1	Ph	THF	−20	no reaction	
2	Ph	Et_2O	−20	no reaction	
3	Ph	CH_3CN	−20	no reaction	
4	Ph	toluene	−20	62	40
5	Ph	toluene	−40	65	64
6	Ph	CH_2Cl_2	−20	71	63
7	Ph	CH_2Cl_2	−40	66	64
8	Ph	CH_2Cl_2	−78	no reaction	
9	4-BnO−C_6H_4	toluene	−20	50	47
10	4-BnO−C_6H_4	CH_2Cl_2	−20	62	49
11	1-Naph	toluene	−20	35	43
12	1-Naph	CH_2Cl_2	−20	57	76

[a] The yields after purification by column chromatography. [b] All enantiomer excesses were determined by chiral HPLC using chiral OD-H or AD columns with isopropyl alcohol and hexane as the mobile phase.

Interestingly, the manner in which the reactants were loaded was found to be very important with regard to both enantioselectivity and yields, as can be seen from Table 2. Firstly, Et_2AlI should be added to the solution of salen ligand over a period of 30 minutes with a syringe pump; the resulting solution should then be stirred at room temperature for about 1 hour. Secondly, the in situ pre-prepared metal complex should be slowly transferred to the mixture of ethyl propiolate and aldehyde.

Based on the optimization results, the reaction was carried out in CH_2Cl_2 solution at −20 °C, with the slow addition of Et_2AlI. In addition, ethyl propiolate was loaded in two portions (as described in Exp. Sect.) which further improves the yields. The results are shown in Table 3.

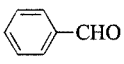
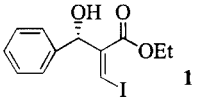
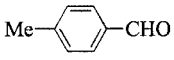
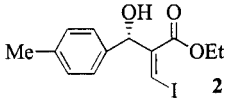
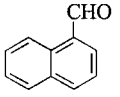
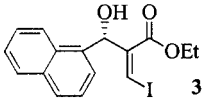
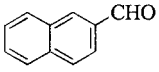
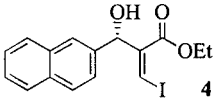
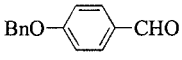
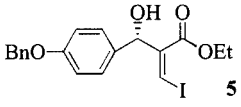
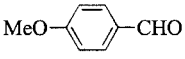
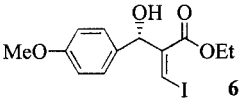
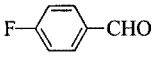
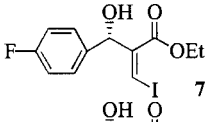
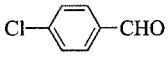
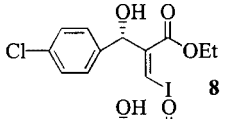
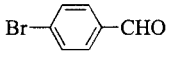
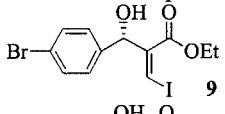
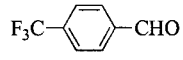
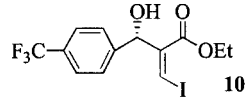
A noteworthy aspect of the optimized conditions is the complete *E*/*Z* selectivity as revealed by proton NMR spectroscopy. Only *Z* isomers were observed in all examples; this is better than the results obtained from our previous asymmetric synthesis of MBH ketones.[4a] The *E*/*Z* configuration was revealed by ROSEY NMR spectroscopic experiments, as mentioned in our previous papers.[8,10] The absolute configuration of the major enantiomeric isomer was determined by chemical correlation. Product 1 (Entry 1, Table 3) was transformed to methyl-α-methoxyphenyl acetate, its ^1H NMR and chiral HPLC data were compared with an authentic sample. The determination of the absolute configuration is done by chemical correlation as demonstrated in Scheme 3.

Table 2. Effect of experimental conditions on the benzaldehyde-based reaction

Entry	Solvent	Addition of Et_2AlI	Temperature (°C)	Yield (%)[a]	*ee* %[b]
1	toluene	slow addition	−40	65	64
2	toluene	dropwise	−40	20	39
3	CH_2Cl_2	slow addition	−20	71	63
4	CH_2Cl_2	dropwise	−20	40	25

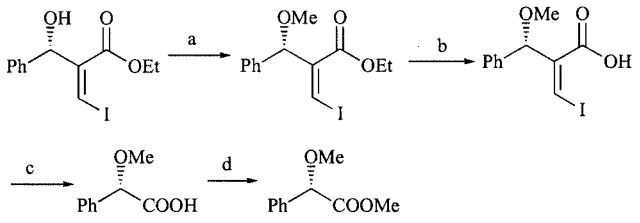
[a] The yields after purification by column chromatography. [b] Enantiomer excesses were determined by chiral HPLC using a chiral OD-H column with isopropyl alcohol and hexane as the mobile phase.

Table 3. Results of asymmetric halo aldol reactions with aromatic aldehydes

Entry	Aldehyde	Product	Reaction time (h)	*ee* (%)[a]	Yield (%)[b]
1		 **1**	36	63	71
2		 **2**	48	63	75(88)
3		 **3**	48	76	57(85)
4		 **4**	48	66	80(92)
5		 **5**	60	49	62(91)
6		 **6**	60	59	55(91)
7		 **7**	36	55	65(82)
8		 **8**	36	59	71(81)
9		 **9**	36	64	74(92)
10		 **10**	36	53[c]	73

[a] In all cases, only *Z* isomers were observed from crude ^1H NMR spectroscopic analysis. Enantiomeric excesses were determined by chiral HPLC using chiral OD-H or AD columns with isopropyl alcohol and hexane as the mobile phase. [b] The yields after purification by column chromatography. Yields in parentheses were calculated based on recovered starting materials. [c] HPLC determination of its mesyl-protected derivative.

As can be seen from Table 3, the reaction worked well for a wide range of aromatic aldehydes. Almost all aromatic aldehydes gave similar enantioselectivities; 1-naphthaldehyde gave the highest *ee* of 76% (Entry 3, Table 3). The aromatic aldehydes that have electron-donating groups required longer reaction times than benzaldehyde (Entries 5 and 6, Table 3). It is worth noting that for the trifluorotolualdehyde-derived product (Entry 10, Table 3) it



Scheme 3. Reaction conditions: a) MeI, Ag_2O, MeCN, reflux for 4 h; b) NaOH, MeOH/H_2O, room temperature; c) H_5IO_6, $RuCl_2$, CCl_4/MeCN/H_2O (v/v, 1:1:2); d) MeOH, TMSCl

was extremely difficult to determine the *ee* value by HPLC. This determination was achieved by converting it into its mesyl-(methylsulfonyl-)protected derivative and by using a chiral AD column with hexane/isopropyl alcohol (v/v, 20:1) as the mobile phase. It should be noted that other protecting groups, such as methyl, benzyl, tosyl groups, among others, were not useful for this determination.

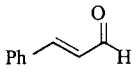
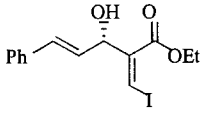
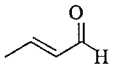
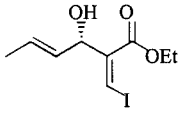
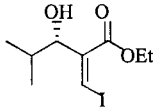
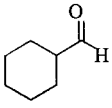
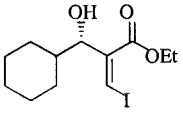
So far, only four aliphatic aldehydes were subjected to the present reaction (Table 4). Unfortunately, the chemical yields and enantiomeric excesses were all lower than those of their aromatic counterparts. Further study of this new asymmetric reaction will be continued in our laboratories.

The *Z*-geometry preference of the product is illustrated in Scheme 4; the *Z* isomer is formed as a kinetically controlled product, which results from the less hindered chair-like transition state.

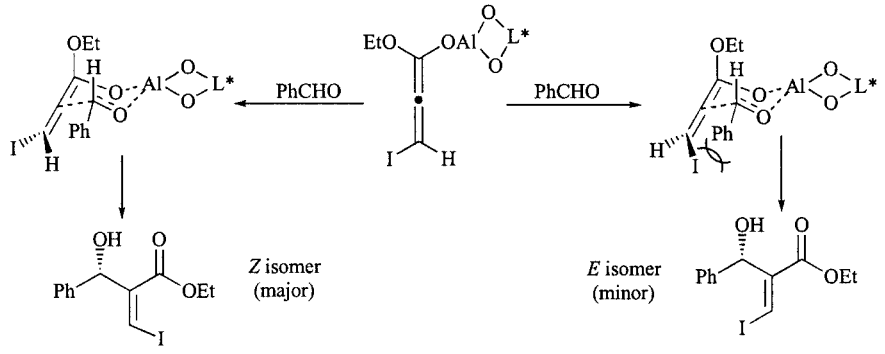
Conclusion

The first enantioselective halo aldol reaction of ethyl propiolate with aldehydes has been developed by using Jacobsen's chiral salen ligand. This method serves as the first enantioselective synthesis of β-iodo Morita−Baylis−Hillman (MBH) esters. The reaction showed broad substrate scope and gave modest to good enantioselectivities and chemical yields. The absolute structure has been unambiguously determined by chemical correlation using ^{1}H NMR spec-

Table 4. Results of asymmetric halo aldol reactions with aliphatic aldehydes

Entry	Aldehyde	Product	*ee* (%)[a]	Yield (%)[b,c]
1		 **11**	33	35 (74)
2		 **12**	36	37
3		 **13**	48	45
4		 **14**	47	46 (60)

[a] Enantiomer excesses were determined by chiral HPLC using chiral OD-H or AD columns with isopropyl alcohol and hexane as the mobile phase. [b] The yields after purification by column chromatography. Yields in parentheses were calculated based on recovered starting materials. [c] All reactions were performed within 48 h.



Scheme 4

troscopy and chiral HPLC. Excellent *E*/*Z* selectivity has been achieved for all examples examined.

Experimental Section

Typical Reaction Procedure: In a dry vial, under inert gas protection, a solution of Et_2AlI (1 M in toluene, 0.41 mL, 0.41 mmol) was added slowly to a CH_2Cl_2 solution (2 mL) of (*R*,*R*)-Salen (0.22 g, 0.40 mmol) with a syringe pump over a period of 30 min. The resulting solution was stirred at room temperature for 1 hour before it was transferred slowly with a syringe pump (≈ 5 h) to a CH_2Cl_2 solution (1.5 mL) of ethyl propiolate (0.035 mL, 0.35 mmol) and benzaldehyde (0.03 mL, 0.30 mmol) at −20 °C. The reaction mixture was stirred at −20 °C for 12 h before another portion of ethyl propiolate (0.025 mL, 0.25 mmol) was added dropwise into the reaction system. The reaction proceeded for another 20 h at −20 °C, after which it was quenched with 1 M aqueous HCl solution (5 mL). The two phases were separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phase was washed with brine and dried with anhydrous sodium sulfate. Purification by flash chromatography (EtOAc/hexane, v/v, 1:5) provided the pure product.

Ethyl 2-[Hydroxy(phenyl)methyl)-3-iodoacrylate (1): Isolated as a colorless oil (72 mg, 71% yield). IR (deposited from CH_2Cl_2 solution on NaCl plate): $\tilde{\nu}$ = 3449, 2982, 1711, 1189 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27−7.37 (m, 5 H), 7.24 (d, *J* = 1.5 Hz, 1 H), 5.52 (d, *J* = 5.5 Hz, 1 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 3.00 (d, *J* = 6.0 Hz, 1 H), 1.20 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8, 145.1, 140.1, 128.6, 128.2, 126.5, 86.7, 76.1, 61.4, 13.9 ppm.

Ethyl 2-[Hydroxy(*p*-tolyl)methyl]-3-iodoacrylate(2): Isolated as a colorless oil (78 mg, 75% yield). IR (deposited from CH_2Cl_2 solution on NaCl plate): $\tilde{\nu}$ = 3442, 2982, 1709, 1638, 1188 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.19−7.24 (m, 3 H), 7.13−7.18 (m, 2 H), 5.51 (d, *J* = 5.5 Hz, 1 H), 4.20 (q, *J* = 7.0 Hz, 2 H), 2.78 (d, *J* = 5.5 Hz, 1 H), 2.34 (s, 3 H), 1.23 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 145.2, 138.1, 137.1, 129.3, 126.5, 86.4, 76.3, 61.4, 21.1, 13.9 ppm.

Ethyl 2-[Hydroxy(naphthalen-1-yl)methyl]-3-iodoacrylate(3): Isolated as a colorless oil (65 mg, 57% yield). IR (deposited from CH_2Cl_2 solution on NaCl plate): $\tilde{\nu}$ = 3432, 1719, 1709, 1191 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.98−8.04 (m, 1 H), 7.80−7.90 (m, 2 H), 7.57−7.62 (m, 1 H), 7.44−7.56 (m, 3 H), 7.05 (d, *J* = 1.5 Hz, 1 H), 6.32 (d, *J* = 4.5 Hz, 1 H), 4.23 (q, *J* = 7.0 Hz, 2 H), 2.85 (d, *J* = 4.5 Hz, 1 H), 1.20 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.3, 145.1, 135.3, 133.8, 130.5, 129.2, 128.8, 126.6, 125.9, 125.3, 124.8, 123.4, 87.4, 72.4, 61.5, 13.9 ppm.

Ethyl 2-[Hydroxy(naphthalen-2-yl)methyl]-3-iodoacrylate (4): Isolated as a colorless oil (92 mg, 80% yield). IR (deposited from CH_2Cl_2 solution on NaCl plate): $\tilde{\nu}$ = 3436, 1710, 1190 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.80−7.85 (m, 4 H), 7.46−7.51 (m, 2 H), 7.39−7.43 (m, 1 H), 7.29 (d, *J* = 1.0 Hz, 1 H), 5.70 (d, *J* = 5.5 Hz, 1 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 3.03 (d, *J* = 6.0 Hz, 1 H), 1.20 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 145.0, 137.4, 133.13, 133.12, 128.5, 128.1, 127.7, 126.4, 126.3, 125.6, 124.3, 87.2, 76.3, 61.5, 13.9 ppm.

Ethyl 2-[(4-Benzyloxyphenyl)hydroxymethyl]-3-iodoacrylate (5): Isolated as a colorless oil (81 mg, 62% yield). IR (deposited from CH_2Cl_2 solution on NaCl plate): $\tilde{\nu}$ = 3349, 2927, 1719, 1709, 1509, 1243, 1175 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.30−7.48 (m, 5 H), 7.22−7.27 (m, 3 H), 6.93−6.97 (m, 2 H), 5.50 (d, *J* = 4.5 Hz, 1 H), 5.06 (s, 2 H), 4.19 (q, *J* = 7.0 Hz, 2 H), 2.70 (d, *J* = 5.5 Hz, 1 H), 1.22 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 158.7, 145.3, 136.7, 132.5, 128.6, 128.0, 127.9, 127.5, 114.9, 86.1, 75.7, 70.0, 61.4, 14.0 ppm.

Ethyl 2-[Hydroxy(4-methoxyphenyl)methyl]-3-iodoacrylate (6): Isolated as a colorless oil (60 mg, 55% yield). IR (deposited from CH_2Cl_2 solution on NaCl plate): $\tilde{\nu}$ = 3468, 2981, 1718, 1512, 1251, 1179, 1031 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.21−7.28 (m, 3 H), 6.84−6.90 (m, 2 H), 5.50 (d, *J* = 5.5 Hz, 1 H), 4.20 (q, *J* = 7.0 Hz, 2 H), 3.80 (s, 3 H), 2.73 (d, *J* = 5.0 Hz, 1 H), 1.23 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 159.5, 145.4, 132.2, 127.9, 114.0, 86.0, 75.7, 61.4, 55.3, 14.0 ppm.

Ethyl 2-[(4-Fluorophenyl)hydroxymethyl]-3-iodoacrylate (7): Isolated as a colorless oil (68 mg, 65% yield). IR (deposited from CH_2Cl_2 solution on NaCl plate): $\tilde{\nu}$ = 3449, 2926, 1710, 1509, 1225, 1190 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27−7.34 (m, 3 H), 7.01−7.07 (m, 2 H), 5.53 (d, *J* = 5.0 Hz, 1 H), 4.20 (q, *J* = 7.0 Hz, 2 H), 2.87 (d, *J* = 5.5 Hz, 1 H), 1.23 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8, 163.5, 161.6, 144.9, 135.9, 128.4, 128.3, 115.6, 115.5, 86.9, 75.6, 61.5, 14.0 ppm.

Ethyl 2-[(4-Chlorophenyl)hydroxymethyl]-3-iodoacrylate (8): Isolated as a colorless oil (78 mg, 71% yield). IR (deposited from CH_2Cl_2 solution on NaCl plate): $\tilde{\nu}$ = 3449, 2925, 1718, 1708, 1190 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.25−7.34 (m, 5 H), 5.50 (d, *J* = 5.5 Hz, 1 H), 4.20 (q, *J* = 7.0 Hz, 2 H), 3.06 (d, *J* = 5.5 Hz, 1 H), 1.24 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7, 144.6, 138.7, 134.0, 128.7, 127.9, 87.3, 75.5, 61.6, 13.9 ppm.

Ethyl 2-[(4-Bromophenyl)hydroxymethyl]-3-iodoacrylate (9): Isolated as a colorless oil (91 mg, 74% yield). IR (deposited from CH_2Cl_2 solution on NaCl plate): $\tilde{\nu}$ = 3437, 2981, 1718, 1486, 1189 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.45−7.50 (m, 2 H), 7.28−7.32 (m, 1 H), 7.18−7.24 (m, 2 H), 5.48 (d, *J* = 5.5 Hz, 1 H), 4.20 (q, *J* = 7.0 Hz, 2 H), 3.06 (d, *J* = 6.0 Hz, 1 H), 1.24 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7, 144.5, 139.2, 131.7, 128.2, 122.2, 87.5, 75.6, 61.6, 13.9 ppm.

Ethyl 2-[Hydroxy(4-trifluoromethylphenyl)methyl]-3-iodoacrylate (10): Isolated as a colorless oil (88 mg, 73% yield). IR (deposited from CH_2Cl_2 solution on NaCl plate): $\tilde{\nu}$ = 3450, 1709, 1322, 1166 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.5 Hz, 2 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 7.35 (d, *J* = 1.0 Hz, 1 H), 5.58 (d, *J* = 6.0 Hz, 1 H), 4.21 (q, *J* = 7.0 Hz, 2 H), 3.21 (d, *J* = 6.0 Hz, 1 H), 1.23 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.6, 144.2, 144.1, 130.3 (q, *J* = 33 Hz), 126.8, 125.5 (q, *J* = 4.0 Hz), 123.9 (q, *J* = 278 Hz) 88.1, 75.7, 61.7, 13.9 ppm.

Ethyl 3-Hydroxy-2-iodomethylene-5-phenylpent-4-enoate (11): Isolated as a colorless oil (36 mg, 35% yield). IR (deposited from CH_2Cl_2 solution on NaCl plate): $\tilde{\nu}$ = 3449, 2981, 1718, 1190 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36−7.39 (m, 2 H), 7.30−7.34 (m, 3 H), 7.24−7.28 (m, 1 H), 6.67 (d, *J* = 16 Hz, 1 H), 6.21 (dd, *J* = 6.5, 16 Hz, 1 H), 5.13 (dd, *J* = 6.0, 6.0 Hz, 1 H), 4.31 (q, *J* = 7.0 Hz, 2 H), 2.76 (d, *J* = 5.5 Hz, 1 H), 1.34 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 144.6, 136.0, 132.4, 128.6, 128.1, 127.8, 126.6, 88.6, 75.0, 61.6, 14.1 ppm.

Ethyl 3-Hydroxy-2-(iodomethylene)hex-4-enoate (12): Isolated as a colorless oil (33 mg, 37% yield). IR (deposited from CH_2Cl_2 solution on NaCl plate): $\tilde{\nu}$ = 3423, 2980, 2920, 1719, 1188 cm^{-1}. ^1H

NMR (500 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 1.0 Hz, 1 H), 5.74−5.83 (m, 1 H), 5.48−5.56 (m, 1 H), 4.89 (dd, *J* = 6.0, 6.0 Hz, 1 H), 4.31 (q, *J* = 7.0 Hz, 2 H), 2.53 (d, *J* = 6.0 Hz, 1 H), 1.69−1.73 (m, 3 H), 1.36 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1, 145.3, 129.9, 129.5, 85.3, 75.1, 61.4, 17.7, 14.1 ppm.

Ethyl 2-(1-Hydroxy-2-methylpropyl)-3-iodoacrylate (13): Isolated as a colorless oil (40 mg, 45% yield). IR (deposited from CH_2Cl_2 solution on NaCl plate): $\tilde{\nu}$ = 3450, 2964, 1719, 1710, 1189 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.02 (d, *J* = 1.0 Hz, 1 H), 4.32 (q, *J* = 7.0 Hz, 2 H), 4.08 (td, *J* = 7.0, 1.0 Hz, 1 H), 2.47 (d, *J* = 7.0 Hz, 1 H), 1.84 (o, *J* = 6.5 Hz, 1 H), 1.36 (t, *J* = 7.0 Hz, 3 H), 0.96 (d, *J* = 6.5 Hz, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7, 146.2, 84.3, 80.9, 61.5, 32.8, 19.2, 17.5, 14.1 ppm.

Ethyl 2-[Cyclohexyl(hydroxy)methyl]-3-iodo-acrylate (14): Isolated as a colorless oil (47 mg, 46% yield). IR (deposited from CH_2Cl_2 solution on NaCl plate): $\tilde{\nu}$ = 3450, 2927, 1710, 1188 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.99 (d, *J* = 1.0 Hz, 1 H), 4.33 (q, *J* = 7.0 Hz, 2 H), 4.08 (t, *J* = 7.0 Hz, 1 H), 2.49 (d, *J* = 7.0 Hz, 1 H), 1.90−1.97 (m, 1 H), 1.69−1.80 (m, 2 H), 1.64−1.68 (m, 1 H), 1.55−1.60 (m, 1 H), 1.46−1.54 (m, 1 H), 1.38 (t, *J* = 7.0 Hz, 3 H), 1.06−1.27 (m, 3 H), 0.92−1.01 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6, 145.9, 84.4, 80.4, 61.5, 42.4, 29.5, 28.2, 26.2, 26.0, 25.8, 14.1 ppm.

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